Chapter 23
Assessment and Management of Psychiatric Symptoms in Neurodegenerative Disorders

Kasia Gustaw Rothenberg

Clinical Pearls

- Neuropsychiatric symptoms (NPS) (apathy, irritability, agitation, depression, delusions, hallucinations, anxiety, disinhibition, aberrant motor behavior, sleep disturbances, appetite and eating abnormalities) can manifest themselves at all stages of neurodegenerative disorders (NDD). NPS often cluster, tend to be persistent, are associated with excess morbidity and mortality, and contribute to patients' distress and caregiver burden.
- Currently, there are no FDA-approved medications for the treatment of NPS with the exception of pimavanserin approved for the treatment of delusions and hallucinations in Parkinson's disease.
- Cholinesterase inhibitors (ChEIs) may reduce the emergence of NPS and have a role in their treatment.
- Although used "off label", a large number of antidepressants, mood stabilizers, typical and atypical antipsychotics are prescribed for NPS. An ongoing assessment of benefit versus harm should continue throughout the course of treatment with periodic consideration of withdrawing the medication.

Introduction

Behavioral and psychological symptoms of dementia (BPSD) also termed neuropsychiatric symptoms (NPS) commonly accompany neurodegenerative diseases (NDD) [1]. Cardinal psychiatric symptoms such as depression, apathy, psychosis or agitation complicate the clinical presentation of Alzheimer's disease (AD) and

K.G. Rothenberg, M.D., Ph.D.
Cleveland Clinic Lou Ruvo Center for Brain Health,
9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: rothenk@ccf.org

B. Tousi, J. Cummings (eds.), *Neuro-Geriatrics*,
DOI 10.1007/978-3-319-56484-5_23

Parkinson's diseases (PD) and some are considered core symptoms of frontotemporal dementia and dementia with Lewy bodies (DLB). NPS are near universal among patients with NDD, thus almost all patients with AD experience at least one of them during the course of their illness [2]. NPS are usually assessed by comprehensive psychiatric evaluation but more structured tools like the Neuropsychiatric Inventory (NPI) commonly used in the setting of trials can be of help in clinical practice [1]. The group of common and debilitating NPS include: apathy, irritability, agitation, depression, delusions, hallucinations, anxiety, disinhibition, aberrant motor behavior, sleep disturbances, appetite and eating abnormalities [1, 2]. NPS can manifest themselves at all stages of NDD (especially when a dementia syndrome is present), often cluster, tend to be persistent, are associated with excess morbidity and mortality contribute to patients' distress and caregiver burden. NPS are linked to increased healthcare use, costs, and institutionalization [3, 4].

The neurobiology of NPS is extremely complex. Dysfunction in frontal-subcortical and cortico-cortical networks was proposed as a model of NPS [5]. Dysfunction in ascending monoaminergic systems involving serotonin, norepinephrine and dopamine, glutamate-mediated excitatory neurotoxicity, tau-mediated pathology, and inflammation may play a role in the occurrence of NPS in NDD [6–8].

Despite the significant burden of these symptoms, there are few recommended, evidence-based treatments including pharmaceuticals [4, 9]. Pharmacotherapy in the geriatric population in general is challenging due to age-associated changes in pharmacodynamics and pharmacokinetics as well as high rates of medical comorbidities and use of concomitant medications, which increases risk for polypharmacy, drug-drug interactions, and adverse drug effects [9]. Additionally, there are risks attributed to use of antipsychotics, antidepressants, anxiolytics and/or mood stabilizers in elderly, and specific risks to patients with dementia [4]. Psychotropics, especially antipsychotic medications, may alleviate certain NPS, but may have severe adverse effects including increased risk of involuntary movements, cerebrovascular events, falls, and death [9].

AD treatments like cholinesterase inhibitors (ChEIs) may reduce the emergence of NPS and have a role in their treatment. These agents may delay initiation of, or reduce the need for other drugs such as antipsychotics thus ChEIs should be initiated, optimized and maintained for the management of both cognitive symptoms as well as NPS [7].

Currently, there are no FDA-approved medications for the treatment of NPS in NDD with the exception of pimavanserin which was recently approved for the treatment of psychosis in the course of PD [10]. Although used "off label", a large number of antidepressants, mood stabilizers, typical and atypical antipsychotics are prescribed for behavioral disturbances in persons with NDD [4, 11].

Parallel to robust efforts in pharmacological trials there is an ongoing need to assess and verify existing, as well as create new nonpharmacologic behavioral strategies. Cohen-Mansfield [12] conceptualizes behavioral disorders in the course of NDD as representing unmet personal needs such as pain and other somatic discomfort, and need for social contact. Those needs should be recognized and addressed

by nonpharmacologic interventions. Therapeutic approaches should be individually tailored to each patient with NPS using behavioral management techniques, caregiver education and support, problem solving and communication skills training, music therapy, aromatherapy, and modified cognitive-behavioral and interpersonal therapies.

With few exceptions initiating pharmacotherapy should occur only after eliminating underlying medical or environmental factors and should be limited to cases where nonpharmacologic measures have failed [11, 12]. All patients should be carefully monitored for development of adverse events and side effects during a time-limited treatment course; symptoms often resolve over time regardless of medication use [11]. An ongoing assessment of benefit versus harm should continue throughout the course of treatment with periodic consideration of withdrawing the medication [4, 13].

This chapter addresses NPS in AD and PD. The principles are applicable to other NDD where supporting data are less well-developed.

Depression of Alzheimer's Disease

Depression of AD concept was defined as a depressive syndrome with prominent decreased affect, irritability, agitation, and anxiety, diminished attention and fatigue but less evidence of guilt and suicidality than major depressive episode [14]. Depression of AD is relatively common (affecting up to 50% of persons with AD) and persistent. More than 50% of untreated depressed patients with AD remaining depressed at 1-year follow-up [14]. A National Institute of Mental Health Work Group developed diagnostic criteria for depression of AD (NIMH-dAD) (Table 23.1) which were derived from DSM-IV criteria for major depression, with some adjustment. The number of symptoms required for a diagnosis of depression was decreased as well as duration and frequency of depressive symptoms. The decreased ability to think and concentrate was eliminated. The criteria for anhedonia were modified to focus on decreased affect and pleasure associated with social and other activities. Social isolation/withdrawal and irritability were added as new symptoms [15].

Despite the widespread antidepressant use (almost 50% of patients with dementia are on antidepressants) there is mixed evidence regarding the benefits for depressed AD patients. Use of antidepressants in AD and other NDD is based on rules developed for major depressive disorder pending better evidence for depression of Alzheimer's disease.

