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Progress in Pharmacologic Management of Neuropsychiatric Syndromes in Neurodegenerative Disorders
A Review

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IMPORTANCE Neuropsychiatric syndromes (NPSs) are common in neurodegenerative disorders (NDDs); compromise the quality of life of patients and their care partners; and are associated with faster disease progression, earlier need for nursing home care, and poorer quality of life. Advances in translational pharmacology, clinical trial design and conduct, and understanding of the pathobiology of NDDs are bringing new therapies to clinical care.

OBSERVATIONS Consensus definitions have evolved for psychosis, agitation, apathy, depression, and disinhibition in NDDs. Psychosocial interventions may reduce mild behavioral symptoms in patients with NDD, and pharmacotherapy is available for NPSs in NDDs. Brexpiprazole is approved for treatment of agitation associated with Alzheimer disease dementia, and pimavanserin is approved for treatment of delusions and hallucinations associated with psychosis of Parkinson disease. Trials are being conducted across several of the NDDs, and a variety of mechanisms of action are being assessed for their effect on NPSs.

CONCLUSIONS AND RELEVANCE Detection and characterization of NPSs in patients with NDDs is the foundation for excellent care. New definitions for NPSs in NDDs may inform choices regarding clinical trial populations and translate into clinical practice. Psychosocial and pharmacologic therapies may reduce behavioral symptoms and improve quality of life for patients and caregivers. Approved agents may establish regulatory precedents, demonstrate successful trial strategies, and provide the foundation for further advances in treatment development.

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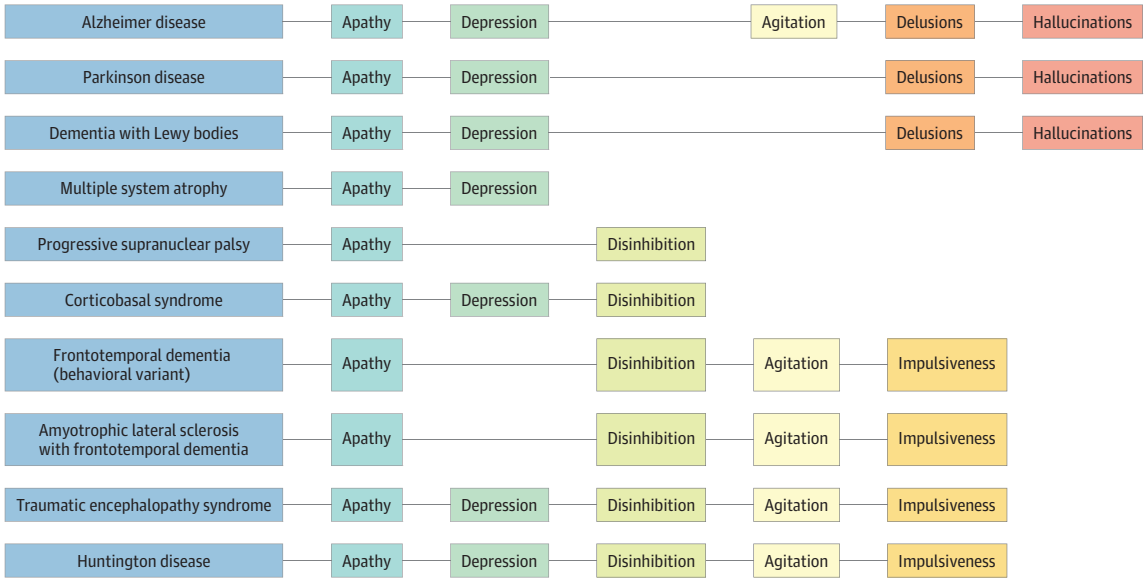
Neurodegenerative disorders (NDDs) include Alzheimer disease (AD), Parkinson disease (PD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), corticobasal syndrome, multiple system atrophy, amyotrophic lateral sclerosis, chronic traumatic encephalopathy and traumatic encephalopathy syndrome (TES), and Huntington disease (HD). Most of these conditions are age related and become symptomatic in late life or late middle age. Their frequency is growing as the world's population ages. The total and projected global burden of NDDs in the US and globally is enormous.[1]

