Major Neurocognitive Disorders (Dementias)

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13.1 Introduction

Consultation-Liaison (CL) Psychiatrists are frequently consulted on patients with Major Neurocognitive Disorders (MNCDs; DSM-5), formerly known as dementia. The questions usually posed include determination of decisional making capacity, management of delirium superimposed on MNCD, diagnosing the etiology of and assisting with the management of behavioral and psychiatric symptoms (e.g., mood, psychotic or behavioral symptoms) due to MNCD.

Thus, it is imperative for CL psychiatrists to be able to recognize and diagnose MNCD, differentiate among the various types and causes of MNCD, and be familiar with management strategies of the various psychological and behavioral manifestations.

Here is a common scenario of such a consult:

> A 72-year-old man with diagnosed "Alzheimer's Dementia" was brought to the hospital by his wife and children, for increased agitation and confusion. The patient had demonstrated worsening of his memory over the last 7 years. During the same period, his wife took over managing the household and finances, the patient stopped driving, and eventually he was no longer allowed to leave the house on his own. Progressively, he required assistance in dressing and bathing and had difficulty recognizing distant family members when they visited. Over the last year, he started accusing his family members of stealing his personal items. During the same period, he called 911 several times to report non-existing intruders. During the week prior to admission, the patient became increasingly irritable and agitated, threatening and scaring his family.

H. Leigh and J. Streltzer (eds.), *Handbook of Consultation-Liaison Psychiatry*,
DOI 10.1007/978-3-319-11005-9_13, © Hoyle Leigh & Jon Streltzer 2015

He charged and attempted to hit his son. He had forcefully pushed his wife when she was attending to him, and was later found barricading in the bathroom. He reported that he saw "a gang of thugs" in his living room and was hiding from them. At this point, his family members feel they can no longer safely manage his behavior at home and thus are requesting evaluation and treatment.

In the emergency department, a medical and laboratory evaluation revealed a urinary tract infection (UTI). Other laboratory data were within normal levels, including normal hepatic and renal function. Electrocardiogram (EKG) revealed normal sinus rhythm without prolonged QTc. The patient was admitted to the medicine unit and started on oral antibiotics.

In the hospital, the patient was agitated, yelling at and attempting to hit the nurse offering him medications. He appeared to swing at imaginary objects and exhibited a reversal of his sleep–wake cycle (i.e., not sleeping at night, but somnolent during the daytime). The patient was disoriented, unable to state where he was or why he was in the hospital.

The CL psychiatrist was consulted to aid in management of the patient's symptoms. After an assessment, the patient was diagnosed with delirium superimposed on MNCD. In addition, to treating his infection, the CL psychiatrist recommended starting a short-term, low dose antipsychotic to treat delirium, as well as to manage the patient's agitation and psychotic symptoms due to MNCD. In addition, the CL psychiatrist recommended initiating treatment with an acetylcholinesterase inhibitor and a selective serotonin reuptake inhibitor (SSRI) for the long-term management of his behavioral symptoms. The staff was instructed on the use of behavioral interventions for redirecting the patient's unsafe behavior.

After 5 days of treatment the patient appeared to be calmer. Yet, due to past experiences, the family did not feel safe having the patient return home and the team thought it was appropriate to pursue a specialized skilled nursing facility. However, the patient expressed a firm desire to return home. Psychiatry was asked to comment on patient's capacity to make decisions regarding discharge planning. The CL psychiatrist again met with the patient, discussing the patient's choice, and further elucidating the patient's understanding of his condition, the team's recommendations, and the risks versus benefits of returning home versus going to a skilled nursing facility (Appelbaum 2007). The patient was found to be unable to appreciate that he had a progressive cognitive impairment and could not verbalize his needs or risks of being at home. He did not understand his family's concerns or the team's recommendations. Thus, he was deemed not to have capacity to make medical or placement decisions, and his family was thought to be an appropriate surrogate decision maker. Finally, the family was encouraged to pursue probate conservatorship in order to facilitate the patient's future care.

Major Neurocognitive Disorders (MNCDs; DSM-5), are major neuropsychiatric conditions affecting an individual's cognitive functioning leading to interference with independence in everyday life activities (APA 2013). By definition, DSM-5 requires that the presenting deficits represent a decline from a previously attained level of cognitive functioning; this will allow distinguishing them from the neurodevelopmental disorders in which a neurocognitive deficit is present at birth or interferes with development. It is possible, however, to develop a neurocognitive disorder superimposed on a neurodevelopmental disorder, for example Alzheimer's disease (AD) in a patient with developmental delay associated with Trisomy 21.

In MNCD various cognitive domains are affected, including complex attention, executive function, learning and memory, language, perceptual-motor, and/or social cognition (Table 13.1). DSM-5 requires that in order to diagnose major NCD, the patient must demonstrate BOTH an acquired cognitive decline in one or more cognitive domains (based on concern about cognition either on the part of the individual, informants, or clinician) AND substantial cognitive impairment preferably documented with evidence from objective testing or quantifiable clinical assessment. In cases of MNCD, performance on objective neuropsychiatric assessment falls usually two or more standard deviations below standardized norms (3rd percentile or below) (APA 2013). These cognitive deficits are attributable to changes in brain structure, function, or chemistry.

13.1.1 Epidemiology

By 2005, 24.2 million people worldwide had MNCD and 4.6 million new cases were arising every year (Ferri et al. 2005; Reitz and Mayeux 2014). It is estimated that the highest prevalence and incidence rates of MNCD can be found in North America and Western Europe, followed by populations in Latin

Table 13.1 Neurocognitive domains affected in MNCD

Complex attention	The patient has increased difficulty in environments with multiple stimuli (e.g., TV, radio, conversation); has difficulty holding new information in mind (e.g., recalling phone numbers or addresses just given; or reporting what was just said).
Executive function	The patient is not able to perform complex projects; needs to rely on others to plan instrumental activities of daily living or make decisions.
Learning and memory	The patient repeats self in conversation, often within the same conversation; cannot keep track of short list of items when shopping or of plans for the day. Requires frequent reminders to complete task in hand.
Language	The patient has significant difficulties with expressive or receptive language; often uses general terms such as "the thing" and "you know what I mean."
	With severe impairment patients may not even recall names of close family and friends.
Perceptual–Motor	The patient has significant difficulties with previously familiar activities (e.g., using tools, driving motor vehicle), and navigating in familiar environments.
Social cognition	The patient may exhibit changes in behavior (e.g., shows insensitivity to social standards); makes decisions without regard to safety. Usually patients have little insight into these changes.

America and China and the western-Pacific region (Ferri et al. 2005). Studies predict that global prevalence of MNCD will quadruple by the year 2050 (Reitz and Mayeux 2014). Much of the increase will be in the developing countries (Alzheimer's Disease International 2013).

Studies have found that the prevalence of MNCD increases exponentially with age (Table 13.2) (Lobo et al. 2000; Alzheimer's Disease International 2008). In 2002, the Aging, Demographics, and Memory Study (ADAMS) estimated the prevalence of MNCD in the USA among individuals aged 71 and older to be 14 %, comprising about 3.4 million individuals, and in those aged 90 and older 37.4 % (Plassman et al. 2007).

Overall, AD accounted for approximately 69.9 % of all dementia, while vascular dementia (VaD) accounted for 17.4 %. Other types of dementia such as "dementia, undetermined etiology," Parkinson's dementia, normal-pressure hydrocephalus, frontal lobe dementia, alcoholic dementia, traumatic brain injury, and Lewy body dementia accounted for the remaining 12.7 % of cases (Plassman et al. 2007). The Global Burden of Disease project DISMOD-II software estimated incidence rates of 4.6 million new cases of dementia every year (about one new case every 7 s). Estimating the number of people living with dementia worldwide in 2001 at 24.3 million, but predicting the number will almost double every 20 years, translates to 42.3 million in 2020 and 81.1 million in 2040 (Ferri et al. 2005).

