

Topic: Overview of Cognitive Remediation for various neuropsychiatric disorders

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Introduction: Concept of cognition

Cognition is the mental action or process by which knowledge and understanding is developing in the mind. It is a process of acquiring knowledge and understanding through thought, attention, language, learning, memory, and perception. It refers to a range of mental processes relating to the acquisition, storage, manipulation, and retrieval of information. It underpins many daily activities in health and disease across age span. Cognition can be separated into multiple distinct functions dependent on brain circuits and neuromodulators.

Cognition can further be categorized into neurocognition and social cognition.” (Elvevåg & Goldberg, 2000) Neurocognition, non-social cognitive processes, involve domains such as attention, memory, and executive functioning. Social cognition refers to psychological processes that are involved in perceiving, inferring, and responding in social situations. (Green et al, 2008)

The ability to test, measure and monitor cognitive performance across the life span opens the chance for patients to be identified earlier, access treatment faster and stay healthy for longer, improving quality of life and reducing cost.

Cognition in Indian literature

In Yajur Veda (ऋग्वेद) Mind has been conceptualized as the inner flame of knowledge. In 34th Chapter of Yajur Veda first six mantras lucidly describe various aspects of mind which says “what is mind? Perceiving knowledge is mind, mind is described as Yog and Samadhi (state of mind), All our sensory organs are under control of mind, and they function under the control of mind.

eu Jks=a eu'p{kq%euks jlue~ euks ?kzk.ke~
euks oS czã bR;qikLo

A considerable part of Indian thought is devoted to the question of consciousness. Yoga Vasistha and Tripurarahasya claim to describe the nature of consciousness. The same is generally true of various works on yoga, the Upanishads, and even the earlier Vedic texts.

Cognitive abilities arise from a continuing reflection on the perceived world.

One Vedic statement tells us that Atman (Soul) consists of three Elements of Soul (Atman)

1.Mind(eu) 2. Vitality (izk.k) 3. Matter (okd~)

We may see these three elements pervading us as well as the whole world. Our mind represents knowledge (Kku), Vitality (izk.k) action (fdz;k) and matter (okd~) represents all worldly objects and all literature ('kCn). One vedic shruti says -

KkutU;k HkosfnPNk] bPNktU;k Hkosr d`frA

d`frtU; Hkosr dEeZ Rnsrr~d`reqP;rsAA

Knowledge begets will and will begets effort and effort begets action, action includes all born.

According to Sankhya, reality may be represented in terms of twenty-five categories. These categories form the substratum of the classification in Saivism. These categories are:

- Five elements of materiality, represented by earth, water, fire, air, ether.
- Five subtle elements, represented by smell, taste, form, touch, sound.
- Five organs of action, represented by reproduction, excretion, locomotion, grasping, speech.
- Five organs of cognition, related to smell, taste, vision, touch, hearing.
- Three internal organs, being mind, ego, and intellect; and inherent nature (prakṛti), and consciousness (puruṣa).

Cognition is set of all mental abilities and processes related to knowledge: attention, memory & working memory judgment & evaluation, reasoning & computation problem solving & decision making, comprehension & production of language (Miller & Wallis, 2009). The concept of cognition and perception have a detailed description in all the six Indian philosophies nyaya (logic), vaishesika (atomic theory), sankhya (analysis of matter and spirit), yoga (the discipline of self- realization), karma-mimamsa (science of fruitive work) and vedanta (science of God realization) with slight variations amongst each of the philosophies. All six schools of Vedic philosophy aim to describe the nature of the external world and its relationship to the individual, to go beyond the world of appearances to ultimate Reality, and to describe the goal of life and the means for attaining this goal. Perception and cognition have been described to have key role in the right means of knowledge (Swami, 2001).

Concept and mechanism of Cognition according to Sāṅkhya

It is a complex process: the senses (such as sight) cognize their respective objects (color and shape) through the physical organs (such as the eye) and these senses are themselves the objects of cognition of the psyche (which in turn is comprised of three faculties the mind (manas), the intellect (buddhi), and the ego (ahankāra). The mind for its part internally constructs is a representation of objects of the external world with the data supplied by the senses. The ego contributes personal perspective to knowledge claims. The intellect contributes understanding to knowledge. The puruṣa adds consciousness to the result: it is the mere witness of the intellectual processes.

Perception, inference, and valid testimony are the means. By these all-other means of right cognition too are established (Virupakṣa, 1995)

Concept and Mechanism of Cognition according to Yoga

According to Patanjali's epistemology (Taimini, 1986), cognition is possible only because citta is coloured by both the object and the mind itself. Sensory impressions from the external world continually bombard the functions of sight, hearing, smell, taste and touch. As the mind defines the object, so the object defines the mind. Manas then registers the objects of

cognition and controls the response. It does so by drawing from the memory bank of karma stored in the mind. So, the model of Cognition according Sāṅkhya and Yoga is almost replicable except for the fact that Buddhi in Yoga is represented by Chitta.

Schematic presentation of mechanism of cognition according to ancient Vedic literature describe as in figure.1 and relation of cognition and consciousness in figure.2

Figure 1: Schematic presentation of mechanism of Cognition - according to Sankhya and Yoga

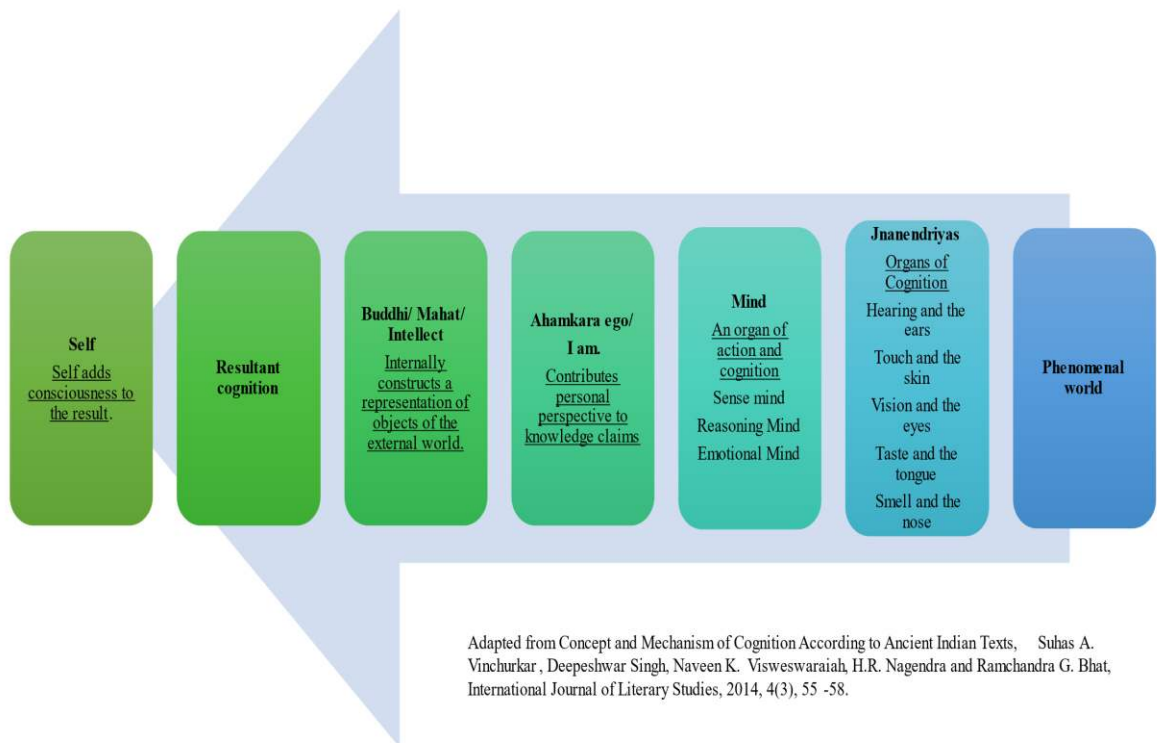
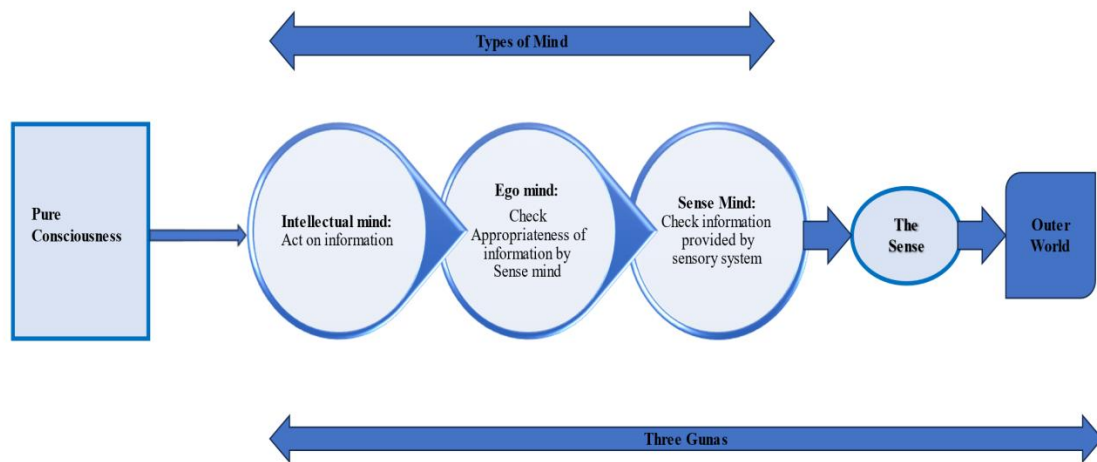


Figure.2 Connection cognition and consciousness as per Indian thought systems

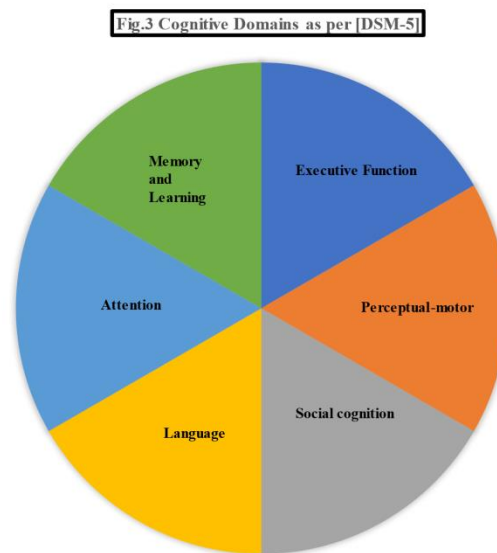


Adapted from How Do Theories of Cognition and Consciousness in Ancient Indian Thought Systems Relate to Current Western Theorizing and Research?

Peter Sedlmeier^{1,*} and Kunchapudi Srinivas² Front Psychol. 2016; 7: 343. Published online 2016 Mar 15

Cognitive function in Modern Medicine

Cognition has served the important function of human existence and area of interest for research for several years. Fig.3 explains the major domains of cognition as described in DSM 5.



Cognitive impairment in Psychiatric disorders

Cognitive function plays an important role in daily life. It is commonly known that widespread impairment in cognitive function is an essential feature of many mental disorders.^{Kurtz} Cognitive deficits may result in poor attention, problems in processing information, difficulties with remembering and recalling, and response-related problems.^{Trivedi}

Cognitive impairments have an impact on several domains, including everyday living, education, employment, and interpersonal relationships^(Goldberg-Green Matrics). Impaired cognitive function leads to poor quality of life and socio-occupational impairment. The World Health Organization's disability model states that these cognitive impairments affect social functioning, community integration, and overall quality of life.^{Quiles C} Impairments in social and occupational functioning in schizophrenia were strongly related to the impairments in neurocognition.^{Green}

In Earlier era, Bleuler and Kraepelin explored cognitive impairment in schizophrenia.^{Bleuler and Krepeline.} However, modern psychiatric disorder nosology and diagnostic criteria often focus on emotional and behavioural symptoms of the condition and undermine cognitive function and cognitive impairment. With advancements in medical science, psychiatric interventions and treatment of cognitive symptoms and cognitive impairment gain further attention in research and clinical practice.

Wide range of prevalence rates of cognitive impairment have been reported in common psychiatric disorders.

Reichenberg et al studied Neuro-cognitive performance in Schizophrenia, Schizoaffective disorder, Bipolar disorder, and Depression. All four groups demonstrated impairments in memory, executive functions, and attention and processing speed. However, more pronounced impairment was noted in the schizophrenia subgroup.

Konstantakopoulos et.al in a study of bipolar and schizophrenia patients highlighted significantly impaired in general intellectual ability, verbal memory and learning, and executive functions compared to healthy controls.

Patients with schizophrenia performed significantly worse than patients with bipolar on verbal memory tasks, whereas the bipolar group did not have a significantly lower score than schizophrenia in any task.

Schizophrenia patients performed worse than a control group on attention, processing speed and immediate memory tests, while Bipolar patients on visuospatial ability and working memory.

Both Schizophrenia and Bipolar groups did not differ from the control group regarding Theory of Mind.

Study results of Konstantakopoulos et.al show stable schizophrenia and euthymic bipolar disorder exhibit similar profiles of cognitive impairment, consistent with previous studies suggesting that the differences are related to the extent and degree of impairments, rather than being qualitative.^{Konstantakopoulos}

Schizophrenia is one of the most severe and disabling psychiatric illnesses. Cognitive impairment in schizophrenia is severe, enduring, and associated with poor outcomes. Nearly 80% of persons with schizophrenia and 40% of patients with depression have cognitive impairment.^{Raffard S and Mokhtari et al}

Cognitive deficits in mood disorders studied extensively but the overall pattern of specific cognitive impairment has not always been consistent. Common problems identify in the area of attention, executive function, and recall memory.^{Marvel}

In depression, cognitive impairment can be severe and generalized. Cognition is considered one of the core features of diagnosing depression for a long period.^{APA} Meta-analysis of the first episode of Major depressive disorder showed cognitive deficits in psychomotor speed, attention, visual learning and memory, and all aspects of executive functioning.^{Rico}

Depressive symptom improvement and the number of previous depressive episodes moderated the extent of cognitive changes. It demonstrates scar-like features of depressive episodes on cognitive domains.^{Ahern}

Cognitive function in depression improves marginally with treatment intervention. Working memory, verbal memory, and verbal fluency were most sensitive to change. Executive function, processing speed, and nonverbal memory were less sensitive to change.^{Bernhardt M}

A study in adolescent patients with depression showed neuropsychological deficits in MDD compared to controls in the cognitive domains of executive function, working memory, psychomotor and processing speed, verbal fluency, and visual (-spatial) memory.^{Baune}

In first-episode bipolar disorders, impairment in psychomotor speed, attention and working memory, and cognitive flexibility were identified, whereas smaller deficits were found in the domains of verbal learning and memory, attentional switching, and verbal fluency.

Cognitive deficits can be identified during euthymic or in remission state of disorder also. Studies have shown structural and functional changes in DLPFC which are consistent with impairment in Attention, Executive function, and memory.^{Marvel}

Commonly identified difficulties in OCD are visuospatial and visuoconstructionl areas. Some Studies identify impairment in non-verbal memory. However verbal memory is usually preserved in most cases.

Memory problems are the core feature of PTSD, studies show verbal and autobiographical memory impairment in PTSD.

A study conducted on individuals with acute PTSD revealed deficits in high-level attentional resources, working memory, executive function, and memory.^{Lagarde}

Cognitive impairment in psychiatric disorders has been reported in most of domains and more pronounced in certain sub domains of the cognition in different disorders.

Multiple factors and interactions at a cellular level are responsible for cognitive impairment in psychiatric patients. We have enlisted some prominent molecular changes responsible for cognitive impairment in Table.1

Tab.1 Molecular Mechanism for Cognitive Impairment in Psychiatric Disorder ^{Wang Y}	
Genetics	The N-methyl-D-aspartate-glutamate (NMDA) network is principally involved in schizophrenia and cognitive trait impairment.
	GWAS of MDD and cognitive function found that there were 48, 116, and 32 SNPs significantly associated with executive function domains, processing speed, and global cognition, respectively.
Epigenetics	DNA methylation and gene silencing
	Histone modifications
	non-coding RNA (ncRNA)
	miRNAs

Neurotransmitter deficits	Cognitive impairment is mostly associated with the glutamatergic system, the dopaminergic neurotransmitter system, the gamma-aminobutyric acid (GABA) system, and the serotonin system.
Proinflammatory cytokines, neurotrophins	IL-6
	TNF- α

Assessment and Quantification of Cognitive Impairment

Assessment of cognitive function is a challenging yet an integral component of psychological, psychiatric, and neurological evaluation. Cognitive assessment tests, tools, scales, and batteries is used for screening for the presence of any cognitive impairment and differential diagnosis, determining the severity of the disorder, monitoring disease progression, and determining treatment efficacy. Cognitive impairments include reductions in general intellectual capacity and domain-specific areas such as memory, attention, processing speed, executive functions, and social cognition. (Sheffield et al, 2018) and assessment in particular domain of cognition helps us to understand and quantify cognitive impairment in better way.

It is mandatory to use relevant normative data to understand the cognitive status of an individual and derive empirical conclusions that are strongly based on well-understood theoretical rationales of psychometrics and neuroscience. Ever since, it was understood that populations differing in their demographic characters show difference in test performance; population-based normative studies have become the need of the hour. Unfortunately, even seemingly homogenous populations exhibit within-group differences, and thus, the task of developing and using theoretically and ecologically valid instruments for the empirical assessment of cognitive function in a known heterogeneous population as in India is proving to be an enormous challenge for researchers and clinicians. The Indian demographics does not just differ by language and religion but also by a myriad of cultural and socioeconomic confounding factors, some of which have not yet even been identified as possible confounders.

The NIH-funded MATRIC project developed a tool for an assessment and quantified change in cognitive impairment in clinical trials. Seven distinct cognitive parameters were identified for measurement; Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory, Reasoning and Problem Solving, and Verbal Comprehension.^{Nuechterlein}

As a result of growing interest in social cognition and further data supporting its applicability to clinical trials assessing the effects of potential cognitive enhancers on cognitive function and performance, the eighth domain—social cognition—was added later.^{Nuechterlein}

Verbal Comprehension was not considered appropriate for a cognitive battery intended to be sensitive to cognitive change, due to its resistance to change.

The remaining seven domains were recommended for inclusion in the MATRICS-NIMH consensus cognitive battery and will serve as the basic structure for that battery.^{Nuechterlein}

- Speed of processing,
- Attention/vigilance,
- Working memory,
- Verbal learning,
- Visual learning,
- Reasoning and problem-solving,
- Social cognition

Major component and subcomponents used in neuropsychiatric assessment listed in Table.2 and common neuropsychiatric tests listed in Table.3

Tab.2 Cognitive domains and commonly used subtypes in Neuropsychiatric assessment

Memory	Executive functioning	Attention and Processing speed	Perceptual and Motor skills	Language /verbal skills	Social Cognition
Working memory	Planning and decision-making	Semantically relevant (fluency)	Object recognition	Naming	Recognition of emotions
Episodic/declarative memory	Problem-Solving	Coding and tracking	Organizational strategies	Fluency	Theory of mind
Procedural memory	Reasoning	Attention span	Construction	Reading	Insight
Semantic memory	Feedback response	Selective attention	Copying	Comprehension	Attributional style
Prospective memory	Inhibition	Sustained attention/vigilance	Drawing		
	Flexibility	Divided attention	Other praxis skills		

Tab.3 Common cognitive domain and test for assessment [Russo M/Organic Psychiatry]

Attention	Continuous Performance Test: Identical Pair
	Trail Making Test Part A
	Digit Symbol Substitution
	Digit span forward; spatial span forward
Working memory	Wechsler Memory Scale; spatial span; letter-number span
	Letter-number sequencing
	Digit span backward; spatial span backward
Verbal learning and memory	Hopkins Verbal Learning Test (HVLT)

	Rey Auditory Verbal Learning Test (RAVLT); Category Cued Recall
	Logical Memory 1 and 2; RAVLT total and delayed recall
	California Verbal Learning Test-second edition (CVLT-II) total recall
	short-delayed free recall and long-delayed free recall
	Buschke Selective Reminding Test (SRT)
	HVLT total and delayed recall
Visual learning and memory	Brief Visuospatial Memory Test
	Rey–Osterrieth Complex Figure Test (RCFT)
	Visual reproduction 1 and 2;;
	Rey Complex Figure Test (RCFT)
	30-min delayed recall
	Wechsler Memory Scale (WMS);
	Visual Memory Index
Executive Function Test; Reasoning and problem solving	Paired Associates Learning test
	Wisconsin card sorting test
	Phonological fluency; semantic fluency
	verbal fluency letter and semantic fluency
	Stroop test
	Trail Making Test Part B
	Modified Card Sorting Test (MCST); CANTAB
Processing Speed	Intradimensional/extradimensional shift (ID/ED)
	Vigilance and Sustained Attention Test (WAFV)
	Trail-Making Test A and Test B
	Symbol digit Modalities test (SDMT)
	Familiar faces; Boston Naming Test
Social cognition	
	Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT)

Tab. 4 Disease wise commonly used cognitive instruments to measure cognitive impairment in psychiatric disorders.

Schizophrenia	Brief Cognitive Assessment Tool for Schizophrenia (B-CATS)
	Screen for Cognitive Impairment in Psychiatry (SCIP)
	Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)
	Cambridge Neuropsychological Test Automated Battery (CANTAB)
	Brief Assessment of Cognition in Schizophrenia (BACS)
	Schizophrenia Cognition Rating Scale (SCoRS)
	Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS)
Bipolar Disorder	International Society for Bipolar Disorders (ISBD) for assessment of neurocognition in bipolar disorder (ISBD-BANC)
ADHD	Questionnaire for Complaints of Cognitive Disturbances

Cognitive remediation: Basic principles

Cognitive remediation also known as cognitive enhancement or cognitive rehabilitation. Its training-based behavioral intervention operates on learning principles.⁰⁰⁰

The “Cognitive Remediation Expert Working Group” has defined cognitive remediation as a behavioral training intervention targeting cognitive deficit, using scientific principles of learning, with the ultimate goal of improving functional outcomes.^{Wyake}

Its effectiveness is enhanced when provided in a context (formal or informal) that provides support and opportunity for extending to everyday functioning.^{Bowie CR}

Specifically, targeting improvement in memory, attention, executive functions, thinking, processing speed, motor tasks, and metacognition.

Studies have shown cognitive remediation improved self-care, social relations, and functionality in the individual.

Cognitive remediation acts as a complement to medication and psychological therapies, which constitute the core methods of treatment for schizophrenia.^{Demily}

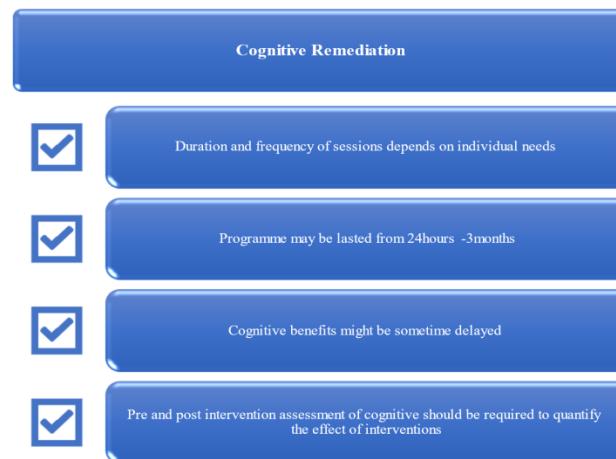
The history of cognitive remediation or rehabilitation techniques date back to times when drill and practice restoration methods were the only behaviour modification techniques in

use.^{tripathi a}The primary goal of the intervention though is the effective use of the obtained skill in independent daily living.^{Zaytseva Y}

Keshavan et.al define cognitive training as behavioural training affecting cognitive or social learning, which can be scalable and reproducible, to potentially improve function.^{keshvan}

Features and Benefits and of cognitive remediation described in Figure 4 and Table 5 respectively.

Figure.4 Features of Cognitive Remediation treatment

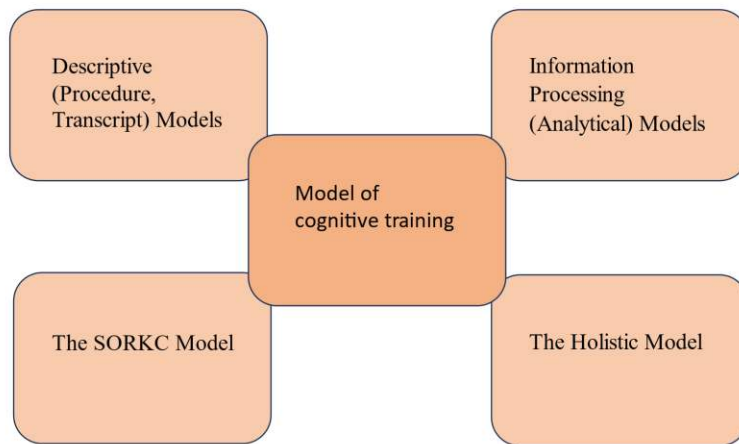


Tab.5 Impact of Cognitive deficits and potential benefits of Cognitive Remediation in Psychiatric disorders (Tripathi et al, 2018)

Impact of Cognitive deficits		Benefits of Cognitive Remediation
1	Impaired neuroplasticity	Increase in neuroplasticity
2	Decreased functional connectivity in brain	Improvement in functional connectivity in brain
3	Decreased physiological activity in specific brain areas	Improvement in physiological activity in specific brain areas
4	Impairment in functioning	Improvement in functioning
5	Disability	Improvement in disability

Cognitive training can be done via various model as described by Malhotra et.al in figure 5

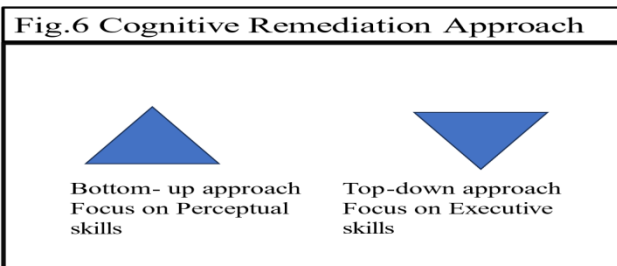
Fig.5 Theoretical model of cognitive training [Malhotra et.al]



Primarily two main approaches use in Cognitive remediation as describe in (Fig 6).Top-down (or executive) and bottom-up (or perceptual) approach.^{Nuechterlein}

The top-down processing strategy concentrates on higher-level cognitive processes that integrate and coordinate lower-level processes.^{Nuechterlein}

The bottom-up processing approach focuses on enhancing lower-level cognitive processes (like attention) and progresses towards higher-level processes.^{Nuechterlein}



Techniques of Cognitive Remediation ^{Fact Sheet}

Various techniques used to improve cognitive function via mental exercise, learning strategies, skills, and awareness Listed in Table-6

Tab. 6 Techniques of cognitive Remediations

Techniques	Explanation	Examples
Restorative task practice	Based on mental exercises	Cogpack, PSS CogRehab, PositScience
Strategy Coaching	Learning strategies to improve cognitive performance	Reading information aloud Story telling
Compensatory Skills training	Training provides to improve cognitive ability in the daily tasks and optimizing community functioning and living.	Activity Scheduling Minimising distractions
Metacognitive training	Increasing awareness about self-mental ability and thoughts and channelised to improved cognitive performance.	Asking the participant to pay attention to how and when they improved their performance on a particular cognitive task Noting what things led them to become distracted.

Although, efficacy of Cognitive remediation on neurocognition and on functional outcome, has been demonstrated, with inconstant continuation of benefit after completion of treatment.
Demily

Over last few years number of programs that were created—like IPT, CRT, NEAR, CET, NET, CRT, and CAT—are starting to be utilized more often. Few commonly used remediation approach and therapy listed in Table-7.

Tab. 7 Commonly used Remediation Approach and Therapy ^{Zaytseva Y}

Strategy coaching	Aim is to develop and maintain motivation via group-based cognitive exercise.
Neuropsychological educational approach to rehabilitation (NEAR)	Uses a strategy-coaching approach, target cognition and problem solving in group and individual setting
Neurocognitive	Computerized cognitive remediation + Social cognition in

enhancement therapy (NET)	individual and group setting.
Cognitive enhancement therapy (CET)	Small-group sessions with a specific emphasis on social cognition and supportive therapy.
Pair cognitive remediation	Embodies cognitive training and a supported employment program aiming to facilitate social recovery in schizophrenia
Cognitive adaptation training (CAT)	Home delivered cognitive rehabilitation strategy which is designed to train cognition in order to offer solutions to the daily life problems, specific and concrete to each individual
Brain fitness program (BFP)	a drill practice method, used in order to improve brain plasticity. The aim of BFP is to restore and amplify auditory perception and working memory processing through six exercises of increasing complexity.
CogPack	Computer assisted intervention, target cognitive function in individual settings
Braingame Brian	Computerised programme for autistic patient

Steps to improve the effects of Cognitive Remediation (Trapp et al, 2022)

- Identify the patient in need
- Assess for cognitive deficits
- Consider augmentation of CR with different components- Social cognition training, combining with Physical exercise, focusing on CR to improve clinical symptoms
- Having fun activities for improving motivation and developing positive state
- Consider utilising hot cognitions (through tasks based on emotionally relevant stimuli)
- Encourage metacognitions (thinking about thinking)
- Helping to build bridges (to improve functioning)
- Training for appropriate period and observing for long term benefit

Predictors of Response in Cognitive Remediation

Various predictors of response in cognitive remediation described in table 8.

Evidence suggests greater role of therapist related factors in form of expertise, training, active engagement, plan of integrated intervention for better response of cognitive remediation (Barlatti et al 2019). Hence, it should be delivered by trained professionals, clinical psychologist with expertise in the area.

(Medalia & Richardson, 2005; McGurk et al, 2007; Wykes et al, 2011; Tripathi et al, 2018; Barlati et al 2019, Vita et al, 2021)

Tab. 8 Predictors of Response in Cognitive Remediation in Schizophrenia		
Domain	Variables	Predictors of better response
Patient profile	Age	Adolescent, young age
	Genotype	COMT Met carrier, presence of BDNF polymorphism in older adults

	Cognitive reserve	Better cognitive / brain reserve, faster processing speed, better visual/verbal learning
	Illness related	Short duration of illness Earlier phase of illness Less severe positive symptoms Symptomatically stable Lower pretreatment negative symptoms, disorganization, hostility
	Motivation	High intrinsic motivation
	Emotional state	Positive mood state
Treatment	Use of precognitive agents	Glycine agonist (D-serine), Ampakines Modafinil, d-amphetamine Dopaminergic and cholinergic agents
	Use of Neuromodulation	Transcranial magnetic stimulation, transcranial direct current stimulation, vagal nerve stimulation
	Adjunctive interventions	Healthy lifestyle, aerobic exercise
	Therapist related	Trained Therapist Therapeutic alliance Active role of therapist
	Therapy related	Use of strategic cognitive remediation Presence of integrated treatment
	Medication related	Lower amount of antipsychotic intake & anticholinergic burden at baseline

Rationale for combining cognitive-enhancing drugs and cognitive remediation.

Cognitive- enhancing drugs have not as yet been successful and cognitive remediation has shown modest success. Therefore, in suitable cases the optimal approach may require a combination of cognitive-enhancing drugs with cognitive remediation. Though there is theoretical rationale, and preliminary evidence available, but there are practical challenges exist in this approach. (Michalopoulou et al, 2013)

Rationale of combining Cognitive Rehabilitation with Psychiatric Rehabilitation

Research indicates that when cognitive training and other psychosocial rehabilitation programs are used in conjunction with the adoption of a strategy coaching approach based on learning techniques, there is a considerable increase in social functioning.^{Lystad}

Meta-analysis by (Duin et al, 2019) included 23 studies on 1819 patients and found enhancing effects of Psychiatric Rehabilitation (PR) with Cognitive Rehabilitation (CR) with significant beneficial effects on vocational outcomes (e.g. employment rate: SMD = 0.41), and social skills (SMD = 0.24). No significant effects were found on relationships and outcomes of community functioning. Effects on vocational outcomes were moderated by years of education, intensity of the intervention, type of CR approach and integration of treatment goals for PR and CR. Type of PR was no significant moderator.

Studies, where cognitive remediation was combined with other forms of rehabilitation and when it included strategy coaching, demonstrated significantly better functional outcomes.
Emily

Brain stimulation modalities, such as repetitive transcranial magnetic stimulation (rTMS), is found to be effective in improving cognitive impairment as well as clinical symptoms of depression (Tikka et al, 2023).

Transcranial direct current stimulation (tDCS) has been found to be effective in improving cognitive functions (Jeon et al, 2018) as well as clinical symptoms (Nayok et al, 2024) in patients with schizophrenia.

Evidence of Cognitive Remediation in Major Psychiatry and Neuropsychiatry Disorder [Early Psychosis, Schizophrenia, Bipolar, Depression, Dementia, Anxiety disorder, Substance use disorders, Autism, ADHD, Eating disorders etc.]

The biological basis of Cognitive Remediation shown by increased brain activation in regions associated with working memory particularly the fronto cortical areas.^{Wykes, T}

Cognitive impairment is prominent in high-risk individuals and early stages of psychosis. Its more responsive to remediation techniques during early stages of psychosis (McGorry et al, 2009; Wykes et al, 2018). CR has been found effective in improving cognitive impairment, community functioning, emotional regulation and clinical symptoms in early-stage of psychosis (Keshavan et al, 2014). CR also influence brain plasticity by targeting neural functions and restoring neural networks in early psychosis (Best et al, 2019).

Cognitive Remediation produces small to moderate improvements in cognition and depressive symptoms in mood disorders.^{Goldberg Z}

Models examining the effects of cognitive remediation versus Control at post-treatment showed medium to large effects of cognitive remediation on processing speed, visual learning, and memory. Cognitive remediation was not associated with change in community functioning, although cognitive change was associated with functional change across the sample.^{Lewandowski}

Metanalysis Cognitive rehabilitation for improving cognitive functions and reducing the severity of depressive symptoms in adult patients with Major Depressive Disorder concluded moderate and significant effects on the executive function, verbal learning, and working memory of MDD patients. However, there were no significant differences between intervention and control groups in attention or depressive symptoms.^{Mokhtari et al.}

Cognitive remediation interventions are potentially effective in improving social cognition and cognitive functioning in autistic spectrum disorder. RCTs supported the efficacy of CR interventions in improving social cognition and executive functioning.^{Dandil Y}

Cognitive remediation effectiveness was demonstrated in children and adolescents with attention deficit hyperactivity disorder (ADHD) [Hamza M], anorexia nervosa [Harrison A, Tchanturia K], specific learning disorder [Azizi A], intellectual disability [Demily C] and in early onset psychosis [Puig O].

CR in patients with Dementia have reported improvement in cognitive functions, behavioral problems and quality of life. Several techniques have been used including validation therapy, reality orientation therapy, digital interventions etc. (Boccardi & Frisoni, 2006)

Vast evidence suggests beneficial effects of CR along with holistic rehabilitation approach through manualised, digital as well as in-person training improve functional outcome and cognitive deficits in person with Traumatic brain injury (TBI) (Lynch, 2002; Khan et al, 2003)

Conclusion

The study by Alice et.al to examine factors influencing positive responses to cognitive remediation in schizophrenia includes patients' motivation, work style, chronicity of illness, intensity, type of treatment, and clinician's experience.^{alice}

The benefits of Cognitive Remediation are especially relevant for chronic and severe patients with schizophrenia. Current evidence indicates that it significantly improves many outcomes, including memory, attention, problem-solving, cognition, social cognition, independent living skills, and social adjustment.

Pharmacological treatment falls short of bringing noticeable changes in cognitive as well as socio-affective processing. Cognitive training-based interventions are safe, preventive remedial measure for individuals at younger ages and at earlier stages of illness.

Considering cognitive heterogeneity in psychiatric disorders, it is crucial to identify whether particular groups of patients benefit from cognitive remediation therapy. Hence, early detection of psychiatric disorder and timely intervention for illness (with comprehensive management) and cognitive symptoms (through remedial measures) may restrict development of stable deficits and disability and likely to improve overall illness course, prognosis, and functioning.

Comprehensive assessment of cognition should focus not only on areas of impairment that may affect function but also on areas of cognitive strength and personal resources that may support the pursuit of stated goals. Assessment will also allow the therapist to tailor remediation to the patient's preferences, strengths, and learning style, which could serve to increase the patient's intrinsic motivation to engage in cognitive remediation. This personalized approach should be maintained throughout the course of the intervention regardless of the illness stage or treatment setting.

Evidence also exists that even after cognitive intervention; there is no noticeable improvement in the outcomes.

Also, Psychiatric disorders are heavily influenced by social-emotional experiences and developmental context. This also calls to improve our understanding mechanism of cognitive defect, training of content, response time.

Gap areas and directions for Future Research

First, it is crucial to detect the impairments that will be targeted in each patient presenting a specific pattern of impairments. For this purpose, validated and customized neuropsychological tests are required. Then, cognitive remediation programs must then be customized to each patient's needs to motivate the patient to participate. Finally, long-term effects must be assessed to verify whether reinforcement is needed. Following these steps, most of the studies show an improvement in the well-being of patients with schizophrenia. These recommendations are also suitable for the cognitive remediation programs, as for treatments with cognitive assistive devices. An important hurdle facing the advancement of cognitive assistive technology programs is that different research groups work individually without a coordinated effort to improve and validate the existing programs.^{seblie}

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CLINICAL PRACTICE GUIDELINES 2024

ASSESSMENT AND MANAGEMENT OF MINOR NEUROCOGNITIVE DISORDER

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INTRODUCTION

Today neuroscience has progressed to understand that dementia is actually a late diagnosis. Just as cholesterol plaques start in the vascular system as early as the first decade of life, so too brain degeneration may pre-date manifestation of frank symptoms by 2-3 decades. Therefore, it is important to understand if clinically there is a grey zone between apparent normal brain functioning and obvious brain decline. This gap is what Mild Cognitive Impairment or Minor Neurocognitive Disorder (Minor NCD) is. A seminal discussion in 2003, led to acceptance of Minor NCD as a separate entity, and definition based on Petersen's criteria. Subsequently, these were modified to Winblad criteria, and those defined by NIA-AA (National Institute of Ageing and Alzheimer's Association) as well as fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-5 (which spoke of Minor Neurocognitive Disorder). The common thread in all of these was—*subjective recognition of cognitive errors, objective decline in neuropsychological tests and relatively intact ability to carry on with activities of daily living*.; the combination of which could lead to adequate distress and anxiety.^[1]

Hence systematic research of the same, and approach to assessment and care, is really the need of the hour. In India, the research is even more limited, and hence this guideline, which is a combination of best advised practices, and those followed easily in the sub-continent, so it can be easy for the treating psychiatrist to approach and manage.

PROCESS OF DEVELOPMENT

The development of the Clinical Practice Guidelines (CPG) for the assessment and management of Mild Neurocognitive Disorder was a rigorous and systematic effort led exclusively by a team of psychiatrists from leading institutions across India. The guidelines were crafted based on an extensive review of the latest scientific literature, including national and international guidelines such as those from the National Institute on Aging-Alzheimer's Association (NIA-AA), the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), and the International Classification of Diseases (ICD-11).

This process was driven by the need to address the specific challenges and nuances of diagnosing and managing MINOR NCD within the Indian population. The expert team engaged in multiple rounds of discussions and deliberations to ensure that the guidelines are evidence-based, clinically sound, and tailored to the Indian context. Following this, the draft was deliberated in a IPS workshop, incorporating the inputs of expert professionals throughout the country. The focus was on creating a comprehensive resource that reflects both the current scientific understanding of MINOR NCD and the practical realities faced by psychiatrists in India. The resulting guidelines aim to standardize and enhance the quality of care provided to individuals with MINOR NCD, ensuring that psychiatrists have a reliable and relevant framework for diagnosis and management. These guidelines may be modified by the clinicians as per individual's need and feasibility.

COGNITIVE RESERVE

When discussing about Minor NCD, it becomes imperative to understand the concept of cognitive reserve and its assessment.

Cognitive reserve (CR) is defined as brain's ability to cope with neuropathology/neurodegeneration by exploiting pre-existing cognitive processes and/or compensatory mechanisms, which is supposedly built

through a number of factors over the years. It reflects brain's flexibility and efficiency in utilizing available resources to maintain cognitive function despite aging or disease[Figure 1].

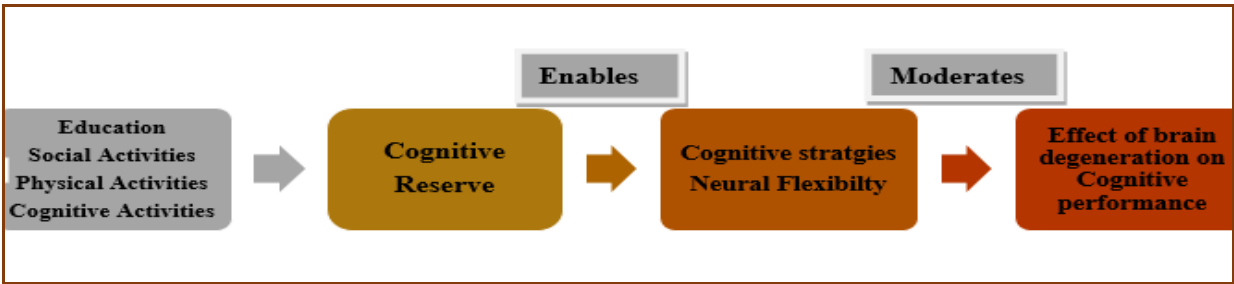


Figure 1: Cognitive reserve and its significance

Assessing cognitive reserve is crucial for understanding individual differences in susceptibility to cognitive decline and dementia. It helps in identifying those at higher risk and in tailoring interventions that can bolster cognitive reserve through lifestyle modifications and targeted cognitive training. Although there are no gold standard test available, however certain proxies are cumulatively reflective of CR. [Table 1]

Proxy	Details
Educational Attainment	Number of years of formal education.
Occupational Complexity	Complexity and intellectual demands of individual's occupation.
Engagement in Leisure Activities	Participation in cognitively stimulating activities such as reading, playing musical instruments, or engaging in social activities.
Premorbid Intelligence	Assessed using tests like the National Adult Reading Test (NART) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R)
Crystallized Intelligence	Measured through vocabulary and general knowledge tests
Physical Activity	Regular engagement in physical exercise
Social Engagement	Participation in social activities and maintaining social networks
Multilingualism	Proficiency in multiple languages

Table1: Proxies of CR and their assessment [2-3]

Some scales also have been formulated using one or more of above proxies or domains but are not widely used and researched. [Figure 2]

Scale	Components
	
☐ Cognitive Reserve Index Questionnaire (CRIq)	☐ Education, Working Activity, Leisure Time
☐ Cognitive Reserve Scale (CRS)	☐ Education, Occupation, Intellectual Activities
☐ Lifetime of Experiences Questionnaire (LEQ)	☐ Education, Occupational Complexity, Social and Cognitive Activities
☐ Cognitive Reserve Assessment Scale in Health (CRASH)	☐ Education, Occupation, Intellectual Activities, Leisure Activities
☐ Battery for the Assessment of Cognitive Reserve (BARC)	☐ Education, Occupational Complexity, Leisure Activities, Social Activities, Cognitive Tests

Figure 2: Scales for assessment of CR. ^[2-3]

MINOR NCD AS A DIAGNOSTIC ENTITY

The transition between normal aging and very early dementia has been described using various terms, such as MinorNCD, dementia prodrome, incipient dementia, and isolated memory impairment. Over the years Minor NCD has become widely used term, will be used here for the purpose of discussion. Minor NCD lies between normal aging and early dementia on the continuum, with overlapping stages at both ends of the Minor NCD [Figure 3], indicating that distinction between normal ageing and Minor NCD can be subtle and clinically challenging. However, Minor NCD has gradually been established as a distinct diagnosis, with specific criteria and intervention strategies. ^[4]



Figure 3: The Cognitive continuum showing the overlap in the boundary between normal ageing and Minor NCD and Early Dementia

Several terms have been used in connection to cognitive decline before Dementia, apart from Minor NCD over time, e.g. Benign Senescence Forgetfulness, Age-Associated Memory Impairment (AAMI), Age-Associated Cognitive Decline (AACD), Cognitive Impairment No Dementia (CIND), and very recently used Mild Neurocognitive Disorder in DSM-5.^[5]

PATHOLOGY IN MINOR NCD

Along with changes in the nomenclature, simultaneous changes occurred in the understanding of Minor NCD, summarized in Table 2. In addition to symptoms and cognitive assessments, brain pathology was also deliberated. The protein theories of Minor NCD emphasize the significant role of abnormal protein accumulation and aggregation in the brain, which can lead to cognitive decline. Table 3 summarizes the key proteins involved, their roles in Minor NCD, and underlying mechanisms.

Source	Designation	Individual's own Complaints	Informant Complaints	Clinical Suspicion	Objective Memory Impairment	Non-Memory Impairment	Social Cognition Impairment	Functional status	To Rule Out
Bly et al., 1995	Cognitive impairment no dementia (CIND)	Memory loss	P	P	P	P	NS	Variable	Dementia, delirium, psychiatric conditions
Petersen et al., 1999	Mild cognitive impairment (MCI)	Cognitive concerns	P	NS	N	NS	NS	Preserved	Dementia
Winblad et al., 2004	Mild cognitive impairment (MCI)	Cognitive concerns	P	NS	P	P	NS	Independent, less efficient at complex activities	Dementia
DSM-5, 2013	Mild neurocognitive disorder (mild NCD)	Cognitive concerns	P	P	P	P	P	Staying independent requires strategies	Delusions, mental disorders
NIA-AA, 2018	Mild cognitive impairment (MCI)	Cognitive concerns	P	P	P	P	P	Mild functional impairment in complex activities	Dementia, delirium, psychiatric conditions
ICD-11, 2019	Mild neurocognitive disorder (mild NCD)	Cognitive concerns	P	P	P	P	P	Mild decline in complex activities	Dementia, delusions, mental disorders, substance use

Table2- Evolution of Minor NCD as an entity.^[6]Foot note- P-present as criterion. N-absent, NS-not specified

Protein	Role and Mechanism in Cognitive Impairment
Amyloid-beta (Aβ)	Forms plaques, disrupting cell communication and inducing neuroinflammation, leading to synaptic dysfunction.
Tau	Forms neurofibrillary tangles inside neurons, disrupting intracellular transport and causing cell death.
Alpha-synuclein	Aggregates into Lewy bodies, disrupting synaptic function and contributing to cognitive decline.
TDP-43	Accumulates abnormally, disrupting RNA processing and causing neurodegeneration.
Ubiquitin	Dysfunction in protein degradation, leading to toxic aggregation of damaged proteins
Prion proteins	Misfolded proteins induce misfolding of normal proteins, causing cell death and neurodegeneration.

Table 3: Protein theories in etiopathogenesis of Minor NCD ^[7]

SUBTYPES OF MINOR NCD

MINOR NCD is heterogenous in presentations, depending upon the affected cognitive domain. Due to this, it has also been classified based on the type of cognitive domain affected. This classification relates to underlying etiology and pathology, clinical presentation, and outcomes. Figure 4 shows various subtypes and their probable outcome.^[8] Today, we understand that this classification is more clinical and less etiopathological, and probably too simplistic to understand Minor NCD. Nevertheless, it is important for the clinician to know.

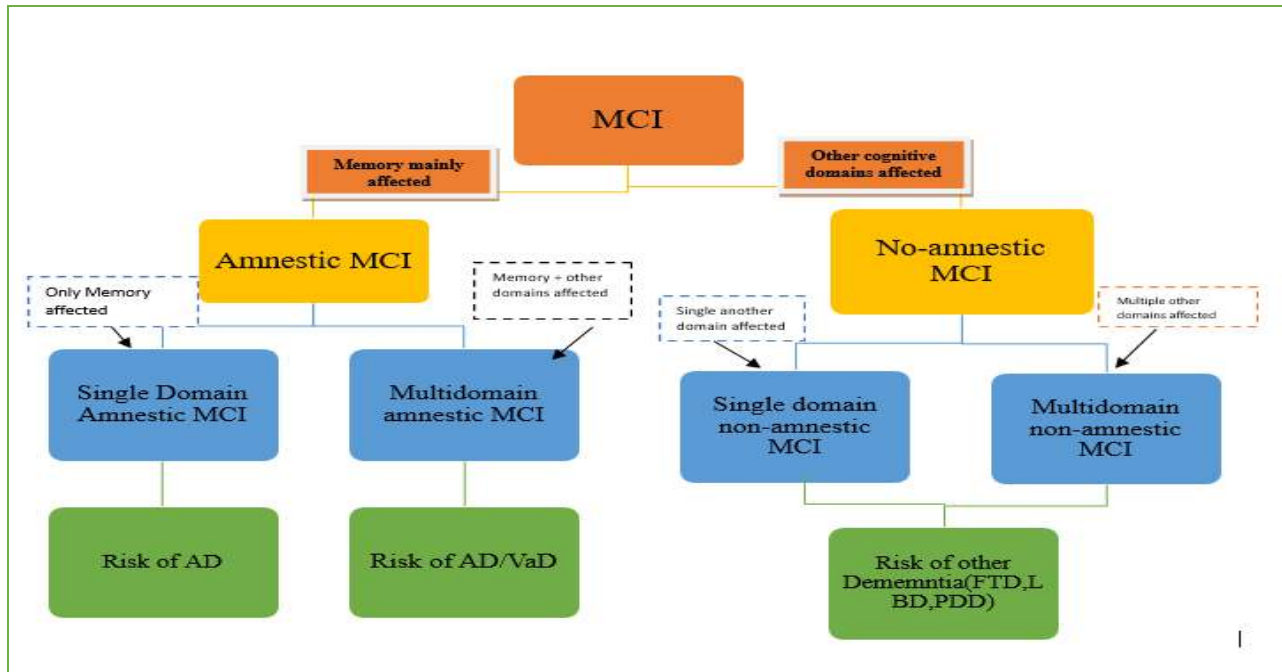


Figure4: Clinical subtypes of Minor NCD and their probable outcomes

PROGRESSION OF MINOR NCD

The course of Mild NCD is variable. It may remain static, gradually improve over time and may progress to dementia or Major NCD. Certain factors are associated with increased risk of progression to dementia which should be specifically looked for while assessment:

MODIFIABLE	NON-MODIFIABLE
High fat diet	Older age
Medical comorbidities: Metabolic syndrome, chronic inflammatory diseases, vascular disease, thyroid disorders, and elevated homocysteine levels	Lower cognitive reserve
Excessive alcohol intake	Presence of apolipoprotein E (ApoE) E4 allele
Stressful lifestyle	Magnetic resonance imaging (MRI), with volumetric measurements of the hippocampus at or below the 25th percentile for matched age and sex
Untreated mental illnesses	

DELAY IN SEEKING TREATMENT

Minor NCD may although affect one or more cognitive domains but does not interfere with person's capacity of independence in everyday activities, and often gets overlooked leading to delays in consultation, along with various other reasons. [Table 4]

Reasons for delay in seeking consultation in persons with MINOR NCD	
1.	Subtle Symptoms: Symptoms can be mild with insidious onset and slow progression, easy to be overlooked or dismissed as normal aging
2.	Stigma and Denial: Fear of diagnosis of dementia or being labelled
3.	Lack of Awareness
4.	Ageism - Perception of both physician and caregiver, as well as society toward the ageing individual, that loss of function/cognitive decline is expected, and does not require any medical intervention.
5.	Compensatory Strategies: Minor NCD patients often develop compensatory strategies in response to their cognitive deficits, such as using notes or relying on family members, which can mask severity of the impairment.
6.	Busy Lifestyles of patient/caregiver, leading them to postpone seeking medical advice.
7.	Healthcare Access: Limited access to healthcare, either due to geographic, financial, or systemic barriers, can delay consultation and diagnosis.
8.	Physician Detection: Even when patients do see a physician, mild symptoms can be missed or not thoroughly evaluated, leading to a delay in diagnosis.

Table 4: Reasons for delay in seeking consultation in person with Minor NCD

Need for assessment and early diagnosis in Minor NCD:

The need for diagnosis and intervention in Minor NCD is often questioned, owing to mild nature of its symptoms. Evidence suggests that Minor NCD may remain stable, return to neurologically intact state, or progress to dementia. However, risk of progressing to dementia than age-matched controls is higher, thus indicating the pathologic disease state of Minor NCD rather than normal aging. Minor NCD needs comprehensive assessment and timely interventions various reasons listed in Table 5.

Need for assessment and early diagnosis in Minor NCD	
1.	Early Intervention: Timely intervention can help manage symptoms, slow progression, and improve quality of life. Treatments and lifestyle changes are more effective when started early.
2.	Monitoring Progression: It can help track changes in cognitive function, allowing for adjustments in treatment plans.
3.	Patient and Family Planning: A diagnosis of Minor NCD enables patients and their families to

	plan for the future, including making financial, legal, and care arrangements, as well as addressing potential safety concerns, such as driving and living arrangements.
4.	Education and Support: A diagnosis allows healthcare providers to educate patients and their families about the condition, its potential progression, and ways to manage symptoms. Support groups and resources can be beneficial for coping with emotional and practical aspects of Minor NCD.
5.	Improving Overall Health: Diagnosing Minor NCD often involves comprehensive evaluation of patient's overall health. This can lead to the identification and management of other medical conditions that may impact cognitive function, such as DM, hypertension, and sleep disorders.
6.	Personalized Care Plans: These plans address specific needs and challenges of a patient, improving their overall well-being and support network.

Table 5: Need for assessment and early diagnosis in Minor NCD

ASSESSMENT OF PERSONS WITH SUSPECTED MINOR NCD

Any patient suspected of having Minor NCD should undergo detailed clinical evaluation and systematic investigations. A thorough history and physical examination, [specifically, central nervous system (CNS) examination] focusing on the status of cognitive functions, status of activities of daily routine, medications, neuropsychiatric evaluation, laboratory testing and neuroimaging are important components of this assessment[Figure 5].

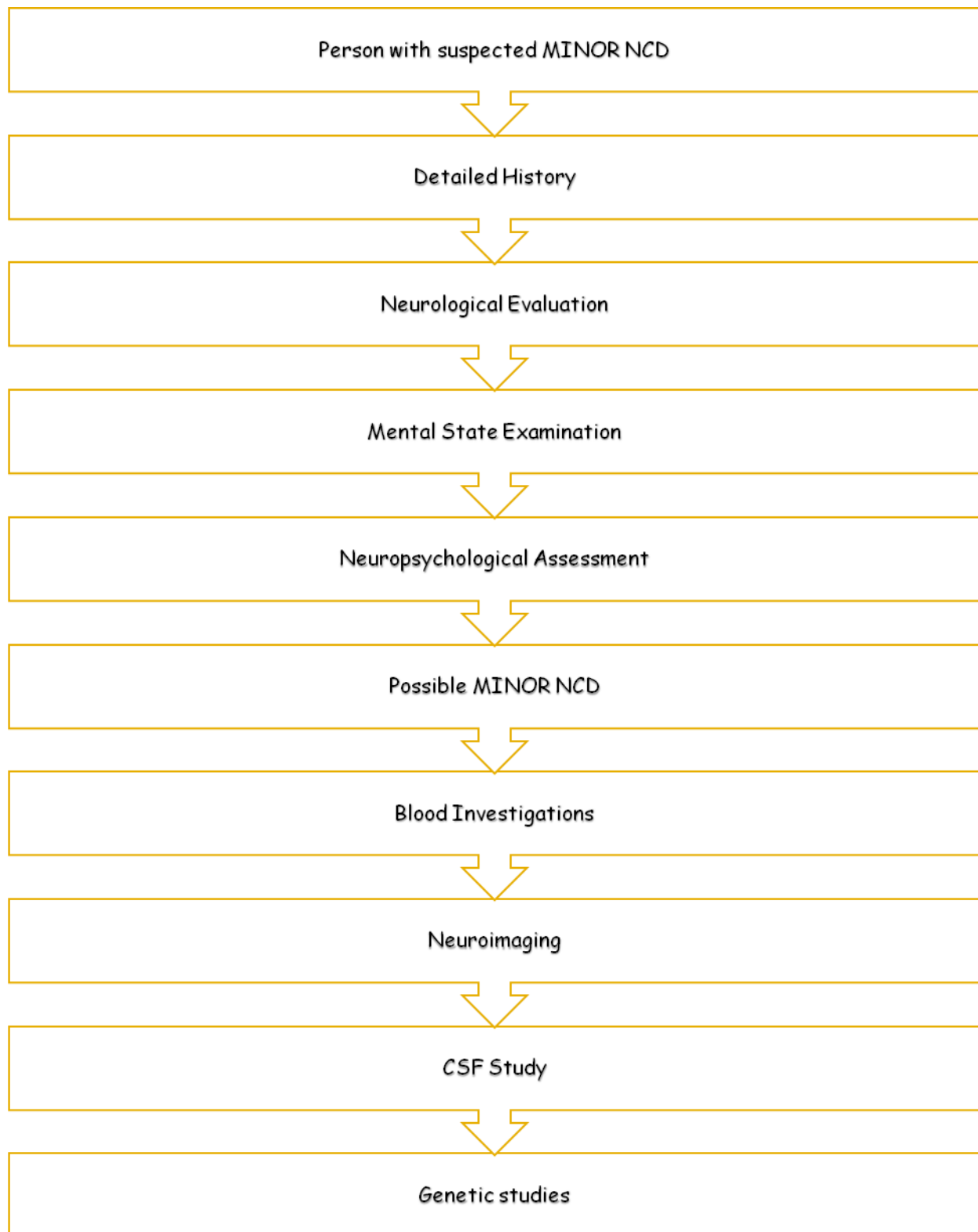


Figure 5: Overview of assessment in cases of a person with suspected Minor NCD

I. HISTORY TAKING

Taking a comprehensive history in patients with Minor NCD is crucial for accurate diagnosis and management. The history may focus on clarifying the points as mentioned in Table 6.

1. Detailed history of onset, duration, and progression of presenting symptoms (commonly cognitive)
2. Assessment for other behavioral and psychological symptoms
3. Effect of symptoms on individual's functioning
4. Establish the premorbid/ baseline functioning of the individual
5. Decline in cognitive reserve
6. Rule out other possible differentials for the cognitive complaints (e.g. normal ageing, dementia, delirium, depression etc.)
7. Elaborate medical history to rule out possible medical causes of the symptoms (utmost importance is to look for reversible causes of the cognitive symptoms)
8. History of substance use or intake of prescription medications

Table 6: Components of history to be elicited in patients with suspected Minor NCD

The history should incorporate the following considerations in detail:

- a) **Cognitive symptoms:** Detailed history of cognitive symptoms needs to be elicited. [Table 7]

• Defining the onset, duration, course, and progression of symptoms e.g., When was he/she last completely normal?
• Defining the nature of cognitive symptoms
• Memory domain: - Specific instances of forgetfulness (e.g., forgetting appointments, conversations, recent events). - Frequency and duration of memory lapses - Impact on daily activities (e.g., losing items, repeating questions)

• Language domain: - Word-finding difficulties (e.g., trouble naming familiar objects or people). - Problems with comprehension or following conversations. - Changes in fluency or coherence in speech.
• Visuospatial domain: - Getting lost in familiar places. - Difficulty judging distances - Problems with tasks requiring spatial orientation (e.g., driving, assembling objects).
• Attention and concentration domain: - Difficulty maintaining focus on tasks. - Easily distracted or trouble following conversations. - Impact on completing tasks or following instructions.
• Executive dysfunction: - Problems with planning, organizing, and problem-solving. - Difficulties in managing finances or medication. - Inability to multitask or follow multi-step instructions. - Preparing a meal - Household repairs - Using tools/appliances
• Social cognition - Difficulty in understanding nonverbal cues such as facial expressions, body language, or tone of voice - Reduced empathy - Avoidance of social interactions - Difficulty in maintaining family or workplace relations
• Situational Triggers - Times of day when symptoms are better or worse. - Specific situations or conditions that exacerbate symptoms (e.g., stress, fatigue).
• Compensatory Strategies - Techniques the patient uses to manage or mask symptoms (e.g., using reminders, relying on others, noting down things etc.). - Effectiveness of these strategies.

Table 7: Pointers in history of cognitive symptoms in suspected **Minor NCD**

The other important parameters to be assessed in history are summarized in the Table 8.

Parameters		Specific points to be explored
b)	Behavioral and psychological symptoms	Mood Changes: Presence of depression, anxiety, irritability, or apathy; and its impact on social interactions and relationships.
		Personality Changes: Noticeable changes in behaviour or personality (e.g., increased aggression, withdrawal, jocularity, disinhibition etc).
		Sleep Disturbances: Changes in sleep patterns (e.g., insomnia, excessive sleepiness).
		Psychotic Symptoms (if any): Presence of hallucinations or delusions
c)	Impact on daily life OR Changes/ decline in ability to perform	Activities of Daily Living(ADLs): Impact on basic activities (e.g., bathing, dressing, eating).
		Instrumental Activities of Daily Living (IADLs): more complex activities (e.g., managing finances, shopping, cooking, using technology)
d)	Past medical history	Medical history, with particular emphasis on prior neurologic (to rule out Parkinson's disease, normal pressure hydrocephalus, stroke, or neuropathy) or psychiatric conditions.
		Complete information should be obtained to rule out potentially reversible causes of cognitive decline (depression, vitamin B12/folate deficiency, thyroid diseases, etc.).
e)	History of ongoing medications	Review of ongoing treatment with special attention to - adherence - drugs with CNS activity, including over-the-counter drugs, illicit drugs, supplements, and alternatives forms of medicines
f)	History of substance use	Assessing chronicity and recent changes in the pattern of substance use
g)	Family History	Presence of family history of cognitive disorders, substance use, psychiatric illnesses, neurological illnesses, any illness with genetic predisposition

h)	Social History	Psychosocial history (family, friends, religious activities, hobbies, social involvement etc.)
		Living situation: Alone, with family, assisted living
		Support system: Family, friends, caregivers
		Daily routine activities and hobbies
		Social and recreational activities
		Educational and occupational background
i)	Diet history:	to rule out any deficiencies
j)	Assess level of physical activity/exercise	
k)	Extent of involvement in cognitively challenging tasks	

Table 8: Specific parameters to be explored in each section of history

II. EXAMINATION

A) Neurological

Some of the relevant findings of neurological system examination are listed in Table 9.^[9] In the most abbreviated neurologic examination, *the extraocular movements and gait* are the most important to test, whenever possible.

Assessment of	Abnormal in conditions
Extraocular movements (cranial nerves III, IV, VI)	- Progressive supranuclear palsy, Parkinson disease - Structural lesions - Drug toxicity
Speech (cranial nerves V, VII, IX, X, XII)	- Bilateral corticobulbar (pseudobulbar) lesions - Bulbar (lower brainstem) lesions - Basal ganglia and cerebellar disorders - Some lateralized structural lesions - Drug toxicity

Pronator drift	▪ One arm pronates, may also drift downward (corticospinal tract lesion) ▪ One arm drifts laterally to 45 degrees (ipsilateral cerebellar dysfunction) ▪ One arm drifts upward (may be central sensory deficit)
Stand	Detects weakness, postural instability
Gait	▪ Lewy body disease - Untreated Parkinson disease - Dementia with Lewy bodies - Multiple system atrophy ▪ Tau disorders - Progressive supranuclear palsy - Corticobasal degeneration - Other frontotemporal dementias ▪ Huntington disease ▪ Post–cardiovascular accident or traumatic brain injury ▪ Normal pressure hydrocephalus ▪ Cerebellar or toxic/metabolic disorders

Table 9: High-yield neurologic examination findings in the evaluation of cognitive symptoms

III. NEUROPSYCHOLOGICAL ASSESSMENTS

The mental state examination in a suspected case of cognitive impairment requires detailed evaluation of higher mental functions. This would include testing the cognitive domains already elaborated in the section of ‘History taking’. Some of the common tests and their usefulness is listed in table 10.^[9,10] The first 6 may be done by the sole practitioner in OPD as well.

Assessment of	Tests
Recent memory	Delayed recall

Language (comprehension)	3-stage commands
Language (semantic fluency): Temporal lobe	Patient given 1 minute to generate as many names, typically of animals or any other category
Language (phonemic fluency): Frontal Lobe	Patient given 1 minute to generate as many words beginning with a specific letter, typically f, a, or s
Visuospatial skills	- Copying intersecting pentagons, in which 2 5-sided figures form a 4-sided intersection. - Copying a cube such that the figure appears 3-dimensional, the appropriate lines are parallel and of equal length, and no lines are added, - Clock draw test
Executive functions	Clock drawing test
Sequencing (executive functioning)	Luria sequencing task (fist-edge-palm test)
Attention	Set shifting
Social cognition (Theory of Mind)	Reading the mind in the eye test
Multiple domains (executive function, attention, and working memory)	Trail B test

Table 10: Cognitive assessment in examination of patient with suspected Minor NCD

IV. DIAGNOSIS

Both DSM-5 and ICD-11, include mild cognitive impairment under the category of Mild Neurocognitive Disorders, with nearly similar diagnostic criteria. ^[9,10] ICD 10 mentions the diagnosis of ‘Mild Cognitive Disorder’ (F06.7) under the head of ‘Other mental disorders due to brain damage and dysfunction and physical disease’. ^[11] [Table 11]

DSM-5	ICD-11	ICD 10
A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive	Mild neurocognitive disorder is characterized by the subjective experience of a decline from a	Mild cognitive disorder may precede, accompany, or follow a wide variety of infections and physical

function, learning and memory, language, perceptual–motor, or social cognition) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and 2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.	previous level of cognitive functioning, accompanied by objective evidence of impairment in performance on one or more cognitive domains relative to that expected given the individual’s age and general level of intellectual functioning that is not sufficiently severe to significantly interfere with independence in the person’s performance of activities of daily living.	disorders, both cerebral and systemic (including HIV infection).
B. The cognitive deficits do not interfere with capacity for independence in everyday activities (that is, complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).	The cognitive impairment is not entirely attributable to normal aging.	Direct neurological evidence of cerebral involvement is not necessarily present, but there may be distress and interference with usual activities.
C. The cognitive deficits do not occur exclusively in the context of a delirium.	The cognitive impairment may be attributable to an underlying disease of the nervous system, a trauma, an infection or other disease process affecting specific areas of the brain, or to chronic use of specific substances or medications, or the etiology may be undetermined.	When associated with a physical disorder from which the patient recovers, it does not last for more than a few additional weeks.
D. The cognitive deficits are not better explained by another mental disorder (for example, major depressive disorder or schizophrenia).		The diagnosis should not be made if the condition is clearly attributable to any other mental or behavioural disorder.

Specify whether due to: • Alzheimer’s disease • Lewy Body Disease • Fronto-temporallobe degeneration • Vascular disease • Traumatic brain injury • Substance/medication induces • HIV infection • Prion disease • Parkinson’s disease • Huntington’s disease • Another medical condition • Multiple etiologies • Unspecified	Code, also the underlying condition	
Specify: • Without behavioral disturbances • With behavioral disturbances		

Table 11: Diagnostic criteria for Minor NCD in different classification systems

CONSIDERATIONS WHILE MAKING A DIAGNOSIS OF MINOR NCD

- Excessive focus on subjective symptoms could lead to missing the diagnosis, where patient lacks insight or/and family is in denial.
- Excessive focus on objective assessments may lead to missing the diagnosis in high functioning individuals, whose currently ‘normal’ performance might be a ‘decline from his/her baseline’.
- Assess the cognitive reserve of the individual (as has been explained earlier). Individuals with high cognitive reserve may not show symptoms of Minor NCD until they have a significant amount of brain pathology, which may delay the diagnosis of Minor NCD. Secondly, standard cognitive tests might not be sensitive enough to detect Minor NCD in such individuals.
- The neuropsychological assessment has a role in reaching to diagnosis. These tests, with performance compared with norms appropriate the patient’s age, educational attainment, and cultural background,

is part of the standard evaluation of neurocognitive disorders (NCD), and is particularly critical to evaluation of Minor NCD.

- It is also interesting to note that, none of the common definitions of Minor NCD list advanced age as a criterion, although most of the research conducted in this area occurs in the geriatric population and is generally presumed to be a disorder of old age.

V. DIFFERENTIAL DIAGNOSIS

When talking about making a diagnosis, it is important to consider the following common differential in relation to Minor NCD (Figure 6).^[11]

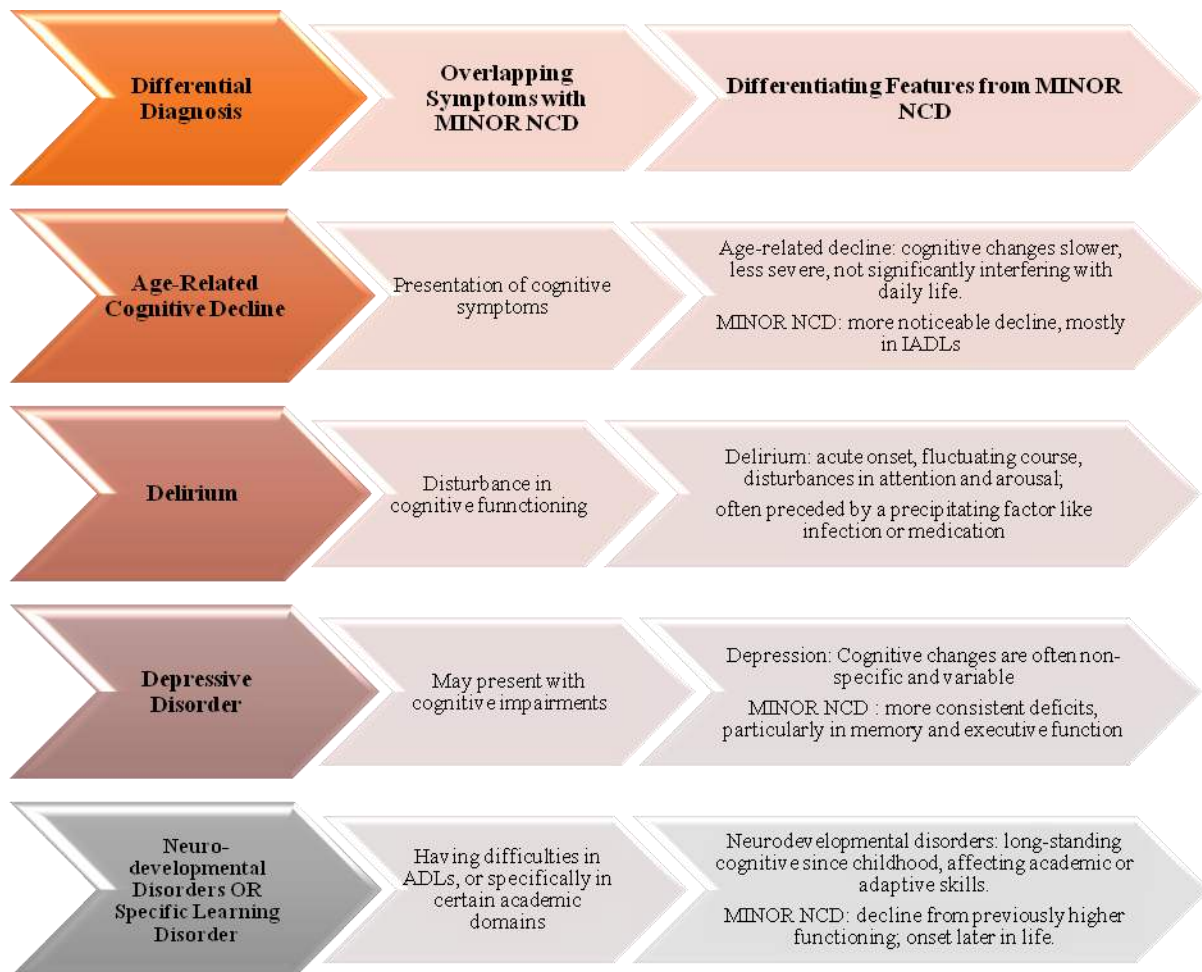
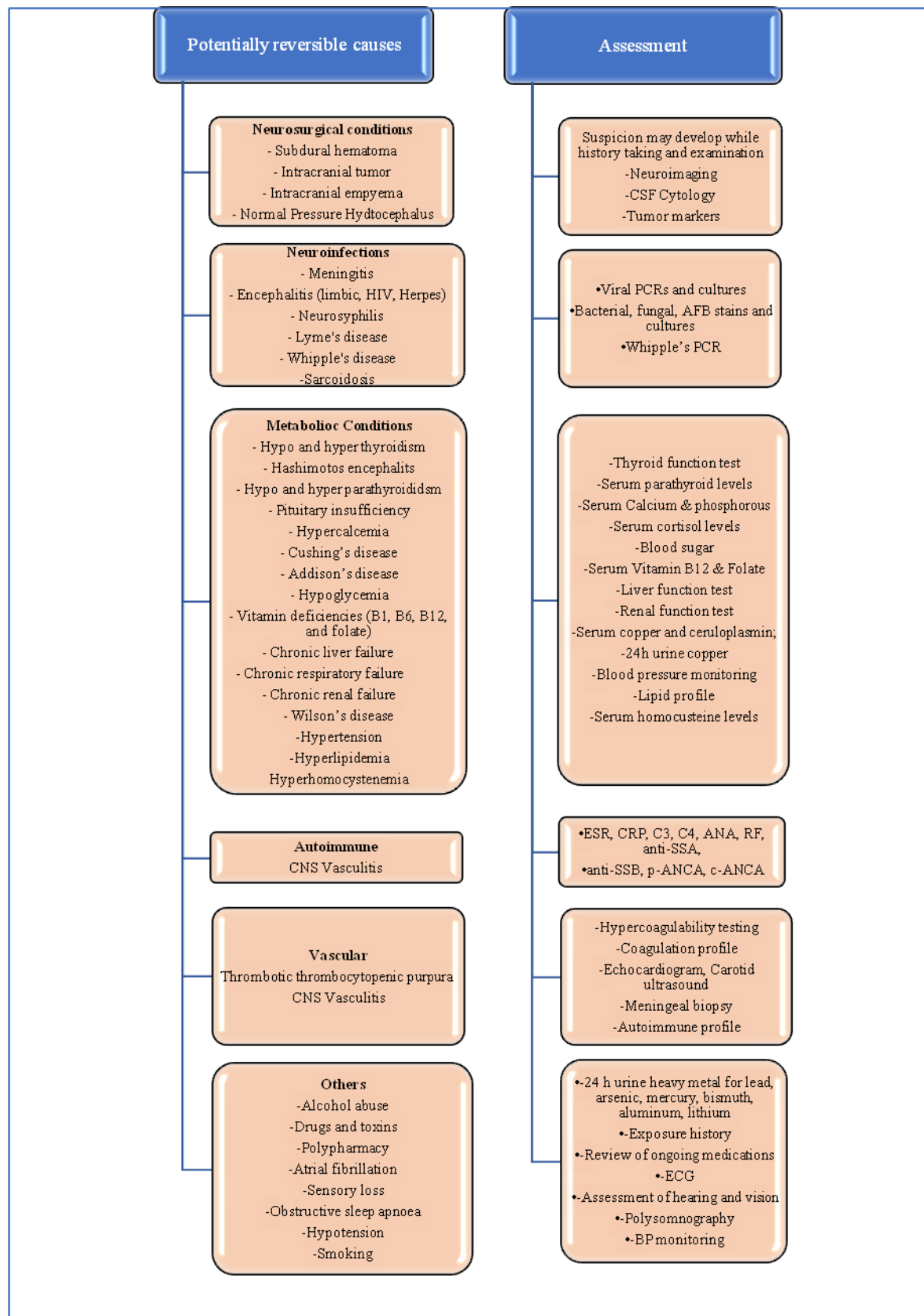


Figure 6: Differential Diagnosis of Minor NCD

VI. INVESTIGATIONS

a) LABS:

The diagnosis of Minor NCD is based on the diagnostic criteria. However, there are a number of underlying factors or causes which may be causative or contributory to the condition. This has been taken into cognizance by the specifier ‘Another Medical Condition’ of the Mild Neurocognitive Disorder in DSM-5.^[11] Similar to dementia, Minor NCD too has many reversible causes, which although less frequent, carry good prognosis with prompt treatment of underlying condition. Thus, such potentially reversible causes should be thoroughly investigated. Some of the common ones are listed in Figure 7, along with the mode of assessment.^[14-16] However, it is essential to elicit symptoms and signs as well, while clinical assessment, which would provide clues to the etiology and accordingly the investigations may be conducted. For example, metabolic causes generally have some or the other clinical manifestation, which can be identified. Atrial fibrillation may cause small, undetectable embolic events, mimicking small strokes or transient ischemic attacks, leading to Minor NCD and ultimately vascular cognitive impairment.



Figure

7: Potential reversible causes/contributory factors for Minor NCD and their assessment

b) **NEUROIMAGING:**

- Neuroimaging has not been routinely recommended in diagnosis of Minor NCD, but may be helpful in evaluating overall brain structure, in addition to serving the following purpose:
 - i. Identifying underlying causative conditions like brain tumours, normal pressure hydrocephalus, vascular malformation, and strokes.
 - ii. Serving as a potential biomarker for progression to Alzheimer's dementia (AD). **However, there is lack of consensus of different guidelines on this.**

Advances in both structural and functional neuroimaging have been providing valuable insights into the structural, functional, and biochemical alterations in the brain, enabling the physicians to make the diagnosis of Minor NCD and in predicting its progression to dementia more accurately. Commonly observed neuroimaging findings have been summarized in Figure 8.^[17-18]

Recently, new processing methodologies for existing techniques have been introduced to increase clinical value of methods that process obtained data. In relation to MRI, different morphometry methods are being used for data processing, e.g., voxel-based, pattern-based, tensor-based and deformation-based. In Alzheimer's dementia, the earliest changes are found in the medial temporal lobe structures, the entorhinal and perirhinal cortex and the hippocampus. Since neuronal damage in the hippocampus is manifested as decreased hippocampal volume, volumetric MRI scan of the hippocampus is a widely accepted method for assessing AD pathology; suggests the anatomic validity of the underlying disease process and is an early indication for AD.

Additionally, Diffusion tensor imaging studies have demonstrated the relationship matter integrity and disease severity. Optical coherence tomography links pathological changes in retina to Alzheimer's dementia.^[17]

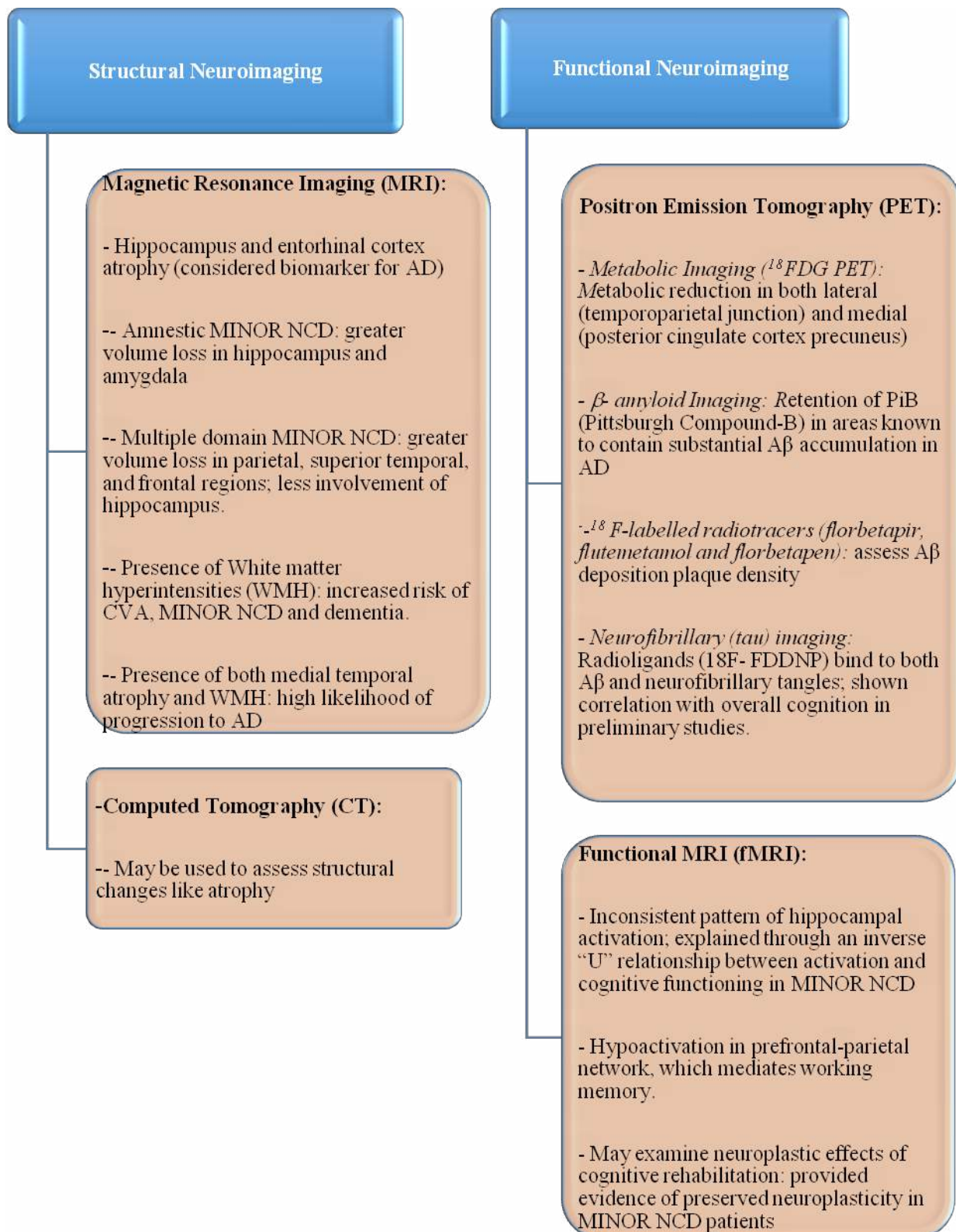


figure 8: Neuroimaging findings in Minor NCD

c) CSF STUDY

A number of CSF biomarkers have been identified in AD.^[19-20] The three CSF biomarkers, namely total tau, phospho-tau and A β 42, are believed to have the highest diagnostic accuracy for early AD diagnosis and the ability to predict AD development in Minor NCD patients. These may be considered if possible/when available.

d) GENETIC TESTING

- Genetic studies may provide potential biomarkers. Testing of genes has not been considered or recommended in any of the recent guidelines. The important features concerning genetic studies are summarized in Figure 9.^[11]
- Patients requiring genetic studies should receive genetic counselling before undergoing testing.