Neuropsychiatric syndromes (NPSs) are common across all NDDs (**Figure**), and for many NDDs, NPSs are included in the diagnostic criteria for the disease.[2] In some common NDDs, such as AD, nearly all patients with the dementia stage of the illness manifest an NPS, and some patients have multiple NPSs simultaneously or sequentially.[3] In AD dementia where these syndromes have been most thoroughly studied, NPSs are associated with more rapid cognitive decline, greater functional impairment, poorer quality of life, greater likelihood of residence in a nursing home, and greater caregiver distress.[4-7] Neuropsychiatric syndromes show highly variable temporal profiles; most NPSs are more common and more severe with disease progression and cognitive decline.[8] Progress has been made in the early identification of NDDs, and NPSs play important roles in the prodromal presentations of AD, DLB, and FTD.[9-11] The COVID-19 pandemic called attention to the high rate of NPSs in patients residing in nursing homes and their vulnerability to exacerbation of symptoms with isolation and changes in daily routines.[12]

The many negative consequences of NPSs in patients with NDDs motivate the search for strategies to reduce these symptoms with the goal of improving quality of life and possibly influencing the long-term trajectory of the diseases. Psychosocial nonpharmacologic interventions have important effects in ameliorating NPSs in patients with NDD and reducing the likelihood of relapse.[13,14] Psychosocial treatment options include environmental modification, activity and exercise programs, music, therapeutic touch (massage and acupressure), animal-assisted interventions, and combined activities (music, art, and exercise), as well as deprescribing potentially agitation-inducing medication.[14-17] Tailored multimodal interventions designed around the specific behaviors and circumstances of the individual appear to be most effective.[14] The high rate of placebo responses in clinical trials of NPSs in NDDs attests to the power of psychosocial and interpersonal interventions to produce symptom reduction.[18] Preliminary studies have indicated that biomarker and digital device changes associated with psychosocial interventions may eventually provide objective evidence to guide these therapeutic programs.[19,20]

Figure. Major Neuropsychiatric Syndromes Occurring in Neurodegenerative Disorders



Pharmacologic interventions are reserved for the treatment of patients whose symptoms do not respond to psychosocial interventions, present a threat of harm to themselves or others, or who may stay in their home for a longer time if the symptoms are ameliorated. Development of drugs to treat the NPSs of NDDs is arduous, and most trials have failed to demonstrate a drug-placebo difference. However, there has been progress in developing new therapies for NPS, and several agents have been approved by the US Food and Drug Administration (FDA) for use specifically in patients with an NDD.

The development of criteria for NPSs in both fully manifested NDDs and prodromal states has contributed to better design of clinical trials and may assist practitioners in identifying appropriate patients for treatment.[21-28] **Table 1** provides the specific diagnostic criteria for NPSs in NDDs. We describe the symptoms, occurrence across NDDs, and appropriate management of 5 major NPSs, including psychosis, agitation, depression, apathy, and disinhibition. Other important NPSs occurring in NDDs include sleep disturbances, anxiety, irritability, and disturbances of sexual behavior.

Best practices for care of patients with an NDD and NPS is a stepwise approach to diagnosis of the NDD using biomarkers, if available; identifying the dominant NPS; and introducing psychosocial treatment or pharmacotherapy as needed. Awareness of drug-induced neuropsychiatric symptoms, such as the impulse control disorders associated with dopamine agonist treatment of PD, is a key aspect of managing NPSs in NDDs.[29]

Psychosis

The criteria for diagnosis of psychosis in NDDs are provided in Table 1. The International Psychogeriatric Association (IPA) consensus criteria for psychosis in major and mild neurocognitive disorders build on the pioneering Jeste and Finkel[30] criteria, which require hallucinations and/or delusions to be present in patients meeting diagnostic criteria for an NDD.[21] The IPA criteria exclude people with delirium or a prior psychotic illness and require a duration of symptoms of at least 1 month. Reversible causes of psychosis, such as delirium, should be investigated and treated appropriately. Challenges include diagnosing psychosis in individuals with more severe dementia, distinguishing confabulation and memory-related errors from psychosis, and assessing psychotic symptoms in predementia states.