Cholinesterase inhibitors studies provide some evidence of benefit in improving mood. Among the NPS in AD apathy and depression (followed by aberrant motor behavior) are the ones to improve [16, 17]. Donepezil reduces behavioral symptoms, particularly mood disturbances and delusions, in patients with AD [7]. A withdrawal study by Holmes et al. [17] provided additional evidence to support the use of donepezil in the treatment of NPS (including depression) in patients with mild to moderate AD with marked NPS. Discontinuation of donepezil corresponded

Table 23.1 Criteria for depression of Alzheimer's disease

Three (or more) of the following symptoms must be present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms must either be (1) depressed mood or (2) decreased positive affect or pleasure
1. Clinically significant depressed mood
2. Decreased positive affect or pleasure in response to social contacts and usual activities
3. Social isolation or withdrawal
4. Disruption in appetite
5. Disruption in sleep
6. Psychomotor changes
7. Irritability
8. Fatigue or loss of energy
9. Feelings of worthlessness, hopelessness, or excessive or inappropriate guilt
10. Recurrent thoughts of death, suicidal ideation, plan or attempt
B. All criteria are met for Dementia of the Alzheimer Type (DSM-IV)
C. The symptoms cause clinically significant distress or disruption in functioning
D. The symptoms do not occur exclusively in the course of delirium
E. The symptoms are not due to the direct physiological effects of a substance
F. The symptoms are not better accounted for by other conditions such as major depressive disorder, bipolar disorder, bereavement, schizophrenia, schizoaffective disorder, psychosis of Alzheimer disease, anxiety disorders, or substance-related disorders

Adapted from: Teng E, Ringman JM, Ross LK, Mulnard RA, Dick MB, Bartzokis G, Davies HD, Galasko D, Hewett L, Mungas D, Reed BR, Schneider LS, Segal-Gidan F, Yaffe K, Cummings JL; Alzheimer's Disease Research Centers of California-Depression in Alzheimer's Disease Investigators. Diagnosing depression in Alzheimer disease with the national institute of mental health provisional criteria. Am J Geriatr Psychiatry 2008 Jun;16(6):469–77

with worsening of NPS and increased in caregiver distress as compared with those who remained on the treatment. Optimization as well as maintenance treatment with ChEIs should be considered as an important step in the management of depression of AD.

As for antidepressants the American Psychiatric Association (APA) recommends their use in persistent depression in patients with dementia. Selective serotonin reuptake inhibitors (SSRIs) are preferred because of their favorable safety profile [18]. Sertraline, citalopram or escitalopram in low doses are the most appropriate first-line agents (Fig. 23.1). The dose can be increased weekly, if tolerated, to a maximum of 150 mg of sertraline or 40 mg of citalopram per day with close monitoring of side effects. Although improvement should occur within 4–6 weeks at the target dose, a longer period may be required for full effect. Other SSRIs like fluoxetine and paroxetine are not recommended as a first-line due to debatable efficacy and unfavorable (mostly anticholinergic) effects [19]. If patients do not respond to SSRI, switching to a different agent or augmenting a treatment with second agent may be considered. Especially for patients who have psychotic symptoms or

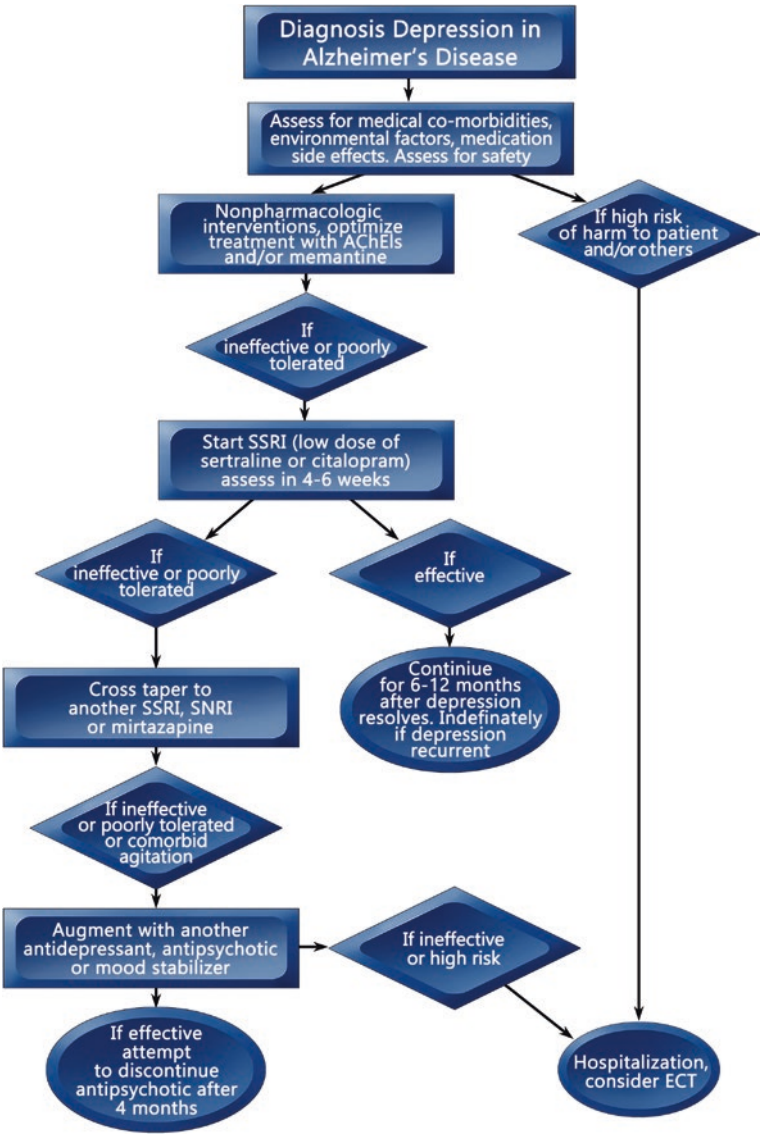

Fig. 23.1 Treatment of depression in Alzheimer's disease

agitation along with depression, an atypical antipsychotic in a small dose might be considered [4, 20, 21]. An anticonvulsant in smaller doses (the best evidence is for carbamazepine) might be considered as additional therapy to an antidepressant if there is moderate or severe agitation [22]. Switching to an antidepressant of a

different class (as opposed to augmentation) is recommended in cases of severe side effects induced by initial medication. Preferred second-line agents are selective norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine or duloxetine, or antidepressants with a mixed pharmacology (mirtazapine, bupropion). Tricyclic antidepressants are not recommended due to lack of convincing evidence and the occurrence of side effects including anticholinergic complications. Psychiatric hospitalization should be considered an option in severe cases.

For patients with severe, refractory depression, electroconvulsive therapy (ECT) might be considered, especially if there is risk of self-harm or harm to others [19]. There is evidence for ECT as an effective and well-tolerated option for treating depression in people with dementia [23].

Therapeutic interventions are being recognized as a valuable treatment modality as well. Interpersonal psychotherapy (IPT) modified to address the needs of older adults with mild cognitive deficits (IPT-CI) [24], cognitive-behavioral therapy (CBT) adapted for depressed older adults with mild stages of dementia [25], home delivered problem adaptation therapy (PATH), or problem solving skills and caregiver training [26] were proved to be beneficial.

Apathy of Alzheimer's Disease

Apathy, often assessed concomitantly with mood symptoms, should be rather considered a disorder of motivation. Conceptualized as diminished goal-directed activity in the domains of behavior, cognition and emotion, apathy is considered one of the most common NPS in AD with a 5-year prevalence of 71%. It can cluster with other NPS and is associated with higher costs and burden of care [2, 27]. Apathy criteria are available (Table 23.2). Diminished motivation in comparison to the patient's previous level of functioning should be noted. Diminished motivation should be observable most of the time for a period of at least 4 weeks and accompanied by additional symptoms like loss or diminished goal-directed behavior or/and cognitive activity or/and emotion. Symptoms should cause clinically significant impairment in personal, social, occupational, or other important areas of functioning and cannot be exclusively explained by physical and/or motor disabilities, diminished level of consciousness or the direct physiological effects of a substance [28]. The approach to management of apathy is illustrated in Fig. 23.2.

Growing evidence suggests that apathy in AD is a manifestation of dysfunction of dopaminergic circuits between the basal ganglia, anterior cingulate, and other frontal cortex structures involved in motivation and reward.