Table 13.2 Incidence and prevalence rates of dementia from the EURODEM meta-analyses for European studies

Age group	Annual incidence per 100		Prevalence (%)	
	Males	Females	Males	Females
60–64	0.2	0.2	0.4	0.4
65–69	0.2	0.3	1.6	1.0
70–74	0.6	0.5	2.9	3.1
75–79	1.4	1.8	5.6	6.0
80–84	2.8	3.4	11.0	12.6
85–89	3.9	5.4	12.8	20.2
90+	4.0	8.2	22.1	30.8

Sources: (Lobo et al. 2000; International 2008)

MNCD has widespread effects on affected individuals, their families, and society. In the report on the state of US Health, Alzheimer's Disease (AD) was ranked as the ninth cause of the years of life lost due to premature mortality and the 12th cause of the years lived with disability (Murray et al. 2013).

Early-onset neurocognitive disorder (NCD) has been increasingly recognized. A study conducted at the university hospital in Cambridge, UK found that the overall prevalence of early-MNCD (i.e., onset <65 y/o) was 81 per 100,000 in the 45–64-year age group (Ratnavalli et al. 2002). Furthermore, they found that AD accounted for 35 % of this early onset dementia, while frontotemporal lobar degeneration (FTLD) accounted for 22 %. As mentioned above, there are multiple etiologies contributing to the dementias, each with its own characteristics and presentation.

Table 13.3 Major neurocognitive disorders—subtypes (as recognized by DSM-5)

Subtypes based on etiology (*in alphabetical order*)
Alzheimer's disease
Due to another medical condition
Due to multiple etiologies
Frontotemporal lobar degeneration
HIV infection
Huntington's disease
Lewy body disease
Parkinson's disease
Prion disease
Substance/medication induced
Traumatic brain injury
Unspecified
Vascular disease
Subtypes based on severity level
Mild—Instrumental ADL's are preserved
Moderate—Basic ADL's affected
Severe—Fully dependent
Subtypes based behavior
With behavioral disturbance
Without behavioral disturbance

Table 13.4 Major neurocognitive disorder due to Alzheimer's disease

1. Diagnostic criteria for major neurocognitive disorder are met.
2. There is insidious onset and gradual progression of impairment in one or more cognitive domains.
3. Criteria met for either probable or possible Alzheimer's disease are as follows:
   (a) *Probable* Alzheimer's disease is diagnosed if either of the following is present:
   - Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing.
   - All three of the following are present:
     – Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detail history or serial neuropsychological testing).
     – Steadily progressive, gradual decline in cognition, without extended plateaus.
     – No evidence of mixed etiology (e.g., absence of other neurodegenerative or cerebrovascular disease or another neurological, mental or systemic disease likely contributing to cognitive decline).

   (b) Otherwise, *possible* Alzheimer's disease should be diagnosed.

The commonest subtypes of MNCD include AD, vascular dementia (VaD), dementia with Lewy bodies, and FTLD. DSM-5 subtypes the various MNCD syndromes based on their etiology, if known (Table 13.3) (APA 2013). These are discussed below.

13.2 Etiologic Factors and Subtypes

13.2.1 Alzheimer's Disease

Alzheimer's disease (AD) is the leading cause of MNCD, estimated to occur in 50–75 % of those afflicted by dementia (Gouras 2009). It is estimated that by 2013 about five million Americans older than 65 have Alzheimer's disease. Further estimates suggest that by the year 2025 up to 7.1 million of Americans older than 65 will suffer from the condition. The disease slowly erodes memory and thinking skills, and eventually makes the affected individual incapable of taking care of their activities of daily living (ADLs). It is characterized by slow progression with an average time from its diagnosis until death ranging from 5 years (Larson et al. 2004) to 10 years (Brookmeyer et al. 2002). MNCD due to AD usually presents with loss of recent episodic memory, with affected individuals becoming forgetful, losing objects, repeating stories, and missing appointments. Word-finding difficulty is common and presents early. Memory deficits are followed months to years by deficits in executive function, visuospatial function, language, and praxis. It eventually manifests in global cognitive deterioration, difficulty with long-term memory and overlearned visuospatial tasks, such as eating and dressing (Table 13.4).

Of note, behavioral changes are common and eventually up to 88 % of patients experience NCD-associated behavioral and psychiatric symptoms, formerly known as Behavioral and Psychiatric Symptoms of Dementia (BPSD) (Mega et al. 1996). These symptoms are usually differentiated into three clusters, i.e., affective symptoms (dysphoria, anxiety, apathy), psychotic symptoms (delusions and hallucinations), and verbal and physical agitation. Of note, psychotic symptoms

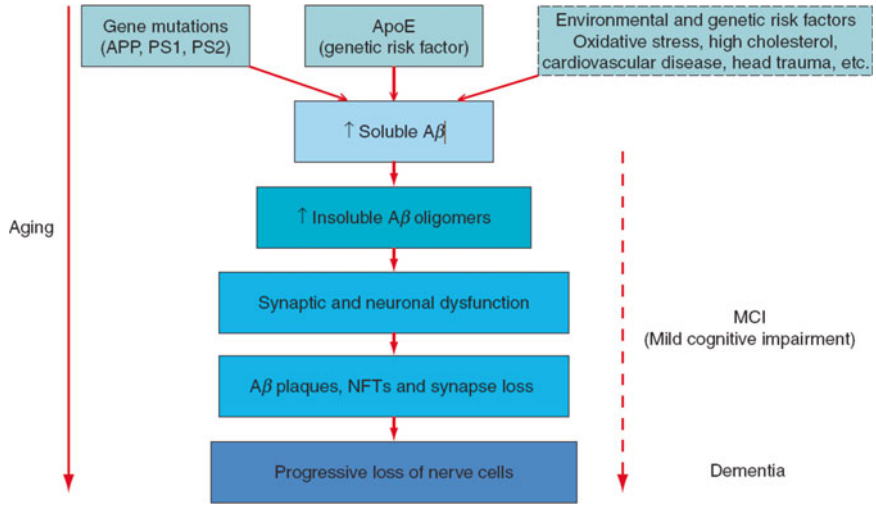

Fig. 13.1 The amyloid cascade hypothesis. *APP* amyloid precursor protein, *PS1, PS2* presenilin proteins 1 and 2, *Apo E* apolipoprotein E, *Ab* b-amyloid, *NFTs* neurofibrillary tangles. From (Gouras 2009 p. 405)

are different from the psychotic symptoms in primary psychotic illnesses: hallucinations are more commonly visual and delusions often relate to the faulty memories. For example, a patient misplaces items and thus concludes that there are intruders in the house who steal, or they have difficult time remembering their spouse and conclude that he/she was replaced with an impostor (Capgras delusion). Usually these behavioral symptoms bring these patients to the attention of a CL psychiatrist and management of agitation in a patient with MNCD is not an uncommon consult question in the general hospital. These neuropsychiatric symptoms also place a huge burden on the family and are frequently the reason behind nursing home placement of such patients. Eventually patients are bedridden, unable to feed themselves or mobilize and they often die from dehydration or sepsis.

The greatest risk factor for developing AD is aging; in addition, history of head trauma and small head size (McDowell 2001) also increase this risk. Higher level of education and occupational attainment may be protective factors (Ngandu et al. 2007), although studies supporting this might have had multiple confounders.

13.2.1.1 Pathology

The "amyloid hypothesis" is at the core of the demonstrated neuropathology of AD development. It proposes that an overproduction and decreased degradation of β-amyloid (Aβ) protein lead to cerebral amyloid angiopathy (CAA), which is characterized by progressive loss of smooth muscle cells in arterioles and accumulation of eosinophilic hyaline material, and formation of senile plaques (SPs), which are comprised of the core of amorphous eosinophilic globule of amyloid surrounded by neuritic corona (Fig. 13.1). Several lines of evidence support that Aβ accumulation precedes and can induce tangle pathology (Gouras 2009). Amyloid precursor protein (APP) is a precursor to β-amyloid and is coded on chromosome 21. Further support comes from the fact that nearly all persons with trisomy 21 (Down's Syndrome) who live long enough develop AD pathology and an accompanying behavioral syndrome. Moreover, mutations in the APP gene lead to the early-onset AD (Goate et al. 1991) as do mutations in two additional identified genes (PSEN1 and PSEN2) (Lippa et al. 2000).

In addition, there has been an established association between polymorphisms of the apolipoprotein E gene (APOE), pleiotropic protein with effects on neurotoxicity, tau phosphorylation, synaptic plasticity, and inflammation, and the risk of onset of AD at least in white populations (Corder et al. 1993). The greatest risk of AD with earlier age of onset is associated with

presence of two copies of ε4 allele; presence of ε3 carries a diminished risk, and ε2—even lower risk.