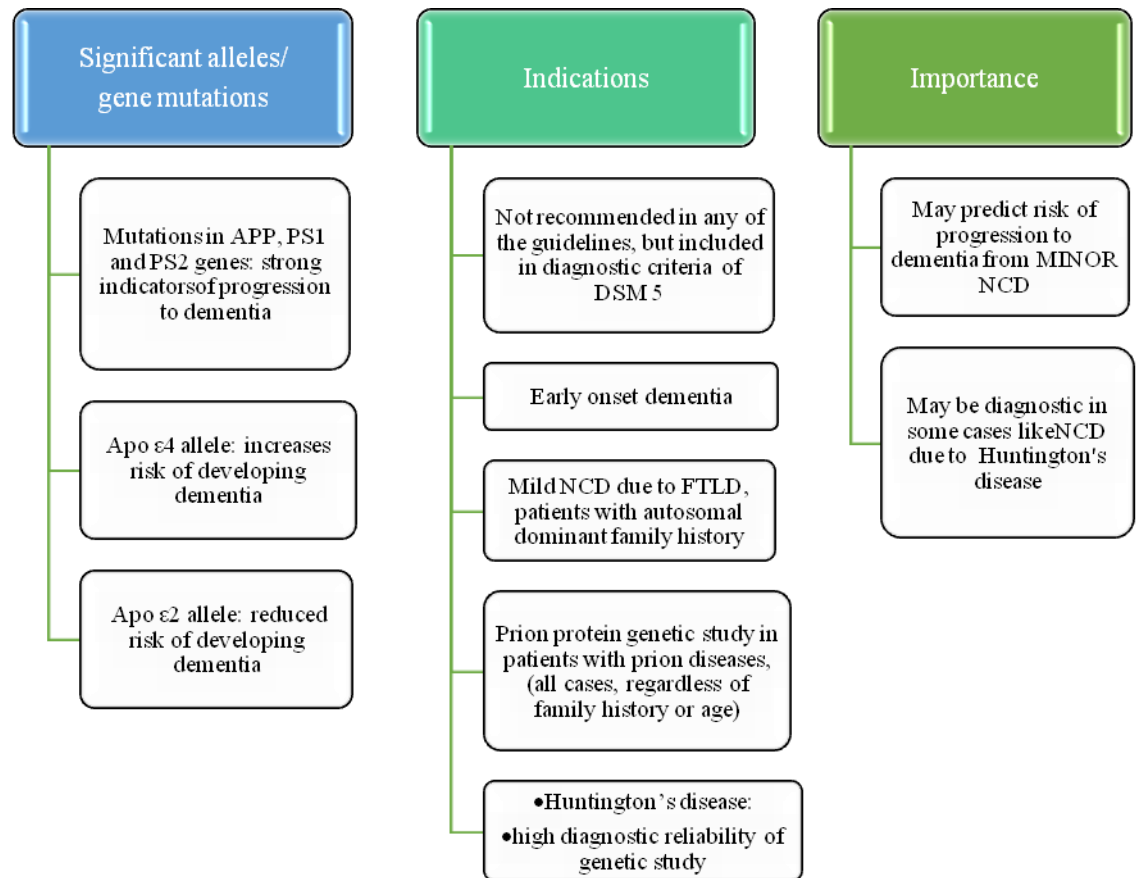


Figure 9: Importance and indications of genetic testing in Minor NCD

VII. DETAILED NEUROPSYCHOLOGICAL ASSESSMENT

- **Assessment of cognition**

Application of appropriate cognitive tests, applicable to patient's age, education and cultural background is another crucial part for evaluation of patients with Minor NCD. The DSM 5 criteria do not require any specific neuropsychological assessment, however cognitive tests within these procedures can be used to measure decline in one or more of the six cognitive domains: complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition. However, no such assessment incorporates all these domains. The performance typically lies in 1-2 standard deviation range (between 3rd and 16th percentile). Some of the commonly used tests along with their properties are listed in Table 12.^[10, 21-23]

Test	Domains Covered	Time for Administration	Screening Capacity for Minor NCD
MMSE	Orientation, Registration, Attention and Calculation, Recall, Language, Visuospatial Skills	5-10 minutes	Widely used but less sensitive to early Minor NCD. HMSE is the modified Hindi version of MMSE for the uneducated individuals
ADAS-Cog	Memory, Language, Praxis, Attention and Concentration, Planning and Sequencing, Visuospatial Skills	30-45 minutes	More comprehensive, better for detecting mild to moderate Minor NCD
CDR	Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, Personal Care	30-90 minutes	Focuses on functional impact, good for staging dementia severity; score of 0.5 suggests Minor NCD
MoCA	Attention and Concentration, Executive Functions, Memory, Language, Visuospatial Skills, Conceptual Thinking, Calculations, Orientation	10-15 minutes	Very sensitive to Minor NCD, recommended for early detection
ACE	Attention, Memory, Fluency, Language, Visuospatial Skills	15-20 minutes	Detailed, good for assessment of mild cognitive impairment
SLUMS	Orientation, Memory, Attention, Executive Function, Language, Visuospatial Skills	7-10 minutes	Good alternative to MMSE, more sensitive than Minor NCD
AD8	Memory, Orientation, Judgment and Problem Solving, Daily Activities	3-5 minutes	Brief informant-based screening tool for dementia or cognitive impairment

Table 12: Properties of Neurocognitive assessment tools in relation to Minor NCD

In addition to above, clinicians may also collect information on cognitive function from informants using standardized tools such as the Informant Questionnaire on Cognitive Decline in the Elderly(IQCODE) and the Dementia Severity Rating Scale (DSRS). Other

tests used are Memory Impairment Screen, Quick Screen for Mild Cognitive Impairment, CDT- Sunderland and CERAD.

- **Assessment of functionality**

Assessment of functional status is also important, to differentiate Minor NCD from dementia. Several scales/tools are available:^[10, 24]

- a) *Lawton-Brody Instrumental Activities of Daily Living*: Subtle deficits in instrumental activities of daily living (IADL) are noticed in Minor NCD.
- b) *Functional Activities Questionnaire (FAQ)*: Assesses functional status, using data from an informant. Score of 6 or more has >85% accuracy in differentiating Minor NCD from dementia.
- c) *Performance Assessment of Self-Care Skills (PASS) test*: It is a valid and reliable tool designed to measure occupational performance of daily life tasks.

- **Assessment of psychological and behavioural symptoms**

The psychological and behavioral symptoms of Minor NCD and the subsequent caregiver distress may be assessed using Neuropsychiatric inventory (NPI) and short questionnaire form of the NPI (NPI-Q), and presence of depression by Geriatric Depression Scale (GDS).^[25-26]

Figure 10 presents an algorithm to approach a person with suspected Minor NCD.

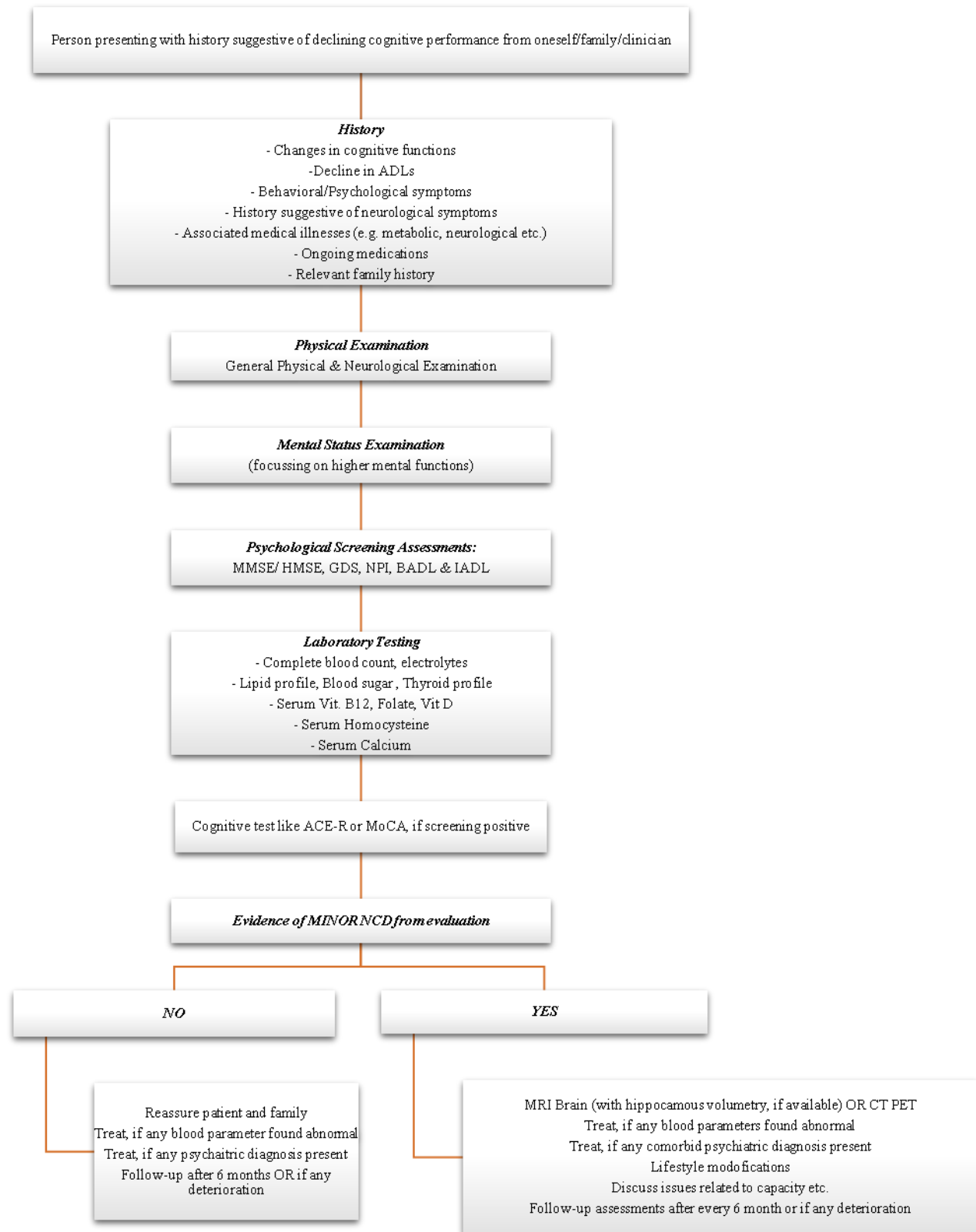


Figure 10: Assessment approach to a person with suspected Minor NCD that can be routinely followed by clinicians.

MANAGEMENT

Managing Minor NCD is challenging due to variability in symptoms, difficulty in distinguishing it from normal aging or Dementia, and lack of universally effective treatments. Effective management focuses on early detection, regular monitoring, and implementing strategies to maintain cognitive function and delay progression to dementia. [Figure 11] Treatment setting is usually outpatient and management relies heavily on non-pharmacological measures due to lack of approved medication and heterogeneity in presentation.

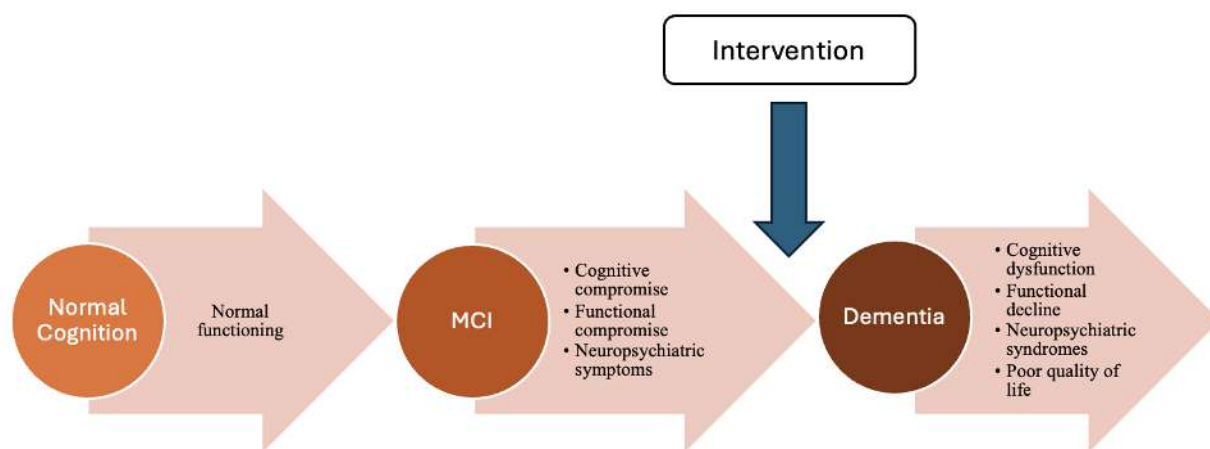


Figure 11: Principle of Interventions in Minor NCD

Goals of management

Management goals for Minor NCD largely include forming a collaborative care approach, aiming for Minor NCD reversal whenever possible, effectively managing comorbidities, promoting overall health, promoting independence, preparing for disease progression, and maintaining continuous monitoring. (Table 13) Helping patients and caregivers to restructure their activities and environment to achieve independence, as is developing a trusting therapeutic relationship to facilitate management process. ^[27]

Goal	Examples
Establishing collaboration with patient and caregiver	• Engage in conversation honestly • Acknowledge uncertainties • Share treatment plans seek, preferences

Managing reversible causes	• Optimize medication number and frequency • Minimize cognitive side effects • Treat underlying conditions
Treat Comorbidities	• Address coexisting health issues, particularly vascular factors • Present treatment options, discuss risk-benefit profiles, and clarify trade-offs for informed decisions
Promote Holistic Health	Encourage - regular exercise - balanced nutrition - adequate sleep - meaningful cognitive and social activities
Promote Independence and Quality of Life	Empower to - self-manage their health - simplify their environment - reduce medication complexity - promote use of technology to assist in daily living
Prepare for Disease Progression	To ensure readiness for potential progression of Minor NCD, address - legal and financial planning - driving safety - retirement - advance directives
Regular monitoring	Schedule regular follow-ups to reassess cognition, function, mood, behavior, physical health, and caregiver burden, ensuring timely adjustments to care plans

Table 13:Goals of management in Minor NCD^[28]

Interventions can be planned at various levels for preventing and managing Minor NCD:

1. Interventions for risk reduction:

The predisposing factors for Minor NCD as highlighted earlier are a potential point for intervention to reduce the risk of developing Minor NCD at a later stage. The common ones along with possible intervention strategies are listed in Table 14.

RISK FACTOR	INTERVENTIONS
Identification and Management of Modifiable Risk Factors like hypertension, diabetes, atrial fibrillation, hyperlipidemia etc.	Antihypertensives, oral hypoglycemics, antiarrhythmic agents, lipid lowering agents
Smoking Cessation	Behavioral support and pharmacotherapy if required
Alcohol Moderation	Psychoeducation Behavioral modifications and pharmacotherapy, if needed
Level of physical activity	Regular physical exercise, particularly aerobic activitiesimprove

	cognitive functions At least 150 minutes of moderate-intensity aerobic exercise per week as per the physical capacity
Insomnia	Behavioral interventions, sleep hygiene and, pharmacological treatments, where warranted
Loneliness and social isolation	Promoting social engagement, referral to community resources, support groups, and social activities
Management of neuropsychiatric symptoms	Management of symptoms like depression, anxiety, and apathy through pharmacological and non-pharmacological (e.g. CBT and other forms of therapy) interventions

Table 14: Interventions for risk reduction in Minor NCD. ^[24, 28]

2. Management of reversible causes of Minor NCD

As discussed in assessment section, numerous treatable factors can contribute to or even cause Minor NCD. Unfortunately, these factors are often overlooked and underestimated, even though some are easily fixable and can greatly improve cognition. Treatment of underlying cause is the principle, discussed in Table 15.

Cause	Description
Polypharmacy	- More number and frequency - Drugs like opioids, muscle relaxants, anxiolytics, antiepileptics, and anticholinergics can affect memory. - Antihypertensives cause hypotension, reducing cerebral blood flow
Depression	Addressing and treating depression can clear cognitive symptoms
Metabolic Deficiencies	Correction of hypothyroidism, hypo/hyperglycemia, dehydration, and vitamin B12 or folate deficiency
Atrial Fibrillation	Anticoagulation can reduce the risk
Obstructive Sleep Apnea	- Causes daytime fatigue and cognitive impairment - Weight loss, frequent physical exercise, reduction of alcohol - Continuous positive airway pressure
Sensory Deficits	Corrective measures like glasses, cataract surgery, hearing aids

Normal Pressure Hydrocephalus	Early detection and treatment can reverse symptoms.
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Table 15: Reversible causes of Minor NCD and their management^[16]

3. Pharmacological Management

Lecanemab (Leqembi), an IgG1 monoclonal antibody received accelerated Food and Drug Administration (FDA) approval for treating Minor NCD and early AD in 2023. In phase III trials, it significantly reduced brain amyloid levels slowing cognitive decline by 27% compared to placebo.

- Mechanism of action: Reduce cerebral amyloid deposition thereby reducing cognitive decline
- Route of administration: 10 mg/kg IV administered once every two weeks
- Safety concerns: Risk of treatment-induced Amyloid-Related Imaging Abnormalities (ARIAs), particularly in individuals with a homozygous ApoE ϵ 4 genotype. Other serious side effects include brain edema (ARIA-E) and microhemorrhages (ARIA-H). Symptoms can include confusion, dizziness, headache, and visual disturbances and close monitoring is warranted.
- Indications: Minor NCD due to AD and early AD
- Not to be used in individuals with MRI evidence of non-AD dementia, and caution in ApoE ϵ 4 carriers due to the risk of ARIAs.
- Considerations around cost, serious adverse effects, need of strict monitoring and lack of long-term safety data needs to be addressed to ensure its wide application.^[29-30]

Currently, there are no other pharmacologic treatments approved by the FDA for treatment of Minor NCD. Table 16 lists medications useful in management of Dementia, tried in Minor NCD, without much effect.^[16] Overall, while various pharmacologic and supplement interventions

have been tested, none have shown significant benefits in delaying the progression of Minor NCD to dementia. Consequently, the focus has shifted to non-pharmacological approaches.

Agent	Evidence Summary	Evidence in MCI
Cholinesterase Inhibitors (ChEIs)		
Donepezil	No significant benefit for delaying MCI to AD conversion over 3 years when combined with vitamin E.	No
Galantamine	Unpublished trial reported 6 deaths in treatment group (2 suicides) vs. 1 death (arrhythmia) in placebo group; significant AEs noted.	No
Rivastigmine	No significant differences in cognitive performance; higher incidence of AEs.	No
Memantine	Not effective for MCI or mild AD. Some studies show small benefit for moderate to severe AD with good tolerability.	No
Selegiline	Efficacious for delaying disease progression in moderate to severe AD when used independently or with vitamin E.	No
Other Antioxidants, Vitamins, and Supplements		
Vitamin C	No benefit on cognition with supplementation unless there is a clear vitamin deficiency.	No
Vitamin B12	Cognition improves with supplementation in those with low serum levels of vitamin B12.	No
Multivitamins	No benefit on cognition with supplementation.	No
Vitamin-E(α-tocopherol)	No benefit found for delaying MCI to AD conversion; risk of side effects such as orthostatic hypotension, falls, diarrhea, nausea, fatigue, and bradycardia.	No
Ginkgo biloba	No benefit on cognition with supplementation.	No
Ginseng	No benefit on cognition with supplementation.	No
Omega-3 fatty acids	Some studies suggest benefits, but evidence is not strong.	Some

Table 16: Pharmacological treatment options for Minor NCD management.^[24]

Further, management of neuropsychiatric symptoms should be done by non-pharmacological measures however when warranted symptomatic management using appropriate Psychotropics as approved in elderly population may be prescribed for symptoms like depression, anxiety, sleep disturbance, apathy etc. ^[16, 24, 27]

4. Non- Pharmacological Management

Cognitive Remediation for Minor NCD aim to improve cognitive function and enhance quality of life. Early and targeted interventions are essential, as they can lead to symptomatic improvements, reduce neuropsychiatric symptoms, and ultimately improve outcomes for individuals with Minor NCD. This can be subcategorized into Cognitive Training (CT), Cognitive Rehabilitation (CR), and Cognitive Stimulation (CS). Each approach has distinct goals, methods, and types of activities.[Table 17]

Aspect	Definition	Principle
Cognitive Stimulation (CS)	Broad engagement in cognitive and social activities to enhance overall cognitive function.	- Aim at improving cognitive & social functions. - Includes stimulating tasks like group discussions, sensory activities, and reminiscence.
Cognitive Training (CT)	Structured practice on tasks designed to enhance specific cognitive abilities.	Focuses on cognitive skills through repetitive practice and exercises targeting memory, attention, problem-solving, and executive functions.
Cognitive Rehabilitation (CR)	Individualized interventions to improve cognitive function and daily living skills.	- Integrates cognitive exercises with practical applications to enhance daily functioning. - Includes compensatory strategies and therapeutic support.

Table 17: Types of Cognitive Remediation and difference in them. ^[31]

These interventions are well-researched and found to have lasting positive effects on the cognitive functioning of healthy older adults. These three approaches involve varying tasks and exercises targeting specific cognitive domain or skill, thereby affecting the overall functioning [Table 18]. ^[31-35]

COMPONENT		DESCRIPTION
U	O	Orientation
		Reinforcement of important information like person, place, and time.

	Validation	Focuses on person's subjective experience.	
	Reminiscence	Discussing past events and reflecting on the person's life, often using props like photographs, music, videos, and objects.	
	Multisensory Therapy	Stimulating senses through activities e.g. fruit tasting, singing, dancing.	
	Cognitive Activities	Mental tasks like puzzle solving, sudoku etc.	
	Implicit Learning	Acquiring knowledge about environment without conscious awareness.	
	ACTIVITY TYPE	DESCRIPTION	EXAMPLES
COGNITIVE TRAINING	Memory Training	Exercises to improve short-term and long-term memory.	Recalling word lists, using mnemonic devices, practicing spaced retrieval.
	Attention Training	Tasks to enhance focus and concentration.	Tracking moving objects, exercises for sustained attention & selective attention
	Problem-solving Training	Activities to develop reasoning and decision-making skills.	Solving puzzles, logical reasoning tasks, real-life scenario simulations.
	Executive Function Training	Exercises to improve higher-order cognitive processes like planning, organizing, and multitasking.	Planning schedules, organizing tasks, managing finances, cooking complex recipes.
	Language Training	Exercises to enhance language skills, e.g. verbal fluency. Vocabulary and comprehension	Reading comprehension exercises, vocabulary games, language learning software, conversation practice.
COGNITIVE REHABILITATION	Assessment	Evaluation of cognitive strengths and weaknesses	Cognitive assessments, interviews, questionnaires.
	Personalized Cognitive Exercises	Activities targeting specific cognitive domains	Memory exercises, attention tasks, problem-solving activities, executive function training, language exercises.
	Compensatory Strategies	Techniques to help manage cognitive deficits, including use	Using calendars, to-do lists, alarms, and organizing the home environment.

		of external aids and environmental modifications	
	Functional Task Practice	Engaging in real-life activities to apply cognitive skills in practical settings	Managing finances, cooking, shopping, organizing daily schedules.
	Psychological Support	Addressing emotional and psychological aspects of cognitive impairment, including building self-efficacy and coping strategies.	Building self-efficacy, coping strategies, therapy sessions

Table 18: Different activities and target domains of various approaches of cognitive remediation in Minor NCD

5. Lifestyle modification for Minor NCD

It is seen that lifestyle modification can greatly help reducing the risk of further cognitive decline and to promote cognitive health in elderly individual. Table 19 below provides with few recommendations for the same. The Nun Study emphasized the protective role of cognitive reserve and healthy lifestyle choices in mitigating cognitive decline. The findings of the study revealed that higher linguistic ability in earlier in life, regular mental and physical activity, and maintaining cardiovascular health significantly reduced the risk of cognitive impairment and dementia despite the presence of Alzheimer's pathology.^[36] In a similar study, from the 10/66 Dementia Research Group indicated that regular consumption of fish, rich in omega-3 fatty acids, is associated with a lower risk of cognitive decline and dementia, highlighting the neuroprotective and anti-inflammatory benefits of omega-3 fatty acids,^[37] reinforcing the importance of dietary practices in maintaining cognitive health.

Intervention Type	Recommendation
Physical Activity	Aerobic exercises like walking, swimming, and cycling are particularly beneficial.
Tobacco Cessation	Quitting smoking can improve overall cardiovascular health, which is linked to brain health.

Dietary Interventions	Mediterranean diet: Emphasizes intake of fruits, vegetables, whole grains, nuts, and healthy fats like olive oil.
Alcohol Use	Reducing alcohol consumption improves cognitive function and overall health.
Social Activity	Engaging in social activities can improve mood and mental health
Weight Management	Maintaining a healthy weight reduces risk of metabolic conditions affecting brain health.

Table 19: Lifestyle interventions in Minor NCD.^[28]

Common myths pertaining to management of Minor NCD

Interventions		Myths	Current Evidence
Diet& Supplements	Mediterranean diet (fruits, vegetables, whole grains, nuts, and healthy fats like olive oil)	Mediterranean diet can cure MINOR NCD	Evidence from RCTs May be prescribed
	Vitamins (B12, Folate)	Vitamin supplementation can improve Minor NCD	Benefit in cognition in those with deficiencies
	Multivitamins, Vitamin E		Level of evidenceto support the same is not robust at present
	Gingko Biloba supplements/food additives	Adding Gingko Biloba in food can improve cognition	Minimal/No benefits seen
	Curcumin	Adding in food may improve cognition or prevent dementia	No robust evidence seen
Nutraceuticals	Gingko Biloba extract 240 mg/day (EGb 761 R)	Gingko Biloba can improve cognition	Benefit shown with dose240 mg/day May be appropriate to incorporate as part of multi domain intervention for MINOR NCD
	Ginseng	Ginseng improves MINOR NCD	Level of evidenceto support the same is not robust at present
	Omega 3 fatty acids	Omega 3 fatty acid can improve MINOR NCD	Level of evidenceto support the same is not robust at present

Pharmacological	Lecanemab	Pharmacological treatment (drugs) can cure MINOR NCD	FDA approved for delaying progression of MINOR NCD (due to AD) and early AD
	Other commonly used drugseg.AChE Inhibitors, Memantine etc		Level of evidenceto support the same is not robust at present

Table 17: Common myths related to management of Minor NCD

6. Tailored interventions

- Based on detailed assessment, a personalized management plan should be developed in collaboration with the patient and family members, which includes relevant cognitive and lifestyle interventions, along with specific goals, plans, and treatment settings.
- Provide resources and support to help patient and family implement the interventions. Schedule regular follow-up appointments to track progress and make necessary adjustments to the plan.
- By tailoring management plan to the individual needs of the patient and involving family members in the process, it is possible to create a supportive environment that promotes cognitive health and improves quality of life for individuals with Minor NCD.
- This personalized approach ensures that the interventions are practical, achievable, and aligned with the patient's lifestyle and preferences.

7. Caregiver Interventions InMinor NCD

Caregiver interventions play a crucial role in managing Minor NCD and supporting both patients and their caregivers. These interventions can significantly improve the quality of life, reduce caregiver burden, and enhance caregiving capabilities. Some key types of caregiver interventions^[38] are listed in Figure 12.

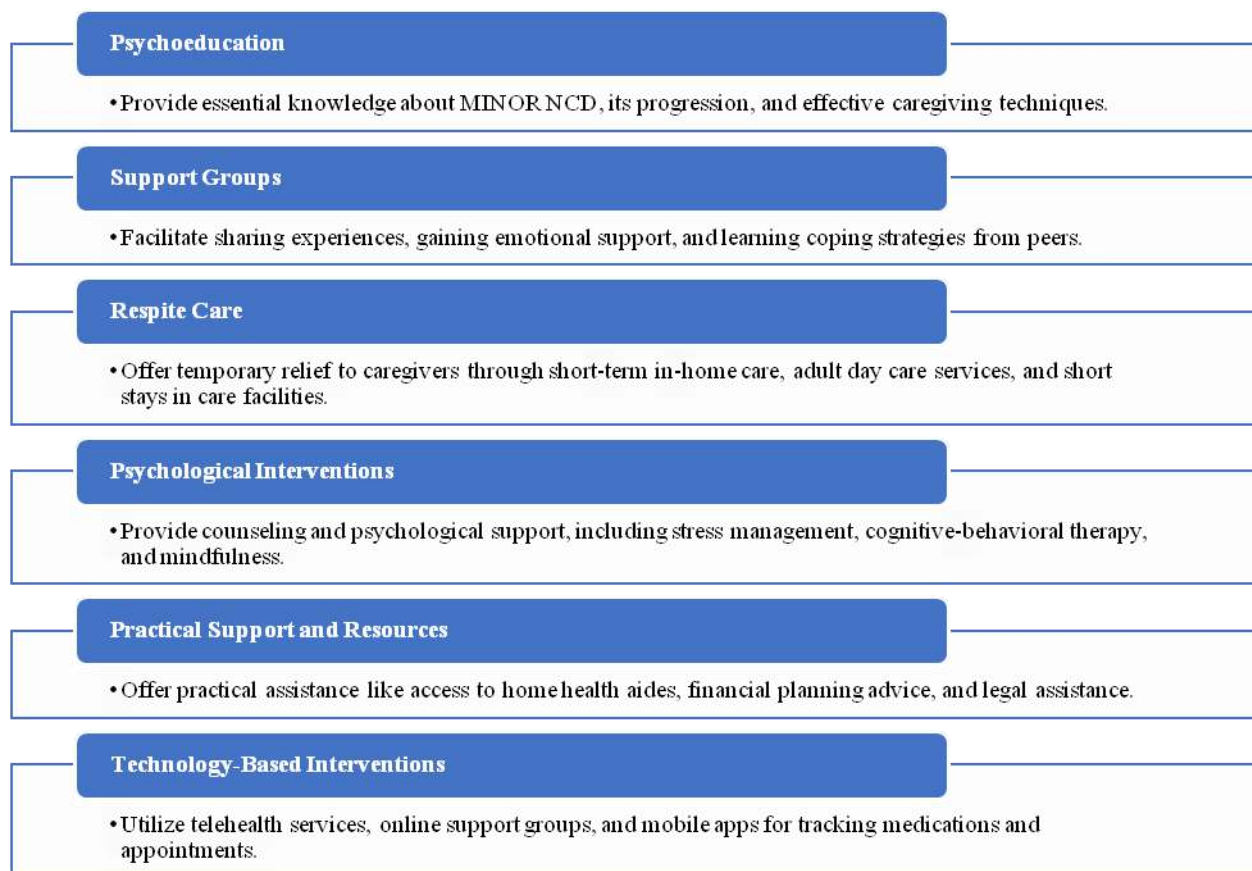


Figure 12: Interventions for care givers of patients with Minor NCD

8. Scheduling follow up assessment in Minor NCD

The following should be included in any follow-up visit for those with Minor NCD:

- A validated cognitive instrument that is consistently repeated
- A comparative structured history from informant
- A comparative structured functional capacity assessment. Details in table 20.

Follow-Up Interval	Components
6-12 Month Follow-Up	• Review by Health professional • Reassessment with cognitive scale • Structured informant report, and • Structured functional assessment.

Earlier Review Triggers	• Patient or family concern, • Recent hospital admission, • Multi-domain amnesic Minor NCD, • Neurological signs, • Mood, or behavioural symptoms, • Unexpected change
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Table 20- Follow up assessments in Minor NCD^[14, 39]

ETHICAL AND RESEARCH CONSIDERATIONS IN MINOR NCD

A number of ethical considerations when dealing with individuals with Minor NCD may arise, especially in context of clinical trials and other research settings. Clinician may also face issues pertaining to assessment, disclosing diagnosis and management of such individuals. Table 21 summarizes the key points and possible ways to navigate:^[40-43]

Category	Key Points	Recommendations
Informed Consent and Participation	- Challenges in obtaining authentic informed consent from cognitively impaired individuals in research trials	- Implement enhanced consent procedures, such as simplified language and repeated consent checks. (May be enforced by IRBs)
	- Ethical issues in including patients lacking decision-making capacity or at risk of losing capacity.	- Ensure regular re-evaluation of the participant's capacity and involve family members or legally authorized representatives from the beginning. - Anticipate the need for continual assessment of capacity with clear guidelines for loss of capacity.
Research Design and Findings Disclosure	- Earlier research did not disclose biomarker study results due to uncertainty.	- Establish clear guidelines for disclosure of biomarker results, including potential risks and benefits.
	- Possibility of negative psychosocial impact of test result disclosure	- Provide pre- and post-test counseling to participants and their families.

Legal Issues	- Lack of laws for protection against genetic discrimination in India.	- Advocacy for legislative changes to protect against genetic discrimination, including protections in insurance and employment. - Apex court in India specified that any act of genetic discrimination, specifically by insurance companies, violates Right to Equality under Article 14 and Right to Health and healthcare under Article 21.
Issues in Disclosing Diagnosis	- Dilemma in disclosing a diagnosis of Mild NCD/Minor NCD with positive biomarkers.	- Develop clear guidelines for diagnosis disclosure, including the involvement of mental health professionals to support the patient.
	- Potential for fear, distress, and loss of hope following the diagnosis.	- Provide psychological support and counseling to patients and their families post-diagnosis.
Medical Decision-Making Capacity	Possibility of decline in decision-making capacity over time.	- As per Section 4 of MHCA 2017, memory loss or cognitive deficits or even a diagnosis does not imply incapacity automatically but emphasizes establishing capacity. - Educate families about the potential for cognitive decline, capacity related issues and the importance of early legal and healthcare planning.
Psychopharmacological Treatment	High possibility of co-morbidities, and susceptibility for side effects, leading to further de-stabilization	- Principle of non-maleficence (Do No Harm) - Conduct thorough risk-benefit analysis for each treatment and involve patients and their families in decision-making. - Monitor patients closely for side effects and adjust treatment plans as necessary.
Assessment Issues	Variability in memory assessment tools affecting diagnosis consistency.	- Guidelines may include Standardize assessment tools and ensure they are validated for use in diverse populations.
	Lack of guidance on assessing non-amnestic Minor NCD.	- Develop and disseminate guidelines for the assessment of non-amnestic Minor NCD.
	Dependence on premorbid level of functioning.	- Include comprehensive assessments that account for premorbid functioning levels.

Stigmatization	Diagnosis of Minor NCD can lead to stigmatization, affecting social functioning and quality of life.	- Implement public awareness campaigns to reduce stigma and promote understanding of Minor NCD.
	Even when having capacity, their autonomy and decision-making may be affected, largely through paternalistic attitudes (e.g., in concerns about them going out alone, driving, and making decisions).	- Education to family members to preserve autonomy of individual. - If and when required, gradual shifting to providing assistance.
Privacy and Confidentiality	Ethical issues in handling information about risk of developing dementia.	- Ensure robust data protection measures and transparent communication about how information will be used and protected.
	Need for greater legal protection for research participants' information.	- Advocate for stronger legal protections for the confidentiality of research data.

Table 21: Ethical and research issues in Minor NCD and recommendations

CAPACITY AND MINOR NCD

Capacity is the ability to understand the benefits and risks of available alternatives, make and communicate an informed decision independently. Minor NCD represents an intermediate or transitional stage between normal aging and more severe of cognitive impairment, and thus raises concerns about the capacity of these individuals to make informed decisions and manage their routine affairs. One such concern was participation in research and clinical decision making, which was addressed in the previous section. Others are tabulated below (Table 22).^[44-45]

Capacity	Key Considerations	Recommendation
Testamentary Capacity (Ability to make or alter a will)	People with Minor NCD may still possess testamentary capacity, but their condition may complicate the assessment	Discussion with the individual and the family members about: - Advance Directives - Power of Attorney - Guardianship

Contractual Capacity (Ability to understand and engage in contractual agreements)	Minor NCD may impair ability to comprehend complex contracts, thus raising concerns about exploitation or undue influence.	Aim is to: Balancing autonomy and protection Preventing exploitation
Financial Decision-Making	Individuals with Minor NCD may struggle with these tasks, increasing vulnerability to financial abuse	
Matters pertaining to court proceedings (depose/stand trial)	Not necessarily impaired May have difficulty in understanding legal proceedings Role of psychological and behavioral symptoms in the crime	• <i>Evaluation of the individual in relation to:</i> - Able to understand the nature and seriousness of the charges - Basic understanding of the court process - Ability to recall and articulate facts related to the case - Able to communicate effectively with their attorney • <i>Providing accommodations and Support:</i> If individual deemed fit to stand trial but has some cognitive limitations- - Provide simplified explanations of legal concepts. - Give regular breaks during the trial. - Presence of a legal guardian or support person. - Aim is to protect rights of vulnerable individuals.
Driving vehicles	Driving, example of complex IADL (requires several abilities, including an intact neurocognitive system, adequate sensory motor & visual functions). Person with Minor NCD might have deficits in one or more cognitive domains, thus facing difficulties in driving.	• As per Motor Vehicles Act 2019, cognitive abilities are not the basis of denying driving license to an individual. • Allow the individual to maintain agency in the decision for as long as it is safe to drive. • Clinical advice may be given by the physician as per the assessments.
Possession of firearms		• No legal provision for denying/withdrawing firearm possession to persons with Minor NCD. • The individual with his/her family members, and health care providers may proactively discuss firearm access and consider setting a “firearm retirement date”

Table 22: Issues related to capacity of persons with Minor NCD in various domains.

OVERVIEW OF MANAGEMENT IN MINOR NCD

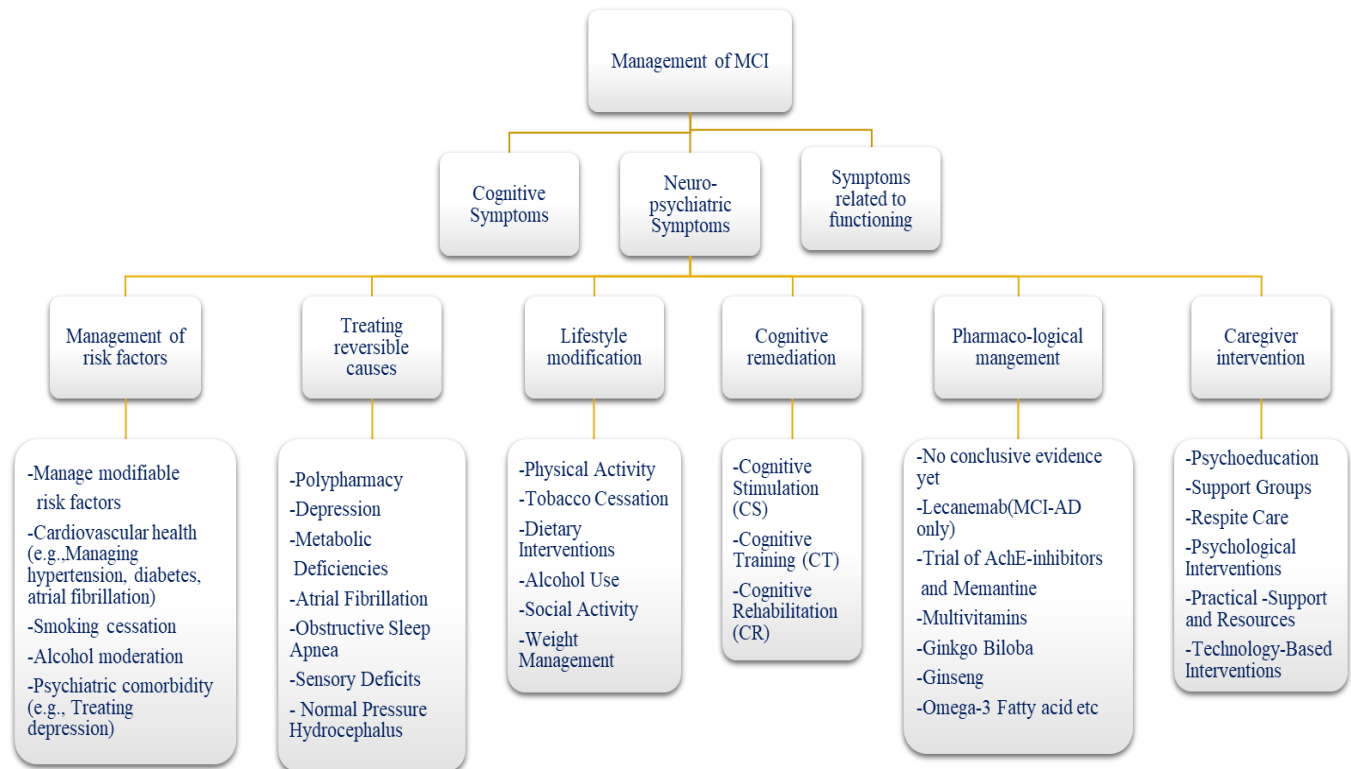


Figure 13: Overview of management in Minor NCD

CONCLUSION

Comprehensive assessment and management of Minor NCD is essential to prevent its progression and to enhance the quality of life of the individuals. Early and precise diagnosis, utilizing clinical assessment, laboratory tests, and neuro-psychological testing, allows for timely intervention. Integrating multidisciplinary approaches, including cognitive training, pharmacological treatments, and lifestyle modifications, can effectively address both cognitive and neuropsychiatric symptoms associated with Minor NCD.

Furthermore, recognizing and managing Minor NCD - related behavioral symptoms is essential in reducing caregiver burden and improving overall patient outcomes. Regular follow-up assessments are

crucial to monitor disease progression and adjust treatment plans accordingly. Continuous research and validation of biomarkers, tests and interventions are necessary to improve diagnostic accuracy and treatment efficacy. By adhering to these clinical practice guidelines, clinicians may ensure a comprehensive yet structured and effective approach to the assessment and management of Minor NCD.

BASILINE ASSESSMENT	INTERVENTION AND FOLLOW-UP	CONVERSION TO DEMENTIA
	6 monthly follow up	Continue 6 monthly follow up
HISTORY - Changes in cognitive functions - Decline in ADLs	-Lifestyle modifications -Cognitive remediation -Non-pharmacological measures	- Continue lifestyle measure, non-pharmacological measure, cognitive remediation -Introduce pharmacology
Baseline Assessment: MMSE	More detailed neuropsychological tests	Serial cognitive profiling
Labs: Rule out reversible causes	Extended labs/genetic/CSF	Regular baseline labs to ascertain no reversible causes have emerged
Imaging: MRI where possible	fMRI/CT-PET	Annual imaging wherever possible, with hippocampal volume measurement
Exclude differential diagnosis	More definitive towards Min NCD	Evolved to frank Dementia

Table :Clinical overview to approach Minor NCD

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Clinical practice guidelines on addressing cognitive impairment in treatable dementias

1. Introduction

In older adults aged 60 years or above the prevalence of dementia in India is 7.4%, which translates to about 8.8 million cases of dementia.^[1] With an estimated increase in the proportion of older adults aged over 60 years to approximately one fifth of the entire population by 2050 due to increasing lifespan, the prevalence of dementia is predicted to increase tremendously.^[2] A proportion of these dementias are considered to be produced by irreversible conditions, while the others by reversible conditions.

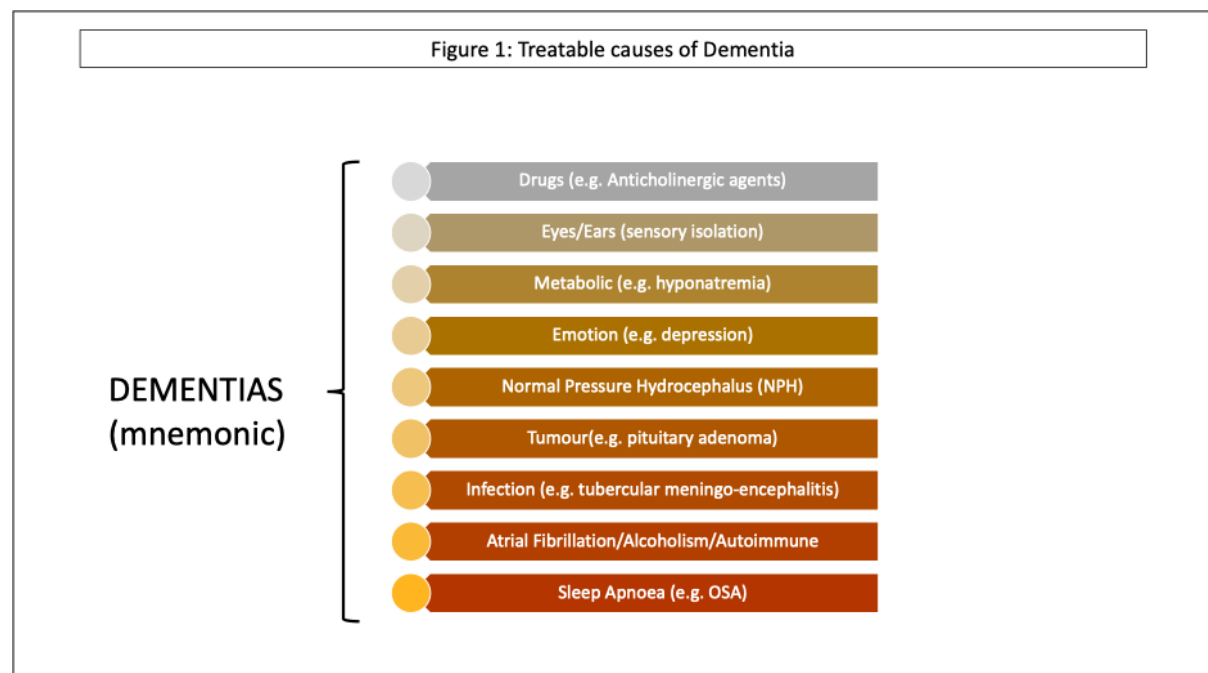
The precise frequency of reversible dementias in the general population is difficult to estimate. This is because of the ambiguity surrounding the terminology used to characterize reversible dementia– the variation in the population being studied, or the existence of subclinical instances that are difficult to diagnose.^[3] By and large however, the proportion of reversible dementias compared to the irreversible dementias is very low. Prevalence is highly variable, with a varied number of studies reporting a range between 0 and 40%, and average approximates to 12 %. While, the prevalence of potentially reversible aetiology has been reported 18% in patients under the age of 65 years, however only 5% in those over 65 years.^[3] A meta-analysis showed that although potentially reversible causes were seen in 9% of the cases, only 0.6% of dementia cases could be reversed.^[4] Optimum assessment of differential diagnosis and prompt treatment are therefore of paramount importance.

While therapeutic strategies are available for both reversible and irreversible dementias, the term ‘treatable dementias’ is assumed to be synonymous with ‘reversible dementias’ as they are ‘readily treatable’.^[5] However, ‘treatable dementias’ include cases with conditions which are irreversible too.^[6] There are definite ‘treatable aspects of irreversible dementias, such as behavioural and psychological symptoms of dementia.’^[6] This chapter does not cover those aspects.

2. Causes of potentially reversible dementias

Little (2018) proposed a mnemonic DEMENTIAS for potentially reversible causes of dementia- **D**rugs, **E**yes/**E**ars (sensory isolation), **M**etabolic, **E**motion, **N**ormal Pressure

Hydrocephalus (NPH), **T**umour, **I**nfection, **A**trial Fibrillation/**A**lcoholism and **S**leep Apnoea (Also see Figure 1).^[5] We recommend adding **A**utoimmune (for A) also to the list.



However, for better understanding the reversible dementias can be broadly classified as:^[6,7] 1. Intracranial (neurosurgical) disorders; 2. Intracranial (neuroinfectious) disorders; 3. Systemic (including metabolic/endocrinal) disorders; 4. toxic disorders and 5. mental and behavioural (psychiatric) disorders.

Depression, alcohol-induced cognitive impairment, normal pressure hydrocephalus (NPH), Vitamin B12 deficiency alone would account for more than half of causes of reversible dementias. Other less common causes are tumours and chronic subdural hematomas, hypothyroidism, and central nervous system (CNS) infections such as neurosyphilis and HIV.^[8] The autoimmune dementia and encephalopathies (ADE) is becoming increasingly prevalent in early onset dementia patients; about 20-25% in dementia of early onset.^[9]

3. Clinical features of potentially reversible dementias

Potentially reversible dementias can be identified and differentiated from irreversible dementias from their clinical presentation. A thorough history often clinches the diagnosis of the underlying condition. Tables 1a-1e show the list of disorders in each of the classified reversible dementia subtypes as mentioned above and their clinical features.

Table 1a: Intracranial (neurosurgical) disorders and their clinical features		
Sl.no	Disorder/condition	Clinical features
1	Traumatic Brain Injury (Subdural/intracranial haemorrhage)	• History of trauma (temporal relationship) • Acute-subacute onset; sometimes late onset • Headache • Characteristic Post Traumatic Amnesia • Seizures (> in cases of intracranial haemorrhage) • Fluctuating course • Psycho-motor slowing • Reduced alertness
2	Intracranial Tumours (meningioma, astrocytoma, solitary metastasis, pituitary adenoma)	• Headache • Seizures • Papilloedema • Gradually progressive focal signs • Visual field defects and endocrinal changes (acromegaly, etc.) in cases of pituitary adenoma
3	Cerebral abscess or intracranial empyema	• Headache • Fever • Focal signs
4	Normal Pressure Hydrocephalous	• Dementia • Incontinence • Gait disturbance, falls

Table 1b: Intracranial (neuroinfections) disorders and their clinical features		
Sl.no	Disorder/condition	Clinical features
1	Meningitis, encephalitis, meningo-encephalitis (Viral (inc. HIV, herpes), Bacterial (esp. tubercular), fungal (esp. cryptococcal) or malignant)	• Subacute course • Lethargy • Fever (may not be present sometimes) • Neck stiffness • Immunocompromised host (esp in HIV, cryptococcal meningitis) • HIV-associated dementia/AID-dementia complex (later stages of HIV infection)
2	Toxoplasmosis	• Immunocompromised host • Focal neurological signs
3	Cerebral Malaria	• Stupor • Fever and chills
4	Neurosyphilis	• Untreated syphilis infection • Headache; neck stiffness; nausea/vomiting (meningeal syphilis) • Stroke (meningovascular syphilis)

		• Personality/mood changes (General Peresis)
5	Whipple's disease	• Constitutional symptoms • Malabsorption • Uveitis • Supranuclear gaze palsy
6	Lyme's disease	• Headache • Fever/feverish and shivers • Muscle and joint pains • Numbness • Tiredness • Signs of meningitis
7	Cerebral vasculitis/arteritis and Giant cell arteritis	• Headache • Stroke-like signs • Systemic arteritis signs- constitutional symptoms, claudication, etc. • Vision loss; polymyalgia rheumatica (in Giant cell arteritis)
8	Systemic Lupus Erythematosus	• Mental and behavioural symptoms • Seizures • Systemic manifestations (fever, fatigue, weight loss)
9	Sarcoidosis	• Systemic manifestations (fever, fatigue, night sweats, skin rashes, changes in skin colour) • Respiratory symptoms- chest pain, cough, wheezing (in pulmonary sarcoidosis)

Table 1c: Systemic (including metabolic/endocrinal) disorders and their clinical features		
Sl.no	Disorder/condition	Clinical features
1	Thyroid disorders • Hypothyroidism • Hyperthyroidism • Autoimmune thyroiditis	• Signs of myxoedema • Delayed reflexes • Restlessness • Anxiety • tremor • tachycardia • exophthalmicophthalmoplegia • These symptoms may be masked in elderly • May present with hypo/hyper/eu-thyroid

		levels
2	Cushing's syndrome	• Central obesity • Striae • Hypertension • Diabetes mellitus • Irritability • Depression • Evidence of exogenous or endogenous corticosteroid excess
3	Addison's disease	• Weakness • Hypotension • Pigment change • Hyponatremia • Hyperkalemia
4	Parathyroid disorders • Hypoparathyroidism • Hyperparathyroidism	• Paraesthesia • Muscle cramps • Mood disturbances • Dry skin • Tiredness • Muscle weakness • Abdominal pain • Mood symptoms- esp. depression
5	Diabetes Mellitus • Hyperglycaemia • Hypoglycaemia	• Hyperosmolar state with stupor: • Minor focal signs • Associated with excess hypoglycaemic agents or Insulinoma
6	Dyselectrolytemia • Hyponatremia • Hypernatremia • Hypocalcaemia	• Weakness • Lethargy • Seizures • Signs of dehydration • Tetany • Seizures • Associated hypoparathyroidism, renal failure, hypomagnesaemia

	• Hypercalcaemia • Hypomagnesemia	• Weakness • Fatigue • Mood changes; • Associated hyperparathyroidism, multiple myeloma, bone metastases, ectopic parathyroid hormone • Tetany • Seizures • Associated alcohol use disorders
6	Cardiac disease	• Heart failure • Arrhythmia esp. Atrial Fibrillation
7	Pulmonary disease	• Headache, tremors and myoclonus • Associated with Chronic Obstructive Pulmonary Disease, Pneumonia and Other conditions causing chronic hypercapnia or hypoxia
8	Hypertensive encephalopathy	• Headache • Retinopathy • Nephropathy • Seizures
9	Anaemia	• Fatigue • Lethargy
10	Chronic Renal Failure	• Associated with Uremia and other metabolic derangements • Fatigue • Apathy • Irritability • Tremor • Asterixis • Myoclonus • Neuropathy
11	Hepatic encephalopathy	• Signs of liver disease- jaundice, weakness • Asterixis • Tremor • Myoclonus • Associated Hyperammonaemia • GI Bleeding
12	Porphyria	• Abdominal pain • Neuropathy • Personality changes • Agitation • Confusion
13	Vitamin B12 deficiency	• Memory loss may precede anaemia

		• Myelopathy • Neuropathy • Perniciousanaemia
14	Folate deficiency	• Myelopathy • Neuropathy • Associated with malabsorption syndromes like alcohol use, and use of phenytoin
15	Thiamine deficiency	• Confusion • Ophthalmoplegia • Ataxia • Neuropathy
16	Niacindeficiency	• Pellagra • Weaknessandlethargy • Dermatitis • Diarrhoea • Neuropathy
17	Sleep apnoea	• Loud snoring • Day time lethargy

Table 1d: Toxic disorders and their clinical features		
Sl.no	Disorder/condition	Clinical features
1	Lead toxicity	• Motorneuropathy • Headache • Seizures • Anaemia • Lead lines
2	Arsenic toxicity	• Somnolence • Sensoryneuropathy • GI Symptoms • Mees lines
3	Mercury toxicity	• Psychosis • Neuropathy
4	Organophosphorous toxicity	• Confusion • Irritability • Aggression
5	Opioids	• Pupillary constriction • Constipation • Respiratory depression
6	Antihypertensives (Esp. Clonidine, propranolol, reserpine)	• Psychomotor slowing • Depression
7	Digoxin	• GI symptoms • Confusion
8	Anticonvulsants	• Cerebellar signs • Sedation • Dizziness and blurring of vision

9	Antibiotics	• Esp. Penicillin and chloramphenicol
10	Antineoplastic drugs	• Esp. Methotrexate
11	Antipsychotics	• Confusion • Parkinsonism
12	Antidepressants	• Confusion • Tremors • Anticholinergic effects
13	Sedatives and hypnotics (Esp. Benzodiazepines)	• Lethargy • Confusion • Withdrawal effects
14	Anticholinergics	• Confusion • Psychosis • Dilated pupils dry skin • Tachycardia
15	Antiparkinsonism drugs	• Confusion • Psychosis

Table 1e: Mental and Behavioural disorders and their clinical features		
Sl.no	Disorder/condition	Clinical features
1	Depression/Depressive cognitive disorder	• Clinical signs of depression • Clinical features of cognitive impairment characteristic of depressive cognitive disorder is discussed in next section on course.
2	Alcohol use disorder	• Alcohol dependence • Associated with Thiamine deficiency or Hepatic encephalopathy • Associated with dyselectrolytemia related to alcohol withdrawals
3	Autoimmune dementia and encephalopathies (ADE) (paraneoplastic and non-paraneoplastic)	• Early age of dementia presentation (<50-60 years) • History of autoimmunity- dermatomyositis, vitiligo, reactive/rheumatoid arthritis, type 1 diabetes mellitus, Hashimoto thyroiditis, etc. • Family history of autoimmunity and dementia • Prominent inattention mimicking delirium • Headache, tremor, myoclonus/seizures, parkinsonism

4. Clinical course of “treatable dementias”

In this section, we briefly describe the course of some of the highly prevalent causes of “treatable dementia” below:

Alcohol-induced (related) Dementia:

Several lines of research suggests that chronic consumption of alcohol leads to permanent damage, both structural and functional, to the brain. Apart from the indirect contribution of thiamine deficiency to this, alcohol too has direct effects- the presentation is named “alcohol related dementia (ARD)”. The umbrella term 'alcohol-related brain damage' includes both ARD and the Wernicke-Korsakoff syndrome. Patients with ARD are mostly male, have their onset of symptoms younger compared to other dementias and lack social support. Visuospatial, memory and executive dysfunction is mainly evident.^[10]

Depressive cognitive disorder (Depressive pseudodementia)

Depressive cognitive disorder is characterised by a cognitive impairment where its “risk factors overlap with those for depression”. The symptoms mimic dementia, but improve with improvements in mood; there is no neuronal degeneration noted. It is prevalent in those aged 50 or above years. The cognitive domains mainly affected are: memory, executive function and speech. Although it may be difficult to diagnose depressive cognitive disorder when there is a significant overlap of depressive and true dementia symptoms, there are aspects that help differentiate it from true dementias.

The onset of cognitive impairment in depressive cognitive disorder is abrupt to acute and usually are precipitated and aggravated by stress. The symptoms show rapid progression as well as fast resolution. There is possibility of previous and family history of mood disorder episodes. More characteristically, they often tend to respond with “I do not know” rather than confabulations, which are noted in other forms of dementia. Other symptoms of depression will be noted.^[11] Table 2 shows the differences between depressive cognitive disorder and dementia.

Table 2: Prominent differences between depressive cognitive disorder and dementia	
<i>Depressive cognitive disorder</i>	<i>Dementia</i>
abrupt to acute	Subacute to chronic
usually are precipitated and aggravated by stress	No
previous and family history of mood disorder	Not frequent
respond with “I do not know”	Confabulations

Autoimmune Dementia and Encephalopathies (ADE)

ADE is broadly divided in paraneoplastic (underlying cancers) and non-paraneoplastic varieties. The non-neoplastic ADEs were considered idiopathic until recently where there has been discovery of many neural-specific autoantibodies.^[9] The various varieties of common autoimmune encephalitis presenting as dementia^[12] is given table 3. A detailed list of neural antibodies, in general, is given by Fernández-Fournier (2022)^[13] Except for conditions like limbic encephalitis where the onset can be abrupt to acute, other conditions run a subacute to chronic course. While memory loss is the most prominent clinical presentation, other cognitive domains, especially attention is also affected. Preservation of memory with behavioural changes such as personality changes and social disinhibition may also be presented and mimic frontotemporal dementia. The course of ADE may be continuous or remitting and relapsing. Spontaneous recovery is also seen in some cases. Once the clinical suspicion is made and investigations show evidence of autoimmunity, the progression, or rather response to steroids and antibody-depleting agents (immunotherapy) is remarkably positive. Relapse after immunotherapy should be looked as a complication of immunotherapy- infectious complications such as progressive multifocal leukoencephalopathy or steroid induced cognitive impairment.

Table 3: Varieties of common autoimmune encephalitis presenting as dementia	
1	anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis
2	anti-NMDA receptor (NMDAR) encephalitis
3	anti-gamma-aminobutyric acid B receptor (GABABR) encephalitis
4	anti-contactin-associated protein-like 2 (CASPR2) encephalitis

Normal Pressure Hydrocephalic Dementia:

The classical triad of NPH is gait disorder, urinary dyscontrol, and dementia. The following examination and historical characteristics support hydrocephalus as the cause of dementia: a history of urinary symptoms (frequency and/or incontinence not related to the urological system), a history of typical gait (wide-based, magnetic, "freezing" gait, with postural instability), and a history of meningitis or subarachnoid hemorrhage of any cause at any point in the past (e.g., head trauma or aneurysmal bleeding). A large volume lumbar puncture is typically part of the evaluation process for hydrocephalus, ideally accompanied by a filmed gait analysis both prior to and in the hours that follow. Following the evacuation of 35 to 50 cc of CSF, improvements in urine and gait are suggestive of possible dementia reversibility.

Over a few years, dementia gradually worsen, albeit more subacute presentations do happen. There may be fluctuations in the course which might invite uncertainties., The neurosurgical installation of a ventriculoperitoneal or ventriculoatrial shunt may offer some reversal of dementia symptoms (especially in more obese people). Improvement in clinical outcomes are reported in 70% to 90% of those with confirmed NPH. However, there may frequently be concurrent neurodegeneration (Alzheimer's disease, vascular, or frontotemporal type) confounding the improvement. Interestingly, shunting may initially improve memory and gait abnormalities and postpone the deposition of beta-amyloid, but it is unlikely to totally stop the progression of the disease.

Metabolic dementias:

Cortical ischemia, vascular dementia, and cognitive decline have all been linked to abnormal thyroid function tests.

Specifically, higher thyroid-stimulating hormone and decreased thyroxine levels have been detected. But the evidence is conflicting. And there is scant data to support that hypothyroidism is the only cause of dementia or that the use of thyroid hormone replacement therapy could reverse cognitive impairment. Similarly, hyperthyroidism is linked to an increased risk of Alzheimer's disease brain pathology due to greater thyroxine levels; however, there is minimal evidence that treating these abnormalities may enhance

cognition. It is still advised to test thyroid function in the workup of cognitive impairment, even though more evidence is required to confirm the relationship between thyroid disease and dementia and the effects of treatment. This is because thyroid disease can result in other problems, such as depression, weight loss, or cardiac arrhythmias, that can affect functional trajectories in dementia.^[14]

Cognitive decline and dementia have been linked to both hypoparathyroidism resulting in hypocalcaemia and hyperparathyroidism resulting in hypercalcemia. Improved mentation has been linked to correction of the parathyroid abnormalities with parathyroid resection (hyperparathyroid) or calcitriol (hypoparathyroid). Importantly, lithium may stimulate PTH secretion resulting in hypercalcemia in around 10% of case and ensuing neuropsychiatric sequelae.

Severe deficiencies in vitamin B12 and folate are linked to anaemia and cognitive impairment since they are essential for healthy brain development. Malabsorption combined with a decrease in oral intake is the most common cause of vitamin B12 insufficiency in elders. Vit B12 deficiency is also more often seen in those receiving proton pump inhibitors, H2 blockers and or metformin in clinical context. Folate deficiency is more commonly seen in nutritional disorders, those with duodenal pathology, patients having chronic haemolytic anaemia, patients receiving antimetabolite agents such as methotrexate. Even in the absence of anaemia, a folate shortage can result in elevated homocysteine levels, which are linked to the pathophysiology of Alzheimer's disease and vascular disease. Regretfully, meta-analyses have not discovered a statistically significant improvement in mood or cognition associated with vitamin B12 or folate replacement. Alcohol misuse is also linked to deficiencies in B12, folate and niacin (vitamin B6). As per naturalistic studies following treatment for a vitamin B12 deficiency, neuropsychiatric symptoms recovery frequently takes longer to manifest (for example, beginning to improve in around three months and lasting up to a year). Duration of untreated period of deficiency becomes critical as it may determine the irreversibility of the symptoms. Interestingly, some experts have pointed out a period of worsening before clinical improvement during supplementation.

A niacin deficiency is also linked to dementia, which is completely reversible once replenished.

Intracranial Tumours:

Prior to twentieth-century imaging, dementia brought on by an undetected brain neoplasm was more typical. Now that neuroimaging techniques have become widely available in clinical practice, it is typically possible to quickly identify the brain lesions that cause dementia. Usually, a diffuse white matter, frontal, or right hemisphere process is responsible for a subacute alteration in mentation that affects every day functioning. Astrocytomas (glioblastomas) and meningiomas with edema are the most prevalent because of the mass effect and increasing edema that lead to abnormal mental status. Steroids are usually used to delay the onset of dementia caused by these lesions, which is then treated with surgery, radiation, and/or chemotherapy.

Other Toxic disorders:

These dementia conditions might reverse with confiscation of the source of exposure, and subsequent clearance of the toxic substance from the body, whether by course of time, or via the aid of therapeutic moieties (see table 1d). The dementia may reverse partially or completely if the harmful exposure is stopped. Chelation therapy helps speed up recovery from heavy metal poisoning.

Sensitivity of drugs may increase (benzodiazepines or narcotics) or decrease (drugs mediated by beta-adrenergic receptors) with age. So, the response in terms of any confusion or memory or cognition in context to any medication can be unpredictable and prompt an investigation into a possible medication reaction. Most of the medications implicated in inducing dementia like those for atopy, upper respiratory infections, urinary incontinence do so via their anti-cholinergic burden. Other group of medications which cause CNS depression and are related to cognitive deficits are benzodiazepines.

Traumatic brain injury related cognitive impairment is described in clinical practice guidelines on TBI. ^[15; Munoli]

Table 4 lists the various criteria's and tools to help clinicians to identify and de-prescribe the offending drugs. Again, dementia would significantly improve once the offending agent is stopped.

Table 4 shows Description of criteria/scales/tools to determine safe net of prescribed medications, their anticholinergic burden and drug-drug interactions.	
Criteria/Tools	Remarks
American Geriatrics Society Beers criteria ^[16]	this set of criteria is based on medications that are available in the United States
European START/STOPP criteria ^[17]	Section D criteria lists, with rationale, medications that may affect the central nervous system
The Anticholinergic Burden Scale ^[18]	
Anticholinergic Risk Scale ^[19]	
UpToDate® Lexidrug ^[20]	Drug-drug interaction screening software; Subscription based
Micromedex ^[21]	Drug-drug interaction screening software; Subscription based
Epocrates ^[22]	Drug-drug interaction screening software; Drug interaction checker, pill identifier, and insurance drug coverage information
WebMD ^[23]	Identify potentially unsafe combinations of prescription medications

5. Cognitive assessment

There are several screening tests and test batteries available for cognitive assessment for adults and elderly.^[24,25] Table 5 shows the list.

Table 5: Global screening measures and cognitive test batteries available for use in Indian population			
Sl.no	Name	Language versions	Free
<i>Global screening measures</i>			
1	Mini mental state examination	No	No
2	Hindi mental state examination	No	No
3	Montreal cognitive assessment (MoCA)	Yes	Yes

4	Addenbrooke's cognitive examination-III	Yes	Yes
5	World health organization's Study on AGEing and adult health survey screening tool	Yes	Yes
6	Cognistat-Indian adaptation	No	No
7	Dementia assessment by rapid test (DART)	No	Yes
8	Hindi adaptation of Mattis dementia rating scale	No	No
<i>Cognitive test batteries</i>			
1	The Post Graduate Institute (PGI) battery of brain dysfunction	No	No
2	NIMHANS neuropsychological battery (versions for adults and for elderly)	No	No
3	All India Institute of Medical Sciences comprehensive neuropsychological battery in Hindi (adult form)	No	No
4	The Indian Council of Medical Research-Neurocognitive Toolbox (ICMR-NCTB)	Language free	No
5	Wechsler Adult Intelligence Scale, India	No	No

6. Investigations and signs of potentially reversible dementias

Once the suspicion for the cause for dementia (as a reversible dementia) is made based on the clinical features, confirmation of the cause is by the choice of correct investigation. Further, identification of the findings of the investigation that characterize those conditions is the next important step. Tables 6a-6c show the investigations to be conducted/ordered for intracranial (neurosurgical), intracranial (neuroinfectious) and systemic (metabolic and endocrine) disorders. They also show the signs characteristic of the particular condition. While toxic conditions are confirmed by toxicology screens, no confirmatory tests are needed to diagnose mental and behavioral disorders; Sleep apnoea however is diagnosed using the Apnoea index in polysomnography.

Table 6a: Intracranial (neurosurgical) disorders, investigations and signs			
Sl.no	Disorder/condition	Investigations	Signs
1	Traumatic Brain Injury (Subdural/intracranial	CT Scan Brain	Crescent-shaped extra-

	haemorrhage)		axial collection (hyperdense during acute phases and hypodense in chronic phase)
2	Intracranial Tumours (meningioma, astrocytoma, metastatic, pituitary adenoma)	• MRI Brain • PET scan • Biopsy	• Mass and mass effect • Features vary with tumour type
3	Cerebral abscess or intracranial empyema	• Contrast enhanced MRI • CSF study	• Multiple brain lesions on neuroimaging • CSF shows leukocytosis
4	Normal Pressure Hydrocephalous	• MRI • CSF flow study • MRS	• Enlarged lateral and third ventricles out of proportion to the cortical sulcal enlargement • Evans index ≥ 0.3 • Callosal angle: 40-90 degrees • DESH sign: Disproportionately Enlarged Subarachnoid Space Hydrocephalus

Table 6b: Intracranial (neuroinfections) disorders, investigations and signs			
Sl.no	Disorder/condition	Investigations	Signs
1	Meningitis, encephalitis, meningo-encephalitis (Viral (inc. HIV, herpes), Bacterial (esp, tubercular), fungal (esp. cryptococcal) or malignant)	• CSF study • FilmArray Meningitis/Encephalitis panel	• Variable for different infective agents
2	Toxoplasmosis	• Antibody testing	• Mass lesions on

		• MRI	MRI
3	Cerebral Malaria	• Peripheral smear • MRI	• Cerebral edema on MRI
4	Neurosyphilis	• CSF study	• WBC count of 20 cells/μL or greater, and/or a reactive CSF VDRL, and/or a positive CSF intrathecal T pallidum antibody index
5	Whipple's disease	• Biopsy • MRI	• PAS-positive foamy macrophages in biopsy • MRI may show atrophic brain changes, hydrocephalus or mass lesions.
6	Lyme's disease	• Antibody test	• Positive for antibodies to Borrelia
7	Cerebral vasculitis/arteritis and Giant cell arteritis (GCA)	• CSF • Artery biopsy for GCA • Angiography	• Inflammatory CSF; Elevated ESR • "Beading" on arteriogram
8	Systemic Lupus Erythematosus	• MRI	• lupus white-matter changes, infarcts
9	Sarcoidosis	• MRI • Chest X Ray	• Thickening and enhancement of the leptomeninges, especially around the base of the brain

Table 6c: Systemic (including metabolic/endocrinal) disorders, investigations and signs			
Sl.no	Disorder/condition	Investigations	Signs
1	Thyroid disorders	• Blood thyroid profile (free T3, T4 and TSH) • Anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-	• Variable for different conditions

		TG) antibody levels	
2	Cushing's syndrome	• midnight salivary cortisol levels • low-dose dexamethasone suppression test (DST)	• cortisol level >1.8mcg/dl on DST
3	Addison's disease	• Serum sodium, potassium and cortisol levels	• low sodium, high potassium or low cortisol level
4	Parathyroid disorders	• Blood calcium, phosphate and parathormone levels	• Low calcium, high phosphate, low parathormone (hypoparathyroidism) • High calcium and high parathormone (hyperparathyroidism)
5	Diabetes Mellitus	• Blood sugars and glycosylated haemoglobin	FBS>140 HbA1c>6.5%
6	Dyselectrolytemia	• Serum electrolyte levels	• Variable
6	Cardiac disease	• ECG; ECHO; Angiography	• Variable
7	Pulmonary disease	• Chest X ray • PFT	• Variable
8	Hypertensive encephalopathy	• MRI • EEG	• Cerebral microhaemorrhages in deep grey matter and brain stem • EEG may show periodic slowing
9	Anaemia	• Complete blood Count test and Peripheral Smear	• Variable
10	Chronic Renal Failure	• Renal Function tests • EEG	• EEG may show periodic slowing
11	Hepatic encephalopathy	• Renal Function tests • Ammonia levels • EEG	• EEG may show periodic slowing
12	Porphyria	• A combination of blood, urine or stool testing to measure porphyrin levels	• Variable
13	Vitamin B12 deficiency	• Blood levels	• Knuckle pigmentation
14	Folate deficiency	• Blood levels	• Deficient levels

15	Thiamine deficiency	Blood levels	Wernicke-Korsakoff's syndrome
16	Niacin deficiency	Blood levels	Deficient levels
17	Lead, mercury and arsenic toxicity	Blood levels- Heavy metal screening panel (lead mercury, arsenic and cadmium)	- Arsenic >13ng/mL - Lead >70mcg/dL (for adults) - Mercury >10mcg/mL

For autoimmune dementia and encephalopathy, cerebrospinal fluid analysis (CSF) , testing for serum autoantibodies, neuroimaging (especially magnetic resonance imaging (MRI)) and complemented by EEG are the suggested investigations. The CSF analysis shows inflammatory picture- increased total white blood cell count, elevated protein >100 mg/dL, elevated oligoclonal bands or IgG index/synthesis rate.^[9] Testing for serum autoantibodies can be done using commercially available kits. Elevated levels of autoantibodies is diagnostic of ADE. MRI has to be looked for mesial temporal signal abnormalities. EEG shows patterns specific to dementia/encephalopathy and may not be clinching.

The table 7 shows recommendations of various professional associations for investigations in cases of dementias. These primarily emphasize on identifying treatable dementias.

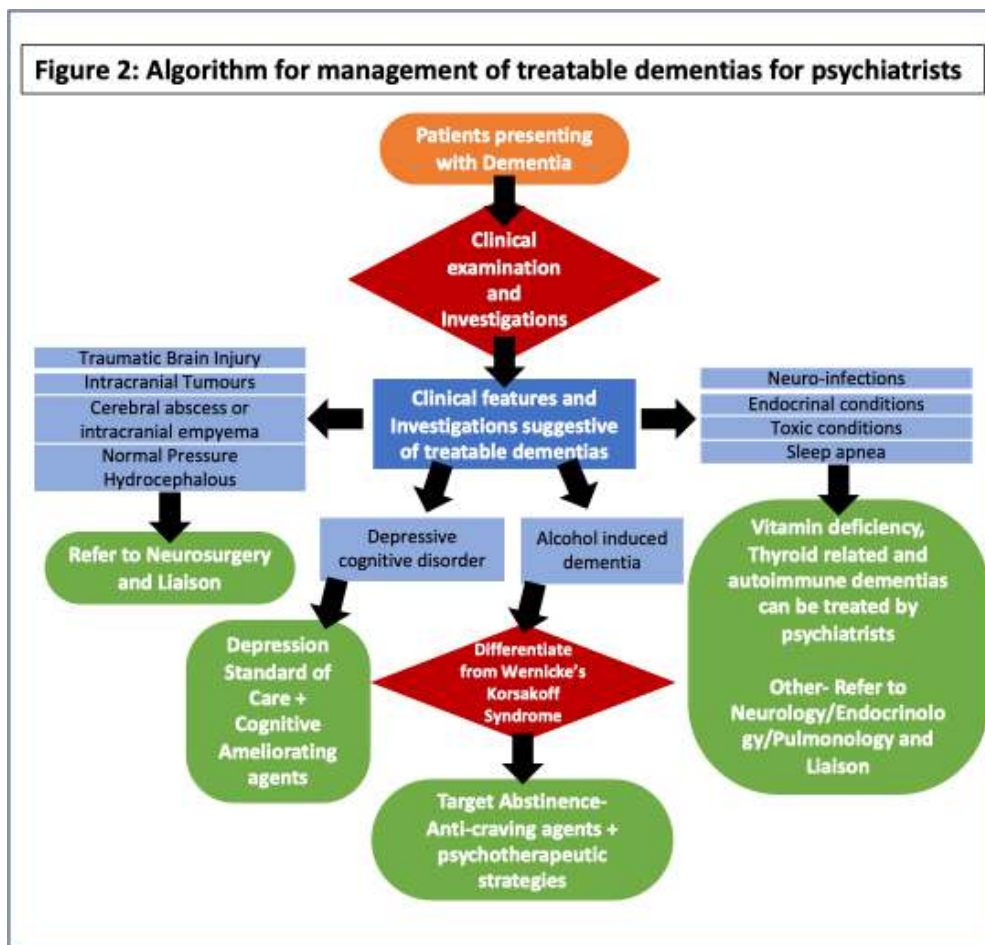
Table 7: recommendations of various professional associations for investigations to identify treatable dementias		
Association	Investigations	Other
American Neurological Association ^[26]	Routine - Structural neuroimaging (non contrast CT or MRI scan) - Depression should be screened - B12 deficiency should be screened - Hypothyroidism should be screened	VDRL: Some specific risk factor or evidence of prior syphilitic infection, or resides in one of ENDEMIC areas
European Academy of Neurology ^[27]	Structural imaging should be used in the evaluation of every patient affected by dementia. They would exclude secondary causes for dementia such as tumour and inflammatory disease, including abscess or normal-pressure hydrocephalus (Level A recommendation)	EEG: There is not enough evidence to consider for the initial assessment of in dementia except in rapid dementia, or when suspecting CJD or

		transient epileptic amnesia
University of Sydney Cognitive Decline Partnership Centre (ENORSED BY RANZAP) ^[28]	Routine <i>Before diagnosing dementia (Expert opinion)</i> 1. A review of medication (including OTC) that may adversely affect cognitive functioning. 2. Consideration of other causes including depression A basic dementia screen should be performed including a. routine haematology, b. biochemistry tests (including electrolytes, calcium, glucose, and renal and liver function), c. thyroid function tests, d. serum vitamin B12 and folate levels.	Structural imaging used in people with suspected dementia (to exclude other cerebral pathologies/establish subtype diagnosis), unless clinical judgement indicates this inappropriate. Not needed in moderate-to-severe dementia, if the diagnosis is already clear. Testing for syphilis serology or HIV should be undertaken only in those with histories suggesting they are at risk. Chest X ray, ECG, EEG not routine. Applicable if clinically indicated.
Japanese Society of Neurology ^[29]	In order not to overlook treatable dementia, it is desirable to perform structural imaging by head CT or MRI when dementia is diagnosed. Blood counts, thyroid hormone, electrolytes, fasting blood glucose, vitamin B12, and folic acid are recommended.	Cerebrospinal fluid test is recommended for patients with atypical types and other conditions that are difficult to differentiate
Indian Journal Of Psychiatry (Indian Psychiatric society) ^[30]	Routine CT scan or MRI scan, CBC, ESR, serum urea, electrolytes, calcium, phosphate, LFT, KFT, TFT, urine analysis, VDRL, Serum B12, Folate levels	HIV status, ECG, Chest radiograph, EEG, Neuropsychological assessment

National institute of health and clinical excellence (NICE) ^[31]	1. Offer structural imaging to rule out reversible causes of cognitive decline and to assist with subtype diagnosis, <i>unless dementia is well established, and the subtype is clear.</i> 2. If dementia is still suspected after initial assessment: undertake appropriate blood and urine tests to exclude reversible causes of cognitive decline.	---
5th Canadian Consensus Conference ^[32]	Neuroimaging is recommended in most situations using the following list of indications: 1. Onset of cognitive signs/symptoms within the past 2 years. 2. Unexpected decline in cognition in a patient already known to have dementia. 3. Recent and significant head trauma. 4. Unexplained neurological manifestations (gait disturbances, new onset severe headache, seizures), at onset or during evolution 5. History of cancer or “at risk” for brain metastases 6. Subject at risk for intracranial bleeding 7. Symptoms compatible with normal pressure hydrocephalus 8. Significant vascular risk factors. MRI (3 T> 1.5 T) > CT Brain	No comments on the biochemical tests.

7. Treatment

Most important role of a psychiatrist is in delineating the clinical features, course and getting appropriate investigations. These steps are crucial in establishing the treatable causes of dementia. Once the cause is established or is indicative of, the next crucial step remains proper referral and liaison with appropriate super-speciality. **Figure 2** shows treatment algorithm of various treatable causes of dementia for psychiatrists.



The two most important reversible/treatable causes that will be primarily managed by psychiatrists are depressive cognitive disorder and alcohol related dementia (ARD).

Depressive cognitive disorder

Treatment of depressive cognitive disorder requires both pharmacological and psychotherapeutic approaches. The standard of care for treatment of depression, including the need for electroconvulsive therapy, must be followed for depressive cognitive disorder.^[33,34] While treatment with antidepressants remains the mainstay of management, certain antidepressants have been found to be more effective for depression associated with cognitive difficulties. These include bupropion, duloxetine, fluoxetine, reboxetine, buspirone, tandospirone, vortioxetine and venlafaxine. Ketamine has also been suggested to be useful. Further, certain cognitive ameliorating agents have also been suggested. These include donepezil, memantine, modafinil and melatonin. Novel agents such as dehydroepiandrosterone and fludrocortisone (targeting neurosteroid dysregulation), erythropoietin, S-adenosylmethionine have also been suggested. Cognitive ameliorating

agents and other newer agents are suggested to be used in combination with antidepressants.^[35] Newer brain stimulation modalities, such as repetitive transcranial magnetic stimulation, is also suggested in cognitive impairment in depression.^[36]

While there are sparse reports on risk of depressive cognitive disorder progressing into dementia, there are reports of late-life depression progressing to mild cognitive impairment (MCI) and dementia. Some report of up to 70% risk.^[37] Also, among cases with MCI, those with depressive symptoms tend to progress to dementia more.^[37] In this context, there is a need to differentiate MCI with depression and depressive cognitive disorder. This differentiation is clinically made based on the antidepressant response to treatment. If cognitive impairments persists beyond improvement in depression symptoms, the possibility of a comorbid MCI is indicated. Neuroimaging based differentiation may not be useful as hippocampal volume deficits are also seen in patients with depressive cognitive disorder.^[38] However, distinct hippocampal functional network correlates have been shown in late-life depression and MCI.^[39]

Delirium

Differentiating delirium from dementia is also an important aspect while discussing treatable dementias. We suggest the readers to refer to the clinical practice guidelines on management of delirium in elderly.^[40]

Psychiatric disorders, in general, and treatable/reversible cognitive impairment

A very recent registry based study from the United Kingdom suggests that severe psychiatric disorders, specifically schizophrenia, bipolar disorder, depression and mania and anxiety disorders, have an increased risk of developing dementia in later life.^[41] Another very large cohort study showed that dementia patients have higher risk of psychiatric disorders both before and after dementia diagnosis.^[42] Therefore, treatment of these disorders with an emphasis on recovery is very important in reducing the risk of later development of dementia.

Further, cognitive impairment across psychiatric disorders (as discussed in various clinical practice guidelines in this supplement issue)^[43-45 grover-schizophrenia, muralidharan-bipolar, avinash-depression]

is considered treatable and responds to the standard care of respective disorders. Further, adding cognitive training for cognitive impairment in these disorders has an important role.