Common delusions include false beliefs of theft, harm, infidelity, or abandonment.[31] More systematized delusions; first-rank symptoms of schizophrenia; and delusions that people, objects, or radiation can pass through walls (delusion of partition), which are common in late-onset schizophrenia, are rare in dementia-related psychosis. Hallucinations can manifest in any sensory modality, but visual (eg, people, animals) and auditory (eg, voices) hallucinations are most common.[31] Misidentification syndromes occur and include beliefs that strangers are residing in one's home (phantom boarder syndrome), loved ones have been replaced by impostors (Capgras syndrome), images on television are real (TV sign), and the person in the mirror is not one's self.[31] Presence delusions (the delusion that someone is standing near them) and passage hallucinations (occurring at the edge of peripheral vision) can occur in NDDs.[32] Growing evidence suggests that delusions and hallucinations have differential associations with specific pathologies of NDDs. Individuals with DLB discovered on autopsy are more likely to have experienced visual hallucinations, misperceptions, misidentification delusions, and the feeling of presence.[33] Patients with FTD induced by transactive response DNA-binding protein 43 were more likely to exhibit delusions, misidentification, and paranoia compared with patients with FTD associated with tau pathology.[33] These studies suggest that specific pathologies in NDDs differentially affect circuits and transmitters, indicating that disease and syndrome-specific pharmacotherapies may be feasible.[34-37]

Delusions and hallucinations have cross-sectional frequencies of approximately 30% and 20%, respectively, in AD, most commonly occurring in the moderate and moderately severe stages of

dementia. Visual hallucinations are more common in DLB (75%) and PD dementia (50%).[32] Psychotic features are less frequent in FTD (10%). In AD, the longitudinal pattern is one of resolution and relapse, with 30% to 50% of people experiencing resolution of the psychotic symptoms within 3 months, and one-half of these individuals experiencing a relapse within 6 to 9 months.[31]

Pimavanserin is the only antipsychotic drug approved for psychosis in an NDD. It is approved for treatment of delusions and hallucinations occurring with psychosis in PD with or without dementia.[38] Pimavanserin is a selective 5-hydroxytryptamine 2A (5-HT_{2A}) inverse agonist without dopaminergic, histaminergic, or muscarinic binding. In AD, a phase 2 trial including participants in nursing homes demonstrated moderate efficacy for the delusions plus hallucinations domains of the Neuropsychiatric Inventory, with substantially larger treatment effects in people with more severe psychosis.[39] A subsequent phase 3 relapse prevention study including people with dementias of various causes demonstrated a significant 2.8-fold reduction in relapse in the pimavanserin-treated group compared with the placebo group over 6 months.[40] The benefit was greatest in PD dementia and did not reach statistical significance in AD or other dementias. Pimavanserin has a black box warning against the use of this agent for the treatment of psychosis in elderly patients with dementia and psychosis unless the psychosis is due to PD.

