Chapter 3
Neurocognitive Disorders and Neuropsychiatric Symptoms

Susan S. Rose

Introduction to Neurocognitive Disorders and Neuropsychiatric Symptoms

The brain is a dynamic process undergoing constant development and reconstruction across the lifespan [7], which can be imagined as a process of pruning, maintenance, and regrowth [30]. However, this dynamic process can be disrupted when an individual develops a neurocognitive disorder, such as dementia, a disruption that is characterized by neuropsychiatric symptoms and eventually leads to death.

Prior to the publication of the 2013 edition of the diagnostic and statistical manual of mental disorders (DSM-5), neurocognitive deficits were referred to by the umbrella term of dementia. This led to confusion on the part of consumers, particularly when terms like Alzheimer's and dementia were used interchangeably. The DSM-5, however, refers to dementia in terms of a more inclusive title: neurocognitive disorders (NCD). There are other disorders where cognitive impairment and functional decline occur outside of the degenerative brain disorders known as dementia. As with other versions of the DSM, the latest version encourages differen-

S. S. Rose (✉)
Legacy Medical Group – Geriatrics, Vancouver, WA, USA

M. Nash, S. Foidel (eds.), *Neurocognitive Behavioral Disorders*, https://doi.org/10.1007/978-3-030-11268-4_3

tiation of *with or without behavior disturbance* [2], but little emphasis is given to the subject of behavior disturbance itself.

This guide strives to rectify the deficit. The use of the phrase *behavioral disturbance* is inherently incomplete. Behaviors are ubiquitous and normal and serve as a principal mode of communication. Behaviors can become the only mode of communication for those who have trouble understanding or using the language. This guide focuses on the prevention and management of neuropsychiatric symptoms (NPS). NPS routinely causes suffering for those individuals with MNCD, as well those who care for and about them. The trajectory of MNCD leads to eventual fatality. Currently, there are no disease-modifying treatments for MNCD. Instead, NPS are quite often the major focus of treatment: Arguably, NPS may be the only current treatment targets for intervention.

The focus on neuropsychiatric symptoms (NPS) is pragmatic as well as compassionate. NPS comprise the leading cause of quality of life concerns for families of individuals with MNCD. It is the NPS, rather than the NCD itself, that leads to placement of individuals in facilities. The authors of this text posit that these abnormal symptoms cause so much suffering that they need to be the major focus of assessment and treatment. Therefore, this chapter will describe types of MNCD in the context of the various NPS that are associated with each NCD. In fact, our focus on NPS is the predominant theme for this chapter.

Neuropsychiatric Symptoms

The term "neuropsychiatric symptom" has historically been used to describe core features of Alzheimer's disease and related dementias [17, p. 532]; however, a formal operational definition of NPS has not been universally embraced. Many studies recognize the contribution of the Neuropsychiatric Inventory (NPI) [8, 9] and define NPS in terms of NPI items [16, 32]. A 2010 Alzheimer's Association Research

Roundtable underscored the difficulty identifying and classifying NPS across system clusters, as well as differentiating clear syndromes [17].

For the purposes of this guide, NPS are defined inclusively and comprise those symptoms described in the NPI, including apathy, agitation, anxiety, irritability, dysphoria, aberrant motor behavior, disinhibition, delusions, hallucinations, and euphoria [8]. Additional NPS that cause distress for individuals with NCD and their caregivers include verbal abuse, physical aggression, sexually challenging behaviors, exit-seeking behaviors, vocal repetitions, and screaming behaviors and are therefore included in the inclusive definition of NPS.

Assessment of Neuropsychiatric Symptoms

There are a number of different scales to measure NPS, including the Neuropsychiatric Inventory [8], Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) [26], Alzheimer's Disease Assessment Scale noncognitive section (ADAS-noncog) [29], Cohen-Mansfield Agitation Inventory [6], and others. The authors of this textbook recommend the Neuropsychiatric Inventory (NPI), developed by the behavioral neurologist Jeffrey Cummings, MD [8, 9].

The NPI is valid, reliable, sensitive to change, and free to use in clinical settings. It is validated across many different NCDs, which differentiates it from many of the other scales that were modelled on the most common NCD, Alzheimer's disease. The NPI uses a screening strategy to *minimize administration time*, examining and scoring only those behavioral domains with positive responses to screening questions. The NPI measures the frequency and severity of each behavior as well as the level of caregiver distress. Information for the NPI is obtained from a caregiver familiar with the patient's behavior.

The NPI covers 12 domains: hallucinations, delusions, elation/euphoria, agitation/aggression, depression/dysphoria,

anxiety, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep, and appetite and eating disorders. There are a number of different forms of the NPI, including the NPI-NH tested in nursing homes and the NPI-C clinician rating scale [10].

Definition of Neurocognitive Disorders

NCDs refer to conditions in which cognitive impairment is a salient characteristic. Although other psychiatric disorders, such as schizophrenia, may affect cognition, only disorders in which cognitive impairment is a core feature are included in the DSM-5 categorization of NCDs [2]. Additionally, NCDs only include disorders in which cognitive dysfunction represents a decline from prior level of functioning, thus excluding conditions such as developmental delay, or other syndromes in which cognition may have been impaired since birth or early life.

Although dementia is subsumed under the entity *major neurocognitive disorder*, the term *dementia* itself has been retained in the DSM-5 for continuity, as it is the common term for degenerative disorders that generally affect older adults. The more inclusive term, neurocognitive disorder, is preferred for conditions that include younger individuals, such as impairment secondary to traumatic brain injury [2].

The diagnosis of a MNCD requires evidence of significant cognitive decline from prior level of functioning in one or more cognitive domains, such as attention, executive function, learning and memory, language, perceptual-motor, and social cognition or metacognition. Diagnostic criteria also specify that the slope of the decline must be sufficient to affect basic activities of daily living (ADLs) or independent ADLs. Further, the cognitive deficits cannot occur in the context of a delirium, nor should they be more completely explained by another psychiatric disorder, such as major depressive disorder, bipolar disorder, or schizophrenia [2].