Autoimmune Dementia and Encephalopathy

The treatment of paraneoplastic variety of ADE depends on the treatment of the cancers. Remission of cancer usually improves the symptoms of ADE. For non-paraneoplastic ADEs, acute treatment is use of corticosteroids, preferred intravenous (1 gram of intravenous methylprednisolone once daily for 3–5 days) or less preferred oral (prednisone (1 mg/kg/day)). The alternate treatment, when there are contraindications for use of steroids or occurrence of adverse effects to steroids, is the use of intravenous immunoglobulins (IVIG) (0.4 g/kg once daily for 3–5 days and then weekly for 6–12 weeks). Some studies have suggested the use of plasma exchange as well. Monitoring of side effects for these treatment lines has to be prompt and comprehensive.^[9]

For patients showing relapses, maintenance treatment is recommended. Oral mycophenolate and azathioprine are the agents of choice in maintenance phase. Agents such as rituximab and cyclophosphamide are also suggested.^[9]

Alcohol related Dementia

The treatment of ARD is two-staged. In the first stage ARD has to be differentiated from WKS. If ARD is established with sufficient confidence, the mainstay of treatment has to focus on maintaining abstinence. Here it is also important to understand that not all cases of ARD show complete reversibility; partial recovery is what is achieved and must be targeted. Evidence suggests that maintenance of abstinence is essential for reaching this target.^[9] Perhaps, the standard of care, consisting of pharmacological management in terms of anti-craving agents and non-pharmacological management in the form of motivational enhancement therapy, relapse prevention therapy and other forms of cognitive behavioural therapy, must be followed.^[46,47] Not only functional but also structural abnormalities tend to partially recover with abstinence.^[9] Detailed management of cognitive impairment associated with alcohol is described in the respective clinical practice guidelines ^[48] Praharaj, Ameen].

Among the other treatable dementias that psychiatrists might consider offering treatments are- cognitive impairment related to B12 deficiency, obstructive sleep apnoea and thyroid dysfunctions.

Vitamin B12

Unless there is a compelling reason not to like in palliative care situation or patient refusal, everyone with a proven vitamin B12 should receive treatment.

A few general principles apply to vitamin B12 mentioned below:

1. *Urgency of correction*: Most people with vitamin B12 exhibit no symptoms at all, developing symptoms gradually or as an accidental laboratory finding. In these cases, weekly supplementation of the vitamin can be implemented. But in circumstances like neuropsychiatric (NPS) abnormalities or neurological abnormalities, pregnancy and newborns, a more urgent correction and intensive monitoring are indicated. In rare cases of severe deficiency (and severe anemia) and associated hemodynamic compromise blood transfusion may be an option.

2. *Route of administration*: Vit 12 are available for oral and parenteral route. VIT B12 IS NOT GIVEN INTRAVENOUSLY. Parenteral administration shall be provided to as said symptomatic individuals, those with NPS and those who do not have the capacity to absorb oral supplementation (eg, pernicious anemia [PA], intestinal blind loop). Oral route is preferred for those with nutritional deficiency, those with lack of access to parenteral administration facilities and/or patient preference. Moreso, high dose oral supplementation can be given in malabsorption states provided adherence is good, dose is sufficient, and a response is documented.

3. *Available preparations*: Two forms of Vit B12 are available i.e., Cyanocobalamin, which has a cyanide (CN) group added during chemical manufacture, and hydroxocobalamin (also known as cobalamin). Both are effective in treatment of vitamin B12 deficiency and are available in India. Though, cyanocobalamin is predominantly used in the United States and hydroxocobalamin is predominantly used in Europe. Citing different kinetics, maintenance dosing frequency of cyanocobalamin is more frequent than hydroxocobalamin.

4. Duration of therapy: Duration depends upon the underlying etiology of deficit. For those with a disease (such as autoantibodies to intrinsic factor [PA] or gastric bypass surgery) that cannot be reversed, lifetime replacement is required. Supplementation can be stopped once the deficiency is resolved if the underlying cause (such as an overly restrictive diet or a drug-induced deficiency) is removed.

5. Dose: Intramuscular (i.m) route is the most recommended route for Vit 12. Typical adult dose would be 1000 mcg intramuscularly once per week. But for NPS or anaemia, the recommended dose would be 1000 mcg intramuscularly alternate days for 1-2 weeks, and if aetiology is not reversible, then maintenance dose of 1000 mcg intramuscularly once a month (cyanocobalamin) lifelong or once every alternate month per month (hydroxocobalamin).

Oral dosing In adults with normal absorption is equally as effective as i.m dosing if given at a dose of 1000 mcg orally/day. But for individuals with impaired absorption, therapy with mega oral doses of oral vitamin B12 for eg, 2000-3000 mcg daily shall be effective.

6. Monitoring: More intensive monitoring may be required during supplementation for e.g., every 2 to 3 days if given for concerning neurological or NPS. Whereas less frequent monitoring like once in 2 to 3 weeks may be required for conditions such as incidental deficiency. But additional testing (methylmalonic acid and homocysteine levels) may be required if there is lack of response. Once therapy is stopped, then it is prudent to monitor vitamin levels at least at 3 months. ^[49]

Folic acid Deficiency

Oral folic acid (1-5 mg/day) is commonly used to treat folate insufficiency. This dosage is typically enough even in the presence of malabsorption because it is significantly higher than the 200 mcg (0.2 mg) suggested daily intake. For those with a reversible cause of deficiency (e.g., nutritional), folic acid is given for 1-4 months. For those with a chronic cause of folate deficiency, such as chronic haemolytic anaemia, therapy may be given indefinitely. Importantly, the neurologic manifestations of vitamin B12 deficiency will not be treated by folic acid. Thus, for NPS like dementia, we need to investigate and supplement with both Vit B12 and folic acid. ^[49]

Routine administration of vitamin B12 or folic acid supplements without documented deficiency is not recommended.

Obstructive sleep apnoea

Use of continuous positive airway pressure for treatment of obstructive sleep apnoea has been shown to have significant positive impact on the cognitive functions too.^[50] Here, strict patient compliance have to be assured. There is no role of cognitive enhancers in patients with obstructive sleep apnoea.

Hypothyroidism

Healthy adults who have been diagnosed with hypothyroidism for a few months should be started with levothyroxine dose of 1.6 mcg/kg/day and increase their dosage by 12.5 to 25 mcg/day every 6 to 8 weeks, depending on the condition. But those with cardiac disease or elderly over 65 years old initial starting dose shall be 25 mcg/day with a dose adjustment of 12.5 to 25 mcg every 4 to 6 weeks as needed. Patient shall be requested to use the same brand because of the narrow therapeutic index. Frequency of monitoring TSH levels shall be approximately 6 to 8 weeks after treatment initiating. Upon reaching the correct dosing of levothyroxine, frequency of monitoring shall reduce to 4 to 6 months and then every 12 months. It is important to note that in patients with *age more than 65 yrs, there is also a physiological rise of TSH levels, so precaution shall be entertained in treating the subclinical phenotype of hypothyroidism.*

Conditions such as normal pressure hydrocephalus do not require and do not respond specific pharmacological treatment for cognitive impairment.

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Title: Clinical Practice Guidelines on Addressing cognitive impairment in dementia due to Alzheimer's disease and other neurodegenerative disorders

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Introduction:

Indian Psychiatric Society (IPS) published Clinical Practice Guidelines (CPGs) for management of dementia, in the year 2007 and its update in 2018. Now the Indian Psychiatric Society has come up with a new supplement of CPGs on “Cognition in Neuropsychiatric Disorders and Management of Long Stay Psychiatric and Substance Abuse Disorder Patients.” This CPG is an update after half a decade since the last published CPG on management of dementia. However, compared to previous CPG, the current article is a comprehensive update on management with regards to specifically cognitive aspects of dementia in Alzheimer’s and other degenerative dementia (Frontotemporal dementia, Parkinson’s and Lewybody dementia). For information about management of other neurocognitive disorders and related conditions (Mild Cognitive impairment, Vascular dementia and reversible dementia) clinicians are suggested to go through other CPGs in this supplement. This CPGs does not comprehensively covers assessment and management of behavioural and psychological symptoms, psychiatric co-morbidity, end of life care needs in persons with dementia and caregiver interventions. Hence the clinicians are requested to visit appropriate resources for information about the same.

Process of development of these guidelines:

The authors of this guideline performed a thorough search of different data bases (Pubmed, Google Search, Science Direct and Scopus) for the relevant peer reviewed articles on this area. The articles were retrieved using combination of search words such as “Alzheimer’s dementia”, “frontotemporal dementia”, “lewybody dementia”, “Parkinson disease dementia”, “management”, “guidelines”, “pharmacological intervention”, “cognitive interventions”, “cognition oriented therapies,” “cognitive stimulation, ” “cognitive training,” “cognitive rehabilitation,” “non-invasive brain stimulation”, “alternative treatments,” “nootropics”, “supplements”.

While considering the literature, we focused mainly on meta-analysis and systematic reviews. Where ever, meta-analysis and systematic reviews are not available on any particular intervention, randomised controlled trails, cross-sectional studies were considered. Along with the global literature, specifically studies done in India were reviewed and included in this guideline formulation wherever applicable. Published guidelines from other regions were also reviewed and compared. Artificial intelligence or chat GPT are not used to during the development of these guidelines.

Dementia:

Dementia is a clinical syndrome characterized by progressive decline in intellectual abilities. Dementia gradually leads to impaired ability to do activities required for independent living. Dementia can be irreversible or reversible depending on the etiology. Irreversible degenerative dementia are classified, depending on the type of predominant neuropathology as Alzheimer’s dementia, Frontotemporal

dementia, Diffuse Lewy body dementia and Parkinson's disease dementia. Alzheimer's disease is the most common cause of dementia, accounting for 60% to 80% of cases.

Epidemiology:

In India, the prevalence of dementia (all cause dementia) using survey method or clinical diagnosis of DSM-IV or ICD-10 reported 0.6 % to 3.5% in rural areas and 0.9% to 4.8 % in urban areas (Shaji et al.,2019). In terms of AD, the prevalence in southern India was reported as 1.3% and northern India-as 0.77% (males) to 0.46% (females). The estimated dementia prevalence from LASI data for adults ages 60 and above in India is 7.4% (Lee et al.,2023). There is paucity of studies on prevalence of other degenerative dementia from India. However, a clinic based dementia registry study reported that Alzheimer's disease was the most common subtype of dementia (38.3%), followed by vascular dementia (25.4%), frontotemporal dementia (18.7%), dementia with Lewy bodies (8.9%) of the patients, and mixed dementia (8.6%) (Alladi et al., 2011).

2. Clinical presentation

Dementia is characterized by a progressive, global deterioration in intellect including memory, learning, orientation, language, comprehension and judgment. Individuals with Alzheimer's dementia experience multiple symptoms that change over a period of years. The pace at which symptoms of dementia advance from mild to moderate to severe differs from person to person.

- a) **Mild Dementia:** Individuals with Mild Dementia may be able to live independently, but some supervision and/or support is often required. However, individuals with Mild Dementia can still take part in community or social activities without help and may appear unimpaired to those who do not know them well. Judgment and problem solving are typically impaired, but social judgment may be preserved, depending on Dementia etiology. The individual may have difficulty making complex decisions, making plans, and/or handling finances (e.g., calculating change, paying bills).
- b) **Moderate Dementia.** Individuals with Moderate Dementia require supports to function outside the home and only simple household tasks are maintained. Individuals with Moderate Dementia have difficulties with basic activities of daily living, such as dressing and personal hygiene. Moderate Dementia is often characterized by significant memory loss. Judgment and problem solving are typically significantly impaired, and social judgment is often compromised. The individual has increasing difficulty making complex or important decisions and is often easily confused. The individual may have difficulty communicating with individuals outside the home without caregiver assistance. Socializing is increasingly difficult as the individual may behave inappropriately (e.g., in disinhibited or aggressive ways), with associated behaviour changes

(e.g., calling out, clinging, wandering, disturbed sleep, or hallucinations). The difficulties are often obvious to most individuals who have contact with the individual.

- c) **Severe dementia:** Severe Dementia is typically characterized by severe memory impairment, but this varies according to the etiology. There is often total disorientation for time and place. The individual is often completely unable to make judgments or solve problems. Individuals may have difficulty understanding what is happening around them. Individuals are fully dependent on others for basic personal care in activities such as for bathing, toileting and feeding. Urinary and fecal incontinence may emerge at this stage.

Table. 1 Stages of AD with clinical features and common neuropsychiatric symptoms

S. No	Stage of dementia	Cognitive symptoms	Behavioural and Psychiatric symptoms
	MCI	Mild difficulty in complex activities (driving, paying bills, working, participating in community affairs, shopping, cooking, managing medication).	Apathy, anxiety, depressive symptoms
1	Mild stage	Difficulty in remembering names, recalling recent events, remembering where objects were kept, making plans, staying organized, managing money	anxiety symptoms, depression, irritability

2	Moderate stage	Increasing difficulty in remembering events, inability to learning new things, difficulty with planning events, difficulty in remembering their own name, but not details about their own life, difficulty with reading, writing, and working with numbers, Knows that some people are familiar, but not remember their names, or forget the names of a spouse or child, Lose track of time and place, Need help choosing the right clothing, getting dressed, and with daily activities.	agitation, aggression symptoms, restless hallucinations, delusional disturbances, wandering, inappropriate sexual behavior
3	Severe Stage	Loses many physical abilities, including walking, sitting, eating, May lose bowel and bladder control, May be able to say some words or phrases, but not have a conversation, Needs help with all activities.	apathy, agitation, suicidal thoughts, incontinence, sleep disturbances, reduced food intake

Rapidly Progressive Dementia:

Dementia due to neurodegenerative disorders like Alzheimer's disease, FTD and DLBD are usually insidious onset and gradually progressive. In some patients they may have an atypical course with rapid progression. Rapid progression is usually defined as the progression from the initial symptom to the development of clear diagnostic features of dementia and functional impairment within one to two years. The evaluation of the persons with dementia having rapid progression requires consideration of the presence of treatable causes like depression, infection, nutritional impairment, Subdural haematoma, iatrogenic adverse effects, autoimmune encephalitis and paraneoplastic conditions etc. The clinical approach for the evaluation of the treatable dementia has been addressed in a separate CPG in this supplement (ref). Rare neurodegenerative disorders like FTD-ALS, Creutzfeldt Jakob Disease can also have rapid progression.

Dementia subtypes with rapid progression- Table (To be added)

Assessment and evaluation

Clinical History:

History taking is a key aspect in the evaluation of dementia. Reliable informant who knows about the person's current and past personal, social and occupational functioning should be interviewed. This will allow discussion of a certain information which may otherwise be difficult in the presence of the patient. A thorough history should include details like the onset of cognitive decline, cognitive domains effected, and duration of each symptom. The pattern of progression, clinical manifestations of cognitive impairment, and impact on functioning need to be enquired. The behavioral as well as personality changes will have to be assessed as well. If the older adults is residing in residential care facility, information from formal caregivers and other inmates becomes vital in arriving at a provisional diagnosis. A review of all previous medical records, review of allopathic and alternative forms of medication needs a detailed check and documentation. Specifically looks for medication that can directly lead to cognitive impairment or worsens the pre-existing cognitive impairment such as sedatives/hypnotics, anticholinergic, antihistamines, opioids etc., While doing the assessments, one has to be mindful of the family's culture, values, primary language, literacy level and also the decision making process.

Physical Examination:

Examination of vitals (pulse rate, blood pressure, respiratory rate, temperature) examination of systems (respiratory, cardiovascular, per abdomen and genitourinary). One should do a thorough neurological examination. Specially look for any bulbar signs (Gaze palsy,), cortical symptoms (agnosia, aphasia, apraxia, amnesia), extrapyramidal symptoms (decreased expressions, resting tremors, rigidity, bradykinesia), involuntary movements (chorea, dyskinesia, rubral tremors) gait abnormalities (festinating, wide based, ataxic) and frontal release signs (palmar reflex, plamomenta reflex, snout, sucking reflex, glabellar tap reflex,). Mental status examination will help in confirming the symptoms found in clinical history. In general appearance and behaviour look for any overt or subtle changes (tense, worried- suggestive of AD, whereas apathy, indifference, jovial nature, utilisation behaviours suggestive of FTD, mask like appearance suggestive of synucleopathy), speech and thought abnormalities (alteration in fluency, perseveration, phonemic or semantic paraphasia suggestive of FTD), mood disturbances (non-pervasive elation suggestive of FTD), Perception abnormalities (visual hallucination suggestive of lewybody dementia).

Diagnostic criteria: The diagnosis for Alzheimer's dementia is a based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* released in 2013. The other well-known criteria is National Institute of Aging- the Alzheimer's Association (NIA-AA) criteria, 2011. The DSM-5

classifies cognition into five domains. These are 1) Complex attention 2) Executive function 3) Learning & memory 4) Language 5) Perceptual-motor 6) Social cognition.¹⁴. The diagnosis of major neurocognitive disorder requires significant Cognitive Decline in two or more cognitive domains, interfere with independence in activities of living, and could not be explained due to delirium and other mental disorder. Criteria for Alzheimer's dementia, frontotemporal dementia, Lewybody dementia and Parkinson's disease dementia are as mentioned in table 2.

Type of dementia	Diagnostic Criteria for Alzheimer's and other degenerative dementia (ICD-11)
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Criteria for Dementia	• Marked impairment in two or more cognitive domains relative to that expected given the individual's age and general premorbid level of neurocognitive functioning, which represents a decline from the individual's previous level of functioning. • Memory impairment is present in most forms of Dementia, but neurocognitive impairment is not restricted to memory and may be present in other cognitive domains such as executive functioning, attention, language, social cognition and judgment, psychomotor speed, and visuoperceptual or visuospatial functioning. • Evidence of neurocognitive impairment is based on: • Information obtained from the individual, informant, or clinical observation; and • Substantial impairment in memory performance as demonstrated by standardized neuropsychological/cognitive testing or, in its absence, another quantified clinical assessment. • Behavioural changes (e.g., changes in personality, disinhibition, agitation, irritability) may also be present and, in some forms of Dementia, may be the presenting symptom. • The symptoms are not better accounted for by disturbance of consciousness or altered mental status (e.g., due to seizure, traumatic brain injury, stroke, or the effects of medication), Delirium, Substance Intoxication, Substance Withdrawal or another mental disorder (e.g., Schizophrenia or Other Primary Psychotic Disorder, a Mood Disorder, Post-Traumatic Stress Disorder, a Dissociative Disorder). • The symptoms result in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning.
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Dementia due to Alzheimer's disease	• All diagnostic requirements for Dementia are met. • Dementia is presumed to be attributable to underlying Alzheimer Disease (8A20) based on quantified clinical assessment or standardized neuropsychological/cognitive testing, neuroimaging data, genetic testing, medical tests, family history, and/or clinical history. • Early clinical history is typically characterized by gradual onset, progressive memory problems and word finding difficulties, as well as mild functional impairment. The most common form of Alzheimer Disease begins with neuronal impairment in the medial temporal lobes (the brain regions involved in memory formation). As Alzheimer Disease progresses and affects other brain regions, neurocognitive symptoms worsen. Atypical forms of Alzheimer Disease are also characterized by progressive neurocognitive and functional impairment, with initial neurocognitive symptoms often corresponding to the brain region(s) initially affected (e.g., visual processing impairment in posterior cortical atrophy, etc.).
FTD	A. The criteria are met for major or mild neurocognitive disorder. B. The disturbance has insidious onset and gradual progression. C. Either (1) or (2); Behavioural variant ◦ a. Three or more of the following behavioural symptoms: ▪ Behavioural disinhibition ▪ Apathy or inertia ▪ Loss of sympathy or empathy ▪ Perseverative, stereotyped or compulsive/ritualistic behaviour ▪ Hyperorality and dietary changes ◦ b. Prominent decline in social cognition and/or executive abilities Language variant a. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension.

DLBD (McKeith, et al.,2017)	Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function and visuo-perceptual ability may be especially prominent and occur early. Core clinical features <i>(the first three typically occur early and may persist throughout the course)</i> • Fluctuating cognition with pronounced variations in attention and alertness. • Recurrent visual hallucinations that are typically well formed and detailed. • REM sleep behaviour disorder (RBD) <i>which may precede cognitive decline.</i> • One or more spontaneous cardinal feature of parkinsonism – these are bradykinesia rest tremor, or rigidity. Supportive clinical features Severe sensitivity to antipsychotic agents ; postural instability ; repeated falls ; syncope or other transient episodes of unresponsiveness.; severe autonomic dysfunction e.g. constipation, orthostatic hypotension, urinary incontinence ; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety and depression. Indicative biomarkers • Reduced dopamine transporter (DaT) uptake in basal ganglia demonstrated by SPECT or PET • Abnormal (low uptake) MIBG myocardial scintigraphy • Polysomnographic confirmation of REM sleep without atonia Supportive biomarkers • Relative preservation of medial temporal lobe structures on CT/MRI scan • Generalised low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity +/- the cingulate island sign on FDG-PET imaging • Prominent posterior slow wave activity on EEG with periodic fluctuations in the pre-alpha/theta range Probable DLB can be diagnosed if: a) <i>two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers or</i> b) <i>only one core clinical feature is present, but with one or more indicative biomarkers</i> Probable DLB should not be diagnosed on the basis of biomarkers alone Possible DLB can be diagnosed if: a) <i>only one core clinical feature of DLB is present, with no indicative biomarker evidence, or</i> b) <i>one or more indicative biomarkers is present but there are no core clinical features</i> DLB is less likely: a) <i>in the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture,</i>
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although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation.

or

b) if parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia

PD Dementia (DSM-5 Criteria, 2013)	A. The criteria are met for major or mild neurocognitive disorder. B. The disturbance occurs in the setting of established Parkinson's disease. C. There is insidious onset and gradual progression of impairment. Major or mild neurocognitive disorder probably due to Parkinson's disease should be diagnosed if 1 and 2 are both met. Major or mild neurocognitive disorder possibly due to Parkinson's disease should be diagnosed if 1 <i>or</i> 2 is met: 1. There is no evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline). 2. The Parkinson's disease clearly precedes the onset of the neurocognitive disorder.
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Table 2. Summary criteria for AD and other degenerative dementia (refer to DSM-5 and ICD-

11)

Laboratory work-up

- Blood counts: complete blood count, Hemoglobin and peripheral smear.*
- Metabolic work up: Liver function test*, Renal functions*, serum Electrolytes*, serum Calcium*
- Endocrine work-up: Thyroid function test*
- Nutritional: Vitamin B12, Folate levels.*
- STD workup: VDRL, HIV.*
- Neuroimaging- CT or MRI-brain. # \$
- Autoimmune work-up and Electroencephalogram need to be considered based on clinical suspicion of other potential etiologies.*
- Advanced investigations: CSF amyloid and tau\$, Amyloid PET\$, FDG-PET\$, Polysomnography, dopamine transporter (DAT) imaging with [123I]-FP-CIT single-photon emission computed tomography (DAT-SPECT) and positron emission

tomography with [18F]-FDOPA (FDOPA-PET) (depending on the availability)

- Genetic analysis: ApoE4 allele, Pre-SEN1 and 2, APP gene, C9ORF72, GRN, MAPT (cases with high family loading or suspected autosomal dominant inheritance)
- *rule out reversible etiology, #extent of brain parenchymal atrophy, \$ diagnostic Biomarker

Screening cognitive assessment tools:

1. Mini-mental status examination (MMSE): MMSE is a 30-point questionnaire that is used extensively in clinical and research settings. A score below 24 is taken as cut-off for cognitive impairment. MMSE has 85% sensitivity and 90% specificity for detecting dementia. MMSE suffers from flooring and ceiling effect.
2. Hindi Mental status examination (HMSE): HMSE is a cognitive screening tool validated for Indian population. HMSE consists of 23 questions with a maximum score of 31. It is suitable for patients with minimal education/illiterates. HMSE has a sensitivity of 81.3% and specificity of 60.2% for detecting dementia.
3. Mini-Cog: Mini-Cog is another screening scale composed of the three objects recall and Clock Drawing Test. Mini-Cog has 79% sensitivity and 88% specificity for detecting dementia.
4. Informant questionnaire on cognitive decline in the elderly (IQCODE): It is a structured interview based on informant responses that is used to assess for possible dementia. It has 26-items and each item was rated on a 5-point scale from 1-“much better” to 5-“much worse.”

Brief cognitive tools:

1. Montreal Cognitive Examination (MoCA): Montreal Cognitive Assessment is a brief 30-item questionnaire with cut-off score of 23. MoCA has a sensitivity of 96% and specificity of 95% in samples of Alzheimer's dementia. It is also available in 8 local Indian languages.
2. Addenbrooke's Cognitive Examination (ACE-III): ACE assess five cognitive domains: attention/orientation, memory, language, verbal fluency, and visuospatial skills on 100 point scale. At a cut-off scores of 88 and 83, the ACE was reported to have sensitivity of 93% and specificity of 82%.. ACE-III in six Indian languages apart from Indian English.
3. Frontal lobe assessment battery (FAB): The FAB is a brief cognitive and behavioural battery that can be used at the bedside to assess frontal lobe functions. It has six components and with maximum score of 18. Using a cutoff score of 12 can reasonably differentiate FTD from Alzheimer's dementia (sensitivity of 77% and specificity of 87%) (Slachevsky et al.,2004).

Detailed cognitive assessments:

1. ICMR Neurocognitive tool box: Neurocognitive Tool Box is a standardized set of cognitive tests that are culturally appropriate. The ICMR-NCTB has been standardized across 5 Indian languages (Hindi, Bengali, Telugu, Kannada, and Malayalam). ICMR-NCTB gives scores across various cognitive domains including attention and executive function, episodic memory, language, visuospatial ability, unilateral spatial neglect, and behavioral scales.
2. NIMHANS neuropsychological battery for the elderly (NNBE): NNBE is a comprehensive and standardized neuropsychological battery, developed for older Indian adults. The tests are described here briefly. Episodic memory was assessed with word list and story recall test assessing immediate and delayed recall. Attention was assessed by digit span test. Constructional ability was assessed with stick construction test. Executive functions were assessed with digit span, Corsi block-tapping test, fluency, and Tower of Hanoi (TOH). Language abilities were assessed by semantic verbal fluency test.

4. Table on recommended tools available for dementia assessment

Management of cognitive impairment:

Treatment options for cognitive impairments-**Pharmacological treatments:**

The treatment is currently targeted towards symptomatic improvement. Several guidelines recommend anticholinesterase inhibitors (ACEI) and NMDA partial antagonist memantine in Alzheimer's and other degenerative dementia.

Anti-cholinesterase inhibitors (ACEI): ACEI are one of the commonly used medication in degenerative dementia especially Alzheimer's, Lewybody and Parkinson's disease dementia. ACEI primarily decreases the catabolism of acetylcholine in the synaptic cleft and thus

Type of intervention	Intervention	Medication and Dosing schedule	Adverse effects	Indication	Level of evidence (RANZCP)
ACEI	Donepezil	5mg(min) increase to 10mg after 4 wks	bradycardia, syncope, vomiting, loss of appetite, insomnia, Muscle cramps	AD, DLBD, PDD	Low
	High dose Donepezil	SR 23mg			
	Rivastigmine oral and Patch	1.5mg BD double the dose every 2 wks to max of 6mg BD 4.6mg/24hr increase to 9.5mg/24hr after 4 weeks.	bradycardia, syncope, Vomiting, loss of appetite, insomnia	AD	Low
	Galantamine	4 mg BD double the dose every 2 wks to 12mg BD	bradycardia, syncope, vomiting, loss of appetite, insomnia	AD	Low
NMDA antagonist	Memantine	5mg OD increase by 5mg wkly to 20mg OD	Headache, constipation	AD	Moderate

symptomatically improves attention and working memory in persons with dementia. Three cholinesterase inhibitors viz., donepezil, rivastigmine and galantamine are approved by the U.S. Food and Drug Administration (FDA) for treatment of mild to moderate Alzheimer's disease and donepezil has been approved by the FDA for severe Alzheimer's disease. ACEI were notorious

to cause gastric adverse effects and sinus bradycardia. It is advised to do baseline ECG and start at low dose and titrate gradually to maximum recommended dose as shown in table 3. The maximum dose for donepezil, rivastigmine and galantamine are 10mg/day, 12mg/day and 24mg/day. Donepezil SR 23mg and rivastigmine patch 13.5 mg/patch are also available, these are used only if there is adequate tolerability and clinical benefit in selective patients.

In terms of evidence, Cochrane systematic review reported positive effect of cholinesterase inhibitors on the Mini-Mental State Examination (MMSE) in patients with PDD (WMD 1.09, 95% CI 0.45 to 1.73, P = 0.0008) but not in DLBD. However, there is no evidence for ACEI in Bv-FTD and though there are prescribed in semantic variant of FTD with modest evidence.

NMDA- antagonist: Memantine is a non-competitive N-methyl-D-aspartate (NMDA) antagonist. Currently memantine is approved by the FDA for use in patients with moderate and severe Alzheimer's disease. Though

NMDA antagonists

Evidence

Table. 5 **Currently recommended pharmacological interventions for cognitive symptoms in AD and other degenerative dementia.**

Table.6 De-prescribing ACEI and Memantine in PwD

S.No.	PwD taking a ChEI or Memantine for Alzheimer disease, dementia of Parkinson disease, Lewy body dementia or vascular dementia for > 12 months, we recommend trial discontinuation if meets at least one of the criteria as below
1	Cognition and/or function has significantly worsened over the past 6 months (or less, as per the individual);
2	No benefit (improvement, stabilisation or decreased rate of decline) was seen at any time during treatment
3	The individual has severe or end-stage dementia (characteristics include dependence in most activities of daily living, inability to respond to environment and/or limited life expectancy)
	Method of de-prescribing ACEI
1	Reduce the dose to half the previous dose every 4 weeks
2	Monitor the cognitive status, functioning and behaviour and psychological of dementia (BPSD) every 4 weeks during de-prescribing period
3	Any worsening or re-emergence of symptoms within 3 months (after ruling out other etiology), clinicians should consider to re-start or go to the previous dose of ACEI or memantine
4	Any worsening or re-emergence of symptoms after 3 months, consider it as probable progression of underlying degenerative condition

De-prescribing cognitively harmful medication:

Clinicians are advised to do thorough review of all medications of PwD during evaluation. Medications such as Opioids, sedatives, hypnotics, anticholinergic and antihimnnics are known to contribute to or worsen the cognitive abilities in PwD. Hence as part of treatment plan, the above medication should be tapered/withdrawn whenever possible or change to dedication which has minimal anticholinergic burden.

Disease modifying agents:

The future of Alzheimer's disease (AD) treatment is focused on developing therapies that go beyond symptomatic relief to target the underlying mechanisms of the disease. Here are some of the promising directions in research and treatment:

Amyloid-targeting therapies have emerged as a promising approach in the treatment of dementia, particularly Alzheimer's disease. These therapies focus on reducing the accumulation of amyloid-beta plaques in the brain, which are believed to play a crucial role in the disease's progression. Several new drugs have been developed and tested, including **donanemab** and **lecanemab**, which have shown significant efficacy in slowing cognitive decline in early-stage Alzheimer's patients. Donanemab, for

instance, demonstrated a 35% reduction in cognitive decline, particularly when administered early in the disease course.

These therapies work by utilizing antibodies to target and clear amyloid plaques, potentially slowing the neurodegenerative processes associated with Alzheimer's. However, while these treatments have shown promise, they also come with risks, such as brain swelling and microhemorrhages, necessitating careful patient selection and monitoring.

Tau-targeting therapies have gained considerable attention as a promising approach to treating Alzheimer's disease and related dementias. Tau proteins, which accumulate abnormally within neurons, are closely linked to cognitive decline in Alzheimer's. Recent studies have focused on developing therapies that reduce tau levels or prevent its aggregation.

One of the significant advancements has been the exploration of drugs that enhance the brain's natural mechanisms to clear tau, such as boosting proteasome activity specifically in affected areas of the brain. This targeted approach aims to reduce tau without causing widespread degradation of other necessary proteins, thereby minimizing side effects.

Oral medications like ALZ-801 have been highlighted as a promising advancement in Alzheimer's treatment due to their ease of administration compared to traditional intravenous therapies. ALZ-801 is an oral amyloid-targeting drug that works by inhibiting the formation of toxic amyloid-beta oligomers, which are believed to contribute to the progression of Alzheimer's disease. ALZ-801's development builds on the success of its predecessor, tramiprosate, but with improved formulation to enhance efficacy and reduce side effects. This oral drug is particularly noteworthy because it offers a more accessible and less burdensome treatment option for patients, which could improve adherence to therapy.

Clinical trials, including the APOLLOE4 study, have shown that ALZ-801 is effective in reducing amyloid levels in the brain, with a favorable safety profile. This makes it a strong candidate for early intervention, especially in individuals with genetic risk factors for Alzheimer's, such as those carrying the APOE4 allele.

These advancements represent a significant shift towards more effective and targeted treatments for Alzheimer's, offering hope for slowing the progression of this challenging disease. However, these therapies are still under investigation, and more research is needed to fully understand their long-term benefits and potential risks.

Non-pharmacological interventions-

As of now pharmacological “cure” for Alzheimer’s dementia and other degenerative dementias remains an unmet need. Even with upcoming disease modifying treatments (DMT) there are

several challenges in terms of clinical efficacy, tolerability, accessibility and affordability especially in low and middle income countries. In view of the above, non-pharmacological interventions (NPIs) have a role in the treatment of cognitive symptoms in dementia.

Cognition-oriented treatments' (COTs), referred to previously as 'cognition-focused interventions' is an umbrella term referring to a group of NPIs that involve a range of techniques to engage thinking and cognition with various degrees of breadth and specificity. COTs are known to increase the brain health, cognitive reserve and flexibility to improve cognitive status and importantly functioning. The positive aspects of COTs are low-cost, scalable, can be done in group, can be delivered via digital mode and delivered by professionals with various backgrounds. It becomes critical that we utilise NPIs to maximize benefits to persons with dementia either as standalone or in addition to pharmacological interventions. Several cognition oriented treatments have been studied in PwD, among them most studied are cognitive stimulation therapy (CS), cognitive training (CT) and cognitive rehabilitation (CR). Computerised cognitive training (CCT), enriched environment (EE) and photobiomodulation (PBM) are some of the newer methods investigated for cognitive symptoms of dementia.

Table 7. Pre-workup of PwD prior to initiating Non-pharmacological interventions

S. No	Details required
1	Personality traits: introvert/extrovert
2	Language and education background
3	Hobbies, likes and dislikes
4	Personal material like- past memories in the form of pictures or videos or objects
5	Acceptability for group interventions
6	Accessibility and comfort with computerised interventions
7	Risk to self or others (aggression, violence, psychotic symptoms, wandering tendencies, loss of inhibition)-might not be suitable for group intervention
8	Assess sensory and comprehension issues

Cognitive stimulation therapy (CST):

Cognitive stimulation therapy (CST) was developed nearly 25 years ago as one of the well tested non-pharmacological therapy for PwD. (CST) is a brief, psychosocial therapy for persons with Alzheimer's disease and other dementias. CST developed by combining techniques of reality orientation therapy, (RO), reminiscence therapy (RT) and cognitive stimulation approach by Breuil's et al. CST involves engagement of PwD in a range of activities and discussions usually done in a group, aimed at general enhancement of cognitive and social functioning. These are nothing but mental exercises to improve global cognitive abilities. CST consists of 14 twice weekly sessions that scheduled over a period of 7 weeks. The variety of activities in CST include puzzles, word or number games, discussion of topics of interest, reminiscence etc as shown in table.

RCTs on CST reported benefits in cognition, quality of life (QoL), communication, social interaction and also better in effectiveness (Aguirre et al.,2013, Knapp et al.,2006). Recent cochrane review of 36 studies (involving 2704 participants; CS: 1432, controls: 1272) reported moderate-quality evidence for a small benefit in cognition associated with CS (standardised mean difference (SMD) 0.40, 95% CI 0.25 to 0.55). In the same review of 25 studies that used MMSE (1893 participants) for assessing cognitive function, found moderate-quality evidence (significant difference of 1.99 points between CS and controls, 95% CI: 1.24, 2.74) (Wood et al., 2023). National Institute for Health and Care Excellence (NICE) recommends group CST for PwD with mild to moderate severity.

In addition to group CST, individual CST (iCST) was studied in caregivers and PwD as a dyad. iCST delivered by caregivers found to have beneficial effects on caregivers in addition to the PwD. Studies reported iCST enhances the positive caregiving experience and carers quality of life (Gibbor et al.,2020)

Culturally adapted CST to suit Indian patients was pilot tested. This version of CST include sessions on "Childhood memories", "traditional south Indian counting game", session on "association of words, faces or scenes" and final session on "budgeting on ordering a meal for

specific number of people”. The adapted program was found to be acceptable, enjoyable, and constructive by PwD and carers (Raghuraman et al.,2017).

Table. 8 Sessions with content details in Cognitive stimulation therapy (CST)

Session	Content/topic	Session	Content/topic
1	Physical games	8	Being Creative
2	Sound	9	Categorizing objects
3	Childhood	10	Orientation
4	Food	11	Using Money
5	Current affairs	12	Number games
6	Faces/scenes	13	Word games
7	Associated words	14	Team games

Cognitive training (CT):

CT is described as method that typically involves guided practice of a set of structured, standardised tasks, designed to train individuals on relatively well-defined cognitive processes and abilities. CT is known by other terms as ‘brain training’, ‘retraining’, or ‘remediation’. CT is primarily based on restorative model and believes that neuroplasticity of brain is responsible for improvement in cognitive abilities. CT initially developed to improve specific cognitive functions in cerebrovascular stroke and traumatic brain injury conditions. This was followed by extensions of its benefits to healthy older adults, persons with subjective cognitive decline and subsequently PwD.

The technique of CT is based on two assumptions. First assumption is that practice has the potential to improve or at least maintain functioning in the given cognitive domain. Second assumption is that any effects of practice will generalise beyond the immediate training context. CT is divided into subtypes of cognitive exercise and strategy training (Gates 2011). The strategy based CT involves instruction and practice in the use of specific cognitive strategies designed to enhance performance, or minimise the impact of impaired cognition (e.g. method of loci, visual imagery). There are several advances have come in CT intervention in the past 3 decades such as transition from fixed program model to individualised program and paper-pencil to computer delivered intervention. CT can be provided in individual session or group sessions.

The earlier RCTs on CT in PwD reported either minimal or no benefits on cognitive aspects, though open label studies promise. This could be due to inclusion of smaller samples, heterogeneity in diagnosis, variable frequency and duration on intervention, concomitant use of ACEI (Clare and Woods, 2008). However, recent cochrane review of 32 RCTs involving majority of patients with AD shown small to moderate positive effects with CT compared to treatment as usual. The sample in each study ranged from just 12 to 653 and duration of intervention ranged from 2 weeks to 104 weeks. There was moderate-quality evidence showing a small to moderate effect of CT on composite measure of global cognition at end of treatment (standardised mean difference (SMD) 0.42, 95% confidence interval (CI) 0.23 to 0.62), and high-quality evidence showing a moderate effect on verbal semantic fluency (SMD 0.52, 95% CI 0.23 to 0.81) at end of treatment, with these gains retained till 3 to 12 months post treatment (Bahar-Fuchs et al.,2019).

In India, a picture based cognitive training intervention (CTI) was developed for patients with AD by Bajpai et al. This cognitive intervention is suitable patients irrespective of literacy. The task include picture recognition task based of episodic memory, spot the differences based on attention and verbal learning task based on errorless learning and spaced retrieval strategy. CTI involves caregiver along with PwD, thus it is suitable as domicillary intervention (Bajpai et al.,2020).

To summarise the evidence for CT is small to poor level in mild to moderate dementia, unlike in healthy older adults and MCI where there is moderate level of evidence. Currently NICE guidelines do not recommend CT to PwD.

Table.9 Cognitive training intervention adopted to Indian Setting. (Bajpai et al.,2020)

Domain	Task	Principle
Episodic Memory	Picture recognition task	Mental Imagery
Attention	Spot the differences	Visual scanning
Language	Verbal learning task	Errorless Learning and spaced retrieval strategy

Cognitive rehabilitation:

Rehabilitation denotes a positive approach to enabling persons to make the most of their functional ability (Poulos 2017). Cognitive rehabilitation (CR) is a person-centered approach that addresses the impact of cognitive impairment on everyday activities and enables the persons to engage in or manage day to day activities at a desired level. CR was originally developed for people with cognitive impairment due to brain injury. Later the CR approach was adapted for people with dementia.

The goal of CR is to improve functioning in areas that are relevant for PwD. These targeted areas are typically outlined in the form of personal goals that the PwD wishes to attain. The expert delivering CR consider three factors while planning this intervention viz., person, context and activity (Clare et al.,2008). There are several strategies and methods that are employed in CR to improve functioning in PwD. The one adopted by Kelly and Sullivan involve methods for better encoding, retrieval and specific interventions as shown in table.

Regarding the evidence, a multicentric trial (GRAET trial) randomised of 475 PwD with dementia (AD, VaD, mixed dementia and MCI) to CR and treat as usual (TAU). There was statistically significant large positive effects for participant-rated goal attainment ($d = 0.97$; 95% CI, 0.75-1.19), corroborated by

informant ratings ($d = 1.11$; 95% CI, 0.89-1.34). The positive effects were maintained at 9 months for both participant ($d = 0.94$; 95% CI, 0.71-1.17) and informant ($d = 0.96$; 95% CI, 0.73-1.2) ratings (clare et al.,2019). In addition, cochrane meta-analysis of 6 RCTs published from 2010 to 2022, included 1702 PwD compared CR with TAU. Positive evidence on participant self-ratings of goal attainment (SMD) 1.46, 95% confidence interval (CI) 1.26 to 1.66; $I^2 = 0\%$; 3 RCTs, 501 participants), informant ratings of goal attainment (SMD 1.61, 95% CI 1.01 to 2.21; $I^2 = 41\%$; 3 RCTs, 476 participants), and self-ratings of satisfaction with goal attainment (SMD 1.31, 95% CI 1.09 to 1.54; $I^2 = 5\%$; 3 RCTs, 501 participants), relative to an inactive control condition. At follow-up (3 - 12 months) the gains of CR were maintained as per the participant self-ratings of goal attainment (SMD 1.46, 95% CI 1.25 to 1.68; $I^2 = 0\%$; 2 RCTs, 432 participants), informant ratings of goal attainment (SMD 1.25, 95% CI 0.78 to 1.72; $I^2 = 29\%$; 3 RCTs, 446 participants), and self-ratings of satisfaction with goal attainment (SMD 1.19, 95% CI 0.73 to 1.66; $I^2 = 28\%$; 2 RCTs, 432 participants), relative to an inactive control condition (Kudlicka et al.,2019)

Table . 10 Commonly used Cognitive rehabilitation techniques for mild- moderate AD

S. NO	Intervention	Procedure
1	Graded Activity	
2	Modelling	
3	Action based learning	
4	Expanded Rehearsal	
5	Prompting and Fading	
6	Mnemonics, elaboration and vanishing cues for learning information	
7	Compensatory strategies such as memory aids	
8	Environmental modification	

Table 11. Strategies and interventions used in Cognitive rehabilitation (Kelly and Sullivan, 2015)

Guiding Principle	Recall strategies	Specific interventions
Effortful Processing	Mnemonics	Face-name Recall
Dual Cognitive Support	Chunking	Story Recall
Errorless Learning	Method of Loci	List/Object Recall
	Cueing	Number Recall
	Spaced Retrieval	Fluency Training
		Procedural Memory
		Semantic Impairments

Enriched environment (EE):

Previous research has shown that participation in activities and emotional support can help enhance cognitive reserves and maintain or improve cognitive functions in older adults (Iwasa et al.,2011). The concept of “enriched environment” was proposed by Hebb in 1947. Enriched environment is defined as an environment with intervention factors and a combination of nonliving things and social stimuli. It included two categories: socially enriched stimuli and physically enriched stimuli. The social enriched stimuli increase the opportunities for interaction among individuals, and the physical enriched stimuli provide a complex and changing environment where individuals live by changing the setting or appliances in the environment.

Creating stimulating environment without putting cognitive overload for PwD should be goal in terms of environmental interventions. This can include pictures of family members, calender, wall clock, jigsaw puzzles, coloured pictures, flower pots and garden.

Cognitive Engagement:

Cognitive engagement is more an informal, structured or un-structured activities delivered by health professionals or caregivers for overall cognitive improvement and to decrease behavioural problems among PwD. Cognitive engagement has similarities with CST in terms of principle of intervention, however, cognitive engagement does not require any specific training or a structured tools to implement.

The activities can range from simple games like chess or board games, drawing, painting, sorting, arranging, planting sampling, gardening etc. deepening on the feasibility and patient prior interests.

Previous studies have shown that nursing home residents spend the majority of their time not engaged in any meaningful activity (Harper-ice, 2002). Lack of stimulation/engagement for sustained periods can have negative impact on PwD as it the worsen apathy, depression, loneliness and deterioration in cognitive abilities. Engaging PwD in age appropriate activities has been shown to yield beneficial effects such as increasing positive emotions, improving activities of daily living (ADL) and improving the quality of life (Orsulic-Jeras et al.,20000).

Digitally delivered non-pharmacological interventions:

The traditional cognitive intervention programs require face-to-face contact, require significant time from therapist and overall more expensive in the long run. In India there are additional barriers such as lack of adequate trained personal who can deliver cognitive interventions, language barriers and commute to training facility frequently.

The merits of digital based cognitive interventions are, these can be tailored to patient requirement, can combine mix of cognitive interventions, gives immersive and enjoyable experience, provide instant feedback and are actively accessible on portable digital devices. The challenges in Indian setting are digital literacy, cooperation of PwD, suitability, affordability and accessability for the digital devices and applications. The experience gained during COVID19 pandemic with widespread lockdowns enabled clinicians to use digital platforms to provide health care to older adults in India. In this way using digital technology to deliver cognitive interventions appears aa a feasible option in current day world than previously thought.

The computersied digital applications are classified depending on the platform used, target group, device and primary intervention approach as shown in table. Here we discussed salient digital applications which are investigated at RCT level.

FESKITS is computer program used for cognitive intervention in PwD. It is designed to improve and maintain cognitive functions. In an RCT by Gaitan et al., 60 patients with MCI and mAD were randomised to traditional CT versus computer based CT (CBCT) and traditional CT (FESKITS) by in Spain for 3 months. Addition of CBCT to traditional CT has shown improvement in executive function but no further in global cognitive improvement compared to traditional CT possibly due to ceiling effect (Gaitan et al.,2013). SOCIABLE is another digital application commonly used for cognitive training

intervention in PwD. SOCIABLE comprises the exercises for the cognitive training and an electronic book called “Book of Life” for the Reminiscence therapy (RT). Barban et al. (2015) in a multicenter RCT examined the effects of using SOCIABLE in MCI, mAD and healthy subjects in Italy for 3 months followed by 3 months of rest. In this study, all three groups, shown improvement in delayed recall. MCI and mAD participants showed a significant improvement on MMSE. Participants with mAD showed more stable instrumental activities of daily living during the training versus the rest period (Barban et al.,2015). Another RCT by Zaccarelli et al., found improvement in memory and executive function among MCI and mAD with 12 week training with SOCIABLE digital application (Zaccarelli et al.,2013).

In terms of cognitive rehabilitation (CR) ComCog, Grader, Brainer, and NeuronUp were been studied in PwD. Computer-Assisted Cognitive Rehabilitation (COMCOG) is a computer based CR intervention program. COMCOG consists of items such as simple recognition memory, simple spatial memory, sequential recall memory, language recall memory, combined recall memory, language categorization memory, and language integration memory. A study from South Korea on 35 AD patients who received COMCOG for 30 minutes per day, 5 days per week for 4 weeks found improvement in delayed recall and recognition memory (Hwang et al.,2015). In an RCT from Italy on 80 Patients with AD receiving CBCT using Brainer for 12 weeks reported a significant improvement in various neuropsychological domains with effect lasting till 6 months (Cavallo et al.,2016). Grador is a neuropsychological assessment system and multi-domain cognitive intervention program. Principles of feedback and difficulty adaptation are used to enhance participation in Grador. In a pilot study (MCI and Healthy) where cognitive exercises using Grador software were combined with physical exercises was found to be feasible and promising. There is an on-going RCT to determine the effectiveness of the cognitive rehabilitation program Grador and the ICT platform ehcoBUTLER among MCI and PwD (Vanova et al.,2018). Another study on cognitive training through a Brain Computer Interface (BCI) and the NeuronUp platform in patients with mild dementia (MSSE:18-23) found delayed cognitive symptom progression as assessed from luria neuropsychological battery Mendoza (Laiz et al.,2018).

Early attempts of examining virtual CST intervention in India was tested in a multicentric study along with Brazil. In this study 17 vCST group sessions were delivered 59 PwD for 7 weeks using manually validated CST protocol. This study reported feasibility and acceptability of digitally delivered CST intervention (Fisher et al.,2024).

Table. 12 Digitally delivered cognitive interventions for PwD

Types	Categories	Examples
Depending on the platform	Native application (can be used offline) Web based application	Brainer, Cogmed, CogniFit, FesKits, NeuronUp, ComCog Captain's Log, CogniPlus, COGPACK, GRADIOR)
Primary approach for cognitive intervention	Cognitive stimulation Cognitive training Cognitive rehabilitation	FesKits Captain's Log, Cogmed, CogniFit, CogniPlus, COGPACK, SOCIABLE Brainer, GRADIOR, NeuronUp, ComCog
Target patients	MCI PwD	SOCIABLE, COGPACK, Cogniplus, Cogmed, Cognifit Feskits, GRADIOR, NeuronUp, ComCog, SOCIABLE

Physical exercise:

Positive effects of physical exercise on overall health is well known. In terms of brain health, physical exercise is known to reduce the atherosclerotic changes in brain, reduce the ageing effects,, promotes neurotropic release, improves cognitive reserve, dampens the pro-inflammation and decreases age related gray matter loss. When it comes to degenerative dementia's several therapeutic interventions aimed to reduce the neurotoxic effect of protein aggregates in degenerative dementia were examined till today. Physical exercise as a natural method, has a potential however small it can be to dampen the relentless progression of degenerative process.

Physical exercise (PE) as a cognitive intervention has shown its positive impact as part of multimodal intervention in MCI patients (FINGER trial and MAPT trial). Among the notable studies on PE in PwD, a multi-centre single blind randomized controlled trial of 200 patients with mild AD compared supervised exercise group (60-min sessions three times a week for 16 weeks) or to a control group in Denmark. In intention to treat analysis, the study did not find significant difference between two groups on attention domain as measured by Symbol Digit Modalities Test (SDMT) (mean:2.5, 95% CI -1.1 to

6.1: $p=0.179$), ability to perform ADL and quality of life. However, PwD who adhered to the protocol, significant change in SDMT was observed in PE group compared with the control group (mean: 4.2, 95% CI 0.5 to 7.9, $p = 0.028$) (Hoffmann et al.,2016). Another large three arm RCT from Finland randomised patients with AD ($n=200$) to home-based exercise (HE) and group-based exercise (GE) or control group. The intervention were done twice weekly for 1 years and assessed for cognitive status. The study found improvement in executive function as measured by clock drawing test (CDT) in HE group at 12 months, whereas there was deterioration of MMSE scores and verbal fluency in all there groups (Ohman et al.,2016).

A meta-analysis in 2019 that included 13 RCT ($N= 673$, AD patients) showed a statistically significant improvement in cognition with PE in MMSE scores ($SMD = 1.12$ CI:0.66~1.59) compared to the control groups (Jia et al.,2019). A recent systematic review on effect of PE on cognitive functions in AD included 22 studies ($n = 1647$, mean age: 77.1 ± 6.3 years) of which sixteen were included in the meta-analysis. In this review 13 studies that used MMSE showed a significant improvement in cognitive function with physical exercise ($n = 820$, $MD = 0.83$, 95% CI = 0.43 to 1.23, $p < 0.00001$; $I^2 = 47\%$, fixed-effect model). Four studies that used ADAS-Cog showed significant improvement in cognitive functions with physical exercise ($n = 335$, $MD = -3.533$, 95% CI = -6.9 to -0.16 , $p = 0.04$; $I^2 = 57\%$, random-effect model). Six studies that used CDT measuring executive function showed no significant improvement with physical exercise ($n = 439$, $MD = 0$, 95% CI = -0.04 to 0.04 , $p = 0.91$; $I^2 = 0\%$, fixed-effects model) (Liu et al.,2022).

Physical exercise has been well studied in PwD. Most common physical exercise (PE) types studied in AD are mixed exercise modalities (aerobic, resistance, balance, and stretching exercises) followed by aerobic exercises. The frequency of PE ranged from 2 to 5 times per week and duration of each session lasting 30–70 min each. The duration of the PE interventions ranged from 9 to 52 weeks. The optimal type, frequency and duration of PE to get desired cognitive benefits in PwD is yet to be established. There is also no specific PE module for PwD, however there are certain strategies that can be used to facilitate PE as shown in table. RANZCP guidelines currently recommends physical activity/exercise for PwD to improve functional independence.

Table.13 Physical exercise adaptations for PwD

Problems Areas	Strategy to facilitate Physical activities
Attention issues unable to persist with exercise	Include a volunteer to support PwD during physical ac

Memory impairment	Employ auditory, visual, and physical cueing to correct patterns
Movement & gait impairments	Adapt exercises to physical capabilities of PwD
Sensitivity to over-stimulating environments	Modify environment to reduce sensory stimulation (e.g. familiar)
Emotional reactivity and agitation	Anticipate these triggers for Agitation Adapting the physical activity depending on the emotion of participant

YOGA -

Yoga encompasses physical postures, breathing exercises, meditation. Yoga is recognised for its role in physical and mental wellness. The Ministry of Ayush, Government of India reorganised Yoga as an independent alternative system of medicine. Therapeutic benefits of yoga in Subjective cognitive impairment and mild cognitive impairment (MCI) are reported. YOGA with its roots in Indian culture has much more acceptance among older adults. Hence, there is a merit in considering yoga for PwD as a part of holistic care.

The usual challenges when considering yoga for PwD are the feasibility and cooperativeness. Regarding this, studies on yoga in PwD found 'Chair Yoga' and 'standardised mindfulness meditation' developed by Massachusetts Medical School as feasible for PwD (Park et al., 2020, Wells et al., 2013).

When it comes evidence, an initial quasi experimental study of yoga exercises in PwD in longterm care setting (cases-33, control group-35) found positive effect on depressive symptoms, flexibility and balance (Fan and Chen, 2011). Similarly Sit 'N' Fit Chair Yoga Program on nine PwD (AD) for 8 weeks found to improve gait and balance (McCaffrey et al., 2014). Study by Salazar et al., investigated the impact of Hatha Yoga (32 one hour session twice a week) on 35 PwD (AD) reported improvement in attention. (Salazar et al., 2017). Another open label study on chair yoga for PwD (AD), reported no significant change in cognitive symptoms after 10 weeks of intervention (Litchke et al., 2012). A recent RCT compared Chair yoga with Music intervention and Chair-based exercise in PwD (n=31, diagnosis: AD, DLBD, PDD) twice weekly 45-min sessions for 12-weeks. In this study Chair yoga was found to improve QoL, mood, functional abilities, interpersonal relationships, ability to participate in meaningful activities (Park et al., 2020). A systematic review of 10 studies on yoga that included predominantly

patients with MCI and lesser PwD, reported cognitive benefits in MCI but not in PwD (Karamacoska et al.,2023). To summarise, Kundalini yoga, chair yoga, followed by Hatha Yoga are the most studied yoga interventions in PwD. Cognitive functions were assessed using caregiver reports, from functioning ability, improvement in ADL and MMSE. Average duration of yoga intervention was 12 weeks.

There are fewer studies so far that systematically assessed effect of yoga on cognitive aspects in PwD. Due to this limitation, yoga is not recommended by current guidelines in PwD for cognitive symptoms, though certainly yoga has a role in engagement and physical health aspects in PwD.

Dietary supplements :

Dietary supplements have garnered significant attention for their potential role in managing Alzheimer's disease (AD) and cognitive decline. Here's an overview of some key supplements being studied:

1. **Omega-3 Fatty Acids:** Found in fish like salmon and sardines, omega-3 fatty acids, particularly DHA (docosahexaenoic acid), are essential for brain health due to their anti-inflammatory properties. Some research suggests that higher levels of omega-3s in the blood are associated with a reduced risk of dementia and better cognitive function. However, while these findings are promising, they are not yet conclusive enough to recommend omega-3 supplements solely for dementia prevention. Including fatty fish in the diet remains a general recommendation for its cardiovascular and cognitive benefits.
2. **Curcumin:** This compound, derived from turmeric, has powerful antioxidant and anti-inflammatory properties. Studies have shown that curcumin might reduce brain inflammation and prevent the accumulation of amyloid plaques, a hallmark of Alzheimer's. Although some clinical trials have reported mixed results, ongoing research continues to explore curcumin's potential to slow Alzheimer's progression. Interestingly, research has shown that curcumin can cross the blood-brain barrier, which makes it a compound of interest for neurological conditions.
3. **Vitamin D:** There is growing evidence that vitamin D deficiency may be linked to an increased risk of cognitive decline and dementia. Vitamin D, particularly in its active form (D3), plays a role in neuroprotection and immune function. Some studies suggest that adequate levels of vitamin D might help clear amyloid plaques from the brain, potentially offering a preventive effect against Alzheimer's. However, more research is needed to establish definitive guidelines on vitamin D supplementation for Alzheimer's prevention.

4. **Other Supplements:** Ginkgo biloba, Vitamin E, and Coenzyme Q10 are other supplements that have been studied for their potential cognitive benefits. Ginkgo biloba is believed to improve blood flow to the brain and has antioxidant properties, though research findings are inconsistent. Vitamin E, known for its antioxidant effects, may slow functional decline in patients with mild to moderate Alzheimer's, while Coenzyme Q10 could protect the brain from oxidative damage, though evidence is still limited.

While these supplements offer hope, it's crucial to approach their use with caution. Supplements can interact with medications and may not be suitable for everyone. A holistic approach that includes a balanced diet, regular physical activity, mental stimulation, and good sleep hygiene is recommended for overall brain health.

Caregiver interventions:

Addressing the needs of Alzheimer's caregivers involves providing comprehensive support, including emotional and mental health resources, respite care, education, and financial and legal guidance. These measures are essential to sustain the health and well-being of caregivers, which in turn benefits the patients they care for.

Caring for Alzheimer's and dementia patients presents unique challenges, and recent studies since 2022 have increasingly recognized the critical needs of caregivers. Caregivers, often family members, face significant physical, emotional, and financial burdens as they provide ongoing support to their loved ones.

Education and Training: Educating caregivers about the progression of Alzheimer's, effective communication strategies, and behavioral management techniques has been identified as a crucial need. Training programs that equip caregivers with these skills can significantly reduce stress and enhance the quality of care provided.

Emotional Support: Caregivers frequently experience high levels of stress, anxiety, and depression due to the relentless nature of Alzheimer's care. Recent literature highlights the importance of providing mental health support, such as counseling and support groups, tailored specifically for caregivers. These resources can help mitigate feelings of isolation and burnout, offering a platform for sharing experiences and coping strategies (Alzheimer's Disease and Dementia).

Respite Care: To prevent caregiver burnout, there is an increasing emphasis on respite care services. These services offer temporary relief by providing professional care for patients, allowing caregivers to rest and attend to their own needs. Access to respite care has been shown to improve the well-being of both caregivers and patients, underscoring its importance as part of a comprehensive care plan.

Financial and Legal Guidance: The financial strain of long-term care, coupled with the complexities of legal issues like power of attorney and guardianship, are significant concerns for caregivers. Recent studies suggest that providing access to financial planning and legal resources can help caregivers manage these burdens more effectively

Table 14. Summary of other Guidelines

Guidelines	ACEI and Memantine	CST, CT, CR	Occupational therapy	Physical Exercise/YOGA
Australian Guidelines (Laver et al., 2016)	Any one of the three acetylcholinesterase inhibitors (donepezil, galantamine or rivastigmine) could be considered for people with AD, DLBD, PDD, VaD or mixed dementia. Combination of an ACEI and memantine could be considered for managing the symptoms of functional decline for people with moderate to severe AD			
RANZCP Guidelines, 2016	Any one of the three ACEI (donepezil, galantamine or rivastigmine) are recommended as options for managing the symptoms of mild, moderate and severe AD (EBR mod), DLBD, PDD, VaD, Mixed dementia (EBR low) Memantine is recommended as an option for people with moderate-to-severe AD who are intolerant of or have a contraindication to ACEI (EBR mod) combination of ACEI plus memantine could be considered in moderate-to-severe AD (EBR low)	No specific recommendation for either CST, CT or CR based of available evidence	Recommends to improve functional independence (EBR low)	PE: Recommends to improve functional independence (EBR low)

NICE Guidelines, 2018	Recommends ACEI as lone medication for AD with mild severity. Recommends combination of ACEI+ Memantine for AD with moderate to severe AD. DLBD: Recommends donepezil or rivastigmine in mild -mod severity (mod. quality evidence) Recommends donepezil in severe DLBD (GC experience) Recommends galantamine in mild- mod DLBD if other ACEI are not tolerated (GC experience) Recommends memantine in DLBD if ACEI are not tolerated or are contraindicated (low-mod. Quality evidence) FTD: Does not recommend ACEI or memantine in FTD [low to mod. quality evidence]	Recommends CST to PwD with mild to moderate severity (based on mod. Quality of evidence) Recommends CR to PwD with mild to moderate severity (based on low to mod. Quality of evidence) Does not recommend CT to PwD	Recommends to PwD with mild to moderate severity (based on low to mod. Quality of evidence)	
Irish College of General Practitioners (ICGP), 2019	Recommends ACEI in mild to mod. AD Recommends memantine either alone or with ACE in mod-severe AD			
Taiwan Dementia Treatment Guideline, 2021	Recommends donepezil, rivastigmine and galantamine in AD Recommends donepezil and rivastigmine in DLBD and PDD Recommends memantine in mod-severe AD. Combination of ACEI and memantine in AD is recommended if cognitive deterioration continues			

Conclusion:

The current CPG recommends ACEI medications for all stages of dementia due to AD, DLBD/PDD but not in FTD for cognitive symptoms. Memantine is recommended for moderate to severe stage of AD, but have poor evidence in other degenerative dementia. In addition, taper or withdraw medications contributing to cognitive impairment. Among the non-pharmacological intervention, CST is

recommended based on current evidence for cognitive symptoms. CT and CR though have low evidence, it is advisable to use these interventions due to their multifaceted benefits for PwD. Training of staff at dementia care facilities is important in effective implication of non-pharmacological cognitive interventions. Digital interventions are feasible based on current evidence and are advised to recommend based on availability and affordability. Non-invasive brain stimulations (rTMS and tDCS) are not routinely recommended for cognitive symptoms based on current available evidence. Nootropics and food supplements are not supported by currently available evidence for cognitive impairment. Regular monitoring of PwD while on ACEI is always recommended and continue or withdraw based on risk-benefit ratio. Holistic person-centred care need to be followed in the management of PwD especially in longterm residential care setting.

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Clinical practice guidelines for addressing cognitive impairment in vascular dementias

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General comments

- Plagiarism- maximum 15% (total), max from single source- 3%
- Please submit to IJP today (and send submission number/acknowledgement mail to CPG committee)
- Quote- International as well as IPS guidelines specifically
- Follow- timeline
- Add section- process of developing the guideline - Done
- Add Indian literature to quote as far as feasible & relevant
- For manuscript-please use IJP format and referencing style.

Specific to topic

1. Please correct typo errors
- Done
2. Use uniform font type
- Done
3. Phrase as Options available, remove not-recommended (as no treatment is recommended)
- Done
4. Role of Imaging to add/ elaborate Hachinshe's index for vascular dementia, CT, MRI, PET → Added
5. Add about procedures available for specific clinical condition, and liaison approach
- Added emphasis on interdisciplinary approach and liaison.
6. Add a section on Mixed dementia.
- Added about prevalence.
7. Add about physical exercise, cognitive impairment and metabolic syndrome
- Physical activity already included in management; Lack of Physical Exercise added in risk factors. Metabolic syndrome already present in risk factors table.
8. Add about anecdotal evidence- Vinpocetine
- Done
9. Re-training to start as early as possible
- Done
10. Add about small vessel disease.
11. Please add tables flow charts.
Tables are already added in the guideline

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Introduction

Vascular dementia (VD) has been recognised for many centuries and was later meaningfully distinguished from dementias due to other ~~etiologies~~aetiologies.^[1] VD is recognised as one of the most common types of dementia in the community across the world second only to dementia due to Alzheimer's disease (DAT) and the prevalence may be even higher in developing countries such as India.^[2] Thus, VD is an important public health challenge and a major contributor to morbidity and mortality worldwide. However, there are issues in the exact classification of the disease and diagnostic criteria. Also, there are no licensed treatments specifically for VD.^[3]

What sets VD apart from other dementias are the following factors. The ~~etiology~~aetiology of VD is clearly associated with brain tissue loss and dysfunction secondary to vascular pathophysiology in which hypertension seems to be the main culprit.^[4] While the exact cellular mechanisms are still not clear, it does imply that VD may potentially be largely preventable through better cardiovascular-metabolic risk modification. VD may also arise from other more gross brain insults such as strokes and infarcts that can lead to a sudden and catastrophic loss of cognitive function unlike the usual stepladder pattern or gradual decline that is classically described in VD or observed in other dementias. This is reflected in the various cerebrovascular disorders that have been described and also different terminologies that have been used by different authors to describe cognitive decline due to brain tissue loss and dysfunction due to vascular reasons.^[5,6] Thus cognitive decline due to cerebrovascular pathophysiology can exist on a spectrum from mild to severe and be correlated with a variety

of brain lesions of vascular origins. Much of the deficit seen in VD may be attributed to the particular brain area that is involved in the insult. Thus, symptoms may vary from patient to patient. It can present itself as problems with memory and attention, confusion, impaired planning and judgment, uncontrolled laughing and crying, declining ability to pay attention, impaired function in social situations, and difficulty finding the right words, changes in personality and ~~behavior~~behaviour, loss of speech and language skills, and sometimes weakness or tremors. Cortical lesions may result in aphasia, apraxia, and seizures while subcortical lesions may present as executive dysfunction, parkinsonism, abnormal gait or urinary incontinence.

Vascular cognitive impairment may be divided into mild and major (VD). VD can be caused by post-stroke dementia, subcortical ischemic vascular dementia, multi-infarct cortical dementia, and mixed dementia (when comorbid with dementias due to other

~~etiologies~~aetiologies).^[7] Dementia of Alzheimer's type (DAT) is the most common type of Dementia across the world followed by Vascular Dementia (VD). However, often due to overlap of symptoms, it becomes difficult to distinguish both the dementia clinically in the later stages of dementia. Mixed Dementia (which is the co-occurrence of DAT and VD) is estimated to be the third most common type of Dementia globally as well as in India^[8,9].

~~It is increasingly recognised that VD may co-occur with Dementia of Alzheimer's type (DAT).~~^[8] ~~However,~~ VD can usually be meaningfully clinically distinguished from DAT and other dementias especially in the early stages which opens up possibilities for early interventions.^[9] This is especially so because most VD seems to have a long incubation period of decades and midlife hypertension seems to be contributory to the development of the same in later life. Unlike DAT where drugs have been designed for modification of disease process, management of VD has largely ~~foesed~~focused on prevention through the modification of risk factors and prevention of further deterioration in established VD.

Comment [pk1]: Custodio N, Montesinos R, Lira D, Herrera-Pérez E, Bardales Y, Valeriano-Lorenzo L. Mixed dementia: A review of the evidence. *Dement Neuropsychol*. 2017 Oct-Dec;11(4):364-370. doi: 10.1590/1980-57642016dn11-040005. PMID: 29354217. PMCID: PMC5769994.

Arshad F, Mm S, Paplikar A, Rajendran Kalkonde Y, Alladi S. Vascular cognitive impairment in India: Challenges and opportunities for prevention and treatment. *Cereb Circ Cogn Behav*. 2021 Nov 25;3:100034. doi: 10.1016/j.cccb.2021.100034. PMID: 36324418; PMCID: PMC9616277.

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In keeping with the mandate provided to the authors, this paper will deal with guidelines that may help clinicians in the prevention and management of VD. The authors have reviewed existing clinical guidelines for VD and vascular cognitive impairment.^[10–20] Other existing relevant data has also been reviewed for this purpose.

Process of Development of the Guideline:

The guideline was developed after extensive review of the scientific literature as well as based on the clinical experience. The authors searched for relevant peer reviewed articles published in both international and national medical journals in English with focus on Vascular Dementia or Vascular Cognitive impairment as well as guidelines from WHO, and various international societies that have focused on vascular dementia or vascular cognitive impairment. Among the journal articles, meta-analysis were preferred whenever available, followed by systematic reviews and randomised Controlled trials. The current guideline, thus developed, was then presented at a workshop to eminent psychiatrists of the Indian Psychiatric Society on August 10, 2024. The comments thus received were incorporated and presented again on August 11, 2024, as well as uploaded on the website of the Indian Journal of Psychiatry for comments and suggestions from all mental health professionals. Following that, the final draft of the guidelines were published.

Guidelines

The guidelines are arranged as follows. Firstly, guidelines that deal with diagnosis of VD will be discussed. This will be followed by guidelines for prevention.^[21] Finally management strategies will be considered.

Diagnosis and assessment

The complexity of vascular dementia often requires a coordinated approach involving multiple specialists – neurologists, endocrinologists, cardiologists, psychiatrists and psychologists to comprehensively assess as well as to manage address the various

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contributing factors effectively. Regular interdisciplinary consultations and collaborative joint care planning are vital to address the multifactorial nature of vascular dementia, and for tailoring interventions that target both cognitive symptoms and underlying vascular risk factors.

As mentioned above, VD is meaningfully different from other dementias with regards to phenomenology and pathophysiology. This provides clinicians and researchers opportunities for interventions. Therefore, it is imperative that sensitive and specific diagnostic schedules be available. Diagnosis is available in the following modalities in addition to routine clinical and lab investigations.

Standardized diagnostic criteria:

Recommended standardized diagnostic criteria for diagnosis of VD and vascular cognitive impairment are presented in Table 1. Most schedules emphasize on a temporal correlation of the cognitive deficit with a cerebrovascular insult, neuroimaging support for the diagnosis of the insult, characteristic clinical picture, manifestations of stroke residua, risk factors of stroke, supportive natural history and familial factors.^[22] Some of these diagnostic criteria have shown to have high inter-rater agreement with items in other schedules and have adequate predictive power with regards to conversion to dementia and mortality.^[23] These diagnostic schedules may be recommended as aids to clinical diagnoses of VD and cognitive impairment.

Radiological diagnosis:

Radiological diagnosis of VD is done preferably via the use of magnetic resonance imaging (MRI) and if not available or contraindicated by the use of computerized tomography (CT) scanning.^[15] This is true for clinical and research settings. This is because MRI has a greater sensitivity and specificity for smaller lesions and microbleeds, as well as cortical atrophy that may reflect concomitant disease processes.^[24] Recommendations have been made for

standardization of imaging protocols for small vessel cerebral disease.^[25] It is recommended that MRI should be mandatorily carried out as a part of the diagnostic work- up and assessment of any patient with suspected or confirmed VD. in the absence of MRI or if it is contraindicated, CT may be a reasonable alternative.

Hachinski Ischemic Score or Hachinski Index:

The **Hachinski Ischemic Score (HIS)**, also known as the **Hachinski Index**, is a clinical tool, often, used to differentiate between vascular dementia and Alzheimer's disease. It was developed by Dr. Vladimir Hachinski and colleagues in 1975. The index assesses various clinical features associated with dementia to determine the likelihood that the dementia has a vascular component (abrupt onset, stepwise deterioration, fluctuating course, nocturnal confusion, relative preservation of personality, presence of depressive symptoms, somatic symptoms, emotional incontinence, history of stroke, presence of focal neurological signs, and presence of focal neurological symptoms). A score of 7 or more indicates vascular dementia. This is not a diagnostic tool. The index is most effective when combined with other diagnostic tools and tests, including neuroimaging and cognitive assessments.

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Prevention

As mentioned above, VD represents a condition which may be uniquely preventable by modification of non-communicable disease risk factors. Various risk factors have been described of which some are modifiable.^[26] Modification of many of these risk factors can presumably reduce the risk of developing VD.^[27]

Universal prevention:

Universal prevention of VD in adults can include strategies for prevention and evidence for prevention of VD in particular. The world health organization (WHO) strategies for prevention of dementia may be recommended as an universal population strategy and may be useful in selective and indicated patients as well.^[28] These include promotion of age appropriate physical activity, tobacco cessation interventions, nutritional interventions, alcohol use interventions, cognitive interventions, management of weight, hypertension, diabetes mellitus, and ~~dyslipidemia~~dyslipidaemia.

Selective and indicated preventive strategies specific to VD:

While a host of modifiable risk factors have been proposed for the development of VD, research has been focussed mainly on prevention and management of hypertension, prevention of stroke and recurrent stroke, the use of acetylsalicylic acid (ASA) in patients with white matter lesions and in patients with brain infarcts without stroke.

Hypertension is an easily identifiable and modifiable risk factor for development of dementia and VD.^[29] While the association is well described, the pathophysiology is not so clear. It seems that midlife hypertension may be more contributory to the development of VD than late-life hypertension.^[30] Thus midlife control of hypertension may be a better preventive strategy. There is modest evidence to suggest that blood pressure interventions across modalities may reduce incidence of dementia later.^[31] A similar finding exists for lowering of blood pressure in the elderly with a greater cardiovascular risk profile. A modest advantage was reported for intensive blood pressure lowering versus standard lowering interventions on development of eventual cognitive impairment or dementia.^[32] However these studies are not generalisable to patients with pre-existing stroke, dementia or diabetes. Also intensive blood

pressure lowering is associated with the risk of cerebral hypoperfusion and concomitant falls and syncope.

However it is reasonable to recommend measures to prevent hypertension as a means to prevent VD and vascular cognitive impairment. In middle-aged or elderly patients with hypertension and associated risk factors, target blood pressure of <120 mm of Hg systolic should be aimed for. In patients with pre-existing cognitive impairment, blood pressure readings of ≥ 90 mm of Hg or systolic readings ≥ 140 mm of HG should indicate the need for hypertension therapy.^[15] Indian guidelines for hypertension may be useful in this regard.^[33]

The calcium channel blocker drugs and angiotensin converting enzyme inhibitor classes of antihypertensive drugs may be useful in this regard.^[34,35]

Stroke prevention is another important aspect of prevention of VD. This includes prevention of first-ever and recurrent stroke. There are various guidelines for stroke prevention and these guidelines from India may also be useful.^[36] Other guidelines include the Berlin manifesto, and the Canadian and American guidelines.^[17,37,38]

Another aspect of prevention of VD is the use of ASA in patients with white matter lesions and brain infarcts without stroke. Both of these conditions may be considered to be proximal to the eventual development of VD. While it is reasonable to expect that such patients would benefit from the use of an antiplatelet and ~~antiinflammatory~~anti-inflammatory agent such as ASA, the evidence base suggests that ASA may not have a role in prevention of VD or cognitive decline in either of these populations or in the prevention of dementia.^[39-41] Use of ASA must be tempered by the possibility that it may lead to a predisposition to bleeding.^[42] Thus the use of ASA must be tempered by an analysis of the risk-reward ratio.

It is worthwhile to suggest that much of what has been discussed above may require a liaison with other specialities such as endocrinology and cardiology, thus a psychiatrist may be encouraged to seek guidance from other specialists.

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Treatment options

Treatment options

Most of the guidelines and literature have focused on prevention of further impairment in vascular dementia by reduction of risk factors that can lead to further vascular events. These include management of Diabetes, Hypertension as well as other vascular risk factors using medications, and lifestyle interventions namely diet, physical activity, avoidance of tobacco and alcohol. While the WHO guidelines recommend these interventions to reduce the risk of cognitive decline in patients with normal cognition and those with mild cognitive impairment to reduce further cognitive decline. However, its effect in improving the cognition among patients with vascular dementia is not known.

Due to the multifactorial nature of vascular dementia, as well as due to the frequent presence of mixed dementia, Management should involve active collaboration and liaison among the various specialists, especially cardiologists, endocrinologists, neurologists, psychiatrists and psychologists. By addressing the underlying vascular and metabolic conditions that contribute to cognitive decline through the collaborative approach, along with interventions for improvement of cognitive functions, one can provide effective and targeted treatment, ultimately improving the quality of life for patients with vascular dementia.

Treatment modalities used are presented in table 3.

Pharmacological Interventions:

No pharmacological treatment modality has been found to consistently lead to clinically significant improvement in treating patients with vascular dementia. Some of the pharmacological agents that have been tried in patients with vascular dementia have been discussed below:

Anticholinesterase agents: Cholinesterase inhibitors that have been tried for cognitive impairment in patients with vascular dementia include Donepezil, Galantamine and

Rivastigmine. Multiple Cochrane reviews as well as multiple meta-analyses have found modest cognitive benefits with cholinesterase inhibitors in patients with mild to moderate dementia.^[3,43–46] The latest Cochrane network-meta-analysis has found Donepezil and Galantamine to have slight but clinically insignificant impairment, while Rivastigmine has little to no effect on cognition.^[47] However, the use of these medications is also associated with higher risk of adverse effects. The most common adverse events include nausea, vomiting and ~~diarrhea~~diarrhoea. Serious adverse events that have been reported include stroke, pneumonia, and myocardial infarction. Most international guidelines support the use of these medications when vascular cognitive impairment has comorbid DAT. However, when there is no comorbid DAT, these medications may be considered for vascular dementia if there is no contra-indication and after fully informing the patient about the potential benefits and risks of these medications.

NMDA antagonist: Memantine is another agent which has been tried for patients with vascular dementia and has shown modest benefits in cognition, similar to AChE inhibitors. However, since the effects are modest, their clinical significance is again a matter of debate. While most available international guidelines recommend use of memantine in vascular dementia in patients with co-morbid DAT, they are divided with respect to recommendations for pure vascular dementia, with some guidelines not recommending its use and some guidelines recommending consideration for use in selected patients. Hence, NMDA antagonist maybe tried and may be useful for selected patients, especially when there is co-morbid Dementia of Alzheimer's type (Mixed Dementia).

Citicoline: Citicoline is an endogenous intermediate in the formation of phosphatidylcholine, the primary neuronal phospholipid. Few studies have tried to assess the efficacy of citicoline mainly in prevention of cognitive impairment after stroke or other cerebrovascular events. The studies have shown some improvement in the executive function, attention and temporal

orientation in patients following stroke. Studies which have used citicoline as an adjuvant along with other modalities of treatment like TMS or memantine have also found additional benefits of combination therapy which included citicoline.^[48–50] None of the international guidelines mention the use of Citicoline in patients with vascular dementia. Until further research is available, Citicoline may be tried and may be useful in selected patients, especially post-stroke patients. is NOT recommended as treatment for patients with vascular dementia.

Vinpocetine: Vinpocetine is a synthetic derivative of vinca alkaloid vincamine, which is extracted from the periwinkle plant, *Vinca minor*. It has several cellular targets – inhibitor of Ca²⁺/ Calmodulin stimulated cyclic nucleotide phosphodiesterase 1 (PDE1), inhibitor of voltage-dependent Na⁺ channel and inhibitor of IκB kinase (IKK). There is very limited literature on the effect of Vinpocetine on Vascular impairment, with the available literature showing mixed results. Anecdotal evidence that Vinpocetine may be useful in vascular dementia, mainly by improving the cerebral blood flow, acting as an antioxidant and reducing cerebral inflammation. More studies are needed to find its effectiveness in patients with vascular dementia.

Non-Pharmacological Interventions:

Neuromodulation: Neuromodulation techniques like repetitive transcranial magnetic stimulation (rTMS) and (tDCS) are recently being tried in research to find its efficacy in patients with vascular dementia. Meta-analyses of rTMS have shown it to lead to medium to large effect on the executive function in patients with vascular dementia. However, the effect of other domains, as well as its impact on activities of daily living is still not known. There are very limited studies on tDCS, with the available studies showing improvement in very few domains like visual memory and reaction time, but not on overall cognitive performance.

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Comment [pk2]: Zhang YS, Li JD, et al. An update on vinpocetine: New discoveries and clinical implications. *European Journal of Pharmacology*. 2018 Jan 15;819:30-34. doi: 10.1016/j.ejphar.2017.11.041. Epub 2017 Nov 26. PMID: 29183836; PMCID: PMC5766389.

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Comment [pk4]: Zhang YS, Li JD, et al. An update on vinpocetine: New discoveries and clinical implications. *European Journal of Pharmacology*. 2018 Jan 15;819:30-34. doi: 10.1016/j.ejphar.2017.11.041. Epub 2017 Nov 26. PMID: 29183836; PMCID: PMC5766389.

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While the available studies show promise, more studies with larger sample size and longer follow-up are also needed to establish its efficacy in the long-term. None of the international guidelines present till now have not mentioned neuromodulation in treatment of vascular cognitive impairment. Neuromodulation can be tried if patient can engage in the intervention, resources are available and there are no contra-indications for the same. Hence, till more evidence becomes available, neuromodulation methods are NOT recommended as treatment for vascular dementia.

Cognitive training and rehabilitation: Studies on cognitive training and cognitive rehabilitation on patients with vascular dementia are again very limited. Cognitive rehabilitation usually involves a combination of restorative and compensatory approaches and focuses on improving the functioning of the individual in everyday activities. Cognitive training focuses on particular cognitive tasks. The available studies have shown either no effect or very minimal effect on cognition. While some guidelines recommend the use of cognitive training or cognitive rehabilitation, some guidelines do not recommend the same or are silent about the same. Until further research is available, it is NOT recommended to provide cognitivesame. Cognitive training and rehabilitation should be offered for patients as soon as possible after a stroke. with Vascular dementia.

Virtual Reality: Recently, research is also focusing on virtual reality in patients with vascular dementia. The available studies have found promising effects in improvement in cognition. However, its clinical significance as well as long term efficacy needs to be researched further. Also, no guidelines till now have mentioned about the use of virtual reality for treatment in vascular dementia. Until more research is available Virtual reality may be considered as an option in selected patients with vascular dementia is NOT recommended as treatment for cognitive impairment for patients with vascular dementia.