In addition to senile plaques, the microscopic lesions of AD include neurofibrillary tangles (NFTs), which are dense intraneuronal cytoplasmic aggregates of paired helical filaments and granulovacuolar degeneration (GVD), characterized by neuronal cytoplasm of hippocampal pyramidal cells replaced by vacuoles with small basophilic granules. Moreover, there is significant synapse loss that can be demonstrated biochemically or by immunohistochemistry in AD brain.

13.2.1.2 Diagnosis

Patients presenting with impairing cognitive or behavioral symptoms should be evaluated carefully and diagnosis of MNCD, and in particular AD, should be considered. Repetition is important to rule out other reversible causes of cognitive impairment, such as etiologies contributing to delirium (infection, medication side effect), hypothyroidism or hyperthyroidism, cobalamin deficiency, and neurosyphilis in some geographical regions. Computed Tomography (CT) brain scan can help to identify significant brain pathology for which interventions might be possible (brain tumor, hydrocephalus, subdural hematoma, large stroke). Brain Magnetic Resonance Imaging (MRI) can provide additional information about subtle white matter ischemic changes and regional cerebral atrophy pattern. It is important to screen for depression and other psychiatric morbidity, as these etiologies can contribute or solely explain the presentation. However, these symptoms might also be a part of MNCD. Cognitive testing must be done, such as the Mini Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MOCA) (see Chap. 4 Appendix for these tests) and if not possible or not enough, formal neuropsychological testing is recommended.

The imaging of the AD patient brain with head CT scan or brain MRI demonstrates cerebral atrophy globally, but in particular in medial temporal lobes. Nuclear Imaging with fluorodeoxyglucose positron emission tomography (FDG-PET) (Benson et al. 1983) or single-photon emission computed tomography (SPECT) (Jagust et al. 1987) shows hypometabolism or hypoperfusion in temporoparietal regions with the sensitivity of 94 % and specificity of 73 % in pathologically proven AD (Silverman et al. 2001). Because this pattern of hypometabolism is so distinctive from that of FTD, distinguishing patterns of hypometabolism between AD and FTD is Medicare-approved indication for nuclear imaging.

13.2.2 Frontotemporal Lobar Degeneration

Frontotemporal Lobar Degeneration (FTLD, *frontotemporal dementia*, FTD) is a heterogeneous group of conditions with prominent early behavioral disinhibition, encompassing a variety of clinical syndromes and pathological substrates. The mean age at onset of FTLD is 52.8 years and there is a striking male preponderance (14:3). (Ratnavalli et al. 2002)

FTLD is usually divided into three clinical variants. These include the frontal-variant or behavioral-variant (fvFTLD); progressive nonfluent aphasia (PNFA); and semantic dementia (SD). The motor syndromes of corticobasal degeneration (CBD); progressive supranuclear palsy (PSP); and motor neuron disease (MND) may also be associated with features of FTLD and its pathology (Weder et al. 2007).

FTLD presents earlier as compared to AD with age of onset varying from 35 to 75, but most typically in 5th and 6th decades. It represents 20 % of degenerative dementias of pre-senile onset. Up to 40 % of patients have family history of FTLD, with another prominent risk factor being history of head trauma (Weder et al. 2007). Median survival from symptom onset is approximately 6 years for FTLD and 3 years for FTLD-MND (Hodges et al. 2003; Weder et al. 2007). Median survival for the entire group is 3 years from initial diagnosis, related to common significant delay in diagnosis.

Patients present with behavioral alterations and tend to lack appropriate basic and social

emotions. Some patients with FTLD present with disinhibition and overactivity, while others show apathy and blunted affect.

Frontal variant of FTLD (fvFTLD) is characterized by insidious onset of personality changes, behavioral abnormalities and poor insight (Weder et al. 2007). Symptoms include disinhibition, poor impulse control, antisocial behavior, and stereotyped/perseverative behaviors. Patients might be interpersonally inappropriate, tactless, and offer and display improper sexual comments and gestures. Apathy and emotional blunting are common. Speech output is attenuated and mutism eventually develops. The most common cognitive deficit in fvFTD is an impairment of executive function or working memory, with other frequently encountered cognitive abnormalities including attentional deficits, poor abstraction, difficulty shifting mental set, and perseverative tendencies. Deficits in planning, organization and other aspects of executive function become universal as the disease progresses.

Semantic dementia (SD) or temporal FTD is associated with bilateral atrophy of the middle and inferior neocortex and is characterized by a loss of word meaning/knowledge. Patients present with abnormal speech, where speech is fluent, but words might be substituted for less specific ones and patients are often unaware of their difficulties with comprehension. Patients lose the ability to name and understand words and to recognize the significance of faces, objects and other sensory stimuli. In addition, they might demonstrate deficits on nonverbal tasks using visual, auditory, and other modalities. Behavioral symptoms may appear early or late.

Progressive nonfluent aphasia (PNFA) is associated with asymmetric atrophy of left hemisphere and is characterized by agrammatic nonfluent speech and decreased speech output leading to mutism. Patients present with changes in fluency, pronunciation, or word finding difficulty. Behavioral problems appear later in the disease.

13.2.2.1 Pathology

Pathology of FTD is heterogeneous and is characterized by gliosis, neuronal loss, and superficial spongiform degeneration in the frontal and/or temporal cortexes. Ballooned neurons, i.e., Pick cells, occur with variable frequency in all subtypes (Kertesz and Munoz 2002). Some cases show tau- or ubiquitin-positive inclusions, or lack any distinctive histological features (Mariani et al. 2006). Mutations in the tau gene, which is involved in the regulation of microtubule assembly and disassembly, lead to tau deposition in neurons and glia; while mutations in the progranulin gene lead to ubiquitin-only immunoreactive inclusions. Both genes are located on chromosome 17.

Neuroimaging shows anterior temporal and frontal atrophy, while functional imaging shows decreased perfusion of both frontal and temporal lobes. The focus of the atrophy is in the left temporal lobe in progressive nonfluent aphasia (PNFA) patients and in both frontal lobes in frontal variety frontotemporal dementia (FvFTD) patients.

Neurochemical changes of FTD differ from those of AD. There is evidence of less cholinergic deficit and more serotonergic disturbance in FTD as compared to AD (Weder et al. 2007). This might explain early increased impulsivity, irritability, affective change, and changes in eating behavior in patients with FTD since these behaviors are modulated by serotonergic dysfunction. Thus, serotonergic agents might have a greater role in managing behavioral symptoms of FTD as compared to cholinergic medications, as is discussed later in the chapter.

13.2.3 Vascular Disease

Vascular disease (VaD) encompasses a variety of vascular etiologies, including multi-infarct MNCD with cortical and subcortical involvement as well as the smaller lacunar and micro-infarcts (Erkinjuntti 2007).

VaD is considered the second most common cause of MNCD accounting for 10–50 % of the cases, with prevalence ranging from 1.2 to 4.2 % in persons aged 65 years and older (Hebert and Brayne 1995). The pathophysiology is attributed to interactions between vascular etiologies (coronary vascular disease and vascular risk

factors, such as hypertension, diabetes, smoking), changes in the brain (infarcts, white matter lesions (WMLs), atrophy), and host factors (age, education) (Erkinjuntti 2007). The main subtypes of VaD include cortical VaD or multi-infarct MNCD also referred as post-stroke VaD, subcortical ischemic vascular disease (SIVD) or small-vessel MNCD, strategic-infarct MNCD, and hypoperfusion MNCD resulting from global cerebrovascular insufficiency (Erkinjuntti 2007).

Cortical VaD (multi-infarct MNCD, post-stroke VaD) is characterized by a relatively abrupt onset (days to weeks), a stepwise deterioration (some recovery after worsening) and a fluctuating course of cognitive functions. It is related predominantly to large vessel disease and cardiac embolic events. The frequency of post-stroke MNCD varies from 12 to 32 % within 3 months to 1 year after stroke (Leys et al. 2005). A history of stroke increases the risk of subsequent MNCD by a factor of 5 (Leys et al. 2005).