Atypical antipsychotics have been the main pharmacologic approach for psychosis treatment in NDDs. Modest efficacy must be balanced against the risk of adverse effects, including stroke, falls, accelerated cognitive decline, and increased mortality.[41] Two small studies indicated substantial treatment benefits with clozapine in people with PD-related psychosis[32] without significant exacerbation of extrapyramidal symptoms; an open-label follow-up from these studies suggested a possible increased mortality risk with clozapine treatment. Quetiapine is commonly used for the treatment of psychosis in NDDs, but placebo-controlled trials did not indicate a significant treatment benefit.[32] Findings from a recent meta-analysis showed antipsychotic efficacy with aripiprazole and risperidone, but tolerability of risperidone in patients with dementia was poor.[42]

Cholinesterase inhibitors reduce symptoms of psychosis in people with DLB[32]; evidence of their efficacy is less clear in PD dementia[32]; and data support modest efficacy in AD.[42] A meta-analysis revealed limited antipsychotic efficacy of memantine.[42] A previous randomized clinical trial of the muscarinic agonist xanomeline demonstrated substantial benefits in the treatment of psychosis, but tolerability was poor, with gastrointestinal adverse effects common.[43] A randomized clinical trial combining xanomeline with a peripheral muscarinic antagonist to reduce adverse effects is ongoing.

Agitation

Agitation is among the most common and troublesome NPSs in NDDs (Figure).[22] Symptoms of agitation include hitting, shoving, kicking, shouting, and actively resisting care. Families and care partners of people with NDDs rarely use the term agitation. They may describe the patient as having a short fuse, being more easily upset or angered, or exhibiting a marked change in personality. Irritability commonly precedes and accompanies agitation.[44] In AD dementia, agitation may lead to accelerated disease progression and earlier

Table 1. Diagnostic Criteria for Neuropsychiatric Syndromes Occurring in Neurodegenerative Disorders

Neuropsychiatric syndrome	Key diagnostic criteria
Agitation in cognitive impairment[22]	In the past 2 wk: Excessive motor activity Verbal aggression Physical aggression
Psychosis in major or mild neurocognitive disorder[21]	One (or more) of the following symptoms present, at least intermittently, for ≥1 mo: Visual or auditory hallucinations Delusions
Psychosis in Parkinson disease[25]	At least 1 of the following symptoms continuously present or recurrent over the past month: Illusions False sense of presence Hallucinations Delusions
Apathy in neurocognitive disorders[23]	One (or more) of the following symptom dimensions present for ≥1 mo: Diminished initiative: less spontaneous and/or active than usual self Diminished interest: less enthusiastic about usual activities Diminished emotional expressiveness or responsiveness
Depression in Alzheimer disease[26]	Three (or more) of the following symptoms present for the same 2-wk period: Depressed mood Decrease positive affect or pleasure response Disruption of appetite Disruption in sleep Psychomotor changes (agitation or retardation) Fatigue or loss of energy Feelings of worthlessness; hopelessness; or excessive, inappropriate guilt Diminished ability to think or concentrate Recurrent thoughts of death or suicidal ideation, planning, or attempt Social isolation or withdrawal Irritability
Depression in Parkinson disease[27]	Five (or more) of the following symptoms present for the same 2-wk period: Depressed mood Diminished interest or pleasure in most activities Loss or gain in weight or appetite Insomnia or hypersomnia Psychomotor agitation or retardation Fatigue or loss of energy Feelings of worthlessness or excessive or inappropriate guilt Diminished ability to think or concentrate or indecisiveness Recurrent thoughts of death, recurrent suicidal ideation, or suicide attempt or plan
Disinhibition in neurodegenerative disorders[28]	Features: Socially inappropriate behavior Loss of manners or decorum Impulsive, rash, or careless actions
Traumatic encephalopathy syndrome[24]	Features: Explosiveness Impulsivity Emotional dyscontrol Affective lability

Table 2. Treatments Commonly Used for Neuropsychiatric Syndromes in Neurodegenerative Disorders[a]