ChEIs may improve symptoms of apathy in AD [16], and symptoms may worsen after discontinuation of ChEIs [17]. Optimization and maintenance treatment with ChEIs is a crucial step in the management of apathy of AD.

Table 23.2 Criteria for apathy in neurodegenerative disorders

A: Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others
B: Presence of at least one symptom in at least two of the three following domains for a period of at least 4 weeks and present most of the time
Domain B1—Behaviour: Loss of, or diminished, goal-directed behavior as evidenced by at least one of the following:
Initiation symptom: loss of self-initiated behavior (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)
Responsiveness symptom: loss of environment-stimulated behavior (for example: responding to conversation, participating in social activities)
Domain B2—Cognition: Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:
Initiation symptom: loss of spontaneous ideas and curiosity for routine and new events (i.e., challenging tasks, recent news, social opportunities, personal/family and social affairs)
Responsiveness symptom: loss of environment-stimulated ideas and curiosity for routine and new events (i.e., in the person's residence, neighbourhood or community)
Domain B3—Emotion: Loss of, or diminished, emotion as evidenced by at least one of the following:
Initiation symptom: loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect)
Responsiveness symptom: loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)
C: These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning
D: The symptoms (A–B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication)

Adapted from: Mulin E, Leone E, Dujardin K, Delliaux M, Leentjens A, Nobili F, Dessi B, Tible O, Agüera-Ortiz L, Osorio RS, Yessavage J, Dachevsky D, Verhey FR, Cruz Jentoft AJ, Blanc O, Llorca PM, Robert PH. Diagnostic criteria for apathy in clinical practice. Int J Geriatr Psychiatry 2011 Feb; 26(2):158–65

Psychostimulants including methylphenidate and modafinil have been used to treat apathy in AD. Methylphenidate acts by blocking the dopamine transporter and norepinephrine transporter, leading to increased concentrations of dopamine and norepinephrine within the synaptic cleft. Methylphenidate (but not modafinil) proved to be effective in reducing apathy in AD in a small cross over trial and larger, multicenter, double-blind controlled trial for Alzheimer's Disease Methylphenidate Trial (ADMET) [29].

In ADMET, methylphenidate (20 mg daily for 6 weeks) was associated with a significant reduction in apathy symptoms. Adverse events and side effects were modest. Methylphenidate treatment may have clinical utility in treating apathy of AD.

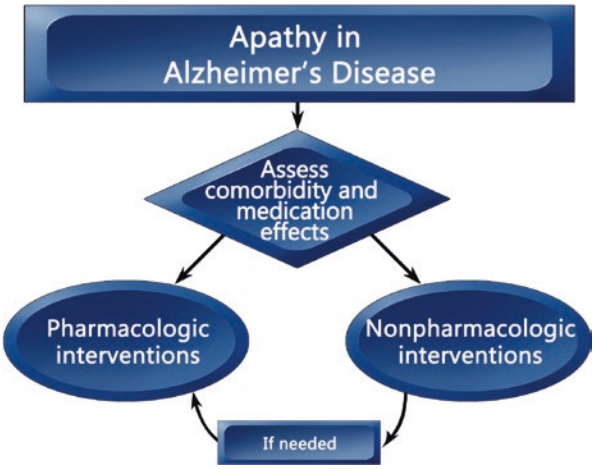

Fig. 23.2 Approach to management of apathy

Psychosis of Alzheimer's Disease

Estimates of the incidence of psychosis in AD range widely from 10 to 75%. (Table 23.3) provides the diagnostic criteria for psychosis of AD. The common psychotic symptoms are delusions and hallucinations followed by misidentification phenomena. Hallucinations are predominantly visual. Auditory phenomena especially of a schizophrenic quality are rare in AD [30]. Delusions in the course of AD are typically paranoid, non-bizarre, and simple. Delusions tend to recur or persist for several years in AD patients. Vivid hallucinations and delusions tend to diminish in intensity in the course of cognitive decline with reduced insight and decreasing ability for verbal expression [30].

Patients with delusions are significantly older, with more advanced age at onset and cognitive impairment, a more severe stage of dementia, and tend to be more depressed than AD patients with no delusional symptoms. Delusional patients showed a higher grade of disability in basic and instrumental activities of daily living [31].

Psychosis of AD is believed to be the result of dysfunction of frontal lobe circuitry with contributions from neurofibrillary tangles in limbic structures as well as neurochemical abnormalities including the cholinergic deficit and dopaminergic dysfunctions. Delusions cluster with hallucinations, agitation/aggression, depression mood, apathy, irritability, aberrant motor activity, sleep disturbances, and eating disorders. More severe cognitive impairment and faster rate of cognitive decline are associated with and predictive of hallucinations and delusions in patients with AD. Parkinsonism is concerned as predictive symptom of imminent psychotic symptoms in AD.

ChEIs may reduce or/and postpone the need for the psychotropics. In a few studies, donepezil reduced delusions, hallucinations and agitation in the majority of subjects.

Memantine appears to provide modest benefit for the management of AD psychosis and has a favorable safety profile. In a pooled, retrospective analysis of data from three placebo-controlled trials in moderate to severe AD, memantine was linked to significant reduction in psychosis, agitation, and aggression [32].

Table 23.3 Diagnostic criteria for psychosis of AD [30]

(a) Characteristic Symptoms
Presence of one (or more) of the following symptoms:
1. Visual or auditory hallucinations
2. Delusions
(b) *Primary Diagnosis*
All the criteria for dementia of the Alzheimer type are met[a]
(c) *Chronology of the onset of symptoms of psychosis vs. onset of symptoms of dementia*
There is evidence from the history that the symptoms in Criterion A have not been present continuously since prior to the onset of the symptoms of dementia
(d) *Duration and Severity*
The symptom(s) in Criterion A have been present, at least intermittently, for 1 month or longer. Symptoms are severe enough to cause some disruption in patients' and/or others' functioning
(e) *Exclusion of schizophrenia and related psychotic disorders*
Criteria for Schizophrenia, Schizoaffective Disorder, Delusional Disorder, or Mood Disorder With Psychotic Features have never been met
(f) *Relationship to delirium*
The disturbance does not occur exclusively during the course of a delirium
(g) *Exclusion of other causes of psychotic symptoms*
The disturbance is not better accounted for by another general-medical condition or direct physiological effects of a substance (e.g., a drug of abuse, a medication)
Associated features: (*Specify* if associated)
With Agitation: when there is evidence, from history or examination, of prominent agitation with or without physical or verbal aggression
With Negative Symptoms: when prominent negative symptoms, such as apathy, affective flattening, avolition, or motor retardation, are present
With Depression: when prominent depressive symptoms, such as depressed mood, insomnia or hypersomnia, feelings of worthlessness or excessive or inappropriate guilt, or recurrent thoughts of death, are present

[a]Note: For other dementias, such as vascular dementia, Criterion B will need to be modified appropriately

In patients with more severe psychotic symptoms which do not respond to ChEIs or/and memantine, antipsychotic medications are used. Olanzapine (up to 10 mg daily) has shown benefit in managing delusions and hallucinations, anxiety and agitation in AD patients [33]. Aripiprazole (5–10 mg/day) was efficacious and relatively safe for psychosis associated with AD, significantly improving psychotic symptoms and agitation [34]. Risperidone (mean doses of 1.5 mg daily) treatment proved efficacious for psychosis of AD in several studies [20, 35].

Quetiapine is commonly used for off-label indications such as NPS of AD. It is believed to have a lower incidence of serious side effects such as extrapyramidal symptoms and tardive dyskinesia when compared with other antipsychotics. Quetiapine can be used in a wide range of doses. Sedating properties are of some use in certain clinical situations in NDD [36]. Results may vary across studies but most show modest benefit for psychosis and agitation with an acceptable side effect profile (Fig. 23.3).