The presenting symptoms include memory impairment, which may be mild, and such cortical symptoms as aphasia, apraxia, agnosia, and visuospatial or constructional difficulty. In addition, most patients have some degree of dysexecutive syndrome. Moreover, patients often have focal neurological impairments apparent on the exam such as visual field deficits, lower facial weakness, focal motor or sensory deficits, and gait impairment (Leys et al. 2005).

Subcortical Ischemic Vascular Dementia (SIVD) or small-vessel MNCD incorporates two entities, "the lacunar state" and "Binswanger's disease." The onset is variable with 60 % of the patients having a slow onset and only 30 % an acute onset of cognitive symptoms (Erkinjuntti 2007). The course is gradual without (40 %) and with (40 %) acute deficits, and fluctuating in only 20 % (Babikian and Ropper 1987). There is often a preceding clinical history of transient ischemic attacks with only mild focal findings (e.g., drift, reflex asymmetry, gait disturbance). SIVD is attributed to small-vessel disease and is characterized by lacunar infarcts, focal and diffuse ischemic white matter lesions (WMLs), and incomplete ischemic injury. Clinically, it is characterized by the subcortical cognitive syndrome with deficits in executive functioning, slowed information processing, mild memory deficits and behavioral symptoms such as depression and emotional lability (Babikian and Ropper 1987). In addition, neurologic symptoms include motor hemiparesis, bulbar signs and dysarthria, and gait disorder. Imaging reveals multiple lacunes and extensive WMLs.

Strategic-infarct MNCD is characterized by focal, often small, ischemic lesions involving specific sites critical for higher cortical functions, such as the hippocampal formation, angular gyrus and cingulate gyrus, and subcortical sites leading to impairment, including thalamus, fornix, basal forebrain, caudate, globus pallidus, and the genu or anterior limb of the internal capsule (Erkinjuntti 2007).

Moreover, AD and vascular disease coexist in a large proportion of patients, making at times distinguishing primary etiology of MNCD difficult (Erkinjuntti 2007).

13.2.4 Lewy Body Disease

Lewy Body Disease (LBD, DLB) represents up to 20 % of all cases of MNCD cases. It presents late, in 6th through 9th decade and affects both genders equally (Ferman and Boeve 2007). The MNCD is characterized by cortical and subcortical cognitive impairments, with worse visuospatial and executive dysfunction as compared to AD. There is usually relative sparing of memory especially early on. Fifty percent of the cases have mixed presentation with AD. The diagnosis is based on presence of MNCD and additional two out of three features: spontaneous parkinsonism, hallucinations, and daily fluctuation in cognition. Parkinsonian signs must be spontaneous and not attributable to neuroleptics; as compared to Parkinson's Disease (PD) or Parkinson's Disease Dementia (PDD), there is more rigidity and bradykinesia than tremor and parkinsonian symptoms are less severe. Tremor, bradykinesia, and rigidity tend to be more symmetric than asymmetric, and tremor tends to be maximal with posture/action rather than at rest (Ferman and Boeve 2007).

Visual hallucinations (VH) in Dementia with Lewy Bodies (DLB) consist of fully formed, detailed, three-dimensional objects, people, or animals. Auditory hallucinations might happen, but mostly in patients who also have VH. VH have been documented to occur in 59–85 % of autopsy-confirmed DLB samples as compared to 11–28 % of autopsy-confirmed AD sample (Ferman and Boeve 2007). The etiology of DLB hallucinations is likely multifactorial, including severe depletion of acetylcholine, depletion of other neurotransmitters such as dopamine and serotonin, as well as intrusion of dream imagery into wakefulness as a potential mechanism due to the dysregulation of rapid eye movement (REM) sleep in many patients with DLB.

The fluctuations of DLB are characterized by a waxing and waning of cognition, abilities, and arousal. Moreover, patients who have DLB often have daytime drowsiness or somnolence. In addition, these patients often have the parasomnia of REM sleep behavior disorder (RBD) due to the loss of normal muscle atonia during REM. The augmented muscle activity during REM sleep occurs along with dream content and can range from elevated muscle tone to complex behavioral sequences.

Of note, REM sleep behavior disorder can precede the onset of neurodegenerative diseases with alpha-synuclein inclusions (i.e., DLB, PD, or multiple system atrophy [MSA]) by years and even decades and is postulated to be a precursor to the disorders (Iranzo et al. 2013).

In addition, autonomic abnormalities, in particular orthostatic hypotension and carotid sinus sensitivity, are more common in DLB than AD or elderly controls.

To make a diagnosis of DLB, please refer to criteria to make a clinical diagnosis (Table 13.1).

13.2.4.1 Pathology

Neuropathologically, DLB is marked by presence of Lewy bodies in cortical and neocortical brain regions. Lewy bodies, typically present in Parkinson's Disease (PD), are concentric, intracytoplasmic neuronal inclusions within monoaminergic and cholinergic neurons of the substantia nigra, locus ceruleus, and basal nucleus of Meynert with dense eosinophilic core surrounded by a lucent halo, easily seen with routine staining. In contrast to PD, the neocortical Lewy bodies seen in DLB are smaller, lack a halo, and are difficult to see under routine staining conditions. PD and cortical Lewy bodies contain a-synuclein, which is a 140 amino acid protein of unknown function. Abnormal protein processing gives rise to the cytoplasmic collections of a-synuclein, which coalesce to form Lewy bodies. Brains of patients with Lewy bodies demonstrate severe depletion of both cholinergic and dopaminergic markers (Walker et al. 2007).

13.2.5 Posttraumatic Brain Injury

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease that occurs in association with repetitive traumatic brain injury (McKee et al. 2014). In most instances, the clinical symptoms of the disease begin after a long period of latency ranging from several years to several decades. The initial symptoms are typically insidious, consisting of irritability, impulsivity, aggression, depression, short-term memory loss, and heightened suicidality. The symptoms progress slowly over decades to include cognitive deficits and MNCD. MNCD has been increasingly associated with traumatic brain injuries. Mildcognitive impairment (MCI) after self-reported head trauma with at least momentary loss of consciousness or memory has been found to be associated with greater amyloid deposition, when compared with cognitively intact individuals, suggesting that head trauma may be associated with the development of MNCD (Mielke et al. 2014).

The underlying pathology of CTE is characterized by the accumulation of phosphorylated tau protein in neurons and astrocytes in a pattern that is unique from other tauopathies, including Alzheimer's disease (McKee et al. 2014). The hyper-phosphorylated tau abnormalities begin focally, as perivascular neurofibrillary tangles and neurites at the depths of the cerebral sulci,

and then spread to involve superficial layers of adjacent cortex before becoming a widespread degeneration affecting medial temporal lobe structures, diencephalon and brainstem. Most instances of CTE (>85 % of cases) show abnormal accumulations of phosphorylated 43 kDa TAR DNA binding protein that are partially colocalized with phosphorylated tau protein. In addition CTE is associated with frontal and temporal lobe atrophy, and is increasingly categorized as an acquired Frontotemporal lobar degeneration. Clinically CTE is characterized by behavioral and personality changes, as well as cognitive impairments. As is the case in AD, at present CTE cannot be definitively diagnosed during life, thus its exact incidence and prevalence remain uncertain.

13.2.6 Rapidly Progressive Dementias

Rapidly Progressive Dementias (RPDs) are neurologic conditions that develop subacutely over weeks to months, sometimes even days, not infrequently quickly leading to death (Geschwind et al. 2007). The differential is extensive and is demonstrated along with suggested workup in Table 13.5.