Behavior	Therapeutic class	Agents[b]	Type of supportive evidence
Psychosis	Antipsychotics	Pimavanserin (psychosis of PD)[c]	Double-blind, placebo-controlled trials
		Aripiprazole	Double-blind, placebo-controlled trials
		Risperidone	Double-blind, placebo-controlled trials
Agitation	Antipsychotics	Brexpiprazole (agitation with dementia due to AD)[c]	Double-blind, placebo-controlled trials
		Aripiprazole	Double-blind, placebo-controlled trials
		Risperidone	Double-blind, placebo-controlled trials
		Quetiapine	Mixed outcomes of double-blind, placebo-controlled trials
	Antidepressants	Citalopram	Double-blind, placebo-controlled trials
	Anticonvulsants	Carbamazepine	Double-blind, placebo-controlled trials
Apathy	Stimulants	Methylphenidate	Double-blind, placebo-controlled trials
		Modafanil	Multiple case observations
Depression	Selective serotonin reuptake inhibitors (for PD)	Paroxetine	Double-blind, placebo-controlled trials in PD
	Selective serotonin and norepinephrine reuptake inhibitors (for PD)	Venlafaxine	Double-blind, placebo-controlled trials
	Selective serotonin reuptake inhibitors and serotonin receptor modulators	Vortioxetine	Open-label clinical trial
	Dopamine agonists	Pramipexole (for PD)	Double-blind, placebo-controlled trials
	Seizure induction	ECT	Multiple case observations
Disinhibition	Antidepressants	Citalopram	Open-label clinical trial
	Anticonvulsants	Valproic acid	Case reports
	Miscellaneous	Methylphenidate	Double-blind, placebo-controlled crossover trial
		Dextromethorphan plus quinidine	Case reports

Abbreviations: AD, Alzheimer disease; ECT, electroconvulsive therapy; PD, Parkinson disease.

[a] Doses should be individualized and aligned with the approved indications for these agents. Adverse effects should be reviewed in the prescribing information prior to use.

[b] Agents with negative clinical trial results are not included in the table. The principal sources of information supporting clinical benefit are shown.

[c] Approved treatment with indication.

death.[45] Agitation is associated with an increased risk of hospitalization[46] and earlier admission to long-term care facilities[47] and substantially lowers the quality of life of patients and their families and care partners.

The prevalence of agitation in NDDs has been best studied in AD dementia. Sixty percent of patients with AD dementia may experience agitation, which can occur at any stage of the disease but becomes more common with disease progression and more severe cognitive decline.[48,49]

Clinical management algorithms provide step-by-step approaches to differential diagnosis of etiologies of agitation, including delirium, pain or discomfort, depression, psychosis, and environmental and psychosocial stressors.[14,15] The algorithms emphasize implementation of trials of psychosocial interventions prior to use of pharmacologic treatments in nonurgent situations. Optimizing dementia treatment with cognition-enhancing agents, such as cholinesterase inhibitors or memantine, may reduce agitation.[50,51]

Pharmacotherapies are used when psychosocial approaches have failed or when acute agitated or aggressive behaviors pose a danger to the patient or others (**Table 2**). Recently, the FDA approved brexpiprazole for the treatment of agitation associated with AD dementia. Brexpiprazole is the first FDA-approved treatment option for this indication in AD or any NDD. It was approved based on positive results from two 12-week-long randomized, placebo-controlled studies in patients with AD who met IPA criteria for clinically significant agitation unresponsive to psychosocial strategies. Brexpiprazole, at a dose of 2 or 3 mg/d (slowly titrated from 0.5 mg/d to 1-2 mg/d over 2 weeks), achieved statistically significant agitation reduction compared with placebo as measured by the Cohen-Mansfield Agitation Inventory (the primary efficacy measure) and the Clinical Global Impression of Severity. Brexpiprazole was well tolerated with similar discontinuation rates due to adverse events with active treatment or placebo.[52,53] Brexpiprazole prescribing information includes a black box warning that it is not indicated for dementia-related psychosis and that antipsychotics are associated with an increased risk of death in older individuals exhibiting dementia-related psychosis. Brexpiprazole is not indicated for as-needed use for agitation in dementia.[54]