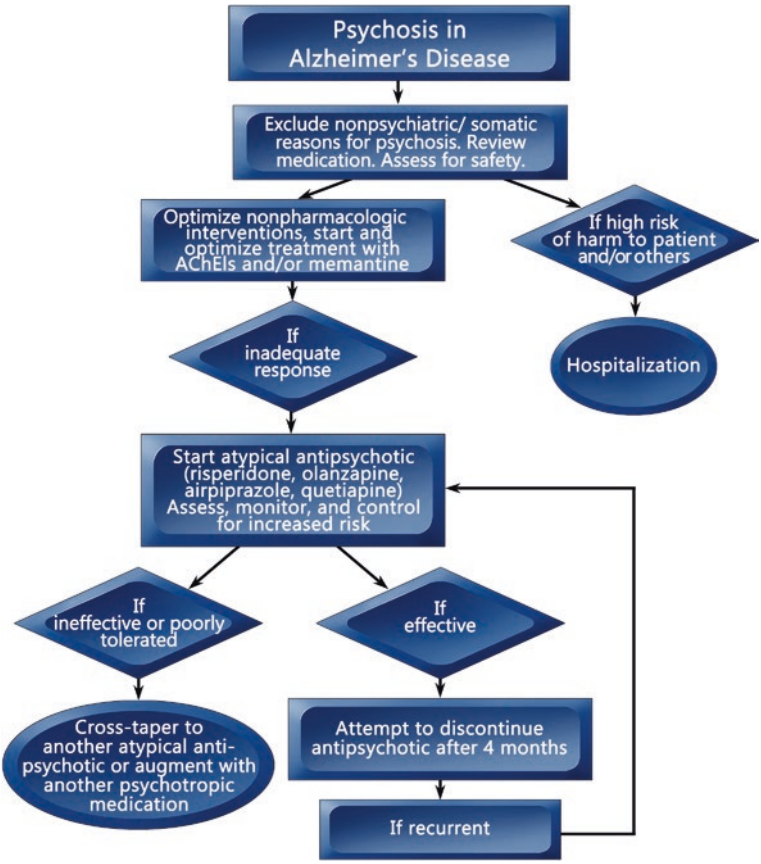

Fig. 23.3 Treatment of psychosis in Alzheimer's disease

Next generation atypical antipsychotics such as pimavanserin—approved for treatment of delusions and hallucinations in PD [10]—may be useful for treatment of psychosis of AD.

Atypical antipsychotics appear to have some impact in reducing psychosis as well as agitation in AD with the best evidence to support risperidone use. Carefully monitored and relative brief courses of antipsychotics are recommended.

Agitation in the Course of AD

Agitation as a symptom of AD is common (prevalence ranges from 20 to 60%) and highly disruptive. Agitation commonly clusters with aggressive behavior and tends to co-occur with sleep disorders, delusions, hallucinations, anxiety and dysphoria [12, 37].

Table 23.4 provides the International Psychogeriatric Association (IPA) criteria for the definition of agitation in cognitive impairment [38].

Table 23.4 International Psychogeriatric Association definition of agitation in cognitive impairment

A. The patient meets criteria for a cognitive impairment or dementia syndrome (e.g. AD, FTD, DLB, vascular dementia, other dementias, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment or other cognitive disorder)
B. The patient exhibits at least one of the following behaviors that are associated with observed or inferred evidence of emotional distress (e.g. rapid changes in mood, irritability, outbursts). The behavior has been persistent or frequently recurrent for a minimum of 2 weeks' and represents a change from the patient's usual behavior
(a) Excessive motor activity (examples include: pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms)
(b) Verbal aggression (e.g. yelling, speaking in an excessively loud voice, using profanity, screaming, shouting)
(c) Physical aggression (e.g. grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things, and destroying property)
C. Behaviors are severe enough to produce excess disability, which in the clinician's opinion is beyond that due to the cognitive impairment and including at least one of the following:
(a) Significant impairment in interpersonal relationships
(b) Significant impairment in other aspects of social functioning
(c) Significant impairment in ability to perform or participate in daily living activities
D. While co-morbid conditions may be present, the agitation is not attributable solely to another psychiatric disorder, suboptimal care conditions, medical condition, or the physiological effects of a substance

Adapted from: Cummings J, Mintzer J, Brodaty H, Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. Int Psychogeriatr 2015; 27:7–17

Frontal-subcortical and cortico-cortical network dysfunction is proposed as of the basis for the agitation syndrome [8].

The symptom of agitation may be caused by pain or any other discomfort, medical comorbidities, environmental factors or drug effects. The optimal approach to treating agitation in AD requires assessing the medical circumstances with careful verification of medications. This step should be followed by thorough assessment of symptom severity, cognitive function, and co-occurrence of other NPS. Additionally individual vulnerability to adverse effects of pharmaceuticals should be considered.

Nonpharmacologic, behavioral interventions are crucial in the management of agitation in AD and are considered first-line treatments. Meta-analyses of various behavioral approaches found that behavior management therapies, care by specific types of caregiver in residential care, and staff education had the most lasting benefits. Music therapy and sensory stimulation had positive but only short-lived effects [39].

When psychosocial approaches are inadequate, antipsychotics, antidepressants, anticonvulsants, and other classes of drugs are utilized.

ChEIs studies provide only modest evidence to support benefit from their use in managing agitation [16]. In clinical practice, ChEIs are not helpful when immediate intervention is required [8]. A study comparing galantamine with risperidone, showed that the levels of agitation decreased in both treatment groups, but the improvement was significantly greater in the risperidone group [40].

Memantine provides modest benefit in the treatment of agitation and aggression in dementia and is well tolerated. In pooled, retrospective analyses of data from three placebo-controlled trials in moderate to severe AD, memantine showed significant reduction in agitation, as well as aggression or psychosis [32].

Atypical antipsychotics are commonly used off label despite modest clinical benefits, side-effect burden and risk of mortality. Atypical antipsychotic were more beneficial than placebo and were associated with decreases in caregiver burden but adverse effects limit their overall effectiveness [41].

There is some evidence to support the use of typical antipsychotics to manage aggression and agitation in the acute clinical setting. Haloperidol is useful in treatment of aggression with agitation [42]. The use of typical antipsychotics in NDD even in acute situations is considered high risk. Typical antipsychotics are not recommended in non-emergent treatment of agitation in dementia [43].

Experts recommend that risperidone, olanzapine and aripiprazole be used for severe agitation, aggression and psychosis associated with AD where there is risk of harm to the patient and/or others [13]. The potential benefit of all antipsychotics must be weighed against the significant risks, such as cerebrovascular adverse events and mortality.

A metaanalysis of four large placebo-controlled clinical trials supported risperidone's efficacy in the management of agitation and aggression even in severely impaired AD patients [35]. Risperidone may be considered as an option for short term intervention in cases of acute, treatment-resistant agitation in AD.

If there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic drug, the medication should be tapered and withdrawn. In cases of adequate response an attempt to taper and withdraw the drug should be made within 4 months of initiation, unless the patient experienced a recurrence of symptoms with prior attempts at dose reduction.