One important category in this class is prion diseases, including Creutzfeldt–Jakob Disease (CJD), characterized by a classic triad of dementia, typical EEG changes, and myoclonus. Most cases are sporadic, with genetic cases comprising 15 % and iatrogenic 2 % (Eggenberger 2007). Prevalence, annual incidence, and yearly mortality of CJD are 0.5–1 per million people. It results from abnormal prion protein form acting in an "auto"-enzymatic fashion, converting normal host prion (prior protein cellular (PrPC)) into the abnormal isoform (protease resistant scrapie form of PrP (PrPSc)) (Eggenberger 2007). The onset of the illness is typically between 50 and 70 years of age with median age of onset at 68 and equal gender distribution. Median survival is 5 months and 85 % of afflicted die within first year of symptom onset. The onset is usually insidious with a nonspecific prodrome in one third, characterized by headache, fatigue, anxiety, changes in sleep, anorexia, weight loss, dizziness, memory difficulties, mood or behavior changes, weakness, and problems with locomotion. These symptoms are followed by progressive aphasia, apraxia, pyramidal signs, myoclonus, and choreiform-athetoid movements. Patients become severely demented within 6 months, with death occurring usually within 12 months of the symptom onset, typically resulting from intercurrent infection. Heidenhain variant is punctuated by visual presentation, most commonly a homonymous visual field defect leading to cerebral blindness early in the course of the disease. EEG can be helpful with the diagnosis, first showing slowing, and later in the course characterized by periodic sharp waves in two thirds of the patients. CSF studies might be remarkable for increased protein 14-3-3, total tau (t-tau), and neuron specific enolase (NSE). Brain MRI demonstrates increased bilateral signal intensity in the basal ganglia, corpus striatum, or thalamus, better visualized on diffusion-weight imaging (DWI) than on fluid-attenuated inversion recovery (FLAIR) sequences (Eggenberger 2007). The definitive diagnosis can be obtained via brain biopsy with tissue pathology demonstrating spongiform degeneration, astrocytic gliosis with neuronal loss, amyloid plaques, lack of inflammatory response, and misfolded prion proteins (PrPs) on immunochemistry (Yung et al. 2010).

13.2.7 Delirium–Dementia Continuum

There seem to be a bidirectional relationship between delirium and dementia. In fact, the presence of baseline cognitive deficits, even those not rising to the level of dementia, significantly increases the risk of developing delirium. The Neuronal Aging Hypothesis (NAH) suggests that the aging process and accompanying physiologic changes constitute an independent risk factor for delirium (Maldonado 2013). The NAH may also explain why the elderly seem to experience a greater chance of developing delirium when challenged by physiological distress that is better tol-

Table 13.5 Differential and suggested workup for rapidly progressive dementias

Category	Differential	Suggested tests
Neurodegenerative	• AD, DLB, FTD • Neurofilament Inclusion Body Disease (NIBD) • Fahr's Disease	• Brain MRI • Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scan
Infectious	• Viral encephalitis, e.g.. HSV • HIV dementia • Progressive Multifocal Leukoencephalopathy (PML) (JC virus) • Opportunistic infections in immunocompromised: Cryptococcus, mycobacteria • Neurosyphilis • Subacute Sclerosing Panencephalitis (SSPE) (measles virus)	• Viral PRCs and cultures • Bacterial, fungal, AFB stains and cultures • RPR • Whipple's PCR
Autoimmune	• Non-vasculitis autoimmune inflammatory meningoencephalopathies: primary angiitis of the CNS (PACNS), polyarteritis nodosa (PAN), sarcoidosis, Systemic Lupus Erythematosus (SLE), Sjögren's syndrome, celiac disease, Behçet's disease, hypereosinophilic syndrome • Cerebral amyloid inflammatory vasculopathy • Hashimoto's encephalopathy • Limbic encephalitis	• ESR, CRP, C3, C4, ANA, rheumatoid factor, anti-SSA, anti-SSB, anti-dsDNA, anti-smith, P-ANCA, C-ANCA, anti-endomysial or anti-gliadin IgA or IgC, SSA, SSB, ACE • TSH, free T4, anti-thyroid peroxidase • Paraneoplastic panel (CSF and serum)
Malignant	• Primary and metastatic solid tumors • Primary CNS lymphoma (PCNSL) • Intravascular lymphoma (i.e., angiotropic lymphoma) • Lymphomatoid granulomatosis	• CT scan body with and without contrast • Whole body PET scan • CSF cytology and flow cytometry • Serum LDH, tumor markers (PSA, CEA, etc.) • Mammogram • Colonoscopy
Vascular	• Strokes • Thrombotic thrombocytopenic purpura (TTP) • Hyperviscosity syndromes: polycythemia vera, gammopathies • CNS vasculitidies	• Brain imaging • Hypercoagulability testing; coagulation profile • Echocardiogram; carotid ultrasound • Cerebral angiogram, meningeal biopsy
Toxic-metabolic	• Vitamin B1, B12, niacin, folate deficiencies • Uremia • Wilson's disease • Portosystemic encephalopathy • Acquired hepatocerebral degeneration • Porphyria • Bismuth, lithium, mercury, arsenic toxicities • Electrolyte abnormalities	• Vitamin B1, B12, niacin, folate • Comprehensive metabolic panel: electrolytes, liver function tests, creatinine/ blood urea nitrogen • Copper and ceruloplasmin; 24 h copper • 24 h urine heavy metal for lead, arsenic, mercury, bismuth, albumin, lithium • Methylmalonic acid levels; thiamine, vitamin E • Exposure history
Prion	• Creutzfeldt–Jakob Disease (CJD)	• EEG • CSF cytology, including protein 14-3-3 • Brain MRI • Brain biopsy

Table 13.6 Mechanisms mediating delirium and cognitive impairment

1. A number of factors and mechanisms leading to delirium, may also directly cause CNS damage and neuronal dysfunction, and thus mediate both the manifestations of delirium and long-term cognitive impairment (e.g., cytokine release and other neuroinflammatory mediators; decrease perfusion and oxygenation leading to decreased cerebral oxidative metabolism; changes in blood–brain barrier permeability; hypercatabolic states; water and electrolyte imbalances; excessive glucocorticoid levels and other HPA axis dysfunctions; melatonin and sleep–wake cycle abnormalities).
2. Pharmacological agents used either to treat the underlying causes of the delirium (e.g., steroids, calcineurin inhibitors, other immunosuppressants, dopamine) or those agents used to treat delirium (e.g., dopamine blocking agents, benzodiazepines) may themselves lead to neuronal damage in a fragile brain.
3. Any of the mechanisms listed above may themselves lead to alterations in neurotransmitter concentration or receptor sensitivity which may underlie the different symptoms and clinical presentations of delirium and/or long-term cognitive dysfunction. Thus, the same mechanisms that cause the substrate for delirium, may mediate the cognitive impairments observed after the acute presentation of delirium has resolved.
4. It is possible that instead of causing cognitive deficits or dementia, delirium (and its underlying causes) only serve as a catabolic agent, leading to an acceleration of normal physiological cerebral aging mechanisms leading to dementia.
5. It is also possible that an episode of delirium simply unmasks subtle cognitive deficits already present, although not yet identified.

Source: (Maldonado 2008a, b, 2013)

erated by younger individuals (Maldonado 2013). Patients with compromised cognitive ability prior to surgery are at greater risk to develop postoperative delirium (Inouye et al. 1998; Litaker et al. 2001; McNicoll et al. 2003; Benoit et al. 2005; Franco et al. 2010; Tognoni et al. 2011). Even subtle deficits in attention or executive function (e.g., problem solving, processing speed, planning, complex sequencing, and reasoning), in the absence of frank cognitive impairment, closely associate with postoperative delirium independent of other risk factors (Rudolph et al. 2006; Lowery et al. 2007; Smith et al. 2009). Similarly, preoperative MMSE scores have been found to be an independent predictor of postoperative delirium (Kalisvaart et al. 2006). A study of elderly subjects undergoing orthopedic surgery demonstrated an increased incidence of postoperative delirium, depending on whether patients suffered from dementia or not (100 % vs. 32 %) (Wacker et al. 2006). Similarly, nearly 70 % of elderly patients admitted to a specialized "delirium ward" carried the diagnosis of "cognitive disorder"—either dementia or mild cognitive impairment (Wahlund and Bjorlin 1999).

Conversely, studies have demonstrated that among elderly surgical patients, delirium is a strong independent predictor of cognitive impairment and the occurrence of severe dependency in activities of daily living. In fact, 38 months after discharge from hospital, 53.8 % of the surviving patients with postoperative delirium continue to experience cognitive impairment, as compared to only 4.4 % of the non-delirious subjects.(Bickel et al. 2008) In some of the studies, the long term outcomes (e.g., mortality, nursing home placement, cognition, function) of patients with persistent delirium were consistently worse than the outcomes of patients who had recovered from delirium (Cole et al. 2009). Similarly, a prospective matched controlled cohort study of elderly hip surgery patients demonstrated that the risk of dementia or mild cognitive impairment (MCI) over a 30-months follow-up almost doubled in inpatients with postoperative delirium compared to those without delirium (Kat et al. 2008). These findings suggest that delirium does not simply persist for a certain time but also predicts a future cognitive decline with an increased risk of dementia.