The most used drugs for agitation have been the atypical antipsychotics, especially sedating agents such as quetiapine and olanzapine (Table 2). Practice guidelines cite small but statistically significant beneficial effects on agitation in dementias with atypical antipsychotics, but due to safety concerns, guidelines recommend the use of antipsychotics for agitation in dementia only when symptoms are severe, cause significant distress, and/or pose a danger to the patient or others.[55]

Benzodiazepines have been used to treat agitation, but these agents are inappropriate for use in older adults due to their adverse effects on cognition, balance, and risk of falls.[56] The selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram has shown agitation-reducing efficacy in a large placebo-controlled trial.[57] The effective dose of citalopram was 30 mg/d, which is higher than the 20 mg/d dose recommended by the FDA for patients older than 60 years because of an increased risk of cardiac QTc prolongation and potentially life-threatening arrhythmias. A follow-up study of escitalopram is being conducted.[58] Development of agitation-reducing pharmacotherapies is currently the most active area of clinical trials for NPSs in NDDs, with trials being conducted for α^2 adrenoreceptor agonists, dextromethorphan plus CYP2D6 inhibitors, endocannabinoids, dual orexin antagonists, 5-HT_6 receptor agonists, SSRIs, anticonvulsants, and atypical antipsychotics.[59]

Depression

Mood symptoms, including clinically significant depression or major depressive disorder (MDD), are common in NDDs (Figure). Anxiety symptoms may accompany the mood disorder, amplifying patient disability. The prevalence of MDD varies among the dementias. Approximately 40% of patients with AD dementia have depression sometime during the course of the disease, with unrecognized, untreated depression leading to accelerated cognitive decline, increased mortality, and suicide risk.[60] Depression may be an early marker and risk factor for AD.[61] Other NDDs may have even higher rates of mood symptoms, and depression occurs in up to 80% of patients with Lewy body disorders (PD, DLB, and multiple system atrophy).[62] The diagnosis of depression in NDDs is often challenging since signs and symptoms may be masked by medical comorbidities, and symptoms of depression may overlap with those of dementia, apathy, and cognition-related reduction of activity. In the dementias, patients may not be able to describe mood symptoms due to cognitive impairment and diminished self-awareness. Clues to the existence of depression in dementias, such as AD, include sudden, unexplained progression of disease, weight loss, or sleep disturbance. The 9-item Patient Health Questionnaire is helpful in detecting and quantifying mood and depression symptoms in NDDs.[63] The clinical interview with care partner and family input is vital to eliciting the core features of depression.[64]

Once a diagnosis of clinically significant depression in a patient with an NDD is made and potentially reversible or contributory factors have been excluded, a biopsychosocial-environmental treatment plan is developed. The plan begins by addressing psychological and environmental stressors. Psychotherapy, particularly cognitive behavior therapy, may be useful in NDDs if cognitive impairment and depression are mild.[65] Interpersonal therapy, counseling, or multimodal interventions have been shown to provide benefit in preliminary studies.[66]

There are no drugs approved by the FDA for the treatment of depression in any NDD, and there are few double-blind, placebo-controlled trials in NDDs to provide evidence-based guidance for treatment. There is preliminary evidence suggesting that an elevated brain amyloid burden may predict a poor response to antidepressant pharmacotherapy in older adults with MDD, suggesting that AD pathology may confer treatment resistance.[67] Pharmacotherapy choices are based on experience with responses in older individuals and idiopathic MDD (Table 2). Pharmacotherapeutic considerations focus on the SSRIs and selective serotonergic and noradrenergic reuptake inhibitors with well-known adverse effect profiles. For severe, psychotic, or life-threatening depression, electroconvulsive therapy is safe and effective.[68]

Apathy

The criteria for the diagnosis of apathy in neurocognitive disorders are shown in Table 1.[23] Apathy is a common symptom in dementia, with increased prevalence as dementia severity increases (Figure).[69] Apathy is found in 24% to 85% of patients with AD dementia, 50% to 100% with FTD, 52% to 76% with HD, 20% to 92% with PSP, 17% to 70% with PD, 35% to 100% with DLB, and 43% to 89% with vascular dementia.[69] The wide variation in the reported prevalence may reflect the different populations assessed and the varying tools used to detect and characterize apathy.