There is modest evidence to support effectiveness of carbamazepine in targeting agitation and aggression in AD [16]. In practice, its use is limited by the risk of common side effects such as dizziness, sedation, ataxia, confusion, headaches, nausea, vomiting, diarrhea, blurred vision. More rare but significant adverse effects include inappropriate antidiuretic hormone with hyponatremia, cardiac and hepatotoxicity, and increased risk of suicidal behavior and ideation [4]. Patients should also be explicitly informed of warnings for aplastic anemia, agranulocytosis, and rare but sometimes fatal dermatologic adverse reactions.

The evidence for valproate in management of agitation in AD is mixed, with a meta-analysis of pooled results proving valproate ineffective and associated with unacceptable rates of adverse events (notably sedation and urinary tract infections) [13]. Among other pharmaceuticals from this category topiramate has some efficacy; gabapentin, lamotrigine, oxycarbamazepine and levetiracetam have been the subject of observational or uncontrolled studies and are considered as low priority agents.

Trazodone, a hypnotic and antidepressant (pharmacologically a serotonin antagonist and reuptake inhibitor), is used for management of irritability, agitation and aggression in AD. Trazodone has sedating properties with minimal anticholinergic activity. Trazodone has a favorable safety profile if administered in small doses and appears to produce a stabilization of the circadian rhythms in individuals with AD

[44]. A few retrospective or observational studies suggest that trazodone may be effective for the treatment of aggression or agitation in AD [45].

The most promising potential pharmacological alternatives to antipsychotics and anti-epileptic agents include citalopram, dextromethorphan/quinidine, and prazosin [46]. Comparator studies indicate that sertraline and citalopram are probably as effective as risperidone in treating agitation in dementia. A recent study had shown that dextromethorphan/quinidine significantly improved AD-associated agitation, reduced caregiver burden, and was generally well tolerated [47].

Depression of Parkinson's Disease

Depression, anxiety, psychosis, cognitive decline, and autonomic or sleep disturbances may be observed during the course of PD. Depression is common in PD, occurring in 40–50% of patients. Depression negatively impacts quality of life and worsens already impaired motor and cognitive abilities [48]. Depression of PD tends to be accompanied by cognitive impairment and emerges in advanced stages of the disease. Depression of PD frequently clusters with other NPSs; co-occurrence with anxiety is nearly universal reaching 92% [49]. PD has a broad range of severity from severe depression consistent with major depressive disorder to undifferentiated and even subclinical forms of depression. The mood disorder may have a fluctuating course in PD. In some cases depression is present only during the "off" period [48]. (Table 23.5) provides the diagnostic criteria for depression of PD [52].

Table 23.5 Criteria for depression of PD modified from DSM-IV criteria for major depression as recommended by NINDS/NIMH Work Group [52]

(a) Persistence and general pervasiveness of 5 or more of 9 potential symptoms during the same 2-week period that represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure that is present most of the day, nearly every day, as indicated by either subjective report or observation made by others.
1. Depressed mood
2. Markedly diminished pleasure from all, or almost all, activities
3. Loss or gain in weight or appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
(b) Symptoms do not meet criteria for a DSM mixed episode (presence of phenomena of both a manic and a depressed episode)
(c) Symptoms cause clinically significant distress or functional impairment
(d) Symptoms are not better accounted for by bereavement

Morphologic and functional neuroimaging studies demonstrate that depression in PD correlates with reduced activity of neural networks including prefrontal cortex, thalamus anterior and posterior cingulate structures. Degeneration of mesolimbic dopamine, norepinephrine, and serotonin pathways in orbital-frontal circuits and subcortical structures, such as the locus coeruleus, dorsal raphe nuclei, and ventral tegmental area, are thought to be associated with depressive symptoms in PD [50]. Functional neuroimaging studies implicate cortical cholinergic circuitry in dementia and depression of PD [51]. Depressive symptoms mainly: anhedonia, anergia, early morning awakening, and psychomotor retardation overlap with features of PD. Despite the overlap of symptomatology, a diagnosis of depression should be made if the core mood features of depression are present. Because of significant risk of under-detection, all PD patients should be screened periodically to detect depression. Additionally, because anxiety and depressive symptoms are frequently co-morbid in PD, a finding of anxiety should prompt screening for mood disorder [52].

Many studies demonstrate the efficacy of medications as well as psychotherapies for PD depression. Ideally in the management of PD depression pharmacological and nonpharmacologic intervention should be initiated concomitantly to promote optimal response.

Use of cognitive behavioral therapy (CBT) for depression and anxiety of PD is supported by strong evidence, including controlled trials [53]. The goal of CBT is to provide a structured approach that helps people to identify maladaptive thoughts contributing to emotional discomfort and to replace them with more enabling alternatives.

In terms of pharmacotherapy, experts recommend dopamine agonists (DA) as a first step in the management of depression of PD assuming it is compatible with the management of the motor symptoms of PD. Pramipexole (range of doses 0.3–4.2 mg/day) and ropinirole (10 mg/day) have antidepressant properties in patients with PD [54–56]. DAs use may be limited since this group of medication is linked to risk for developing impulse control disorders. Regular monitoring to capture symptoms like pathologic gambling, hypersexuality, and overspending in the course of DA therapy is crucial.

If an antidepressant agent is warranted, tricyclic antidepressants (TCAs) should be considered first (unless cognitive impairment is present). TCAs inhibit reuptake of dopamine, norepinephrine, and, to a lesser extent serotonin. TCAs also possess alpha-adrenergic antagonist, antimuscarinic, and antihistaminic properties. Almost all TCAs: amitriptyline, desipramine, imipramine, and nortriptyline (with the exeption of doxepine) have been demonstrated to be potent antidperessants in randomized controlled trials involving patients with PD. The secondary amine TCAs (e.g., desipramine and nortriptyline) are preferred due to better tolerability and fewer anticholinergic effects. Desipramine and imipramine may improve motor symptoms of PD [49, 51]. In a subset of patients, such as those with hypersalivation or overactive bladder, the antimuscarinic activity of TCAs may be of additional benefit. Sedating TCAs may be helpful for the treatment of depression with insomnia.

In general, anticholinergic properties of TCAs limit their use in PD patients with existing or emerging cognitive dysfunction. Although infrequent, the TCAs also have the potential to induce cardiac conduction disturbances. If the use of a TCA is limited

due to cognitive impairment, comorbid medical conditions or treatment-emergent adverse effects, the SSRIs should be considered. SSRIs are well tolerated with the exception of tremor, which may be induced or worsened by SSRIs. Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline were similarly effective for the treatment of depression in PD. Among the SSRIs, citalopram and sertraline are preferred due to efficacy, tolerability, and low drug interaction potential. In addition to SSRIs and TCAs, several other antidepressants including bupropion, duloxetine, mirtazapine, moclobemide, nefazodone, and venlafaxine have been evaluated in controlled trials for the management of depression in PD. Both open label and placebo-controlled data demonstrate that duloxetine and venlafaxine are well tolerated and improve depressive symptoms in patients with PD. SNRI's however were found to have lower acceptability and tolerability than SSRIs in PD [57].

Nonselective monoamine oxidase (MAO) inhibitors (isocarboxazid, phenelzine, and tranylcypromine) should be avoided especially in levodopa-treated patients because of the risk of hypertensive crisis. The selective MAO-B inhibitors (selegiline) may be beneficial in the treatment of PD depression. MAO-B inhibitors should be however regarded as higher risk and low on the list of therapeutics for this indication.

Mirtazapine, a multiple-mechanism antidepressant (presynaptic alpha-2 antagonist blocker of 5-HT2a, 5-HT2c, 5-HT3, and H-1 receptors) is a promising treatment option for depression of PD. Evidence suggests that mirtazapine may also improve tremor and levodopa-induced dyskinesias [58].