Computer Assisted Cognitive Rehabilitation: While recent studies are focusing on computer assisted cognitive rehabilitation, the beneficial effects of these interventions over standard cognitive rehabilitation is questionable. While many guidelines do not mention this intervention, American heart association/ American stroke association scientific statements have mentioned that computerized cognitive training is better if they are part of clinician directed programs.

Physical activity: Studies on physical activity have provided mixed results, with some studies showing positive effects and some showing no effect. The main reason for the varied results could be the variation in the type and amount of physical activity across studies. Aerobic exercise and mixed physical activity which involves aerobic exercise has in general been found to be better in improving cognition. Guidelines either have not mentioned physical activity or have advised physical activity for overall improvement and prevention of future vascular events. Only WHO guidelines for dementia overall have mentioned physical activity to be recommended to individuals with normal cognition or mild cognitive impairment. However, it is also silent about physical activity for patients with dementia. Even though the quality of evidence is low with respect to the effect of physical activity on cognitive impairment in patients with vascular dementia, since physical activity improves the overall physical health and brings about improvement in co-morbid conditions like diabetes, as well as it helps the person to become as much independent as possible, Physical activity should be advised to persons with vascular dementia unless there is a contra-indication.

Acupuncture: There have been limited studies on acupuncture, with the available studies showing minimal improvement on cognition, but with no effect on activities on daily living.

None of the guidelines currently mention acupuncture as a treatment for vascular dementia.

~~Due to paucity of literature, acupuncture is NOT recommended for treatment of cognitive~~

impairment in vascular dementia. Acupuncture may be tried as an option in selected patients if patient can engage, resources are available and there is no contraindication for the same.

Table 4 presents a summary of recommendations for VD across different contemporary international guidelines.

Table 1. Recommended standardized diagnostic criteria for VD and cognitive impairment.

Vascular ~~behavioral~~ <u>behavioural</u> and cognitive disorders (VASCOG) criteria ^[51]
DSM-5 criteria ^[52]
The consensus statement of the American Heart Association and American Stroke Association ^[16]
Vascular Impairment of Cognition Classification Consensus Study ^[7]

Table 2. Commonly described risk factors for VD

Non-modifiable risk factors	Modifiable risk factors
Age	Hypertension
Sex	Diabetes
Family history	Sedentary lifestyle
Genetic predisposition	Obesity
Race	~~Dyslipidemia~~ <u>Dyslipidaemia</u>
	Smoking and alcohol use
	Atrial fibrillation
	Hypercoagulable states
	Metabolic syndrome
	Cardiovascular events
	<u>Lack of Physical Exercise</u>

Table 3. Evidence Base on Management of Cognitive Impairment in Vascular Dementia

Pharmacological Interventions			
Medication type	Dosage	Type of Study	Results
Cholinesterase Inhibitors	Donepezil 5 to 10 mg Galantamine 16 to 24 mg Rivastigmine 3 to 12 mg	A network meta-analysis of 8 RCTs including 4373 participants [47]	Donepezil 5 mg, 10 mg and Galantamine 16 to 24 mg – slight, but clinically insignificant improvement Rivastigmine 3 to 12 mg – little to no effect on cognition
	Donepezil 5 to 10 mg, Galantamine 24 mg, Rivastigmine 12 mg	Network Meta-Analysis of 11 RCTs (Comparison of ChE inhibitors with memantine) [53]	Donepezil 5 mg, 10 mg, galantamine 24 mg showed better effects in ADAS-cog Donepezil 5 mg, 10mg , rivastigmine 12mg exhibited superior benefits in MMSE. Donepezil 10 mg better effects in executive function and global status
	Donepezil 5 to 10 mg, Galantamine 24 mg, Rivastigmine 3 to 12 mg	Network Meta-analysis of 12 RCTs [54]	Donepezil, Rivastigmine significantly more effective in cognition based on MMSE Donepezil, galantamine, and memantine significantly more effective in cognition based on ADAS – Cog scale
NMDA antagonist	Memantine 20 mg	Network Meta-Analysis of 11 RCTs (Comparison of ChE inhibitors with memantine) [53]	Memantine exhibited superior benefits in ADAS-Cog. Memantine was better in terms of acceptability.
	Memantine 20 mg	Network Meta-analysis of 12 RCTs [54]	Memantine more effective in cognition based on ADAS-Cog score Memantine improved global status based on clinician's interview based impression of change scale plus caregiver's input
Citicoline	Citicoline 1 g/day for 12 months Given 6 weeks after stroke	Open-Label, randomized parallel trial of 347 participants [49]	Cognitive functions improved 6 and 12 months after stroke in the entire group Citicoline showed better outcome compared to controls in (A)Attention-executive functions &

			(B) temporal orientation at 6 and 12 months follow-up. Citicoline group showed a better functional outcome (modified Rankin scale ≤ 2) at 12 months without statistically significant difference.
Non-Pharmacological Interventions			
Cognitive rehabilitation / training	Systemic Cognitive training: 12-weeks training 60 minutes / day (Attention, Memory, Orientation, Visuospatial perception, re-telling and naming intervention)	A RCT of 73 patients with Vascular Cognitive impairment but no dementia ^[55]	Significant improvement in memory, language, attention, and visuospatial function after intervention ($p < .05$) except Stroop ~~Color~~ Colour-Word Test.
	Cognitive training: Guided practice on a set of standardized tasks designed to reflect particular cognitive functions such as memory, attention or problem-solving. Cognitive rehabilitation: Individualised approach to help people with cognitive impairment to improve functioning in everyday context.	Meta-analysis of 11 RCTs (Included patients with Alzheimer's dementia or Vascular dementia)	Cognitive training did not lead to significant improvement in cognitive function. There was only one eligible RCT on cognitive rehabilitation that showed a positive effect on mood and other outcomes.
Neuromodulation	Repetitive Transcranial Magnetic Stimulation (rTMS): Stimulation on Left DLPFC 20 sessions in most studies	A meta-analysis of 20 high-quality RCTs with 1049 participants ^[56]	Significant improvement in executive function: Large effect size (SMD 0.93) in executive sub-item of cognitive scale. Medium effect size (SMD 0.69) on executive specific scale. Theta burst stimulation (iTBS), higher frequency, lower intensity, longer duration and combined comprehensive therapy show superior efficacy

	tDCS: Anode – Left DLPFC Cathode – Right Supraorbital area 20 sessions	RCT of 21 patients with mild vascular dementia ^[57]	No significant difference between real and sham intervention in overall ADAS-Cog Scale. However, there was statistically significant improvement in visual recall and reaction time in the intervention group compared to control.
Virtual Reality	Virtual Reality (VR) and Computer Assisted Cognitive Rehabilitation (CACR) VR immerses participants in a computer-generated analog world that changes naturally with head and body movements CACR: Computer-based cognitive training program that includes computer exercises and computer games	A network meta-analysis of 21 RCTs (1,047 patients) ^[58]	VR group and CACR groups were found to be superior to Conventional therapy group, but not significant in change in MMSE VR and CACR showed significantly better outcomes compared to CT in MoCA. CACR had the best treatment effect, followed by VR.
Physical Activity	Physical activity definition varies across studies (Ranges from >0.25 miles walked per day to involving activities other than walking) Once per week to more than three times per week	Meta- Analysis of 9 observational prospective studies (preventive role) ^[59]	Only three individual studies reported significant associations. However, on meta-analysis, overall effect was statistically significant, with higher levels of physical activity associated with a smaller risk of VCI and Vascular dementia
	Physical activity : Stretching and toning / physiotherapy Aerobic exercise (treadmill, bicycle) Mixture of aerobic and stretching and toning exercise	Meta-analysis of 14 studies with 736 participants. ^[60]	Physical activity showed an overall positive effect on cognitive performance. Combined aerobic and strength training programs produced better cognitive performance. The positive effects were found in processing speed and attention even in chronic stroke phase (mean – 2.6 years after stroke)
Acupuncture	Acupuncture	Meta-analysis of 34 RCTs with	Significant improvement in Hasegawa dementia scale (HDS) and

		2672 patients ^[61]	MMSE. However, no significant change in Activities of daily living (ADL)
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Table 4. International Guidelines on Management of Cognitive Impairment in Vascular Dementia

Pharmacological Interventions		
Medication type	Name of Guideline	Recommendation
Cholinesterase Inhibitors (Donepezil, Galantamine, Rivastigmine)	Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD)5: Guidelines for management of vascular cognitive impairment, 2020 [62]	May be considered for treatment of vascular cognitive impairment in selected patients

	NICE Guidelines, 2018 ^[20]	Consider ~~AChE~~ <u>AChE</u> inhibitors for people with vascular dementia only if ~~g#here~~ <u>there</u> is suspected co-morbid Alzheimer's dementia, Parkinson's disease or Dementia with Lewy bodies
	American Heart Association/American Stroke Association, 2011 ^[63]	Donepezil can be useful for cognitive enhancement in patients with VaD Administration of galantamine can be beneficial for patients with mixed Alzheimer disease/VaD The benefits of rivastigmine are not well established in VaD
	American Heart Association / American Stroke Association, 2023 ^[64]	Cholinesterase inhibitors are sometimes prescribed for patients with dementia after stroke, although more work is needed to define the safety and efficacy RCTs provide moderate-quality evidence for small improvements in cognition, of uncertain clinical relevance.
	Australian Family physician guidelines, 2016 ^[65]	Evidence has shown the benefit of AChE inhibitors in vascular dementia. Medications when given should be reviewed within one month for evaluating appropriate dose and adverse effects. Review within six months should also be considered to find if there is improvement in quality of life, ~~behavior~~ <u>behaviour</u> and cognitive symptoms.
	European Stroke Organisation and European Academy of Neurology joint guidelines on post-stroke cognitive impairment ^[66]	There is insufficient evidence to make a recommendation for use of cholinesterase inhibitors.
	British Association for Psychopharmacology, 2017. ^[67]	Cholinesterase inhibitors are beneficial in mixed dementia
Memantine	Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD)5: Guidelines for management of vascular cognitive impairment, 2020. ^[62]	May be considered for treatment of vascular cognitive impairment in selected patients.

	Australian Family physician guidelines, 2016. ^[65]	Evidence has shown the benefit of memantine in vascular dementia. Medications when given should be reviewed within one month for evaluating appropriate dose and adverse effects. Review within six months should also be considered to find if there is improvement in quality of life, behaviour and cognitive symptoms.
	American Heart Association/American Stroke Association, 2011. ^[63]	The benefits of memantine are not well established in VaD
	American Heart Association / American Stroke Association, 2023. ^[64]	Memantine is sometimes prescribed for patients with dementia after stroke, although more work is needed to define the safety and efficacy RCTs provide moderate-quality evidence for small improvements in cognition, of uncertain clinical relevance.
	European Stroke Organisation and European Academy of Neurology joint guidelines on post-stroke cognitive impairment. ^[66]	There is insufficient evidence to make a recommendation for use of memantine
	NICE Guidelines, 2018. ^[20]	Consider ~~AChE~~ EACHe inhibitors for people with vascular dementia only if there is suspected comorbid DAT, Parkinson's disease or Dementia with Lewy bodies
SSRIs and Dopamine agonists	American Heart Association/American Stroke Association ^[64]	No consistent beneficial effects on cognition in patients with vascular dementia.
Non- Pharmacological Interventions		
Intervention	Name of Guideline	Recommendation
Physical Activity	American Heart Association/American Stroke Association. ^[64]	Physical activity may have a positive impact on cognitive function after stroke, with a possible advantage for aerobic compared with ~~non-aerobic~~ non-aerobic exercise.

	Australian Family physician guidelines, 2016. ^[65]	Exercise is important for persons with dementia
	European Stroke Organisation and European Academy of Neurology joint guidelines on post-stroke cognitive impairment. ^[66]	Interventions to improve lifestyle (includes exercise) may have many health benefits but a beneficial effect on cognition is not proven.
	WHO recommendations, 2022. ^[28]	Physical activity should be recommended to individuals with normal cognition and those with mild cognitive impairment to reduce the risk of cognitive decline
Cognitive training and rehabilitation	American Heart Association/American Stroke Association. ^[67]	Cognitive rehabilitation (including restorative cognitive training and functional cognitive rehabilitation) after stroke results in small improvements in cognitive functioning
	WHO recommendations, 2022. ^[28]	Cognitive training may be offered to individuals with normal cognition and those with mild cognitive impairment to reduce the risk of cognitive decline or dementia
	European Stroke Organisation and European Academy of Neurology joint guidelines on post-stroke cognitive impairment. ^[66]	There is insufficient evidence to make a recommendation for use of cognitive rehabilitation.
Computer based cognitive rehabilitation	American Heart Association/American Stroke Association. ^[64]	Benefits of computerized cognitive training over standard cognitive rehabilitation are inconsistent but tend to be better with clinician-directed programs

Table 5. Recommendations for Assessment and Management of Cognitive Impairment in Vascular Dementia

Assessment: ● Use standardized criteria from ICD-11 or DSM-5 for diagnosis of Vascular Dementia ● <u>Assessment should include active collaboration among different disciplines – especially, neurologists, cardiologists, endocrinologists, psychiatrists and</u>
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psychologists for comprehensive assessment of cognitive impairment as well as associated risk factors.

- Assessment should include clinical assessment, neuropsychological testing and neuroimaging when feasible.
- Standard Neuropsychological testing should be used for assessment of neuropsychological functioning. In addition to global cognitive assessment, more in-depth tests to assess the different cognitive domains, including memory and learning, attention, orientation, executive functions, visuospatial abilities, language and social cognition should be done.
- Magnetic resonance imaging (MRI Brain) is recommended for investigating vascular lesions to diagnose vascular dementia. When MRI is not available or contraindicated, Computed Tomography (CT Head) should be used.

Universal Intervention:

- Physical activity, preferably, aerobic exercise, should be recommended to all
- Healthy balanced diet should be recommended to all. Mediterranean diet may be recommended.
- Avoidance of smoking should be recommended to all
- Limiting intake of alcohol should be recommended to all
- Weight management should be recommended to all
- Stress management strategies may be recommended.

Selective Intervention:

- Management of vascular health through management of vascular risk factors should be recommended
- Management of blood pressure in patients with hypertension through medications, diet and lifestyle intervention
- Management of blood sugar in patients with diabetes through medications, diet and lifestyle intervention
- Management of cholesterol levels in patients with ~~dyslipidemia~~dyslipidaemia through medications, diet and lifestyle interventions
- Provide help for tobacco cessation in patients who use tobacco
- Provide treatment for alcohol use disorder

Indicated Intervention / Management:

- Screening for cognitive impairment in patients with stroke or other vascular events should be done
- Management of Vascular health through management of vascular risk factors to prevent recurrence of future vascular events and further cognitive decline
- Management should involve active liaison among the various disciplines, especially neurologists, cardiologists, endocrinologists, psychiatrists and psychologists for comprehensive and holistic care.
- All interventions mentioned under selective intervention should be followed to prevent recurrence of future vascular events and further cognitive decline

- Cholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine) and Memantine can be offered in patients with vascular dementia co-morbid with Alzheimer's dementia, Parkinson's dementia or Dementia with Lewy bodies
- Cholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine) and Memantine may be considered in selected patients with pure vascular cognitive impairment.
- Cognitive training and Cognitive rehabilitation may be considered in selected patients with **vascular** cognitive impairment **and should be offered as early as possible after the vascular event**
- Neuromodulation techniques like rTMS, and tDCS may be tried in selected patients if patient can engage in the intervention, resources are available and there are no contra-indications for the same
- Acupuncture may be tried in selected patients if patient can engage in the intervention, resources are available and there are no contra-indications for the same

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Cognitive Impairment and ADHD – Assessment and Management

ADHD is a common disorder seen in children and adolescents. It is one of the most common disorders diagnosed in childhood and affects children across populations. In about 5% of cases, it progresses to adulthood and may manifest as adult ADHD. Boys are more commonly affected than girls. The ratio of boys to girls affected is 3:1 to 5:1, most of which is attributed to biological factors such as differences in male and female biology along with hormonal factors but there may be other psychosocial and parenting factors such as child-rearing practices where boys are allowed to be behaviorally less inhibitive and physically more active as compared to girls. The condition is associated with deficits in basic cognitive processes like attention and also higher abilities like planning and organization, with varying degrees across children. Cognitive impairments contribute to significant dysfunction in ADHD. Although the prevalence of ADHD in adulthood is reported to be about 4-5 % of the population, not much research is available on ADHD in adults.^[1-2] This paper primarily deals with cognitive dysfunctions in children and adolescents with ADHD.

Symptoms of ADHD

Children who have symptoms of inattention may:

- Be easily distracted, miss details, forget things, and frequently switch from one activity to another
- Have difficulty focusing on one thing
- Become bored with a task after only a few minutes, unless they are doing something enjoyable
- Have difficulty focusing attention on organizing and completing a task or learning something new
- Have trouble completing or turning in homework assignments, often losing things (e.g., pencils, toys, assignments) needed to complete tasks or activities
- Not seem to listen when spoken to
- Daydream, become easily confused and move slowly
- Have difficulty processing information as quickly and accurately as others
- Struggle to follow instructions.

Children who have symptoms of hyperactivity may:

- Fidget and squirm in their seats
- Talk nonstop

- Dash around, touching or playing with anything and everything in sight
- Have trouble sitting still during dinner, school, and story time
- Be constantly in motion
- Have difficulty doing quiet tasks or activities.

Children who have symptoms of impulsivity may:

- Blur out inappropriate comments, show their emotions without restraint, and act without regard for consequences
- Have difficulty waiting for things they want or waiting for their turns in games
- Often interrupt conversations or others' activities.
- Be impatient.

Process of developing these guidelines

These guidelines have been developed by reviewing the available literature on cognitive impairment and cognitive assessment in ADHD. Only reviews and meta-analyses or synthesis papers of multiple meta-analyses or position papers and white papers have been reviewed. For India data, a specific search has been done for the published work of the centers, institutes, and professionals long associated with the research work on ADHD, especially in neurocognitive assessment and intervention. The findings in the clinical guidelines below are based on a combination of the findings of the studies reviewed above and the clinical experience of all authors writing the paper. The findings have been posited in a manner that shall be clinically useful for the busy clinician and also from an academic and research standpoint.

Cognitive Impairments seen in children with ADHD

More recently, it has become clear that whereas ADHD is associated at the group level with a range of cognitive impairments, no single cognitive dysfunction characterizes all children with ADHD. Patients with this syndrome do not fit into any one category and are present with widely differing co-occurring disorders-including varying cognitive profiles. Cognitive impairments constitute secondary features that often accompany the disorder and need to be considered as part of a comprehensive clinical formulation and multidisciplinary treatment plan. For a comprehensive plan of intervention, cognitive deficits need to be considered.^[3-4]

The types of cognitive deficits seen generally in children with ADHD are as follows:

Attention Deficits:

1. **Sustained Attention:** Difficulty maintaining focus over extended periods, especially on tasks that require prolonged mental effort (e.g., classroom activities, homework).

2. **Selective Attention:** Problems filtering out distractions and focusing on relevant information, resulting in being easily distracted by external stimuli.
3. **Divided Attention:** Challenges in managing multiple tasks simultaneously, often leading to incomplete or poorly done tasks.

Processing Speed Deficits:

1. **Slow Cognitive Processing:** Reduced speed in processing information, which can affect the ability to complete tasks efficiently and keep up with peers in fast-paced environments.
2. **Reaction Time:** Slower reaction times, impacting activities that require quick responses, such as sports or timed academic tasks.

Executive Functioning Deficits:

1. **Working Memory:** Difficulty holding and manipulating information in mind for short periods, affecting tasks like following multi-step instructions or solving problems.
2. **Inhibition Control:** Challenges in suppressing impulses, leading to behaviors such as interrupting others, difficulty waiting their turn, and acting without thinking.
3. **Cognitive Flexibility:** Problems shifting attention between tasks or adjusting to new rules, which can lead to difficulties in adapting to changing situations or perspectives.

Planning and Organization Deficits:

1. **Task Initiation:** Difficulty starting tasks, often leading to procrastination or avoidance.
2. **Organization:** Problems organizing thoughts, materials, and tasks, resulting in disorganized workspaces, forgotten assignments, and missed deadlines.
3. **Time Management:** Challenges in estimating time needed for tasks, leading to poor time allocation and inability to meet deadlines.

Memory Deficits:

1. **Short-Term/ Working Memory:** Issues with retaining information for short durations, affecting ongoing tasks like remembering instructions or recalling recent events.
2. **Long-Term Memory:** Difficulty with the retrieval of stored information, impacting the ability to recall learned material and apply it in different contexts.

Emotional Regulation Deficits:

1. **Emotional Control:** Difficulty managing emotions, leading to frequent mood swings, frustration, and difficulty coping with stress.
2. **Motivational Deficits:** Problems with intrinsic motivation, often requiring external rewards or stimuli to initiate and complete tasks.

Language and Communication Deficits:

1. **Verbal Fluency:** Difficulty retrieving words, leading to struggles with expressive language and slower conversational exchanges.
2. **Pragmatic Language:** Challenges in using language appropriately in social contexts, affecting the ability to follow conversational rules and interpret social cues.

Note: Similar cognitive impairments may also be present in Adult ADHD but may be significantly affected by the presence of comorbid psychiatric disorders like depression, bipolar disorder, personality disorders, and other comorbidities unlike in childhood ADHD. The current guidelines focus only on child and adolescent ADHD. We recommend, the assessment of development, intellectual functioning, cognitive abilities, and learning problems in that order because each of the first-level domains helps understand the subsequent domains better.

Children with ADHD will have specific developmental delays

Developmental skill repertoire is a good indicator of intellectual levels and cognitive abilities, especially in young children. For example, cognitive maturity can be understood from motor abilities, language and communication skills, and social and emotional skills. Therefore, a thorough developmental assessment is necessary for ADHD. There could also be clinically significant developmental conditions that limit cognitive functioning. However, there is not much research in this area as compared to the focus given to other comorbid conditions like, externalizing disorders (e.g. conduct disorder, oppositional and defiant disorder), internalizing disorders (e.g. anxiety), and other psychiatric disorders (e.g. mood disorders, substance use disorder). Since ADHD is a neurodevelopmental disorder, it shares many neurobiological, neuropsychological, and clinical features with other neurodevelopmental disorders, especially autism spectrum disorder, and global developmental delay/ intellectual disability. Therefore, persons with ADHD, especially children, should be examined for specific developmental delays or deficits rather than ignoring them as features of ADHD. In this regard, pertinent clinical questions are *-what is the nature of developmental delays, and how to assess and intervene the same?*

Recent studies have indicated that persons with ADHD can at least have mild delays or deficits or deviations in specific domains like motor coordination, language processing, pragmatic communication, socialization/interpersonal, and adaptive behavior. It should not be assumed that all these problems are secondary to ADHD, and assessment or intervention is carried out only after the ADHD symptoms are resolved. Rather, it is important to note that clinically significant developmental deficits were 2 to 7 times as common in children with ADHD as in non-ADHD children. It implies that the specific developmental delays are not a consequence of ADHD but independently occur maybe due to the same neurobiological mechanism that mediates the ADHD symptoms. Specific deficits (e.g. language and interpersonal skills) may interact with the other impairments responsible for ADHD to make the disorder more severe and more disabling. Therefore, the identification of developmental problems is necessary for a detailed assessment, program planning, referrals, and the prediction of the course and prognosis.^[5] For children below the age of 15 years, the Developmental Screening Test, Vineland Social Maturity Scale, or any other standardized, culturally appropriate tests can be used to identify gross developmental problems. It is better to avoid paper-pencil or computer-based specific cognitive tests under the age of 4 years. If needed, cognitive assessment should be restricted to developmental assessments in which there are specific subscales for cognitive assessment (e.g. Developmental Assessment for Indian Infants; Bayley Scales of Infant and Toddler Development). The assessment report should inform the nature of the developmental problems (i.e. delay, deficit, or deviation), the affected domains (e.g. single or multiple), and the permanence of the condition (e.g. transient or global), and link all of these to intervention plan including appropriate referrals. It is preferable to repeat the developmental assessments at 6-month intervals if the child is below 5 years of age because development during this period is diffused yet rapid, and intellectual disability or other specific developmental difficulties are difficult to ascertain without any evidence of stable deficits.

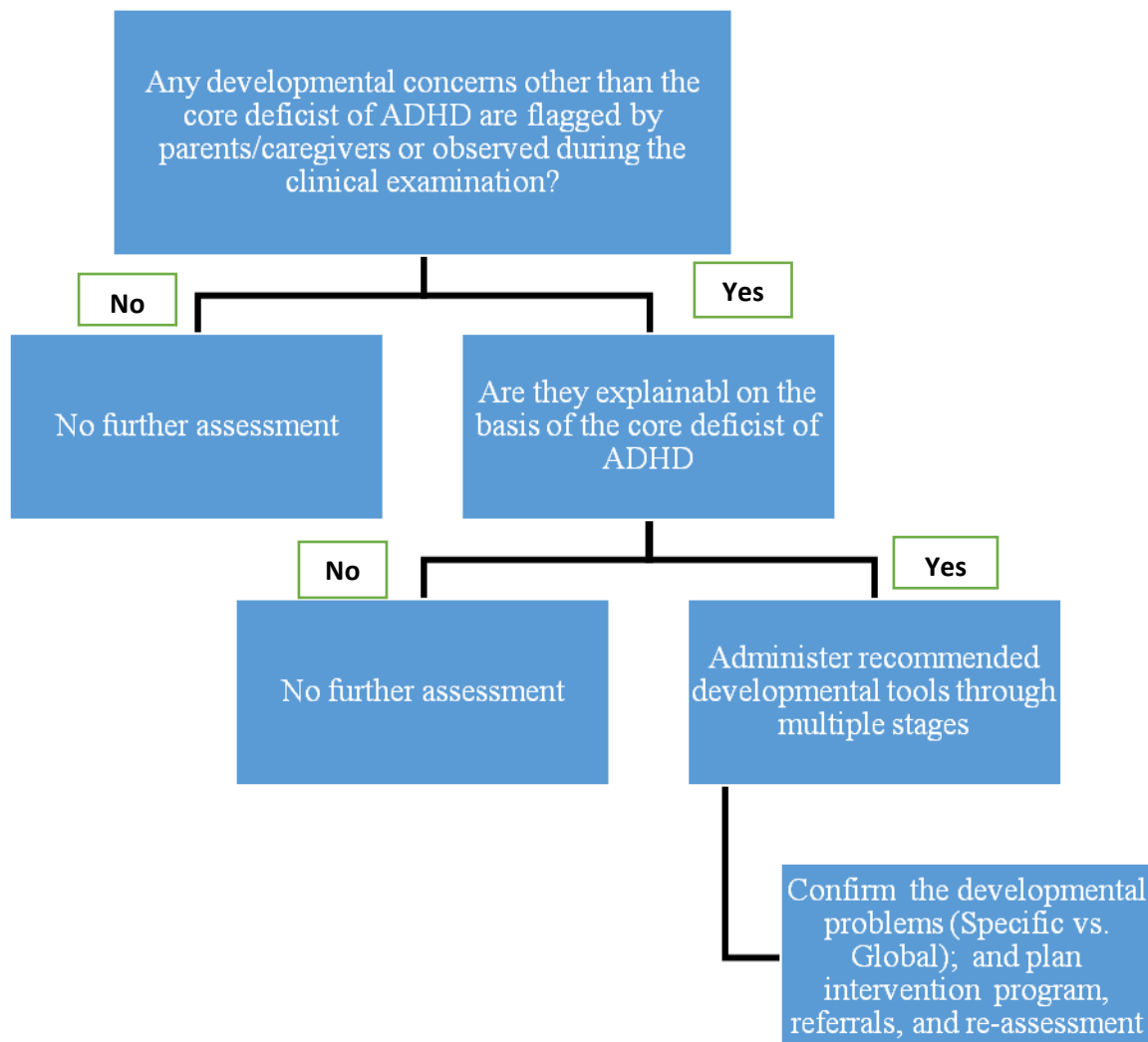


Figure 1: *Screening Developmental Problems in ADHD*

Intellectual impairments in ADHD could be a function of core symptoms and also an artifact of testing

Most intelligence tests are long and require focused and sustained attention of the individuals to perform adequately. Some tests may require planning and specific problem-solving skills to achieve the tasks. Further, the individual's motivation is also important. Given that the deficits in these areas are characteristic of ADHD, they can affect global

intellectual capacities. Therefore, it is not surprising that meta-analyses have found low IQ in children with ADHD as compared to non-clinical controls. Since most studies have not included persons with IQs below 80, it is difficult to comment on how common borderline intelligence or intellectual disability is in ADHD.^[6] Nonetheless, the relevant clinical questions are- *does the individual have below-average intellectual functioning (i.e. borderline functioning or intellectual disability)? Are the intellectual impairments a function of the core symptoms of ADHD? How to check the artifact of testing? Which measures are best suited for intellectual assessment in ADHD?*

How to differentiate between low IQ and cognitive deficit typical of ADHD?:

It is easy to understand how inattention, impulsivity, and low motivation affect test performance. However, it is also true that those with low intelligence may also show less interest and become easily distracted if presented with a complex task. Therefore, a thorough developmental history must be taken to identify clinically significant delays (see the first statement on developmental delays for specific guidelines). If the developmental delays are significantly sub-average in two or more important areas, the diagnosis of global developmental delay or intellectual disability should be considered as per the chronological age cutoff. Further, clinical observations must be validated by appropriate developmental or intelligence measures. Clinical history should always precede psychometric assessment and not vice versa. Concerning the assessment measures, it is preferable to use developmental and adaptive behavioral measures for children under five years of age. Those measures will yield developmental and social quotients, respectively. The test quotients can be interpreted the same way as the intelligence quotient to identify the severity of the developmental delay. For children aged six and above, age-appropriate intelligence scales can be administered. For further details on the intelligence scales, the Indian Psychiatry Society's clinical practice guidelines on intellectual disability can be referred to (see, Appendix 2 of the document).^[7]

It is preferable to start the intellectual assessment with non-speed performance tests (e.g. Gessell's Drawing Test, Progressive Matrices), examine how basic cognitive processes affected the test performance, and proceed with global intelligence scales that contain both verbal and non-verbal items and timed and un-timed items. Otherwise, a child's poor performance on an intelligence scale is not necessarily due to intellectual impairment but unsuitability of the test for the individual (i.e. artifact of the test). To illustrate further, a child may find it difficult to sustain attention as the complexity of items increases on speed tests. Conversely, with adequate breaks and appropriate reinforcement, the child may complete a complex test like progressive matrices. Notwithstanding these, IQ assessment should not be

used as a standalone method. Rather, it should be complemented with developmental measures (especially, for children below 5 years) and adaptive behavioral assessment (a rule applicable for any age group) because impairments in both will suggest intellectual impairments. Conversely, a relatively better performance on adaptive behavior measure than on an intelligence scale may denote the adverse effects of cognitive impairments on global intelligence. If the results of the non-speed tests and adaptive behavioral measures match, an appropriate diagnostic code should be used to highlight the intellectual level.

Regarding the effects of ADHD symptoms on intelligence scores, studies indicate that inattentive and the combined subtypes, compared with the normative sample, show lower IQ scores on global intelligence scales (e.g. Wechsler's). However, the ADHD combined type was better on dynamic tests (i.e. novel problem-solving tasks).^[8] Therefore, tests that measure rule-learning to solve problems progressively (e.g. Progressive Matrices) must be a part of the assessment. Lastly, the intelligence test profiles should not be considered a marker of ADHD subtype.

Figure 2: Summary of Guidelines on Intellectual Functioning in ADHD

- Persons with ADHD can have intellectual impairments.
- Core deficits of ADHD can affect the individual performance on intelligence scales.
- A thorough developmental history should precede intellectual assessment
- A combination of static and dynamic intelligence tests should be used for assessment, preferably, starting with non-speed, and non-verbal tests.
- Intelligence test results should not be considered to classify ADHD subtype
- Intelligence tests should always be combined with adaptive behavior measures for a final interpretation of intellectual impairments

Cognitive deficits with robust individual variations are common in ADHD

It is imperative to assess cognitive impairments given that the major diagnostic systems recognize inattention, distractibility, and impulsivity as important features of ADHD implying the underlying neurocognitive processes. However, the clinical questions one needs to ask are-

- a) *What kind of cognitive impairments are typically found in ADHD? And how robust are they?*
- b) *What is their significance for clinical diagnosis and a person's functionality?*

c) *How to assess them?*

There are 34 meta-analyses on the neurocognitive performance of individuals with ADHD to that of healthy controls as of 2024. A summary of those meta-analyses by Pievsky and McGrath^[6] indicates that the neurocognitive performance of the children with ADHD is poorer than the control groups in 96% of the instances, with substantial heterogeneity, and low- to moderate effect sizes. Nonetheless, the group effects for neurocognitive impairments were far smaller compared to that of behavioral symptoms of ADHD. It means that not all ADHD children will have substantial cognitive impairments. However, when cognitive impairments were noted, medium effect sizes were reported for the following: *reaction time variability, intelligence/achievement, vigilance, working memory, and response inhibition*. That is, both basic and higher-order cognitive functions are affected. The group effects appear to be a function of age, with greater differences among children and adults than adolescents or young adults. For instance, performance on executive function tasks in preschool children is probably related to state regulatory impairments rather than insufficiently developed executive function systems. Higher-order executive functions (e.g. working memory, inhibition, response variability, and set-shifting) are easily discernable in adolescents. Measures of response/reaction time variability yielded the strongest effect sizes for school-age children. Less effortful, bottom-up, cognitive processes generally differentiated those with childhood ADHD from controls irrespective of adolescent/young adult clinical status.^[9-11] Another important finding in the literature is that results can vary depending on the assessment methods (i.e. direct performance versus caregiver reports). Parents usually report higher inattention and lower executive function skills than what is generally noted on direct assessment, however, it was strongly associated with ADHD diagnosis. Parents' or caregivers' lived experiences with ADHD children may help them provide a comprehensive picture of cognitive impairments noted in their children. However, no such effects were noted for motor skills. Further, performance-based measures of cognitive and motor skills do not have incremental predictive validity compared to parent reports. Another study indicates that cognitive profiles are similar in ADHD inattentive type and combined type.^[12] Although neurocognitive tests are important, approximately 50% of pediatric ADHD cohorts perform in the "normal" range on any given neurocognitive measure, suggesting poor sensitivity. Further, the absence of an "impaired" score on neuropsychological tasks seldom rules out the presence of ADHD, contributing to reduced specificity. However, the neurocognitive measures are useful in differential diagnosis, identification of individual learning styles (e.g. speed, accuracy), and establishment of

context-specific interventions.^[9] These findings have implications for the purpose and scope of assessment.

Guidelines on Cognitive Assessment in Children with ADHD:

The purpose of the cognitive assessment is to understand how effectively an individual with ADHD can switch from a resting mode to an active functional mode in a way that is developmentally appropriate. Since it cannot be achieved by a single measure, a combination of direct testing and parental behavioral ratings of key cognitive domains mentioned above are essential.^[13-14] Tests should be able to assess *basic* (i.e., processing speed and distractibility) and *higher-order* cognitive functions (i.e., working memory, planning, cognitive flexibility, memory functions) to understand how much the basic functions have contributed to impairments in the higher functions.^[15] Further, it would be better if the assessment informs whether the impairments in basic cognitive processes are at a perceptual or a motor execution phase of information processing.^[16] There are many neuropsychological scales widely used in India (see, Bhullar et al., 2023).^[17] Relevant individual scales or a neuropsychological battery can be selected based on their scope, cultural validity, and other logistics like availability of test material, affordability, and qualified test administrators. Since cognitive profiles are broadly similar across the subtypes of ADHD, they should not be used for clinical diagnosis of ADHD. Special efforts must be made in older adults to distinguish pre-existing cognitive difficulties from ‘mild cognitive impairment’.^[18] Further, symptom severity measures should always be a part of the comprehensive assessment plan because some cognitive impairments can be a function of non-ADHD psychiatry symptoms such as low mood and anxiety.^[14] For broad guidelines on neurocognitive measures, Table 1 can be referred.

[Table 1 here]

Figure 3: Summary of Guidelines on Cognitive Impairments in ADHD
• Neurocognitive impairments are not necessary for diagnosing ADHD • Deficits related to reaction time variability, intelligence/achievement, vigilance, working memory, and response inhibition are typical of ADHD and will interfere with the individual’s adaptive functioning • The deficits are pronounced more in young and older populations but not in adolescents or young adults • Any single measure is not adequate to assess cognitive impairments • A combination of parental measures and direct testing is necessary for a robust

cognitive assessment. The necessary assessment measures listed in Table 1 can be referred for this purpose.

Table 1: *Neurocognitive measures based on domain and age*

	Domain	Measure	Age	Administ ration time (min.)	Focus
I	Processing Speed				
	Processing Speed	Pattern Comparison Processing Speed Test	5+ years	4 minutes	An assessment of processing speed. Participants are asked to quickly determine whether two stimuli are the same or not the same. [available at: https://nihtoolbox.org/test/pattern-comparison-processing-speed/
II	Attention				
	a). Attention span	Digit span	4+ years	1-3	Forward digit span is regarded as the general attention span but very specifically the short-term or verbal working memory.[Note: It can be obtained from any intelligence scale like the Wechsler's, Malin's or Binet-Kamat Test of Intelligence]
	b1). Sustained attention	Colour cancellation test [#]	5+ years	5	Omission errors indicate poor visual scanning and poor selective attention. Commission errors indicate problems in the inhibition of rapid responses.
	b2). Sustained	Open-source open-access	14-89 years	Several minutes	It evaluates the central processing speed which correlates with

	attention and Alertness	reaction time test (OORTT)			cognitive efficiency, namely sustained attention and alertness (Open access: https://osf.io/xvcg6/)
	b3). Arousal, Activation and/or Effort	Continuous Performance Test	5+ years	Several minutes to over 20 minutes	It includes a serial presentation of visual or auditory target and non-target stimuli (numbers, letters, number/letter sequences, or geometric figures). The test provides the response time (RT) and RT variability besides “omission error” (failing to respond to a target stimulus), “commission error” (a response to a non-target stimulus), and the number of correct responses.
II I	Executive Functions				
	Sustained selective attention and Working memory	New Minimally Linguistic Tasks	4-10 years	25 minutes	It includes nonlinguistic, visual stimuli to reduce bias resulting from differences in language experiences or abilities. The tasks are fully automated, and they are freely available (Key article available at: https://doi.org/10.3758/s13428-023-02078-5 ; Tool available at: DOI 10.17605/ OSF.IO/HP4GS).
	Inhibition	Flanker Inhibitory Control and Attention Test	4+ years	3 minutes	An assessment of inhibitory control and attention. The participant is asked to focus on a particular stimulus while inhibiting attention to the stimuli flanking it. (Available at:

					https://nihtoolbox.org/test/flanker-inhibitory-control-and-attention-test-age-12/)
	Cognitive flexibility	Dimensional Change Card Sort Test	4+ years	4 minutes	An assessment of cognitive flexibility and attention. The participant is asked to match a series of picture pairs to a target picture. (Available at: https://nihtoolbox.org/test/dimensional-change-card-sort-test/)
	Working Memory	List Sorting Working Memory Test	5+ years	7 minutes	An assessment of working memory. The participant is asked to recall and sequence different stimuli that are presented visually and via audio
	Ability to inhibit cognitive interference	The Stroop Color and Word Test	5+ years	Below 5 minutes	This test assesses the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute, well-known as the Stroop Effect. A comprehensive review of the test is provided by Scarpina et al. (2017) [available at: doi:10.3389/fpsyg.2017.00557].
	Verbal fluency	Phonemic Fluency Test	5-15 years	Under 5 minutes	Individual is asked to produce as many words starting with F,A, and S letters or beginning with phonemes of <i>ka</i> , <i>pa</i> , and <i>ma</i> . Each letter or sound is given a minute to complete.
	Motivation	Children's Motivation	6-17 years	Under 10 minutes	Parent ratings of children's motivation and apathy. Higher

		Scale			scores indicate low motivation.[liable at: Gerring JP, Freund L, Gerson AC, Joshi PT, Capozzoli J, Frosch E, Brady K, Marin RS, Denckla MB. Psychometric characteristics of the Children's Motivation Scale. Psychiatry Res. 1996 Jul 31;63(2-3):205-17. doi: 10.1016/0165-1781(96)02841-7. PMID: 8878317.
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Note:

1. The above list is different from the widely used cognitive scales and tests. Since the popular tests are only commercially available, and it has implications for cost and expenditure on end-users, a conscious effort has been made to source open-access material. However, clinicians can use popular tests as per the requirement as the above list is not exhaustive or compulsory.
2. Under group II (b), either one or all from b1 through b3 can be administered as per the need.
3. Under group III, any one test of inhibition can be administered. The motivation scale is optional.
4. For some of the above measures, norms can be accessed from NIMHANS Neuropsychological Batteries
5. Some IQ measures (e.g. Wechsler scales) are considered as neurocognitive measures but training and expertise are needed for such application.

Appendix A: List of Important Tests

Domain	Measure
For comprehensive neuropsychological functioning	• Rao SL, Subbakrishna DK, Gopukumar K. NIMHANS neuropsychological battery-2004. Manual. Bangalore: NIMHANS, 2004 [For age 16-65 years]

	• Kar BR, Rao SL, Chandramouli BA, Thennarasu K. NIMHANS neuropsychological battery for children-manual. Bangalore: NIMHANS, 2004 [For age 5-15 years] • AIIMS Neuropsychological Battery (Hindi) [For age 8-14 years; 15-80 years]
General Intellectual Functioning	• Wechsler Intelligence Scale for Children® – Fourth Edition (WISC-IV) (for 6-16 years 11 months) • Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) India (For 16+years) • Coloured Progressive Matrices • Standard Progressive Matrices
Academic Achievement	• Wide Range Achievement Test, Fifth Edition-India (WRAT 5 – INDIA) • Grade Level Assessment Test (NIEPID Publication) • NIMHANS Index for Specific Learning Disability (NIMHANS Publication)
Working Memory	
Verbal	N-back Task by Smith and Joindes
Non-verbal/Visuospatial	Visuospatial Working Memory Span Task by Miller
Planning	Porteus Maze Test
Set Shifting	Wisconsin Card Sorting Test
Memory	
Verbal Learning and Memory	Rey's Auditory Verbal Learning Test
Visual Learning and Memory	Memory for Design*

Note:

1. All of them are proprietary items. All of them have user guidelines in terms of the qualifications of the examiner, scope of assessment, etc. Except for Memory for Design Test, they are not freely available in the public domain. Hence, user discretion is recommended in using the above tests in regular clinical practice.

2. The manual of the Memory for Design is available at Graham, F. K., & Kendall, B. S. (1960). Memory-for-Designs Test: Revised General Manual. *Perceptual and Motor Skills*, 11(2), 147-188. <https://doi.org/10.2466/pms.1960.11.2.147>

Children with ADHD will have learning difficulties, which amounts to learning disability in some instances

Learning problems are common in ADHD. Inattention and other symptoms of ADHD can adversely affect an individual's performance in school and on standard ability tests. It is also possible that the learning difficulties could be an independent entity therefore they are not fully explainable by ADHD symptoms. While some may have mild learning problems that resolve as the ADHD symptoms improve, others persist with significant difficulties that necessitate reasonable educational accommodations. In this regard, important clinical questions are- *how do we identify the learning difficulties in the backdrop of ADHD symptoms and related cognitive deficits? How do we identify specific learning disability in ADHD?*

First, it is important to recognize that learning problems are common in ADHD, and the nature and severity of the issues widely vary. Unlike the previous versions, DSM-5 and ICD-11 do not automatically exclude the diagnosis of learning disabilities on account of other psychiatric disorders such as ADHD. Learning abilities are acquired through the teaching-learning process, mediated by cognitive abilities and motivational factors, and moderated by language proficiency, instruction methods, and settings. Therefore, assessment should explore all these aspects rather than simply attributing the learning difficulties to ADHD symptoms or ignoring the learning disability.

The diagnosis of a learning disorder should not be contingent upon ADHD symptom recovery. As a first step, it is most important to establish the presence of learning and academic difficulties during the developmental period, and noticeable difficulties with phonological processing skills.^[19] At the next level, cognitive, intellectual, and achievement assessments must be planned. Regarding the cognitive abilities underlying reading, writing, and arithmetic skills, there is no consensus on what the core abilities are.^[20] However, both basic (i.e. attention, information processing) and higher-order cognitive abilities (e.g. planning) are implied in learning difficulties and academic achievement. A meta-analysis indicates that these cognitive processes (i.e. planning, attention, and simultaneous processing) are strongly associated with reading English, mathematics, and problem-solving skills independent of age and grade level.^[21] Those with ADHD and specific learning disability

have more severe cognitive deficits than either of the conditions alone.^[22] Similar studies are not there in India, but these findings are also relevant to Indian settings.

Regarding achievement testing, the focus must be on reading, writing, and arithmetic in school-age children. There is no clarity on what and how to assess learning problems in adults. However, the following issues can be considered in assessing learning difficulties at any age. Reading abilities are understood from three parameters-*accuracy* of text-to-speech conversion, *speed*, and *comprehension*. The first two can be directly affected by the ADHD symptoms like inattention and distractibility, which in turn can affect comprehension. Therefore, assessment should delineate the effects of inattention and distractibility on reading comprehension. Writing skills generally comprise composition abilities and motor abilities and are moderated by motivation. Given that motor abilities and motivational resources are generally affected in ADHD, they should be given due consideration while commenting on the severity of writing difficulties. It is also important to consider the effects of multilingual and multicultural factors on learning skills.^[23-24] After identifying the learning problems clinically, mandated procedures must be initiated to assess learning disability (see, Shah et al., 2019).^[25] Further, specific plans should be drawn to work with the schools to help the child continue education because studies indicated that those who attended school regularly had better cognitive outcomes and stability of ADHD symptoms in young adulthood. Parental involvement enhanced those effects; therefore, the plan should include addressing their concerns and involving them in the intervention.^[26]

Figure 4: Summary of Guidelines on Learning Difficulties in ADHD

- Learning problems are common in ADHD, and they may cause significant impairment in some cases.
- ADHD does not disqualify the diagnosis of specific learning disability
- Both basic (i.e. attention, information processing) and higher-order cognitive abilities (e.g. planning) should be assessed
- Assessment should delineate the effects of inattention and distractibility on reading comprehension; and the effects of motor and motivational issues on writing abilities.
- After identifying the learning problems clinically, mandated procedures must be initiated to assess learning disability

Neurotherapeutics and psychosocial interventions are effective in improving cognitive deficits

The rationale for cognitive training in ADHD is based on the premise that cognitive deficits (e.g. inattention, information processing speed, executive functions) are widely prevalent in ADHD. The deficits have a strong neurobiological and neuropsychological base. Therefore, there is a need for intervention in this area. In this regard, a few important clinical questions are-

- a) *Which functions should be targeted?*
- b) *Who is suitable for cognitive intervention?*
- c) *Which intervention methods have maximum effects?*

Studies indicate that the focus should be on neurocognitive deficits beyond attention. Therefore, all the core deficits (e.g. *reaction time variability, intelligence/achievement, vigilance, working memory, and response inhibition*) should be targeted because they are associated with ADHD. However, targeting basic cognitive processes such as processing speed and distractibility could generalize to improvements across several higher cognitive domains.^[13] Children with ADHD *combined type* adapt more easily to education with visualized methods (e.g., graphs, figures, and behavioral modeling) as compared to those with predominantly *inattentive type* due to perceptual reasoning differences.^[27] Working memory and prosocial behavior were related to behavioural regulation, and hyperactivity/inattention difficulties in 7-8 year olds. Therefore, promoting prosocial behavior and improving working memory skills in school-aged children are necessary for a positive outcome.^[28]

Cognitive interventions primarily include ***Cognitive training, Neurofeedback, and Cognitive-Behavioural Interventions.***

Cognitive training for ADHD refers largely to the use of computerized training programs to improve aspects of cognition such as attention and memory, and ultimately broader aspects of functioning as well as ADHD symptom severity. However, cognitive training has been of limited use in children and adolescents and of no use to adults. Cognitive behavior therapy is more beneficial than cognitive training for adults. Any small effects noticed are not sustainable or effective in vertical skill transfer. Overall, there is no evidence that multi-process training was superior to working memory training. Therefore, Computerized cognitive training cannot be a stand-alone intervention for ADHD symptoms.^{[29-}

^{33]}Behavioural interventions are effective for parenting and parents' sense of empowerment and independently corroborated effects on conduct problems in children with ADHD at least

during a short term.^[34] For optimum outcomes, interventions must focus on deficits that extend beyond attention, and include a human element to promote treatment compliance, motivation, self-efficacy, social cognition, and transfer to real-life benefits.^[31,35]

Neurofeedback: It is based on a brain-computer interface. It involves calculating the pre-selected brain parameters (i.e. a specific frequency band or a brain potential) online and translating them into signals that are fed back to the user in real-time. Through this feedback, the participant can learn to self-regulate his or her brain activity to directly alter the underlying neural mechanism of cognition and behavior. Initial studies indicate mixed results though later studies renewed the interest in this technique because of the limited effects of pharmacotherapy and behavioral intervention. Recent meta-analyses indicate that three standard neurofeedback training protocols, namely theta/beta, sensory-motor rhythm, and slow cortical potential are ‘efficacious’ and ‘specific’.^[36-38] Two studies done in India indicate that NFT is superior to treatment-as-usual conditions and has better long-term effects on core ADHD symptoms and multiple cognitive abilities and learning.^[39-40] However, there is a need for standardized protocols on these as they seem to be safe and have minimal or no side effects.

Cognitive-behavioral interventions could be offered in combination with other pharmacological and psychosocial interventions across the age groups more so for older age groups. When CBT is offered to children, it should be based on the developmental capacities of the children to self-reflect, articulate their thoughts, and their ability to influence their thinking processes. The intervention should balance the challenges faced by the individual and the individual strengths, values, and interests.

Parent and family training:

Parent and family training is also beneficial for children under 18 years. The themes can be grief and adjustment to their child’s diagnosis; adjustment of interpersonal dynamics within the family; management of family members’ needs; self-care; mental health and educational support for the child; and advocacy for the child. Both CBT and parent training can be delivered in an individual or a group format.^[30]

Figure 4: Summary of Guidelines on Neurotherapeutic and Psychosocial Interventions in ADHD

- Core deficits (e.g. reaction time variability, intelligence/achievement, vigilance,

working memory, and *response inhibition*) should be targeted for assessment and intervention

- Basic cognitive processes could be targeted to provide a base for higher-order cognitive functions.
- Cognitive training could be offered to children and adolescents
- Standard protocols of any of the three forms of neurofeedback namely theta/beta, sensorimotor rhythm, and slow cortical potential could be offered to all age groups depending on the resources.
- Cognitive behavioural therapy should be offered to adults.
- Behavioural interventions should be offered to parents to improve parenting and parents' sense of empowerment
- Cognitive-behavioural interventions could be offered in combination with other pharmacological and psychosocial interventions across the age groups.
- CBT for children should be based on the developmental capacities of the children to self-reflect and their ability to influence their thinking processes.

Assessment and intervention are dynamic processes based on scientific and ethical processes.

- Clinicians should make a distinction between clinical management of ADHD and research investigations. Accordingly, assessment and interventions should be need-based, and judicious (see, Appendix A for a list of important tests).
- Assessment is a dynamic process. Therefore, it should involve *multiple informants* (e.g. parents, teachers, caregivers), *diverse methods* (e.g. clinical history, observation, mental status examination, and testing), *settings* (e.g. home, school, and community), and *time points* (e.g. baseline assessment, formative evaluation, summative evaluations).
- Clinicians should select the assessment measures based on the purpose, ecological validity, reliability, norms, affordability, and simplicity.
- An important ethical issue is that the clinician should have the required training and skills to conduct assessments and deliver interventions as some methods mandate specific training and certification by authorized agencies.

- Assessment should inform the strengths and deficits of the individual with leads for intervention and reassessment.
- Clinicians should understand that the test report will be referred to by different stakeholders, therefore, the language and content of the report should be *simple, clear, informative, inclusive, respectful* (i.e., devoid of any biased/stigmatizing language), and *strongly appeal for appropriate support and evidence-based interventions* for the individual with ADHD.
- Some children that are being assessed may be on medication for the treatment of ADHD like Atomoxetine and Methylphenidate, which may cause some cognitive side effects. While this association is not robust, the pre-existing cognitive impairments may be compounded by these medications. Therefore, individual medical profiles of children or adolescents undergoing assessment must be taken into cognizance on a case-to-case basis.^[41]

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Clinical Practice Guidelines for cognitive impairment in autism spectrum disorders- Assessment and Management

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication, repetitive behaviours, and a restricted repertoire of interests and activities. It has its onset during early childhood, and the functional deficits often persist throughout the individual's lifespan. (American Psychiatric Association. 2013). The estimated prevalence in India ranges between 0.74-1.68% in children aged 2-9 years, according to which 1 in every 68 children is affected with autism. (Panda et al., 2019).

The clinical presentation of ASD is very heterogeneous, attributed to differences in developmental trajectories, gender, language abilities, cognitive functioning, adaptive behaviours, and associated medical and psychiatric comorbidities. (Kamp-Becker et al, 2024). In addition to the core deficits, children with ASD often face significant difficulties in the cognitive domain. Cognitive functioning varies across the spectrum, with some children having mild deficits, others (30- 70%) having significant delays or intellectual disability (Fodstad et al.,2020), and some with extraordinary abilities or 'splinter skills' in a specific domain. (Howlin et al. 2009) Cognitive functioning is essential in determining the type of service, the level of support, and the educational placement required for the child. (White et al. 2007).

Children with ASD and comorbid intellectual disability (IQ <70) are more likely to present early in the course of the disorder, given caregiver concerns about the overt delays or cognitive impairments noted in the child. However, children with higher-functioning ASD (without comorbid intellectual disability or significant language delay) often have challenges due to less apparent impairments in cognitive functioning. While research into the cognitive impairments in children with higher-functioning ASD has many gaps in its evaluation and implementation, the scope of this guideline is to attempt to translate this into practice.

Diagnostic criteria for ASD – ICD 11

- Persistent deficits in initiating and sustaining social communication and reciprocal social interactions that are outside the range of typical functioning given the person's age and level of intellectual development
- Persistent restricted, repetitive and inflexible patterns of behaviour, interests, or activities that are clearly atypical or excessive for the person's age and sociocultural context
- The onset of the disorder occurs during the developmental period, typically in early childhood, (note that characteristics might not fully manifest until later in life due to increased social demands)
- Characteristics result in significant impairment in personal, family, social, educational, occupational or other important areas.
- Specifiers for characterizing features within the autism spectrum:

These specifiers enable the identification of co-occurring limitations in intellectual and functional language abilities, which are important factors in the appropriate individualization of support, selection of interventions, and treatment planning for individuals with autism spectrum disorder. A qualifier is also provided for loss of previously acquired skills, which is a feature of the developmental history of a small

proportion of individuals with Autism Spectrum Disorder.

Need for the guideline

- Specific cognitive impairments are noted in children with average/low average or borderline intelligence and ASD
- Cognitive functioning needs to be assessed for planning intervention
- Cognitive assessment is required for academic guidance and support

Challenges in assessment of children and adolescents with ASD

- Children with ASD can have comorbid developmental delay or intellectual disability
- Children with ASD with average development or intellectual functioning can have specific cognitive deficits
- The impairment could be at the sensory perception level, cognitive processing level or can affect learning and memory.
- There are no specific diagnostic criteria for cognitive impairment in ASD
- The deficits identified are not specific to ASD

Process of development of this guideline

Pubmed search was done using relevant terms, like: “cognitive impairment”, “cognitive deficits”, “assessments and interventions for specific cognitive deficits in ASD”. The specific guidelines for ASD, developmental delay assessments and interventions, were also reviewed, and the information was amalgamated in the current guidelines.

Scope of the guideline

Children with ASD can be broadly classified into 2 categories based on the developmental/ cognitive functioning –

- a. ASD with developmental delay/intellectual disability (DQ/IQ <70)
- b. ASD with borderline/low average/ average/ above average development/intelligence (DQ/IQ >70)

This guideline will focus on the second group of children. A brief note on the relevant developmental assessments and tests of intelligence will be made, highlighting the specific profiles noted in children with ASD. Specific screening measures and diagnostic assessments for development/intelligence will not be elaborated in this document. (Please refer to the Clinical Practice Guidelines for Assessment and Management of Intellectual Disability, Indian Journal of Psychiatry, 2019).

Specific screening and diagnostic tools for ASD will not be elaborated in this document. (Please refer to the Clinical Practice Guidelines for Assessment and Management of ASD, Indian Journal of Psychiatry, 2019)

Cognitive deficits in ASD

Cognitive functions are the primary mental processes involved in acquiring information, knowledge, and reasoning. The DSM 5 has defined six main domains of cognitive functioning: complex attention, memory and learning, executive function, perceptual-motor control, language and social cognition. Individuals with ASD can have both delayed and atypical cognitive profiles, and even in those without associated intellectual disability, impairments in cognitive functioning have been documented. (Bölte S et al, 2002, Velikonja T et al 2019).

Neurobiological theories of cognitive impairments in ASD

a. *Executive function and frontal lobes:*

Damasio and Maurer, in 1978, put forward the Executive dysfunction theory in ASD, postulating that individuals with ASD have deficits in executive functions similar to that seen in patients with frontal lobe damage. The frontal lobes, primarily the pre-frontal cortex, have been associated with goal-oriented behaviours which require planning and execution of appropriate action plans. This appears to be a significant deficit in individuals with ASD, as they struggle to complete a plan effectively and lack the flexibility needed to adapt to change. (Goel et al., 1995).

b. *Social cognition and limbic associated neural pathways:*

While higher cortical structures play a significant role in cognitive intelligence, dysfunction in the ventromedial prefrontal cortex, amygdala and limbic system associated with processing of emotions, may explain social cognitive deficits seen in ASD. (Bechara A et al., 2000)

c. *Spatial reasoning, memory and hippocampus*

The hippocampus has been implicated in impaired cognitive functions of spatial reasoning, as well as episodic memory in ASD. As the timeline of the development of the hippocampus and the emergence of the core symptoms of ASD coincide, studies have noted structural abnormalities and functional connectivity deficits. Episodic memory impairments in ASD have been attributed to both encoding and retrieval process deficits in the hippocampus, revealed through fMRI studies. (Cooper RA et al. 2017, 2019)

d. *Sensory processing*

Cognition can be affected at the cellular and genetic levels. (Lee YS et al, 2009). Visual, auditory and tactile sensory perceptions are all integrated and need to function optimally for effective cognitive processing. Individuals with ASD are noted to have sensory perception abnormalities, leading to sensory integration difficulties. Problems in visual processing, which are often seen in ASD, have led to studies looking at retinal changes as early markers of cognitive impairments in these individuals.

e. *Systemic causes*

Neurological, immune, oxidative stress and gastrointestinal dysfunction have been hypothesized to lead to cognitive impairments in ASD. Immune dysfunction is shown to cause neuroinflammation; this, in turn, affects neural connectivity, glutamate/gamma-aminobutyric acid (GABA) balance, cognitive processing, memory, learning and brain plasticity. (Al-Mazidi SH, 2023, Morimoto K et al, 2019). Oxidative stress and dysfunctional mitochondria affect the myelination of neurons directly or indirectly. The activation of multiple cortical areas, adequate functional connectivity, and balance in GABA, glutamate, oxytocin, and vasopressin are required for adequate cognitive flexibility, which is often impaired in ASD. (Heise KF et al, 2022). However, while neuroinflammatory biomarkers have been identified in ASD, they are not specific to ASD and treatments targeting chronic inflammation have not been effective to date, requiring more clinical trials.

Cognitive processing in ASD

Various psychological theories have been proposed to explain cognitive processing differences in individuals with ASD.

a. *Central coherence dysfunction and local processing bias*

Central coherence is the ability to integrate information in context for higher-level meaning or gestalt. Individuals with ASD appear to show "weak" coherence, attending preferentially to details at the expense of the whole or gestalt. Weak coherence has been postulated to result in symptoms like insistence on sameness, rigidity in thinking and uneven cognitive profile seen in ASD. While both global and local processing is a requirement for normal sensory processing, atypical and preferential local processing with impairment in global processing in ASD can lead to difficulties in making sense of the world around (Happé et al. 2006) and this in turn can affect social cognition. (Joseph R M et al, 2009).

b. Theory of mind (ToM) deficits

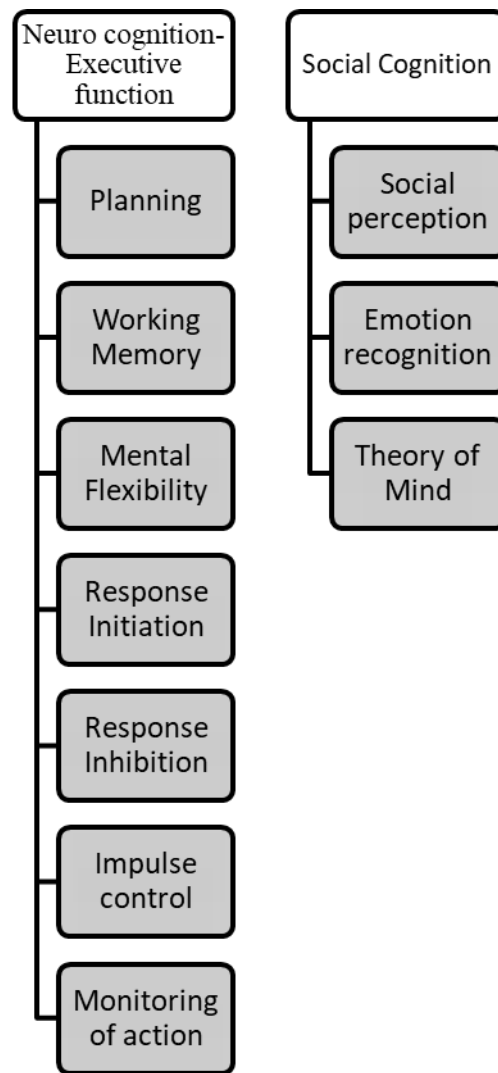
The ToM concept, otherwise known as 'mind-blindness' or 'mentalization failure', was described by Baron-Cohen in his study of children with ASD. (Baron-Cohen 1993). ToM is the ability to infer the mental states of others and understand that this can differ from one's own belief. Individuals with ASD are known to have deficits in this process, often leading to difficulties in understanding social nuances.

c. Joint attention difficulties

Joint attention is the ability to coordinate attention between a social partner and an object or event, resulting in ongoing engagement with a communication partner and object. (Bakeman & Adamson, 1984) There are two types of joint attention described, namely supported and coordinated. Joint attention is a predictor of language and higher social skills as children grow. Individuals with ASD have delays in developing joint attention.

Cognitive impairments associated with ASD:

The cognitive impairments in ASD are broadly classified into non-social or neurocognitive impairments and social cognitive impairments (Hajri M, et al., 2022). (Figure 1)



A. Neurocognition/ non-social cognition

Griffith et al. (1999) defined executive functions "as a flexible, strategic plan of action to solve a problem or attain a future goal". Deficits in executive functioning affect the routine day-to-day activities in children with ASD due to perseverative responses, rigidity in routines, repetitive behaviours, and decreased impulse control.

Executive functions can be divided into 2 groups:

a) Higher-order executive function skills of organization, planning, working memory (WM), mental flexibility, response initiation, response inhibition, impulse control, self-regulation and action monitoring.

b) Lower-order skills like motor skills, short-term memory, and language. (Spear LP. 2010). The primary lower-order skills are simple and develop by 2 -4 years, while the higher-order skills are more complex and develop later, by 4 – 7 years. (Jeffrey D. Drayer, 2008)

The significant components of executive function, influencing multiple components of learning are briefly mentioned below (Hill et al, 2004)

a. **Organize/plan-** the ability to plan, organize and problem-solve effectively.

- b. **Working memory** - a type of short-term memory that stores information temporarily during the completion of a task and actively manipulates and transforms the information needed to complete the cognitive task. It comprises the central executive, visuo-spatial sketch pad and the phonological loop.
- c. **Cognitive/ mental flexibility**- the ability to change thought and behaviour, according to changes in the environment
- d. **Response initiation/fluency**: the ability to generate verbal and non-verbal stimuli including ideas, designs, words and spontaneously engage in purposeful goal directed activities.
- e. **Inhibition**: the ability to deliberately inhibit automatic, dominant responses when required.
- f. **Impulse control**: set of behaviours that help us think before acting
- g. **Self-monitoring** - regulating emotions and behaviour to accommodate social situations.
- h. **Shifting set** – the ability to shift back and forth between multiple stimuli, operations, or mental sets.

B. Social cognition

Social cognition refers to the perception and interpretation of social information. Individuals with ASD have social and communication deficits, with trouble in understanding people's goals, intentions and emotional states. (Pagni BA et al, 2020). Social cognition includes three main domains: social perception, emotion recognition and theory of mind.

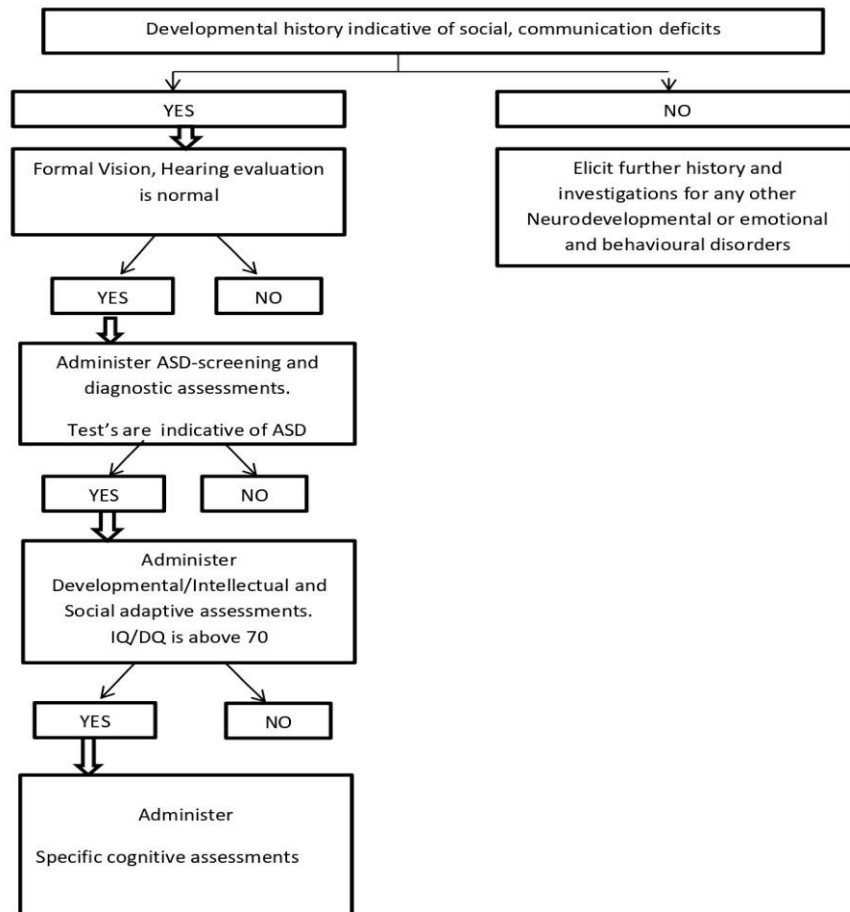
- a. **Social perception** -the ability to be aware of the cues and rules that occur in social situations
- b. **Emotional recognition** -the ability to recognize the feelings of self and others
- c. **Theory of mind**-the ability to attribute beliefs and intentions to oneself and others

Assessment of cognitive function in ASD

Assessment of cognitive functions in a child with ASD should be done by trained personnel only, following evaluation by a child psychiatrist, paediatric neurologist or developmental paediatrician. This is important for confirming a diagnosis of ASD and ensuring that medical and psychiatric comorbid conditions have been addressed before assessment and treatment plans are formulated.

Before proceeding with assessments looking at specific cognitive impairments in children who are the target of this guideline, developmental/ intellectual testing and adaptive functioning assessment using standardized tests will need to be done. This will help first to delineate those children with ASD without comorbid developmental/ intellectual/ language impairments and secondly plan further assessment based on the unique cognitive profile of the individual child.

Flow chart for evaluating a child with ASD (Figure 2)



Developmental assessments are administered for children who are nonverbal/less than 6 years of age. Cognitive/ intellectual tests are administered for children and adolescents who can speak in sentences and comprehend the test instructions. Adaptive functioning will also need to be evaluated along with developmental and intellectual assessments, as discrepancy between the cognitive and adaptive functioning may be seen.

A. Developmental/cognitive assessments in ASD: Table 1

Assessments	Age group	Domains	Deficits specific to ASD
DEVELOPMENTAL			
Bayley Scales of Infant and Toddler Development™, Fourth Edition (Bayley™-4) (Balasundaram et al 2022)	16 days to 42 months	It assesses the development of infant and toddlers in 5 major domains- Cognitive, Language, Motor, Social–Emotional, and Adaptive behavior.	Uneven developmental profile has been noticed in children with ASD. The overall developmental level has been affected by the severity of autism, age and sex of the child. (Li HH et al 2020) Relative weakness has been seen in language and communication and personal-social-emotional scales (Taddei M et al 2023)
Developmental Assessment Scale for Indian Infants (DASII), an Indian adaptation of Bayley Scales (Madaan P et al, 2021)	Birth to 2 years	Body control, locomotion, manipulation, cognition, memory, social interaction, language development & manual dexterity	
Griffiths Scales of Child Development 3rd Edition [GRIFFITHS-III] (Pino et al 2024)	Birth to 6 years	It provides an overall measure of a child’s development along with an individual profile of strengths and weaknesses across 5 areas-foundations of learning, Language and communication, Eye hand coordination, Personal-social-emotional, Gross motor	
COGNITIVE/ INTELLECTUAL (Kishore MT,2019)			
Binet Kamat test of intelligence-adapted by Kamat (1967) and Reappraised by Venkatesan (2002a)	3 years and above	It measures six dimensions like -Language, memory, reasoning, conceptual thinking, visuo-motor and social intelligence	Uneven profile has been seen across the subtests. Inter/Intradomain unevenness leads to superior skill in one area. Weakness/low performance is seen in processing speed and working memory with typical performance in verbal and perceptual reasoning (Kishore TM et al 2012)
Malin’s Intelligence Scale for Indian Children.	6 -16 years	It has both verbal and performance components. It measures 10 domains-	
Bhatia's Battery of Performance Test of Intelligence	11 years and above	It is a performance test hence it can be administered to people with poor verbal abilities. It has	

		5 subtests like Kohs' Block Design, Alexander's Pass-along, Pattern Drawing, Picture Construction and Immediate Memory Tests.	
<i>Wechsler Intelligence Scale for Children, fourth edition (WISC IV) India</i>	6 - 16 years	It measures 4 subdomains like-Verbal comprehension, perceptual reasoning, working memory and processing speed using 10 subtests.	
<i>Wechsler Abbreviated Scale of Intelligence second edition (WASI-II) India</i>	6-90 years	It has 2 and 4 subtest version. 4 subtest form measures Vocabulary, Similarities, Block Design, Matrix Reasoning and provides Full scale IQ, Verbal comprehension and perceptual reasoning. 2 subtest form measures Vocabulary and Matrix Reasoning and provides full scale IQ to estimate general cognitive ability	

Assessing developmental age in an uncooperative child with ASD:

Some children with ASD, may not cooperate for a formal assessment of DQ or IQ, in such cases, the Psycho-educational Profile revised -PEP R can used to assess the developmental age, and the interventions can be planned accordingly.

Psycho-educational profile revised PEP-R

Alwinesh MT et al reported that PEP-R could be effectively used in individuals with ASD to assess the developmental quotient. It measures the developmental age and the emerging age across various domains like, imitation, perception, fine motor, eye-hand integration, cognitive performance, and cognitive verbal. PEP- R has strong psychometric properties in children with dual disability and can be used in children across the ages and with varying severity of autism. (Alwinesh MT et al, 2012)

B. Psychometric assessments to measure adaptive skills (Table 2)

Assessment	Age	Domains	Specific deficits in ASD
<i>Adaptive Behaviour Assessment System (ABAS)-3 (Anna Prokopiak et al, 2020)</i>	Birth to 89 years Parent and/or teacher rating scale for ages birth-21 years Adult self-report and other report for ages 16-89 years	Assesses 3 major adaptive domains – (conceptual, social and practical) along with 11 skill areas	Social and adaptive domains are predominantly affected. Adaptive functioning is below the cognitive level (McDonald et al 2015). Lowest scores

			are obtained in socialisation domain (Yang et al 2016)
<i>Vineland Adaptive Behaviour Scales (VABS) (Yang et al 2016)</i>	Birth to 90 years	Assesses domains like communication, Daily living skills, socialization, motor skills and maladaptive behaviour	
<i>Vineland Social maturity scale –Indian Adaptation (VSMS) (Roopesh, 2022)</i>	0 to16 years	Self-help general, Self-help dressing, Self-help eating, self-direction, locomotion, communication, occupation and socialization	

Note - Some of these assessments require training and certification, hence clinician discretion to be used

Specific assessments for cognitive impairments in children in ASD without comorbid intellectual disability

A. Assessment of executive functions(Demetriou EA et al, 2019):

1. Delis - rating of executive functioning (D- REF): It is a standardized assessment tool used to evaluate and measure the frequency of behaviors related to executive functions like planning, organization, inhibition, and flexibility across various situations in children and adolescents between the ages of 5 and 18 years.

2. Delis- Kaplan Executive function system (D KEFS): It is a battery of tests designed to assess a wide range of executive functions including cognitive flexibility, problem-solving, conceptual reasoning, inhibition, multitasking, and nonverbal and verbal creativity in children and adults

3. Behavioural assessment of dysexecutive syndrome in children (BADS – C): It is a battery of tests to evaluate the executive functioning of children with neurodevelopmental disorder between 8 to 16 years of age.

4. Behaviour rating inventory of Executive function – (BRIEF): It is a parent and teacher rated questionnaire to assess the executive function and self-regulation in children and adolescence between the ages of 5 to 18 years

5. Behaviour rating inventory of Executive Function-Preschool Version (BRIEF-P): It is a standardized parent/teacher rating scale for children from 2 years to 5 years 11 months to measure the executive function in preschool children with developmental conditions

6. NEPSY - Developmental Neuropsychological Assessment (Korkman, Kirk, & Kemp, 1998). It is a developmental neuropsychological assessment, used to assess children between the ages of 3 and 12 years, including children with developmental disabilities. It measures five functional domains/subtests- Attention/Executive Functions, Language, Sensorimotor Functions, Visuospatial Processing, and Memory and Learning

7. The Cambridge Neuropsychological Test Automated Battery (CANTAB®): It is a computerized, Non-linguistic, culturally blind tool used to measure cognitive functioning in domains like induction, visual memory, executive function, Attention, Verbal/Semantic Memory, Decision Making and Response Control, Social Cognition. It is sensitive for assessing developmental changes in children between 4 to 12 years of age.

8. Barkley Deficits in Executive Functioning Scale children and adolescents (BDEFS-CA): It is an empirically based tool for evaluating executive functions and impairments in daily living activities like time management, organization and problem solving, self-restraint, self-motivation, and self-regulation of emotions for children and adolescence of ages 6 through 17 years.

B. Domain specific tests of executive functions: (Table 3)

Domain	Name of the tests	Age range	Deficits seen in ASD
<i>Planning</i>	Porteus Maze ,1965 (NIMHANS neuropsychological battery for children, Kar et al 2004)	5-15 years	Children with ASD have deficits in planning leading to difficulty in organizing and sequencing a task (Larson et al 2021)
	Maze (Malin's Intelligence Scale for Indian Children.)	6-16 years	
	Tower of London tests-DX second edition	7-15 years	
<i>Working memory-A. Verbal working memory</i>	Letter number sequencing (working memory index of WISC-IV)	6-16 years	Significant working memory deficits have been reported in children and adolescence with ASD. Deficits are more in spatial working memory compared to verbal working memory (Rabiee et al 2020)
	Digit span backwards (working memory index of WISC-IV. Also seen as a subtest in MISIC, BKT	6-16 years	
	Arithmetic (Subtest in working memory index of WISC-IV	6-16 years	
	N-back test-verbal, (Smith &Jonides 1995) (NIMHANS neuropsychological battery for children)	5-15 years	
<i>B. Visuospatial working memory</i>	Visuospatial working memory span task, Milner, 1971 (NIMHANS neuropsychological battery for children)	5-15 years	Lower scores in verbal working memory were associated with greater problems in adaptive behaviour and more restrictive and repetitive behaviour. (Suneeta et al 2014)
	N-back task of visuospatial working memory, Smith Jonides,1995 (NIMHANS neuropsychological battery for children)	5-15 years	
<i>Mental Flexibility/set shift</i>	Wisconsin Card Sorting Test (WCST) (Heaton,1993) (NIMHANS neuropsychological battery for children)	5-15 years	Individuals with ASD show reduced cognitive flexibility, which could reflect difficulty shifting
	Trail making Tests-B in young children	2-6 years	

	(TRAILP-P) Trail making test for children	9- 14 years	from a previously learned response pattern or a failure to maintain a new response set (Miller et al 2015)
	Stroop colour and word test	5-14 years	
<i>Response initiation-Fluency</i> <i>a. Verbal fluency</i>	FAS Phonemic fluency, Lezak 1995 (NIMHANS neuropsychological battery for children)	5-15 years	Children with ASD have overall difficulty in generating words. (Andreou et al, 2022).
	Semantic fluency (Strauss et al 2006)	5-11 years	
<i>b. design fluency</i>	Design Fluency, Jones-Gotman & Milner, 1977 (NIMHANS neuropsychological battery for children)	5-15 years	Number of repetitive items and errors predict symptoms of ASD related to language and social and self-help. (Tian et al 2022)

C. Assessment of central coherence (Table 4)

Name of the test	Age range	Deficits seen in ASD
<i>Children Embedded figures Test (Witkin 1971)</i>	5-10 years age	Weak central coherence in ASD has been reported to be a root characteristic of ASD symptoms such as insistence on sameness, attention to parts of objects, and uneven cognitive profile, including savant skills (Happé et al 2006). Impaired central coherence has been noted to have an impact in learning such as performance in reading comprehension (Alijunied et al 2013)
<i>Rey-Osterrieth Complex Figure Test-ROFT (Rey 1941)</i>	6 years and above	
<i>Central Coherence Test –CCT (Gambra et al 2020)</i>	6 years and above	

D. Assessments of social cognition (Table 5)

Domain	Name of the test	Age range	Deficits noted in ASD
<i>Social perception</i>	"The Awareness of Social Inference Test" (TASIT)-Part 1	13 years and above	People with ASD score low on cognitive empathy
	Edinburgh social cognition test (ESCoT) adapted and validated in India (Bhutani S, 2024)	18 years and above	

<i>Emotional recognition</i>	The Movie for the Assessment of Social Cognition [MASC]	12 years and above	Difficulty in recognizing emotions however the intelligence level has a significant role
	The emotional bias and recognition task	6-16 years	
<i>Theory of Mind</i>	Reading the mind in the eyes test-Children version	6-16 years	Impaired development of theory of mind is observed in ASD. Impaired and prolonged sequence generation is also observed
	Strange stories task	6-12 years	
	Faux Pas Recognition Test	7-11 years	
	"The Awareness of Social Inference Test" (TASIT)-part 2 and 3	13 years and above	
	Picture sequencing task	3 years and above	
	False belief understanding task-Sally Anne test	4-5 years and above	
	Social stories -second order false belief, emotional display rules, violation of social rules, double bluff and irony (Scheeren, Begeer & Koot, 2012)		

Interventions for cognitive deficits in ASD

Non-pharmacological interventions

Interventions for the cognitive impairments in ASD should be planned, targeting the specific non-social and social impairments that are seen in the individual. Many of these strategies have been extrapolated from interventions carried out in adults with brain damage or schizophrenia and tried in other disorders like ASD, ADHD and learning disabilities. While some of these interventions are listed below, they are still relatively new in children and need to be further studied.

1. Cognitive Remediation Therapy (CRT)

Cognitive Remediation Therapy (CRT) is a therapeutic approach which has been extensively studied in schizophrenia. It improves cognitive processes through individual behavioural training using repetitive exercises and positive reinforcement. (Hajri M et al, 2022). CRT has been tried for the executive functioning deficits seen in adults and children with ASD, comprising of modules working on cognitive flexibility, working memory and planning. A systematic review by Dandil et al. showed that cognitive remediation approaches in ASD individuals effectively addressed cognitive deficits of working memory and phoneme flexibility, suggesting growing evidence for cognitive training in improving executive functions in individuals with ASD. (Pasqualotto, A, 2021)

2. Cognitive flexibility training

Cognitive flexibility is an ability that allows people to shift their attentional focus on complex tasks, and deficit in the same is seen in children with autism spectrum disorder. Cognitive flexibility training uses play and games to improve cognitive flexibility, planning ability, and use of language among children and adolescents with autism. (Varanda et al, 2017)

3. Cognitive Enhancement Therapy (CET)

Research on the cognitive impairments in ASD and domain-specific interventions have shown that executive functioning impairments can, in turn, affect social cognitive functioning. The need to consider interventions that can be more integrative in cognitive rehabilitative approaches led to the development of therapies like CET, a multidimensional program integrating neurocognitive training targeting attention, memory and problem-solving, as well as social cognitive training. Participants are initially paired for initial sessions in neurocognitive training with coach trainers. Small social-cognitive groups are then formed with structured sessions to work on socialization, problem-solving, and perspective-taking, with homework assignments to generalize skills to their daily life over 18 months. While the effectiveness of CET has been found in schizophrenia, its potential effectiveness with minor adaptations in adults with ASD has also been shown. (Eack SM et al., 2018).