Mild Neurocognitive Disorder

MC is a 64-year-old retired secretary. A few months ago, she noticed that she was having trouble remembering tasks. For example, she would go to the grocery store and forget to buy one or two important items. She went to the post office to mail a letter and became distracted by a friend that she met in line. After buying a book of stamps, she was dismayed to find the unmailed letter in her purse. MC recent called you to ask for a referral to a neurologist. "I am sure that I have Alzheimer's!" she tearfully recounted.

Major and mild NCDs occur on a continuum of cognitive and functional impairment. In prior versions of the DSM, MNCD was referred to as dementia, and mild NCD was referred to as mild cognitive impairment.

Mild NCD is an umbrella term that refers to disorders in which the severity of the impairment does not cross the threshold of function. While individuals with mild NCD may demonstrate evidence of decline in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition), the deficits do not interfere with the individual's capacity to live independently or manage instrumental activities of daily living [2].

Structural differences exist between the mild NCD subtypes. Peterson [24] found that individuals with amnestic mild NCD were found to have decreased sizes of the hippocampus and the amygdala, compared to individuals with nonamnestic mild NCD [24].

Differences in neuropsychiatric examination include more impairment in memory functions in individuals with amnestic mild NCD, compared to language impairment in individuals with nonamnestic mild NCD [24], consistent with the prevailing theory of amnestic mild NCD as an AD prodrome and nonamnestic mild NCD as a non-AD prodrome [25, 31]. Table 3.1 compares amnestic and nonamnestic mild NCD and major NCD.

Table 3.1 Amnestic vs nonamnestic mild NCD vs MNCD

Nonamnestic mild NCD	Amnestic mild NCD	Major NCD/ dementia
Memory may be normal, but impairment exists in other cognitive domains, such as attention or language	Memory is impaired but does not cause problems with function	Impairment in memory plus one or more other cognitive domains
Likely non-AD prodrome	Likely AD prodrome	Deficits cross the threshold of functional impairment
Screen for conversion to amnestic mild NCD	Screen for conversion to Major NCD	Treatment is indicated

Individuals with mild NCD should be followed clinically. Currently, annual screening for memory disorders is part of the Medicare guidelines for primary care [5].

Degenerative Neurocognitive Disorders

Neurocognitive Disorder Due to Alzheimer's Disease

AD is an 82-year-old retired dentist. Over the past several years, he has had several minor car accidents, predominantly fender benders. He comes to you for help "dealing with those idiots from the DMV" after having his driver's license suspended. He mentions that he is no longer talking to his daughter, although they have had a close relationship in the past. He pounds his fists on your desk as he complains that she will no longer allow his grandchildren to ride with him. You notice that AD seems more disheveled and disinhibited than he has in the past.

The most commonly diagnosed neurocognitive disorder in older adults is Alzheimer's disease (AD), accounting for

nearly 500,000 new cases of Alzheimer's disease each year [12]. Major or mild NCD due to AD should be suspected when there is evidence of (1) a causative Alzheimer's disease genetic mutation from family history or genetic testing, (2) declining in memory and learning plus one other cognitive domain, (3) steady and progressive decline, without extended plateaus, and (4) no evidence of any other contributory neurodegenerative, cerebrovascular, or other systemic disease or condition to explain the cognitive decline. Probable AD is diagnosed if a family history or genetic mutation is present or if the individual meets all of the remaining criteria; otherwise possible AD should be diagnosed. Mild neurocognitive disorder due to probable or possible AD should be considered for cases that meet the appropriate criteria, but the deficits have not yet begun to affect daily functioning [2].

Neuropsychiatric Symptoms Due to Alzheimer's Disease

NCD due to AD presents with an insidious onset, best described as slow and gradual. Depression and anxiety are increasingly recognized in mild NCD due to AD; in fact, approximately 80 percent of individuals with minor NCD due to AD experience NPS of depression or apathy [2]. Other early symptoms include impaired ability to form new memories; both registration and recall are affected. Language impairment occurs early in the trajectory, and word-finding difficulties are common. Visuospatial impairment also occurs early in the course of the disease; in fact, parking lot accidents and near-misses are common red flags.

As the NCD moves from mild to major, the severity of NPS grows to more commonly include psychotic features, irritability, agitation, combativeness, and wandering. Affect and personality changes may occur in the early stages, but impairment in executive functioning tends to be progressive, as the disease progresses. Paranoia and delusions, most commonly persecutory delusions, are prevalent in mild-moderate

Alzheimer's disease. Sleep disturbances and apathy are frequently found in both mild and MNCD due to AD.

Later stages of MNCD due to AD are commonly associated with motor impairment, gait disturbance, dysphasia, incontinence, myoclonus, and seizures [2]. Agitation, including combativeness, as well as disruptive motor and vocalizations, is common in moderate to severe Alzheimer's. Delusions may occur early in the course of the disease, but hallucinations tend to occur later in the trajectory [11].

Etiology and Treatment of NCD Due to Alzheimer's Disease

Risk factors for Alzheimer's disease include age, family history, and head trauma. Although the aging process does not cause AD per se, age remains the most salient example of correlation without clear etiology of causation.

There are numerous theories for the development of AD, most having to do with cholinergic deficiency. The nucleus basalis of Meynert located in the basal forebrain is the principal site of cholinergic cell bodies thought to mediate memory, learning, and judgment. Deficiency in cholinergic functioning causes disruption in memory. Cholinergic neuronal functioning is one of the earliest neurotransmitter changes in AD. Progressive and downhill, the most damage to the cholinergic system occurs during the first year of symptoms. Unfortunately, by the time the cognitive deficits become apparent, damage has already occurred to the amygdala and hippocampus.

Because Alzheimer's is considered a deficiency of acetylcholine, a trial of cholinesterase inhibitor (ChEI) is considered first-line treatment for MNCD due to AD. The most commonly used ChEIs in the USA include donepezil, galantamine, and rivastigmine. Other ChEIs, such as tacrine, are not currently available.

ChEIs are the most effective for cognition in the early stages of AD. ChEIs require intact postsynaptic cholinergic

receptors in order to receive the benefits of enhanced choline; thus they have the most efficacy when postsynaptic cholinergic targets are still present. That said, ChEIs have considerable utility in management of NCD-related NPS, especially as the severity of the NPS increases [22].