In cases where response is inadequate, switching to an agent from a different class (as opposed to augmentation) is recommended. Most antipsychotics are poorly tolerated in PD patients because of their antidopaminergic properties. Clozapine and quetiapine are exceptions and their use in complicated cases of mood disorders that accompany PD may be considered.

Use of mood stabilizers is limited by side effects: lithium requires very close monitoring and usually worsens motor symptoms in PD [48] and valproic acid is not routinely recommended since it is known to cause parkinsonism in the elderly and likely has a similar effect in those with PD [59].

ECT should be considered for patients with severe and treatment-resistant depression especially when complicated by psychosis or when the patient is at high risk for self-harm. ECT is a safe and effective modality in the treatment of depression in PD (Fig. 23.4).

Psychosis of Parkinson's Disease

Psychosis is debilitating symptom of PD, it is an independent risk factor for nursing home placement, and, increases caregiver distress and patient mortality [51].

Visual hallucinations are the most common psychotic manifestation in PD. Auditory, olfactory, tactile and gustatory hallucinations are infrequently found and usually coexist with visual ones. Minor hallucinations such as presence and

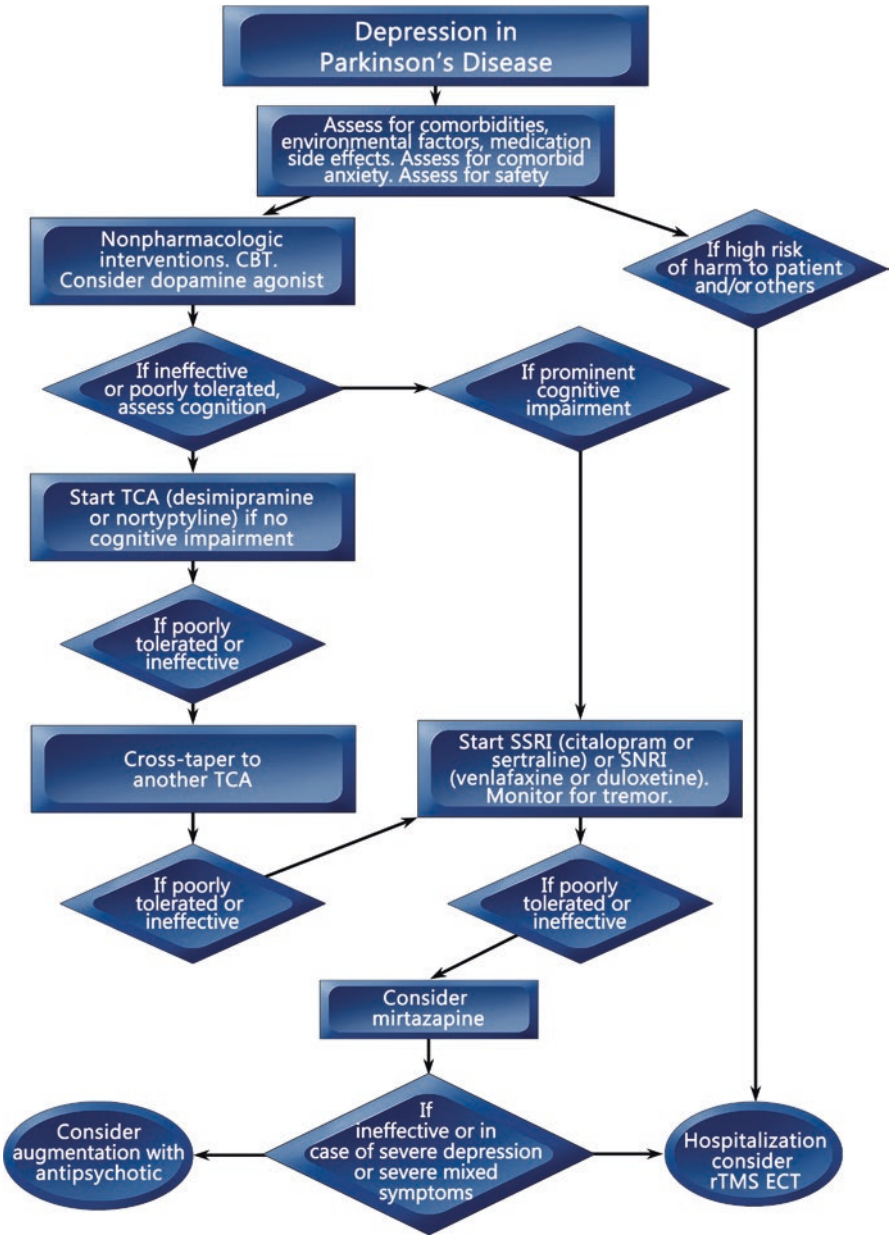

Fig. 23.4 Treatment of depression in Parkinson's disease

passage hallucinations may precede structured visual hallucinations. Delusions occur in about 5% of PD patients Dopaminergic medications, cognitive dysfunction, depression, sleep disturbances, and longer duration of PD are risk factors for the emergence of psychosis in PD [60]. (Table 23.6) provides the criteria for psychosis of PD [66].

Table 23.6 Proposed diagnostic criteria for PD associated psychosis [66]

(a) Characteristic symptoms
Presence of at least one of the following symptoms (specify which of the symptoms fulfill the criteria):
1. Illusions
2. False sense of presence
3. Hallucinations
4. Delusions
(b) Primary diagnosis
UK brain bank criteria for PD
(c) Chronology of the onset of symptoms of psychosis
The symptoms in Criterion A occur after the onset of PD
(d) Duration
The symptom(s) in Criterion A are recurrent or continuous for 1 month
(e) Exclusion of other causes
The symptoms in Criterion A are not better accounted for by another cause of Parkinsonism such as dementia with Lewy bodies, psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features, or a general medical condition including delirium
(f) Associated features: (specify if associated)
With/without insight
With/without dementia
With/without treatment for PD (specify drug, surgical, other)

The pathophysiology of psychosis in PD is most likely multifactorial with disruption of serotonin, dopaminergic, and acetylcholine systems [61]. Neuropathological studies link the development of psychosis with progressive formation of Lewy bodies in cortex, amygdala, hippocampus [62].

The only agent with FDA approval for treatment of PD psychosis is pimavanserin a selective-serotonin inverse agonist that preferentially targets 5-HT2A receptors, while avoiding activity at dopamine and other receptors commonly targeted by antipsychotics. Pimavanserin was shown to be effective in a trial in which adults with PD psychosis were randomly assigned to take 40 mg of pimavanserin or placebo daily for 6 weeks. Patients taking pimavanserin experienced fewer and less severe hallucinations and delusions without worsening the primary motor symptoms of PD. The most common adverse effects reported by patients taking pimavanserin included peripheral edema, nausea, and confusion [10] (Fig. 23.5).

Efforts to treat psychosis of PD with antipsychotics commonly used for primary psychotic disorders to date have been futile and associated with significant deterioration of the motor symptoms [63]. Typical antipsychotics, especially potent blockers of dopaminergic receptors are in general contraindicated in PD. Novel, atypical antipsychotics although safer seem to be of limited efficacy in managing symptoms of PD.

Risperidone has been to some extent beneficial in managing psychotic symptoms of PD Dementia (PDD). Treatment with risperidone improved levels of social, occupational, and psychological functioning [64]. In practice however worsening of parkinsonism limits use of this agent.