4. Cognitive training using video games

Wagle et al., in their study, showed that smartphone-based games can be used to train working memory in children with ASD. The team developed five games- basket game, train game, piano game, face game and shape game, and studied the effectiveness of the same in improving working memory. The games were open-source, free of cost to the community, and designed to match the children's behavioral preferences and sensorimotor abilities. A preliminary one-month intervention trial was conducted to test the effectiveness of the intervention. Though no statistically significant change was noted, children who performed better on the games appeared to improve in their working memory, suggesting that a longer game-based intervention might help improve working memory. (Wagle S et al, 2021)

5. Physical exercise

A recent network meta-analysis looked at the effect of different types of physical exercise on executive function in children with ASD. A medium effect size was seen in the domains of inhibitory control and cognitive flexibility with certain physical sports like mini-basketball, ping pong, exergaming and martial arts, with differential effects in specific sports and overall more effects in inhibitory control. While there were some improvements in working memory, especially in games like ping-pong, the effect size was lower than in the other two domains. The analysis suggests that certain physical sports can be recommended to improve executive functioning in children with ASD. (Yaoqi Hou et al, 2024)

6. Social Skills Training (SST)

SST refers to a wide range of group-based interventions and instructional methods commonly used to help understand and improve social skills. It focuses on developing effective communication skills, enhancing social interaction skills, improving the ability to initiate and maintain conversations, enhancing perspective-taking (ToM) and empathy skills, building self-awareness and self-regulation skills, and promoting emotional understanding and emotional control. SST programs can vary according to the child's chronological age and skill level. Social skills for younger children with autism address fundamental play skills like eye contact and turn-taking. In adolescents and young adults, the focus shifts to expressing opinions, initiating and maintaining conversations, maintaining friendships and workplace behaviour. Standard techniques used in social skills training are peer-mediated interventions and instructions, modelling and role-playing, social narratives, visual supports, video modelling and cognitive behaviour therapy (Wong, et al., 2014).

Social skills group training for children and adolescents with ASD has shown to have modest and inconsistent effects according to a randomised control trial done by Olson. (Choque Olsson N et al 2017). School based social skills training has also been shown to have minimal

evidence in children with ASD. (Bellini, S et al, 2007)

Recently there has been increasing focus on the use of “behavioural intervention technologies” in social skills training. (BITs - SST) (Soares EE et al, 2021).

Some examples of SST programs are:

a. *Social Cognition and Interaction Training (SCIT)*- SCIT is used in adolescents to improve social attention, social cognition and social skills.

b. *Education and Enrichment of Relational Skills (PEERS)* - PEERS is a group-based program developed at UCLA for children with ASD. The program involves 90-minute weekly sessions targeting social skills for 3-4 months. The children are taught these skills through role-play, group activities, and parent involvement to ensure the skills are practised at home and in the community. This intervention has shown to be beneficial even after the training sessions are over.

c. *Assistive Soft Skills and Employment Training (ASSET)*: ASSET is an intervention focussing on work-related social skills.

Non-pharmacological management (Table 6)

Therapy	Domain used in	Evidence	Evidence level
<i>Cognitive remediation therapy</i>	Cognition, executive functions, social cognition	Cognitive remediation interventions have been shown to be effective, in improving social cognition and cognitive functioning in ASD. However, RCT's with larger samples are needed to study long term benefits. Executive function training is shown to have positive effects, more when it is computerised. However more studies are needed.	Systematic review (Dandil et al, 2020, Pasqualotto et al, 2021)
<i>Cognitive flexibility training</i>	Cognitive flexibility	Children with ASD are shown to have benefit from strategies to improve the cognitive flexibility. However more research in this area is needed with larger samples.	Interventional study (Varanda et al, 2017)
<i>Cognitive enhancement therapy</i>	Cognition – in adults	Cognitive Enhancement Therapy has been shown to be effective in the treatment of core cognitive deficits in ASD in adults.	Randomized control trial (Eack SM et al, 2018)
<i>Cognitive training using video games</i>	Working memory	No significant change was noted in the working memory at the end of 1-month training, in all the	Interventional study (Wagle S et al, 2021)

		children. But the study suggested that a longer intervention maybe beneficial in improving the working memory.	
<i>Physical exercise</i>	Inhibitory control, cognitive flexibility, and working memory	Improvement in the executive functions in children with ASD, medium effect noted	Network meta- analysis (Yaoqi Hou et al, 2024)
<i>Social skills training</i> <i>a. Social skills group training</i> <i>b. School-based social skills intervention</i> <i>c. BITs SST</i>	Social skills	Modest to inconsistent effects Minimal evidence for school-based interventions for social skills There is no significant difference between the face-to-face SST and the BITs SST	Randomised control trial (Choque Olsson N et al 2017) Meta-analysis Bellini, S et al, 2007 Soares EE et al, 2021

Pharmacological interventions

Specific evidence-based pharmacological management is recommended for ASD in the presence of severe levels of stereotypies, self-injurious behaviour, hyperactivity and sleep dysregulation or to manage other comorbid medical or psychiatric disorders. (Please refer to the Clinical Practice Guidelines for Assessment and Management of ASD, Indian Journal of Psychiatry, 2019).

While the potential benefit of non-pharmacological interventions to address cognitive deficits in individuals with ASD is noted, the evidence for pharmacotherapy in this specific area is limited.

Current evidence base for pharmacological interventions (Table 7)

Medication	Domain used in	Evidence	Evidence level
N-acetylcysteine (NAC) - antioxidant	Social awareness skills as measured by the Social Responsiveness Scale	Some evidence reported, however further evidence should be sought before a general recommendation.	Meta-analysis (Lee TM et al 2021, Aishworiya et al, 2022)
Dietary Supplements Sulforaphane – found in broccoli and other	Social responsiveness – as measured by SRS	Minimal evidence currently	Randomized control trial (Zimmerman AW et al, 2021)

cruciferous vegetables Omega 3 fatty acid			
Oxytocin	Social interaction – as measured by Aberrant Behavior Checklist modified Social Withdrawal subscale (ABC-mSW) Social functioning	No change in social and cognitive functioning Some benefit reported	Randomised, placebo-controlled, study in children and adolescents with ASD (Sikich L et al, 2021) Meta analysis – includes studies done in adults (Huang Y et al 2021)
Bumetanide	Core symptoms of ASD – as measured by SRS-2	No benefit reported	Double-blind, placebo-controlled, phase 2 superiority trial (Sprengers JJ et al, 2021)
Cannabinoid	Social communication – SRS 2	Some benefit, but insufficient evidence currently, needs further studies	Randomized control trial (Aran A et al, 2021)
Memantine	Cognition and memory	Some improvement in memory No change in nonverbal IQ. Controlled studies are needed to substantiate preliminary findings.	Open label trial (Owley T et al, 2006)
Acetylcholinesterase inhibitors	Core features of ASD	Effectiveness in children-uncertain	Systematic review (Ure A, et al 2023)
L Carnosine	Social, communication domains	Current data do not support the use of L-Carnosine in the management of children with ASD	Meta-analysis (Abraham DA et al, 2021)

As seen in the table given, current evidence for pharmacological management specifically for cognitive impairments in ASD is weak and therefore is not recommended.

Conclusion

In summary, ASD, being a very heterogeneous condition, can present with varying levels of cognitive functioning, ranging from average -above average intelligence to children having developmental delays or intellectual disability. However, even among individuals with ASD in the absence of comorbid intellectual disability, cognitive profiles can differ from the norm, with specific impairments in social and non-social cognitive domains. As these impairments can impair day-to-day functioning, it is essential to evaluate them to tailor interventions to suit the child's needs. Research addressing specific assessments and interventions addressing these cognitive impairments in children with ASD is still relatively new and ongoing. The neuropsychological concepts and assessments for cognitive impairments in ASD without an intellectual disability have been highlighted in this guideline, along with suggestions for interventions.

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Clinical Practice Guideline on the Assessment and Management of Cognitive Impairment in Major Depressive Disorder

INTRODUCTION

Cognitive dysfunction is a common and often overlooked symptom of major depressive disorder (MDD), a prevalent and debilitating mental health condition that can profoundly influence an individual's living experiences and daily functioning(1). The global prevalence of MDD is staggering, with the World Health Organization estimating that it affects nearly 350 million people worldwide, making it the leading cause of disability (2). India itself contributes 280 million to this prevalence. One or more cognitive faculties in MDD patients is adversely affected and tends to persist despite the remission of the episode fig. 1 (3). Upon resolution of an Major depressive episode, although the affected individual may show or experience considerable improvement in measures of psychomotor speed, learning, planning and memory, there are still residual cognitive symptoms that continue to exist,highlighting the need for a comprehensive assessment and management approach (Table 1) (4).The deficit in one or more cognitive faculties has been reported to be one or more standard deviations below normal value, in 25-50% of subjects with MDD. Therefore it furthers the need to proper assessment and diagnostic approach of these affected individuals (5).The existing qualitative research suggests that while the improvement in patient related quality of of life measures is held as a priority by a large number of mental healthcare professionals. These measures are somehow connected to cognition but do not present a distinct cognitive profile (6).

Table 1: Cognitive domains affected in Major depressive

Domain	Description
Attention	Reception, selection, and filtering of information
Memory and learning	Acquisition, storage, recollection, and manipulation of information; includes the following types: • Semantic memory, or memory of learned factual knowledge; • Episodic memory, or memory of events and experiences; • Working memory, or short-term retention and manipulation of information.
Executive functions	Higher-level cognitive processes, including planning, decision-making, mental flexibility, inhibition, task initiation and monitoring, and multi-tasking
Psychomotor processing	Fundamental sensory, perceptual, and motor operations

The prominent classification system DSM5 profiles the symptomatology into various type specifiers; such as, with melancholic features, with anxious distress, with atypical features, with psychotic features, with mixed features, with peripartum onset. Williams et. al. 2013, took to a neural circuitry-based approach to defines biotypes of depression and anxiety (Table 2) Fig. 1 (7).

Table 2: Different Biotypes of Depression biotypes based on neural circuitry

	Biotype	Neural circuit dysfunction
1.	Rumination	Hyperconnectivity in default mode network
2.	Anxious avoidance	Salience circuit
3.	Negative bias	Increased connectivity between the anterior (sub genual ACC and dorsal medial prefrontal cortex) nodes of the negative affect network and the default mode network
4.	Threat dysregulation	A reduction in the uncinate fasciculus white matter connections that support functional communication between the amygdala and ACC
5.	Anhedonia	striatal hypoactivation in positive affect circuit
6.	Context insensitivity	overactivation of the anterior cingulate and midfrontal region
7.	Inattention	Hypoconnectivity within the frontoparietal attention circuit
8.	Cognitive dyscontrol	ACC and dorsolateral prefrontal cortex hypoactivation

A specific group of depressed individuals identified as having “cognitive biotype”, respond poorly to antidepressants,. These individuals continue to struggle with their suboptimal cognitive function, which negatively impacts their overall wellbeing. Through mediation models, it was conceived that the extent of improvement in measures of cognitive control influenced the extent of posttreatment relief from depressive symptoms and quality of life in such individuals. The findings challenge the prevailing assumption that cognitive impairments resolve as a secondary effect of improving overall severity(8).

Another modifier in the poor post-treatment response in cognitive profile and quality of life is the existence of comorbidities in depressed subjects. This adds to the complexities faced in treating depression. This guideline aims to provide evidence-based recommendations for the assessment and management of cognitive impairment in individuals with depressive disorders.

2. OBJECTIVES

- To standardize the assessment of cognitive impairment in depressive disorder.
- To standardize the assessment of cognitive impairment in depressive disorder patients once they achieve remission.
- To outline evidence-based management strategies for cognitive impairment during and persisting after the remission is achieved

- To enhance awareness and understanding of cognitive impairment in depressive disorders among end users i.e. Psychiatrists and other mental health professionals

3. SCOPE

This guideline is intended for use by psychiatrists, clinical psychologists, and other mental health professionals involved in the care of individuals with depressive disorders.

4. ASSESSMENT OF COGNITIVE IMPAIRMENT

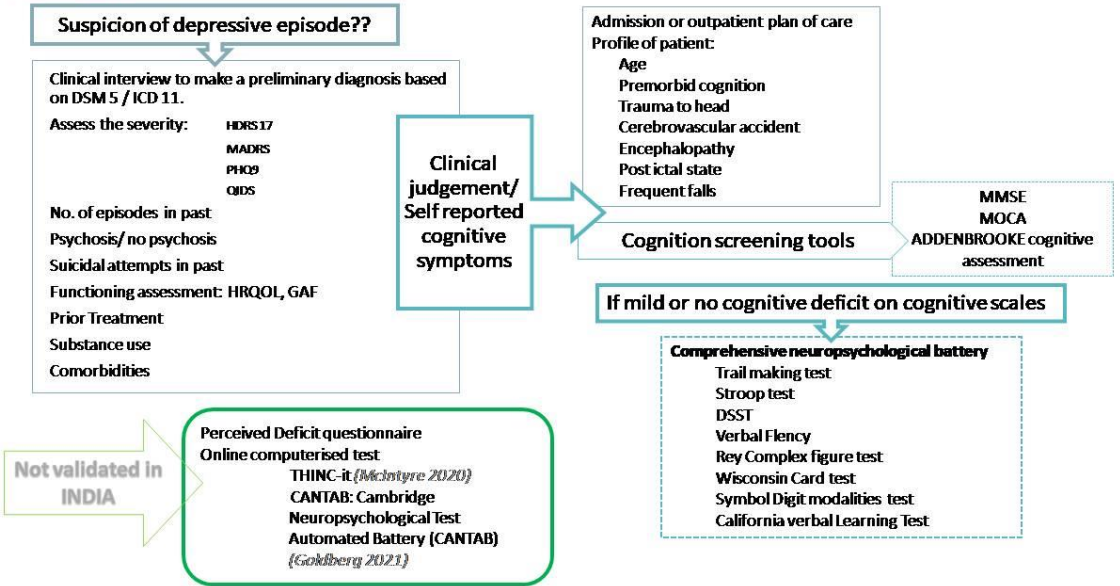
I. General evaluation of Depressive features:

Any individual in clinical setting undergoes preliminary assessment which screens them for any psychopathology, its severity. The clinical presentation should fulfil the criteria required to reach a diagnosis of Major depressive disorder. These set of criteria are defined within prominent diagnostic classification systems ICD 10 and DSM5. The clinical presentation of subjects with depression is not unanimous. DSM 5 has included course and severity specifiers to phenotype the MDD symptomatology. Either of these classifications do not mention cognitive dysfunction as a phenotype.

II. Factors influencing cognitive symptoms in MDD (Ref)

- Age
- Age at onset of depression
- Education level
- Baseline functioning
- Psychiatric co-morbidities
- General Medical co morbidities
- Subtype of MDD
- Duration of illness
- Episodic frequency
- Treatment selection and history
- Symptomatic status

GENERAL EVALUATION OF DEPRESSIVE FEATURES



Suspicion of depressive episode??

- Clinical interview to make a preliminary diagnosis based on DSM 5 / ICD 11.
- Assess the severity
 - HDRS 17
 - MADRS
 - PHQ9
 - QIDS
- No. of episodes in past
- Psychosis/ no psychosis
- Suicidal attempts in past
- Functioning assessment: HRQOL, GAF
- Prior Treatment
- Substance use
- Comorbidities

Clinical judgement: Self reported cognitive symptoms

- Admission or outpatient plan of care
- Profile of patient:
 - Age
 - Premorbid cognition
 - Trauma to head
 - Cerebrovascular accident
 - Encephalopathy
 - Post ictal state
 - Frequent falls

Cognition screening tools

- MMSE
- MOCA
- ADDENBROOKE cognitive assessment

If mild or no cognitive deficit on cognitive scales

- Comprehensive neuropsychological battery
 - Trail making test
 - Stroop test
 - DSST
 - Verbal Flency
 - Rey Complex figure test
 - Wisconsin Card test
 - Symbol Digit modalities test
 - California verbal Learning Test

III. **Evaluation of Cognitive features:** A baseline cognitive assessment entails ruling out other cognitive illnesses. The cognition itself is not the primary pathology. Hence while it is not relevant to have an exclusive assessment of the same, it is empirical to be cognizant that cognitive deficits might be a predictive and prognostic marker of treatment outcome and functioning. The forgoing cognitive domains (i.e., executive function, attention, memory, processing speed and psychomotor skills) are affected at varying levels during all phases in MDD (ie, symptomatic phases and remitted phases).

a. **The widely used scales such as HAM-D 21 and MADRS** have 2 items each assessing cognitive symptomatology. These scales provide insufficient information

b. **Comprehensive neuropsychological tests:**

- i. Trail making test :visual attention, processing speed and cognitive flexibility
- ii. Digit span test: evaluating working memory
- iii. Verbal fluency:
 1. Semantic
 2. Phonemic
- iv. Stroop test: measures selective attention and response inhibition
- v. Rey Complex figure test: visuospatial memory and organizational skills
- vi. Wisconsin Card test: Cognitive flexibility, set shifting and abstract reasoning
- vii. Symbol digit modalities test: Processing speed and attention
- viii. California Verbal Learning Test: Verbal learning and memory
- ix. Clock drawing test
- x. Wechsler adult intelligence scale: comprehensive battery that includes assessment of verbal comprehension, perceptual reasoning, working memory, and processing speed.
- xi. PGI battery for memory assessment
- xii. NIMHANS neuropsychological battery
- xiii. ICMR Neurocognitive tool box

c. Other tests: not validated in India yet

- i. **Perceived Deficits Questionnaire-Depression (PDQ-D)** is a 20-item questionnaire. It was developed by Michael Sullivan initially for patients with multiple sclerosis. However, later on, it was validated for use in depression in several countries.. The scale measures subjective cognitive deficits in 4 domains of cognition, namely:

attention/concentration, retrospective memory, prospective memory and planning/organization. Brief tests for assessment of Cognitive function in MDD: India is yet to adapt and validate existing tools specific to measuring cognitive function in MDD.

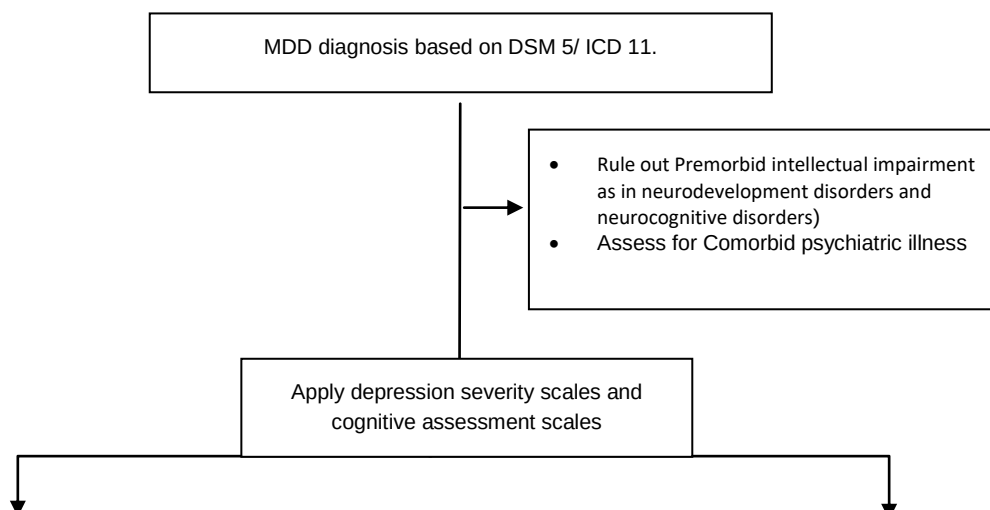
ii. Online computerized tests:

1. **THINC-it®** tool is a valuable screening resource for assessing cognitive functioning in patients with major depressive disorder (MDD). Here are the key features:

a. **Components:**

- i. **PDQ-5D:** A 5-item Perceived Deficits Questionnaire completed by the patient.
- ii. **Neuropsychological Tests:**
 1. **Spotter:** A gamified assessment.
 2. **Symbol Check:** Evaluates attention and processing speed.
 3. **Code Breaker:** Assesses working memory and cognitive flexibility.
 4. **Trails Test:** Measures visual attention and task switching.
- iii. **Purpose:** THINC-it® helps physicians identify cognitive dysfunction in MDD patients. It combines subjective and objective measures, providing valuable insights

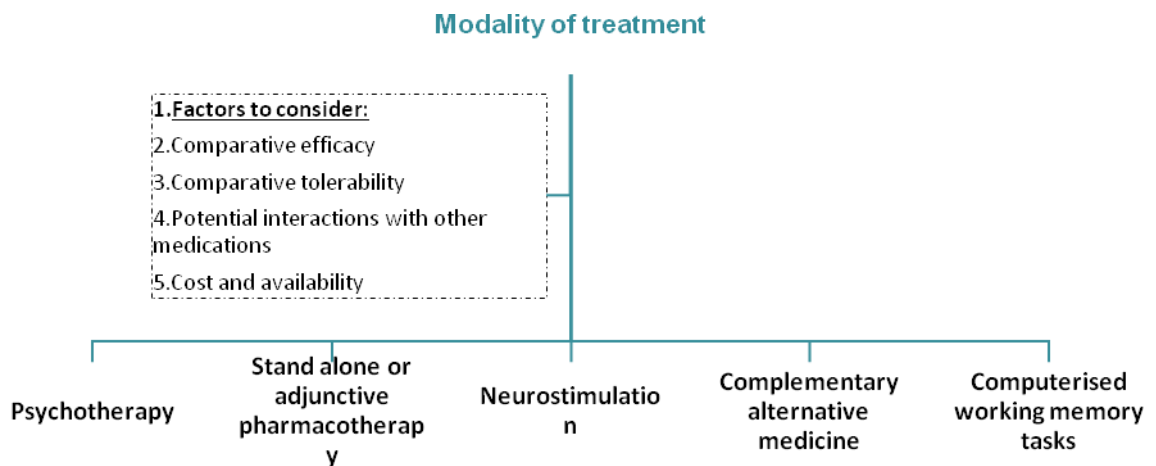
2. **CANTAB: Cambridge Neuropsychological Test Automated Battery (CANTAB)** is a computer-based cognitive assessment system. CANTAB covers various cognitive domains, including attention, psychomotor speed, executive function, emotion, social cognition, and memory.



- HDRS-17
- MADRS,
- PHQ-9

MANAGEMENT

- MMSE
- MoCA

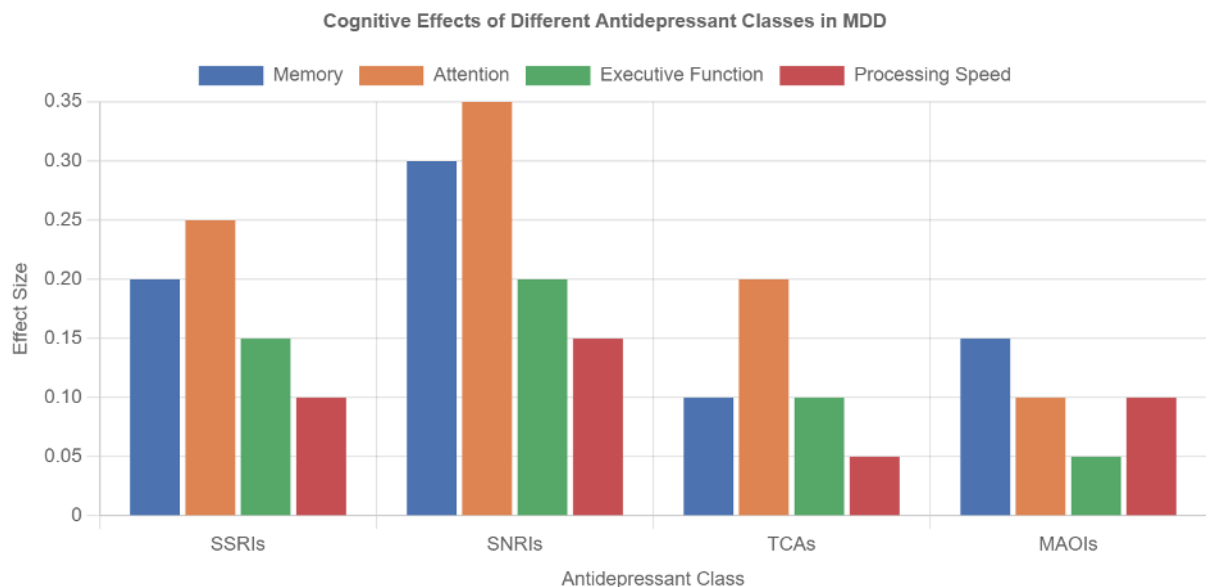


A. Stand alone or adjunctive pharmacotherapy

1. Conventional antidepressants(9)

The meta-analysis by Shilyansky et al. (2016) provides evidence that antidepressants can lead to small to moderate improvements in cognitive symptoms in patients with MDD, particularly in memory, attention, and executive function. This study highlighted following cognitive effects of different classes of conventional antidepressants:

1. Selective serotonin reuptake inhibitors (SSRIs) were found to have a significant positive effect on cognitive symptoms, particularly in memory and attention.
2. Serotonin-norepinephrine reuptake inhibitors (SNRIs) also showed positive effects on cognitive symptoms, with a notable impact on executive function.
3. Tricyclic antidepressants (TCAs) had a smaller effect on cognitive symptoms compared to SSRIs and SNRIs.



2. **Atypical antipsychotics** could potentially lead to better overall cognitive performance in patients with MDD and psychotic features. The change in cognition of antipsychotics has never been studied as primary outcome measure. The cognitive improvements are in most cases a secondary or exploratory outcome. The cognitive improvement is likely to be an indirect effect of remission of psychotic symptoms and stabilizing mood(10).
3. **Multimodal Agents:**
 - a. Vortioxetine consistently outperformed other common antidepressants in terms of its cognitive benefits across multiple studies and across different cognitive domains (11–13).
4. **Non-conventional Drug therapies**
 - a. Ketamine modulates glutamate neurotransmission, which can have rapid antidepressant and procognitive effects. Three and more studies report beneficial effects of ketamine on cognition. (14–16). Pragmatic questions linger about the cognitive safety of long-term prescribed ketamine or esketamine for depression. Further research is needed to confirm these effects (17).
 - b. Cholinesterase inhibitors, such as donepezil and galantamine, have showed limited for their effects on cognitive symptoms in MDD. These inhibitors have been found to ameliorate subsyndromal depression in patients with dementia and improve cognition and behavioral symptoms.

However, the effects of these inhibitors on cognitive function and mood in older adults with MDD are inconsistent (18,19).

- c. Eugeroics: These agents promote wakefulness and enhance cognitive function by modulating dopamine and other neurotransmitters. Few studies show that modafinil and armodafinil improve symptoms of depression, reduces fatigue and improves cognition(19,20) .

5. Psychological treatments

- I. Cognitive Remediation Therapy (CRT) is an evidence-based intervention designed to improve cognitive functioning in individuals with conditions like Major Depressive Disorder (MDD). Here are the key points about CRT:
 - a. Purpose: CRT aims to enhance cognitive abilities such as attention, memory, and executive functions.
 - b. Components:
 - i. Computerized Exercises: Patients engage in structured computer-based tasks that challenge cognitive processes.
 - ii. Strategy Training: Participants learn compensatory strategies to manage cognitive difficulties.
 - iii. Group Sessions: CRT often involves group-based training to foster social interaction and support.
 - c. Benefits:
 - i. Cognitive Improvement: CRT can lead to better attention, memory, and problem-solving skills.
 - ii. Functional Outcomes: Improved cognition may positively impact daily functioning.
 - d. Individualization: CRT is tailored to each person's specific cognitive deficits and needs.
 - e. Integration: It can be combined with other therapies (e.g., psychotherapy, pharmacotherapy) for comprehensive treatment.
- (21)

II. Cognitive behavior Therapy:

In a meta-analysis by Cristea et al. (2015), CBT showed a significant positive effect on improving dysfunctional thinking in adults with depression. Rather than comprehensive cognitive efficacy, this analysis measured change in dysfunctional thinking as a secondary outcome. CBT for depression had a robust medium effect on dysfunctional thoughts. The only difference between CBT and other psychotherapies was found for the DAS. Its ability to improve cognitive restructuring and behavioral activation seems to be a key advantage over some other therapies, based on the available

evidence. There were no differences between CBT and pharmacotherapy on dysfunctional thoughts. More research is needed to fully understand the differential cognitive effects of various psychotherapies for depression (22,23).

- III. Other Psychotherapies: There is less extensive data on effect of other psychological therapies on cognitive outcome.

6. Neurostimulation

- a. Transcranial Magnetic Stimulation (TMS): Individual studies report improvement in cognitive functioning however there is heterogeneity in the montage used, stimulation intensity and pulse pattern(24,25). Clinical practice guidelines for therapeutic responses of rTMS in neuropsychiatric disorders mentions evidence supporting role of rTMS in relative improvement of executive functioning with improvement in depression outcome(26).
- b. tDCS
- c. ECT

7. **Complementary and Alternative medical treatments** : It is defined as “a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine.’

a. Nootropics:

- i. Recombinant erythropoietin (EPO): In a double-blind, randomized, placebo-controlled, recombinant erythropoietin showed significant improvement in verbal learning and memory in a mood-independent manner(27).
- ii. Other potential Nootropics: The evidence for cognitive efficacy of various other nootropics is still limited. Well-designed, large-scale randomized controlled trials are needed to further investigate their efficacy and safety. However, we describe below the nootropics with potential cognitive deficits(28).
 - 1. Minocycline
 - 2. Insulin and Antidiabetic Agents (e.g., Thiazolidinediones).
 - 3. S-Adenosyl Methionine (SAME)
 - 4. Omega-3 Polyunsaturated Fatty Acids

5. N-Acetylcysteine (NAC)
6. Curcumin
7. Statins
8. Coenzyme Q10
9. Gingko biloba extract EGb761(29)

8. **Computerized working memory tasks** such as the Paced Auditory Serial Addition Test, have shown potential in improving the cognitive skills in MDD patients. A study measuring effect of Paced Auditory Serial Addition Test on mental abilities, conducted by Siegle et al., reported enhancement in metacognitive skills, decrease in maladaptive thought patterns (i.e., rumination), and improvement in depressive symptom severity. Moreover, Computer based, mental arithmetic exercises, that focus on sequencing, have been shown to improve intelligence quotient (IQ), increase psychosocial functioning, as well as hippocampal and frontotemporal activation in MDD patients(30).

1. Remove neurocircuitry diagram (due to less relevance and copyright issues)

Have removed the neurocircuitry diagram from the guideline to avoid potential copyright issues and because of its limited relevance in the context of cognitive impairment in MDD. Instead, I will focus on explaining the underlying neurobiological mechanisms in a descriptive format, citing relevant literature, such as Drevets et al. (2008) on the neuroanatomy of depression and how it relates to cognitive function.

2. Title to update with Major Depressive Disorder (MDD)

We have updated the title of the guideline to explicitly include "Major Depressive Disorder (MDD)" to ensure clarity and specificity in the document. The revised title will better reflect the focus on MDD, aligning it with the clinical and research terminology widely accepted in the psychiatric community.

3. cognitive deficits after depression improves

When a patient recovers from depression, cognitive deficits can persist despite improvements in mood. These deficits often include difficulties in attention, memory, executive functioning, and processing speed. Patients might struggle with concentrating on tasks, recalling information, or making decisions, even after their depressive symptoms have lessened. The

persistence of these cognitive impairments can hinder the patient's ability to fully reintegrate into daily activities, work, or social interactions. It is crucial for clinicians to monitor these cognitive aspects also.

4. CPG on management of depression

To maintain the focus on cognitive impairment, we will revise the guideline to refer to the established Clinical Practice Guidelines (CPG) on the management of depression, removing detailed descriptions of depression treatment. This will streamline the document and allow readers to consult the relevant CPG for comprehensive treatment strategies for MDD, while this guideline will focus solely on cognitive aspects. For example, the CPG by the Indian Psychiatric Society on depression management will be referenced for readers seeking guidance on broader treatment approaches.

5. cognitive problems as part of diagnosis of depression

Assessment of cognitive problems is also an integral part to the diagnosis of MDD, as cognitive impairments are common symptoms that can significantly affect a patient's daily functioning. During a diagnostic evaluation of MDD, clinicians assess cognitive domains such as attention, memory, executive function, and processing speed. Patients with depression often report difficulties with concentration, decision-making, and remembering details, which can interfere with their ability to work, maintain relationships, or perform routine tasks.

These cognitive symptoms are not only a reflection of the severity of depression but also provide insight into the disorder's impact on the patient's overall functioning. The presence and extent of cognitive deficits can influence treatment planning, as persistent cognitive problems may require additional interventions beyond standard antidepressant therapy. Furthermore, understanding these cognitive aspects helps in predicting the course of the illness and the risk of relapse, making it a crucial component of comprehensive depression diagnosis and management.

6 level of evidence with regard to contributing factors for cognitive impairment and management

A detailed examination of the contributing factors to cognitive impairment in MDD will be included, categorized by the level of evidence. This will cover neurobiological factors (e.g., neuroinflammation, hippocampal atrophy), psychological factors (e.g., rumination, anxiety comorbidity), and social factors (e.g., socioeconomic status, social isolation). Management strategies will be discussed with evidence graded according to established hierarchies, from meta-analyses and systematic reviews to randomized controlled trials and observational studies. Key references will include Bortolato et al. (2016) on inflammation and cognitive impairment, and Kiosses et al. (2011) on psychosocial interventions.

7. physical comorbidities, their assessment and management

Patients with depression often have physical comorbidities such as cardiovascular disease, diabetes, obesity, chronic pain, and gastrointestinal disorders. These conditions can be both a consequence and a contributing factor to depression, creating a bidirectional relationship that complicates the patient's overall health. For instance, depression can exacerbate symptoms of physical illnesses, impairing immune function and increasing inflammation, while chronic health issues can trigger or worsen depressive symptoms due to ongoing stress and disability. Unmanaged physical conditions can reduce the effectiveness of depression treatment, increase the risk of relapse, and lead to higher healthcare costs. A comprehensive approach that includes monitoring physical health, coordinating care between mental health and other medical professionals, and addressing lifestyle factors such as diet, exercise, and sleep is essential. This holistic management helps in improving both mental and physical well-being, leading to better overall prognosis for the patient.

8 ECT as cognitive deficits are part of depression and ECT related cognitive problems in due course of time

Electroconvulsive Therapy (ECT) is a critical treatment option for severe MDD, and its cognitive side effects are a concern. However, research indicates that ECT-related cognitive impairments, such as memory disturbances, typically improve over time. Studies like Semkovska & McLoughlin (2010) on cognitive outcomes post-ECT, and Sackeim et al. (2007), provide a comprehensive overview of ECT's cognitive effects. These studies conclude that while ECT can initially exacerbate cognitive deficits, these often remit, and the overall cognitive benefit due to mood improvement is substantial.

9 CBT related benefits on cognitive impairment, if strong evidence available

There is evidence supporting the benefits of Cognitive Behavioral Therapy (CBT) in improving cognitive impairments secondary to depression, though the strength of this evidence varies. CBT is primarily designed to address mood symptoms, but it can also positively influence cognitive functioning by helping patients develop better coping strategies, reduce rumination, and improve problem-solving skills.

Some evidence and Key Studies:

1. Shilyansky et al. (2016): conducted a review that found CBT can improve cognitive deficits, particularly in executive function and attention, by addressing the maladaptive thought patterns that contribute to these impairments. The study highlights that the structured nature of CBT can help patients regain cognitive control, which is often compromised in depression.

2. Motter et al. (2016): conducted a meta-analysis that examined the effect of CBT on cognitive impairments in depression and anxiety. The analysis found small to moderate improvements in cognitive functions, particularly in attention and memory, suggesting that CBT can have a modest positive impact on cognitive deficits associated with depression.

3. Porter et al. (2013): in their review of psychological interventions, noted that while CBT is effective in treating depressive symptoms, its direct effects on cognitive impairments are less robust compared to its impact on mood. However, they also noted that CBT can indirectly improve cognitive function by alleviating depressive symptoms, which are closely linked to cognitive deficits.

Conclusion:

While CBT is not specifically designed to target cognitive impairments, there is evidence suggesting that it can lead to improvements in cognitive functioning, particularly by reducing the cognitive symptoms associated with depression. However, the magnitude of these effects can vary, and more targeted cognitive therapies may be necessary for more pronounced cognitive deficits.

References:

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10 NCD related cognitive impairment, assessment strategies, comprehensive management

A new section will be added to address cognitive impairment related to Neurocognitive Disorders (NCDs) in the context of MDD. This will include assessment strategies for differentiating between MDD-related cognitive deficits and those due to NCDs, such as Alzheimer's disease or vascular dementia. Comprehensive management strategies, including pharmacological and non-pharmacological interventions, will be discussed. Key references

will include Petersen et al. (2014) on mild cognitive impairment and Alzheimer's disease, and Butters et al. (2004) on depression and cognitive decline in older adults.

11 medication related cognitive impairment

Medications used to treat depressive disorders, particularly certain antidepressants, can sometimes lead to cognitive impairments as a side effect. Commonly prescribed antidepressants, such as tricyclic antidepressants (TCAs) and some selective serotonin reuptake inhibitors (SSRIs), may affect cognitive functions like memory, attention, and processing speed.

Mechanisms of Cognitive Impairment:

1. **Anticholinergic Effects:** TCAs and some other antidepressants have anticholinergic properties, which can impair cognitive functions by blocking acetylcholine, a neurotransmitter essential for memory and learning.
2. **Sedation and Fatigue:** Medications with sedative effects, such as mirtazapine or some SSRIs, may cause drowsiness and mental fog, leading to difficulties with concentration and memory.
3. **Delayed Cognitive Processing:** Some patients may experience slowed cognitive processing, which can manifest as a delay in thinking and reaction time.
4. **Dose-Dependent Effects:** Higher doses or polypharmacy can exacerbate these cognitive side effects.

While these cognitive impairments are generally reversible upon discontinuation or adjustment of the medication, they can impact a patient's quality of life and adherence to treatment. Therefore, it is important for clinicians to monitor cognitive function during antidepressant therapy and adjust treatment as needed to minimize these side effects.

12 strategies on when and how to assess cognitive impairments in depression

Assessing cognitive impairments in clinical depression is essential for a comprehensive treatment approach, as these impairments can significantly affect a patient's quality of life and treatment outcomes. Here are strategies on when and how to assess these cognitive issues:

When to Assess:

1. Initial Diagnosis: Cognitive assessment should be part of the initial evaluation to establish a baseline and identify the presence of any cognitive deficits that may need addressing.
2. During Treatment: Ongoing assessment is crucial during treatment to monitor changes in cognitive function, as some antidepressants and therapies may impact cognitive abilities differently.
3. Post-Treatment: After depressive symptoms have improved, assess cognitive function to determine if deficits persist, which may require targeted cognitive interventions.

How to Assess:

1. Clinical Interview: Start with a clinical interview to gather subjective reports of cognitive difficulties, such as problems with memory, attention, or decision-making.
2. Standardized Cognitive Tests: Use standardized tools like the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), or more specific neuropsychological tests to objectively measure cognitive domains like memory, executive function, and attention.
3. Observational Data: Collect information from family members or caregivers who may notice cognitive issues that the patient may not report.
4. Functional Assessments: Evaluate how cognitive impairments affect daily functioning, such as work performance, social interactions, and the ability to manage personal affairs.

By integrating these assessments into clinical practice, clinicians can tailor treatment plans to address mood and cognitive symptoms, improving overall outcomes for patients with depression.

13 Depression as a risk factor for dementia

Depression is increasingly recognized as a significant risk factor for dementia. Research suggests that the presence of depressive symptoms, particularly in mid to late life, may accelerate cognitive decline and increase the likelihood of developing dementia, including Alzheimer's disease. The relationship between depression and dementia is complex and may involve several overlapping mechanisms.

Chronic depression can lead to changes in the brain, such as increased inflammation, alterations in neurotransmitter systems, and hippocampal atrophy (because of increased level of cortisol due to depression led chronic stress), all of which are implicated in the pathophysiology of dementia. Additionally, depression often involves cognitive impairments,

such as difficulties in memory, executive function, and attention, which can serve as early indicators or accelerants of dementia.

Depression can also lead to lifestyle changes, such as reduced physical activity, poor diet, and social isolation, which are themselves risk factors for dementia. Furthermore, depressive symptoms like apathy and withdrawal can lead to reduced cognitive engagement, hastening cognitive decline.

14 comprehensive neuropsychiatric assessment through battery/tools

A comprehensive neuropsychiatric assessment of cognitive impairment in depressive disorders typically involves a battery of standardized tools designed to evaluate various cognitive domains. These assessments help identify the specific areas of cognitive dysfunction that may be associated with depression, such as memory, attention, executive function, and processing speed.

Some commonly used tools are:

1. PGI Battery for memory dysfunction
2. NIMHANS neuropsychological battery
3. ICMR neurocognitive tool box
4. Trail making Test
5. Stroop test
6. DSST
7. WCST
8. California verbal learning Test
9. Rey complex figure test
10. WAIS
11. Verbal fluency –Semantic and Phonemic
12. Symbol digit modalities test

Other tests not validated in India yet

- PDQ- D(20)
- Thinc- it
- CANTAB

Most have been mentioned already, we will expand them with description.

A combination of these tools is often used to gain a complete picture of a patient's cognitive functioning. By using a battery of tests, clinicians can identify specific cognitive impairments, track changes over time, and tailor interventions accordingly. The choice of tools depends on the cognitive impairment suspected through screening

CLINICAL PRACTICE GUIDELINES ON COGNITIVE IMPAIRMENT IN BIPOLAR
DISORDERS – ASSESSMENT AND MANAGEMENT

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Running Title: Cognitive Impairment in Bipolar Disorder

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CLINICAL PRACTICE GUIDELINES ON COGNITIVE IMPAIRMENT IN BIPOLAR DISORDERS – ASSESSMENT AND MANAGEMENT

1. INTRODUCTION:

Bipolar Disorder (BD) affects about 0.5% of the Indian population (1). Individuals with BD experience residual symptoms between episodes and manifest significant functional and cognitive impairments, even during remission. Patients with BD show notable cognitive impairment across all clinical states, including euthymia, even when potential confounding factors like demographic variables, medication effects, and residual depressive symptoms are controlled for (2). Neurocognitive deficits are not only a persistent aspect of the illness but are also postulated to be a fundamental primary characteristic, rather than a result of the mood state or medication (3). Significant and widespread neurocognitive deficit reportedly exists even before the first onset of mood symptoms, persists through various phases, and often deteriorates as the illness progresses (4–6). Cognitive functioning is a key predictor of occupational functioning in BD and may exert a greater influence than other clinical factors. Considering the widespread and negative psychosocial impact of cognitive dysfunction in the illness, it is crucial to utilize appropriate cognitive measures to enhance our understanding of the nature, severity, and correlates of cognitive deficits in the illness, and to develop effective therapeutic strategies to address this cognitive impairment in BD.

PROCESS OF DEVELOPMENT OF GUIDELINES

A thorough literature search was conducted using the key words/MeSH terms neurocognition, cognitive function, cognitive deficits OR executive functions Or working memory, cognitive domains AND bipolar disorder, mania, bipolar depression. The 1643 articles that were returned, were scrutinised for relevance. In addition, the Medline search returned about 63 systematic reviews and 46 meta-analysis on the search terms neurocognition and bipolar disorder. The articles were then screened for relevance on the title and abstract. The ones that were more recent were included in the review, on the understanding that they would include the previous articles. Search for Indian literature using the same search terms returned about 30 articles, most of which have been included in this guideline. Weightage was given to meta-analysis where available. The manuscript has been organised in a manner that would provide good flow for the reader, including what is the evidence available including social cognition, what assessments are possible, time taken for each assessment, what are the treatment options investigated and which of these are feasible in clinical practice. A flow chart is incorporated to highlight the same.

2. COGNITIVE DEFICITS IN BD – EVIDENCE SO FAR:

To understand cognition in BD let's try to answer a few questions that commonly arise when we talk about cognition in this group of patients

3.1 Are cognitive deficits present in BD?

Many studies have supplemented the clinical observation that not all BD patients have cognitive deficits. Three distinct cognitive subgroups have been identified in BD subjects in remission – those with intact cognition, those with selective cognitive impairment and those with global cognitive impairment (Burdick, 2014; Lima, 2019). These differences remained over a five year longitudinal course, thereby further highlighting that cognitive deficits in BD could represent a significantly heterogeneous group (Elhrich, 2022) and the cognition remained intact in the high-performance group relative to healthy subjects. Cognitive heterogeneity is now being increasingly recognised and cognitive trajectory of BD is a subject of scholastic debate and enquiry (Van Rheenan, 2020)

Despite this, there is a consensus that performance on neurocognitive tasks in nearly every major domain is disrupted during not only manic, depressed, or mixed phases of BD but the deficits persist even in euthymia. Studies have noted that in euthymic BD, domain-specific deficits have been demonstrated in attention, verbal learning memory, and executive functions (7). Attention is a complex neurocognitive domain with several subcomponents and is essential to all higher cognitive functions. Sustained attention is impaired in BD in all phases of the illness and these impairments do not remit completely during euthymia. Selective attention deficits present in the acute episodes also persist during euthymia (8). Verbal immediate and delayed recall is also impaired in remitted BD. Executive function deficits are the most consistent neurocognitive deficit reported in euthymic BD, in different aspects of executive function like planning, set-shifting, cognitive control, and verbal fluency (8–10). In summary multiple investigations have consistently provided evidence of neurocognitive deficits in individuals with bipolar disorder (BD) across all clinical stages, including euthymia. These impairments have been found to have moderate to high effect sizes. Deficits in verbal memory and certain aspects of executive functioning seem to be more pronounced compared to other cognitive domains. The findings of various studies are summarised below (Table 1).

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Table 1: Summary of Studies on Cognitive deficits in BD

Study	Groups Compared & Markers studied	Number of Subjects	Results of Group Comparisons	Correlation with illness related variables
Robinson et al, 2006	• Metaanalysis – 26 studies • BD Vs HC ✓ Executive measures ✓ Verbal learning and memory ✓ Attention and psychomotor speed	BD euthymic = 689 HC = 721	• BD poor performance on all measures	-----
Torres et al, 2007	• Metaanalysis – 39 studies • BD Vs HC ✓ Premorbid intellect ✓ Attention/processing speed ✓ Memory Learning ✓ Executive/working memory	BD euthymic = 948 HC = 1128	• BD group performed poorly on all measures	-----
Kurtz et al, 2009	• Metaanalysis – 60 studies • BD euthymia • BD Mania/Mixed • BD Depression • HC ✓ Attention ✓ Working Memory ✓ Verbal Memory ✓ Non-verbal Memory ✓ Visuospatial Function ✓ Language ✓ Psychomotor Speed ✓ Executive Function	BD euthymia = 42 studies, 1197 patients BD Mania/Mixed = 13 studies, 314 patients BD Depression = 5 studies, 96 patients	Euthymia Vs HC 1. Attention 2. Working memory 3. Verbal memory 4. Non-verbal memory 5. Visuospatial-block design 6. Language 7. Psychomotor speed 8. Executive function Mania/Mixed Vs HC 1. Attention 2. Verbal memory 3. Language 4. Executive functions Depression Vs HC 1. Attention 2. Verbal memory 3. Language 4. Executive functions	-----
Bourne et	• Metaanalysis	BD euthymic	• BD group performed	• Neither lithium or

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al, 2013	• BD Vs HC • Re-analysis of 31 primary data sets as a single large sample (N=2876) • 11 measures from 4 common tests: CVLT, TMT, Digit Span and WCST	=1276 HC = 1609	poorly on all measures	antidepressants affected performance on any of the measures • Antipsychotics and no. of manic episodes showed decreased performance on verbal learning • No. of depressive hospitalizations affected TMTA • Total no. of hospitalisations affected TMTA, TMTB, WSCT.
Daglas et al, 2015	• Systematic review (7 studies) • FEM acute and remission phases • Intelligence, Processing speed, Attention, Memory, executive functions, Verbal fluency, visuospatial orientation	3 studies with FEM 4 studies of FEM in remission BD FEM=230 HC= 345	• FEM acute Vs HC Executive functions: differences • FEM remission Vs HC Attention, Memory, Response inhibition, Spatial planning, verbal working memory and Spatial working memory was poorer for the remission group	• Patients on lithium treatment performed poorer on memory tasks • Patients in remission taking lithium performed significantly better in spatial reasoning/orientation and executive functioning tasks than those on divalproex • One study reported that increased daily dosage of antipsychotic medication correlated with a slower performance

3.2 At what stages are cognitive deficits noted?

At what stage in the course of the illness do cognitive deficits occur, does illness progression has an impact on the progression of the cognitive deficits and what is the potential for intervention at each stage, are some questions that are of clinical relevance. Some studies (individual and reviews/meta-analyses) have evaluated cognitive deficits in the different stages of BD and the correlation between illness progression and the progression of cognitive deficits. The individual studies are mostly cross-sectional though longitudinal studies would be more

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informative. Most of these studies have reported that cognitive deficits are present from the very early stages i.e. even in the first-degree unaffected family members also, and these are more pronounced after the onset of the first episode. A recent study by Reddy et al, 2023 done at NIMHANS also showed similar results(11). A study done at NIMHANS(12) that evaluated cognition across stages of BD also noted that those with a higher number of episodes, especially more than three manic episodes show higher deficits than those with one or two episodes. Some of these studies are summarised below.

Table 2: Summary of studies on cognitive deficits across stages of BD

Study	Groups Compared & Markers studied	Number of Subjects	Results of Group Comparisons	Correlation with illness related variables
Manteiga et al, 2018	• Cross-sectional study • Four stages of BD • Evaluated staging, neurocognition and social functioning	• Euthymic type I BD patients in the early (n = 25) • Late (n = 23) stages • Healthy siblings (latent stage; n = 23) • HC (n = 21)	• Early-Stage Patients vs. Controls: early-stage patients showed a deficits • Early-Stage Patients vs. Siblings: early-stage patients had significantly worse performance • Late-Stage Patients vs. Controls: late-stage patients had a deficit • Late-Stage Patients vs. Siblings: late-stage patients had significantly worse performance • Early-Stage vs. Late-Stage Patients: No significant differences between both groups of patients were detected in any of the neurocognitive variables	• Social functioning: Late-stage patients had a worse performance than early-stage patients, both clinical groups had a worse performance than healthy siblings and controls. And siblings' functioning was comparable to that of controls

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Torres et al, 2020	- Longitudinal study 3 time points (Baseline, one year, 3 years) - Newly diagnosed BD Vs HC	- BD = 91 - HC = 61	- At baseline, patients showed significantly lower performance across all domain scores and effect sizes moderate to large range. - Only significant trajectory difference between groups was observed for processing speed significant difference between patients and controls at baseline but not at 1-year or 3 years	- Lower executive functioning in patients with substance abuse relative to those without substance abuse at 1-year but not at baseline or 3-years - Illness duration by time interaction was not noted for any of the cognitive domain scores - Change in cognition was not significantly associated with the number of manic, depressive, or total mood episode recurrences nor with change in mood symptom ratings - Patients who discontinued antipsychotics from baseline to 3 years showed more improvement in verbal memory than those who had no change in antipsychotics or those who had an antipsychotic added
Achalia et al, 2020	- Cross-sectional study - BD FEM - BD Multiepisod HC a) Continuous performance test-identical pairs (CPT) to measure sustained attention (b) Stroop test measuring response	- BD FEM= 13 - BD multiepisod e= 17 - HC= 30	- BD as a group had significant impairment in all three cognitive tests compared to HC - There was no significant difference between first episode mania and BD with multiple episodes on any cognitive measure	- Positive correlation between YMRS score and WCST-nonperseverative error - No significant correlation between other clinical variables, namely HDRS score, Simpson Angus scale score, age at onset of

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	inhibition and (c) Wisconsin Card Sorting Test (WCST) to measure set shifting			illness, duration of illness or antipsychotic dose measured using chlorpromazine equivalent
Chandrasekaran et al, 2020	• Cross-sectional study • Unaffected siblings of BD patients • HC • Addenbrooke's Cognitive Examination III Revised (ACE-III R) • Trail Making Test (TMT) A & B • SOFAS	• Unaffected siblings =60 • HC =60	• The siblings had underperformed significantly low scores in memory tasks of ACE-III R Cognitive domains of memory and the total score in ACE-III R were positively correlated with better functioning • TMT-A correlating negatively with psychosocial functioning	• Psychosocial functioning as dependent variables was significant for predicting attention score on ACE-III R
Miskowiak et al, 2022	• Systematic review • BD euthymic • HR	• Total number of studies =19 • BD euthymic = 36–76, studies 12 • HR = 84–234, studies 7	• (Hypo) manic episodes relapse were predicted by general cognitive impairments and by verbal learning and memory impairments • Depression relapse results are conflicting • HR group showed mixed results, fMRI based studies differential neural response in the insula, ACC and thalamus during executive functions and emotional processing in the high-risk individuals with subsequent onset of illness compared to the groups that remained well.	-----

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Reddy et al, 2023	• Cross-sectional study • FEM, HR and HC	• Each group n=25	• Compared to the HC group, the FEM group performed poorly on multiple cognitive domains • The performance of the HR group was comparable to the FEM group, but they showed significantly poorer performance compared to HC on verbal fluency and visual learning, and memory	-----
Reddy et al (Unpublished data)	• Cross-sectional Study • Multiple Episode BD, FEM, HR and HC	• Each group n=42	• The ME group with higher number of manic episodes higher cognitive deficits compared to FEM in processing speed, set shifting, verbal and visual memory • In terms of the cognitive test raw scores, the processing speed domain showed a pattern of deficits (ME>FEM>HR>HC) • The FEM group lies in between the ME and HR groups in verbal learning memory and visual memory HR were similar to controls. • The HR group was comparable with the FEM and they lie between the ME and control group in set-shifting and visual memory	• Total duration of illness correlated: processing speed, set shifting, response inhibition, verbal and visual memory • Total no. of Manic episodes correlated: processing speed, set shifting scores, verbal memory • Total no of depressive episodes correlated: response inhibition, visual memory

3.3 Are there distinct cognitive subgroups of BD?

Some of the studies have attempted to investigate this question. Bora (2018) examined the impact of a history of psychotic characteristics and full manic episodes on neurocognitive performance. The results showed that those with a history of psychotic symptoms and individuals with a history of full manic episodes, i.e. BD-I, had slightly more severe cognitive deficits. BD-I significantly underperformed BD-II in global cognition, verbal memory, and processing speed. Psychotic BD was associated with significantly impaired cognition in global cognition verbal memory processing speed, EF-speed, EF-accuracy, working memory and Social cognition (13). Studies have also attempted to see the difference between BD I and BD II and they reported similar cognitive profiles. A recent systematic review reported similar cognitive profiles in BD I and BD II (14).

Lima et al in 2019 did a hierarchical cluster analysis to investigate the presence of discrete neurocognitive subgroups, using a neurocognitive battery as the basis for classification. The Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) and Functioning Assessment Short Test (FAST) were employed to evaluate self-reported cognitive challenges and the extent of functional impairment. The study identified three separate subgroups: the first grouping consisted of individuals with normal cognitive function (43.5%), the second subgroup consisted of individuals with specific cognitive impairments (33.3%), and the third category consisted of individuals with overall cognitive impairments (23.3%). The intact group had significantly greater levels of schooling and higher estimated IQ compared to both the generally and selectively affected groupings. In addition, they were diagnosed with bipolar disorder at an earlier age and experienced their first hospitalisation at a younger age compared to persons with overall cognitive impairment. Evidence supports the presence of a spectrum of severity ranging from patients without any impairment to those with significant cognitive dysfunction. Patients in the intact group exhibit a greater level of cognitive reserve compared to the other two groups. Nevertheless, they also encountered cognitive grievances and a certain level of functional debilitation(15). These findings indicate that it is crucial to utilise a combination of tools, such as objective and subjective cognitive measures along with functioning instruments, in order to fully evaluate patients with BD. The above studies suggest that we definitely need a better understanding of the determinants of cognitive deficits in BD patients. Let's discuss these determinants in further detail.

DETERMINANTS OF COGNITIVE DEFICITS IN BD

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Determinants	Evidence
Single vs multiple episodes	As mentioned earlier in this chapter early stage BD and late stage BD performed equally and both had deficits compared to healthy subjects. In one longitudinal study with three years follow up only the processing speed domain showed a trajectory of decline over the years (16). The rest of the deficits remained stable with the progressive course. Similarly, a PhD study done in NIMHANS (12) also noted a difference between first-episode mania and multiple-episode BD in the processing speed domain, especially after the third manic episode.
Manic vs depressive episodes	Individuals in the early stages of bipolar disorder reportedly experience deficits in all cognitive domains, depressive episodes do not impose any additional burden on cognitive performance, unlike mania (17). Nevertheless, those with lower verbal memory indicates a higher likelihood of experiencing a depressive relapse in the early stages of the illness. The residual depressive symptoms and number of manic episodes seem to have a negative impact on cognition especially in the attention and verbal learning and memory domains (18).
Predominant polarity	As discussed above the existing literature highlights that cognitive deficits are probably mania-driven. This finding is of utmost importance to the Indian subcontinent because most of our studies have reported a mania-predominant course in our population compared to the depression-predominant course in the West (19).
Medications – valproate, lithium, second generation antipsychotics	Lithium: Early in the course of BD, treatment with valproate, rather than lithium, may lead to working memory problems (20). A large meta-analysis of cognitive studies in BD reported that lithium-treated patients are more likely to present with learning and encoding difficulties and poor cognitive flexibility when compared with unmedicated patients. Follow up studies did not find any notable deficits with lithium treatment for 4 or 6 years.

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	Valproate and anticonvulsants: anticonvulsants generally lead to psychomotor retardation and memory and attentional decline. Valproate, rather than lithium, may lead to working memory problems. 6-month follow-up study found that lamotrigine treated BD patients obtained better scores on phonemic verbal fluency and, to a lesser extent, verbal memory tasks Antipsychotics: The inclusion of risperidone alongside a mood stabilizer adversely affects executive function and verbal learning, a finding that is not observed with quetiapine (21). Olanzapine and quetiapine treated patients perform better than risperidone treated patients.
Obesity	Early in the course of BD, overweight-obesity does not have a detrimental impact on cognitive performance. Considering the available research that suggests obesity can have a detrimental effect on the progression of illness, it is possible to intervene and address obesity at an early stage of BD (22).
Psychotic symptoms	Executive functioning and cognitive flexibility in particular appeared to be a deficit area in BD with psychotic symptoms. Studies suggest that there may be slight cognitive variations between BD patients with or without psychotic symptoms as well as between patients with mood-incongruent and mood-congruent psychotic symptoms, immediately after the onset. Therefore, it may be worthwhile to investigate early intensive techniques to maintain cognitive function in these specific groups of patients (23).
Gender differences	Research examining sex differences has found notable effects on tasks involving spatial working memory and sustained attention, with males outperforming females in healthy individuals. Patients with early BD, who have recovered from a first episode of mania,

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	continue to exhibit healthy cognitive sex differences (24).
Childhood Trauma	A study by Hsueh et al. 2024 explored the impact of childhood trauma on cognition in BD patients using cluster analysis. The cluster characterized by neglect had significant instances of both physical and emotional neglect, accounting for 41.8% of the cases. Patients with bipolar disorder (BD) in this particular group had poorer performance in the Brief Assessment of Cognition in Affective Disorders (BAC-A) when compared to patients in the cluster with multiple trauma. This difference was particularly evident in tasks related to working memory and processing speed. The group that was focused on neglect had a noteworthy adverse impact on the composite score as well as working memory (25).
Thyroid functions	Assess for thyroid function
Vitamin deficiencies	assess

3. ASSESSMENT OF COGNITIVE FUNCTIONS:

The assessment of cognitive deficits can be outlined in two steps:

- a. Screening for cognitive deficits
- b. Evaluation of cognitive deficits

Like Schizophrenia, where researchers have developed cognitive batteries like the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), researchers working on cognition in BD have developed screening tools that can identify cognitive deficits in BD.

Before we screen the patient for cognitive deficits, assessment of the baseline IQ is very important. Screen patients when they are in remission (currently euthymic).

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Clinicians can use the Wechsler Abbreviated Scale of Intelligence® - Second Edition (WASI®-II) to assess the IQ. The WASI is intended to provide estimates of Verbal and Performance intelligence consistent with previous Wechsler tests in addition to measuring general, or Full Scale, intelligence(26). The screening tools that have been validated for use in BD have been listed below (Table 3)

Table 3: Screening Tools for Cognitive Deficits in Bipolar Disorder

Name of the screening tool (author & year)	Brief description
Cognitive Complaints in Bipolar Disorder Rating Scale - COBRA (Jensen et al. 2015)(27)	16-item self-report tool/ Validated for use in India measures subjective cognitive difficulties, encompassing areas such as executive function, processing speed, working memory, verbal learning and memory, attention and concentration, and mental tracking Time 10 mins
Screen for Cognitive Impairment in Psychiatry - SCIP (Schmid et al. 2021) (28)	Paper and pencil screening tool identifies cognitive deficits in psychiatric populations using tests for immediate and delayed verbal learning, a working memory test, a Verbal Fluency Test, and a processing speed test Time 15 mins
THINC- Integrated Tool- THINC-IT (McIntyre et al. 2017) (29)	web-based, patient-administered cognitive screening tool Uses gamified cognitive tasks to engage patients in completing the tests. It measures both subjective and objective cognition by employing four objective tests (attention & executive functions, working memory, and processing speed) and one self-report questionnaire (PDQ-5-D) measuring attention and concentration, prospective memory, retrospective memory, planning, and organization. 15 mins
Internet Based Cognitive Assessment – ICAT (Hafiz et al. 2019) (30)	modified web-based version of the SCIP includes five subtests that assess four cognitive domains: verbal learning, working memory, delayed verbal learning, and psychomotor speed (35 min)

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Among the computer based tests, THINC-IT takes less time (15 minutes) when compared to ICAT (35min) but THINC-IT is validated only for bipolar depression and has poor psychometric quality, so ICAT is a better screening instrument.

Among the paper pencil screening tests, COBRA takes 10 minutes and is a self-report based test, whereas SCIP takes 15 minutes is a clinician assessed, performance based tool.

The International Society of Bipolar Disorder (ISBD) formulated a task force to develop a consensus statement about the neurocognitive deficits in BD. This team reviewed various available cognitive batteries and the individual domain tests for their utility in BD (31). ISBD Battery for Assessment of Neurocognition (ISBD-BANC) outlines the cognitive domains and neuropsychological tests relevant to BD. The NIMHANS neuropsychological battery which is validated for use in the Indian population has tests that can be used to assess the same cognitive domains (Table 4).

Table 4: Proposed Cognitive Battery for Bipolar Disorder

Cognitive Domain	Neuropsychological test (Tests from MATRICS Consensus Cognitive Battery MCCB subtests)	Indian Adaptation (Tests from NIMHANS Neuropsychological Battery) Permissions/Purchase
Speed of processing	Brief Assessment of Cognition in Schizophrenia (BACS): Symbol Coding	Digit symbol substitution test (DSST)
	Category Fluency: Animal Naming	Controlled oral word association test (COWA)
Attention/Vigilance	Trail Making Test–part A	Color trails test (CT) 1
	Continuous Performance Test–Identical Pairs (CPT-IP)	Digit Vigilance test
Working Memory	Wechsler Memory Scale–3 Letter-Number Sequencing	N- Back-test

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	Wechsler Memory Scale–3 Spatial Span	Spatial Span
Verbal learning/memory	Hopkins Verbal Learning Test-Revised	Rey’s auditory verbal learning test (AVLT)
	California Verbal Learning Test	
Visual learning	Brief Visuospatial Memory Test-Revised	Complex figure test (CFT)
Executive functions		
Response Inhibition	Trail Making Test–part B	Color trails (CT) 2
Set Shifting	Stroop test	Stroop test

Adapted from The International Society for Bipolar Disorders–Battery for Assessment of Neurocognition (ISBD-BANC), Yatham, et al; 2010

Out of the other cognitive batteries that could be relevant in BD but warrant further studies include:

1. Hayling Sentence Completion Test (HSCT) for testing Inhibitory control,
2. Cambridge Neuropsychological Test Automated Battery intra-dimensional / extra-dimensional (CANTAB-IDED) set-shifting task,
3. Tower of London (and variants) for planning, inhibition, working memory
4. Balloon Analogue Risk Task (BART) for Decision-making/risk-taking and
5. Theory of Mind Advanced Test for Theory of Mind.

Keefe et al group also working on cognition in BD adopted the Brief Assessment of Cognition in Schizophrenia (BAC-S) scale for assessing cognition in BD and called it Brief Assessment of Cognition in Affective Disorders (BAC-A). This battery has been studied extensively and validated for assessing cognition in BD patients (32). The tests included in the BAC-A battery are as mentioned in the below table (Table 5).

Table 5: BAC –A Subtests

Cognitive Domain	Neuropsychological tests
Affective Learning and Memory	Affective Interference test (Affective Auditory Verbal learning test)
Emotional Inhibition	Emotional Stroop
Verbal Learning/Memory	Rey’s auditory verbal learning test (AVLT)
Working memory	Digit sequencing task

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Motor Speed	Token Motor Task
Verbal Fluency/Category Fluency	Controlled oral word association test (COWA)/Animal Naming
Executive functions (Planning)	Tower of London test
Attention and Motor Speed	Digit Symbol Substitution test

Recommendation: If cognitive impairment is suspected during clinical evaluation, initially screen and/or monitor the patient's cognitive performance using one of four instruments (THINC-it, ICAT, COBRA, and SCIP). If deficits are identified then we can proceed to the next level of assessment, choosing between BAC-A and ISBD-BANC (Figure 1).

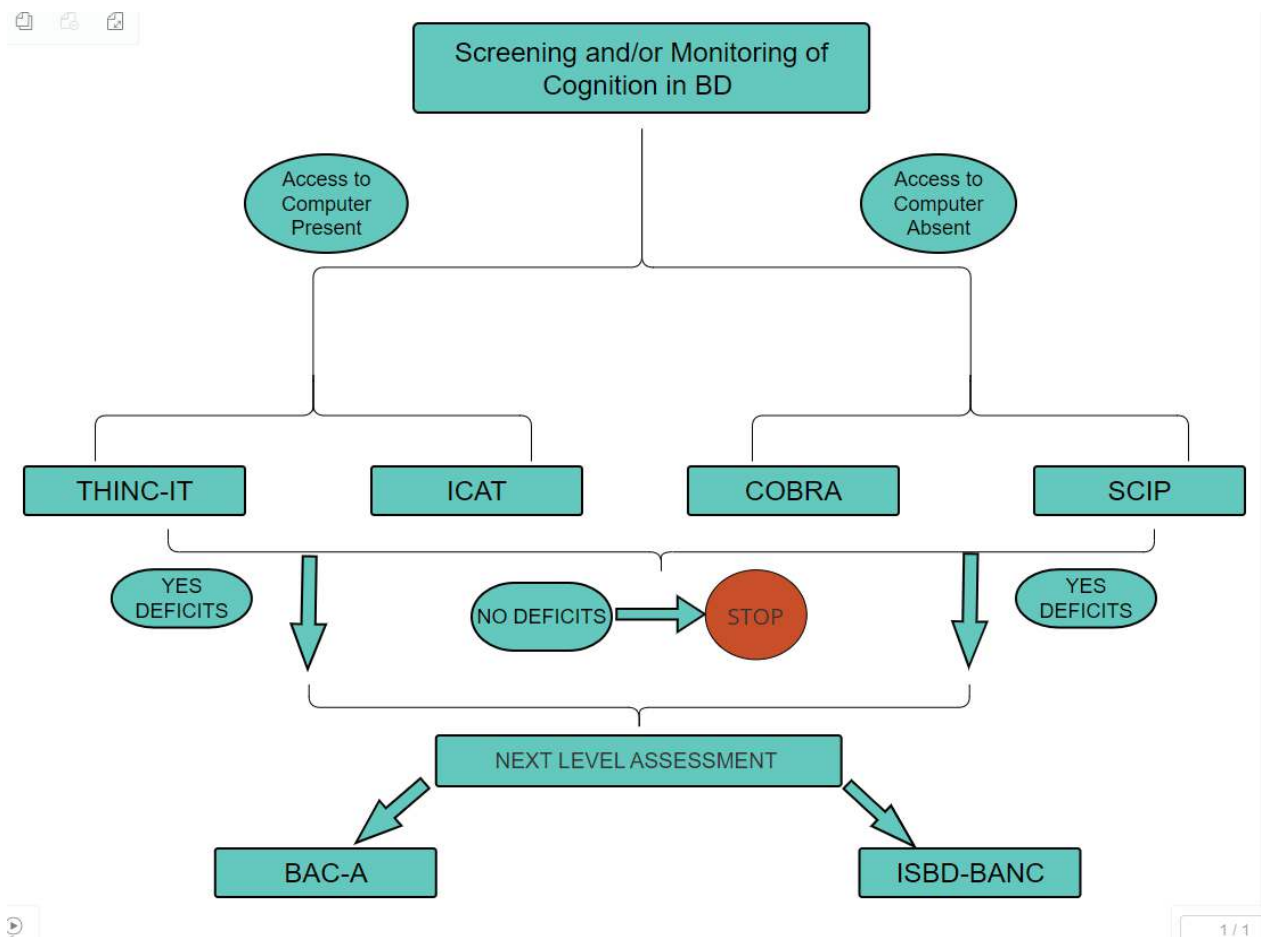


Figure 1: Algorithm for the type of tests to be used for screening and assessing cognitive deficits in BD

BAC-A takes 45 minutes, clinician assessed, performance based tests and ISBD-BANC takes around 90 minutes, clinician assessed, performance based tests. Since BAC-A

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assesses a component of affective memory and emotional inhibition, also takes lesser time, it might be more feasible in clinical settings.

SOCIAL COGNITION IN BIPOLAR DISORDER

Social cognition (SC) is a discipline that seeks to understand how brain function facilitates the cognitive processes that underlie social behavior. It encompasses a range of intricate processes that enable us to engage in adaptive social interactions. These processes include representing internal bodily states, self and other knowledge, interpersonal motivations, and the ability to respond appropriately to socioemotional information (33). The National Institute of Mental Health (NIMH) has categorized five fundamental areas within this concept: Theory of Mind (ToM), Social Perception, Social Knowledge, Attribution Bias, and Emotion Processing (EP) (34). The concept of theory of mind refers to the ability to understand and attribute mental states, such as beliefs, desires, and intentions, to oneself and others. Mentalizing talents also referred to as the capacity for understanding and attributing meaning to mental processes in oneself and others. Attributional bias refers to the inclination to attribute the reason for occurrences to oneself, others, or the situation to understand social events and interactions. Emotional processing refers to the cognitive and psychological mechanisms involved in understanding and managing emotions. Emotional intelligence is the capacity to accurately observe and interpret facial expressions that convey emotions, as well as effectively utilise and regulate one's own emotions. Social perception refers to the process by which individuals interpret and understand the behavior, intentions, and characteristics of others in social situations. Social competence refers to the capacity to recognize, assess, and effectively utilize social cues to make accurate assessments about social roles, norms, connections, and the circumstances of others. Social knowledge, also known as social schema, is the understanding of the rules, objectives, and roles that define social circumstances and facilitate social interactions.

Patients with euthymic BD experience a decline in Theory of Mind (ToM) function, particularly in verbal ToM. Regarding Theory of Mind (ToM) abilities in individuals with Bipolar Disorder (BD), there is a widespread observation of impairment during the acute periods of the illness (35,36). However, the evidence of abnormalities in remission samples has been less compelling. The study of sociocognitive impairment in euthymic states is highly

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significant since these deficiencies can significantly hinder social reintegration and rehabilitation (37). Considering the significance and influence of Theory of Mind (ToM) performance on various aspects of life such as quality of life, social perception, and social behaviour, it is crucial to conduct additional research on the psychological and neurobiological mechanisms behind these impairments. This research is necessary to identify specific areas to focus on in the development of personalised Social Cognition (SC) training for this particular population. A study conducted by Choudary et al in 2021(38) indicates that individuals with BD (Bipolar Disorder) exhibit the lowest performance, while the HC (healthy controls) demonstrate the highest performance on the majority of SC (social cognition) tasks. Siblings, on the other hand, fall in between the patients and HC in terms of performance on all SC subtests, except for the faux pas composite index and externalizing bias, where siblings performed worse than the patient group. Within the several areas of social cognition (SC), the faux pas index, which reflects deficiencies in Theory of Mind (ToM), could potentially be explored as a potential endophenotype for Bipolar Disorder (BD). Nevertheless, it is necessary to reproduce these findings using a larger sample size, conduct normality tests for task performances, and evaluate biomarkers to confidently draw conclusions from these findings. In the overall population of patients with BD, there is no association between SC and demographic and clinical factors. Nevertheless, SC exhibits a notable correlation with neurocognition in both patients and siblings of patients with BD.

4. MANAGEMENT OF COGNITIVE DEFICITS IN BD

Cognitive dysfunction has been linked to psychosocial dysfunction and reduced quality of life in individuals with BD. Secondary expenses associated with BD (such as unemployment and reduced workplace efficiency) present a significantly larger economic burden. There is a pressing need for pro-cognitive treatment to enhance the functioning and quality of life in individuals with cognitive impairment in BD (39). Below we present the evidence from various trials that have looked at pharmacological and non-pharmacological interventions (Tables 6 & 7 respectively)

Table 6: Summary of pharmacological interventions study details and results

Study and year	Pharmacological Intervention and the doses	Design	Treatment groups	Significant Results
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Toniolo et al. 2017	Creatine Monohydrate 6 g/day	Sub-analysis of a randomized, double-blind, placebo- controlled trial; 6 w treatment, no follow-up	Creatine monohydrate (9) vs placebo (9)	Significant improvement in verbal fluency
Miskowiak et al. 2014	Erythropoietin 40,000 IU Infusions weekly	Double-blind, randomized, placebo- controlled trial; 8 w treatment, 14 w follow-up	EPO (23) vs Placebo (20)	Significant improvement in tests for verbal memory, sustained attention, attention, executive function, and social cognition
Ghaemi et al. 2009	Galantamine 8-24 mg/day	Double-blind, randomized, placebo- controlled trial; 12 w treatment, no follow-up	Galantamine (6) vs Placebo (10)	Placebo was superior to treatment in a single measure of verbal fluency
McIntyre et al. 2012	Intranasal insulin 40 IU q.i.d.	Double-blind, randomized, placebo- controlled trial; 8 w treatment, no follow-up	Insulin (34) vs Placebo (28)	Significant improvement in one test of executive function (trail making B)
Yatham et al.2017	Lurasidone 20–80 mg/ day	Open-label randomized controlled pilot trial; 6 w treatment, no follow-up	Lurasidone (17) vs TAU (17)	Improvement in global cognitive function and one measure of working memory (letter number sequencing)
Alda et al.2017	Methylene blue 195 mg	Double-blind crossover study; 3 months treatment, 1 week washout	n = 37 Therapeutic dose methylene blue vs subtherapeutic dose methylene blue crossover	No significant changes in cognitive function
Young et al.2004	Mifepristone 600 mg/day	Double-blind crossover trial 1 w treatment 2 w washout	n = 20 Mifepristone vs Placebo crossover	Significant Improvement in visuo-spatial learning, spatial working memory, and executive function.

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Watson et al. 2012		Double-blind, randomized, placebo-controlled trial; 1 w treatment, 7 w follow-up	Mifepristone (30) vs Placebo (30)	Significant improvement in spatial working memory
Dean et al. 2011	N-acetyl cysteine 2000 mg/day	Sub-analysis of a double-blind, randomized, placebo-controlled trial; 6 m treatment, no follow-up	NAC (16) vs placebo (13)	No significant changes in cognitive function
Burdick et al. 2004	Pramipexole	Double-blind, placebo-controlled trial; 8 w treatment, no follow-up	Pramipexole (24) vs placebo (26)	No significant between-group differences in cognition were reported
KauerSant'Anna et al. 2019	Tianeptine 12.5–37.5 mg/day	Double-blind placebo-controlled maintenance trial; 8 w open-label phase, 24 w RCT	Tianeptine (36) vs placebo (33)	Significant improvement in one test of working memory (letter number sequencing)
Chengappa et al. 2013	Withania Somnifera 500 mg/day	Double-blind, randomized, placebo-controlled trial; 8 w treatment, no follow-up	WSE (30) vs Placebo (30)	Significant improvement in social cognition and two tests of attention.

Table 7: Summary Psychosocial and other Biological Interventions study details and results

Study and Year	Intervention	Design	Treatment groups	Significant Results
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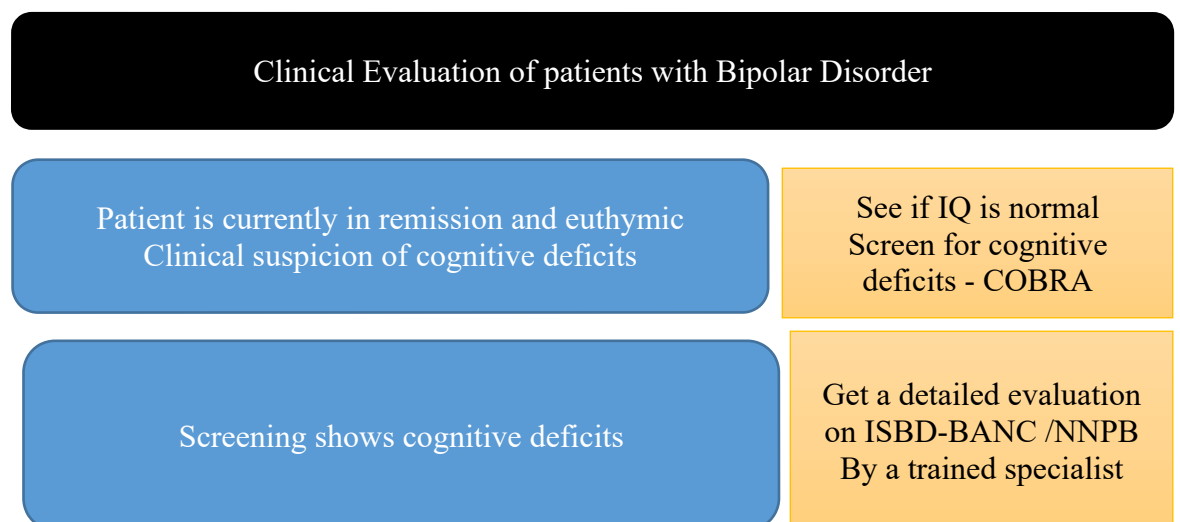
Torrent et al.2013	Functional remediation and psychoeducation	Randomized, rater blind, controlled trial 21 w treatment No follow-up	Functional remediation (77) vs psychoeducation (82) vs TAU (80)	No significant changes in cognitive function in both the functional remediation and psychoeducation groups
Demant et al.2015	Cognitive remediation	Randomized, rater blind, controlled trial 12 w treatment 26 w follow-up	CR (23) vs TAU (23)	Significant improvement in subjective cognitive abilities, but in no objective cognitive assessments.
Lewandowski et al.2017		Randomized, rater blind, controlled trial; 24 w treatment, 6 m follow-up	CR (39) vs active control (36)	Improvement in verbal learning and a composite cognitive score
Gomes et al.2019	Cognitive behavioural rehabilitation	Randomized, rater blind, placebo controlled trial 12 w treatment 24 w follow-up	CBR (31) vs TAU (29)	Significant improvement in reaction time and emotion recognition.
Myczkowski et al.2018	rTMS	Randomized, double-blind, sham controlled trial; 4 w treatment, 4 w follow-up	Active rTMS (20) vs sham (23)	Significant improvement in the language domain
Lin-Lin et al.2019		Single-blinded randomized sham controlled trial; 10 d treatment, 2 w follow-up	Active rTMS (25) vs sham (27)	Significant improvement in visual learning and processing speed.
Bersani et al.2017	tDCS	Double blind controlled trial; 3 w treatment, no follow-up	tCDS (21) vs sham tDCS (21)	Significant improvement in executive function and visuospatial memory.

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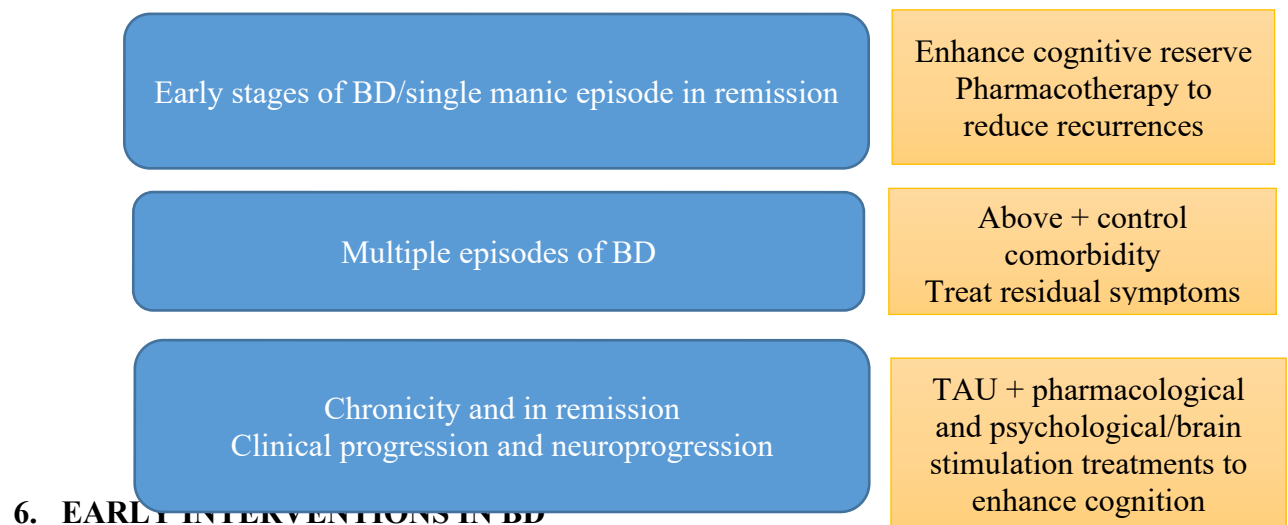
To summarize the above findings at present, no intervention has shown strong, separate, and beneficial effects on cognitive function in adults with BD, as indicated by findings from randomized, double-blind, placebo-controlled investigations. It is recommended to consider methodological concerns such as enriching the study population with persons who have pre-treatment cognitive impairment, and include those who are in remission. The field must also determine a cognitive measure that is thorough, with a little impact from repeated practice, and is capable of detecting changes as a dependent measure. Since we do not have any agent or therapy that can improve or reverse cognitive deficits in BD it becomes important that we focus on intervening before these deficits set in, i.e. the prevention of cognitive impairment. This can be done first by identifying the mediators of the cognitive impairments and second by intervening early.

The mediators of cognitive deficits of BD are educational attainment and premorbid intelligence quotient (proxy variables of cognitive reserve), clinical symptomatology (remission vs acute episode), subclinical depressive symptoms, psychotic symptoms, bipolar diagnostic subtype, psychiatric or medical comorbidity, illness duration (chronicity), number of episodes, pharmacological treatment, childhood adversity. The potential prevention strategies would be to prevent multiple episodes with effective pharmacotherapy and the implementation of psychoeducation programs, avoid concomitant medications that interfere with cognitive function, treat subclinical depressive symptoms, control comorbidity (mental and psychiatric), promote healthy habits, aerobic physical exercise. Implement cognitive or functional remediation, prescribe adjunctive pro-cognitive treatment, and use noninvasive brain stimulation techniques (TMS, tDCS) wherever indicated, early in the course of the illness i.e. after the first episode (40).