Glutamate antagonists, such as memantine, are also useful for AD. These agents inhibit the excitotoxic action of glutamate by blocking noncompetitive N-methyl-D-aspartate (NMDA) receptors and are thought to help restore physiologic function of neurons [14]. They can also play a role in mitigating NPS, such as anxiety. More consistently calming than ChEIs, glutamate antagonists have an appreciable anxiolytic benefit because they block the excitatory properties of glutamate.

Depression and anxiety are commonly seen in individuals with NCDs. Unlike a primary depression, dementia-related depression and anxiety are treated differently than primary anxiety and depressive disorders that developed prior to the onset of dementia. While antidepressants may be the staple for primary anxiety and depressive disorders, they tend to be much less helpful for NPS [21]. In Alzheimer's, for example, apathy may be due to hippocampal degeneration, rather than a reflection of an underlying depression. In fact, depression is a common prodrome to emergence of Alzheimer's dementia. There is also evidence that social interventions and dementia-specific medications such as ChEIs and glutamate antagonists decrease depression and anxiety [22].

Psychosis and aggression are common in those living with Alzheimer's disease and usually respond to certain antipsychotic medications. The standard of care recommends an informed consent discussion of risks, benefits, and alternatives to antipsychotic use as well as regular monitoring of NPS with a valid scale such as the NPI. Currently, the only antipsychotic medications supported by a large body of evidence are risperidone, aripiprazole, and in certain situations olanzapine [3].

Frontotemporal Neurocognitive Disorder

FD is a 62-year-old male who was brought into the emergency department after assaulting his son. His family reports the patient has been argumentative, disinhibited, and exhibiting very poor judgment. Last week, he set fire to a tree in his backyard and was threatened with arrest. His wife pulls you aside and whispers, "I think he has manic depression, but why would he get it at his age?"

Major frontotemporal NCD, formerly referred to as frontotemporal lobe dementia or degeneration (FTLD), refers to a number of syndromes characterized by frontotemporal lobar dysfunction in the absence of Alzheimer's pathology.

Frontotemporal NCD should be considered when (1) there is clinically detectable evidence of decline in one or more cognitive domain, (2) the disturbance has insidious onset and gradual progression, (3) there is relative sparing of memory and perception, and (4) the disturbance is not better explained by another process, such as cerebrovascular disease, another neurodegenerative disorder, substance use, or another mental, neurological, or systemic disorder [2]. Diagnosis of frontotemporal NCD also includes behavioral and language variants, which further complicates the diagnostic conundrum.

Neuropsychiatric Symptoms in Frontotemporal NCD

Characterized by progressive personality change, behavioral challenges, and impaired judgment and executive function, the behavioral variant of frontotemporal NCD generally involves a "fast and furious" decline. Attention and memory may be normal in frontotemporal NCD, which clouds the diagnostic picture. Further adding to diagnostic uncertainty is an early onset of symptoms, around age 40–60, which is far sooner than what is typically seen in other forms of NCDs.

Paranoia and delusions, particularly persecutory, as well as occasionally euphoria, are seen in mild-moderate frontotemporal NCD. Sleep disturbances and apathy are common in FT NCD. When the major FT NCD is moderate to severe, agitation, combativeness, disruptive motor, and vocalizations are all common.

Roughly 60 percent of all frontotemporal NCDs involve the *behavioral variant*, in which emotional dysregulation can cause mania that can mimic a bipolar disorder. It is not uncommon for individuals with the behavior variant form of frontotemporal NCD to present to the emergency department as floridly manic, with no measurable memory impairment. Further, many individuals with behavior variant frontotemporal NCD may develop obsessive or compulsive behaviors and fetishes, which also make diagnosis difficult. The behavioral variant of frontotemporal NCD was previously referred to as behavior variant frontotemporal lobe dementia (bvFTLD) and includes either (1) prominent decline in social cognition and/or executive abilities or (2) three or more of the following: (a) behavioral disinhibition; (b) apathy or inertia; (c) loss of sympathy or empathy; (d) perseverative, stereotyped, or compulsive/ritualistic behavior; or (e) hyperorality and dietary changes [2].

The *language variant* of frontotemporal NCD is characterized by language impairment, either in the form of speech production, word finding, object naming, grammar, or comprehension [2]. Under the umbrella of language variant frontotemporal NCD is another division, namely, fluent and nonfluent forms. Primary progressive aphasias (PPA) include progressive nonfluent aphasia (PNFA), which is characterized by slow, effortful speech, a semantic fluent aphasia (SFA) in which speech rate may be normal but the meaning of the words is lost, and logopenic progressive aphasia (LPA), in which the words themselves are lost. While a discussion of the various forms of language variant frontotemporal NCD is beyond the scope of this text, it underscores the wide variation in which an individual may present for care and the difficulty with diagnostic certainty.

Treatment of Frontotemporal NCD

Treatment is complicated in frontotemporal NCD. First-line treatment involves behavioral, environmental, and social interventions. There is no evidence of benefit from cholinesterase inhibitors. Glutamate antagonists also lack an evidence base supporting their use. Low-dose serotonergic medications can occasionally be helpful, but the majority of treatment is aimed toward mitigating behavioral symptoms. Mood stabilizers may be helpful in this regard if there is no response to behavioral, social, and environmental interventions. Psychosis and aggression usually respond to certain antipsychotic medications. The standard of care recommends an informed consent discussion of risks, benefits, and alternatives to antipsychotic use as well as regular monitoring of NPS with a valid scale such as the NPI. Currently, the only antipsychotic medications supported by a large body of evidence are risperidone, aripiprazole, and in certain situations olanzapine [34].

Consistent with other NCDs, the differentiation of major versus mild depends on whether the NCD has crossed the threshold of function. Also consistent with other NCDs, the designation of probable vs possible depends on evidence of causative frontotemporal NCD genetic mutation from family history or genetic testing or neuroimaging evidence of frontal and/or temporal lobe degeneration. Differences between NCD due to AD and frontotemporal NCD are portrayed in Table 3.2.