The relationship between cognitive deficits and dementia seems to be reciprocal, with episodes of delirium causing the development of a new cognitive or accelerated the course of a preexisting dementing process. Data suggests that among the elderly, there is a significant acceleration in the slope of cognitive decline in patients with Alzheimer's disease (AD) following an episode of delirium (Fong, Jones et al. 2009). In fact,

a substantial proportion of delirium survivors are left with post-delirium cognitive impairment (Wacker et al. 2006; Griffiths and Jones 2007; Bickel et al. 2008; Kat et al. 2008; Maldonado 2008a, b; Fong et al. 2009; MacLullich et al. 2009; Girard et al. 2010).

Among medically ill, elderly subjects, those suffering from baseline dementia and developing prevalent or incident delirium during the first week of hospitalization were found to meet persistent delirium criteria at discharge (39 %), 6 (38.5 %) and 12-month (48.9 %) follow-ups, compared to only 11.1, 8.8 and 14.8 % of non-demented subjects (McCusker et al. 2003). Another study found that only 4 % of delirious patients experienced full resolution of all symptoms of delirium before discharge from the hospital; with an additional 20.8 and 17.7 % of subjects experiencing symptom resolution by 3 and 6 months after hospital discharge (Levkoff et al. 1992).

Studies have demonstrated a consistent relationship between delirium and post-delirium cognitive decline (Macdonald 1999; Rockwood et al. 1999; Jackson et al. 2004; MacLullich et al. 2009). A study in an elderly orthopedic population found that among those experiencing postoperative delirium the risk of mild cognitive impairment (MCI) or dementia was almost doubled that of non-delirious subjects (Kat et al. 2008). Another study in the same population showed that up to 53.8 % of patients who developed postoperative delirium continue to experience cognitive impairment 38 months after hospital discharge, compared to only 4.4 % of the non-delirious subjects (Bickel et al. 2008). These studies and others also suggest that delirium duration was also independently associated with long-term cognitive outcome (i.e., the longer the duration of delirium the more significant the cognitive deficits). For example, an increase in the length of delirium from 1 to 5 days was independently associated with nearly a 5-point decline (i.e., a one-half SD decline) in the cognitive testing scores (Girard et al. 2010).

These findings raise questions regarding whether prevention of delirium might ameliorate or delay cognitive decline in patients at risk, particularly those with dementing processes.

13.3 Management of Major Neurocognitive Disorder

13.3.1 Treatment of Behavioral and Psychological Symptoms of MNCD (BPS-MNCD)

Consultation-liaison psychiatrists, especially in inpatient settings, are often consulted for treatment of behavioral symptoms of patients with MNCD, since these symptoms not only contribute to patient suffering, but also place significant burden on caregivers, and are not an uncommon reason for bringing these patients to the emergency rooms.

Aggression and nonaggressive agitation occur in approximately 20 % of people with AD living in community, and in 40–60 % of those who live in care facilities (Ballard and Corbett 2013). Delusions and hallucinations are present in 25 % of people with MNCD in clinical settings, while depression occurs in 20–30 % of people with AD (Ballard et al. 2009; Enache et al. 2011). In patients with Lewy-Body and Parkinson's disease-associated MNCD (PD-MNCD), visual hallucinations, delusions and depression are even more significantly frequent as compared to AD patients, and visual hallucinations are also significantly more intense and persistent (Ballard et al. 2009). Depression is significantly more frequent and persistent in patients with VaD than in AD (Ballard et al. 2009).

While agitation manifests as restlessness, pacing, excessive fidgeting, shouting, and screaming, aggression is usually characterized by verbal insults, hitting, biting and throwing objects, and can be particularly common during personal care (Ballard and Corbett 2013). In almost all individuals, agitation and aggression significantly affect their daily lives, are distressing to individuals themselves and their caregivers, and serve as a significant factor in placement of these patients in institutionalized care facilities (Ballard and Corbett 2013).

When these patients come to the attention of physicians, it is important to (1) identify target symptoms, (2) pursue and address etiology of

behavioral disturbance, (3) employ behavioral approaches, and, if all fails, (4) apply pharmacological interventions. When choosing pharmacological interventions, it is important to identify specific psychiatric symptoms to address in patient's presentation: aggression, psychosis, depression, mania or spontaneous disinhibition. The differential of the etiologies leading to a patient's behavioral dysregulation can be broad and includes medical etiologies leading to delirium (e.g., urinary tract infection, poor oxygenation, pneumonia, encephalitis, meningitis, and dehydration), neurological causes (e.g., seizure, cerebrovascular accident, and tumor), exacerbation of primary psychiatric illness, pain which is often poorly communicated, changes in environment and psychosocial stressors, sensory disturbances (e.g., cataract, hearing loss), and finally Behavioral and Psychiatric Symptoms of Dementia (BPSD). Pain and dehydration are not uncommon contributors to agitation and aggression. While assessment of pain may be difficult in patients with MNCD, a thoughtful approach to its management has been shown to significantly reduce agitation in patients with MNCD (Husebo et al. 2011).

13.3.1.1 Depression in Patients with MNCD

Early and late-life depression has been found to be a risk factor and a prodrome for development of MNCD (Enache et al. 2011). Moreover, approximately 20–30 % of patients with AD have depression (Enache et al. 2011). The proportion seems to be relatively similar across MNCD stages and is higher in patients with vascular depression (VaD) and Lewy Body disease than in Alzheimer's disease (Enache et al. 2011).

The pharmacological treatments for depression in demented patients have not shown consistent benefit. In a Cochrane review (Bains et al. 2002) on the effect of antidepressants for depression in MNCD, only 4 studies with a total of 137 participants reported sufficiently detailed results to enter into meta-analysis. The authors concluded that the evidence offered weak support for the hypothesis that antidepressants are effective for patients with depression and MNCD. They pointed out that the medications are not "necessarily ineffective but rather that there is not much evidence to support their efficacy."

In another meta-analysis based on seven studies with a total of 299 patients, neither response rates (OR 2.12, 95 % CI 0.95–4.70) nor remission rates (OR 1.97, 0.85–4.55) were significant enough between placebo and active treatment (Nelson and Devanand 2011). Thus the authors concluded that the evidence for antidepressant treatment of people with depression and MNCD, although suggestive, did not confirm efficacy. Of note, the studies were underpowered to detect the differences. A recent review of the topic that included in their own analysis 11 randomized placebo-controlled drug trials for depression associated with MNCD, with a total of 1,514 patients, noted that five studies reported that the antidepressant was more effective than placebo (sertraline, clomipramine, maprotiline, moclobemide, citalopram), whereas six were negative (sertraline, mirtazapine, venlafaxine, imipramine, fluoxetine, and estrogen replacement therapy) (Enache et al. 2011). Finally, the largest to date trial on antidepressants in patients with MNCD, Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD) enrolled 326 patients with probable or possible Alzheimer's disease and randomized them to placebo, mirtazapine, or sertraline (Banerjee et al. 2011). The investigators did not find difference in efficacy between three treatment groups as monitored via scores on Cornell scale for depression in dementia (CSDD), but noted more side effects in both treatment groups.

Electroconvulsive therapy (ECT) is the most effective treatment for depression, but few studies have been performed in patients with MNCD. Current evidence suggests that ECT might be an effective treatment for depression in MNCD, although the relatively small number of controlled studies makes the comparison of effectiveness between healthy non-geriatric patients and those with MNCD difficult (Oudman 2012). Of course, there is at least theoretical concern that cognitive side effects of ECT might further worsen cognitive impairment of MNCD. In one study, depressed patients with

mild cognitive impairment or MNCD had a similar improvement of depression as compared to subjects with normal cognition (Hausner et al. 2011). In all three groups, initial non-significant cognitive worsening was followed by cognitive improvement. In patients with mild cognitive impairment, the cognition actually improved 6 months after ECT compared with baseline, and a similar but non-significant improvement was noted in patients with MNCD, with significant improvement among those taking anti-MNCD drugs. Thus, ECT might be considered in patients with MNCD and medication-resistant severe depression.