5. APPLICATION IN CLINICAL PRACTICE



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6. EARLY INTERVENTIONS IN BD

The early interventions can again be divided into two, one in the people who have developed the illness and are in the early course and second in those who are at high risk of developing BD. In BD patients in the early course of illness, the ISBD task force has given certain recommendations after a detailed systematic review. They recommend that the combination of psychological and pharmaceutical interventions may provide synergistic effects, although the most effective interventions or combinations for this specific group in the early stages are yet uncertain. They also suggest considering the potential benefits of lithium in reducing relapses in the early stages of illness, along with the data supporting the use of both medication and psychoeducation, it is important to assess the effectiveness of combining lithium and psychoeducation therapies in the early stages of illness. Based on the available evidence supporting the use of both medication and psychological treatments, individuals in the early stages of bipolar disorder should be provided with the opportunity to receive safe and effective interventions (41).

Another systematic review that evaluated the efficacy of early intervention in high-risk individuals (with an affected FDR) concluded that existing studies provide limited data regarding the conversion to bipolar disorder, which is the primary outcome measure in early intervention research. Conducting multicentre, prospective randomized studies with large sample numbers, confirmed familial risk and a homogeneous group of participants would provide valuable insights into the impact of a single intervention. Several therapies with documented efficacy in treating mood episodes, such as cognitive behavioral therapy, atypical antipsychotics, and moderate physical exercise, should be considered for implementation in this particular population. It is important to carefully assess the ethical implications of

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providing antipsychotics to a high-risk group. Early intervention in the initial phases of a problem can help avoid the long-term impact of the disease and yield significant advantages in terms of both human well-being and economic considerations and will greatly contribute to the prevention onset of BD (42).

7. SUMMARY AND CONCLUSION

Many individuals with BD exhibit measurable cognitive impairment in all clinical phases, including euthymia, even after accounting for potential confounding factors such as demographic characteristics, drug effects, and residual depressed symptoms. This cognitive impairment affects all domains, although it is especially pronounced in verbal memory and executive functioning. Several studies provide evidence suggesting that lithium treatment has a slight detrimental effect on cognitive performance in a certain subset of people with bipolar disorder who do not respond well to the medication. Valproate is linked to poorer cognitive function in comparison to other drugs used to stabilize mood, although the effect of second-generation antipsychotics on cognition is still uncertain. Existing research indicates that, in contrast to individuals with schizophrenia, the majority of people with BD exhibit cognitive abilities that are average or higher than normal prior to the onset of the disorder. Nevertheless, a portion of individuals with BD has below-average premorbid intellectual ability, suggesting that early neurodevelopmental issues may contribute to the development of BD in this specific group of patients. The available prospective studies do not provide evidence to support the notion of gradual cognitive loss in BD after the initial episode. In contrast, certain research indicates that patients may observe enhancements in cognitive performance through suitable treatment following the initial manic episode. Cognitive functioning plays a crucial role in predicting how well people with BD can do their everyday activities and work. Initial results from limited studies have indicated the potential cognitive-enhancing effects of behavioural interventions (Cognitive Remediation), as well as pharmacological interventions (erythropoietin, intranasal insulin, lurasidone, and mifepristone), and neurostimulation interventions (rTMS and tDCS).

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Conducting longitudinal studies on the neurocognitive functioning of individuals at high risk of BD can enhance our understanding of how neurocognitive impairment develops and progresses in BD. This knowledge can then be used to develop specific early intervention strategies that aim to prevent or slow down and potentially reverse cognitive decline. Furthermore, it is crucial to acknowledge the significant influence that cognitive abilities have on the overall functioning of individuals with BD. Therefore, future efficacy trials should also prioritise investigating the possible positive and negative effects of therapies on cognitive performance and functional outcomes.

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Clinical Practice Guidelines for Assessment and Management of Cognitive Impairment in Schizophrenia

Introduction

Schizophrenia is a heterogeneous disorder that usually has an onset in the second decade of life and often runs a chronic course. Traditionally, schizophrenia is characterized by positive (in the form of delusions and hallucinations) and negative symptoms. However, over the years, the understanding of the range of symptoms of schizophrenia has improved. It is now understood that a person with schizophrenia may present with positive symptoms, negative symptoms, disorganized speech, disorganized behavior, catatonic symptoms, depressive symptoms, manic symptoms, and cognitive symptoms. Among all these symptoms, cognitive impairment, although it has been reported to be associated with marked disability, has not been formally included in the current nosology despite initial consideration (ICD-11; DSM-5). The non-inclusion of cognitive impairment in the nosology was attributed to these being non-specific with an overlap of cognitive impairment in patients with bipolar disorder, due to which these not being of diagnostic value¹⁻³.

In the contemporary literature, cognitive disturbances are considered to be the central feature of schizophrenia, which is seen in more than 80% of the patients, and is considered to be the main contributor to functional disability, indirect cost, unemployment, and inability to live independently^{4,5}. There is a consensus that cognitive impairments in schizophrenia are often present before the emergence of psychotic symptoms, are present during the acute psychotic episode, and also persist even after remission of the psychotic⁴.

Considering the importance of cognitive impairment in schizophrenia, it is important to have a clear understanding about its assessment and management. Accordingly, this guideline attempts to discuss the extent of cognitive impairment in schizophrenia, factors associated with cognitive impairment and management of cognitive impairment in schizophrenia. This guideline provides a broad framework for assessment and management of cognitive impairment in schizophrenia. These guidelines can be modified for implementation as per the need and feasibility.

Process of development of these guidelines

For development of these guidelines, a thorough search of different search Engines (PUBMED, Google scholar, Science Direct and Scopus) was done to search for the relevant peer reviewed literature by using the combination of key words- Schizophr*, Cognit*, Social Cognition, Cognitive remediation (CR), course of cognition, antipsychotic medications, pharmacological management. A search for available guidelines, recommendations, and consensus papers was also done. Separate searches were also done to identify assessment tools and interventions that have been developed and validated/tested in India.

While considering the literature, we focused primarily on systematic reviews and metanalysis. Whenever, metanalysis and systematic reviews were available, these were given more weightage and were included. If no systematic review and metanalysis was available, we considered randomised controlled trials or cross-sectional studies. However, for Indian data open-label studies were also considered. Information published only in the form of abstract was not included.

Cognitive Domains Affected by Schizophrenia

In terms of cognitive impairment, the existing literature suggests that schizophrenia patients show impairment in general intelligence along with deficits in other cognitive domains. The variation in the level of impairment is 1.5 to 2 standard deviations below in patients with schizophrenia as compared to healthy controls^{4,5}. Initial studies varied in the assessment instruments for the assessment of cognitive domains, due to which it wasn't easy to reach a consensus. At the beginning of the twenty-first century, a review of factor analyses of studies

evaluating the cognitive impairment in patients with schizophrenia identified seven cognitive domains, viz., attention/vigilance, processing speed, working memory, verbal learning and memory, visual learning and memory, reasoning, and verbal comprehension. However, verbal comprehension was considered resistant to change and hence was dropped. During this time, there was increasing interest in SC, and it was also considered to be significantly impaired in schizophrenia patients (Nuechterlein et al, 2004) (figure-1, Table-1)⁶. Based on this review, the National Institute of Mental Health (NIMH) designed the Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS) test battery for assessment of cognitive functions in patients with schizophrenia⁶. Later, a confirmatory factor analysis study suggested that these seven domains could be further reduced to three domains: attention/working memory, processing speed, and learning. The most robust predictors of these three factors were symbol coding, spatial span, and visual learning, with symbol coding emerging as the single best predictor of overall cognitive performance⁷. The most affected cognitive domain in patients with schizophrenia that correlates with general cognitive performance is processing speed.

SC is not a single domain but comprises five domains, i.e., theory of mind, emotional processing, social perception, social knowledge, and attribution style (Table 1). A recent meta-analysis suggests that compared to the healthy controls, patients with schizophrenia perform poorly in all the SC domains⁸.

Figure 1: Cognitive Domains Affected in Patients with Schizophrenia

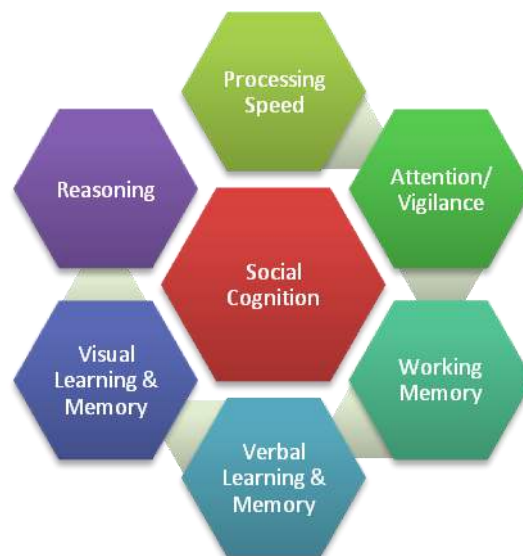


Table 1: Cognitive Domains Affected in Patients with Schizophrenia^{8,9}

Cognitive Domain	Definition
Processing speed	The capability to automatically carry out known and learned tasks
Attention	The capacity to focus on a single stimulus when present with several stimuli, to process the information
Working memory	A system that converts sensory information into long-term, permanently stored information
Verbal learning	The acquisition and retaining verbal information
Visual learning	The acquisition and retaining visual information
Reasoning and problem solving	Ability to foresee and plan things when exposed to a problem
Social cognition	Encoding, retrieval, and processing of information in a social setting
	Theory of mind/Mentalizing: The capacity to decipher someone's spoken words and acts with respect to their intentions, knowledge, and beliefs
	Emotional perception: The ability to correctly recognise and label the emotions of others, primarily based on their facial expressions
	Emotional processing: the capacity to recognize and differentiate different emotions, as well as the capacity to control emotions and emotional responses
	Social perception: The ability to recognize and evaluate social norms, regulations, and circumstances
	Social Knowledge: It is the understanding of the roles, norms, expectations, and goals that guide social situations or representational templates of social situations
	Attribution style/bias: it is the tendency to attribute good and bad occurrences to internal (self), external (other people), or situational variables

The course of Cognitive Functioning in Schizophrenia Patients

The course of schizophrenia can be divided into premorbid functioning, prodrome, first episode, and chronic course. In general, there is some consensus that the majority of the persons who ultimately develop schizophrenia have neurocognitive (NC) and social cognition (SC) impairment starting from childhood, the severity of which, especially non-verbal deficits, increase during adolescence. This increase in deficits in adolescence is considered to be a stronger predictor of the subsequent development of schizophrenia^{4,5}.

From a clinical perspective, evidence suggests that when assessed at the age of 16 years, compared to those who do not manifest schizophrenia, those who go on to manifest features

of schizophrenia have significantly poorer academic performance and poorer performance in mathematics several years before the onset of schizophrenia¹⁰. Data also suggests that persons with schizophrenia are less likely to enter higher education¹⁰.

There is some evidence to suggest that possibly there is some further worsening in the cognitive functioning in the prodromal phase among those at high risk of developing psychosis. A meta-analysis showed that among the clinically high-risk groups, compared to those who do not go on to develop psychosis, those who go on to develop psychosis have a worsening processing speed from their baseline performance¹¹. Further, available evidence suggests that among the clinically high-risk group, those who finally go on to develop psychosis have much more severe cognitive impairment¹². Compared to healthy controls, the clinical high risk for psychosis (CHR-P) group shows poorer performance in the domains of executive function, attention, processing speed, verbal fluency and visual, verbal and working memory and general intelligence¹².

Compared to healthy controls, drug naïve patients with first episode schizophrenia (FES) also have cognitive deficits in the domains of verbal memory, processing speed and working memory¹³.

There is a lack of consensus on the course of cognitive symptoms after the psychotic breakdown due to methodological issues related to the available data. Accordingly, available evidence supports further decline and also improvement in cognitive functioning^{4,5}.

Studies that have evaluated the course of SC in patients with schizophrenia, especially during the first five years of illness suggest that these are relatively stable¹⁴.

To summarize, compared to healthy controls, patients with schizophrenia perform poorly on various NC domains since childhood, which becomes much more prominent during the adolescence; with further decline during the prodromal phase and peaks at the first psychotic breakdown. After recovery from the first episode, the cognitive impairment, improves slightly and the patient then continues to have cognitive deficits that are either stable or show further decline over the years.

Factors influencing Neurocognitive impairment

Schizophrenia as a disorder has multifactorial etiology and the same is true for cognitive impairment as a symptoms. Genetic factors, antenatal (obstetric complications, influenza infection, preterm birth), natal, and postnatal factors are considered to increase the risk of cognitive impairment in childhood in patients with schizophrenia. In terms of genetic factors, the cognitive impairment is considered to be polygenic. Early childhood environmental factors such as childhood trauma and socioeconomic deprivation have also been linked to cognitive impairment in schizophrenia patients⁵.

The clinical factors that are reported to influence cognitive impairment in different metanalysis include age of onset¹⁵, chronic smoking¹⁶, metabolic syndrome, diabetes mellitus, hypertension, dyslipidemia^{17,18}. The evidence of association of cognitive impairment and cannabis use in schizophrenia is contradictory and inconclusive⁵ (Table 2).

Factor analyses studies of the Positive and Negative Syndrome Scale (PANSS) suggest that among the different symptom domains of schizophrenia, only disorganization domain is significantly associated with cognitive impairment¹⁹. Some of the studies have also linked level of cognitive impairment with level of physical activity. One study showed that compared to patients who were less physically active, patients who indulged in light physical activity had better cognitive performance in the domains of attention/concentration and processing speed²⁰.

A recent metanalysis concluded that duration of untreated psychosis does not have significant impact on the NC deficits²¹.

Table 2: Factors that influence neurocognitive impairment in patients with schizophrenia (Findings from metanalysis and network analysis)

Variable	Reference number	Findings
Chronic Smoking	22	• Compared to non-smokers, schizophrenia patients with chronic smoking have more impairment in the domains of attention, working memory, learning, reasoning/problem-solving, and processing speed. • Meta-regression analysis suggested that age and PANSS total score could influence impairment in attention.
MetS	17	• Presence of MetS is associated with more severe global cognitive impairment and impairment in the domain's memory, attention, processing speed, executive function, • Each component of MetS is associated with cognitive impairment • Presence of comorbid diabetes mellitus is associated with more severe impairment in global cognition, memory and processing speed; longer duration and younger age of onset of diabetes mellitus are associated with cognitive impairment • More severe cognitive impairments are associated with comorbid hypertension, obesity, dyslipidemia
	18	• Higher global cognitive impairment is associated with presence of metabolic syndrome, diabetes mellitus, hypertension • Presence of diabetes mellitus is significantly associated with more severe impairment in 5 domains (attention/vigilance, processing speed, verbal learning, visual learning, and reasoning and problem-solving) • Presence of hypertension is significantly associated with more severe impairment in 4 domains (processing speed, verbal learning, working memory and reasoning and problem solving) • Presence of dyslipidemia was significantly associated with more severe impairment in 5 domains (attention/vigilance, processing speed, verbal learning, working memory and reasoning and problem solving) • Obesity, overweight, and obesity/overweight significantly associated with more severe dysfunction in the domain of visual learning
Negative symptoms	23	• Negative symptoms have a small but significant impact on the severity of memory impairment
Age of onset	15	• Lower age of onset associated with more severe cognitive impairments • Compared to late-onset schizophrenia (age of onset ≥ 40 years), youth onset schizophrenia (age of onset ≤ 19 years) is associated with more severe cognitive impairments in the domains of arithmetic, executive function, Intelligence quotient, processing speed and verbal memory
Physical	20	• Light physical activity associated with better attention and

Activity		processing speed
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MetS- Metabolic Syndrome

There is lack of metanalysis evaluating the factors influencing SC.

Consequences of Cognitive Impairment in Schizophrenia

NC impairment in schizophrenia is associated with multiple negative consequences⁵ (Figure 2). SC impairment has also been linked to the level of community functioning, with SC having larger impact than the NC impairment²⁴. Further, emerging evidence suggests that SC mediates the relationship of NC deficits and functional outcomes²⁵.

Figure-2: Negative Consequences of Cognitive impairment in schizophrenia⁵



Impact of antipsychotic medications on cognition

As per the available evidence, there is a differential effect of various antipsychotic medications on cognition. Different metanalysis and network metanalysis have attempted to synthesize the available evidence in the last one decade or so (Table-3). A metanalysis of randomised controlled trials that evaluated the impact of second-generation antipsychotic medications (SGAMs) on cognition and included 37 studies involving 3576 participants reported that sertindole was better than clozapine, quetiapine and first-generation antipsychotic medications (FGAMs) on the composite cognitive score. On verbal working memory ziprasidone performed better than clozapine, olanzapine and quetiapine. The FGAMs performed poorly than risperidone on the verbal working memory. In terms of executive functioning, clozapine, olanzapine, quetiapine, ziprasidone and FGAMs performed

worse than sertindole. When the effect was seen on the processing speed, FGAMs performed worse than sertindole and quetiapine. In terms of long-term verbal working memory, olanzapine performed better than clozapine, whereas on verbal fluency, FGAMs performed worse than olanzapine and clozapine. On visuospatial abilities, olanzapine performed better than the FGAMs and clozapine²⁶. Another meta-analysis compared the effect of two classes of SGAMs (i.e., -pines and -dones) on cognition in schizophrenia and reported that the -pines (olanzapine, clozapine, quetiapine) improve attention/working memory, processing speed, executive functioning, fluency, nonverbal memory, and verbal memory. In terms of -dones (risperidone, and ziprasidone), improvement was noted in attention/working memory, executive functioning, motor function, nonverbal memory, processing speed, and verbal memory. However, the effect sizes for both the group of medications were small (effect sizes for dones = .254; pines = .202). Both the group of medications did not have any significant effect on language, motor functioning, or visuospatial skill. In the studies that compared the -pines and -dones, the majority (four studies) did not find any difference between the two groups of antipsychotic medications; two studies suggested pines to be better than -dones and one study found -dones led to more cognitive impairment than -pines²⁷. A meta-analysis that compared the effect of oral and long-acting injectables on various outcomes in patients with schizophrenia and evaluated the impact on cognitive functions as a secondary outcome reported that there is no difference between the two groups, with 16 out of the 19 studies reporting lack of difference between the two groups, 2 reporting long-acting formulations to be better than oral agents in terms of cognitive outcome and only one study considered oral agents to be better than the long-acting injectables²⁸. A network meta-analysis of 54 trials involving 5866 patients evaluated the effect of various antipsychotic medications on cognition. The meta-analysis included FGAMs (chlorpromazine, haloperidol, fluphenazine, perphenazine) and SGAMs (amisulpride, clozapine, lurasidone, olanzapine, quetiapine, remoxipride, risperidone, sertindole, and ziprasidone) and showed differential effect of various antipsychotics on various domains (Table-3). Overall, amisulpride, lurasidone, and sertindole were shown to have a positive impact on cognitive function and occupied the first-ranking positions in multiple cognitive domains. Olanzapine, on the other hand, improves the greatest number of cognitive domains, including the composite score. On the other hand, placebo was found to be better than remoxipride, clozapine, and haloperidol, on most of the cognitive domains and the composite score²⁹.

Another meta-analysis suggests that compared to patients on SGAMs, patients on haloperidol perform poorly in the domains of cognitive composite (mean difference: -0.13; 95% CI: -0.33 to -0.03), processing speed (mean difference: -0.17; 95% CI: -0.28 to -0.07), attention (mean difference: -0.14; 95% CI: -0.26 to -0.02), motor performance (mean difference: -0.17; 95% CI: -0.31 to -0.03), memory and verbal learning (mean difference: -0.21; 95% CI: -0.35 to -0.08), and executive function (mean difference: -0.27; 95% CI: -0.43 to -0.11). However, no significant difference was noted in the domains of working memory, visual learning, visuoconstruction, and SC³⁰.

Emerging preliminary evidence from different studies has reported beneficial effect on third-generation antipsychotic medications (i.e., Cariprazine and Lumateperone) on some of the domains of cognition^{31,32}. However, it is important to note that the data is not robust enough to make any conclusions.

Recently, the European Psychiatric Association evaluated the available evidence for treatment for cognitive impairment in schizophrenia and made three important recommendations with

respect to antipsychotic medications. First, compared to the FGAMs, the SGAMs have a favourable cognitive profile. Second, patients with cognitive impairment currently receiving FGAMs, should be switched to SGAMs. Third, no one SGAM is superior to others in terms of beneficial effects on cognition³³.

In the Indian context, atypical antipsychotic medications are the most commonly prescribed antipsychotic medications in schizophrenia patients and FGAMs form very small proportion (8-15%) of all the prescriptions, either as monotherapy or part of polypharmacy^{34,35}. Accordingly, the need to change from FGAMs to SGAMs, may be applicable to a very small proportion of patients in the Indian context.

Table-3: Effect of Antipsychotic medications on cognition in patients with schizophrenia

Author, year	Cognitive domain	Comparative effect of various antipsychotic medications
Nielsen et al ²⁶ , Metanalysis	Composite cognitive score	• Sertindole > clozapine (ES: 0.87; 95% CI: 0.12–1.63) • Sertindole > quetiapine (ES: 0.75; 95% CI: 0.00–1.49) and • Sertindole > FGAMs (ES: 0.89; 95% CI: 0.14–1.64)
	Verbal working memory	• Ziprasidone > clozapine (ES: 0.37; 95% CI: 0.00–0.74) • Ziprasidone > olanzapine (ES: 0.31; 95% CI: 0.02–0.59) • Ziprasidone > quetiapine (ES: 0.37; 95% CI: 0.03–0.64) • Risperidone > FGAMs (ES: 0.31; 95% CI: 0.04–0.58)
	Executive function	• Sertindole > clozapine (ES: 0.82; 95% CI: 0.06–1.58) • Sertindole > olanzapine (ES: 0.81; 95% CI: 0.07–1.55) • Sertindole > quetiapine (ES: 0.76; 95% CI: 0.02–1.51) • Sertindole > ziprasidone (ES: 0.90; 95% CI: 0.14–1.67) • Sertindole > FGAMs (ES: 0.83; 95% CI: 0.08–1.58)
	Processing speed	• Sertindole > FGAMs (ES: 0.97; 95% CI: 0.02–1.91)

		• Quetiapine>FGAMs (ES: 0.36; 95% CI: 0.01–0.72)
	Long-term verbal working memory	• Olanzapine> clozapine (ES: 0.41; 95% CI: 0.06–0.76)
	Verbal Fluency	• Olanzapine > FGAMs (ES: 0.26; 95% CI: 0.01–0.50) • Clozapine >FGAMs (ES: 0.44; 95% CI: 0.06–0.81).
	Visuospatial abilities	• Olanzapine > FGAMs (ES: 0.41; 95% CI: 0.04–0.78) • Olanzapine > Clozapine (ES: 0.44; 95% CI: 0.05–0.83)
Clissold & Crowe ²⁷ Metanalysis	Attention/working memory Executive functioning Fluency Nonverbal memory Processing speed Verbal memory	Pines (olanzapine, clozapine, quetiapine) > Dones (risperidone, and ziprasidone)
Kishimoto et al ²⁸ Metanalysis	Different cognitive domains	Oral $\approx$ LAIs
Baldez et al ²⁹ Network Metanalysis	Processing speed	Best Ranked: sertindole & Amisulpride Worst Ranked: remoxipride and haloperidol
	Attention	Best Ranked: amisulpride & lurasidone Worst Ranked: haloperidol and placebo
	Motor performance	Best Ranked: olanzapine & clozapine Worst Ranked: chlorpromazine, haloperidol and placebo were ranked the worst
	Visuoconstruction abilities	Best Ranked: olanzapine & fluphenazine Worst Ranked: quetiapine and haloperidol

	Memory and verbal learning	Best Ranked: amisulpride & perphenazine Worst Ranked: clozapine and haloperidol
	Working memory	Best Ranked: ziprasidone & lurasidone Worst Ranked: placebo and haloperidol
	Executive functions	Best Ranked: perphenazine & sertindole Worst Ranked: remoxipride and haloperidol
	Composite cognitive score	Best Ranked: lurasidone & amisulpride Worst Ranked: haloperidol and clozapine
	Overall positive impact on multiple cognitive domains	Best Ranked: amisulpride, lurasidone & sertindole
	Antipsychotic with positive impact on largest number of domains	Best Ranked: Olanzapine
Baldez et al ³⁰ Metanalysis	Composite Cognition Processing speed Attention Motor performance Memory & verbal learning Executive function	SGAMs>HPL

FGAMs: First generation of antipsychotic medications

SGAMs: Second generation of antipsychotic medications

Effect of other agents on cognition in patients with schizophrenia

Many other medications have been evaluated for their impact on the cognition in patients with schizophrenia (Table 4). The evidence for antidementia drugs plus antipsychotic medications in patients with schizophrenia was evaluated by a meta-analysis that included data from 7 double-blind, randomised, placebo-controlled trials with a sample size of 225 participants. The results showed that the overall effect of adding antidementia was superior to the combination of antipsychotic medications and the placebo in terms of cognition as measured by using mini mental status examination scores (standardised mean difference = -0.79 , 95% CI = -1.23 to -0.34 , $P = .0006$)³⁶. A systematic review that evaluated the impact

of psychotropics on SC showed that benzodiazepines (i.e., diazepam) have negative impact on the emotional recognition among the healthy volunteers³⁷. Available data from large sample size cross-sectional studies suggests that anticholinergic agents and long-term use benzodiazepines have been shown to have negative impact on the cognitive functioning in schizophrenia patients^{33,38-40}. With respect to antidepressants, again available data suggest lack of pro-cognitive effect or minimal pro-cognitive effect⁴¹⁻⁴³. One meta-analysis that included 17 studies and data of 466 patients evaluated the effect of intra-nasal oxytocin on SC. The metaanalysis found a small significant effect on theory of mind (ToM), but no significant effect of intra-nasal oxytocin on emotion recognition, empathy⁴⁴. A metaanalysis that evaluated the effect of anti-inflammatory agents (i.e., aspirin, davunetide, estrogen, erythropoietin, selective estrogen receptor modulators, omega-3, minocycline, or pregnenolone) reported that augmentation with minocycline and pregnenolone is associated with significant beneficial effect on some of the domains of cognition⁴⁵. There is preliminary evidence from a review that included 5 randomised controlled trials and one open-label study suggests the beneficial effect of modafinil on cognition (short-term memory, attention, and the ability to shift mental sets⁴⁶. Available evidence do not support the role of cannabidiol⁴⁷, Glutamate modulators⁴⁸, and Varenicline⁴⁹.

Table 4: Effect of other pharmacological agents on Cognition in Schizophrenia Patients

Agent/class	Reference Number	Study Design	Effect	Remark
Antidementia agents	36	Metanalysis	Pro-cognitive effect	Quality of evidence is poor
Benzodiazepines	40	Cross-sectional study	Negative impact on cognition	Quality of evidence is poor
Anticholinergic agents	38,39	Cross-sectional studies	Negative effect on cognition	No metanalysis available
Antidepressants	41-43	Metanalysis	Lack of or minimal precognitive effect	Quality of evidence is poor
Cannabidiol	47	Metanalysis	No positive effect	-
Minocycline	45	Metanalysis	Beneficial effect on the domains of visual learning, executive function, and attention	Quality of evidence is poor
Pregnenolone	45	Metanalysis	Beneficial effect on the domains of	Data from only one study

			visual learning, and attention	
Intranasal Oxytocin	44	Metanalysis	Small effect on the Theory of Mind, but no effect on other SC domains	The quality of evidence is limited
Modafinil	46	Review	Improves cognition (short-term memory, attention, and the ability to shift mental sets)	The quality of evidence is limited
Glutamate modulators	48	Metanalysis	No significant benefit	-
Varenicline	49	Metanalysis	No significant benefit	-

SC-Social Cognition

Psychosocial Interventions for Management of Cognitive impairment in schizophrenia

Different interventions have been evaluated to address cognitive impairment in schizophrenia patients. These include CR, exercise and lifestyle interventions. Among these, CR is the most commonly used intervention to improve the cognitive functioning in schizophrenia patients.

Cognitive remediation: The Cognitive Remediation Expert Working group⁵⁰ defines CR as “a behavioral training intervention targeting cognitive deficit (attention, memory, executive function, SC, or metacognition), using scientific principles of learning, with the ultimate goal of improving functional outcomes. Its effectiveness is enhanced when provided in a context (formal or informal) that provides support and opportunity for extending to everyday functioning”⁵⁰. Different interventions are reported to fulfil the definition of CR and these are categorized as individual- or group based, pencil-and-paper or computerized, bottom-up or top-down, and different combinations of these elements. The studies that have evaluated the beneficial effect of CR have varied in terms of frequency and structure of the sessions and the duration of the intervention. Over the years, many metanalysis have evaluated the efficacy/effectiveness of CR in schizophrenia. A recent large meta-analysis included information from 130 studies involving 8851 participants. Of these 57 studies were performed in Europe, 38 in the United States, 22 in Asia, 4 in Canada, 4 in the Middle East countries, 3 in Australia and 2 in Brazil. The majority (n=89) of the studies were single-centre studies. The studies included participants from inpatient (n=35), outpatient (n=79), and both settings (n=16). About one-sixth of trials (17.7%) were blinded trials. Comparison groups included treatment as usual in one-third of the studies (34.3%), active treatment as usual group (15.1%) studies, nonspecific control (30.8%), and active intervention (19.9%) group. The metanalysis showed that CR was useful for improving cognition (global cognition and various cognitive domains) and global functioning. An engaged and skilled therapist, the systematic development of cognitive strategies, integration with psychosocial rehabilitation, and the length of therapy were considered to be critical components of cognitive rehabilitation that were essential to its effectiveness. The format and delivery of CR did not

significantly influence the efficacy. In terms of patient-related factors, lower number of years of education, lower premorbid intelligence quotient, and higher severity of baseline symptoms were associated with higher improvement in cognition⁵¹. Other meta-analysis have also reported beneficial effect of CR in improving cognition in schizophrenia. In this meta-analysis, the variables that have been shown to impact the effect of CR were: strategy-coaching (episodic memory) and a discussion group (also called a "bridging") to assist in applying learnt cognitive abilities to daily life (on verbal memory and global cognition)⁵². The severity level of psychopathology was not found to influence the impact of CR on cognition^{51,52}.

Different meta-analyses have also evaluated the impact of social-cognitive training on SC. A meta-analysis that included 42 controlled trials involving 1868 patients showed that the intervention was associated with improvement in emotion recognition, mental state attribution, and social perception. In terms of patient-related variables, the lower number of years of education of the participants was associated with larger effects of social cognitive training on mental state attribution. Studies with smaller samples showed larger effect of social cognitive training⁵³. Another meta-analysis included 46 randomised studies involving 1979 participants. The social cognitive training was categorized as focused focus (targeted/broad-based) and inclusion of cognitive remediation therapy (CRT). Compared to treatment as usual, it was seen that targeted (i.e., interventions targeting 1 or 2 domains of SC) social cognitive training without CR led to improvement in emotion perception. Further, individual treatment performed better for emotion perception. All treatments (i.e. social cognitive training with or without CR) significantly improved social perception. Only broad-based social cognitive training improved the Theory of Mind. Overall combining social CR with CRT did not influence the impact of social CR⁵⁴. Based on the available evidence, the European Psychiatric Association recommended use of CR training and social cognitive training for management of cognitive deficits and social cognitive deficits in schizophrenia patients⁵¹. It also recommended that the CR should be carried out by a trained therapist and should be integrated in a psychosocial rehabilitation⁵¹.

Physical Exercise and Lifestyle Interventions: Physical exercise and lifestyle interventions have also been evaluated for their impact on the cognitive deficits in schizophrenia patients. Many meta-analyses have evaluated the role of physical exercise on cognition in schizophrenia patients. A meta-analysis that included data from 10 controlled trials involving 385 participants showed a beneficial effect of aerobic exercises on global cognitive performance, working memory, attention/vigilance, and SC. However, heterogeneity was noted for the effect of aerobic exercises on working memory, attention/vigilance, and SC⁵⁵. The duration of aerobic exercise/physical activity in different studies have varied from 20-60 minutes sessions, with 2 to 4 sessions per week for 4 to 12 weeks. Other meta-analyses have evaluated the role of improvement in diet alone or in combination with physical activity and did not find any significant beneficial effect of the intervention on the cognitive functioning^{56,57}. Another meta-analysis that evaluated the role of mindfulness-based exercises (such as Yoga, tai-chi, and qigong) showed that there is small benefit of these interventions on the working memory⁵⁸. However, it is essential to note that these interventions have been evaluated in limited number of studies that have limited sample size.

Role of Brain Stimulation Treatments in management of Cognitive impairment in schizophrenia

At present, three brain stimulation techniques, i.e., electroconvulsive treatment (ECT), repetitive transcranial brain stimulation (rTMS), and transcranial direct current stimulation (tDCS), are used in the management of schizophrenia. Since the beginning, ECT has been reported to have a negative impact on cognition. A systematic review that evaluated the role of ECT in management of schizophrenia and included studies reporting the cognitive

outcomes showed lack of negative impact of ECT on the cognition, with some of the studies actually report beneficial effect of ECT on cognition⁵⁹. Another review evaluated the role of electrode placement on the cognitive outcomes and showed that right unilateral or bifrontal ECT have more favourable cognitive outcomes when compared to bitemporal ECT⁶⁰. A recent study attempted to evaluate the predictors of cognitive changes in schizophrenia patients receiving ECT, reported that lower pre-ECT Montreal Cognitive Assessment (MoCA) scores and female gender predicted improvement in MoCA post-ECT. On the other hand, age and voluntary admission predicted deterioration in MoCA score⁶¹. Systematic reviews also suggest lack of adverse impact of ECT in treatment-resistant schizophrenia patients⁶².

There are few studies from India, that have evaluated the cognitive outcome in patients with schizophrenia undergoing ECT. A study from India showed deterioration in cognitive function with ECT, with threshold bitemporal ECT being associated with more cognitive impairment when compared to right unilateral and bifrontal ECT⁶³. Another study from India showed bifrontal ECT was associated with lower cognitive impairment when compared to bitemporal ECT at the end of the ECT course⁶⁴. In a follow-up study, that compared the cognitive performance of patients who received bifrontal and bitemporal ECT, it was evident that after a mean duration of about 98 days, the acute cognitive deficits induced by ECT actually improve by 3 months with electrode placement having no significant impact on the cognitive outcomes⁶⁵.

Different studies have attempted to evaluate whether treatment with rTMS or tDCS is associated with improvement in cognitive functioning. A meta-analysis evaluated the cognitive benefits with rTMS and tDCS across different neuropsychiatric conditions, including schizophrenia. This metanalysis included 24 (14 studies on rTMS and 10 studies on tDCS) studies involving patients with schizophrenia and reported lack of improvement in cognitive functions with these treatments in schizophrenia patients⁶⁶. Similar outcomes have been reported in other systematic reviews and metanalyses^{67,68}. However, another metanalysis showed that compared to rTMS with sham rTMS, included 9 studies involving 351 patients with schizophrenia showed that high-frequency rTMS, positioned on the left dorsolateral prefrontal cortex with a total pulse <30,000, were associated with improvement in working memory⁶⁹. Similarly, another metanalysis showed beneficial effect of multi-session tDCS on working memory⁷⁰. On the other hand, another meta-analysis that evaluated role of tDCS on multiple cognitive domains reported some beneficial role in working memory, attention and SC. However, it is crucial to remember that there was a great deal of variability in the included research⁷¹. Other meta-analyses have also confirmed the beneficial role of transcranial electrical stimulation on the working memory⁷².

Emerging evidence is inconclusive about combining CR measures and tDCS or rTMS for incremental benefit^{73,74}.

Overall, it can be concluded that the current level of evidence suggests that ECT does not lead to significant cognitive impairment in the long run and there is some beneficial effect of other brain stimulation treatments on working memory. However, the evidence is not robust to recommend use of rTMS and tDCS for cognitive impairment in schizophrenia patients.

Tests for Assessment of Cognition in Schizophrenia

Many test batteries are recommended for assessment of NC deficits and SC in patients with schizophrenia. These can be understood as test batteries or screening instrument (Table 5).

Table 5: Tests for Assessment for Neurocognition and Social Cognition

Neurocognition	Social Cognition tools validated in India
• Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS™) • Brief Assessment of Cognition in Schizophrenia (BACS) • Brief Cognitive Assessment Tool for Schizophrenia (B-CAT) • Montreal Cognitive Assessment (MoCA) • Screen for Cognitive Impairment in Psychiatry (SCIP) • Self-Assessment Scale of Cognitive Complaints in Schizophrenia (SASCCS)	• Social Cognition Rating Tools in Indian Setting (SOCRATIS) • Tool for Recognition of Emotions in Neuropsychiatric Disorders (TRENDS) • Facial Emotion Recognition Deficits (FERD) • AIIMS Facial Toolbox for Emotion Recognition (AFTER) • Facial Emotion recognition task by Mandal • The Indian Spontaneous Expression Database for Emotion Recognition • Observable Social Cognition A Rating Scale (OSCARS)

In the following section, we will discuss some of the important and commonly validated instruments in schizophrenia patients.

The ***Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS™)***, was designed by the National Institute of Mental Health (NIMH), to improve research in the area of cognition in schizophrenia while evaluating the psychopharmacological agents and CR. The MATRICS Consensus Cognitive Battery (MCCB) is now considered to be the gold standard battery for assessing cognitive impairment in schizophrenia patients. It is also available in Hindi, Marathi, Tamil and Telugu. It includes ten tests covering the seven recommended domains of cognition to be assessed in schizophrenia patients (Table-5). It is validated for persons aged 20-59 years and takes 60-90 minutes to complete^{75,76}. It has been demonstrated that the battery has good test-retest reliability⁷⁷. However, one of the limitations for using this test battery in routine clinical practice is the long duration required for its administration. The Hindi version of the MATRICS has been used in a multicentric study funded by the National Institute of Mental Health (NIMH)⁷⁸. Tests equivalent to MATRICS battery have been validated in India^{79,80}.

Brief Assessment of Cognition in Schizophrenia (BACS) is a brief test battery that can be completed in 30 minutes. It includes tests for 6 NC domains (Table-6). The results of these tests can be summed up to create a composite score. The composite score has been shown to have high test-retest reliability⁸¹. It has been demonstrated to outperform the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in terms of test-retest reliability and internal consistency⁸².

Table 6: MATRICS Consensus Cognitive Battery (MCCB)

MATRICS Consensus Cognitive Battery	Brief Assessment of Cognition in Schizophrenia (BACS)
Speed of processing • Brief Assessment of Cognition in Schizophrenia (BACS): Symbol Coding • Category Fluency: Animal Naming • Trail Making Test: Part A Attention/vigilance • <i>Continuous Performance Test</i>—Identical Pairs (CPT-IP) Working memory • Wechsler Memory Scale-3rd Edition (WMS®-III): Spatial Span • Letter-Number Span Verbal learning • <i>Hopkins Verbal Learning Test-Revised</i> (HVLTR) Visual learning • Brief Visuospatial Memory Test-Revised (BVMTR) Reasoning and problem solving • Neuropsychological Assessment battery (NAB): Mazes Social cognition • <i>Mayer-Salovey-Caruso Emotional Intelligence Test</i> (MSCEIT™): Managing Emotions	Verbal Memory: • List Learning Working Memory • Digit Sequencing Task Motor Speed • Token Motor Task Verbal Fluency • Tests of Category Instances (Semantic Fluency) and Controlled Oral Word Association Test (Letter Fluency) Reasoning and Problem Solving • Tower of London Attention and Processing Speed • Symbol Coding

The **Schizophrenia Cognition Rating Scale (SCoRS)** is an 18 items scale that evaluates 6 cognitive domains (attention, reasoning and problem solving, memory, working memory, language production, and motor skills). Each item is rated on a 4-point scale (none-1; mild-2; moderate-3; and severe-4) pertaining to cognitive functioning in the last 2 weeks. The rating is done by an interviewers based on the information provided by the patient, an informant (usually a family member)⁸³.

Brief Cognitive Assessment Tool for Schizophrenia (B-CATS) is a brief battery that can be administered in less than 12 minutes and it includes 3 tests, i.e., Trail making test, category fluency (animals, fruits, vegetables) and digit symbol⁸⁴. It has good internal consistency and test-retest reliability⁸⁵.

The **Montreal Cognitive Assessment (MoCA)** includes an assessment of executive functions, visuospatial abilities, naming, memory, attention, language, abstraction, recall, and orientation. It is also available in Hindi. The maximum attainable score on MoCA for any participant is 30 points. One-point correction is made if the person is educated for less than 12 years⁸⁶. It requires 10-15 minutes to be administered, and this has been validated in

schizophrenia patients against MCCB. Significant associations were noted between 5 out of the 7 subtests of MoCA (visuospatial-executive, attention, language, abstraction and delayed recall) and MCCB subtests. No correlation was noted for the MoCA subtests of the naming and orientation. A cut-off of <25 is considered to an indicator of cognitive impairment in schizophrenia, rather than the original <26⁸⁷. The Hindi version of MoCA has been adapted and validated in India in elderly subjects⁸⁸.

Screen for Cognitive Impairment in Psychiatry (SCIP), is a paper-pencil screening tool for assessing cognitive impairment in patients with psychotic or affective disorders. It consists of five subscales. Total score is calculated by summing up the scores for each of the subscale, with higher scores indicating better cognitive functioning. It can be completed in 15 minutes. It is available in three different forms, so that the test can be repeated and the learning effect can be avoided. The test has good psychometric properties⁸⁹. A cut-off score of <70 indicates cognitive impairment, with a sensitivity of 87.9 and specificity of 80.6⁹⁰.

Cognitive Screening Scale for Schizophrenia (CSIS), is a short screening instrument of 11 subscales, that has good internal consistency. The initial scale included subscales for assessment of larger number of cognitive functions. However, the final scale includes 6 subscales. A cut-off score of 16 was found to have a sensitivity of 86% and specificity of 70%⁹¹.

The **Self-Assessment Scale of Cognitive Complaints in Schizophrenia (SASCCS)** is a 21 item self-rated questionnaire that assesses five cognitive domains - memory, attention, executive functions, language and praxia. It has good psychometric properties (internal consistency and reliability)⁹².

Social Cognition Rating Tools in Indian Setting (SOCRATIS) is a battery of tests designed to evaluate three areas of social cognition (SC): theory of mind (ToM), attribute styles, and social perception. It was created in India. Two first-order activities (the Sally-Anne and Smarties task), two second-order tasks (the Ice Cream Van and the Missing Cookies narrative), two metaphor-irony tasks, and the faux pas detection test are among the adaptations of the ToM tests. A modification of the Social Cue Recognition examination is the social perception test that is part of the battery. The Internal, Personal, and Situational Attributions Questionnaire (IPSAQ) served as the model for the attributional bias test. Every SOCRATIS exam has recognised groups validity and strong content validity (> 4 score by > 75% of experts).

All tests of the SOCRATIS have good content validity (> 4 score by > 75% of experts) and known groups validity⁹³.

Tool for Recognition of Emotions in Neuropsychiatric Disorders (TRENDS), created in India, assesses a person's capacity to identify the whole spectrum and variety of emotional emotions. The instrument consists of 52 still photos and 28 films, each lasting four seconds, that show six fundamental emotions with neutral face expressions and two variable intensities—high and low. The images are arranged in a random order⁹⁴.

Facial Emotion Recognition Deficits (FERD) is a modification of TRENDS for used in mothers with severe mental illness that uses images of the children. It covers six basic emotions, presented at two different intensities along with neutral facial expressions. The scale has good inter-rater agreement and internal consistency⁹⁵.

AIIMS Facial Toolbox for Emotion Recognition (AFTER) include static facial images covering the eight emotions- neutral, happiness, anger, sadness, disgust, contempt, fear, and surprise. Each emotion is expressed as high and low. It has good inter-rater reliability⁹⁶.

Facial Emotion recognition task by Mandal, includes five photographs each for six basic emotions. It has been evaluated in a group of patients with schizophrenia⁹⁷.

The Indian Spontaneous Expression Database for Emotion Recognition consists of spontaneous facial expressions presented as 428 segmented video clips, validated using machine learning algorithms. The Kappa coefficient between the four raters was 0.85⁹⁸.

Observable Social Cognition A Rating Scale (OSCARS) is an 8-item scale that can be administered as a semi-structured interview. The interview can be conducted with the patient or the informant. It can also be used as an Informant based questionnaire. Both methods take approximately 15–20 minutes. Each item is rated on 7-point scale, based on the anchor points given in the scale⁹⁹. The scale has been developed in English and has been recently translated to Hindi.

Revised reading the mind in the eye test for the Theory of Mind has validated the Bengali version of the revised reading the mind in the eye test and showed it to be a valid test for assessment of the theory of mind in the Indian context¹⁰⁰.

However, it is important to note that all the above-described assessment methods have only been used in research settings and normative data is not available for these scales. Hence, their utility in clinical practice is doubtful.

Data from India

Many Indian studies have compared the NC functioning of schizophrenia patients and healthy controls and suggest that patients perform poorly when compared to the healthy controls¹⁰¹⁻¹⁰⁷. Studies from India that have compared SC of schizophrenia patients and healthy controls suggest that patients perform poorly than the healthy controls^{100, 108,109}. A study from Chandigarh documented higher SC deficits in patients with first episode psychosis, when compared to healthy controls¹¹⁰.

Studies also suggest that among schizophrenia patients NC deficits are associated with functioning/dysfunction^{111,112}, insight¹¹³, and employment¹¹⁴. Data also suggest that SC in schizophrenia influence functioning/dysfunction^{112,115}, and disability¹¹⁵. One study showed that cognitive functions of motor speed, attention and executive functions have significant correlation with negative symptoms (Hedge et al, 2013). Other studies suggest association of higher cognitive impairment with longer duration of illness^{105,116}, positive^{105,116}, and negative symptoms¹⁰⁵. One study did not find association of cognitive functions with current employment status and performance at work¹⁰⁵. The information that is now available indicates that childhood/adolescent-onset schizophrenia is linked to greater deficiencies in NC in the areas of verbal fluency, processing speed, and cognitive flexibility than does schizophrenia that manifests in adults¹¹⁷.

Many NC tests and SC batteries have been validated in India (refer to the above section for the same).

In terms of effect of pharmacological intervention, one study suggests that three-month clozapine therapy leads to improvement in SC, but not NC deficits¹¹⁸.

Many studies have evaluated the role of CRT in schizophrenia. A study from NIMHANS evaluated the role of Home-Based cognitive retraining for FES patients showed significant benefit in the domains of divided attention, concept formation and set-shifting ability, and planning. However, overall sample size for the study was small¹¹⁹. Another multinational study involving patients from India and United States showed that CRT leads to significant gains in the domains of Verbal Working Memory, and a trend toward improvement in Attention/Vigilance¹²⁰. Another study from NIMHANS, compared the efficacy of caregiver assisted home-based CR program with clinic-based CR program and reported that it is feasible to provide CR to the schizophrenia patients with the help of caregivers in home setting and there is no significant difference in the efficacy of both the intervention programs

¹²¹. Another study from Chandigarh evaluated the role of computerized CRT and showed significant beneficial effect on the same on sustained attention and the processing speed, when compared with treatment as usual¹²². One study from Lucknow evaluated the role of add-on family assisted cognitive remediation therapy (FACT) in schizophrenia patients, and compared it with treatment as usual (pharmacotherapy and brief counselling), reported that there was improvement with FACT on attention/vigilance, working memory, processing speed, household responsibility and SC¹²³. Second study from the same centre evaluated the role of home-based CR and showed that compared to treatment as usual, CRT is associated with significant improvement in cognitive functioning, reduction in disability, and improvement in quality of life¹²⁴. Other studies have also shown beneficial effect of yoga on cognitive functions¹²⁵.

Studies have also evaluated the add-on role of yoga on cognitive functions and these suggest that add-on yoga to the ongoing treatment leads to significant improvement in the facial emotion recognition deficits, plasma oxytocin levels and socio-occupational functioning^{126,127}.

Assessment of Schizophrenia Patients from the Perspective of Managing Cognitive Impairment

Indian Psychiatric Society (IPS) has already published the clinical practice guidelines for management of schizophrenia in adults, children and also in the elderly¹²⁸⁻¹³⁰. Accordingly, the general principle of assessment and management of schizophrenia as laid down in the above-mentioned guidelines must be followed. Here we would discuss the specific issues pertaining to assessment and management of cognitive impairment (Table 7, Figure-3).

While history taking, whenever possible, clinicians should focus on the assessment of the level of cognitive functioning of patients with schizophrenia. Although the initial assessment and management of schizophrenia focus on the reduction in psychopathology, the available literature suggests that psychopathology does not have much impact on cognitive functioning. Hence, cognitive functions should be assessed at the earliest opportunity when the patient is cooperative for the same and then these should be monitored on a regular basis. In high-risk groups, such as those with a family history of schizophrenia and children of patients with schizophrenia, cognitive assessment should be done at the earliest, and if they are found to have a cognitive impairment, the cognitive remedial measures should be instituted at the earliest. Assessment instruments may be chosen based on the feasibility. However, wherever feasible and whenever feasible, patients should undergo a comprehensive assessment for cognitive impairment.

Additional assessment should also focus on the impairment in various domains of life (function, education, work, quality of life, social functioning, etc), that are being affected by the NC and SC deficits. If required these could be assessed by using structured instruments to understand the exact level of the deficits in various domains of life. Considering the side-effect profile of the atypical antipsychotic medications and the negative impact of adverse metabolic parameters on cognitive functions, the importance of assessment and monitoring of body weight, body mass index, and metabolic parameters should be understood, and this needs to be incorporated in the day-to-day management of schizophrenia. Assessment of level of physical activity should also be incorporated in the routine clinical assessment.

A detailed history of substance use should be obtained and all the efforts must be made to keep the patient in an abstinent state.

Table 7: General Principles of Assessment and Management of Cognitive impairment in Schizophrenia

Assessment and Management of cognitive impairment should start as soon as possible

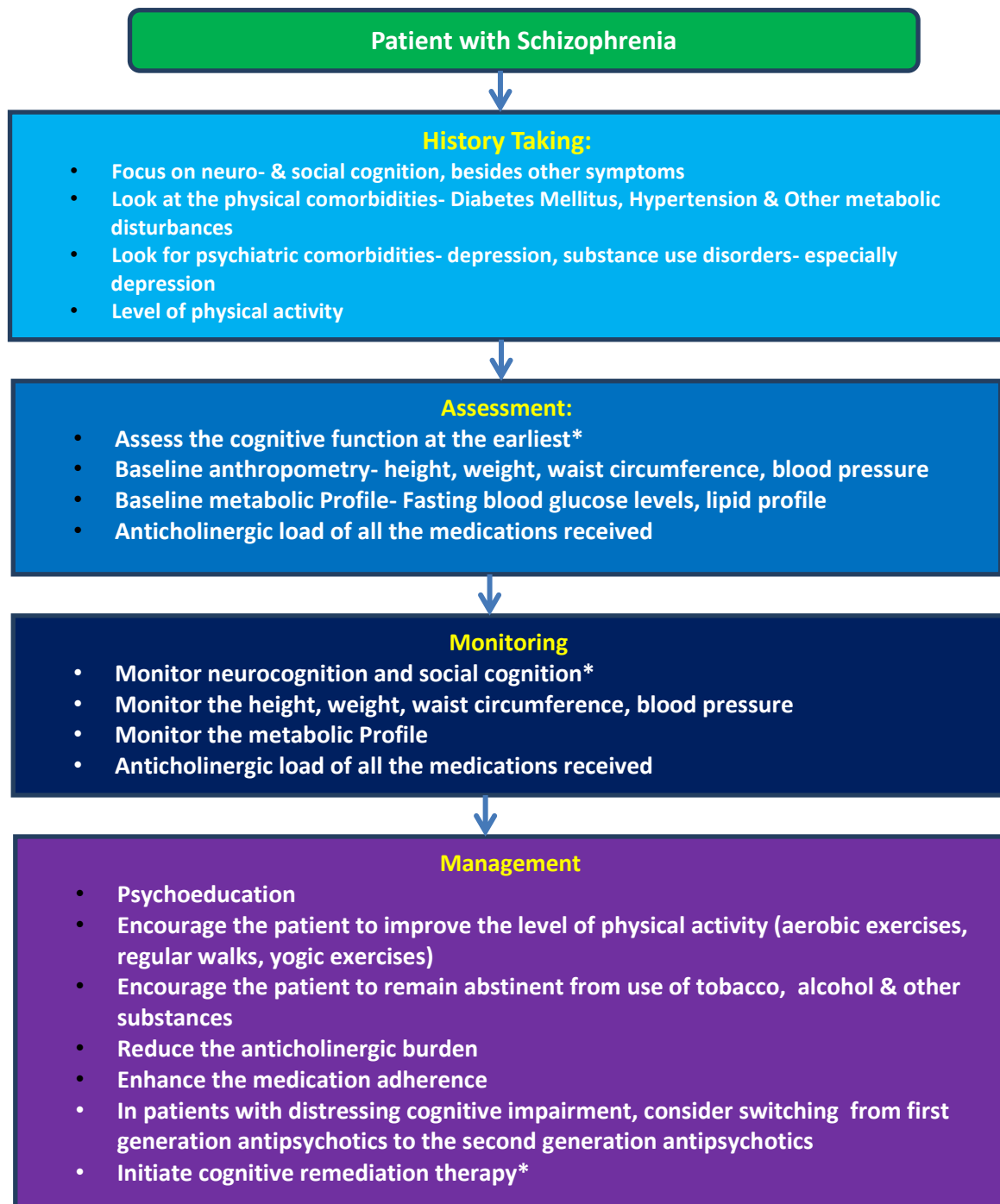
- **Adequately assess comorbidities including depression and substance use disorders**
- **Assessment of cognitive functions (NC and SC) should be done on regular basis***
 - Cognitive functions should be assessed at the earliest opportunity
 - Cognitive functions should be monitored on regular basis
 - In children of patients with schizophrenia, cognitive assessment should be done at the earliest and they are found to have cognitive impairment, the cognitive remedial measures should be instituted at the earliest
 - Cognitive assessment battery should be chosen as per the feasibility
 - Baseline recording of body weight, body mass index, metabolic parameters (Fasting blood sugar, lipid profile, blood pressure) and regular monitoring of the same as per the standard recommended guidelines
 - Level of physical activity
 - Current status of substance use
- **Psychoeducation**
 - Focus on informing the patient and the caregivers about the associated cognitive impairment
 - Emphasize that cognitive impairment is a manifestation of the disorder
 - Encourage the patient to do regular aerobic exercise
 - Encourage the patient to healthy diet, to avoid weight gain
 - Encourage the patient to have adequate sleep
 - Avoid smoking, use of alcohol and other substances
- **Ensure medication Adherence**
- **Monitor metabolic parameters as per the recommendations**
- **Institute cognitive remediation measures* along with measures for rehabilitation**
- **Monitor the anticholinergic burden and whenever feasible stop the anticholinergic agents at the earliest**
- **If a patient is on the FGAMs and is reporting of significant cognitive impairment, consider changing to a SGAMs**

FGAM-First Generation Antipsychotic Medications

SGAM-Second Generation Antipsychotic Medications

*** Wherever possible, this should be done by mental health professionals formally trained in administering these, e.g., clinical psychologists / neuropsychologists**

Figure-3: Assessment and Management of Cognitive Impairment in Schizophrenia



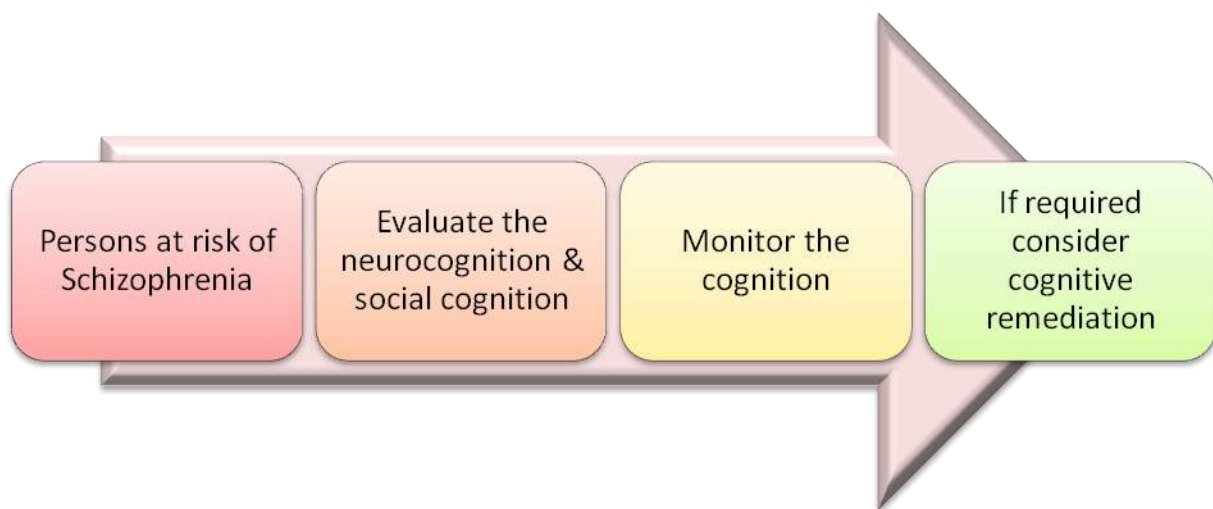
*** Wherever possible, this should be done by mental health professionals formally trained in administering these, e.g., clinical psychologists / neuropsychologists**

Management of Cognitive Impairment in Schizophrenia

The management should include multiprong strategies to prevent development or progression of cognitive impairment and to reduce the existing NC and SC deficits. The strategies can be broadly understood as psychoeducation, pharmacological measures including selection of antipsychotic medications and use of anticholinergic agents, considerations while using somatic therapies, and non-pharmacological measures.

Among the people at risk of schizophrenia, efforts should be made to evaluate, monitor and if required manage the cognitive impairment, even before the emergence of other symptoms of schizophrenia (Figure-4).

Figure-4: Assessment and Management of Cognitive Impairment in persons at risk of schizophrenia



Psychoeducation

The psychoeducation for patients with schizophrenia should cover all the important aspects of the illness such as understanding the knowledge of the patient and the caregivers about the illness, and providing information about the diagnosis, symptoms, etiology, treatment options, course and outcome, pharmacological management, non-pharmacological management, the importance of medication and treatment adherence, need for abstinence from substances, role of communication patterns including the expressed emotions, issues related to marriage, pregnancy and child-birth, relapse and identifying the early signs of relapse, role of stress in relapse and continuation of symptoms, and improving the adaptive coping mechanisms to deal with the residual psychopathology¹²⁸⁻¹³¹. However, from the perspective of NC, patients and caregivers should be informed that cognitive symptoms are part and parcel of the illness and do not improve much with the available antipsychotic medications. They should be informed that non-pharmacological measures such as CR and, aerobic exercises can lead to improvement in the cognitive functioning. Similarly, the patients and caregivers must be informed about the adverse impact of weight, high body-mass index and abnormal metabolic parameters on the NC functions. The patients should also be asked to take a healthy diet, do regular physical activity, and remain abstinent from substances to avoid further weight gain and the development of abnormal metabolic parameters. Those with pre-existing obesity, diabetes mellitus and hypertension should also be encouraged to take their medications for these illnesses regular and consult their physician from time to time

to minimize the impact of these on cognitive functions. Studies in healthy controls and persons with different illnesses suggest that a lack of sleep can also have adverse impact on the cognitive functioning¹³². Hence, the patients must be encouraged to have adequate sleep. Additionally, the patients and caregivers should be informed about the increased risk of dementia in patients with schizophrenia¹³³.

Selection of Antipsychotic medications

Besides the other consideration¹²⁵, the selection of antipsychotic medications in schizophrenia patients should take into consideration the anticholinergic properties of the medications and where ever feasible medications with lower anticholinergic properties may be considered. However, it is important to maintain a balance between achieving adequate symptom controls versus the lower anticholinergic properties. Considering the negative impact of FGAMs on NC functions, whenever feasible, in patients with cognitive impairment, the FGAMs should be changed to a SGAMs. However, current level of evidence suggests that there is lack of difference among various SGAMs on the cognitive functioning³³. In patients with treatment resistant schizophrenia clozapine will remain as a medication of choice. However, while using clozapine all other listed measures need to be considered for a comprehensive management of the patient.

Whenever feasible anticholinergic agents should be used sparingly and when used should be used in the lowest effective dose for the shortest duration. While prescribing medications for other illnesses too, the clinicians should be aware about their anticholinergic potential and choose medications accordingly.

Consideration while using ECT

There is lack of conclusive evidence for the adverse effect of ECT on cognitive functions in schizophrenia patients on the long-term. Hence, ECT should not be withheld when clinically indicated, just because of fear of worsening of the cognitive functioning. However, while using ECT measures such as use of right unilateral or bifrontal ECT may be considered initially. However, if patient does not respond to these electrode placements, bitemporal ECT should be considered.

rTMS and tDCS

There is lack of conclusive evidence at present to suggest that rTMS and tDCS leads to improvement in cognitive functioning in patients with schizophrenia. Accordingly, there is a need for further good quality evidence to prove the beneficial effect of these interventions on the cognitive functioning.

Cognitive Remediation

As per the Cognitive Remediation Experts Group, CR for schizophrenia is “a behavioral training-based intervention that aims to improve cognitive processes (attention, memory, executive function, SC, or metacognition) with the goal of durability and generalization”. CRT involves use of various cognitive exercises and techniques to improve the cognition. It basically adopts a strength-based approach and utilizes the concept of neuroplasticity of the brain and aims to improve the cognitive skills of the persons to improve the overall functioning and the quality of life. CR should be started as early as possible, provided patient is cooperative for the same. The duration of CR can vary from patient to patient depending on their progress and level of improvement.

In terms of approaches for CRT, two approaches have been documented, i.e., the compensatory approach and the restorative approach. The compensatory approach involves use of aids such as smart phone and other aids to compensate for the cognitive difficulties.

This is also known as cognitive adaptation training¹³⁴. In real sense, the compensatory approach is not CRT. The restorative approach involves improving the cognitive functioning in a particular domain by using the behavioral training involving a combination of ‘drill and practice’ and methods to generalize these skills. The drill and practice can be done by pen and pencil method or by computerised method¹³⁴.

The different techniques used in majority of the CT programmes include errorless learning, self-monitoring, and scaffolding.

The ‘errorless learning’ involves teaching the participants to carryout various cognitive tasks by minimizing the opportunity for making mistakes. This means that that participants are presented the task in which the task or the therapist supports all the steps required to complete the task. Further to facilitate the errorless learning, sometimes the task is build-up backwards from the end result to the beginning, and sometimes the tasks are presented in a graded manner, i.e., initially the tasks are presented slowly and then speeded up or initially, the participant is asked to start with simpler tasks and then the level of difficulty is increased. With continued training sessions the support provided to patient is withdrawn so that they become independent of the support provided by the therapist or the task¹³⁵.

The second technique known as “self-monitoring” involves allowing the person to develop a rehearsal technique with respect to the instructions of the task and the task completion. This can involve verbalization of the instructions for the given task, initially overtly and later covertly¹³⁵.

The third technique is known as “scaffolding”, that is understood as linking the complexity of the task to the level of ability of the participants. However, it is important to note that this is not same as errorless learning which involves increasing the complexity of the task with learning¹³⁵.

Different packages are available for the CRT. One such approach is the Neuropsychological Educational Approach to Cognitive Remediation (NEAR) Model¹³⁶. In routine clinical practice some of the simple measures as listed in Table 8 can be used.

Table 8: Cognitive Remedial Measures for different Cognitive Domains^{120,122, 125}

Cognitive Domain	Tasks used for remediation	Procedure
Attention	Letter cancellation	• The participant is asked to cancel a specific letter, such as, ‘a’, ‘b’, or ‘m’ • In the second step the procedure can be made more complex and participants may be asked to cancel 2 letters • Further, complexity may involve asking patient to cancel a particular alphabet, such as ‘a’; however, this should only be done when this is not preceded by alphabet “m” or let’s say, not succeeded by alphabet “d” • This can be adapted for use in any language • If the person is not able to understand the alphabets, a number sequence can be used
	Bead/Grain sorting	• The beads of different colours, shapes and sizes are given to the participant, with the instruction to sort them according to shape, size and colour • This can be adapted by using different types of grains

	Colouring	- Participant is provided with a design, outlining a particular image/picture and they are asked to colour the image/picture of the design, using even strokes and making sure that the colour do not spill outside the design - The design can be made more complex depending on the mastery of the participant
	Finding hidden objects	The participant is provided with different pictures and are asked to search different hidden objects in the picture
	Digit symbol	- As done in digit symbol substitution test, participants are provided with a reference set of numbers/digits (1-9) along with a corresponding symbol - This is followed by handing over a paper with symbols to the participant and asking them to fill the corresponding digits in the shortest possible time
	Words in passage	The participant is read out a passage. While listening to the passage, the participant is required to note the number of times a given word is read and is expected to answer a few questions about the passage.
	Visual scanning	This involves using the Trail making test-A and B and they are expected to complete the same, as per the instructions used for trail making test A and B.
Memory	Memorization/ Recognition	- A picture is shown to the participant for 15 seconds with the instruction to memorize the items present in the scene - In the second step, they are shown another picture (which has some of the items of the first picture and additional items) and are asked to identify the things present in the first picture
	Reading passage and remembering facts	Initially the participant is requested to read a passage and then they are requested to recall maximum number of facts from the read passage
	List learning	Like, the Rey's Auditory Verbal Learning Test, this requires the subject to recall a list of words in the order of their choosing after being given the list
	Learning visual patterns	After presenting a visual pattern for ten seconds, the subject is given a blank matrix, that is to be filled out by the participant in accordance with the pattern visible in the provided visual pattern
	Jumbled words	- The participants are asked to construct a coherent sentence using a random set of words - The intricacy and length of the phrases is increased gradually, raising the challenge level
	Route memorization	- Initially, a map with various routes is shown to the participant - Subsequently, participants are asked to find routes on a blank map connecting two locations

	Visual N. Back 1	• One by one, cards containing dots and circles are shown to the participant • The participants are supposed to learn where each dot and circle appears on the cards, and then they are supposed to tap the table to show that the dots' locations match each time a dot or circle appears in that same spot
	Remembering designs	• Specific designs are shown to the individual • After ten seconds of close observation, the participant is asked to sketch the same design without glancing at it.
	Remember the previous word	• The participants are informed that words with three or four letters will be displayed to them. Every word will be written on a single card, which will be displayed one after the other • They must pay attention and memorize the words because, at random, during presentations, a blank card will be shown • They must then say the word that was shown right before the blank card
	Star counting	• Participants are presented with a set of stars with plus and randomly placed minus signs in between • There is a two-digit number printed in the upper left corner. Additionally, a single digit with the word forward (like 3 forward) and a single digit with the word backward (like 2 backward) are put on top • Beginning with the double digit in the left upper corner, the participant is instructed to add or subtract numbers (based on the digits written with "forward" or "backward") with each star, matching the plus or minus signs that come before it
Reasoning and problem-solving	Find hidden words	• A matrix made up of alphabets is shown to the participants • The participant must find and mark a few significant words that are concealed in the alphabetic matrix
	Mirror images	• When presented with a design, the task for the participant is to determine which of the four designs below is the mirror image of the stimulus design
	Where next	• The participants in each trial are given three designs, each of which is arranged on a card in a predictable way • They are given a blank box with the three designs on it • After that, they're prompted to select the correct response from the four provided options to complete the blank box
	Decoding words	• 26 alphabets are given to the participants; each alphabet corresponding to a symbol • Then, a set of symbols is supplied to the participant. Every group of symbols represents significant English words • Every symbol denotes an English alphabet letter from A to Z • To decode the word, they must replace the symbols with the appropriate alphabet
	Number game	• A set of numbers are presented to the participants in a specific order. Any number may be missing in the given series

		• To determine which number is missing, the participant must decipher the order in which the numbers are written
	Mazes	• The participants are shown an image of a maze • They must follow the path from the starting point of the maze to its conclusion; but, they can't start following the path until they have a mental picture of it • Once they begin drawing the trail, they are not permitted to stop or retrace any of the lines
	Writing a short essay	• The task for the participant is to produce a 500 word essay on a certain topic • The topics ranged from everyday activities to prevalent social issues • The task's difficulty increases gradually

Wherever feasible, patients with significant cognitive impairment should be evaluated by a clinical psychologist trained in neuropsychology or a psychiatrist with adequate training to use different cognitive tests. They should conduct assessment based on locally validated tools to identify cognitive deficits and plan individualized cognitive retraining programs. The CR measures should be carried by mental health professionals trained to administer these interventions.

However, in Indian setting very few patients can access the services of such specialists. Hence, in the absence of trained mental health professionals, mental health professionals with various levels of training may encourage patients to go through the cognitive exercises as listed in table-8. The patients can also be encouraged to use cognition enhancing apps (e.g., lumocity, mindlamp, etc). Patients may also be encouraged to engage in cognitively stimulating activities, e.g., grain sorting, rangoli making, solving crosswords, sudoku, puzzles, playing chess or cards with increasing cognitive demand, etc.

Aerobic Exercises/Physical Activity: Evidence from metanalysis suggests that aerobic exercises improve global cognition, working memory, attention/vigilance, and SC. It was also seen that the higher level of exercise associated with more positive impact on the cognition. Further, when exercise is supervised by physical activity professionals, it is associated with better outcome¹³⁷. Accordingly, clinicians should encourage the patients to do regular aerobic exercises and if feasible, the patients should be encouraged to do so under the supervision of a physical activity professional. In the inpatient setting, physical activity professionals can be included as part of the team to train patients for various aerobic exercises. The duration of aerobic exercise/physical activity in different studies have varied from 20-60 minutes sessions, with 2 to 4 sessions per week can be recommended. Based on the interest of the patients, mindfulness based exercises can also be considered.

Use of Yoga

The preliminary evidence from a randomized controlled trial suggests that use of yoga (loosening exercises, breathing practices, Suryanamaskāra, sitting and supine and prone posture Āsanās along with Prāṇāyāma and relaxation techniques) for a period of one month can lead to improvement in SC¹²⁷. Hence, whenever feasible and if patient is interested in doing so, the same must be encouraged to be done on regular basis.

Meaningful Occupation

There is some evidence from a randomized controlled trial to suggest that providing employment helps improve patients' cognitive functions¹³⁸. Accordingly, all the patients should be assisted to follow any occupation, particularly, income-generating ones in addition to other cognitive enhancing measures¹³⁹.

Conclusions

NC impairment and social cognitive deficits are part and parcel of clinical presentation of schizophrenia. These deficits often emerge before the actual development of psychotic symptoms. These deficits have an adverse impact on the overall functioning, social functioning, educational attainment, work performance, and overall quality of life of the patients. Accordingly, assessment and management of cognitive impairment should be an integral part of holistic care. The assessment should be an ongoing process and the management should involve multiprong strategies to improve the overall outcome of patients with schizophrenia.

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CLINICAL PRACTICE GUIDELINES FOR PERSONS WITH MENTAL ILLNESS IN LONG STAY AT PSYCHIATRIC INSTITUTIONS: MENTAL HEALTHCARE ACT, 2017 PERSPECTIVE

INTRODUCTION:

World Health Organization(WHO)'s Comprehensive Mental Health Action Plan 2013-2030 recommends systematically shift the locus of care from long-stay psychiatric hospitals to non-specialized health settings.¹ This includes expanding the coverage of evidence-based interventions through a network of linked community-based mental health services, which encompass short-stay inpatient and outpatient care in general hospitals, primary care, comprehensive mental health centers, day care centers, support for Persons with mental illness (PWMI) with mental disorders living with their families, and supported housing. This shift allows PWMI to regain independence and engage in social and vocational activities, significantly improving their overall well-being.

The WHO has released a document on transitioning mental health care from institutions to community settings in the South-East Asia Region. It provides statistics and recommendations related to residential facilities for PWMI in India. In 2020, India had 136 psychiatric institutions, of which 46 were operated by the government, and the country had a total of 1.43 psychiatric beds per 100,000 people, a relatively low figure. India also recorded the highest number of involuntary admissions in the region, with 15,890 cases, accounting for 28% of all admissions. Additionally, 68% of inpatients stayed for less than a year, yet over 2000 individuals continued to reside in institutions despite having recovered, representing 12% of all admissions. Regarding community-based care, India had 223 residential facilities, and recent initiatives have increased this number to 330 across various states.²

The Mental Healthcare Act (MHCA) 2017, a landmark legislation, emphasizes a rights-based approach and mandates the provision of high-quality, humane, and patient-centred care within the community, aligning with international standards.³

SCOPE

The clinical practice guidelines aim to provide comprehensive and practical guidance for healthcare professionals, (Mental health establishments) MHEs, and stakeholders involved in the care of PWMI in MHE including long stay. The guidelines address key aspects of long-stay care, aligning with the principles and provisions of the MHCA 2017, which are admissions to a MHE, management of PWMI in MHE, and transfer/discharge from a MHE.

However, they do not address stay of person with intellectual disabilities without a concurrent mental disorder diagnosis. By adhering to these guidelines, mental health professionals and institutions can ensure that PWMI in long-stay care receive optimal treatment and support, while upholding their rights, dignity, and autonomy. These guidelines are designed to be a practical and adaptable resource, evolving with new evidence and best practices to continuously improve the quality of care for this important population.

GUIDING PRINCIPLES FOR CARE AT LONG STAY

- The Mental Healthcare Act (MHCA) , 2017, strives to ensure access to mental healthcare services for PWMI while simultaneously protecting, promoting, and fulfilling their rights during treatment and recovery, recognizing that these two objectives are intrinsically linked in the journey towards well-being. (Preamble of MHCA 2017)
- The MHCA 2017 presumes all PWMI have the capacity to make decisions about their mental healthcare, including admission and continued stay at a MHE unless there are reasonable reasons to doubt the presumption. [Section 4(1)]
- This principle of "least restrictive alternative" or "least restrictive environment" mandates that PWMI should be offered treatment options and settings that meet their treatment needs while imposing the least possible restriction on their rights and freedoms. In alignment with this principle, admission to a mental health establishment should only be considered when it is deemed the least restrictive care option available, after considering any existing advance directives. [Section 89(1)(b), and Section 90(2)(b)]
- All admission to a MHE should be independent admission as much as possible, including long stay, unless supported admission is unavoidable. [Section 85(2)]
- Supported admission should be provided only to those who lack capacity to make MHTD. No one deemed to have capacity to make MHTD should be forced to remain in a MHE against their will or without providing ongoing consent. [(Section 89(1)(c), Section 90(2)(c)]
- All treatment decision related to care of PWMI in a supported admission who lacks capacity to make MHTD, should be made in discussion with and consent of the NR, then a 'best interests' decision needs to be made with the temporary consent of the NR for treatment plan. [Section 89(7), Section 90(13)]
- Long-stay MHE should only be considered in exceptional circumstances, for the shortest possible duration, and as a last resort after appropriate community-based treatment options have been exhausted. [Section 18(5)(c)]
- Every PWMI has right to community living, and PWMI who no longer require treatment at a restrictive Long stay psychiatric hospital should be supported through community based establishments such as half way homes, by the appropriate government. [Section 19(3)]
- The MHCA 2017 explicitly prohibits the continued confinement of PWMI in MHE solely due to factors such as lack of family support, rejection by family, homelessness, or the absence of community-based facilities. [Section 19(2)]

This Clinical Practice Guideline (CPG) for Long Stay in psychiatric settings will adopt a comprehensive approach encompassing admission, treatment, and discharge processes, aligning with relevant sections of the Mental Healthcare Act (MHCA) 2017. Each phase will be discussed in detail, outlining the types of admissions, criteria or requirements for each, and the resources and facility types necessary for providing care. The Role of MHRB in each type of admission is summarized in table 1.

Table 1: Role of MHRB based on type admission as per Mental Healthcare Act 2017

Relevant section	Role of MHRB (Mental Health Review Board)
Section 86	- The MHRB does not need to be informed, nor is their permission required for admissions under Section 86. However, the facility where the admission takes place must be registered as MHE. - The MHRB's role primarily comes into play in cases when there are appeals or complaints regarding mental healthcare decisions in any type of admission or service provision.
Section 87	- All admissions of minor have to be reported to concerned MHRB within 3 days. - Admission extending beyond 30 days will be reviewed by MHRB - ECT can only be used with prior permission from the Board and with the consent of the NR
Section 89	- To receive intimation of supported admissions: Ensuring proper documentation and adherence to legal procedures. - To receive and decide applications for the appointment of NR. - To receive any enquiry and decide on any request to complaints related to treatment received by the PMWI at the MHE within the stipulated time. Till the time decision is pending, the treatment should continue with the consent of the NR. - To procure monthly reports on use of restraints at the MHRB - To ensure patient rights are not violated during care at the MHE
Section 90	- To receive intimation of supported admissions, and decide application of the supported admission under section 90. If a decision is not reached within this 21 days, the treating psychiatrist can proceed with the planned treatment after obtaining consent from the patient's nominated representative in accordance with Section 90. - The MHRB should periodically review need for continued admission which is at 90 days, 120 days, and then 180 days subsequently. - To receive any enquiry and decide on any request to complaints related to treatment received by the PMWI at the MHE within the stipulated time. Till the time decision is pending, the treatment should continue with the consent of the NR. - To procure monthly reports on use of restraints at the MHRB - To ensure patient rights are not violated during care at the MHE: Upholding the dignity and well-being of PWMI throughout their admission.

ADMISSION OF PWMI IN LONG STAY

1. INDEPENDENT ADMISSION UNDER SECTION 86:

A person with mental illness(PWMI) can be admitted as an independent patient and continue as an inpatient for an extended period. However they have to meet criteria for admission to a Mental Health Establishment(MHE), which has to be periodically reviewed.

a. Criteria for admission under section 86:

- To be admitted under Section 86, a PWMI should have a mental illness of sufficient severity that necessitates admission to the (MHE) as . This determination should be made by qualified professionals authorized to make such decisions, in accordance with the established policies of the MHE. In addition to the severity requiring admission, there must be a reasonable likelihood that the admission will benefit the PWMI.
- Continued stay in an MHE requires the written consent of the PWMI. Furthermore, no treatment should be initiated or continued without the informed consent of the PWMI, as mandated by the MHCA

b. Professional opinion: The professional to determine the need for admission must be a medical officer or mental health professional. The definition and minimal qualification of these professional should be as defined in the MHCA 2017.

c. Capacity requirement: While capacity is presumed to be present, before admission, irrespective of the type or setting of the admission, it is required to do a capacity assessment as per capacity guidance. It is important because a PWMI who lacks the capacity to make MHTD should not be admitted under Section 86. As a routine, capacity assessment is not required to be repeated for independent admission during a long stay at any MHE as a periodic legal need, unlike supported admission. But it is important to note that capacity is a dynamic ability, specific to time and task. Therefore, any time during the inpatient care as an independent admission, if the PWMI is found to be unable to understand the nature or purpose of their treatment decision, capacity assessment has to be repeated as per guidance document. If deemed not having the capacity to make MHTD, the admission under Section 86 should be terminated

d. Resources required: While the MHCA does not explicitly mandate specific infrastructure for independent admissions under Section 86, it emphasizes the principle of the least restrictive environment. Therefore, if a hospital-based MHE admits a PWMI (Person With Mental Illness) under this section, it is preferable to have less restrictive facilities within the MHE. The minimum standards for the MHE will be as prescribed by respective state/central MHCA regulations.

The MHE can establish its own policies regarding the admission and treatment of PWMI, as long as these policies do not violate the provisions of the MHCA. A lack of less restrictive facilities should not be a reason to keep the PWMI in a more restrictive environment than necessary for treatment of the PWMI.

If a PWMI admitted under Section 86 finds the facility too restrictive and requests discharge, they should be discharged within 24 hours, as their admission is considered independent and voluntary. Since these patients are not deemed to pose a significant risk of harm to themselves, others, or of self-neglect, acute care services focused on crisis management are not a necessity.

Therefore, even low-resource facilities can cater to the needs of PWMI admitted under Section 86. However, a comprehensive community treatment plan is essential at all levels of facilities, especially if the PWMI is a long stay. This plan should focus on reintegrating the PWMI into the community and providing ongoing support to ensure their well-being.

All long stay PWMI should have access to rehabilitation service. So, MHE should develop a model of care for transitioning patients of long-term psychiatric facilities to the community. The focus of these model should be to reduce length of hospital stay, and reduced readmission..

- e. Type of MHE: Independent admission under Section 86 of the MHCA, can occur at any registered MHE, whether it is a community-based MHE or a hospital-based MHE. The essential requirement is that the PWMI provides informed consent for their stay and meets the admission criteria outlined.

Major difference between the H-MHE and C-MHE with respect to provisions, level of resources needed and type of admissions allowed as per MHCA 2017 are summarized in table 2.

Table 2. Classification of Mental Health Establishment based on residential care provision.

Setting	Hospital based Establishment	Community based Establishment
Residential services	• Inpatient and long stay residential services provided at Psychiatric hospitals/institutions • Inpatient care services provided at Psychiatry ward in a general hospital	• Mental health community residential services • General care residential facilities not specifically designed for persons with mental health needs, where <i>Person with Mental Illness(PWMI)</i>[†] resides.
Provision for acute care service	Present	Absent
Level of resource required	High	Low
Level of restrictive environment	High with or without provision of less restrictive environment	Less restrictive environment
Need for registration as <i>Mental Health Establishment</i> [†]	Present	Present
Sections [§] under which admission of PWMI can occur	Both independent and supported admission (Section 86, Section 89 and Section 90) [§]	Independent admission only (Section 86) [§]

Terms in italic before [†] are as defined in the “Mental Healthcare Act 2017”;

[§] : Section of Mental Healthcare Act, 2017

2. SUPPORTED ADMISSION OF MINOR UNDER SECTION 87: Admissions of minor in a MHE comes under section 87 of the MHCA 2017

- a. Criteria for admission under section 87: The independent assessments must be conducted on the day of admission or within the preceding seven days. Both professionals involved in the assessment must independently conclude, based on their examination and any additional relevant information, that:
 - The minor has a mental illness severe enough to require admission to a mental health establishment.
 - Admission is in the best interests of the minor, considering their health, well-being, safety, and ascertainable wishes.
 - The minor's mental healthcare needs cannot be adequately met outside of a mental health establishment.
 - All community-based alternatives to admission have been explored and have either failed or are inappropriate for the minor's situation.
- b. Professional opinion: For admitting a minor, the assessor has to be either two psychiatrists, or by one psychiatrist along with either a mental health professional or a medical practitioner, as defined in the MHCA 2017.
- c. Capacity requirement: For minors, there is no capacity assessment required, and all decision related to MHTD, has to be made by the consent and request of the NR or an appointed attendant.
- d. Resources required :
 - Separate accommodation facility for minors: MHE should have separate accommodation facility separately from adults in an environment that considers their age and developmental needs, ensuring it meets or exceeds the quality of care provided to other minors admitted to hospitals for various medical treatments.
 - This can be within the same compound, but has to be physically separate facility. Additionally, it is preferable to have separate facility for adolescent and children to meet the different developmental needs.
 - Recommendations regarding the clinical indications for using ECT in minors and the review process by the MHRB has been discussed comprehensively elsewhere.⁵
- e. Type of MH: Minor can be admitted to any MHE, however during the entire period of a minor's admission to the MHE, the NR or an appointed attendant must stay with the minor at all times. Additionally, only a female attendant should accompany minor girl.