Neurocognitive Disorder with Lewy Bodies

LB is a 74-year-old retired grocery clerk. He was forced into retirement after repeatedly stumbling and falling at work. He has had several visits to the emergency department and is frustrated that he has not been given a diagnosis. He is anxious and dismayed when he presents to your office. After a bit of coaxing, he discloses that he has been seeing a little girl in a red apron standing at the end of his bed. "Please tell me I'm not crazy," he begs.

Table 3.2 NCD due to Alzheimer's disease vs frontotemporal NCD

NCD due to Alzheimer's disease	Frontotemporal NCD
Insidious onset, delusions, and memory impairment occur early in the disease	Fast and furious onset, problems with judgment and impulse control. Memory not impaired until late in the disease
Age of onset is late; 60–90 or later	Age of onset is early; 40–60
Language deficits involve word-finding difficulties	Language deficits may range from word-finding difficulties to nonsensical language
Mood is generally stable	May present as manic
Treatment with ChEI is beneficial	ChEI ineffective, may make things worse
Glutamate antagonist is generally beneficial	Glutamate antagonist not helpful

Neurocognitive disorder with Lewy bodies (NCDLB) is the most common neurocognitive syndrome associated with parkinsonism. Unlike Alzheimer's disease, which involves amyloid bodies, NCDLB is considered a tauopathy and is often overlooked pathologically because of the difficulty identifying cortical Lewy bodies.

Major or mild neurocognitive disorder with Lewy bodies should be considered when (1) there is clinically detectable evidence of decline in one or more cognitive domain, (2) there is insidious onset and gradual progression, and (3) the disorder meets a combination of core diagnostic features (fluctuating cognition with fluctuating levels of awareness, recurrent and detailed visual hallucinations, spontaneous features of parkinsonism that developed prior to the onset of cognitive decline) and suggestive diagnostic features (REM sleep behavior disorder, severe neuroleptic sensitivity). As with other neurocognitive disorders, the disturbance is not better explained by another etiology [2].

Neuropsychiatric Symptoms in NCDLB

Like other neurocognitive disorders, NCDLB is characterized by decline in cognitive and functional performance with deficits in attention and executive functioning. Unlike other NCDs, however, memory function may remain robust, and the initial symptom may be the onset of vivid hallucinations and delusional content.

Neurocognitive disorder with Lewy bodies is felt to exist on a continuum with Parkinson's-related disorders, so parkinsonism is a key characteristic in NCDLB. Specifically, individuals with NCDLB typically exhibit spontaneous motor features of parkinsonism, including slowed motor speed, shuffling gait, dyskinesia, masked facies, and tremor. The motor symptoms present later than other symptoms in NCDLB. Severe fluctuations and pronounced variation in alertness are also common, as well as frequent falls, syncope, autonomic dysfunction, and transient loss of consciousness. Language functions appear slowed, and visuospatial abilities are abnormal. NCDLB also has a high rate of depressive NPS.

Most individuals with parkinsonism exhibit neuroleptic sensitivity, so individuals with NCDLB also tend to be intolerant of moderately potent antipsychotics. For example, an individual with NCDLB or parkinsonism will likely develop increased muscle tone and tremor when prescribed neuroleptic agents, such as haloperidol.

NCDLB has other defining features that differentiate it from other types of NCDs. They may also have complex and well-formed visual hallucinations. For example, an individual with Alzheimer's-related hallucinations may describe them as "children playing in the hallway." In contrast, an individual with Lewy body-related hallucinations may experience them in greater detail, such as "a little girl wearing a yellow bonnet with an apple."

The onset of hallucinations is also different in NCDLB versus AD. Hallucinations are fairly rare in early Alzheimer's, tend to last days or weeks, and may be associ-

ated with an acute illness or delirium. In contrast, NCDLB-related hallucinations may last months or years in duration [21].

Additional features suggestive of NCDLB pathology include rapid eye movement (REM) sleep behavior disorder (RSBD), the onset of which may precede parkinsonism by a decade or more.

The progression of NCDLB is considered to be more rapid than Alzheimer's. If AD were to be visualized as a ball rolling down a hill, NCDLB would be seen as a ball bouncing erratically down a hill [28].

Treatment of Major Neurocognitive Disorder with Lewy Bodies

Neurodegeneration in NCDLB includes deficits in choline transmission; therefore, a ChEI is indicated. Because of the fluctuating nature of NCDLB, the use of a steady distribution agent such as a transdermal patch can be useful. For that reason, many individuals with NCDLB are tried on a rivastigmine patch. Interestingly, the hallucinations and delusions experienced by those living with NCDLB often respond robustly to ChEIs. If psychotic NPS are causing significant distress or dangerousness and do not respond to a ChEI, the addition of low-dose quetiapine or clozapine can be quite successful.

Glutamate antagonists can be helpful with NCDLB, although the evidence is mixed. It is worth noting that cholinergic deficiency in NCDLB is greater than that seen with Alzheimer's, so minimizing anticholinergic medications is particularly important.

Consistent with other NCDs, the differentiation of major versus mild depends on whether the NCD has crossed the threshold of function. Unlike other NCDs, however, family history is not a common prognostic factor in NCDLB. Genes have been identified that may point to a vulnerability, but there is little other criteria to assist in

Table 3.3 Alzheimer's vs. Lewy body

NCD due to AD	NCD with Lewy bodies
Insidious onset, delusions, and memory impairment occur early in the disease	More rapid onset; visual hallucinations may occur early in disease; memory may not be affected until later
Motor symptoms do not occur until later	Parkinsonism is a core feature
Neuropsychiatric symptoms such as visual hallucinations are common but tend to be vague and nondescript	Neuropsychiatric symptoms such as visual hallucinations are common, complex, and well-defined
Language may be impaired; word-finding difficulties	Language is slowed
Generally tolerant of antipsychotics	Generally intolerant of antipsychotics
Treatment with ChEI is beneficial	Treatment with ChEI is beneficial
Treatment with glutamate antagonist is generally beneficial	Treatment with glutamate antagonist may or may not be beneficial

the designation of probable vs possible NCDLB. Table 3.3 outlines differences between dementia due to AD and dementia due to Lewy bodies.