Apathy is associated with negative outcomes in NDDs. There is a 2-fold higher risk of progression from mild cognitive impairment to dementia in patients with apathy compared with those without symptoms of apathy[70] and a 3-fold increase in short-term mortality.[71] Correlates of apathy include increased caregiver distress, higher risk of frailty, greater cost of informal and formal care, and poorer treatment responses.[70,72]

Dysfunction of frontal-subcortical circuits is the common correlate of apathy in NDDs.[73] Patients with apathy have reductions in gray matter in the medial frontal and prefrontal cortices and reduced white matter and greater white matter hyperintensities in the frontal lobes.[74] Patients with both AD and apathy exhibit lower metabolic activity with ^{18}F-fluorodeoxyglucose positron emission tomography in the anterior cingulate and medial orbitofrontal regions bilaterally compared with patients with AD dementia without apathy. Apathy in AD has been linked to frontal lobe neurofibrillary tangle burden and, less consistently, with amyloid plaque deposition on amyloid positron emission tomography.[74]

There are no approved treatments for apathy in NDDs. Moderate-quality evidence supports psychosocial interventions for apathy in NDDs, with music and physical activity showing the most consistent results.[69,75] Randomized placebo-controlled trials have focused on apathy in dementia associated with AD, with fewer studies in other NDDs. Noninvasive brain stimulation, particularly transcranial direct stimulation and repetitive transcranial magnetic stimulation, has been tested for the treatment of apathy in NDDs, with preliminary positive results.[69,72] Clinical trials of methylphenidate for apathy in AD dementia have shown positive outcomes.[76,77] Data for the effect of modafinil on apathy are inconclusive.[69,72] Nonpsychostimulant pharmacologic interventions may also provide positive outcomes for apathy; a meta-analysis suggested that cholinesterase inhibitors may be of modest therapeutic value for the treatment of apathy in NDDs.[78]

Disinhibition

Disinhibition is characteristic of the behavioral variant FTD (bvFTD) and occurs in a variety of other NDDs, including PSP, AD, and HD

(Figure).[79] Disinhibition is characterized by socially inappropriate behavior that violates social norms, including approaching or touching strangers or committing improper sexual acts. There is a loss of decorum, including inappropriate laughter, cursing, speaking loudly, telling offensive jokes, making crude or sexually explicit remarks, or sharing personal information. Patients may drive recklessly, shoplift, steal, buy goods, or sell possessions without regard for consequences.[28]

In a recent comparative study of individuals with clinically diagnosed dementia, disinhibition was most common in those with bvFTD (42.3%) compared with AD (30.7%), DLB (26.3%), and PD (22.3%).[44] Patients with bvFTD were more likely to have more severe disinhibition than was evident in other dementia types. Behavioral variant FTD can co-occur with amyotrophic lateral sclerosis, with disinhibition as one manifestation of the behavioral disorder.[80] Some forms of bvFTD, such as those due to the microtubule-associated protein tau variants, have particularly high frequencies of disinhibition, ranging from 80% to 100%.[81] Where longitudinal data are available, patients with bvFTD show increasing severity of disinhibition during the illness.[81] Patients with HD often exhibit irritability and impulsive behavior.[82] Similarly, TES (the clinical syndrome associated with chronic traumatic encephalopathy) is manifested by neurobehavioral dysregulation with outbursts of rage, impulsive behavior, and affective lability that shares features with the disinhibition of bvFTD.[24] Convergent evidence indicates that orbitofrontal dysfunction is the common shared anatomic substrate across NDDs with disinhibition.[83]