3. ADMISSION INVOLUNTARY PATIENTS IN LONG STAY ~~SUPPORTED ADMISSION UNDER SECTION 89:~~

~~For the first thirty days the supported admission~~ All involuntary falls under section 89, and stay beyond 30 days or long stay comes under Section 90. The detailed process for supported admission under both these section has been summarized in table 3.

Table 3: Process for Supported admission and continuation under the Mental Healthcare Act, 2017 (Sections 89 & 90)

Time Period	Action Required	Additional Notes	Section
a. Processes under section 89			
	Request from Nominated Representative (NR) for supported admission		Section 89(1)
	Two independent examinations (psychiatrist + medical officer OR mental health professional)	Confirming eligibility for supported admission under section 89	Section 89(1)
	Admission to mental health establishment under section 89	Limited to 30 days	Section 89(2)
	Inform MHRB within 3/7 days (woman/minor or others)	As per Section 89(9)	Section 89(9)
Weekly (During Section 89 Admission)	Capacity assessment	As per capacity guidance document	Section 89(8)
<i>Before 30 days expire (If continuation is needed)</i>			
	Request from Nominated Representative (NR) for continuation		Section 90(2)
	Two psychiatrists independently examine	Confirming eligibility for supported admission under section 89	Section 90(2)
b. Process under section 90			
Within 7 Days of Admission/Re admission	Medical officer/Mental Health Professional reports admission/readmission to MHRB		Section 90(3)
Fortnightly	Capacity Assessment	As per capacity guidance document	Section 90(13)
Up to 90 Days	Initial supported admission period	Maximum duration for initial admission under Section 90	Section 90(8)
Within 21 Days of Admission/	Approval from Mental Health Review Board	Required for continuation under Section 90	Section 90(4)

Continuation			
	(If required) Board may request community treatment plan and progress report	For readmission or continued admission	Section 90(6)
<i>At every review (Up to 120, 180 Days)</i>			
	Request from NR for continuation		Section 90(2)
	Two psychiatrists independently recommend continuation		Section 90(2)
	(If required) Board may request community treatment plan and progress report	For readmission or continued admission	Section 90(6)
Within 7 Days of Admission/Re admission	Medical officer/Mental Health Professional reports admission/readmission to MHRB		Section 90(3)
Fortnightly	Capacity Assessment	As per capacity guidance document	Section 90(13)
First extension at 120 days	First extension period	Maximum duration for extended admission under Section 90, after completion of 90 days under Section 90	Section 90(9)
Subsequent extension at 180 days each time	Subsequent supported admission period	After completing 120 days of extension under section 90	Section 90(9)
Within 21 Days of Admission/Continuation	Approval from Mental Health Review Board	Required for continuation under Section 90	Section 90(4)

a. Criteria for admission under section 89: We can divide the admission criteria as severity criteria, least restrictive criteria and capacity criteria. The detailed admission criteria for these have been provided in table 4.

b. Professional opinion: The need and criteria for supported admission under section 89 is by independent examination by two professionals (one psychiatrist and one other mental health professional or medical officer), the qualification of whom should be as defined in the MHCA 2017.

c. Capacity requirement:

- ***At the time admission:*** Capacity assessment done as per capacity guidance document by the professions should ascertain that the PWMI lacks capacity to

make MHTD. No PWMI who has capacity to make MHTD should be admitted as supported admission.

- **Periodic reassessment under Section 89:** There should be a reassessment of capacity to make MHTD every week under Section 89(8). If the PWMI regains capacity during these weekly assessments, their admission under this section must be immediately terminated. At the end of 30 days, there should be a review in accordance with Section 90(1) to assess for continued admission under Section 90. This review should also involve capacity assessment.

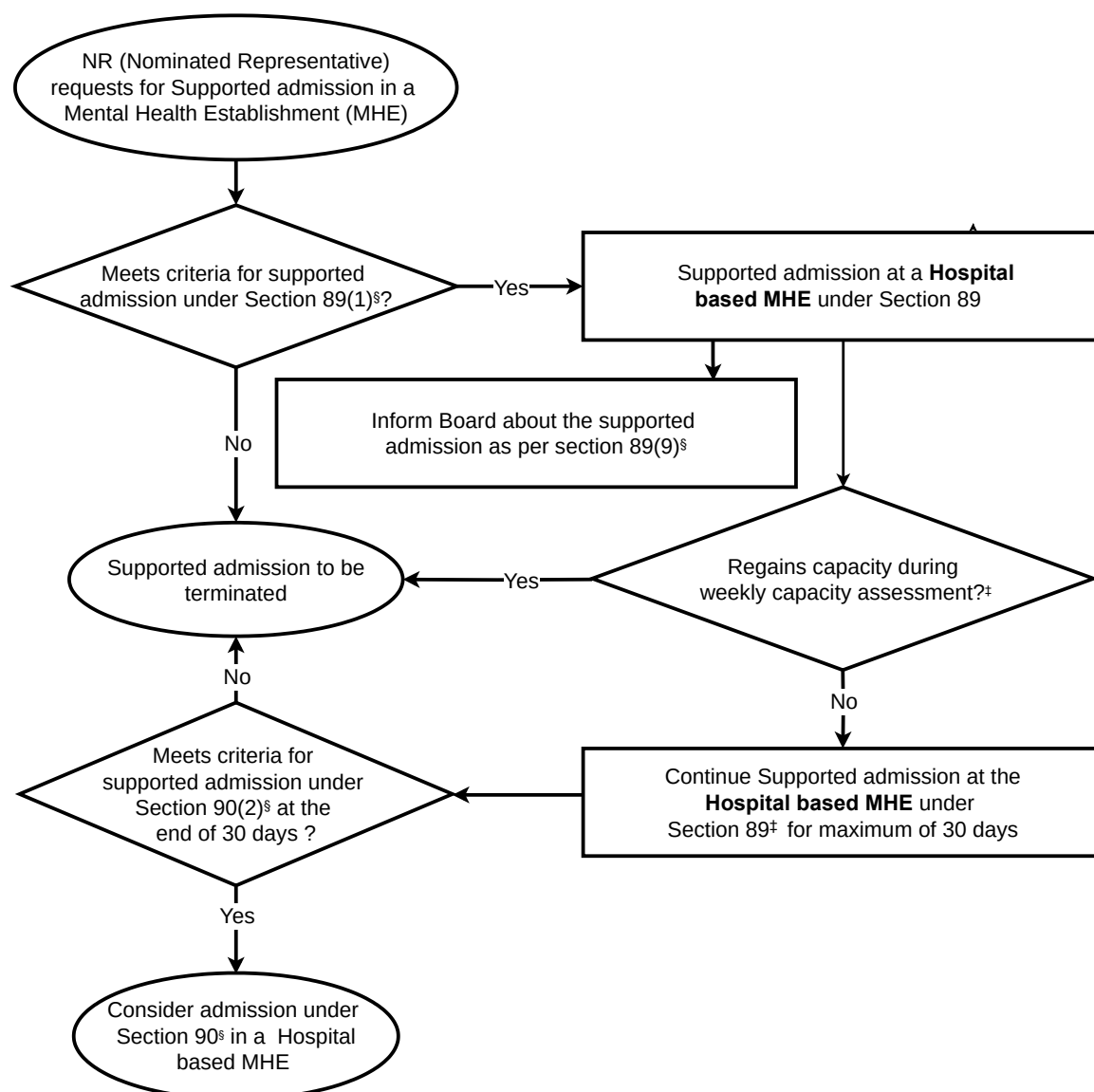
Type of supported admission	Under Section 89	Under Section 90
1. Pre-requisite criteria	• Request from Nominated Representative for supported admission of Person with mental illness (PWMI) at the MHE • The establishment should have valid registration as MHE	
2. Assessor criteria	1. One Psychiatrist, and 2. One Mental health professional <i>or</i> Medical practitioner	Two psychiatrists
3. Admission criteria		
3.a. Severity criteria:		
Criteria to be met	PWMI Has recently (i) Threatened or attempted or is threatening or attempting to cause bodily harm to himself; or (ii) behaved or is behaving violently towards another person or has caused or is causing another person to fear bodily harm from him; or (iii) shown or is showing an inability to care for himself to a degree that places the individual at risk of harm to himself;	PWMI Consistently over time, has (i) Threatened or attempted to cause bodily harm to himself; or (ii) behaved violently towards another person or caused another person to fear bodily harm from him; or (iii) shown an inability to care for himself to a degree that places the individual at risk of harm to himself;
3.b. Least restrictive criteria: Admission to the MHE least restrictive care option		
3.c. Capacity criteria: Needs very high support from his nominated representative in making decisions		

Table 4: Relevant section and criteria for supported admission [§]

[§] Subsection (1)&(2) under Section 89 and 90 of Mental Healthcare Act, respectively describes criteria for Supported admission to Mental health Establishment(MHE), which are as following

- d. Resources required: Supported admission typically will require high resource setting. There should be provision of acute care services as defined. These settings being restrictive should have additional human resources to adhere to the MHCA 2017 rules. For example, there should be monthly reporting of the restraint orders, and documentation related to the stay including steps taken to discharge from the restrictive environment.
- e. Type of MHE: Admission under section 89 should only occur at hospital based MHE. As the PWMI meeting the criteria for admission include risk of harm to self, others or severe neglect, they will be restrictive and inclusive of medical intervention. The decision pathway for supported admission under section 89 is depicted in figure 1.

Figure 1: Decision Pathway for Supported admissions under Section 89[§] (until 30 days)



[§] Section of Mental Healthcare Act, 2017

[‡] Capacity assessment to be done as per capacity guidance

* Board refers to respective Mental Health Review Board

4. SUPPORTER ADMISSION UNDER SECTION 90

- a. Criteria for admission under section 90: Continuation of admission beyond 30 days in MHE, necessitates a re-assessment by professional and periodic review by the MHRB. The criteria for admission under section 90 has been provided in table 5. The behavioural criteria for continuation are stricter, requiring the behaviours mentioned above to have occurred "consistently over time."

b. Professional opinion: Section 90 necessitates a re-assessment by two psychiatrists

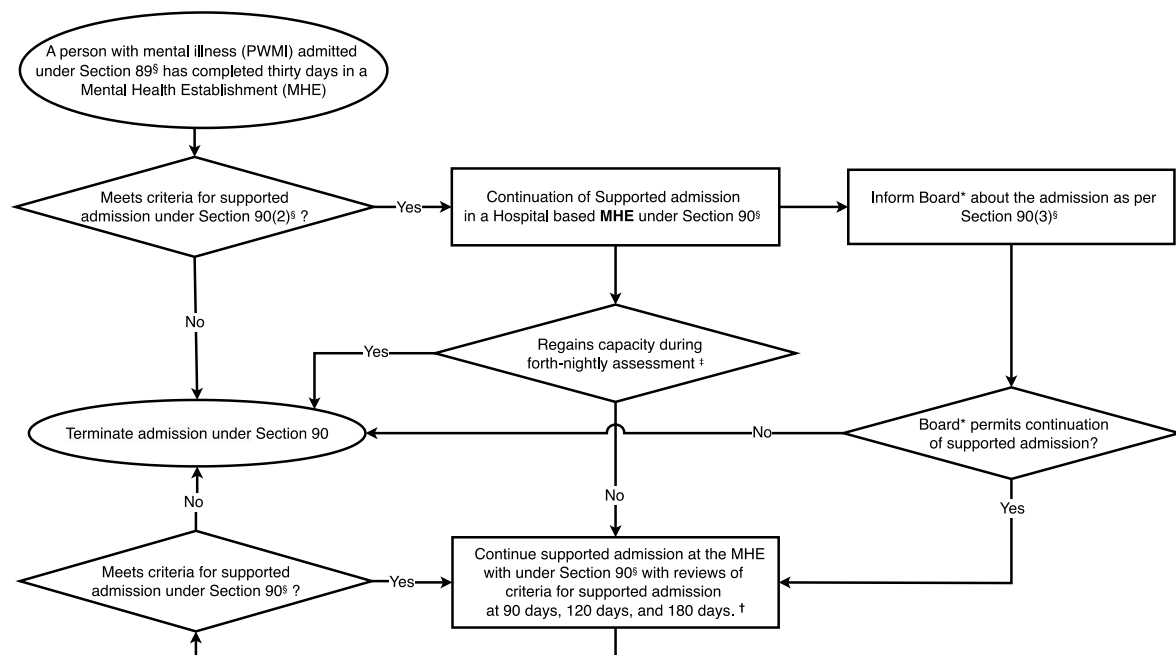
- c. Capacity requirement:

- Assessment before admission under section 90: As a part of the admission criteria, the professionals should assess for capacity. Only those who lacks capacity to MHTD should be considered of continuous admission under section 90.

- **Periodic reassessment under Section 90:** Capacity assessments should occur every fortnight for those admitted under Section 90(13). Those who regain capacity will be discharged, while those lacks capacity under Section 90(13) support can continue as supported admissions under Section 90 with treatment decision by the nominated representative temporarily for 14 days.

- d. Resources required: Since the criteria for supported admission under section 90 is stringent, characterised by consistent self-harm risk, violent risk or significant self-neglect, despite stay of 30 days, there should be specialised intervention plan with resource to handle the need of these PMWI. Additionally, it should have community treatment plan to reintegrate the PWMI into the community, which can be requested by the MHRB at the time of review
- e. Type of MHE: Similar to section 89, the admissions under section 90 should occur only at hospital based MHE. The decision pathway for supported admission under section 90 is depicted in figure 2.

Figure 2: Decision Pathway for Supported admissions under Section 90 (beyond 30 days)



§ Section of Mental Healthcare Act, 2017

‡ Capacity assessment to be done as per capacity guidance

† The admission shall initially be limited to 90 days. Beyond this period, the admission may be extended for an additional 120 days initially, and thereafter for periods of 180 days each

* Board refers to respective Mental Health Review Board

MANAGEMENT OF PWMI IN LONG STAY

1. PHARMACOLOGICAL MANAGEMENT IN LONG-STAY.

- a. Medications for the PWMI admitted as independent admission should be done with informed consent of the PWMI, after providing reasons for the medication. If a PWMI is refusing treatment, they should be provided with information of the consequence of not taking medication, and refusal should be documented. No PWMI who has capacity to make MHTD should be forced or given medication covertly.

- b. **Covert medication:** Covert medication should only be considered in PWMI who lacks capacity to make MHTD, when admitted at the MHE by the care team, when indicated, with the consent of NR for PWMI under section 89(8) and 90(13). Covert medication is known to be prevalent by the caregiver in the community care⁶, which is not recommended. Also, this should be avoided in PWMI who is willing to take oral medication. The decision pathway for covert medication when the medications are refused by PWMI, and the medication is deemed essential in the care plan is as depicted in figure 3. The pre-requisite for covert the medications are

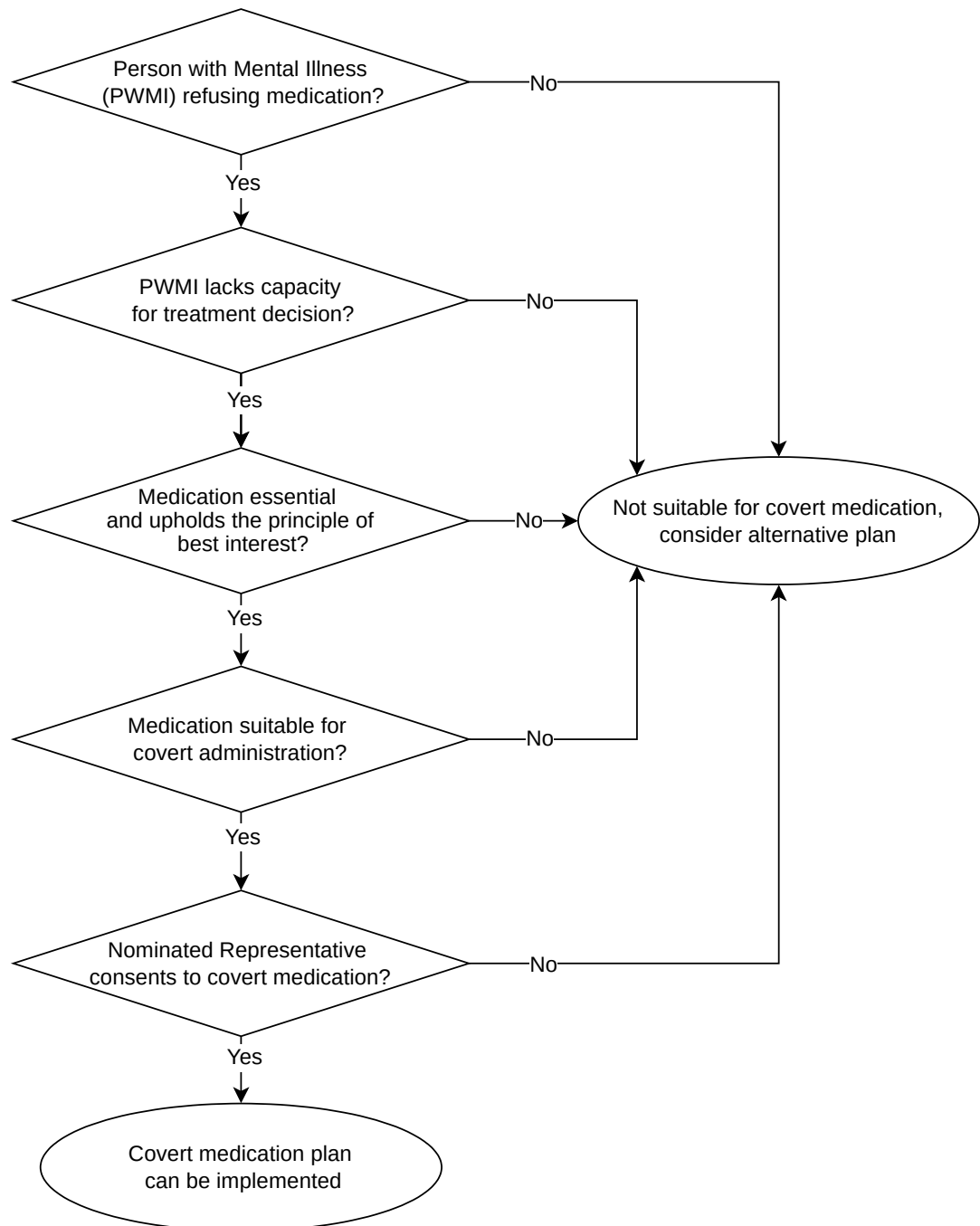
- Lacking capacity to make MHTD during capacity assessment
- Refusal by PWMI of the medication which is deemed essential in the care plan
- Written consent from the NR agreeing to covert medication, which is valid for a temporary period.
- After ascertaining that the covert medication is the least restrictive of the treatment care plan, with documentation of alternative options which has failed or rejected.

Important consideration when covert medication is to be initiated

- The initiation of covert medication has to be by a health care provider, with clear documentation to avoid duplication.
- After ascertain whether the PWMI has made an advanced directive to refuse a particular medicine that can be used to inform decision-making.
- A review of treatment response and consideration of suitability of crushing tablets, safety of crushing, interaction with food and absorption of medicine.
- Covert medication should not be done for the convenience of the staff, or as a routine, or to make up for the deficiency in the care provision.

Covert medication should not be continued if the person regains capacity to make MHTD.

Figure 3: Decision pathway for covert medication at a hospital based mental health establishment



Covert medication refers to the practice of administration of oral medication in disguised form

- c. **Parenteral medication:** Parenteral depot and rapid tranquillisation are considered restrictive practices. As a general rule, the benefits of using chemical restraints or parenteral depot for the PWMI must outweigh the potential negative effects and risks associated with not using the restrictive practice.

Rapid tranquillization: The chemical restraint can be fixed dose or symptoms triggered. In both scenarios, the use of chemical restraints (intramuscular or intravenous) as a restrictive practice may be considered under the following conditions at a MHE, with consent from the NR, in PWMI who lacks capacity to make MHTD:

- When it is the least restrictive option to prevent the PWMI's behaviour from causing harm to themselves or others taking into account the severity of the illness, and the history of multiple tranquilization in last 24 hours.
- As a temporary measure when there is a need to protect the PWMI and others from significant harm.
- As part of a treatment strategy that aims to create a safer environment for the PWMI and others, ultimately leading to reduced or eliminated need for restrictive interventions. The strategy can be fixed dose chemical restraint like twice a day, but has to be reviewed every day.

Additional considerations

- Less restrictive options have been evaluated and deemed unsuitable or ineffective.
- Mechanisms are established at the MHE to enable continuous monitoring and evaluation of the practice's use.
- Chemical restraint shouldn't not be used as a form of punishment or to make up for logistic difficulty such as shortage of staff at the MHE.

Parenteral depot: The decision to start parenteral depot should be done with consent of the PWMI. In rare cases, where the PWMI needs parenteral depot, and needs 100% support, the decision to start parenteral depot should be done with written consent of the NR for a temporary period, with each dose preceded by a capacity assessment if not done in preceding 14 days, which is done in accordance with Section 89(8) and Section 90(13). Consent has been obtained from the NR prior to implementation.

2. USE OF RESTRAINTS AND SECLUSION IN LONG-STAY : Restraint guidelines for mental health services in India has been discussed comprehensively in the earlier IPS guidelines on restraint.⁷

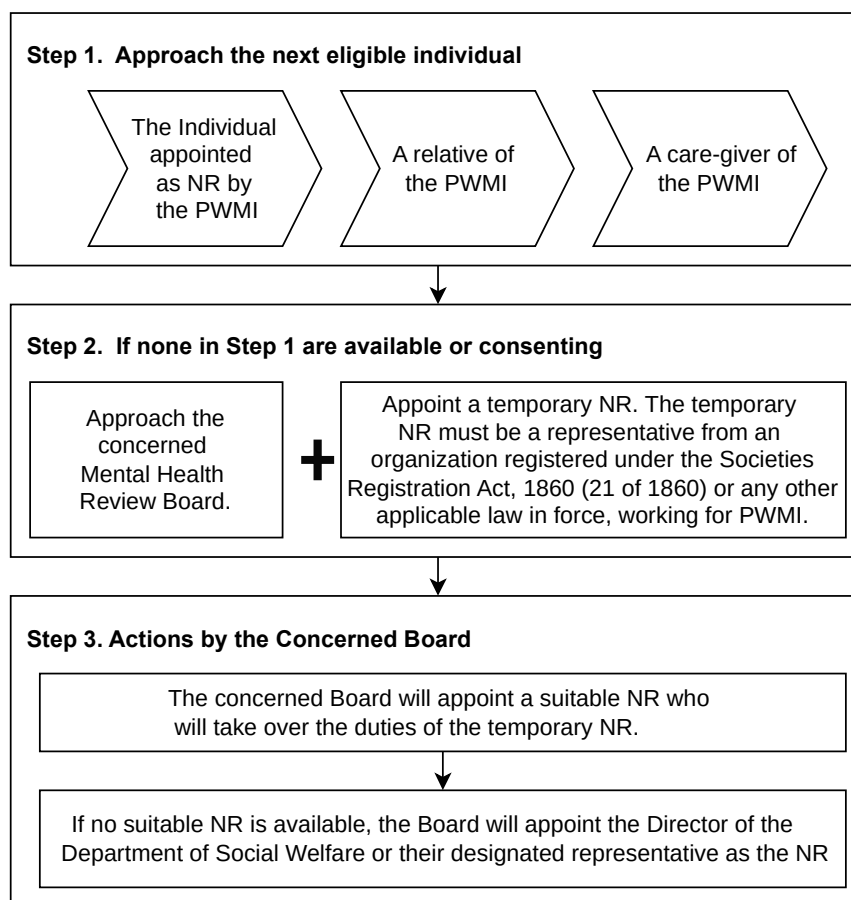
3. COMMUNICATING WITH THE NOMINATED REPRESENTATIVE (NR) OR FAMILY

- Independent admission, the presence of caregiver is not required, unless the policies of the MHE advocated for the same.
- For PWMI admitted under supported admissions, periodic capacity assessments occurs periodically, contingent upon the PWMI not regaining capacity. These interactions provide an opportunity to update the NR on the PWMI's health status, treatment progress, and any modifications to the treatment plan, ensuring that the NR is informed and involved in the ongoing care process. Decisions such as covert medication, ECT should be done only after taking written consent of the NR.

- When the NR is not available, the steps to be followed has been mentioned has been described in Section 14(4) of Mental Healthcare Act, 2017 to make MHTD. The details of these steps is depicted in figure 4.
- In the event of emergencies or significant changes in the PWMI's condition, the NR must be promptly informed. All communication with the NR or family should be thoroughly documented, including the date, time, content of discussions, and any decisions made. This documentation ensures transparency and accountability while safeguarding the PWMI's confidentiality and privacy as per legal requirements.
- Additionally, MHEs should make attempts to provide support and educational resources to NRs and families to help them understand the PWMI's condition, treatment options, and the role they play in the recovery process. This can include informational brochures, workshops, support groups, and individual counselling, fostering a supportive and collaborative environment for all stakeholders involved.

4. Minimum standards for MHE: The minimum standards for registration of the MHE has to be in accordance with rules and regulations prescribed by the respective authority in accordance with MHCA 2017.

Figure 4: Step wise procedure when Nominated Representative (NR) is not available⁵



⁵In accordance with Section 14(4) of Mental Healthcare Act, 2017

DISCHARGE PROCEDURES UNDER THE MENTAL HEALTHCARE ACT, 2017:

The Mental Healthcare Act (MHCA), 2017, outlines specific procedures for the discharge of patients admitted to mental health establishments (MHEs). These procedures vary depending on the type of admission and the patient's condition

1. Discharge Planning (Section 98)

Discharge plan is a mandatory requirement for all discharge from a MHE, irrespective of type and setting of admission as per Section 98 of the MHCA,

Community treatment plan should be made with available resource. It is important to note that discharge planning is an ongoing process, and it should start from the time a PWMI is admitted to MHE. A community treatment plan is required to be presented to MHRB, when PWMI is admitted under section 90, when applying for review to the MHRB, for continued supported admission.

Collaborative Planning: Before a patient is discharged, the psychiatrist responsible for their care must consult with the patient, their nominated representative, family members, caregivers, and other relevant parties to develop a discharge plan.

Post discharge plan: The plan should outline the treatment and services that will be provided to the patient after discharge, ensuring continuity of care and support in the community. This includes providing emergency contact number in case of crisis, with mentions of follow up date.

The post discharge plan should consider relevant practices in the country such as proxy consultation⁸, however ensuring that the provisions of the MHCA 2017 are not violated. Refill medication has been practiced in developed countries(UK and Australian reference). The refill prescription has to be for the shortest duration, and with prior authorization and the duration not more than 6 months, and can be with caution and proper monitoring mechanism for medication which require frequent monitoring such as clozapine.

2. Discharge of Independent Patients (Section 88)

Right to Request Discharge: PWMI admitted as independent patients (under Section 86) have the right to request and obtain immediate discharge from the MHE. This right is subject to certain exceptions.

Exception for discharge of independent admission: A mental health professional may prevent the discharge of an independent patient for up to 24 hours for assessment if they believe the person:

- Is unable to understand their decisions and needs substantial support.
- Has threatened or attempted bodily harm to themselves or others.
- Has behaved violently or
- Shown an inability to care for themselves.

After the assessment, the PWMI will either be admitted as a supported patient under Section 89 or discharged within 24 hours

3. Discharge/ leave of absence for supported admission:

- **Discharge of supported admission:** The decision on discharge of PWMI who regains capacity to make treatment decision under specific section has been well addressed in the respective section related to supported admission in MHCA 2017. PWMI lacking capacity to MHTD admitted under section 89, 90 will undergo periodic capacity assessment as stipulated, with termination of supported admission once the PWMI regains capacity to MHTD. The PWMI can decide further management, which option of him continuing admission as independent discharge or discharge. However in those who continues to lack capacity to make MHTD, a request from NR is deemed appropriate for to initiate discharge procedure for PWMI under section 89(8) and 90(13), when mental health professionals of the MHE also determine that continued admission is not necessary. However if the mental health professionals determine that continued admission is necessary for the safety and well-being of the patient, but the nominated representative disagrees, the matter needs to be resolved through the Mental Health Review Board.
- **Leave of Absence (Section 91):** The medical officer or mental health professional in charge of the MHE can grant leave of absence to any PWMI under supported admission, or admission of minor. The NR of the PWMI will request for leave of absence for the PWMI lacking capacity to MHTD, following which the medical officer or psychiatrist in charge of the PWMI admitted, will determine the duration and conditions of the leaves.

4. Transfer Between MHEs

- ~~Transfers of independent patient between (From H MHE to C MHE):~~ The discharge of long stay PWMI in psychiatric hospitals is often hindered by complex barriers such as the unwillingness of families to take patients back, patients' inability to communicate their address, and logistical issues when patients belong to different states or countries.⁷ In such cases, the continuation of admission in a restrictive MHE should be avoided. Long stay patients in H MHE who have the capacity for MHTD should be transferred to a less restrictive environment, such as community based MHE like half way homes, if no alternative facility is available or deemed appropriate. Capacity assessment should occur at the H MHE before transfer, where the PWMI is residing suitability to be shifted to C MHE. The admission of the independent PWMI should be done with the informed consent of the PWMI. The PWMI should be provided with sufficient information about the C MHE, before making the consent.

~~Transfer of PWMI admitted under supported admission:~~ The transfer of the PWMI admitted under section 87, 89 and 90 can occurs between MHEs as per the provisions of Section 93. Transfers within the same state must follow the Mental Health Review Board's orders, while transfers to another state require the Central Authority's consent. For PWMI admitted under supported admission (Sections 89 and 90), both the PWMI and their NR must be informed in writing about the transfer, including the reasons for it.

● Transfers of PWMI admitted as supported admission between H-MHEs:

Transfers between two MHEs might be necessary for various reasons, including access to specialized care not available at the current facility, geographical considerations (e.g., proximity to family), or a better suited therapeutic environment based on the NR's preferences or needs. This should be done in accordance with section 93.

Transfer from C MHE to H MHE: A PWMI admitted at C MHE, who needs care at high resource setting, as supported admission needs to be promptly transferred to H MHE.

Transfer between two facilities within a MHE, need not be informed to the Board, unless specifically requested by the board. PWMI can continue with the same documentation related to MHCA within different facilities of the same MHE. However if the PWMI is deemed having lacking capacity during the admission as independent admission, the further admission occurs as supported admission under section 89, the process of admission under section 89 should be initiated, as described including informing the boards in the stipulated time. As far as possible, when transfer occurs between two services within the MHE, the treating team should be same, ensuring continued relationship between the treating team and PWMI.

PWMI admitted under reception order before the notification of the MHCA 2017, should be converted as independent admission or supported admission under section 90. PWMI admitted with order from the Magistrate after the notification of MHCA, comes under section 102, and should be dealt in accordance of the provisions of the MHCA within 10 days, i.e. discharged, admitted as independent patient or as supported admission under section 89.. Additionally in the both the situation, the Magistrate have to be provided with report pertaining care of the PWMI.

5. Role of stakeholders in discharge from long stay

For successful deinstitutionalization, it is crucial to establish comprehensive community resources such as housing, employment opportunities, vocational training, empowerment programs for individuals with lived experience, and robust social support networks.⁴

The social welfare department is essential in the rehabilitation of long stay PWMI, particularly in discharge planning and providing necessary social support to facilitate community integration.⁹

NGOs play a vital role in addressing service gaps by rescuing PWMI from the streets and providing rehabilitation and reintegration support, thereby filling a critical need in the mental health care system.¹⁰

6. Managing the Demise:

Demise of the PWMI in the MHE needs to be informed to the police at the earliest. The NR and family must be promptly informed if not present at the premise. A copy of the medical record has to be preserved. A qualified medical professional should certify the death, adhering to legal requirements. Thorough documentation of the cause of death, care provided, and communications with the NR/family is important. Post-demise, grief counselling and bereavement support should be offered to the NR and family.

RESEARCH IN LONG STAY

Any research involving a PWMI who is unable to give informed consent must obtain permission from the concerned State Authority in accordance with Section 99 of the MHCA 2017, in addition to registering with the CTIRI and adhering to ICMR ethical guidelines.

KEY DEFINITIONS

For the purposes of this paper, the following terms shall be defined based on the existing guidance, MHCA 2017 ³ and Mental health atlas of WHO ⁴. The definition of Mental health professional, psychiatrist, medical officer will be as defined in the MHCA 2017.

Definitions for various residential Facilities for PWMI: A PWMI can reside with friends and family, independently in community based facilities, or at Mental health establishments.

Any residential setting, excluding family residences, where a PWMI resides as defined in Section 2(p) of MHCA constitute Mental Health Establishment (MHE). These facilities should be registered as Mental Health Establishments (MHEs) in accordance with MHCA 2017, and can be classified as hospital based or community based MHE.

a. **Hospital based Mental Health Establishment (H-MHE):** These establishments registered as MHE as per MHCA 2017 are located within a hospital setting and provide inpatient and residential care to PWMI along with provision for acute care intervention, and includes

i. **Psychiatric Institution:** These are standalone specialized facility providing inpatient care and long-stay for PWMI. These includes, but not limited to State Mental Health Hospitals and Institutes of Mental Health, and can operate independently or maintain connections to the broader healthcare system,. The range of services offered by psychiatric institutes varies greatly. Most will have provision for long-term custodial care and provide short-term services, while some will have and specialized services like rehabilitation, child and adolescent units, and geriatric care.

Includes : This category encompasses both public and private psychiatric institutions/nursing homes/hospitals, including non-profit and for-profit institutions. Hospitals/clinics meant to provide mental health care of specific population such as elderly, children and adolescents, and persons with substance use disorder, with provisions for inpatient care.

Exclusion: Standalone community-based establishments are excluded from this definition. Additionally, facilities exclusively treating intellectual disabilities without a concurrent mental disorder diagnosis are not considered psychiatric hospitals. Those providing standalone outpatient services to PWMI are not considered Psychiatric institutions/MHE.

- ii. **Psychiatric Units/Psychiatric ward in a General Hospital:** These are specialized facility within a general hospital, medical college or a multispeciality hospital/polyclinic/nursing home, that provide inpatient care for PWMI experiencing acute mental issues. These units typically offer short-term stay of few weeks to months, and focus on managing the acute concerns.

Includes : Both public and private psychiatric units are included in this category, encompassing non-profit and for-profit organizations. This also extends to specialized units in general setting catering to substance use disorder and specific populations, such as children, adolescents, and the elderly.

Exclusion: Psychiatric institutions, community residential facilities, and facilities exclusively treating intellectual disabilities without a co-occurring mental disorder diagnosis are excluded from this definition.

- b. **Community based - Mental Health Establishments(C-MHE):** These establishments are located outside of a hospital setting and provide residential services for PWMI in the community/ These facilities cater to PWMI whose conditions are relatively stable and do not require acute care services.

- i. **Mental health community residential facilities:** These are registered MHE, which are non-hospital setting that provides overnight accommodation and primarily built to support PWMI. The range of facilities in this category are broad, and includes half way homes for PWMI discharged from a hospital, quarterly home and hostels with varying level of staff support and therapeutic communities.

Includes : Both public and private facilities, including non-profit and for-profit organizations, fall under this umbrella. Non-hospital facilities specifically designed for PWMI with substance use disorder and for mental health concerns of special population (such as children, adolescents, or the elderly) are included here.

Exclusion : Facilities exclusively treating intellectual disabilities, residential facilities within psychiatric institutions, and general care facilities not specifically designed for persons with mental health needs (such as nursing home for elderly people, and long stays for treating for physical disabilities, neurological disorder) are excluded from this definition

- ii. **Other residential facilities:** Refers to residential facilities where PWMI resides, which does not fit in the criteria of hospital based mental health facilities or Mental health community residential facility, and needs to be registered as MHE. These includes general care facilities not specifically designed for persons with mental health needs but having persons with concurrent mental disorder diagnosis (such as nursing home for elderly people with dementia, residential facilities specifically for persons with

intellectual disability and palliative care residential facilities housing person with diagnosable mental illness).

Community based Residential Facilities: These are facilities PMWI reside independently with support such as supported accommodation as defined in in Rule 2(i) of the Mental Healthcare (Rights of Persons with Mental Illness) Rules, 2018, and group homes. This support helps the person live independently and safely within the privacy of their home.

Definitions for various Services for PWMI admitted to Mental Health Establishments : MHEs provide a range of residential services with varying levels of intensity and duration, tailored to the individual needs of PWMI. These include:

- a. **Acute care services (ACS):** ACS are specialized medical interventions provided at H-MHEs to address immediate and significant risks of self-harm, harm to others, or self-neglect in PWMI in the acute phase of treatment. Due to the need for intensive monitoring and intervention, ACS are typically provided in more restrictive H-MHEs, such as mental health hospitals or psychiatric wards of general hospitals as defined. These services prioritize safety while facilitating a transition to appropriate community-based treatment.
- b. **Rehabilitation services:** As defined in MHCA Rules 2(e), these services focus on reintegrating PWMI into the community by utilizing existing resources. They aim to empower individuals to become independent in various aspects of life, including financial self-sufficiency, social interactions, and relationship building. Typically these are provided at less restrictive environment.
- c. **Covert medication:** In this CPG, covert medication refers to the practice of administration of medication in disguised form (e.g., in food or drink) to a PMWI who lacks capacity to make mental health and treatment decisions, without their knowledge or consent, within a Hospital based MHE. This does not include the administration of medication in food or drink to aid swallowing or through medical tubes, as long as the PWMI is aware of the medication.

Definitions related to capacity to make mental health care and treatment decision: The capacity guidance document, prepared by the expert committee as per Section 81 of the MHCA 2017, stipulates that after the assessment, the decision should be categorical, specifying either that the PWMI has the capacity to make Mental healthcare and treatment decisions (MHTD) including admission or that the PWMI needs 100% support from their nominated representative(NR) in making treatment decisions including admission. However, it is important to note that in the MHCA 2017, capacity is a dimensional concept, based on the degree of support needed by a PWMI to make decisions, viewing it as a continuum rather than a binary state, with levels such as high support, very high support or 100% support. Having an operational definition of capacity as either having or lacking it is important for several reasons: it provides clarity in decision-making, consistency in care, ease of assessment, maintaining high standards and facilitates documentation and accountability, providing a clear basis for tracking and reviewing decisions regarding capacity to make MHTD.

- a. **Lacks capacity to make Mental Healthcare and Treatment Decisions (Lack capacity to make MHTD):** A PWMI is determined to lack capacity to make mental health and treatment decisions if, assessment based on capacity guidance through examination and relevant history, behavioural observation, clinical findings, and mental status examination findings noted in the medical records, the psychiatrist/mental health professional/medical practitioner believes that the PWMI needs 100% support from his/her NR in making treatment decisions, including admission. The presence of cognitive deficits does not necessarily translate into a lack of capacity to MHTD. Therefore, a capacity assessment should be conducted whenever major decisions regarding MHTD needs to be made, in addition to cognitive assessment.
- b. **Has capacity to make Mental Healthcare and Treatment Decisions (Has capacity to make MHTD):** A PWMI is determined to have capacity to make mental health and treatment decisions if, based on capacity guidance through examination and relevant history, behavioural observation, clinical findings, and mental status examination findings noted in the medical records, the psychiatrist/mental health professional/medical practitioner believes that the PWMI can make treatment decisions, including admission.

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Clinical Practice Guidelines

Assessment of Needs among Persons with Mental Illness and Persons with Substance Use Disorders with Long Stay in Psychiatric Institutions.

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Introduction

While there is variance in what can be termed as long-term hospitalisation, persons with mental illnesses (PMI) may rarely require more than 90 days of continuous hospitalisation. Section 90 (8) of the Mental Health Care Act (MHCA) 2017 states that if a PMI requires more than 30 days of supported admission, the need for such admission should be limited to 90 days in the first instance [1]. A few researchers have defined more than one year of stay in psychiatric hospitals as long stay [2]. We have used the term long stay PMI to denote those who require more than 90 days of hospitalisation in psychiatric hospitals and those who could not be discharged due to deficiencies in their support systems, such as absent family caregivers or unwilling family caregivers or lack of a safe place to live or deficits in independent living ability if they were to live alone in the community.

The needs of PMI and, therefore, the support needed can vary based on underlying mental illnesses, personality characteristics and psycho-social circumstances. In this article, we have arranged the needs assessment of PMI with severe mental disorders (SMD) like Schizophrenia and Bipolar affective disorders (BPAD) separately from the needs assessment of PMI with substance use-related disorders. However, such a distinction is artificial, and often, there would be similarities than differences between needs.

Process of development of guidelines:

A PubMed search using terms relevant terms of needs, long stay, severe mental illness, and substance use disorders was done. A grey literature review of various government documents, independent documents from various NGOs, and consultation with domain experts were done for the development of this document.

Purpose of Assessment:

1. Discharge from hospital
2. Community re-integration
3. Least restrictive environment
4. Participatory rights-based and recovery-oriented approach
5. Holistic and person-centered care – focus on psychological, lifestyle, social, and economic interventions, not merely pharmacological interventions.

Needs of Persons with Severe Mental Illness (PMI) in psychiatric hospitals

(NHRC reports, NCW report on women, Hans Foundation Survey)

The Hans Foundation survey in 2019 surveyed 43 psychiatric institutions across India and observed that 4935 PMIs stayed on average for more than six years in the closed wards. About one-third of them were admitted by their family members in these psychiatric

hospitals. This report further stated significant variations in the number of PMIs across India. Maharashtra, Tamil Nadu, and West Bengal had over half of all PMI. This report further stated that half of long-stay PMI had Schizophrenia, 22% had Intellectual Disability (ID), and 17% had Psychosis, not otherwise specified. [3]

A range of reasons contributed to the extended stay of PMI in psychiatric hospitals. In many instances, family caregivers were untraceable for a planned discharge and to ensure family reintegration [4-5]. Poor social functioning and independent living abilities were observed in PMI admitted for longer periods [6]. PMI may have one or more medical conditions that require frequent medical supervision, or they may have patterns of behaviour that pose significant challenges for living in supported living facilities [7]. Negative symptoms of schizophrenia are observed to be associated with unmet rehabilitation needs [8]. PMI may have cognitive impairment with a range of medical problems which interfere with their ability to live independently in the community [9]. Lack of homes to live in and poor community living facilities for PMI could contribute to such long stays [10]. Apart from the patient characteristics like age at the time of admission and functional ability, intellectual disability, personality characteristics, socio-economic issues, institutional characteristics, such as whether the institute is an academic institution, appear to play a role in the extended stay of PMI [11]. Irrespective of a range of reasons contributing to the long stay of PMIs in psychiatric hospitals, many PMIs admitted under long stay were observed to have the ability to live independently if a safe place to live was offered with adequate and a range of required support [12].

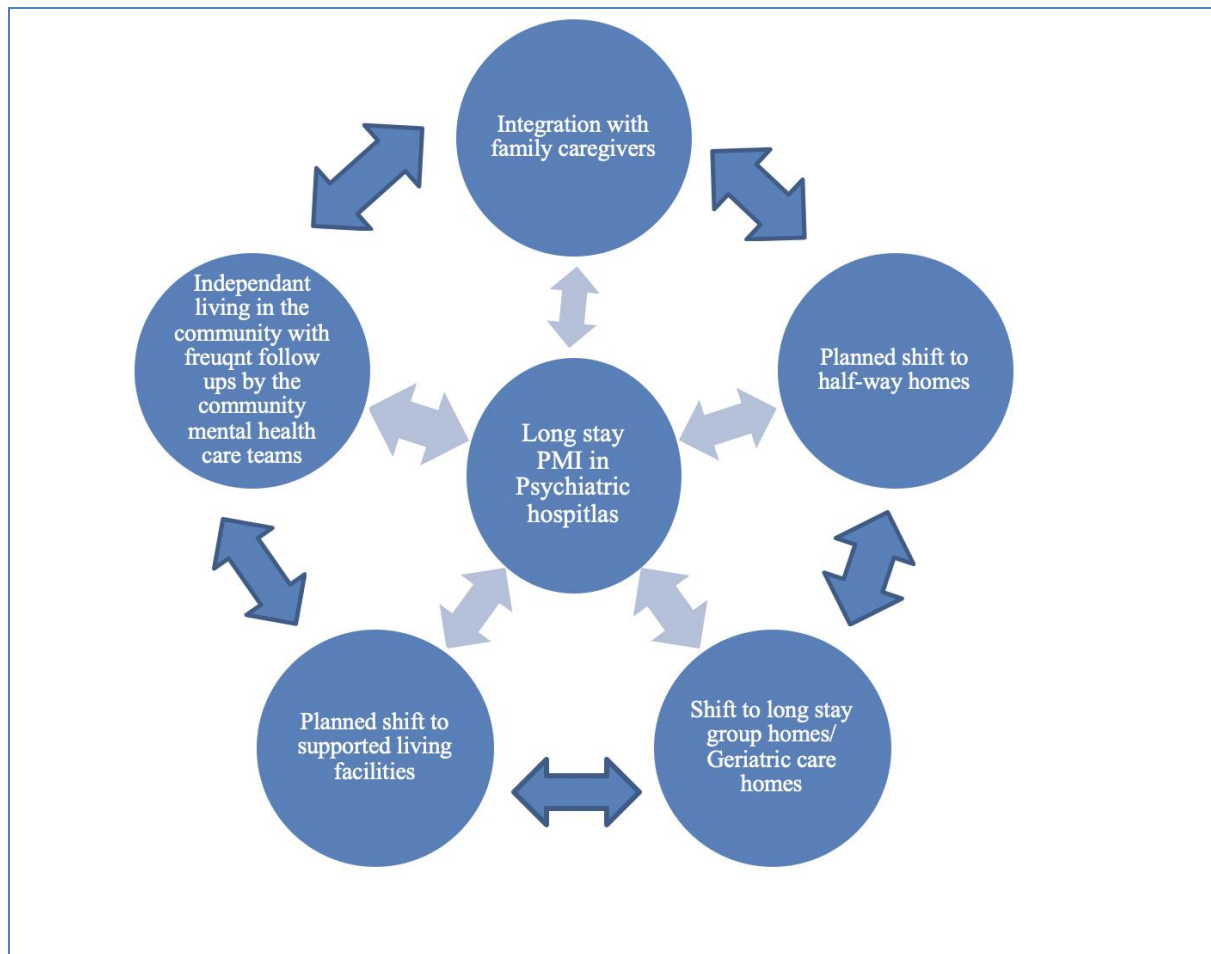
From the above discussion, we can presume that the extended stay of PMI in psychiatric hospitals is multifactorial, ranging from patient characteristics which impact ability to live a quality life post-discharge to the availability of adequate and appropriate community mental health care facilities. Therefore, to understand the needs of PMI admitted for longer periods in psychiatric hospitals, we should examine it from a multi-dimensional perspective. Often, the needs of PMI during the initial period of psychiatric hospitalisation are related to control of symptoms irrespective of their clinical diagnosis. It includes improving the disturbances in biological functions and controlling the behaviours, thoughts, or perceptual disturbances that may endanger their safety and others. In contrast to this, the need for PMI to stay in psychiatric hospitals for a long time is often related to PMI's medical and mental health morbidities, strengths and deficits, socio-economic situations, homelessness, family support, substance use, availability of community care facilities and access to such facilities. Section 98 of MHCA 2017 has stated that the treating psychiatrist of a PMI in any mental health

establishment (MHE) should plan the continuity of mental health care after understanding the choices of PMI, discussing with relevant mental health professionals in the community where the PMI is going to reside, and the caregivers/ family members/ nominated representatives [1] Following the steps as mentioned earlier before the discharge planning of PMI who do not have family caregivers may be difficult and can be challenging.

Assessment of the needs of PMI admitted in psychiatric hospitals for prolonged periods may be conceptualised into two categories. One category of evaluations would be related to the severity of mental illness, activities of daily living, meaningful engagement, and level of awareness about the need for mental health care and treatment. Another category is related to their ability to return to work, reality orientation, strengths and deficits that influence their ability to make choices, and support in the place where they will stay after discharge. However, assessment of needs only helps to understand the types of support and intensity of support needed for PMI. A range of community-based mental health care services will be essential for offering continuous medical care. Often, such assessment should also include the readiness of PMI to go back into the community, as prolonged stays in psychiatric hospitals may also lead to the development of pessimistic attitudes towards living in the community [13]. A few other assumptions or even experiences of psychiatric hospital authorities that could prolong the stay of some PMIs are related to frequent and repeat hospitalisations, which further could be related to poor symptom control and personality trait-related challenges to adjust in the community. Yet, a slow transition of them through a range of community care facilities is likely to enhance their community reintegration [14]. Needs assessment of PMI should be person-centred as significant differences have been observed between the self-reported needs of PMI in comparison to those as assessed by professionals [12]

The Hans Foundation survey, 2019 stated that about 80% of PMIs staying in Indian psychiatric hospitals for more than one year were likely to face mild to moderate challenges in leading a quality community life, and the remaining 20% were likely to face severe to profound difficulties if left alone. They all required some form of support of variable frequency and intensity. Based on our experience, we formulated a model in which the PMI can move to any one of the standard living options, subject to the availability of a range of supports and services, personal preferences and functional abilities. PMI can move from one to another as each conceptualised option offers a range of freedom, restrictions, scope for exercising their choices and autonomy.

Figure 1: A model to describe the transition of PMI with SMD requiring continuous support



To understand more about to which long-stay PMI can be transitioned, mental health professionals should know not only the strengths and deficits of PMIs but also the availability of community mental health care facilities in a geographical location. A simple generic approach that may be considered for comprehensive needs assessment can be the World Health Organisation Community-based rehabilitation matrix, which includes five components (Health, Education, Livelihood, Social and Empowerment). [15]. A comprehensive assessment might require many hours of assessments and several interactions with PMI and other important stakeholders.

The following tools can be helpful to mental health professionals/ trainees to have a broader understanding of the multi-dimensional needs of PMI staying in psychiatric hospitals for a prolonged period. However, these tools cannot replace the subjective judgement of the psychiatrist who understands the pragmatic needs and the rights of PMI.

Tool to assess capacity to make treatment choices

1. Capacity Assessment Guidance Document for PMI admitted in Psychiatric hospital (Prepared by Expert Committee as per Section 81 of Mental Healthcare Act, 2017) [18].

Tools to assess Activities of daily living (ADL)

1. Katz Index of Independence in ADL [16]: 6 items (Bathing, Dressing, Toileting, Transferring, continence, and feeding) are scored from 0 to 1 on each item.
2. Barthel Index of Daily Living [17]: 10 items that measure a person's daily functioning, specifically the activities of daily living and mobility. The items include feeding, moving from wheelchair to bed and return, grooming, transferring to and from a toilet, bathing, walking on a level surface, going up and down stairs, dressing, and continence of bowels and bladder.
3. Everyday abilities scale for India

Tools to assess Instrumental Activities of Daily Living(IADL)

1. Lawton Instrumental Activities of Daily Living (IADL) The scale measures eight function domains: food preparation, housekeeping, and laundering. Individuals are scored according to their highest level of functioning in that category. [19]

Tools to assess clinical and personal recovery

1. Recovery Assessment Scale (RAS) [20]: This scale measures personal confidence and hope, reliance on others, goal success and orientation, and willingness to ask for help.
2. The Recovery Star is designed for adults managing their mental health and recovering from mental illness. It was developed by Triangle in collaboration with the Mental Health Providers Forum. It assesses 10 domains and is underpinned by a five-stage journey of change model: stuck, accepting help, believing, earning and self-reliance [21]

Tools to assess readiness to discharge

1. Readiness for Discharge Questionnaire (RDQ) [22]: 6 items assessing suicidality/homicidality, control of aggression/impulsivity, activities of daily living, medication-taking, delusions/hallucinations interfering with functioning and global status

Tools to assess overall functionality

1. Global Assessment of Functioning (GAF) Scale [23]: This scale measures global functionality on a linear scale of 1-100. The higher the score, the greater the functionality

2. The Clinical Global Impression (CGI) Scale [24]: The severity of illness and Global improvements are measured on a 7-point scale. Higher scores indicate severe illness and poor improvement.
3. Social Occupational Functioning Scale (SOFS) [25]: A brief yet comprehensive, easy to administer measure of social functioning in persons with schizophrenia. It measures adaptive living skills, social appropriateness and interpersonal skills

Tools to assess social living skills and community support required

1. The Social Network Map [26]: This measure helps to map the supports available in drawn circles around the PMI under different ecosystems.
2. Camberwell Assessment of Needs (CANSAS) [27]: This scale is used to assess the unmet needs across the domains and to track the changes in the felt needs over a while.
3. Life Skills Profile: A 20-item questionnaire is available to assess the community living needs of persons with Schizophrenia. [28]. Others with fewer and more items (16 and 39) are also available.
4. Social Functioning Scale [29]: It is used in persons with Schizophrenia and contains 79 items. It measures social engagement, interpersonal behaviour, prosocial activities, independence, and participation in recreational and employment activities.
5. SCARF Social Functioning Index [30]: It rates the individual's social functioning in the areas of self-concern, occupational performance, role in the family, and other social role performances.

Tools to assess vocational potentials in PMI

1. Vocational Potential Assessment Tool (UDYOG): It assesses the strengths, deficits, aspirations and suitability to potential employment in PMI [31]

Tools to Assess Disability

1. Indian Disability Evaluation Assessment Scale (IDEAS): IDEAS measures disability by assessing self-care, interpersonal relationships, communication and understanding, and work domains in addition to calculating duration spent with mental illness over the preceding two years [32].
2. World Health Organisation Disability Assessment Schedule (WHODAS) 2.0: This scale SS measures six domains: cognition, mobility, self-care, getting along with people,

life activities and participation. [33]. There is a longer 36 item and a shorter 12 item version.

Tools to assess Health related Quality of Life

1. World Health Organisation Quality of life (WHO-QOL, WHO-QOL BREF): It measures individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. [34].
2. Euro-QOL
3. Disorder-specific scales: Schizophrenia, Bipolar disorder, etc.

Tools to assess well-being:

1. WHO-5 well-being index
2. Warwick-Edinburgh Mental Wellbeing Scales

Assessment of physical health

1. Multimorbidity assessment- disease counts, composite measures
2. Health risk behaviours – tobacco use, diet, and physical activity- WHO STEPS manual
3. Guidelines for monitoring physical health-LESTER Tool

Psychosocial assessment

1. Income: Below Poverty Line (BPL) card
2. Citizenship status: Aadhar card, Passport, Voter ID, Bank account
3. Social protection measures: UDID, Disability pension etc.

Long-term rehabilitation for persons with substance use disorders (SUDs)

Substance use disorders are chronic relapsing-remitting illnesses that require long-term care. Whether it is on an outpatient or inpatient-based care, evidence suggests that long-term treatment for substance use disorders has better outcomes compared to short-term treatment [35]. The history of long-term rehabilitation or long-term residential programs started in the 1950s as therapeutic communities (TCs) and drug-free residential programs. There was a paradigm shift in looking at addiction recovery from a treatment perspective. Therapeutic communities is a generic term in some countries for long-term and short-term residential programs. Long-term treatments worldwide are known by various names: extended intervention, continued care, stepped care, recovery management, or aftercare. These

treatments have different approaches. Therefore, there are no standardized definitions in terms of the model of care.

In the USA, the duration of long-term rehabilitation of substance use disorders is around three months, and short-term rehabilitation is around three weeks. A majority of people received short-term care compared to long-term care. While such data is lacking from India, published data from private rehabilitation centers suggest a 4-6 weeks stay [36-37]. In NIMHANS, the duration of inpatient care is around three weeks [38]. In India, data from government-run integrated rehabilitation centers for addicts (IRCAs) suggest that the duration of stay is around three months [39]. The camp approach followed in different places across India the duration of stay has varied. For example, in camps at Chandigarh, patients were admitted for ten days, and in Manjakuudi, Tamil Nadu, they were admitted for 15 days [40-41]. In Karnataka, the camp duration was eight days [42].

Needs of long-stay persons with SUD

“Need” is the requirement of the individual that enables them to achieve, maintain, or restore an acceptable level of social independence or quality of life [43]. “Need” is the discrepancy between the current and desired states [44]. While the needs of the long-stay patients are diverse, a broader goal is recovery (Figure 2). Before we understand the needs of a person seeking addiction treatment, it is crucial to understand what recovery means in persons with substance use disorders.

Addiction recovery is a gradual, complex, long-term process, different for every individual (personalized) [45-46]. While clinical recovery is staying abstinent from drugs, a broader definition of addiction recovery is associated with various life domains beyond abstinence [47]. These include health, work, education, housing, legal, social, and economic well-being. Overtime control over substance use, along with abstinence, is included in the definition. Support to individuals and families generally helps in the recovery process. Individual, family, and treatment perspectives on the meaning of recovery might differ.

Stages of Addiction Recovery

1. Early (<1 year)
2. Sustained (1-5 years)
3. Stable (>5 years)

The recovery duration is associated with reduced crimes and better occupational and housing outcomes [48]. Retention in treatment, engagement in meaningful activities, and availability of support and resources are common factors that support addiction recovery.

Needs vary based on the acuity of the problem, chronicity, and complexity [49]. A needs assessment can be based on an individualized approach or using tools to understand the needs.

Recovery-oriented treatment at an institutional level

A minimum infrastructure and functional services are necessary for the long-term care of patients with SUDs. The National Action Plan on Drug Demand Reduction (NAPDDR) recommends guidelines followed by the Integrated Rehabilitation Centre for Addicts (IRCA), which include minimum infrastructure and the standard of care that needs to be provided [50]. It is mandatory for the institutions providing care for people with substance use disorders to register with the state mental health establishments and follow the Mental Health Care Act (MHCA) of 2017 [51]. These institutions need to be periodically assessed by state mental health review boards.

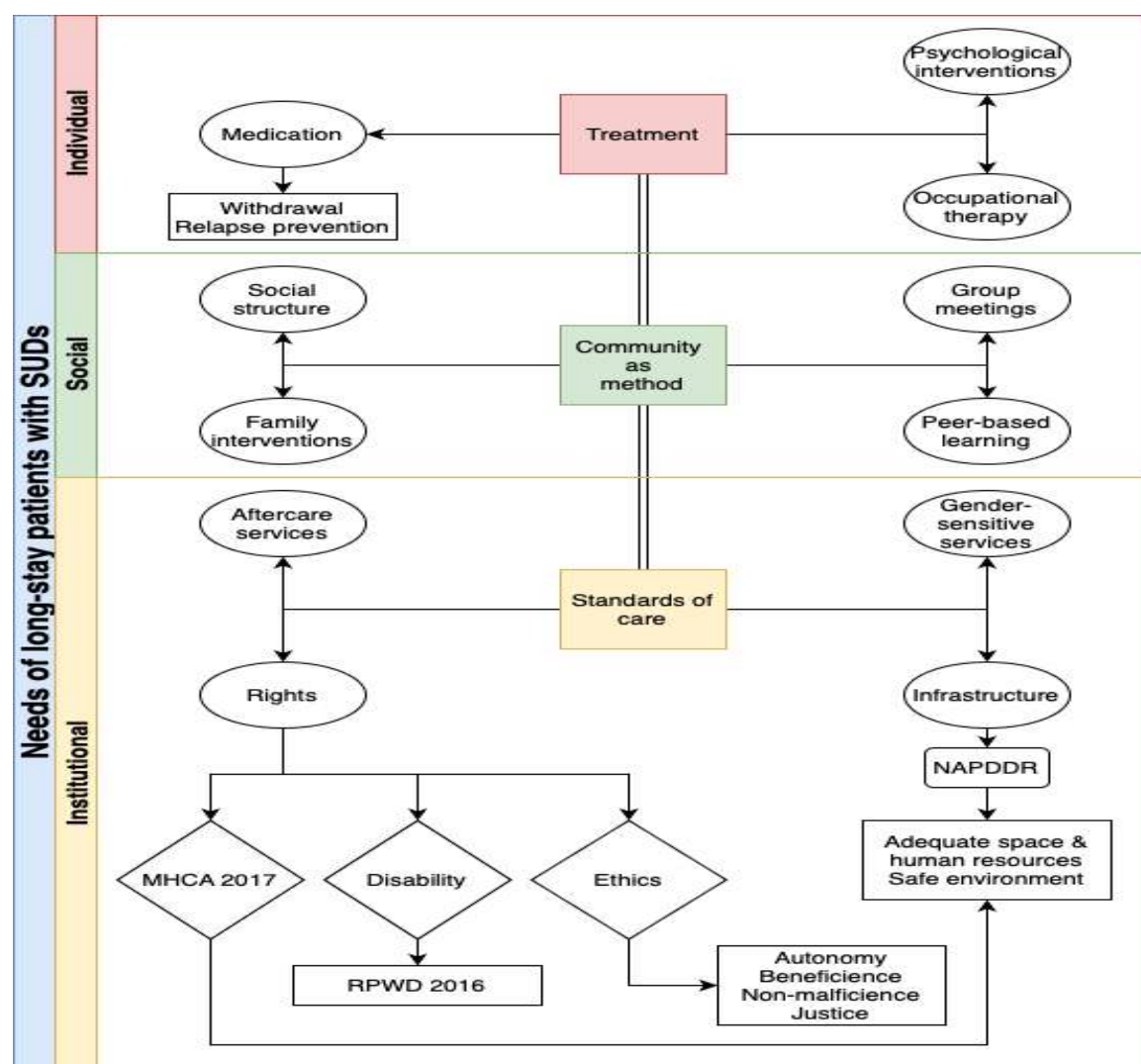


Figure 2: Needs of long-stay patients with substance use disorders (MHCA- Mental Health Care Act; RPwD- Rights of persons with disability; SUDs- Substance Use Disorders)

A breach of ethical principles is commonly observed during long-term care for people with SUDs across many settings [52]. For example, if a patient with cirrhosis of the liver continues to drink alcohol, can he be admitted to a rehabilitation center if he is not willing for admission? If forcefully admitted, there is a breach of autonomy. Although certain situations result in a clinical dilemma for treating physicians, it is important to adhere to the ethical principles of autonomy, beneficence, non-maleficence, and justice in treating people with SUDs.

Community as “method” learnings from TCs

It is the first program to see addiction from a treatment perspective. The program follows the principle of “community as a method.” The key components of the program model are its social organization (structure), peer and staff roles, group and individual counseling, community enhancement meetings, community management elements, and program stages. The original treatment was for 24 months; now, it has been shortened. The social structure emphasizes mutual responsibility at various levels and peer-based learning. TCs focus on providing a safe physical and psychological environment to the population. Community enhancement meetings occur daily, with multiple scheduled meetings. The focus of these meetings is to instil the spirit of community. Therapeutic educational activities involve group and individual counselling.

While TCs are modified for special populations (comorbidity) and settings (prisons), most services in India are “TC-oriented services.” TC-oriented services incorporate select elements of the TC (community meetings, peer support groups) but mainly utilize services and practices that are not specific to the TC. Post-treatment aftercare is a part of traditional TC services.

At an individual level:

A recent study examined treatment-related needs identified from a patient's perspective. The needs included individual needs, family-related needs, treatment-related needs, and community-related needs (16). Among individual needs- medication-related, psychological, and occupational were prominent. Addressing family conflict and supporting the family were the significant sub-themes for family-related needs. The behaviour of the treating team, environmental needs, and diverse services were the significant hospital-related needs.

Awareness, accessibility, availability, and affordability of treatment services were the major community-related needs.

The socio-cultural needs can be different for men, women, and the LGBT community [53]. While the needs assessed from short-term care suggest the quality of therapeutic relationships, stigma and discrimination from the health care system, support needs, and informational needs were the prominent needs of women with substance use disorders, the long-term needs of women not been well understood. In India, very few women-only centers provide care. Gender-sensitive services like addressing sexual abuse, domestic violence, child care, and protection become important during the treatment [54].

Recovery Capital:

An inter-related concept is to look at the strengths of individuals in the recovery process, “recovery capital.” Defined as “the breadth and depth of internal and external resources that can be drawn upon to initiate and sustain recovery from substance use problems (19).” These strengths are commonly assessed in individual, interpersonal (social), and community-related domains (environmental). This helps in understanding the unmet needs of a person's duration of long-term care [55].

Disability:

As a consequence of harm sustained due to alcohol, a proportionate amount of individuals develop disability. For example, patients who develop dementia secondary to alcohol, like alcohol-related dementia or due to Wernicke Korsakoff syndrome. These individuals require disability assessment and certification as per the Rights of Persons with Disability (RPwD) Act 2016. Memory rehabilitation measures are effective if delivered interventions are focused, individualized, and cohesively integrated into comprehensive learning methods[56]. Various interventions, encompassing compensatory memory-enhancement techniques, including traditional aids like agendas, memory cards, and digital tools such as smartphones and smartwatches, show significant promise.

Needs Assessment tools in persons with SUD

Although there are direct needs assessment tools focussed on people with SUDs, there are some indirect ways. To gain insight into someone's needs, it is essential to understand their strengths and difficulties.

A commonly used tool to assess the strengths of individuals with SUDs is Addiction Recovery Capital. In the Indian context, a Hindi version of the tool has been validated [57].

A widely used tool to determine the severity of addiction is the Addiction Severity Index

(ASI). A similar Indian tool developed recently ASSORT, can help understand the severity of Addiction. WHODAS 2.0 [33] and WHO Quality of Life (WHO-QOL) assessment are other commonly used tools for assessment of disability and quality of life that can assist in understanding the needs [34]. Another important tool that can help during the stay is understanding the motivation based on the transtheoretical model of change (pre-contemplation, contemplation, preparation, action, maintenance). The readiness to change questionnaire, a 12-item tool, assists in allocating and predicting outcomes [59].

Further, the Treatment Readiness Tool (TReaT) helps understand the motivation (pre-contemplation, contemplation, and preparation) to seek treatment [60]. The government of India empowers state mental health authorities to frame guidelines for a minimum standard of care in deaddiction centers, considering recommendations from the Ministry of Social Justice and Empowerment [61]. These guidelines are updated regularly. Institutions should follow the previous recommendations until the updated version is released [62-63].

Barriers to assessment of needs in long stay of SMDs & SUDs

A significant proportion of PMI admitted to psychiatric hospitals may have comorbid intellectual disability and speech and language deficits. Understanding their preferences and choices can be challenging. Several psychiatric hospitals may not have multi-disciplinary professionals to assess the post-discharge needs of long-stay PMI, and a limited number of mental health professionals are often overwhelmed with PMI with acute mental health problems. A major barrier to needs assessment for long-term rehabilitation of persons with substance use disorders is high variability in terms of definition (duration), settings (government vs private), regional variations of substance use problems (opioids in north India vs alcohol in southern India), and lastly, lack of structured validated scales.

Pragmatic needs assessment is less likely to be covered under any structured tools.

Tools mentioned above, while trying to capture the information related to strengths, deficits, and choices, professionals should be aware that such tools cannot assess several other complex needs. When PMI are homeless and are admitted to psychiatric hospitals for years or even for decades, they may not have documents such as a Voter card, Bank account, Disability card (if applicable), residence certificate, or below poverty line card which entitles them to several state social justice measures for community living.

Conclusion

Understanding and assessing the needs of long stay PMI in psychiatric hospitals is complex and multi-dimensional and continuous process as needs can change over time. We should strive towards assessments and services becoming recovery oriented and person centred. A

structured multimodal approach is essential at the individual, social, and institutional levels. Professionals caring for the long stay PMI with severe mental disorders should also be aware of various community mental health care facilities as their transition to facilities that could cater to their needs. Therapeutic communities suggest that most learning is through the social community in long-term residential programs. Although abstinence in persons with SUD is the major goal, identifying and strengthening the recovery capital assists the recovery process.

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Cognitive impairment in alcohol use disorder and guidelines for management of long stay alcohol use disorder patients

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Cognitive impairment in alcohol use disorder and guidelines for management of long stay alcohol use disorder patients

Introduction

Cognitive disorders affect over half of patients with alcohol use disorder (AUD) (Alarcon et al. 2015), even without neurological impairments. Identifying these cognitive deficits is important for several reasons. First, some deficits can progress to severe conditions like *Korsakoff disease* (amnesic disorder), which is difficult to recover from. Early detection and treatment during Wernicke encephalopathy may prevent this progression (Praharaj et al. 2021). Second, while abstinence from alcohol can improve cognitive function, it may persist for longer periods in some individuals (Mulhauser et al. 2018; Kaur et al. 2020; Powell et al. 2024). Third, recognizing cognitive impairment can help identify patients who are less likely to follow treatment plans. Studies show that these patients retain less treatment-related information (Teichner et al. 2002) and learn fewer skills to refuse alcohol (Smith and McCrady 1991).

Several terminologies have been used to describe cognitive impairments in AUD. They are: Korsakoff syndrome (KS), Alcohol-Related Brain Damage (ARBD), alcohol-related cognitive impairments (ARCI) (*Table 1*).

Table 1: Conditions/Terminologies related to cognitive impairment in AUD

	Condition	Elaboration
1	Alcohol related brain disorder (ARBD)	Includes brain disorders related to alcohol use such as Wernicke-Korsakoff syndrome, Marchiafava-Bignami syndrome, alcohol-related dementia, etc.
2	Wernicke-Korsakoff syndrome (WKS)	Wernicke encephalopathy is an acute neuropsychiatric disorder, while Korsakoff syndrome is a persistent amnesic disorder.
3	Alcohol-related dementia (ARD)	This is a severe cognitive impairment related to alcohol including varying etiology (thiamine and other deficiencies, direct toxic effects of alcohol, metabolic disorders, trauma, vascular disorder); Oslin et al. (1998) criteria suggests that ARD may be reversible.
4	Alcohol related cognitive impairment (ARCI)	Broader term to include all cognitive impairments related to alcohol including major disorders such as WKS, ARD, and milder impairments

Specific criteria for alcohol-related dementia have been suggested by Oslin et al. (1998) that helps characterize probable or possible diagnosis (*Table 2*). However, there is no criteria for definitive diagnosis.

Table 2: Diagnostic criteria for alcohol-related dementia (Adapted from Oslin et al. 1998)

Diagnosis	Criteria
Probable	<i>Criteria for clinical diagnosis</i>

	1. Dementia diagnosis after 2 months of last alcohol use 2. “Significant alcohol use,” i.e. 35 SD per week for men and 28 SD for women for more than 5 years; this period must occur within 3 years of dementia onset <i>Supportive criteria:</i> 1. Physical complications of alcohol use (e.g. alcoholic liver disease, pancreatitis, neuropathy, cerebellar syndrome) 2. Cognitive impairment becomes stable or improves after 2 months of abstinence 3. Neuroimaging evidence of cerebral atrophy (e.g. widened sulci) improves after 2 months of abstinence 4. Neuroimaging evidence of cerebellar atrophy (e.g. atrophy of vermis) <i>Criteria suggestive of other diagnosis:</i> 1. Language impairment 2. Focal neurological signs or symptoms 3. Neuroimaging evidence of stroke (cortical or subcortical infarction, subdural hematoma) 4. High Hachinski Ischemia Scale Score <i>Criteria which neither support or suggest other diagnosis:</i> 1. Neuroimaging evidence of cortical atrophy 2. WMH (periventricular or deep) in the absence of focal infarct 3. Apoprotein e4 allele
Possible	<i>Criteria for clinical diagnosis</i> 1. Dementia diagnosis after 2 months of last alcohol use 2. <i>Either</i> of the following: a) “Significant alcohol use,” i.e. 35 SD per week for men and 28 SD for women for more than 5 years; this period must occur between 3 to 10 years of dementia onset b) “Possibly significant alcohol use,” i.e. 21 SD per week for men and 14 SD for women for more than 5 years; this period must occur within 3 years of dementia onset

SD: Standard drink; WMH: White matter hyperintensities

Prevalence of cognitive impairment in AUD

Bruijnen et al. (2019) in a cross-sectional multicentric study of outpatients from specialty addiction clinics found that 31% of those with substance use disorder screened positive for cognitive impairment, with 34% of those with AUD. Alcohol users had notably lower cognitive test scores compared to cannabis users. A previous study also found 38% of substance users had cognitive impairment (Copersino et al. 2009). Both studies suggest the need for early cognitive screening in AUD to improve treatment outcomes.

Profile of cognitive impairment in AUD

Four cognitive profiles have been identified in AUD: 1) unimpaired cognitive functioning, 2) representative dysexecutive syndrome with preserved memory and intelligence, 3) modified dysexecutive pattern with impaired memory and executive functions but preserved intelligence, and 4) global deterioration in memory, intelligence, and executive functions. The dysexecutive syndrome involves deficits in mental processes such as working memory, set-shifting, divided attention, problem-solving, and decision-making (Ihara et al. 2000).

Episodic memory deficits are more relevant to AUD than semantic or implicit memory deficits (Fama et al. 2021). These deficits in AUD typically involve difficulty in new long-term learning. Alcohol primarily impairs the encoding process that converts short-term memories into long-term ones, while short-term encoding is less affected. People with AUD also have trouble retrieving long-term memories, sometimes even after one or two drinks. These memory processes can be so severely affected that, once sober, individuals struggle to recall key details or entire events that occurred while they were intoxicated; this phenomenon is known as blackouts (White 2003, Bernardin et al. 2014).

Other features include gaps in visuospatial functioning, including impaired visuospatial processing, greater impairment in visual memory and visual learning compared to verbal learning, and deficits in perceptual-motor tasks and visuospatial organization (Ratti et al. 2002, Oscar-Berman et al. 2007). The domains are summarized in *Table 3*.

Table 3: Cognitive domains impaired in AUD

	Domain	Comments
1.	Attention	Selective and divided attention
2.	Memory/Learning	New learning, episodic memory, autobiographical memory, long-term memory, visual memory, prospective memory
3.	Fluency	Verbal fluency
4.	Executive function	Working memory, response inhibition, self-monitoring, cognitive/mental flexibility
5.	Fluid abilities	Concept formation, planning, abstraction, visuospatial abilities, problem solving, decision making
6.	Psychomotor skills	Proprioception, gait stability

How may AUD drive cognitive impairment?

Several explanations have been proposed to explain the typical cognitive impairments seen in AUD, which can be broadly divided into three hypotheses. The first is the *right hemisphere hypothesis*. This follows from the impaired cognitive functions mentioned earlier, which are mostly served by the right hemisphere (RH). The strongest evidence for RH dysfunction in AUD comes from electrophysiological studies showing significant abnormalities in RH structures (Oscar-Berman et al. 2007). However, not all studies have supported the RH hypothesis (Mungas et al. 1994).

The second hypothesis involves *frontal lobe damage*, which explains the centrality of executive function deficits seen in alcohol-related cognitive impairment. This is supported by clinical studies showing impairments in prefrontal neurobehavioral functioning (Oscar-Berman et al. 2004, Dirksen et al. 2006), structural imaging showing decreased frontal lobe volumes in AUD (Pfefferbaum et al. 1997), functional imaging showing that have consistently showing reduced frontal lobe circulation (Tapert et al. 2001), and lower levels of glucose metabolism (Volkow et al. 1995), all indicating a “hypofrontal” condition. Personality traits linked to frontal lobe involvement, such as disinhibition and impulsivity, may predispose individuals to alcohol dependence, especially early onset (Streeter et al. 1998). Additionally, the genetic predisposition to AUD may partly be due to genetic predisposition to impairments in frontal lobe circuitry (Pihl et al. 1993).

The third hypothesis is the *global brain damage/premature ageing theory* (Oscar-Berman et al. 2007). Like the earlier theories, it draws evidence from neuropsychological deficits noted in AUD. This hypothesis tries to reconcile differences in the literature: some researchers have shown a preferential RH vulnerability to chronic alcohol consumption (Oscar-Berman and Marinkovic 2003), while others have found that frontal lobe and executive function deficits are most affected and worsen with age (Stephan et al. 2017). A meta-analysis of neuropsychological functioning in chronic alcohol users after abstinence highlights the diffuse nature of deficits involving the RH, frontal lobes, medial temporal, subcortical, and cerebellar structures (Crowe et al. 2020).

Risk factors for cognitive impairment with alcohol

Age

As people age, their body water content decreases and their ability to metabolize alcohol reduces. This means that, for the same amount of alcohol consumed, older people will have a higher blood alcohol concentration compared to younger people. Additionally, brain changes in chronic alcohol users and non-alcoholic elderly individuals are similar (Gansler et al. 2000), including prominent frontal lobe atrophy, widened cerebral sulci, and enlarged ventricles. These observations support the premature ageing hypothesis mentioned earlier.

Gender

Men seem to be more vulnerable than women to the cognitive adverse effects of moderate to heavy drinking, although there are gender differences in specific cognitive domains. For example, women with AUD often perform better on episodic memory tests, while men tend to do better on visuospatial tasks (Yonker et al. 2005). Some of these differences continue even after achieving sobriety (Sullivan et al. 2002). Neuroimaging study findings are inconsistent: some suggest women experience greater reductions in grey and white matter than men (Hommer et al. 2001), while others do not (Pfefferbaum et al. 2001). A recent review found that women generally perform worse than men on tasks involving divided attention, memory, and decision-making (Fama et al. 2020). Additionally, women often experience a faster progression of alcohol-related problems and their consequences, known as “telescoping,” which highlights differences in how alcohol affects cognition and psychological health between the sexes (Fama et al. 2020).

General health

When evaluating the relationship between alcohol and cognitive impairment, it's important to consider physical and mental health conditions that may mediate or moderate this relationship. Relevant physical conditions include liver dysfunction, cardiovascular impairment, and poor nutritional status. For example, vitamin B1 deficiency from poor nutrition can lead to persistent cognitive deficits after chronic alcohol use and can cause persisting amnesic disorder, also known as *Korsakoff syndrome* (Oscar-Berman et al. 2007).

Mental health conditions associated with chronic alcohol use include externalizing disorders such as conduct disorder, depression, anxiety disorders, bipolar disorder, and schizophrenia. Any of these conditions may moderate or mediate the relationship between alcohol and neurobehavioral outcomes. Although it is challenging to determine the exact contribution of each variable, it is important to consider their role when developing management or prevention strategies.

Family history

Hereditary factors influence vulnerability to AUD. Research from the Collaborative Studies on the Genetics of Alcoholism (COGA) involving multiplex families suggests that several

interacting genetic loci, each with modest effects, contribute to AUD vulnerability (Edenberg and Foroud 2006). Associations between dopamine gene polymorphisms and reward-dependent behaviors that influence AUD vulnerability have also been found (Blum et al. 2000). More research is needed to understand the causal variants of these genes, their contribution to medical and psychiatric co-morbidity, and their role in brain damage susceptibility in AUD.

Indian evidence

Prevalence of cognitive impairment in AUD: Community/hospital-based studies

Several Indian studies have examined the prevalence of cognitive impairment in AUD. A hospital-based study found that 4 out of 5 patients with AUD who completed detoxification showed signs of global cognitive impairment (Vishwam et al. 2018). Another facility-based study reported that the mean score on cognitive impairment screening tools for patients with alcohol dependence was below the cutoff (Ram et al. 2018). Two community-based studies on adults (Ghogare and Saboo 2019) and older adults (Muhammad et al. 2021) found that over 50% of individuals with AUD had cognitive impairment. Additionally, a hospital-based study on patients with schizophrenia found that nearly 3 out of 4 patients had cognitive impairment, with half of the sample having comorbid AUD (Faye et al. 2022).

Factors influencing the association between AUD and cognitive impairment

Alcohol use has been linked to different levels of cognitive impairment in community-dwelling older adults compared to those who never use alcohol (Mohan et al. 2019, V et al. 2024). However, some studies have found no such association (Paul et al. 2022). Factors related to alcohol use—such as drinking patterns, duration of use, type of alcohol consumed, severity of dependence, family history, concurrent smoking, and age of onset of alcohol use—have been consistently correlated with cognitive impairment across these studies (Ghogare and Saboo 2019, Muhammad et al. 2021, Khan 2022).

Follow-up studies

Investigators have found that neurocognitive functioning improves in the short term with abstinence from alcohol. This highlights the importance of maintaining sobriety as a goal in AUD management (Kaur et al. 2020).

Impact of cognitive impairment in AUD

Cognitive deficits can affect the treatment and outcomes in AUD. They can impact the patient's understanding of the problem and acceptance of treatment. Motivational enhancement therapy and cognitive behavioral therapy are challenging for these patients, necessitating more behavioral treatment strategies along with pharmacotherapy (Suresh et al. 2023). Assessing cognitive deficits is important for treatment plans, as treatment with a heavy cognitive component may be more effective after cognitive processes relevant to the therapy have recovered (Bates et al. 2013). Additionally, cognitive deficits can hinder medication adherence.

Assessment of cognitive impairment in AUD

Screening for cognitive deficits in AUD patients is important in alcohol treatment units, as it can help tailor therapeutic programs. A simple, rapid screening test with good sensitivity, specificity, and reproducibility is needed. The Montréal Cognitive Assessment (MoCA) (Nasreddine et al. 2005), a general cognitive screening tool, is widely used for this purpose.

In AUD patients, the MoCA allows for rapid and confident screening of cognitive deficits (Alarcon et al. 2015; Copersino et al. 2009) and helps evaluate cognitive changes following alcohol withdrawal (Likhitsathian et al., 2013; Pelletier et al., 2016). The other commonly used tools are Mini Mental State Examination (MMSE; Folstein et al. 1975), and Addenbrooke's Cognitive Examination – Revised (ACE-R). Comparing the MoCA, MMSE, and ACE-R suggests that the MoCA and ACE-R are valid and time-efficient for detecting cognitive impairment in substance use contexts (Ridley et al. 2018). The MoCA is also useful for measuring changes in cognitive performance in AUD (Pelletier et al. 2016). In India, the MoCA has been used to evaluate cognitive functions in AUD patients (Vishwam et al. 2018; Ram et al. 2018), but its scores are heavily influenced by education, presenting some challenges.