Neurocognitive Disorder Due to Parkinson's Disease

PD is an 83-year-old retired piano teacher. Slowly, almost painstakingly, she describes her sadness at no longer being able to play her beloved piano, due to the severity of her tremor. "Of course," she says, "I actually had to stop performing a few years ago, when I found that I couldn't keep up with the tempo. I tried to join a choir instead, but I sound like Kate Hepburn, and my voice is also thinner than it used to be. Do you think I am just depressed?"

Individuals with Parkinson's disease (PD) have an almost sixfold increase in prevalence of neurocognitive disorder, compared to those individuals without the disorder; however, the anatomic and pathologic basis of PDD (Parkinson's disease dementia) is not fully understood.

As above, PDD and NCD with Lewy body dementia are thought to exist on a continuum. Therefore, differentiating between PDD and NCDLB is based on history and what is referred to as the "1 Year Rule" [15, p. 2]. If the NPS precede the parkinsonian symptoms by 1 year, then the etiology is presumed to be NCDLB. If the parkinsonian symptoms precede NPS, then the diagnosis is most likely PDD.

Diagnostic criteria for PDD includes (1) documented decline from baseline, (2) disturbance occurs in the setting of established Parkinson's disease, (3) insidious and gradual progression of impairment, and (4) NCD is not attributable to another etiology. Probable NCD with PD is presumed when there is no evidence of mixed etiology and the PD precedes the onset of the NCD. Possible NCD with PD is assigned for individuals in which there may be a mixed etiology or the temporal relationship between diagnosis of PD and onset of NCD has been established. As with all other NCDs, the designation of mild versus major depends on whether the impairments affect functional outcomes [2].

Neuropsychiatric Symptoms in PDD

Unlike other neurocognitive disorders, the onset of PDD involves motor symptoms early in the disease. Motor signs may include tremor, stiffness, and gait instability. Attention and visuospatial function may be normal. Attention and language tend to be slowed. Affect is restricted or blunted. Executive functioning and thought processes will be slowed but may be normal. Depression is very common in PDD. Because PDD and NCDLB exist along a continuum, NPS commonly seen in NCDLB will also be commonly seen in PD, including depression, apathy, and vivid visual hallucinations.

Treatment of PDD

As with other NCDs, cholinesterase inhibitors may be helpful for those with PDD. Evidence on the utility of glutamate antagonists is mixed, as is similar to NCDLB. Cholinesterase inhibitors may help with visual hallucinations, paranoia, delusions, and other NPS in individuals with PD. Rivastigmine remains the best studied and only FDA-approved treatment for PDD, although some evidence supports the use of donepezil and galantamine [34].

As with NCDLB, individuals with parkinsonism tend to have neuroleptic sensitivity, so moderate to high potency antipsychotics should be avoided. Clozapine has the best data for reduction of visual hallucinations but is associated with serious side effects and requires active monitoring. Quetiapine is currently the most commonly used atypical antipsychotic in individuals with neuroleptic sensitivity due to better tolerability, although has less evidence to support relief of hallucinations, and may be overly sedating at higher doses [34].

Quetiapine has brief receptor occupancy, so low and frequent dosing is preferable. Quetiapine and carbidopa/levodopa have similar half-lives, so low doses of quetiapine given at the same time as carbidopa/levodopa can help mitigate carbidopa-induced psychosis.

Table 3.4 compares differences between NCD due to AD, Lewy body, and Parkinson's, and Table 3.5 helps differentiate between the main types of NCDs in terms of onset, cognitive domains, and treatment.

Neurocognitive Disorder Due to Huntington's Disease

Huntington disease (HD) is an inherited progressive neurodegenerative disorder characterized by choreiform movements, NPS, and neurocognitive impairment. The pathophysiology of HD is not fully understood, although it is thought to be related to toxicity of the mutant huntingtin

Table 3.4 AD vs NCDLB vs PD

NCD due to AD	NCD with Lewy bodies	NCD due to PD
Memory impairment occurs early. Delusions may occur early. Hallucinations occur later. Motor symptoms occur late.	Visual impairment occurs first, then motor symptoms. Memory may not be affected until later	Motor symptoms occur first, then visual hallucinations. Memory may not be affected until later.
NPS such as visual hallucinations are common but tend to be vague and nondescript	NPS such as visual hallucinations are common, complex, and well-defined	NPS such as visual hallucinations are common but less complex than NCDLB
Language may be impaired; word-finding difficulties	Language is slowed	Language is slowed
Generally tolerant of antipsychotics	Intolerant of antipsychotics	Intolerant of antipsychotics
Treatment with ChEI is beneficial	Treatment with ChEI is beneficial	Treatment with ChEI may be beneficial
Treatment with glutamate antagonist is generally beneficial	Treatment with glutamate antagonist may or may not be beneficial	Treatment with glutamate antagonist may or may not be beneficial

protein. Symptoms begin insidiously with movement abnormalities and/or with neuropsychiatric or neurocognitive symptoms. The course is one of slow but relentless deterioration in cognitive and motor function. There is currently no cure, and treatment is supportive and symptomatic [33].

Chorea is a key feature of NCD due to HD and the most salient symptom at the time of diagnosis. Chorea is a characterized by brief, abrupt, involuntary, non-stereotyped movements involving the face, trunk, and limbs [13]. These

Table 3.5 Differentiating types of NCDS

	Alzheimer's dementia	**Vascular dementia**	**Frontotemporal dementia**	**Parkinson's disease dementia**	**Lewy body dementia**
History/ onset	Insidious, presents *w/*depression, vague sx2–3 years before dx. Memory, language, visual-spatial problems, indifference, delusions, agitation	Hx of HTN, vascular disease, CAD, abrupt onset but may be insidious. Stepwise deterioration	Insidious, personality change, apathy, disinhibition	Motor signs precede dementia by at least 1 year	Prominent detailed visual hallucinations precede motor signs
Motor signs	Late	Motor signs, balance deficits, or hemiparesis	Apraxia, gait instability	Tremor, stiffness, gait changes	Parkinsonian signs; motor signs and dementia may occur in same year
Attention	Normal	Difficulty with mental tracking	Normal	AMS, marked fluctuation in alertness, attention	
Memory	Early: difficulty learning new info and retaining it	Decreased memory retrieval	May be normal	Slowed	Mildly impaired early