13.3.1.2 Treatment of Agitation/ Psychosis as a Part of Behavioral and Psychiatric Symptoms of Dementia (BPSD)

Agitation, aggression and psychotic symptoms of dementia cause tremendous suffering and place significant burden on caregivers. There have been a variety of non-pharmacological interventions studied to address these symptoms. They have included resource demanding treatments, such as intensive 6–12-month programs educating staff in person-centered care as a first line management to less intensive treatments such as "validation therapy and reminiscence," structured social interaction, personalized bathing and music, and aromatherapy (Ballard et al. 2009). The findings from a large open trial suggested that social interaction confers benefit even when delivered in a simplified form for as little as 10 min per day by a care assistant (Ballard et al. 2009). A recent meta-analysis of 23 studies found that non-pharmacological interventions delivered by family caregivers, consisting of 9–12 sessions tailored to the needs of the person with MNCD and the caregiver in the home using multiple components, have the potential to reduce the frequency and severity of BPSD with effect sizes at least equaling those of pharmacotherapy, as well as to reduce caregivers' adverse reactions (Brodaty and Arasaratnam 2012). In a meta-analysis of 40 studies of non-pharmacological interventions in long-term care facilities, 40 % of included studies reported statistically significant results in favor of non-pharmacological interventions on at least one measure of neuropsychiatric symptoms (NPS), with interventions including staff training in NPS management strategies, mental health consultation and treatment planning, exercise, recreational activities, and music therapy or other forms of sensory stimulation (Seitz et al. 2012). Of course, these interventions often require a lot of resources inside and outside the facilities. Moreover, many of the studies had methodological limitations that placed them at potential risk of bias. Although it is important to know and appreciate non-pharmacological interventions, when psychiatric consultation is requested, it is often a matter of behavioral emergency.

13.3.1.2.1 Antipsychotics

The limitation of the non-pharmacological interventions, lack of appropriate resources, and often the acute need to stabilize the behavior in inpatient setting leads to CL psychiatrists employing pharmacological means to address agitation and psychosis in patients with MNCD. At this time, there are no FDA approved treatments for agitation or psychosis in MNCD. Of interest, in Germany, risperidone does carry the approval for this indication.

Antipsychotics are often thought to be the first-line treatment, but it is important to appreciate their limited effectiveness and significant risks associated with their use.

Conventional antipsychotics have been among first agents used for treatment of agitation and aggression in patients with MNCD. Eleven RCTs, mostly small in size and over 4–12 weeks, have shown a significant but modest improvement compared with placebo, with haloperidol holding the most comprehensive evidence base for treatment of aggression, but not agitation (Ballard and Corbett 2013). Of course, these agents come with significant risks, such as parkinsonism, dystonia, tardive dyskinesia, acceleration of cognitive decline and prolongation of the QTc interval on electrocardiogram (ECG), leading to added risk of cardiac arrhythmias, and thus have been mostly replaced by atypical

antipsychotics which have perceived improved tolerability (Ballard and Corbett 2013).

The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease(CATIE-AD) study was a randomized control trial of 421 patients with Alzheimer's disease and symptoms of psychosis, aggression, or agitation, who were randomized to olanzapine, quetiapine, risperidone, or placebo and followed for up to 36 weeks (Schneider et al. 2006). The trial demonstrated no difference in primary effectiveness outcome of the time to treatment discontinuation for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks) ($P=0.52$). Of note, the times to treatment discontinuation due to lack of efficacy were longer in the olanzapine group (22.1 weeks) and risperidone group (26.7 weeks) as compared to the placebo group (9 weeks). On the contrary, the time to discontinuation due to intolerance, adverse effects, or death favored the placebo arm.

In a meta-analysis by Schneider of 15 trials with atypical antipsychotics (olanzapine, risperidone, aripiprazole, quetiapine) of 3,353 patients randomized to drug and 1,757 to placebo, there was a small but significant improvement on rating scales for risperidone and aripiprazole, but not for olanzapine (Schneider et al. 2006). Smaller effects were observed for less severe MNCD, outpatients, and patients selected for psychosis. One third of the patients dropped out across the groups. The side effects included somnolence, urinary tract infections, or incontinence across drugs; extrapyramidal side effects or abnormal gait with risperidone or olanzapine; and importantly worsening of cognitive tests for all drugs. There was significant risk for cerebrovascular accidents (CVAs) (OR 2.13) with 1.9 % of events in the medication group as compared to 0.9 % in the placebo group. Risperidone had the greatest risk for CVA with OR of 3.43, with 3.1 % versus 1.0 % pooled. The authors concluded that "antipsychotics are modestly effective when used judiciously and there are no demonstrated, effective pharmacologic alternatives."

The 2006 Cochrane review that deemed only nine RCTs to have sufficient data to be included in meta-analysis (Ballard and Waite 2006), concluded that risperidone and olanzapine had small, but significant effects on treatment of aggression and risperidone only—for treatment of psychosis. Risperidone- and olanzapine-treated patients had higher rates of cardiovascular events, extra-pyramidal side effects, other adverse outcomes and were associated with significant increase in drop-outs.

In agreement with previous findings, a more recent meta-analysis of 18 placebo-controlled trials, concluded that aripiprazole, olanzapine, and risperidone, but not quetiapine, had small but statistically significant benefits for global behavioral symptom scores associated with MNCD in elderly patients, with aripiprazole and risperidone having significant effects on psychosis and all three agents on agitation (Maher et al. 2011).

The use of antipsychotics for treatment of behavioral symptoms in patients with MNCD has become controversial since an initial 2003 warning by Food and Drug Administration (FDA) regarding increased risk of cerebrovascular adverse events including stroke in MNCD patients treated with risperidone, extending to similar warnings for other antipsychotic medications and culminating with 2005 warning highlighting a significant increase in mortality risk (OR 1.7) for this population, based on 17 placebo-controlled studies of six atypical antipsychotics versus placebo.

Schneider reviewed the evidence on the association of mortality and antipsychotic use in this patient population from 15 of these trials (9 unpublished), generally 10–12 weeks in duration, including 3 trials with aripiprazole, 5 trials with olanzapine, 3 trials with quetiapine, and 5 trials with risperidone with a total of 3,353 patients randomized to study drug and 1,757 randomized to placebo (Schneider et al. 2005). The meta-analysis confirmed a significant increase in mortality (OR 1.54) with the absolute risk difference of 1–2 % between antipsychotic- and placebo-treated patients and with no difference between specific agents.

Studies have also demonstrated that conventional antipsychotics might have even greater risk of death in this patient population. For example in a retrospective cohort study by Wang and colleagues of patients aged 65 years and older with drug insurance benefits in Pennsylvania and first prescribed antipsychotic drug, the mortality was greater for those patients prescribed conventional antipsychotics as compared to atypical (OR 1.27–1.56) (Wang et al. 2005). The greatest increase in risk of death for conventional as compared with atypical antipsychotics occurred with higher doses and during the first 40 days after treatment initiation. The limitations of the study included the fact that these patients were not officially diagnosed with MNCD.

In another population-based cohort study of 75,445 new users of antipsychotic drugs (haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone), aged 65 and older and living in nursing homes, 180-day risk of mortality as compared for risperidone was more than doubled for haloperidol (HR 2.07) and slightly lower for quetiapine (HR 0.81) (Huybrechts et al. 2012). The effects were noted to be strongest shortly after the start of treatment and in response to increased dose.

It has also been shown that the mortality risk further increases with continued use of antipsychotics. In the MNCD antipsychotic withdrawal trial (DART-AD), patients from UK care facilities were randomized to continue the antipsychotic ($N=64$) (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) for 12 months or be switched to the placebo ($N=64$) (Ballard et al. 2009). There was an impressive reduction in survival in patients who continued to receive antipsychotics compared with those who received placebo: at 12 months, 70 % in the continue treatment group survived as compared to 77 % in the placebo group; at 24 months, the difference was 46 % versus 71 %; and at 36 months, it was 30 % versus 59 %.