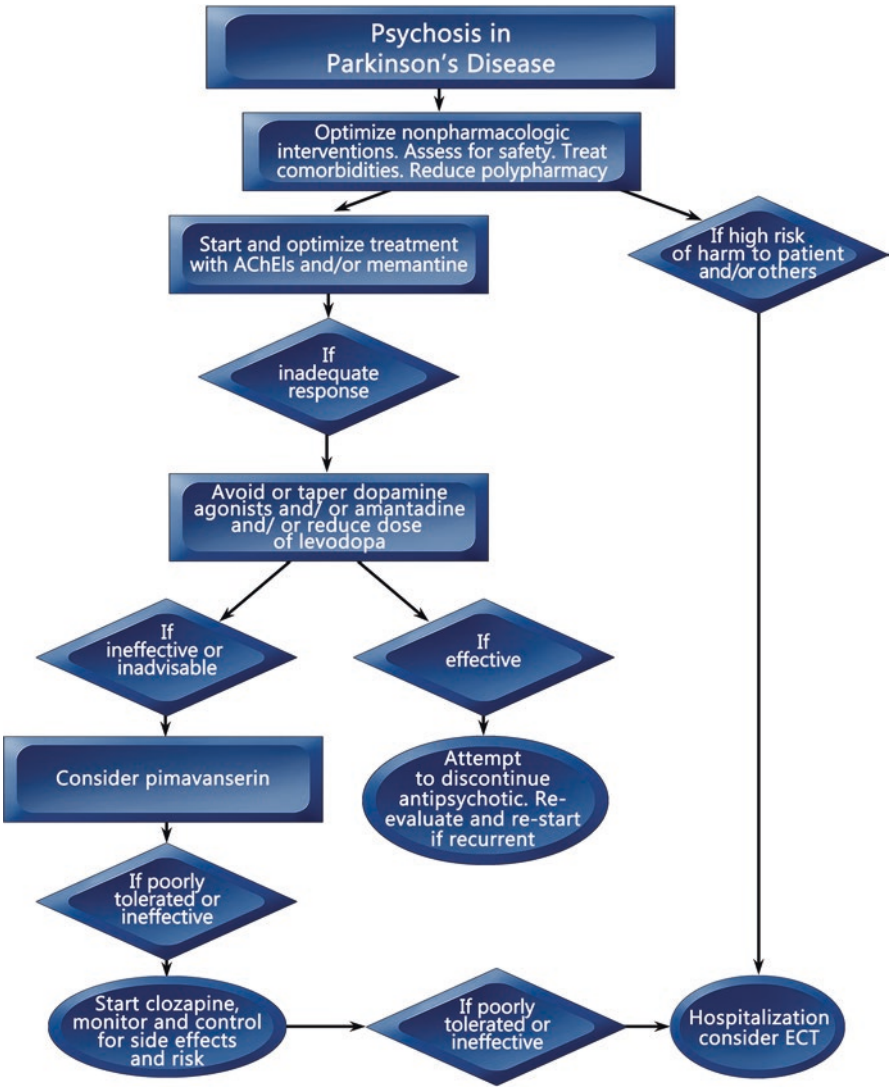

Fig. 23.5 Treatment of psychosis in Parkinson's disease

Clozapine is efficacious in the treatment of PD psychosis in randomized controlled trials even in very small doses (6.25–50 mg daily) [63, 65]. The risk of agranulocytosis and the necessity of blood monitoring with clozapine leads to choice of other antipsychotics, mainly quetiapine (12.5–150 mg) before attempting use of clozapine [63]. Quetiapine is the most frequently prescribed antipsychotic to target psychotic symptoms in PD. Firm conclusions about its efficacy cannot be drawn. Studies show that patients taking quetiapine experienced fewer side effects than reported with other antipsychotics, but it has yet to be proven to be more effective than placebo in the treatment or psychosis in this population.

In severe cases hospitalization should be considered. Somatic therapies may be an option in such a cases as well. In PD, ECT was proved to be effective not only for depression and motor symptoms but for psychosis. It might be considered to treat psychosis that has not responded to other interventions [51].

ICD-10 Codes

G30 Alzheimer's disease

G30.0 Alzheimer's disease with early onset
G30.1 Alzheimer's disease with late onset
G30.8 Other Alzheimer's disease
G30.9 Alzheimer's disease, unspecified
or
G30.9 Major neurocognitive disorder due to probable or possible Alzheimer's disease

Additional codes

F02.80 without behavioral disturbance,
F02.81 with behavioral disturbance
F06.31 Depressive disorder due to Alzheimer's disease with depressive features,
F06.32 Depressive disorder due to Alzheimer's disease with major depressive–like episode
F06.34 Depressive disorder due to Alzheimer's disease with mixed features

G20 Parkinson's disease

Additional codes

F06.2 Psychotic Disorder Due to Parkinson's disease with delusions
F06.0 Psychotic Disorder Due to Parkinson's disease with hallucinations
F06.31 Depressive disorder due to Parkinson's disease with depressive features,
F06.32 Depressive disorder due to Parkinson's disease with major depressive-like episode
F06.34 Depressive disorder due to Parkinson's disease with mixed features

Disclosures Dr. Rothenberg reports no disclosures.

References

1. Cummings JL. The neuropsychiatric inventory: assessing psychopathology in dementia patients. Neurology. 1997;48:10–6.
2. Steinberg M, Shao H, Zandi P. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the cache county study. Int J Geriatr Psychiatry. 2008;23(2):170–7.
3. Steele C, Rovner B, Chase GA, Folstein M. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. Am J Psychiatry. 1990;147:1049–51.
4. Rothenberg KG, Wiechers IR. Antipsychotics for neuropsychiatric symptoms of dementia—safety and efficacy in the context of informed consent. Psychiatr Ann. 2015;45(7):348–53.