Language	Aphasia, anomia, decreased verbal fluency	Variable depending on lesion Most have prominent aphasia	Progressive nonfluent (logopenic) or fluent (semantic) aphasia	Slowed, dysarthria is common
Thought disorders	Delusions			Visual hallucinations and delusions
Visual spatial	Mild early and progressive	Variable, depending on lesion	Relative preservation of visual-spatial skills	Prominent visual-spatial abnormality
Mood, affect	Apathy, depression, personality change	Behavioral changes	Marked apathy, disinhibition, personality change	Apathy
Executive function	Mild early and progressive	More prominent than memory loss	Abnormal frontal lobe, judgment	Slowing of thought process impaired
Treatment	Start early with ChEI, add NMDA antagonist. Avoid anticholinergics	ChEI NMDA antagonist. Treat vascular risk factors	Low-dose SSRI helpful. Avoid ChEI; may worsen symptoms. Antipsychotic variable, can be helpful. Consider mood stabilizer	Avoid all neuroleptics except low-dose quetiapine or pimavanserin. Possible role for low-dose ChEI, rivastigmine patch best. NMDA antagonist variable, possibly unhelpful

movements are mild and may be misinterpreted as restlessness. Individuals may be unaware of the movements and may incorporate the chorea into purposeful actions, a phenomenon termed parakinesia, which can affect up to one half of all individuals with HD, thus complicating the diagnostic picture [20].

Neuropsychiatric Symptoms in HD

Cognitive decline is inevitable in HD. The dominant cognitive feature of HD is executive dysfunction with diminished ability to make decisions. Anosognosia into cognitive and motor impairment is common [23].

NCD due to HD is described as *subcortical*; meaning it refers to a clinical model of cognition that highlights frontostriatal pathways as facilitators of speed and efficiency of thought. Unlike cortical NCDs, such as those seen with Alzheimer's disease, individuals with NCD due to HD tend to do better with cueing, suggesting that memory problems are due to organization, rather than retrieval. Psychosis and motor symptoms in those with HD are treated with antipsychotics, usually haloperidol.

Injury-Related Neurocognitive Deficits

Vascular Neurocognitive Disorder

VD is a 92-year-old retired truck driver that has suffered a series of small strokes over the past several years. He has reached a plateau in rehabilitation, and his insurance will no longer authorize his recovery in a skilled nursing facility. He is described as apathetic and amotivational. He is sent to you for treatment of depression. You notice that his speech is slow, and he is passive with examination.

There are a plethora of names for cognitive deficits following a vascular event, including stroke-related dementia,

multi-infarct dementia, and vascular dementia. A lack of uniform diagnostic criteria clouds the naming conventions; however, all refer to the onset of cognitive deficits associated with cerebrovascular disease. In the DSM-5, cognitive disorders for which cerebrovascular disease is the predominant, if not exclusive pathology, are referred to under the umbrella of major or mild vascular neurocognitive disorder. Major or mild vascular NCD is the second most common cause of NCD after Alzheimer's disease.

Diagnostic criteria for major or mild vascular neurocognitive disorder follow the same format as other NCDs: (1) there is clinically detectable evidence of decline in one or more cognitive domain; (2) clinical features are consistent with a vascular etiology that includes a temporal relationship to a cerebrovascular event or decline in complex attention, processing speed, or frontal-executive function; (3) there is empirical evidence of cerebrovascular disease from history, physical examination, or neuroimaging that is sufficient to account for the neurocognitive deficits; and (4) symptoms are not better explained by another etiology [2]. Evidence of injury on neuroimaging is generally combined with neurological deficits on examination to confirm the diagnosis.

Consistent with other NCDs, the differentiation of major versus mild vascular NCD depends on whether the NCD has crossed the threshold of function. As with other NCDs, the differentiation of probable vs possible depends on neuroimaging evidence of significant parenchymal injury due to cerebrovascular disease, a temporal relationship to a vascular event, or a combination of clinical and genetic evidence of cerebrovascular disease [2].

Neuropsychiatric Symptoms in Vascular NCD

In general, onset of vascular neurocognitive disorder is abrupt, followed by a stepwise deterioration. Motor and balance deficits may be prominent. Unlike other degenerative neurocognitive disorders, however, abnormalities in

cognitive functioning will depend on the location of the vascular event or lesion.

Depression, apathy, and amotivation are common early neuropsychiatric symptoms of vascular NCD, owing to the common comorbidity of depression and cerebrovascular stroke. Hallucinations and other psychotic symptoms depend on the location of the lesion.

As you may recall, we conceptualized the trajectory of NCD due to AD as a ball rolling down a hill and NCDLB as a ball bouncing erratically down a hill. In the same manner, the visualization of vascular NCD would be a ball rolling down an uneven set of stairs [27, 28]. Deterioration tends to occur suddenly, in the context of a vascular event, followed by a period of stability, followed by another sudden drop due to a subsequent injury. As well, there are a significant number of people living with both AD and VD.

Treatment of Vascular NCD

Cholinesterase inhibitors are a cornerstone of treatment for vascular NCD. In general, higher doses of ChEIs are generally used for individuals with vascular neurocognitive disorder than other NCDs such as those due to AD. Unlike other NCDs, however, there is no clear role for glutamate antagonists in slowing down the disease process; however, they remain useful for mitigation of NCD-related NPS.

The most salient treatment for a vascular neurocognitive disorder is reduction of risk factors for a subsequent vascular event. Smoking cessation is vital, as is attention to high-risk comorbidities such as hypertension and diabetes. Reducing stroke risk is the single strongest factor in reduction of vascular NCD.

Psychosis and aggression are common in those living with VD and usually respond to certain antipsychotic medications. The standard of care recommends an informed consent discussion of risks, benefits, and alternatives to antipsychotic use as well as regular monitoring of NPS with a valid scale such as the NPI. Currently, the only antipsychotic medica-

tions supported by a large body of evidence are risperidone, aripiprazole, and in certain situations olanzapine [34].