However, there is also emerging evidence indicating that it is psychosis and not antipsychotics, either conventional or atypical, leading to increased mortality in this patient population. In fact, in a study of 957 patients with diagnosis of probable AD where 241 patients (25 %) were exposed to antipsychotics (conventional, $N=138$; atypical, $N=95$; both, $N=8$), only conventional antipsychotics were associated with the time to admission to the nursing home and this association was no longer significant after adjustment for the severity of psychiatric symptoms (Lopez et al. 2013). The study found that psychosis was strongly associated with nursing home admission and time to death, but neither conventional nor atypical antipsychotics were associated with time to death.

A recent 2013 Cochrane review on withdrawal of long-term antipsychotics including nine trials with 606 randomized participants indicated that only one of these trials with patients with psychosis or agitation who had responded well to risperidone therapy for 4–8 months, reported that discontinuation led to an increased risk of relapse (Declercq et al. 2013). The only pooled outcome (full NPI score) used in two studies, had no significant difference between people withdrawn from and those continuing on antipsychotics at 3 months. In both studies, there was evidence of significant behavioral deterioration in people with more severe baseline NPS who were withdrawn from antipsychotics.

Of likely importance is that the use of second-generation antipsychotics was also associated with a small but significant effect on caregiver burden (Mohamed et al. 2012) and this is likely to contribute to continued frequent use of the medications.

In conclusion, given that the pharmacological interventions are limited, it is important to consider risks versus benefits of the treatment with antipsychotics for behavioral symptoms of MNCD in each patient and advise of these benefits and risks the patient and their family. If treatment with antipsychotic is warranted, it is imperative to continue treatment short-term and attempt to taper off this medication at most 12 weeks after initiation.

13.3.1.2.2 Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors have also shown promise in decreasing behavioral symptoms, in particular that of agitation, in MNCD. Several

meta-analyses demonstrated a small but significant overall advantage of cholinesterase inhibitors (ChEIs) over placebo with regard to the treatment of behavioral and psychiatric symptoms (BPSD) in AD (Trinh et al. 2003; Rodda et al. 2009). Moreover, in a randomized withdrawal study, cessation of donepezil was associated with a significant worsening of the total Neuropsychiatric Inventory (NPI) score within 6 weeks (Holmes et al. 2004). In addition, while there was no short-term benefit for treatment of clinically significant agitation with donepezil over 12 weeks in a large RCT (Howard et al. 2007), an ad hoc analysis of 978 patients randomized to galantamine or placebo demonstrated that patients with behavioral symptoms at baseline had significant reduction (29–48 %) in aberrant motor behavior, agitation, and anxiety (Cummings et al. 2004). In addition, it demonstrated concomitant decrease in caregiver-reported distress.

Trials of rivastigmine in Lewy Body disease and Parkinson's disease dementia (McKeith et al. 2000; Emre et al. 2004) also indicate a significant improvement in BPSD over 6 months in treated individuals. Since there is significant cholinergic deficiency in Lewy Body disease which might even mediate hallucinations, acetylcholinesterase inhibitors might be especially helpful in treatment of psychotic symptoms in this patient population. On the contrary, in frontotemporal dementia (FTD), the cholinergic system is likely intact and so far, the evidence for use of acetylcholinesterase inhibitors for treatment of behavioral symptoms in FTD is questionable (Manoochehri and Huey 2012).

13.3.1.2.3 NMDA Antagonists

Memantine, a NMDA-antagonist has some encouraging evidence for its ability to treat agitation and aggression in MNCD, supported by findings from individual studies, meta-analyses, and pooled analyses (Gauthier et al. 2005, 2008; McShane et al. 2006), but little RCT evidence. While a recent RCT did not show benefit of memantine in controlling agitation in moderate to severe MNCD over 12 weeks (Fox et al. 2012), a post hoc analysis (Wilcock et al. 2008) and a recent RCT (Howard et al. 2012) have suggested that memantine may be of value in reducing the emergence of overall behavioral and psychiatric symptoms.

Thus, the current evidence indicates that memantine may confer benefit in the prevention and treatment of mild-to-moderate agitation and aggression in longer-term use.

13.3.1.2.4 Antidepressants

Evidence for the use of antidepressants is promising and growing. A Cochrane review on the subject including nine trials with a total of 692 individuals with five studies comparing selective serotonin inhibitors (SSRIs) to placebo, found overall significant difference between antidepressants and placebo on measures of agitation on Cohen-Mansfield Agitation Inventory (CMAI) total score and good tolerability (Seitz et al. 2011). It concluded that although there are "relatively few studies …, the SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation compared to placebo in two studies. Both SSRIs and trazodone appear to be tolerated well when compared to placebo, typical and atypical antipsychotics." In particular, a 12-week RCT of 103 non-depressed patients with MNCD hospitalized secondary due to behavioral symptoms, including aggression, agitation, hostility, suspiciousness, hallucinations, and delusions, and randomized to citalopram versus risperidone, demonstrated similar improvement in symptoms of agitation and psychosis with both medications much better tolerability of citalopram (Pollock et al. 2007). The results from the recent "Citalopram for Agitation in Alzheimer Disease Study" (CitAD) support the usefulness of SSRIs in the long-term management of agitation in dementia (Porsteinsson et al. 2014). In this randomized, double-blind, placebo-controlled study, patients with probable AD ($N=186$) were randomized to receive either citalopram (up to 30 mg) or placebo for 9 weeks. Patients in the citalopram group showed significant improvement (compared to placebo) on both primary outcome measures: the Neurobehavioral Rating Scale agitation subscale (NBRS-A) and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change

(mADCS-CGIC). In fact, using mADCS-CGIC, 40 % of citalopram participants had moderate or marked improvement from baseline compared with only 26 % of those on placebo(odds ratio [OR] 2.13 (95 % CI, 1.23–3.69), $P=0.01$). Moreover, caregivers of patients in the citalopram group reported less distress. Unfortunately, the use of citalopram was associated with worsening of cognition (−1.05 points Mini Mental Status Examination (MMSE); 95 % CI, −1.97 to −0.13; $P=0.03$) and QT interval prolongation (18.1 ms; 95 % CI, 6.1–30.1; $P=0.01$). Similarly, trazodone has been shown to be effective in decreasing agitation in patients with FTD (Lebert et al. 2004).

Both acetylcholinesterase inhibitors and SSRIs might be reasonable medications for long-term treatment of agitation and possibly psychotic symptoms in patients with MNCD. It might be reasonable to use an antipsychotic agent initially to control acute symptoms, while initiating and optimizing long-term agents, such as acetylcholinesterase inhibitors and/or SSRI's. Our clinical experience suggests that having optimal doses of both an acetylcholinesterase inhibitor and an SSRI facilitates the tapering off antipsychotic agents, maximizes control of behavioral symptoms, and minimizes side effects.

13.3.1.2.5 Anticonvulsants

There have been two studies of showing effectiveness of carbamazepine in reduction of aggression and one study of oxcarbazepine. The use of these agents, especially the former, is associated with significant side effects and drug–drug interactions. Although valproic acid (VPA) seemed to be promising (Konovalov et al. 2008), as of yet there is no evidence that it is effective. The latest Cochrane review does not support the use of VPA for agitation in demented patients (Lonergan and Luxenberg 2009). However, there are certainly individual patients who can benefit from the thoughtful use of this medication, especially when other agents are not effective or contraindicated.

There is emerging, but still limited, evidence, supporting use of low-dose gabapentin in the management of agitation in patients with MNCD (Kim et al. 2008; Cooney et al. 2013). The benefits of gabapentin include absence of hepatic metabolism, although sedation may be a significant side effect, and thus its use has to very cautious.

13.3.1.2.6 Melatonin

Since there seems to be a relationship between decline in melatonin function and behavioral symptoms in MNCD (Jansen et al. 2011), various studies have investigated melatonin's effects on neurobehavioral symptoms. While some trials have supported melatonin's usefulness (Asayama et al. 2003), others have not (Gehrman et al. 2009). A Cochrane review analyzed five clinical trials and concluded that while there was no evidence to support the effectiveness of melatonin for cognitive impairment, it demonstrated significant improvements in psychopathologic behavior and mood (Jansen et al. 2011).

13.4 Conclusion

MNCD is common and has profound effects on the quality of life of those affected and their families. Psychiatrists are often consulted in the management of behavioral and psychological symptoms of MNCD and thus it is imperative that they are familiar with the literature behind the effectiveness and risks associated with so far limited treatments.

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