Several specific tools for measuring cognitive impairment in AUD have been developed. A new screening tool of cognitive impairment specifically devoted to AUD patients, the BEARNI (Brief Evaluation of Alcohol-Related Neuropsychological Impairments) score, was recently developed (Ritz et al. 2015). It explores five cognitive and motor functions that are impaired in AUD: episodic memory, working memory, executive functions, visuospatial abilities, and ataxia.

A Brief Cognitive Screen for Alcohol Use Disorder (BCS-AUD) (Gupta et al. 2018) was developed from the NIMHANS battery for neurocognition consisting of three tests: Finger tapping, N-back, and RAVLT, for rapid screening of cognitive impairment in AUD. Other tools are Alcohol and Drug Cognitive Enhancement (ACE) Screening Tool (Berry et al. 2022), Barkley Deficits in Executive Functioning (BDEFS) (Barkley 2010), Comprehensive Executive Function Inventory – Adult (CEFI-A) (Naglieri and Goldstein 2017), Neuropsychological Assessment Battery – Screening Module (NAB-SM) (Stern and White 2003), Battery for Executive Functions in Addiction (BFE-A) (Balconi et al. 2022), Repeatable Battery for Assessment of Neuropsychological Status (RBANS) (Randolph 1998), and Brief Executive Function Assessment Tool (BEAT) (Berry et al. 2021). (Table 4)

Table 4: Screening tools for cognitive function in AUD patients

Test	Domains	Comments
General Screening Tools		
Montréal Cognitive Assessment (MoCA) (Nasreddine et al. 2005)	Attention, orientation, language, visuospatial, memory, executive function, abstraction	Developed primarily for dementia, has been used in AUD. Indian adaptations available, versions for illiterate persons. Norms available in India.
Mini-Mental State Examination (MMSE) (Folstein et al. 1975)	Orientation, repetition, verbal recall, attention and calculation, language, visual construction	Does not assess executive functions, not sensitive to alcohol-related memory disorders
Hindi Mental State Examination (HMSE) Ganguly et al. 1995	Orientation, repetition, verbal recall, attention and calculation, language, visual construction	Developed and validated in Indian population
Addenbrooke's Cognitive	Attention, memory, verbal	Maximum score 100

Examination-Revised (ACE-R)	fluency, language, visuospatial ability	Available in 30 languages Does not assess executive functions. Indian adaptations available (Hindi, Kannada).
AUD Specific Tools		
Brief Cognitive Screen for Alcohol Use Disorder (BCS-AUD) (Gupta et al. 2018)	Finger tapping, N-back, RAVLT	Three domains selected from NIMHANS Neuropsychological battery
Brief Evaluation of Alcohol-Related Neuropsychological Impairments (BEARNI)	Episodic memory, working memory, executive functions, visuospatial abilities, and ataxia	Cognitive test sub score total 22; cut off 16 (or 17 for 12 years of education)
Test of detection of cognitive impairment in alcoholism (TEDCA)	Visuospatial Cognition, Memory/Learning and Executive Function	Brief, reliable, and valid test
Barkley Deficits in Executive Functioning (BDEFS) Barkley 2010	5 domains, 89 items	ADHD population Language dependent
Comprehensive Executive Function Inventory – Adult (CEFI-A) Naglieri & Goldstein 2017	9 domains, 80 items	Education and language dependent
Neuropsychological Assessment Battery – Screening Module (NAB-SM) Stern & White 2003	attention, language, memory, visuospatial, and executive	
Battery for Executive Functions in Addiction (BFE-A) Balconi et al. 2022	short- and long-term verbal memory, working memory, cognitive flexibility investigated with both verbal and nonverbal materials, focused attention, attention regulation, suppression of interference and inhibitory control	Digital administration
Repeatable Battery for Assessment of Neuropsychological Status (RBANS) Randolph 1998	12 subtests, 5 domains (Immediate memory, Visuospatial/constructional, Language, Attention, and Delayed memory)	Overall performance score Available in 20 languages
Brief Executive Function Assessment Tool (BEAT) Berry et al. 2021	20 items, domains	

RAVLT: Rey's Auditory Verbal Learning Test

Tools to measure specific cognitive domains in AUD include Iowa Gambling Task for decision making (Bechara et al. 1994, Kovács et al. 2017), balloon analogue risk task

(BART) for risk taking (Lejuez et al. 2022, Canning et al. 2022), Wechsler Memory Scale -III (Wechsler 1997) and P.G.I. Memory Scale (Pershad and Wig 1977) for memory (*Table 5*).

Several neuropsychological batteries such as the National Institute of Mental Health and Neurosciences (NIMHANS) battery for neurocognition (Rure et al. 2024), AIIMS Comprehensive Neuropsychological Battery (Gupta et al. 2000, Dixit et al. 2020), Indian Council of Medical Research – Neurocognitive Tool Box (ICMR-NCTB), Cambridge Neuropsychological Test Automated Battery (CANTAB) (Irwin et al. 2013), Luria–Nebraska Neuropsychological Battery (LNNB) (Chmielewski and Golden 1980), and Halstead-Reitan Neuropsychological Test Battery (Leckliter and Matarazzo 1989) have also been used to assess cognitive deficits in AUD (*Table 6*).

Management of cognitive impairment in AUD

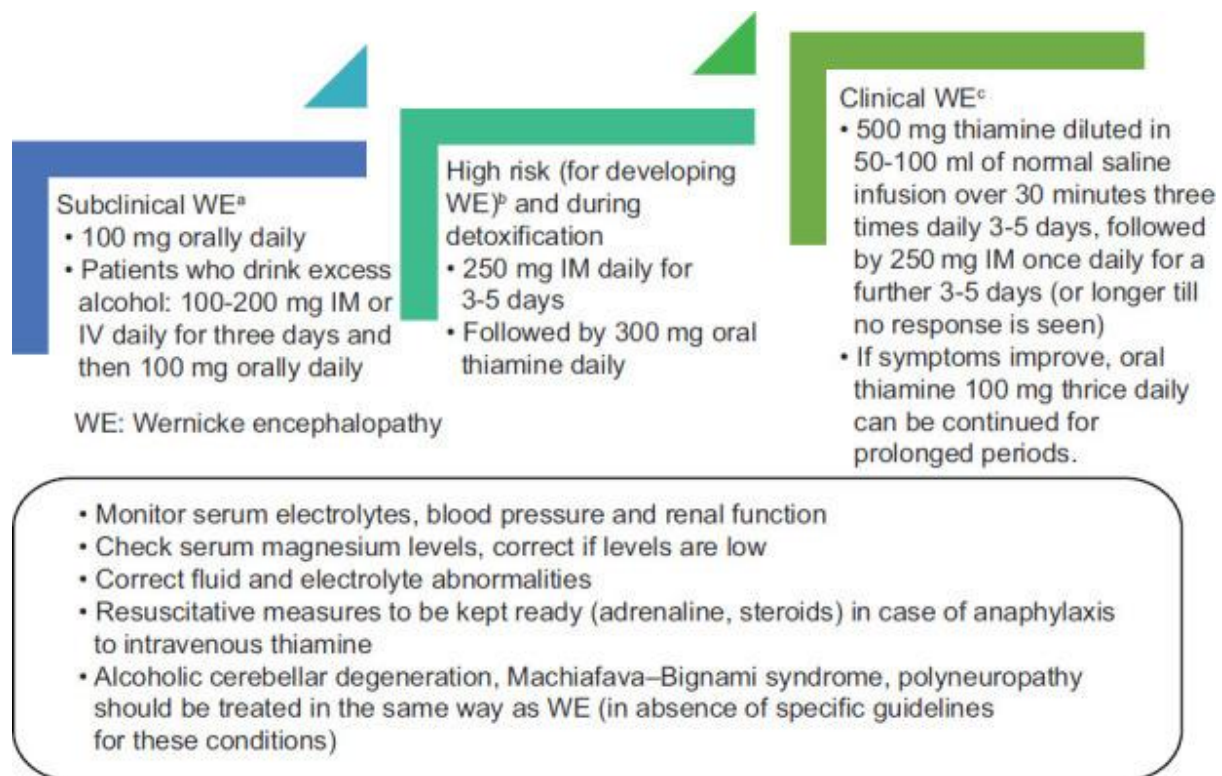
The consistent observation that alcohol-related cognitive decline can resolve with time and abstinence suggests that the brain can recover even after long-term heavy alcohol use. This type of recovery, termed *time-dependent recovery* (Goldman 1990, 1995), shows substantial cognitive recovery in the short term (1 month), with more modest improvements in the mid-term (up to 1 year) and long-term across multiple cognitive domains. Recent literature continues to explore the spatial and temporal aspects of structural and functional recovery (Schulte et al. 2012; Buhler and Mann 2011).

Current gold standard treatments for SUD primarily focus on substance use related outcomes, such as reducing drug use or achieving abstinence, often without addressing cognitive deficits or assuming that cognition will recover after successful remission from substance use. However, cognitive deficits can persist even after long-term abstinence and may contribute to relapse, reduced quality of life, and difficulties in reintegrating into society.

Pharmacological strategies

Wernicke-Korsakoff and related conditions such as acute cerebellar syndrome, alcoholic peripheral neuropathy, and Marchiafava-Bignami syndrome, are linked to thiamine deficiency, other vitamin deficiencies, and alcohol's toxic effects (Praharaj et al. 2021). These conditions should be treated with thiamine to prevent long term cognitive consequences. *Fig 1* outlines the thiamine treatment strategy for AUD. High dose thiamine is recommended for those with or at risk for WKS or related syndromes. For individuals with established amnestic disorder, a daily dose of 300 mg of thiamine or higher may be beneficial, but results vary. Acamprosate helps reduce relapse risk in AUD and may offer additional neuroprotective benefits through NMDA action (Koob et al. 2002).

Fig 1: Thiamine recommendations for patients with alcohol use disorder (Praharaj et al. 2021). ^aHistory of alcohol use, but no clinical features of WE; ^bNo clinical features of WE, but with risk factors such as complicated withdrawal (delirium, seizures); ^cClinical features of WE (ataxia, ophthalmoplegia, global confusion)



A systematic review (Mistarz et al. 2021) found that modafinil is most effective in improving cognitive functions in AUD patients, enhancing executive functions, attention, processing speed, and working memory. Other treatments have shown varying results: dopaminergic agents like levodopa/carbidopa and the dopamine stabilizer OSU, the glutamatergic agent memantine, noradrenergic agents like clonidine and methylphenidate, serotonergic agents such as fluvoxamine, and the opioidergic agent nalmefene can improve some cognitive functions in patients with WKS (Mistarz et al. 2021) (*Table 7*). Preliminary evidence also suggests that modafinil and nalmefene may be effective for reward processing in AUD patients (Mistarz et al. 2022).

Medications found ineffective for cognitive impairment in AUD include cholinergic drugs like rivastigmine, choline chloride, and physostigmine, noradrenergic agents such as reboxetine, methysergide, ephedrine, and amphetamine, and other medications including apomorphine, citicholine, and desglycinamide-arginine vasopressin (Mistarz et al. 2021). However, galantamine 8 mg/day has improved response inhibition in cannabis use disorder (Sugarman et al. 2019) and may potentially benefit AUD, as seen in animal studies (Macht et al. 2021).

Table 7: Pharmacotherapy for cognitive impairment in AUD

Medication	Domains	Comments
Thiamine and Benfotiamine (300 mg)	Verbal memory	WKS patients
Modafinil (100-300 mg)	Improves executive functions, attention,	AUD, WKS, and alcohol-related dementia

	processing speed, working memory, and reward processing	
Clonidine (0.2 mg qd)	Improve verbal memory and response inhibition	WKS patients <6 months duration
Fluvoxamine (100-200 mg)	Improves verbal memory	WKS and alcohol-related dementia
Levodopa/carbidopa (110 mg qd)	Improves response inhibition	Commonly used in Parkinson's disease
OSU6162 (10-30 mg bd)	Improves executive functions (planning and problem solving), verbal fluency	Not available currently
Memantine (10 mg bid)	Improves global cognition	In moderately severe WKS
Methylphenidate (10 mg tid)	Improves verbal memory	WKS patients, moderate to severe
Nalmefene (18 mg od)	Improves impulsivity and reward processing	AUD patients

WKS: Wernicke-Korsakoff Syndrome

Nonpharmacological strategies

Cognitive recovery is not solely due to intrinsic neurophysiological healing but can also be influenced by environmental factors, known as *experience-dependent recovery* (Goldman 1990, 1995). These factors involve cognitive stimulation, similar to physical exercise. Strategies for cognitive recovery include repeated practice, breaking complex tasks into components, and practicing tasks designed to require attention and effortful cognitive functioning (Goldman 1995). Studies have shown that practicing cognitive tasks, termed *cognitive remediation*, can enhance basic cognitive skills and improve performance on various cognitive measures among individuals recovering from AUD (Table 8).

Cognitive retraining has been shown to improve cognitive functioning, specifically working memory and visual learning and memory, in AUD patients (Mathai et al., 1998). Newer approaches include virtual reality-based protocols, such as the Rehabilitation Gaming System (RGS), for cognitive impairment in AUD patients (Caballeria et al. 2022).

Neuropsychological interventions for decision-making have shown moderate (medium-large) beneficial effects when targeting specific mechanisms, such as Goal Management Training (for cognitive control and emotional systems via mindfulness) and Contingency Management (for the reward system). Evidence is mixed for less specific interventions like computerized Working Memory Training and Cognitive Behavioral Therapy (Verdejo-García et al., 2019). Goal Management Training (GMT) is a validated intervention for executive function impairment (Stamenova and Levine 2019).

Table 8: Psychotherapeutic approaches for cognitive impairment in AUD

Therapy	Details	Comments
Cognitive bias modification - Retraining Automatic	Retrain implicit biases towards drug-related cues.	Interrupts automatic approach tendencies toward

Action Tendencies (Wiers et al. (2010))	CBM approaches include retraining of drug-related attentional, approach and/or memory biases, as well as drug cue-related inhibitory control training	alcohol stimuli
Contingency management (Feldstein Ewing et al. 2011)	Retraining the reward system. Using immediate tangible incentives (a voucher, exchangeable for retail goods and services) are provided contingent on objective evidence of behaviour change (e.g., negative urine drug test).	reduce the appeal of reward-like signals in risk-taking tasks, and increase the value of non-drug, delayed rewards in delay discounting tasks
Cognitive remediation / rehabilitation	A therapeutic process targeting cognitive deficits to improve an individual's functioning in everyday life. This includes methods to train and restore cognitive functions and strategy learning techniques. Examples of specific cognitive remediation techniques are goal management training, episodic future thinking / implementation of intentions, spaced retrieval / memory reconsolidation and errorless learning.	
Emotional regulation training	Training patients to use adaptive emotion strategies and regulate maladaptive emotion strategies.	
Working memory training (Rass et al. 2015)		Reduced discounting rates
Goal Management Training (Alfonso et al. 2011) (Levine et al. 2011)	Trains cognitive control using response inhibition and sustained attention exercises, and emotional awareness via mindfulness practice. integrated in a concrete decision-making strategy (Stop – State goal – Check outcomes), which is practiced in real-life projects.	
Chess training (with MI)	Cognitive control and	Improves attention skills

Gonçalves et al. (2014)	planning abilities	
Reality Therapy (Yao et al. (2017)	Planning strategies, mindfulness practice	Improves delay discounting
Heart Rate Variability (HRV) Biofeedback	HRV biofeedback involves learning to breath at a rate that synchronizes cardiac oscillations being driven by respiratory sinus arrhythmia	enhances neurocardiac signaling, improving communication between cardiovascular and neural control systems
Mental and Physical (MAP) Training	Aerobic physical training with breathing meditation (mental training)	Physical exercise enhances executive functions, facilitate cognitive flexibility

Brain stimulation

Brain stimulation techniques have been shown to improve cognition in healthy individuals and various psychiatric disorders and have also been studied for cognitive impairment in AUD. Excitatory stimulation over the left dorsolateral prefrontal cortex (DLPFC) using transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) has been associated with improved inhibitory control, lower risk-taking, decreased delay discounting, reduced attention to alcohol cues, and enhanced executive function (Naish et al. 2018). Excitatory stimulation over the right DLPFC has also been linked to reduced risk-taking, improvements in memory, and consistent response times (Naish et al. 2018).

Management of long stay AUD patients

Patients of alcoholism may at times require long-term inpatient stay because of reasons like a history of repeated relapses despite sufficient short-term admissions where appropriate pharmacological and psychosocial interventions were provided, severe physical comorbidities like cirrhosis, or conditions with cognitive impairment like Korsakoff's syndrome.

Levels of care for AUD

Relevant legal aspects

If the patient has capacity, as per section 86 of the Mental Healthcare Act 2017, the patient can continue to stay in a Mental Health Establishment as long as the person is willing to stay there (Mental Healthcare Act 2017). However, if the patient lacks capacity due to reasons like alcohol-induced dementia, amnesic disorder, hepatic encephalopathy (HE), or comorbid or induced psychiatric illnesses that impair capacity, the initial admission will have to be under section 89 of the Act. If the patient does not gain capacity even after a month of admission and cannot be managed in community-based services, further inpatient stay must be under section 90 of the Act, and the matter has to be reported to the Mental Health Review Board. Beyond a period of 90 days, if the stipulated conditions still apply, the Board may allow an

extension for 120 days at the first instance and after that for 180 days each time if the patient still meets the provisions of the relevant sub-sections of the Act.

Psychosocial interventions

Motivational interviewing: If the person has capacity and has consented to long-term inpatient stay, it is presumed that the person is in the preparation stage of the cycle of change and, hence, may not need motivational interventions. However, the cycle of change is not always unidirectional, and the person may go back from preparation to contemplation at times and, in such instances, may require motivational interviewing (Miller and Rollnick 2012). This includes eliciting change talk through techniques such as open-ended questions, importance ruler, looking back, looking forward, etc., and responding to the elicited change talks with techniques such as elaboration, affirmations, reflections, and summarizing.

Relapse prevention: If the person has been undergoing repeated relapses despite having sufficient motivation, then the psychiatrist may have to employ techniques such as cognitive behaviour therapy (CBT) (Spada 2010), solution-focused therapy (SFT) (Berg and Miller 1992), acceptance and commitment therapy (ACT) (Karekla and Kelly 2022), narrative therapy (Diamond 2002), family therapy (McCollum and Trepper 2014), etc. In CBT, the thoughts and cognitive distortions that lead to the lapse and relapse are identified and corrected. In SFT, the techniques the patient had successfully used in the past to remain abstinent for at least a short while are identified and reinforced. In ACT, the patient is trained to accept the cravings and overcome such moments by engaging in activities that align with their values.

Management of physical complications of alcoholism

Chronic liver disease: According to the latest reviews and guidelines, abstinence from alcohol remains the mainstay of treatment of alcoholic liver disease, and no pharmacological agent has received strong enough recommendations because the available studies are small in number and of low quality (Thursz and Lingford-Hughes 2023, Buzzetti et al. 2017). Liver transplantation has a clear role in decompensated alcoholic liver disease (Thursz and Lingford-Hughes 2023).

Hepatic encephalopathy: According to the European Association for the Study of the Liver Clinical Practice Guidelines on the management of HE (Montagnese et al. 2022), in patients with suspected HE, alternative or additional causes of neuropsychiatric impairment should be ruled out or identified. In patients with delirium and liver disease, a normal plasma ammonia value brings the diagnosis of HE into question. Brain imaging by CT scan or MRI should be performed in case of diagnostic doubts or non-response to treatment. In patients with cirrhosis and no history of overt HE, screening for covert HE should be performed with tests for which experience/tools and local norms are available. The Animal Naming Test (i.e. the number of animals listed in one minute) has recently been shown to compare favourably with more established covert HE measures (Weissenborn et al. 2001) and to predict overt HE (Campagna et al. 2017).

Patients with covert HE should be treated with nonabsorbable disaccharides (and/or rifaximin) and, if beneficial, this also helps confirm the diagnosis. In patients with HE, precipitating factors should be sought and managed (e.g., infection and bleeding). Rapid removal of blood from the gastrointestinal tract (lactulose or mannitol by nasogastric tube or

lactulose enemas) (Tromm et al. 2000) and rapid resolution of constipation (Rahimi et al. 2014) have been shown to improve recovery from overt HE. Lactulose is recommended as secondary prophylaxis following a first episode of overt HE and should be titrated to obtain 2-3 bowel movements per day. Rifaximin as an adjunct to lactulose is recommended as secondary prophylaxis following ≥ 1 additional episodes of overt HE within six months of the first one. In patients with recurrent/persistent HE, replacement of animal protein with vegetable and dairy protein can be considered, provided that overall protein intake is not compromised, and the patient's tolerance is considered.

According to a recent review, studies on branched-chain amino acids, probiotics, zinc supplementation, and L-ornithine-L-aspartate (LOLA) have all demonstrated mixed results. So, their use in treating hepatic encephalopathy must be considered on a case-by-case basis (Khalessi and Pyrsopoulos 2024).

Peripheral neuropathy: Abstinence from alcohol helps improve alcoholic peripheral neuropathy. In one study, improvement in sensory symptoms was seen within a few days, though improvement in strength took weeks to months in some patients, while the most severe cases needed up to two years. Mild impairments in vibration sense or pinprick sensation in the feet or loss of deep tendon reflexes in the ankle persisted even after that (Hawley et al. 1982). According to a systematic review and meta-analysis, vitamin supplementation (with various studies using combinations of thiamine, benfotiamine, nicotinic acid, pantothenic acid, pyridoxine, riboflavin, pyridoxine, folic acid, and vitamin B12) appears to have the best evidence (Julian et al. 2019).

Management of Korsakoff's syndrome

Differential diagnoses: a) If the memory loss is accompanied by executive dysfunctions and disinhibition, consider frontal lobe atrophy that resulted from alcohol dependence itself or head injuries. b) Localized brain lesions, such as trauma, infection, or cancer, that are a consequence of alcoholism or cardiovascular disorder. c) Nutritional deficiencies, especially those of other vitamin B, vitamin C, or protein (Westermeyer et al. 2021).

Course: Thiamine treatment, even if delayed by a day or two, can result in partial recovery. In case of a partial response, continued thiamine treatment over months to a year can lead to slow, incremental recovery with some persisting amnesia. However, if thiamine administration has been delayed by a week or two, even partial recovery cannot be assured and permanent impairment may ensue (Thomson et al. 2012).

Management: Adequate assessments should be performed to identify strengths and deficits so that an appropriate treatment plan can be constituted. The interventions rely extensively on language-free approaches, such as emotional arousal, state-dependent paradigms, and other skills that are typically spared in WKS (Westermeyer et al. 2021).

Cognitive training

Operant conditioning: For example, an after-dinner treat for clearing the table can elicit participation in daily chores.

Classical conditioning: For example, to establish daily schedules and prevent oversleeping, breakfast may be available only for a reasonable period after a morning alarm.

Other psychological approaches include contingency contracting, errorless learning, and affective recruitment (Westermeyer et al. 2021).

Calendars and smart phones: Modern technologies can facilitate the constant supervision WKS patients often need and also alleviate the spatial and temporal constraints that can restrict the patients and their caregivers (Westermeyer et al. 2021). A promising area is the use of memory compensation methods, including the use of agendas, memory cards, smartphones, and smartwatches. Traditional and digital assistive technologies can benefit individuals with amnesic disorder, provided that the goals are clearly defined, ample time is allocated to assist the patient, and the technologies are integrated holistically or combined with detailed learning strategies (Arts et al. 2017).

Pharmacological management

In Korsakoff's syndrome, no evidence exists of any beneficial effect of pharmacotherapy (Arts et al. 2017). Once Wernicke's encephalopathy has been addressed with thiamine replacement, the role of pharmacological interventions is limited to enhancing the remaining skills and suppressing the symptoms that interfere with normal functioning. Appropriate medications can be prescribed for associated problems like depression, anxiety, psychosis, or insomnia, but they do not relieve uncomplicated WKS amnesia (Westermeyer et al. 2021).

Anti-craving medications: Though anti-craving medications may not be necessary as long as the patient is in a secured inpatient facility, they may have to be started before discharge. According to the 2023 Canadian guidelines, naltrexone and acamprosate are the first-line agents, while topiramate and gabapentin are second-line agents (Wood et al. 2023). A 2023 systematic review also suggested naltrexone and acamprosate to be the first-line agents (McPheeters et al. 2023).

Conclusions

Cognitive impairments in AUD are common and may persist even after abstinence. Early identification of WKS and related conditions, along with high-dose thiamine treatment, can help prevent long-term cognitive effects. Regular screening of AUD patients may be necessary to identify cognitive deficits that impact treatment and outcomes. Advances in pharmacotherapy, cognitive remediation strategies, and brain stimulation could provide management options for cognitive impairment in AUD. Long-term patients with AUD may present additional challenges in management.

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Post traumatic cognitive impairment: Assessments and remedial measures

Traumatic brain injury (TBI) is an increasingly urgent public health issue and a major cause of morbidity and mortality in India. As India advances in urbanization and experiences rapid motorization, the incidence of traumatic brain injuries (TBIs) is expected to rise significantly. Individuals who survive a traumatic brain injury (TBI) often face chronic disabilities. These disabilities have a profound impact on various aspects of life, including cognitive, behavioural, psychosocial, physical, and vocational areas. Cognitive impairments are frequently the most challenging and distressing for the individuals affected, their families, and society. Such deficits can severely hinder daily activities, employment, social relationships, recreational activities, and active community participation.

Traumatic brain injury (TBI) is categorized as mild, moderate, or severe based on the level of consciousness, particularly the duration of coma and posttraumatic amnesia (PTA). In cases of moderate to severe TBI, significant cognitive impairments are typically observed around one month after the injury or shortly after PTA resolves. Persistent cognitive impairments beyond three months are associated with a higher frequency of disability. Cognitive recovery in moderate to severe TBI often does not return to baseline even after two years, whereas patients with mild TBI generally experience rapid recovery, with cognitive functions nearly returning to baseline within three months^[1].

Research and literature indicate that timely and effective cognitive rehabilitation interventions following TBI can significantly improve the recovery process and reduce functional disability. To ensure effective treatment, it is crucial to develop detailed guidelines for cognitive rehabilitation in individuals experiencing multiple cognitive impairments as a result of traumatic brain injury (TBI). Indian literature in this domain is limited. Hence, global studies and intervention modules have laid path to develop management strategies and guidelines in the Indian context. Cognitive testing itself is still in infancy in Indian context^[2]. Cognitive rehabilitation recommendations should become a priority in the Indian context for various reasons as mentioned in table 1. Further, there are many challenges in formulation of guidelines for cognitive remediation and implementation in Indian context which are outlined in table 2.

Table 1 Why should cognitive rehabilitation in TBI patients be a priority?

Table 1 Why should cognitive rehabilitation in TBI patients be a priority?
1. Nature of TBI: Traumatic brain injury (TBI) results in extensive damage to brain networks essential for attention, memory, executive functions, and cognitive communication.
2. Expanding Research: The field of cognitive rehabilitation is experiencing rapid growth, with numerous international intervention studies, randomized controlled trials, and two versions of the INCOG (International Network of Cognitive Researchers and Clinicians) guidelines ^[3] . However, research specific to practice guidelines in India is still in nascent stage.
3. Impact on Daily Life: Although rehabilitation often emphasizes inpatient care and daily living activities, cognitive function is vital for instrumental activities of daily living

(IADLs) and returning to normal life, particularly for younger individuals.

4. Knowledge-to-Practice Discrepancy: Clinicians encounter difficulties in implementing evidence-based cognitive rehabilitation due to the complexity and individualized nature of the field, creating a notable gap between research findings and practical application.

5. Inadequate resources: Qualified and trained clinical psychologists in the domain are not available in all places and psychiatrists alone may find it difficult to provide a comprehensive care.

6. Lack of Awareness: Family members of patients with TBI have limited understanding of services for the cognitive impairments and invariably their priorities will be to ensure survival of the patient like survival.

7. Poor Liaison: TBI patients are referred to mental health professionals by Neurosurgeons invariably for the assessment of disability mainly. Creating awareness about services available and the need of cognitive rehabilitation may aid in better outcome.

Table 2 Challenges in Formulation and Barriers for Implementation of Guidelines for Cognitive rehabilitation in patients with TBI

Challenges in Formulation of Guidelines

1. There is limited scientific literature about post traumatic cognitive impairment assessment and management in the Indian context.
2. Assessment tools need to be standardized for the Indian context and need to be validated for various languages.
3. Research evidence for cognitive interventions in traumatic brain injury patients in Indian context is limited.

Barriers for Implementation

1. Nature of the Intervention: Cognitive rehabilitation involves complex processes that require thorough assessments of a TBI patient's cognitive functions, lifestyle, and support systems. Neurosurgeons and other clinicians often lack the necessary training for these methods, and research studies frequently provide incomplete information about treatment specifics, such as exact interventions and their duration^[4].

2. Adopter Awareness and Tools: Currently guidelines for cognitive remediation in this population in Indian context is inadequate. Clinicians, insurance agencies, and policy makers often lack awareness of need of such guidelines or inadequately equipped to work along those lines. In the global scenario also, only a small fraction of clinicians are familiar with relevant practice guidelines, and an even smaller number apply guidelines that meet the necessary criteria^[5].

3. Practice Environment: Cognitive rehabilitation success will depend on a multidisciplinary team, family involvement, and clear goal setting. However, optimal conditions for practice are not always feasible due to limited resources, particularly in Indian context and especially when it is planned in an out-patient setting^[6,7].

4. Comorbidities and Impairments: Other comorbidities like depression and anxiety, as well as pre-existing personality disorders can complicate the process. These challenges, combined with variations in access to rehabilitation services, can impede effective treatment^[8].

Scope and Purpose of the present document

This document provides evidence-based guidelines for evaluating and rehabilitating cognitive function in individuals with moderate to severe traumatic brain injury (MS-TBI) across all phases of care. The primary focus is on enhancing patient outcomes and managing cognitive impairments post-TBI. While some aspects may apply to mild TBI, the guidelines are specifically tailored to MS-TBI due to the increased complexity of cognitive issues associated with it. Key details including target population, process, limitations, and evidence level are summarized in Table 3.

Table 3: Cognitive Rehabilitation post TBI: key areas, target population, the process followed and limitations

Key areas covered include

Assessment and intervention for posttraumatic amnesia (PTA)
Attentional deficits
Memory impairment
Cognitive-communication disorders
Executive dysfunction

Target Population

Adults 18 years and older with moderate to severe traumatic brain injury (MS-TBI) and cognitive impairments.
MS-TBI is characterized by a Glasgow Coma Scale score of less than 13 at any point following the injury. The guideline does not address children, as there is limited research and difficulties in assessing cognitive rehabilitation in developing brains.

Process

- Literature search from 1990 to July 2024 in PubMed
- Relevant studies in the area were searched: mainly systematic reviews, RCTs, and meta-analyses
- New guidelines on MS-TBI and cognitive rehabilitation were identified and evaluated
- Focused on cognitive assessment and remediation
- Evidence was mapped from the INCOG 2023 recommendations
- Clinical algorithms from the INCOG group were adapted for this document.
- Indian evidence in this area was hand searched in data bases and in Google.

Limitations

The recommendations are derived from evidence provided by the global scientific committee. Given the limited Indian literature in this area, it is not yet sufficient to establish as practice guidelines. Future research and new evidence may influence these recommendations. Clinicians should exercise their judgment, consider patient preferences, and take resource availability into account when applying these guidelines.

Degree of evidence used in this document

A: Recommendation backed by at least one meta-analysis, systematic review, or adequately powered randomized controlled trial with a relevant control group.
B: Recommendation supported by cohort studies with at least one comparison group (including small randomized controlled trials) and well-structured single-case experimental designs.
C: Recommendation based mainly on expert opinion and experience, though it may

also include uncontrolled case studies or series.

Defining traumatic brain injury

According to ICD 11 “Damage inflicted on the tissues of the brain as the direct or indirect result of an external force, with or without disruption of structural continuity” constitutes traumatic brain injury^[9]. Further, a case is defined as a head injury (brain) caused by blunt force, penetration, or acceleration-deceleration forces if it leads to one or more of these signs: changes in consciousness (noticed by others or reported by the person), memory loss, visible neurological or psychological issues, or an identified brain injury.

Severity grading

Next step in the process is severity grading. Based on the Glasgow coma scale^[10], the severity of traumatic brain injury is classified into mild, moderate and severe. A GCS score of 8 or lower on admission indicates severe TBI, a score of 9 to 12 is typically considered moderate TBI, and a score of 13 to 15 is classified as mild TBI. These scores are in the time frame of within 30 minutes of the injury. However, clinical evaluation and neuroimaging findings need to be included while assigning a severity grade.

Confirm that the cognitive impairments are due to TBI

After confirming a traumatic brain injury (TBI) in a patient, the next step is to determine if their cognitive issues, such as complaints or impairments, are attributable to the injury. Although cognitive difficulties immediately following the injury might appear directly related to the TBI, the underlying causes can be varied. Considerations include the patient’s pre-existing cognitive abilities, other neurological, medical, or psychiatric conditions, additional physical problems from the injury (like headaches or seizures), the influence of substances or medications on cognition, trauma-related dissociative states, and the possibility of exaggeration or malingering.

It is also crucial to compare the patient’s cognitive difficulties and functional limitations with what is expected for their specific type and severity of injury. Cognitive impairments are typically most pronounced right after the injury and tend to improve over time, though not always completely. If the patient’s cognitive issues do not follow this expected trajectory or cause functional impairments that cannot be fully explained by the TBI alone, further investigation into alternative or additional causes (including medications as mentioned table 4) is necessary.

Table 4: Medications that can significantly impact cognition in patients with TBI

- **Opiate analgesics**
- **Sedative-hypnotics**, like benzodiazepines
- **Dopamine type-2 (D2) receptor antagonists** and medications that reduce cerebral norepinephrine activity, such as typical antipsychotics
- **Anticholinergic agents**, including those for dizziness (e.g., meclizine, scopolamine), tricyclic antidepressants, and paroxetine

Note: Given that individual clinical needs might require these medications; a strict prohibition isn't practical. However, it's important to be aware of their potential cognitive effects. If possible, minimizing the use of these drugs, using the lowest effective doses, and discontinuing them when feasible is advisable. This approach helps in accurately assessing the severity, prognosis, and need for treatment of posttraumatic cognitive impairments

Before initiating evaluations and medication trials, it is essential to conduct thorough investigations. Hematological and biochemical investigations are essential and are part of routine care: hemogram, serum electrolytes, blood sugar, hormonal assay when needed, cardiac evaluation, infection work up as and when indicated. In clinical practice, getting an MRI scan done before starting a neuropsychiatric evaluation and intervention plan is needed. Invariably, MRI brain would have been done. Brain imaging will help us to locate the damage to specific part of the brain indicating probable impairment in a cognitive domain linked with that region of brain, in addition it will help us to know the nature of injury also. When it is felt that remedial measures may not be of help considering the extent of injury, interventions will be planned accordingly such as modifications in environment, family education, supportive strategies. When MRI brain reveals relatively intact brain structures, pharmacological treatments aimed at enhancing brain function may be more effective. The usual recommended MRI brain sequences include T1, fluid-attenuated inversion recovery (FLAIR), T2 gradient echo, susceptibility-weighted, and diffusion-weighted imaging. Utilizing a checklist (Table 5) at the start of the assessment for individuals with TBI can be highly beneficial.

Table 5 Checklist to document factors which may contribute to the cognitive impairments independently

A. Personal domain		
Can the following factor contribute in index person?	Yes	No
Cultural factors?		
Language barriers?		
Education, academic history, prior learning difficulties?		
Premorbid cognitive functioning/intelligence?		
Occupational history?		
Special skills/hobbies?		
Gender?		
B. Pre-existing medical conditions		
Substance dependence?		
Diagnosed psychiatry disorder?		
Epilepsy?		
Dementia?		
Visual or hearing impairment?		
Diabetes?		
Hypertension?		
C. Trauma related factors		
Mood disorder		
Fatigue, pain, lack of motivation		

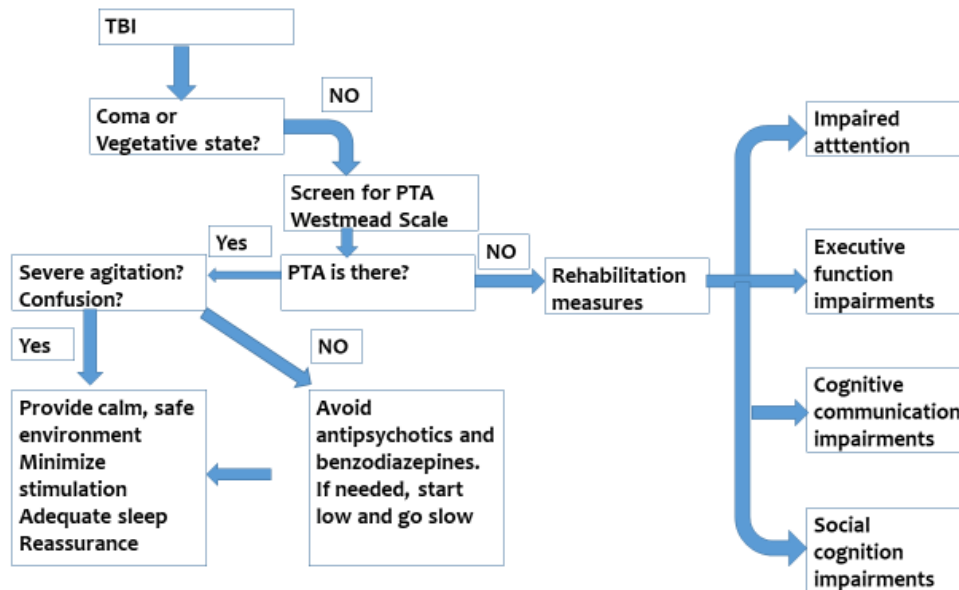
Sleep disorder		
Medications (given prior or after the injury)		
Seizure		
Sensorimotor changes include language changes (aphasia), vision/hearing impairment, incoordination)		
D. Post trauma factors		
Coping skills, cognitive status		
New onset of psychiatry disorders		
New onset of medical conditions – seizures, hormonal changes, pain, fatigue, insomnia		

Assessment Recommendations

Assessment of persons with TBI needs to be fine-tuned for the phase of TBI. The goal of this evaluation is to develop a treatment plan. It can be either standardized or non-standardized based on various factors, including the observed recovery rate and the need for data to guide future planning. This evaluation should involve observing how cognitive impairments affect daily functioning in real-life situations. It is important to complete a formal standardized assessment before starting a cognitive rehabilitation program. When choosing tests, factors such as language, race/ethnicity, acculturation, and cultural background should be taken into account^[3].

Assessment should involve gathering information from the individual with TBI, as well as from family members and others who were familiar with the person before the injury and those who may be caring for them afterward (i.e., close contacts and friends) (Grade B evidence). This helps in understanding changes across various domains. Assessment should be a collaborative process where all professionals work together to combine their findings. They should strive to avoid redundant testing or repeating tests unnecessarily (Grade C evidence). Flowchart to plan assessment of TBI is as in Figure 1.

Figure 1: Traumatic Brain Injury Assessment plan flowchart



Who should conduct cognitive assessments? (Level C evidence)

Patients with TBI have to be evaluated by a clinical psychologist or a psychiatrist who are trained in neuropsychological assessment using batteries/tools which are specific to the geographic location. Effect of cognitive impairment on functioning has to be assessed by an occupation therapist and communication aspect need to be assessed by a speech and hearing therapist.

Posttraumatic Cognitive Impairments in early phase of TBI

The neurological and behavioral manifestations and their recovery after a TBI, usually progresses in some predictable pattern^[11], as illustrated in Figure 2. There is no consensus on the best terminology for describing neurobehavioral changes during this early phase after moderate-to-severe TBI. Typically, individuals with moderate-to-severe TBI experience a period of unconsciousness followed by posttraumatic amnesia (PTA). The patients who are still having PTA will be better suited for rehabilitation programs which will focus on functional improvement instead of a complete neuropsychological testing

and remedial measures^[3]. After PTA resolves, neuropsychological testing can be planned and specific remedial measures can be outlined. Initial assessment procedures are outlined in Table 6. According to the INCOG guideline algorithm, after a thorough cognitive assessment, four primary cognitive domains may benefit from intervention: attention and processing, executive function, cognitive communication, and memory^[3]. The progression after TBI can also be effectively divided into five stages: posttraumatic coma, posttraumatic delirium, posttraumatic amnesia, posttraumatic dysexecutive syndrome, and recovery, as shown in Table 7. Each stage is marked by specific cognitive, emotional, and behavioral disturbances^[12].

Figure 2 Typical trajectories through the stages of posttraumatic encephalopathy following mild, moderate, and severe TBI are depicted. The lines representing these trajectories for each severity level are idealized.

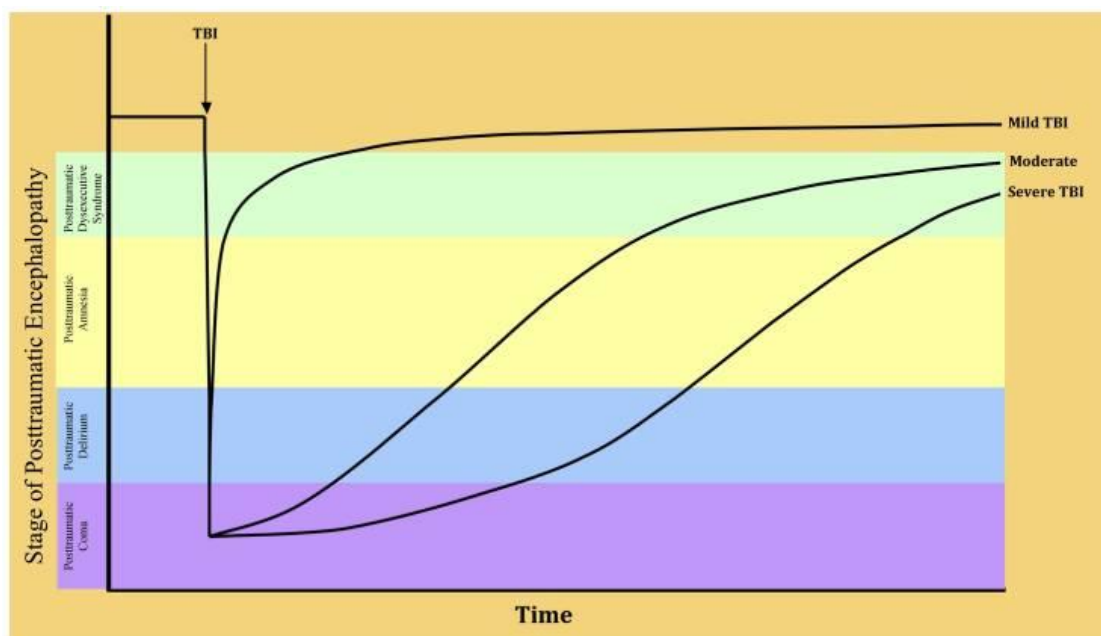


Table 6 Initial assessment after TBI
All individuals with TBI who are conscious, including those in posttraumatic amnesia should be assessed for common impairments including^[3] (Grade of evidence C): - Motor impairments, such as weakness, altered tone, balance, and incoordination - Previously missed musculo-skeletal injuries/skeletal fractures - Pain - Bulbar problems affecting speech and swallowing - Sensory dysfunctions that may impact on safety including hearing loss, numbness, visual problems (eg, reduced acuity, visual field loss, and gaze palsies) - Autonomic dysfunction Cognitive dysfunctions such as impairments in attention, communication, orientation,

and memory

Behavioral dysregulations including potential emotional/behavioral issues.

After emerging from posttraumatic amnesia, all individuals with TBI should be assessed for the presence of cognitive impairments in the following areas^[3] (Grade of evidence C):

Attention (including speed of processing)

Executive function

Language, social communication

Social cognition

Cognitive communication

Learning and memory

Awareness of impairments

Detection/expression of emotion

Visuospatial function

Table 7 An overview of post TBI early phase changes

TBI Stage	Key Neurobehavioral Feature	Description
Posttraumatic Coma	Impaired arousal	A complete impairment of arousal (wakefulness) in which there is no response to sensory input and no spontaneous behavior (purposeful or non-purposeful).
Posttraumatic Delirium	Impaired attention	A state in which there is reduced clarity of awareness of the environment, as evidenced by a reduced ability to focus, sustain, or shift attention.
		Additional features may include: alterations of arousal, which may fluctuate over minutes, hours, or days; disturbances of sleep-wake cycle; motor restlessness; impairments of processing speed, working memory, episodic memory (including orientation), language/communication, and executive function; perceptual disturbances (i.e., illusions, hallucinations) emotional lability; verbally, physically, and/or sexually disinhibited behavior, agitation, and/or aggression.
Posttraumatic Amnesia	Impaired episodic memory	This condition is marked by difficulties in acquiring new declarative information, such as orientation to time, place, and situation, as well as autobiographical details related to the period immediately before and after the injury. These issues are not due to disturbances in wakefulness (e.g., coma) or awareness (e.g., delirium). In this

		state, selective and sustained attention are generally preserved, but higher-level attention (e.g., alternating, divided), working memory, and executive functions (including insight) are impaired. Emotional and behavioral issues such as emotional lability, irritability, depression, anxiety, psychosis, apathy, and aggression may also persist. These problems are not linked to posttraumatic delirium but are instead the neuropsychiatric consequences of focal brain injuries (e.g., orbitofrontal syndrome) or damage to critical neurobehavioral networks.
Posttraumatic Dysexecutive Syndrome	Executive dysfunction, including executive control of 'basic' cognitive abilities	A condition marked by deficits in intrinsic executive functions, such as conceptualization, judgment, and insight, as well as difficulties in managing other cognitive functions, including attention (e.g., alternating, divided), working memory, language (e.g., impaired word retrieval rather than naming), motor planning, and declarative memory (e.g., impaired retrieval rather than new learning). In this condition, emotional and behavioral issues may persist, such as emotional lability, irritability, depression, anxiety, psychosis, apathy, and aggression. These issues are not due to posttraumatic delirium but are indicative of neuropsychiatric effects resulting from focal brain injuries (e.g., orbitofrontal syndrome) or damage to key neurobehavioral networks.

The initial period may be masked by delirium. Confusion Assessment Method (CAM) tool can be considered for assessing delirium^[13]. In this phase, patient needs to be assessed on O-Log^[14] tool every day till the patient meets criteria for emergence from PTA (if patient meets O-Log of ≥ 25 for 2 consecutive days).

At this stage, further cognitive functioning can be tested using Mini-Mental State Examination (MMSE)^[15]. In addition, it is advisable to do frontal lobe testing using Frontal Assessment Battery (FAB)^[16]. These will help give a clear cognitive picture after PTA. It is advisable to go ahead with assessment tools (neuropsychological) whenever feasible during the admission for the purpose of rehabilitation. The tools which are commonly used for neuropsychological testing for cognitive functioning are depicted in table 8. In Indian context, many neuropsychological assessment batteries have been developed and these are outlined in table 9. Based on the need and geographical location, one of the battery can be used.

Table 8 Commonly used standardized neuropsychological assessment

scale (Indian norms are available for the highlighted tests)		
Cognitive Domain	Ares of Assessment	Standard Assessment Tools
Attention-visual and auditory	Orientation, concentration, vigilance, mental speed and attention, distractibility, working memory and multitasking	Visual attention - CCPT-II, symbol digit modalities test (written and oral) Auditory Attention - PASAT, WAIS-III
Learning and memory	Explicit/implicit and verbal/visual memory, working memory Logical memory ^[17] CERAD Word list ^[18,19]	Visual learning and memory - CVMT Verbal learning and memory - CVLT Working memory - Digit span backward, letter number sequencing from WAIS-III
Visuo-spatial	Constructional praxis	
Language	Language comprehension and understanding naming, receptive vocabulary and verbal fluency Categorical fluency Phonemic fluency Object naming test Naming test	Multilingual Aphasia Examination Token Test, Boston Naming Test, Peabody Picture Vocabulary Test, Controlled Oral Word Association Test
Executive function	Planning, goal setting, monitoring performance and flexibility	Wisconsin Card Sorting Test, Trail Making Test, Stroop test, backwards spatial and digit span test
General intellectual function	Overall mental function	Wechsler Adult Intelligent Scale, Wechsler Abbreviated Scale of Intelligence
Psychomotor function	Motor function	Grooved pegboard, Purdue pegboard, finger tapping test
Functional Assessment		EASI: Everyday Ability Assessment Scale for India ^[20]

CCPT-II – Conners' Continuous Performance Test-II; PASAT – Paced Auditory Serial Attention Test; WAIS-III – Wechsler Adult Intelligence Scale-III;
CVMT – Continuous visual memory test; CVLT – California verbal learning test

Table 9 Tools for cognitive testing in Indian context

1. Mini-Mental State Examination (MMSE)^[15]: It is widely utilized by Indian clinicians for global cognitive screening, both in outpatient settings and at the bedside. This paper-

and-pencil assessment has a maximum score of 30, with lower scores indicating more severe cognitive impairments. A score of 24 or below is commonly used as a threshold to identify cognitive dysfunction.

2. Hindi Mental State Examination (HMSE)^[21]: It is a translated and adapted version of the MMSE designed for use with Hindi-speaking, illiterate elderly individuals in rural areas. Like the MMSE, it has a maximum possible score of 30 if all items are answered correctly.

3. Montreal Cognitive Assessment (MoCA)^[22]: It is a brief and user-friendly global cognitive screening tool that is freely accessible and increasingly favored for its availability in numerous languages, including several Indian languages such as Bengali, Kannada, Malayalam, Marathi, Tamil, Telugu, Hindi, and Urdu. The MoCA, which has a maximum score of 30, allows for adjustments based on educational level, visual impairments, and physical disabilities. It demonstrates strong test-retest reliability for repeated measures. A cutoff score of 26 is used to differentiate between normal cognitive function and mild cognitive impairment. Compared to the MMSE, the MoCA exhibits superior sensitivity and specificity.

4. Addenbrooke's Cognitive Examination-III^[23]: It is a straightforward, 100-point paper-and-pencil test designed to assess overall cognitive function and can be administered at the bedside. It is offered in various languages, including Tamil, Hindi, Indian English, Kannada, Telugu, Urdu, and Marathi. This test is freely accessible, with cut-off scores of 88 for clinical purposes and 82 for research applications.

5. Cognistat^[24] (Gupta & Kumar, 2009): It was previously referred to as the Neurobehavioral Cognitive Status Examination, is a concise cognitive screening tool that has been modified for the Indian population and has demonstrated strong validity in assessing traumatic brain injury patients. Despite its proven reliability and validity in smaller studies, normative data derived from the broader population are still lacking.

6. The PGI Battery of Brain Dysfunction^[25]: It includes five sub-tests: the PGI Memory Scale, Bhatia's Short Scale, the Verbal Adult Intelligence Scale, the Nahor-Benson Test of Perceptual Acuity, and the Bender Visual Motor Gestalt Test. This comprehensive battery evaluates cognitive dysfunction through 19 different test variables. Developed in 1990, it provides established normative data for individuals aged 20 to 59 years.

7. The PGI Memory Scale^[26]: It comprises 10 subtests that evaluate various types of memory, including verbal and nonverbal, remote, recent, short-term, and long-term memory. Created at the Postgraduate Institute of Medical Education and Research in Chandigarh, this scale has been standardized with normative data for adults aged 20 to 45 years.

8. The NIMHANS Neuropsychological Battery^[27]: It is the pioneering neuropsychological test battery developed in India. Based on Luria's principles of cerebral localization and lateralization of higher mental functions, this battery includes approximately 20 tests. It integrates several adapted Western tests along with an indigenous delayed response test designed to evaluate working memory.

For adults, the NIMHANS Neuropsychological Battery comprises 19 well-established Western neuropsychological tests that have been adapted and standardized for the Indian population. It includes population-specific norms for individuals aged 16 to 65 years and has been validated for use in various neurocognitive disorders.

9. The comprehensive neuropsychological battery^[28] in Hindi, developed by the All India Institute of Medical Sciences (AIIMS) for adults, is a detailed assessment tool

designed for individuals aged 15 to 80 years. This battery, based on the Luria-Nebraska Neuropsychological Battery, includes 160 items organized into ten primary scales and four secondary scales. It is the sole Indian test battery available in Hindi that has been developed domestically.

10. The 10/66 Dementia Research Group cognitive test battery^[29]: It was employed in studies conducted by the 10/66 Dementia Research Group and includes assessments of general cognitive function, verbal fluency, and both immediate and delayed verbal recall. Derived from the Community Screening Instrument for Dementia (CSI 'D') and the Consortium to Establish a Registry for Alzheimer's Disease, it features site-specific norms for individuals aged 65 to 80 years. This battery is particularly valuable for cross-cultural research, having established norms across seven countries, including Cuba, the Dominican Republic, Venezuela, Peru, Mexico, China, and India.

Posttraumatic Encephalopathy Following Mild TBI

In the early stages following a mild TBI, many patients experience significant impairments in various areas. These impairments can be in attention domain mainly. The processing speed of the information, working memory, memory retrieval (as opposed to new learning) may be impaired. In addition the communication aspect is impaired based on the region of the brain damage. Lastly, the domain of executive functioning is commonly seen. Behavioral and emotional problems will be there along with cognitive problems. These are indicative of impairments in frontal lobe related functions and impairments in control of more emotions and behaviors. At times, 'posttraumatic dysexecutive syndrome' term is also used to describe it.

Late Posttraumatic Cognitive Impairments

Posttraumatic encephalopathy resolves gradually, albeit sometimes incompletely, in the weeks and months after TBI.

Post-traumatic amnesia

This is seen in most individuals who regain awareness after a period of coma. Patients may not have memory of this period. PTA is commonly defined by "disorientation in time, place, and identity, as well as anterograde amnesia, which impairs the ability to form new memories"^[3]. Retrograde amnesia is also frequently seen. This retrograde amnesia can remain for longer period also. PTA can be considered as resolved when the patient's memory gets restored, this should be for the ongoing events mainly. Prior memories like marriage day or face of person recover faster when compared to abilities which warrant new learning. PTA duration is measured as the duration from the time of injury until the person can reliably store and retrieve new information. Additional impairments during PTA may include difficulties in perception, language expression and comprehension, executive function, attention, information processing speed, and capacity. Basic attentional functions typically recover before more complex ones.

Assessment: For Indian context, memory component from any of the above mentioned batteries can be used. Global guidelines have mentioned about using Westmead Post-Traumatic Amnesia Scale^[30]. This has Grade B evidence^[31,32].

Management:

Non-pharmacological measures with a goal to address confusion can be a priority in this phase. This confusion will also manifest as agitation. Managing these at home will be difficult and in patient care is advised till the patient becomes manageable. This has grade C evidence^[33,34].

During the stay activities which are required for daily living need to be addressed as a priority taught. This has grade A evidence^[35].

The non-pharmacological recommendations are outlined the table 10. This has grade C Evidence^[36]. Pharmacological management recommendations are outlined in table 11 and this has grade C evidence^[37,38]. The flowchart of management of PTA is depicted in Figure 3.

Table 10 Managing post-traumatic amnesia

Non-pharmacological

- Maintain a calm, safe, and consistent environment while avoiding overstimulation.
- Use low-stimulation rooms if needed.
- Assess the effects of visitors, evaluations, and therapies, and limit these activities if they lead to agitation or excessive fatigue.
- Allow adequate rest and sleep, supporting night-time sleep and daytime wakefulness as tolerated.
- Minimize the use of physical restraints to enable free movement.
- Ensure that the person with TBI interacts with consistent healthcare professionals or trained caregivers.
- Establish and use the most effective and straightforward communication methods.
- Offer frequent reassurance.
- Introduce familiar information at a pace that the person can tolerate.
- Identify and address triggers of agitation.
- Supervised listening to preferred music may help reduce agitation.
- Educate family members about PTA and effective strategies to engage with the person and minimize agitation.

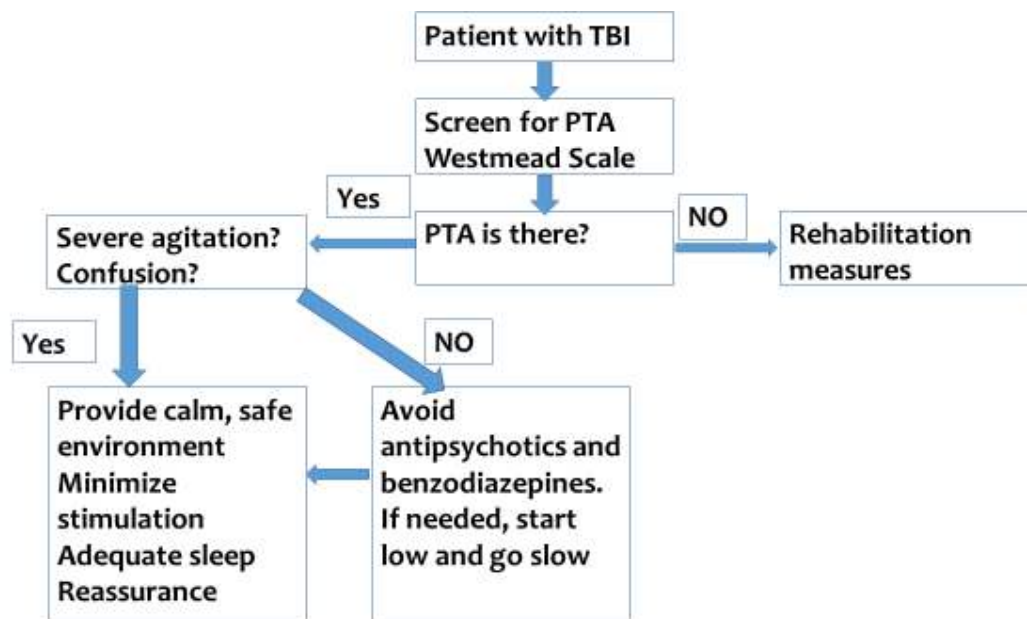
Table 11 Pharmacological management of PTA

Agitation and aggression: Benzodiazepines and antipsychotics are used

Concerns: these may slow recovery after brain injury and may have a negative effect on cognition.

Recommendation: Restrict the use of antipsychotics for more severe levels of agitation and aggression that threaten patient and/or staff safety. In unavoidable circumstances, when medications are required, it is recommended to **start low, go slow**, and it is essential to monitor the impact on agitation and cognition using CAM scale.

Figure 3: Flowchart of management of PTA



Post traumatic attention impairment

After PTA, person needs to be evaluated for attention impairment. This includes both visual and verbal attention. The areas which needs to be assessed in this domain are: orientation, concentration, vigilance, mental speed and attention, distractibility, working memory and multitasking. These can be part of routine clinical evaluation. However, standard assessment tools can be used as mentioned in the table 8 and 9.

Interventions:

The management algorithm has been depicted in Figure 4. Once attentional impairments are identified through neuropsychological assessments and their impact on daily life is considered, it's crucial to address potential exacerbating factors. These factors include disruptions in hearing and vision, fatigue, sleep disturbances, anxiety, depression, pain, medication effects, and substance use. Efforts should be made to manage these factors where possible. Additionally, evaluating the individual's motivation, self-awareness, memory, and executive functions is essential for determining their capacity to adopt effective strategies. The level of support from family and other environmental factors should also be considered.

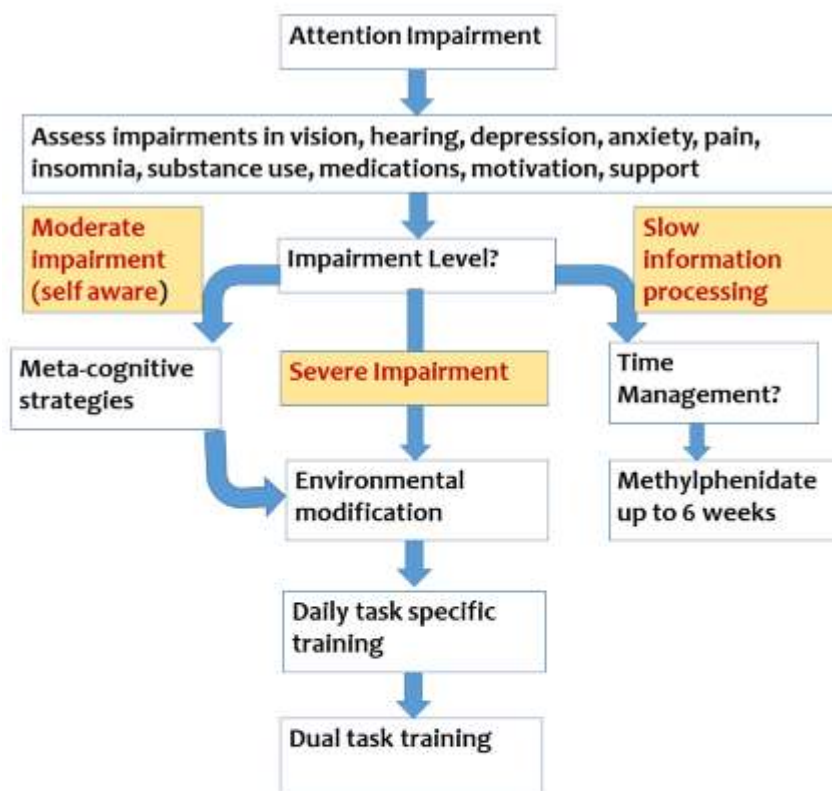
For individuals with mild to moderate attentional impairments and some degree of self-awareness, training in metacognitive strategies tailored to everyday attentional challenges has been shown to be beneficial^[39]. Managing time pressure can help address issues with information processing speed. Training may include specific tasks like dual tasking or coping with background noise, though the focus should remain on practical, everyday tasks rather than abstract computer exercises^[40] due to limited evidence of generalization.

For those with severe attentional impairments, poor self-awareness, and limited executive function, modifications to tasks or the environment—such as reducing attentional demands or eliminating distractions—might be useful^[41]. Attention Process Training (APT) is a targeted program aimed at restoring and enhancing both visual and

auditory attention through direct training methods. However, further research is needed to validate these approaches. Research on these strategies has involved participants with a range of injury severities, generally between 16 and 60 years old, who had adequate visual acuity, hand function, and cognitive ability to perform assessments and training. Individuals with other neurological or developmental conditions, or pre-existing psychiatric or substance use disorders, were typically excluded. Training was conducted from three months to several years post-injury. Neuropsychological tests such as the PASAT, Trail Making Test, cancellation tasks, Digit Span, and Digit Symbol substitution tasks were used for screening and evaluating outcomes, which were also assessed through subjective reports, real-world data entry tasks, and activity and participation scales.

Methylphenidate, administered at 0.3 mg/kg in divided doses, has shown to enhance information processing speed in individuals aged 16 to 60 years recovering from mild to severe TBI^[42,43], either in acute stages or more than six months post-injury, provided they have no history of attention deficit hyperactivity disorder, previous stimulant use, substance dependence, or other psychiatric disorders. Amantadine has demonstrated short-term benefits in arousal and function for inpatients in a vegetative state or emerging from coma, but its effectiveness in improving attention after coma emergence remains unproven^[44].

Figure 4: Impaired attention management algorithm



Impairment of Memory

Memory impairment is the commonest cognitive impairment post TBI^[45]. It is frequently the first function to be notably impaired and one of the last function to be regained in the recovery process. The most commonly reported memory impairments are in prospective and episodic (retrospective) memory^[46]. Prospective memory involves the ability to remember to perform a planned action or intention at a future time, while episodic memory pertains to recalling past information or events^[47]. Both types of memory require the encoding, storage, and retrieval of information. However, prospective memory also involves additional executive functions such as planning, initiating, and monitoring the outcomes related to the future intention or action.

Management strategies for prospective and episodic memory impairments can be divided into compensatory and restorative methods^[48]. Compensatory strategies aim to mitigate the effects of memory impairments on daily tasks, while restorative techniques involve repeated practice to try to restore memory function^[49].

Assessments can be done using tests as mentioned in Table 8 and 9.

Management strategies

Algorithm to manage memory impairment post TBI is as in the figure 5.

Some of the useful strategies for patients with some preserved skills have been mentioned here. As part of instructional techniques, PQIRST method can be used and in this method there is Preview, Question, Read, State, Test. In addition, practicing repeatedly can be considered as an interventional measure, practicing retrieval of information can also be tried and patient can be made to practice visual imagery. Another technique is using metacognitive concept where patient is explained about the concept of self in domains of awareness and regulation. Mix and match of these is used as per the need. These can be part of individual or group therapy. These are internal compensatory strategies and these can be used in addition external memory aids. This has level A evidence^[50,51]. A memory notebook can be used. This has section of orientation (injury related information), memory log, calendar, to-do lists, transportation (maps, public transportation schedule, and taxi phone numbers, a feelings log, names, etc.) Smart gadgets like smart phones or traditional notepads, and whiteboards, can be used in patients with severe memory issues. Training should focus both on patient and the caretaker about these aids. This has grade A evidence^[52]. It is important to note that remediation plan and implementation should be done by a therapist with expertise in this domain. This approach helps ensure that the strategies are integrated into meaningful and practical tasks. There is limited evidence supporting the effectiveness of restorative techniques, such as computerized cognitive training (CCT), when used in isolation^[40].

There are several key instructional practices that can promote learning for individuals with TBI memory impairments and these are outlined in table 12. This has grade A evidence^[1].

Table 12 Standard practices to promote learning in patients with TBI memory impairments

- Clearly defined intervention goals
- Selection of and training of goals that are relevant to the person with TBI (ie, ecologically valid)
- Allow sufficient time and opportunity for practice
- Breaking down tasks into smaller components such as task analysis when training multistep procedures
- Use of distributed practice
- Teach strategies using variations in the stimuli/information being presented (eg, multiple exemplars)
- Teach strategies to promote effortful processing of information/stimuli (eg, verbal elaboration and visual imagery)
- Use of techniques that constrain errors (eg, errorless, spaced retrieval)
- Consider use of behavioral memory strategies with a focus on context and imagery in the acquisition phase of learning

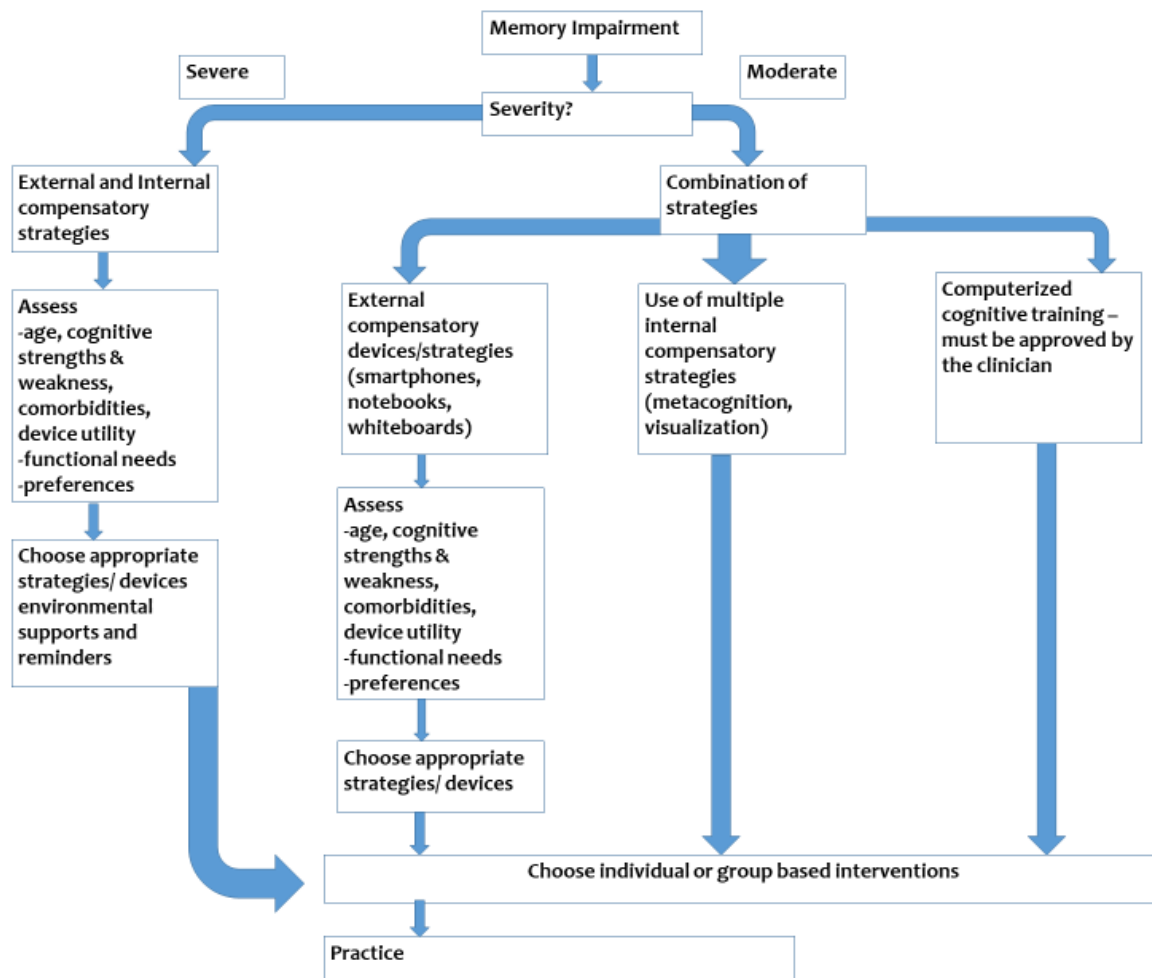
Group-based interventions can be used to address memory impairments but the evidence to support this as more effective than one-on-one intervention is lacking. To enhance effectiveness, it is advisable to minimize variability among group members,

ensure adequate participation through a sufficient number of sessions, and focus on teaching the generalization of acquired skills. This has level A evidence^[53,54].

Pharmacological interventions:

Donepezil for memory impairments during the chronic phase can be used. Periodic objective assessment can be done and need to monitor adverse effects (diarrhea, stomach upset, and nausea)^[55,56]. Methylphenidate^[42] and amantadine^[57] do not have support for use for improving memory in this. Non invasive brain stimulation(Transcranial direct current stimulation (tDCS)) use has been restricted to the randomized controlled trials^[58].

Figure 5 Memory impairment management algorithm



Executive function Impairments

Executive function indicates all cognitive abilities which are usually higher order and are for planning and execution^[59]. These have multiple components beginning from being aware of oneself, planning a task, execution as per the plan, judgement in a situation,

problem assessment and solving, thinking in abstract, reasoning, managing own emotions and behaviours as per the need. Impairments in these sub-components have been found to be strong predictors of functional, interpersonal, and psychosocial outcomes^[60], often providing greater predictive value for clinical outcomes than attention, processing speed, and memory^[61].

Assessment: Executive functions can be assessed by any of these tests: Wisconsin Card Sorting Test, Stroop test, backwards spatial and digit span test. Standard tests to assess this domain is integral to neuropsychological batteries mentioned in table 8 and 9.

Management strategies

After the assessment it will be clear whether the patient is self-aware of the impairments. For individuals with TBI who have impaired self-awareness, strategies that promote self-monitoring and include feedback should be utilized. Self-awareness training methods, such as video feedback, can be considered to enhance the ability to identify and correct errors during task performance. This has grade A evidence^[62].

Metacognitive strategies, can be used. These include dividing the task into sub components like plan a task, do it then check it then review the performance or define a goal as per the abilities or assess one's own abilities and predict one's own performance. These will help in planning a task, improves organization skills and problem solving abilities of the patient. Core aspect in this revolves around concepts of monitoring self, using feedback to fine tune the performance, managing emotions via training. These can be used for simple routine day-to-day issues which will be part of functioning^[63].

Strategies to improve reasoning skills: These will be helpful in TBI patients.

Group-based interventions

Group-based interventions can be used^[63].

Rhythmical/music therapy

To address executive functioning, implementing a structured music therapy program is recommended in global guidelines but Indian evidence is lacking. This program should include (1) rhythmical training, (2) structured cognitive-motor training, and (3) personalized music playing activities to suit a patient's interests and progress^[64].

Rhythmical training: "playing sequences of musical rhythms and coordinated bimanual movements on a djembe drum and own body"^[65].

Structured cognitive-motor training: "playing musical exercises on a drum set with varying levels of movement elements and composition of drum pads, accompanied by the therapist with piano".

Assisted music playing: "learning to play the participant's own favorite songs on the piano with the help of the therapist and using figure notes"

Virtual Reality

Where feasible, virtual reality programs alongside in-person visits can be considered. This has grade A evidence^[66,67] (Alashram et al., 2019; Manivannan et al., 2019). But evidence in Indian context is lacking.

Cognitive communication and social cognition impairments

Communication dysfunction stemming from underlying cognitive impairments is known as a cognitive-communication disorder. These disorders are prevalent following severe TBI, affecting over 70% of individuals with some degree of communication disability due to their injury^[68]. The multifaceted nature of TBI often leads to a complex combination of cognitive, physical, behavioral, emotional, linguistic, and psychosocial effects that contribute to the communication challenges faced by individuals^[69]. Symptoms can vary widely, from reduced communication abilities (such as flat affect, difficulty finding words, and problems maintaining or generating topics) to excessive talking, tangential discussions, dominating conversations, and repetitiveness^[70]. Communicating with someone who has TBI can be challenging, potentially leading friends, caregivers, and family members to avoid the individual, which can strain preinjury relationships. Cognitive-communication disorders can significantly impact psychosocial outcomes, affecting employment, friendships, education, and community involvement^[71]. Overall, a loss of communicative competence is a significant barrier to reintegration into the community.

Social cognition concept is essential component of communication competence. It has both cognitive and affective components: it involves conceptualizing thoughts and beliefs of other people (theory of mind, ToM) in addition, it includes perceiving emotions and demonstrating emotional empathy^[70]. Those with TBI may exhibit egocentric communication, fail to respond to social cues, overlook implied meanings, display excessive familiarity with acquaintances, and breach social norms such as appropriate interpersonal space. These impairments can lead to misjudgments in social situations, hindering their ability to form and sustain relationships^[72].

Evaluation and intervention

This domain needs to be evaluated and addressed by speech and hearing therapists. The assessments will focus on competence of patient in communication. Here the caretaker is used as Communication partners because the patients may communicate more with friends and family members.

Social cognition can be assessed using Indian tool SOCRATIS^[73]. Components of social cognition namely, emotion perception, theory of mind (ToM), and emotional empathy need to be evaluated.

Interventions:

When a severe cognitive communication disorder is considered, interventions can be planned which can be direct or indirect at any level of impairment and include:

Communication partner training. This has grade A evidence^[74].

Communication strategy and metacognitive awareness training. This has grade A evidence^[75].

Reintegration to daily functions, productive activities, participation and competence, modification of the communication environment, assistance with adjustment to impairments.

Communication coping treatment (grade C evidence).

Focus on confidence, self-esteem, and identity formation (grade C evidence).

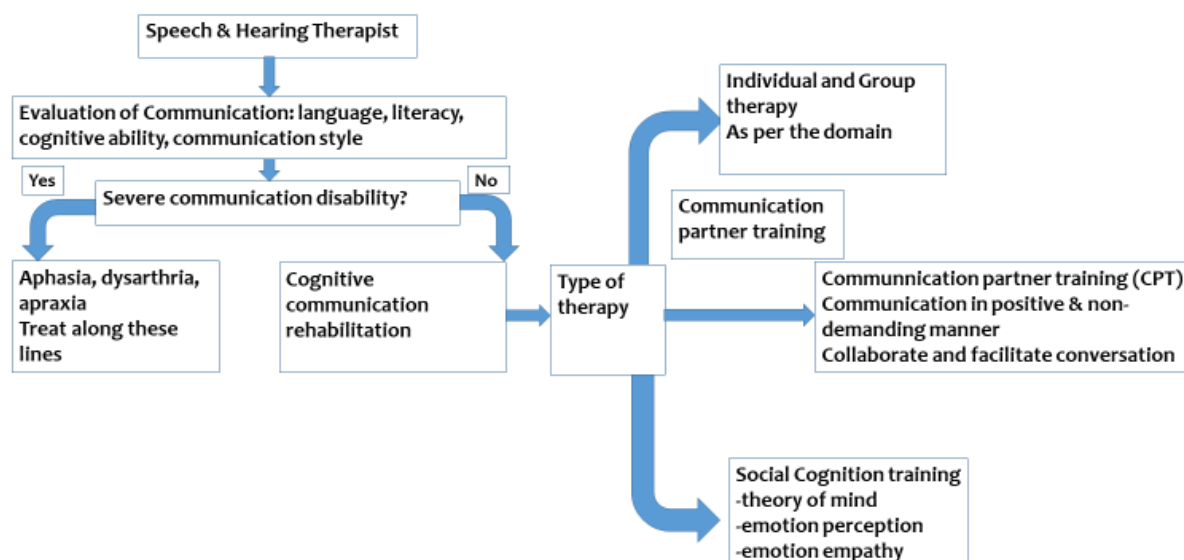
Provision of education and information regarding the nature of acquired cognitive-communication disorders to both the patient and close other and communication partner.

A cognitive-communication rehabilitation program for individuals with TBI should offer opportunities to practice and apply communication skills in real-life contexts relevant to their daily activities, such as living, working, studying, and socializing. Goal attainment scaling is recommended as a method for assessing the effectiveness of person-centered interventions.

Computerized social cognition treatments, which target specific skills like emotion recognition or training in cognitive biases, emotional processing, and theory of mind through photographs and videos, have shown improvements on isolated outcome measures. However, these studies do not demonstrate that these skills generalize to everyday activities. Therefore, computer-based, decontextualized social cognition skills training is not recommended due to the lack of evidence supporting the transfer of these skills to real-life situations.

Algorithm for management is as in Figure 6

Figure 6 Algorithm of management of cognitive communication and social cognition impairment in TBI



General principles for the management of cognitive impairments have been outlined in table 13 and 14 (Bayley et al., 2023).

Table 13 General principles for cognitive rehabilitation with traumatic brain injury

General principle/Recommendation	Grade of Evidence
Individuals with ongoing cognitive deficits from TBI should undergo functionally oriented cognitive rehabilitation. Treatment should be framed within the context of the person's preinjury characteristics, developmental stage and recovery progress, as well as their personally meaningful daily activities, life contexts, and goals.	B
Cognitive rehabilitation should include, when relevant:	C

• Restorative treatments centered on real-world activities • Training in compensatory strategies • Caregiver training • Education on the cognitive effects of TBI • Functional adaptations • Environmental modifications	
Cognitive rehabilitation should: • Emphasize participation in activities that are meaningful to the individual with TBI and relevant to those involved in their care. • Include therapeutic interventions within the person's own environment or those applicable to their daily life. • Integrate strategies to promote the generalization of skills.	C
Group-based interventions can be considered as part of cognitive rehabilitation to address: • Social skills • Emotional self-regulation • Goal achievement • Problem-solving • Communication • Attention • Memory	B
Cognition should be reassessed regularly using standardized and functional outcome measures to evaluate the effectiveness of interventions.	C
Consider implementing non-pharmacological interventions before starting pharmacological treatments.	C

Table 14 General principles for pharmacological management of cognitive functions in TBI

General principle/Recommendation	Grade of Evidence
Medications of TBI patients should be reviewed regularly	C
When initiating pharmacological interventions for TBI, it is crucial to carefully select and monitor drugs to minimize potential adverse effects on arousal, cognition, motivation, and motor coordination. Objective outcome and assessment measures should be utilized.	C
It is advisable to use medications that address multiple brain injury-related symptoms or syndromes when possible (e.g., a single agent that targets both mood and insomnia, or headache and insomnia).	C
When introducing medications for individuals with TBI, start with the lowest effective dose and gradually increase it based on tolerability, clinical response, and urgency of the situation. Ensure that drug trials have sufficient duration and dosing. Clearly define therapeutic goals to gauge efficacy. If these goals are not achieved, reconsider the continuation of the	C

medication.	
Medications that may have harmful side effects or contribute to confusion or sedation should be gradually reduced when feasible, while continuing regular monitoring of the patient.	C
Serum drug levels in individuals with TBI should be monitored as needed to avoid toxicity.	C
Given the potential limitations in self-awareness of patients with TBI, collaborating with family members or significant others, if feasible and accepted by the patient, can be helpful in monitoring the effectiveness and side effects of treatment.	C
The use of antipsychotics and benzodiazepines to manage agitation or aggression in individuals with TBI should be minimized, as these medications may hinder recovery and negatively impact cognition. It is advisable to start with the lowest dose, increase gradually, and assess their effects on agitation and cognition using standardized tools.	C
Anticonvulsants, especially phenytoin and levetiracetam, are recommended to reduce the incidence of posttraumatic seizures within the first 7 days after injury. However, routine use of anticonvulsants to prevent late posttraumatic seizures beyond 7 days post-injury is not advised.	A
Amantadine may be considered to improve arousal and consciousness and to speed up functional recovery in the short term for individuals in a vegetative or minimally responsive state, or in coma, following TBI.	A

Conclusion

Despite more than a century of advancements in psychology, neurology, and neuropsychology in India, cognitive assessments and interventions for patients with traumatic brain injury remains underdeveloped. The need of assessment and intervention is not felt amongst stakeholders namely patients, family members and primary physicians. This can be made possible by creating awareness amongst this population by developing and demonstrating assessment and intervention tools in Indian population. Norms for various cognitive functions have been developed in India but they are not used routinely unless there is a need for disability certification or other legal purposes.

Post traumatic brain injury cognitive deficits will depend on various factors including premorbid cognitive functioning status, severity of brain injury and intervention modalities of brain injury. Initial post traumatic period is marked by confusion and amnesia. This phase mainly involves acute management of behavioural disturbances using pharmacological and non-pharmacological measures. Subsequently post-traumatic memory impairment, executive function impairment, social cognition impairment, language impairment will manifest based on the region of the brain involved and the severity of impairment. Assessments for specific cognitive tasks can be undertaken using standard neuropsychological assessment batteries. Intervention modules in Indian population are limited in terms of research and evidence.

There is a need for collaborative research and resource sharing with global scientific committee which will help to bridge the gap between the need for brief, sensitive, and

psychometrically robust cognitive intervention the practicalities for effective management, and research.

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