Neurocognitive Disorder Due to Traumatic Brain Injury

Traumatic brain injury (TBI) is a leading cause of death and disability. Major or mild neurocognitive disorder due to TBI is caused by a severe and abrupt displacement of the brain within the skull, typically the result of an impact to the head. Specific criteria for major or mild NCD due to TBI include the following: (1) diagnostic criteria for major or mild NCD; (2) evidence of brain injury with one or more of the following, (a) loss of consciousness, (b) post-traumatic amnesia, (c) disorientation and confusion, and (d) neurological signs such as evidence of injury on neuroimaging, new onset of seizures, worsening of premorbid seizure disorder, visual field cuts, anosmia, and hemiparesis; and (3) a temporal relationship between the NCD and the TBI, either immediately or persistent after the acute post-injury period [2].

Neuropsychiatric Symptoms in NCD Due to TBI

Cognitive impairment varies, depending on the severity of the TBI. The term "concussion" is commonly used as a synonym for mild TBI but is formally defined as a trauma-induced alteration in mentation that may or may not involve loss of consciousness [1]. Individuals with mild NCD due to TBI may experience cognitive inefficiencies and difficulty performing daily activities but with less severity than individuals with MNCD due to TBI. Common features of MNCD due to TBI may include disturbance in emotional functioning, irritability, personality changes, physical disturbances, or neurological symptoms. Depression is a common comorbidity, which can worsen functional outcomes and compound difficulties with independent living and self-care [2].

There is evidence that repeated concussions can cause chronic traumatic encephalopathy, with increased severity and duration of mental status abnormalities after each incident [19]. The sequelae of TBI can cause cumulative neuropsychiatric deficits, chronic traumatic encephalopathy, cognitive impairment, and NPS such as personality changes, behavioral challenges, depression, suicidality, parkinsonism, and speech and gait abnormalities [36].

Treatment of NCD Due to TBI

Although there is a dearth of research on the use of cognitive enhancers for treatment of major neurocognitive disorder due to TBI, treatment options can be borrowed from similar NCDs. A history of TBI is a strong risk factor for development of NCD due to Alzheimer's disease. Additionally, the mechanism and trajectory of NCD due to TBI is similar to vascular neurocognitive disorders. Therefore, treatment recommendations center around promotion of NCD-specific medications, such as cholinesterase inhibitors and glutamate antagonists, as well as reduction of risk factors for subsequent injury.

Psychosis and aggression occur in those living with MNCD TBI and usually respond to certain antipsychotic medications. The standard of care recommends an informed consent discussion of risks, benefits, and alternatives to antipsychotic use as well as regular monitoring of NPS with a valid scale such as the NPI. Currently, the only antipsychotic medications supported by a large body of evidence are risperidone, aripiprazole, and in certain situations olanzapine [34].

Delirium

HD is a 75-year-old retired carpenter that was brought in to the emergency department for confusion. He is unable to remember his age, wife's name, or what he did for a living. He has

been described as "quiet and befuddled" by the day shift nursing staff, but the night staff describe him as "wild and wooly." He is currently picking at unseen items on his bedclothes. His wife mentions that he made a hole-in-one on the golf course on Sunday.

No description of NCD would be complete without reference to one of the major confounders when diagnosing dementia: delirium. Delirium can be misinterpreted as dementia, due to presentation in various stages of arousal, which complicates the diagnostic process. Derived from the Latin term meaning "off the track", delirium refers to a transient global cognitive disorder or group of symptoms associated with complex medical comorbidities. Defining characteristics include disturbance in attention and awareness that develops acutely and is characterized by fluctuation [18]. Delirium should be considered when there is evidence of (1) disturbance of attention and awareness; (2) acute onset, with fluctuating severity; and (3) disturbance in cognition, such as memory, disorientation, language, visuospatial ability, or perception; (4) the disturbance is not explained by another neurocognitive disorder or occur in the context of a severely reduced level of awareness, such as a coma; and (5) there is empirical evidence, such as physical exam or diagnostic data, that the disturbance is caused by a physiological condition, such as a medical etiology, substance intoxication or withdrawal, exposure to a toxin, or due to multiple etiologies [2].

Forms of Delirium

Three forms of delirium are described in the literature: hyperactive, hypoactive, and mixed. The *hyperactive* form of delirium often presents with psychomotor agitation and a plethora of psychiatric symptoms, such as confusion, hallucinations, or delusions. The hyperactive form is the most recognized form of delirium and is associated with perceptual disturbances and delusions in more than 70 percent of sufferers [4]. In contrast, the *hypoactive* form of delirium may mimic a stupor or coma

and occurs more commonly than the hyperactive form. Hypoactive delirium has a higher mortality rate than hyperactive delirium, largely due to the effects of immobility [27]. Often called "quiet" delirium because it is characterized by a flat affect or apathy and often present in otherwise calm and seemingly alert patients [35], this type of brain dysfunction carries a grimmer prognosis than hyperactive delirium and is the most commonly missed subtype of delirium. The *mixed* form of delirium is the most frequent subtype of delirium and presents with both hyperactive and hypoactive features. It is not uncommon for delirious individuals to have daytime somnolence, accompanied by nocturnal agitation and insomnia. Alternatively, individuals may fluctuate between the hyper- and hypoactive forms during the course of a few hours.

Delirium accelerates the pace of underlying cognitive decline. It is not uncommon for the presence of an underlying neurocognitive disorder to "declare itself" after an episode of delirium [27, 28]. Although delirium may mimic other neurocognitive disorders, delirium is a separate syndrome and differs from other NCDs in key areas, including onset of symptoms and attention. The most important distinction between delirium and other NCDs is the potentially reversible attribute of delirium. Unlike most NCDs, which are chronic, progressive, and ultimately fatal trajectories, delirium is an abrupt onset of confusion with an optimistic rate of reversibility. With aggressive treatment of underlying causes, it is possible to return the individual to his or her pre-delirium baseline.