There are no approved treatments for disinhibition in NDDs. Three general pharmacologic classes have dominated the treatment of disinhibition, including SSRIs, atypical antipsychotics, and antiepileptic or mood stabilizing agents (Table 2).[84] None of these agents are specific to disinhibition; clinical observations of response of the disinhibition syndrome in concert with treatment of mood abnormalities, psychosis, or agitation guide their use. Paradoxically, stimulants have been shown in some studies to reduce disinhibition in bvFTD.[84] The combination of dextromethorphan and quinidine is approved for the treatment of pseudobulbar affect and has been observed to suppress disinhibited behaviors beyond those of affective lability.[85] The evidence base for choosing an agent for the treatment of disinhibition is limited, and the clinician may approach therapy sequentially from most likely to succeed to less predictably successful based on the quality of the available evidence (Table 2). Adverse effects should be carefully monitored, doses optimized for the syndromic response, and treatment durations abbreviated to the extent possible.

Discussion

There have been advances in the pharmacotherapy of NPSs in NDDs. Although there are few approved drugs and a limited number of controlled clinical trials on which to base evidence-informed recommendations, substantial progress has been made in developing drugs now approved for NPSs in NDDs. Approval of pimavanserin for the treatment of hallucinations and delusions associated with PD psychosis and of brexpiprazole for the treatment of agitation associated with AD dementia has established regulatory precedent, illustrated successful clinical trial designs, demonstrated useful outcome measures and analytic strategies, and encouraged development of treatments for a wider array of NPSs in more types of NDDs.[38,86] There is a low rate of inclusion of members of underrepresented groups in trials (ethnic, racial, geographic, gender, and socioeconomic), and generalization to patients from populations not represented in trials must be done with caution.[87]

Disease-modifying therapies have been introduced for treatment of AD and have been shown to slow disease progression by approximately 30%.[88] With reduced AD pathology, decreased emergence or improvement of NPSs may be observed as demonstrated in studies of aducanumab.[89] Disease-modifying treatments may change the treatment landscape for NPSs in NDDs.

There are critical gaps and controversies in the field of therapeutic development for NPSs in NDDs. The black box warnings associated with both brexpiprazole and pimavanserin discourage the use of these drugs. Many treatments take several weeks to provide relief from the symptoms, and complete remission of symptoms with treatment is rare. The magnitude of improvement may be less than desired. Pharmacokinetic, pharmacodynamic, and safety improvements are needed for optimal pharmacologic management of NPSs in NDDs.

Progress in establishing research criteria for the diagnosis of an NPS in NDDs and related prodromal states is critical to advancing clinical trials and appropriate use of pharmacotherapy in clinical care. Research diagnostic criteria are available for psychosis, agitation, apathy, depression, and disinhibition in NDDs.[21-23] Psychiatric syndromes have been included in the research diagnostic criteria for several of the NDDs, including AD, FTD, PSP, corticobasal degeneration, DLB, TES, and HD.[2] Evolving precision in the diagnosis of NDDs with biomarkers and improved definitions of NPSs in NDDs may facilitate recruitment of accurately diagnosed trial participants and application of treatment to appropriate patients when new therapies are approved and implemented in clinical care.

The pathobiology of NDDs is increasingly well understood, including the pathophysiologic basis of NPSs in NDDs. Structural and functional imaging, genetic studies, molecular imaging, fluid biomarkers, and autopsy investigations provide the foundation for increased accuracy in the diagnosis of NDDs. Advances in pharmacogenomics, clinical trial design and analysis, and clinical and biomarker outcome assessments are leading to improved translational neuropharmacology.

Clinicians must respond to the needs of their patients regardless of the limitations of the evidence-based guidance available. A minority of NPSs for NDDs have a specific FDA-approved indication; most prescribing is off label based on available clinical observations, clinical trials, expert guidance, and extrapolation from similar clinical conditions that have responded to treatment. Advances in neuropsychiatric drug discovery and development strategies promise to deliver new therapies for a wider range of NPSs in NDDs.

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