References

1. American Academy of Neurology. Practice parameter: the management of concussion in sports (summary statement). Report of the quality standards subcommittee. Neurology. 1997;48(3):581.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
3. American Psychiatric Associations' Practice guideline on the use of antipsychotics to treat agitation or psychosis in

patients with dementia. 2016. https://doi.org/10.1176/APPI.BOOKS.9780890426807.
4. Boettgera S, Breitbart W. Phenomenology of the subtypes of delirium: Phenomenological differences between hyperactive and hypoactive delirium. Palliat Supportive Care. 2011;9(2):129–35.
5. Center for Medicare and Medicaid Services. Yearly "Wellness" visits. 2018. Retrieved from https://www.medicare.gov/coverage/yearly-wellness-visits.
6. Cohen-Mansfield J, Marx M, Rosenthal A. A description of agitation in a nursing home. J Gerontol. 1989;44(3):M77–84.
7. Cozolino L. The neuroscience of psychotherapy: building and rebuilding the human brain. New York: Norton; 2002.
8. Cummings JL. The neuropsychiatric inventory: assessing psychopathology in dementia patients. Neurology. 1997;48(Supp16):SlO–16.
9. Cummings JL, et al. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44:2308–14.
10. de Medeiros K, Robert P, Gauthier S, Stella F, Politis A, Leoutsakos J, Taragano F, Kremer J, Brugnolo A, Porsteinsson AP, Geda YE, Brodaty H, Gazdag G, Cummings J, et al. The Neuropsychiatric Inventory-Clinician rating scale (NPI-C): reliability and validity of a revised assessment of neuropsychiatric symptoms in dementia. Int Psychogeriatr. 2010;22(6):984–94.
11. Early-stage caregiving/Caregiver Center/Alzheimer's Association; 2018. Retrieved from https://www.alz.oper-ceptual-motorrg/help-support/caregiving/stages-behaviors/hallucinations
12. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurology. 2007;68:32637.
13. Ho SL, Chorea. The International parkinson and movement disorder society; 2018. Retrieved from https://www.movement-disorders.org/MDS/About/Movement-Disorder-Overviews/Chorea%2D%2DHuntingtons- Disease.htm.
14. Institute of Medicine (US) Forum on Neuroscience and Nervous System Disorders. Glutamate-related biomarkers in drug development for disorders of the nervous system: workshop summary. Washington, DC: National Academies Press (US); 2011. 2, Overview of the Glutamatergic System. Available from: https://www.ncbi.nlm.nih.gov/books/NBK62187/
15. Lewy Body Dementia Association. When Parkisonism does not mean Parkinson's. ScienceDaily. ScienceDaily, 21 January 2015.

16. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment results from the cardiovascular health study. JAMA. 2002;288(12):1475–83. https://doi.org/10.1001/jama.288.12.1475.
17. Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, Cedarbaum J, Brashear R, et al. Neuropsychiatric symptoms in Alzheimer's disease. Alzheimers Dement. 2011;7(5):532–9.
18. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med. 2017;377:1456–66.
19. McAllister TW, Flashman LA, Maerlender A, Greenwald RM, Beckwith JG, Tosteson TD, Crisco JJ, Brolinson PG, Duma SM, Duhaime AC, Grove MR, Turco JH. Cognitive effects of one season of head impacts in a cohort of collegiate contact sport athletes. Neurology. 2012;78(22):1777–84.
20. McCusker EA, Gunn DG, Epping EA, Loy CT, Radford K, Griffith J, Mills JA, Long JD, Paulsen JS. PREDICT-HD investigators of the Huntington study group. Neurology. 2013;81(13):1141–7.
21. Nash, MC. Lewy who? A discussion of Lewy body dementia. Alzheimer's Resource of Alaska, Anchorage, Alaska, November 2013.
22. Nash M, Swantek SS. Neuropsychiatric symptoms of dementia: monotherapy, or combination therapy? Curr Psychiatr Ther. 2018;17(7):21–5.
23. Paulsen JS. The cognitive disorder. In: Nance M, Paulsen JS, Rosenblatt A, Wheelock V, editors. A Physician's guide to the management of Huntington's disease. 3rd ed. New York: Huntington's Disease Society of America; 2011. p. 51. Retrieved from http://hdsa.org/wp-content/uploads/2015/03/PhysiciansGuide_3rd-Edition.pdf.
24. Petersen RC. Mild cognitive impairment. N Engl J Med. 2011;364(23):2227.
25. Petersen RC, Negash S. Mild cognitive impairment: an overview. CNS Spectr. 2008;13:45–53.
26. Reisberg B, Auer SR, Monteiro IM. Behavioral pathology in Alzheimer's disease (BEHAVE–AD) rating scale. Int Psychogeriatr. 1996;8(Suppl 3):301–8, 507–550.
27. Rose SS. Delirium. In: Mauk K, editor. Gerontological competencies for care. 4th ed. Burlington: Jones & Bartlett; 2018a.

28. Rose, SS. Geropsych pearls; 2018b. Retrieved from www.geroconsult.org.
29. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatr. 1984;141:1356–64.
30. Schore A. Early relational trauma, disorganized attachment and the development of a predisposition to violence. In: Solomon M, Siegel DJ, editors. Healing trauma: attachment, mind, body and brain. New York: Norton; 2003.
31. Smith GE, Bondi MW. Mild cognitive impairment and dementia: definitions, diagnosis, and treatment. New York: Oxford University Press; 2013.
32. Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, Breitner JC, Steffens DC, Tschanz JT, Cache County Investigators. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. Int J Geriatr Psychiatr. 2008;23(2):170–7.
33. Suchowersky O. Huntington disease: clinical features and diagnosis, UpToDate; 2018. Retrieved November 19, 2018.
34. Taylor JP, Collerton D. Advances in the treatment of visual hallucinations in neurodegenerative diseases. Future Neurol. 2013;8(4):433–44.
35. Truman B, Ely EW. Monitoring delirium in critically ill patients. Critical Care Nurse. 2003;23:25–36.
36. Wang HK, Lin SH, Wu MH, Hung KW, Wang LC, Huang CY, Lu K, Chen HJ, Tsai KJ. Population based study on patients with traumatic brain injury suggests increased risk of dementia. J Neurol Neurosurg Psychiatr. 2012;83(11):1080–5.