5. Lanari A, Amenta F, Silvestrelli G, et al. Neurotransmitter deficits in behavioral and psychological symptoms of Alzheimer's disease. Mech Ageing Dev. 2006;127:158–65.
6. Murai T, Muller U, Werheid K, et al. In vivo evidence for differential association of striatal dopamine and midbrain serotonin systems with neuropsychiatric symptoms in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2001;13:222–8.
7. Cummings J, Lai TJ, Hemrungrojn S, Mohandas E, Yun Kim S, Nair G, Dash A. Role of donepezil in the management of neuropsychiatric symptoms in Alzheimer's disease and dementia with lewy bodies. CNS Neurosci Ther. 2016;22(3):159–66.
8. Panza F, Solfrizzi V, Seripa D, Imbimbo BP, Santamato A, Lozupone M, Prete C, Greco A, Pilotto A, Logroscino G. Progresses in treating agitation: a major clinical challenge in Alzheimer's disease. Expert Opin Pharmacother. 2015;16(17):2581–8.
9. Kales HC, Gitlin LN, Lyketsos CG, Detroit Expert Panel on A, Management of Neuropsychiatric Symptoms of Dementia. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. J Am Geriatr Soc. 2014;62(4):762–9.
10. Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, Dhall R, Ballard C. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2014;383(9916):533–40.
11. Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. Am J Psychiatry. 2012;169(9):946–53.
12. Cohen-Mansfield J. Nonpharmacologic interventions for inappropriate behaviors in dementia: a review and critique. Am J Geriatr Psychiatry. 2001;9:361–81.
13. Herrmann N, Lanctôt KL, Hogan DB. Pharmacological recommendations for the symptomatic treatment of dementia: the Canadian Consensus Conference on the diagnosis and treatment of dementia 2012. Alzheimers Res Ther. 2013;5(Suppl1):S5:1–S5:12.
14. Olin JT, Schneider LS, Katz IR, Meyers BS, Alexopoulos GS, Breitner JC, Bruce ML, Caine ED, Cummings JL, Devanand DP, Krishnan KR, Lyketsos CG, Lyness JM, Rabins PV, Reynolds CF 3rd, Rovner BW, Steffens DC, Tariot PN, Lebowitz BD. Provisional diagnostic criteria for depression of Alzheimer disease. Am J Geriatr Psychiatry. 2002;10(2):125–8.
15. Teng E, Ringman JM, Ross LK, Mulnard RA, Dick MB, Bartzokis G, Davies HD, Galasko D, Hewett L, Mungas D, Reed BR, Schneider LS, Segal-Gidan F, Yaffe K, Cummings JL, Alzheimer's Disease Research Centers of California-Depression in Alzheimer's Disease Investigators. Diagnosing depression in Alzheimer disease with the national institute of mental health provisional criteria. Am J Geriatr Psychiatry. 2008;16(6):469–77.
16. Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A, O'Brien J, Everratt A, Sadler S, Maddison C, Lee L, Bannister C, Elvish R, Jacoby R. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ. 2005;330(7496):874.
17. Holmes C, Wilkinson D, Dean C, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. Neurology. 2004;63:214–9.
18. Rabins PV, Blacker D, Rovner BW, et al. Practice guideline for the treatment of patients with Alzheimer's Disease and other dementias. 2nd ed. Arlington: American Psychiatric Association; 2007. http://www.psychiatry.org/practice/clinical-practice-guidelines.
19. Lyketsos CG, Olin J. Depression in Alzheimer's disease: overview and treatment. Biol Psychiatry. 2002;52(3):243–52.
20. Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. J Clin Psychiatry. 1999;60(2):107–15.
21. Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN, Mitan SJ, Kadam DL, Sanger TM, Feldman PD, Tollefson GD, Breier A. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry. 2000;57(10):968–76.
22. Tariot PN, Erb R, Podgorski CA, Cox C, Patel S, Jakimovich L, Irvine C. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. Am J Psychiatry. 1998;155(1):54–61.
23. Hausner L, Damian M, Sartorius A, Frolich L. Efficacy and cognitive side effects of ECT in depressed elderly inpatients with co-existing mild cognitive impairment or dementia. J Clin Psychiatry. 2011;72:91–7.

24. Miller M, Reynolds CF. Expanding the usefullness of interpersonal psychotherapy (IPT) for depressed elders with co-morbid cognitive impairment. Int J Geriatr Psychiatry. 2007;22:101–5.
25. Teri L, Gallagher-Thompson D. Cognitive-behavioral interventions for treatment of depression in Alzheimer's patients. Gerontologist. 1991;31:413–6.
26. Kiosses DN, Arean PA, Teri L, Alexopoulos GS. Home-delivered problem adaptation therapy (PATH) for depressed, cognitively impaired, disabled elders: a preliminary study. Am J Geriatr Psychiatry. 2010;18:988–98.
27. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991;38(2):143–62.
28. Mulin E, Leone E, Dujardin K, Delliaux M, Leentjens A, Nobili F, Dessi B, Tible O, Agüera-Ortiz L, Osorio RS, Yessavage J, Dachevsky D, Verhey FR, Cruz Jentoft AJ, Blanc O, Llorca PM, Robert PH. Diagnostic criteria for apathy in clinical practice. Int J Geriatr Psychiatry. 2011;26(2):158–65.
29. Rosenberg PB, Lanctôt KL, Drye LT, Herrmann N, Scherer RW, Bachman DL, Mintzer JE, ADMET Investigators. Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: a randomized, placebo-controlled trial. J Clin Psychiatry. 2013;74(8):810–6.
30. Jeste DV, Finkel SI. Psychosis of Alzheimer's disease and related dementias: diagnostic criteria for a distinct syndrome. Am J Geriatr Psychiatr. 2000;8(1):29–34.
31. D'Onofrio G, Panza F, Sancarlo D, Paris FF, Cascavilla L, Mangiacotti A, Lauriola M, Paroni GH, Seripa D, Greco A. Delusions in patients with Alzheimer's disease: a multidimensional approach. J Alzheimers Dis. 2016;51(2):427–37.
32. Wilcock GK, Ballard CG, Cooper JA, Loft H. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. J Clin Psychiatry. 2008;69(3):341–8.
33. Moretti R, Torre P, Antonello RM, et al. Olanzapine as a treatment of neuropsychiatric disorders of Alzheimer's disease and other dementias: a 24-month follow-up of 68 patients. Am J Alzheimers Dis Other Demen. 2003;18:205–14.
34. Mintzer JE, Tune LE, Breder CD, Swanink R, Marcus RN, McQuade RD, Forbes A. Aripiprazole for the treatment of psychoses in institutionalized patients with Alzheimer dementia: a multicenter, randomized, double-blind, placebo-controlled assessment of three fixed doses. Am J Geriatr Psychiatry. 2007;15(11):918–31.
35. Katz I, de Deyn PP, Mintzer J, Greenspan A, Zhu Y, Brodaty H. The efficacy and safety of risperidone in the treatment of psychosis of Alzheimer's disease and mixed dementia: a meta-analysis of 4 placebo-controlled clinical trials. Int J Geriatr Psychiatry. 2007;22(5):475–84.
36. El-Saifi N, Moyle W, Jones C, Tuffaha H. Quetiapine safety in older adults: a systematic literature review. J Clin Pharm Ther. 2016;41(1):7–18.
37. Soto M, Andrieu S, Nourhashemi F. Medication development for agitation and aggression in Alzheimer disease: review and discussion of recent randomized clinical trial design. Int Psychogeriatr. 2015;27:181–97.
38. Cummings J, Mintzer J, Brodaty H. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. Int Psychogeriatr. 2015;27:7–17.
39. Livingston G, Kelly L, Lewis-Holmes E. A systematic review of the clinical effectiveness and cost-effectiveness of sensory, psychological and behavioural interventions for managing agitation in older adults with dementia. Health Technol Assess. 2014;18:1–226.
40. Freund-Levi Y, Jedenius E, Tysen-Bäckström AC. Galantamine versus risperidone treatment of neuropsychiatric symptoms in patients with probable dementia: an open randomized trial. Am J Geriatr Psychiatry. 2014;22:341–8.
41. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med. 2006;355(15):1525–38.
42. Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. Cochrane Database Syst Rev. 2002; (2):CD002852.
43. APA Practice Guideline Writing Group's "Practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia." http://psychiatryonline.org/doi/book/10.1176/appi.books.9780890426807.

44. Grippe TC, Gonçalves BS, Louzada LL, Quintas JL, Naves JO, Camargos EF, Nóbrega OT. Circadian rhythm in Alzheimer disease after trazodone use. Chronobiol Int. 2015; 32(9):1311–4.
45. Kitamura Y, Kudo Y, Imamura T. [Trazodone for the treatment of behavioral and psychological symptoms of dementia (BPSD) in Alzheimer's disease: a retrospective study focused on the aggression and negativism in caregiving situations]. No ToShinkei. 2006;58(6):483–8.
46. Antonsdottir IM, Smith J, Keltz M, Porsteinsson AP. Advancements in the treatment of agitation in Alzheimer's disease. Expert Opin Pharmacother. 2015;16(11):1649–56.
47. Cummings J, Lyketsos C, Tariot P. Dextromethorphan/quinidine (AVP-923) efficacy and safety for treatment of agitation in persons with Alzheimer's disease: results from a phase 2 study (NCT01584440) (S16.007). Neurology. 2015;84(14 Suppl):16–007.
48. Chen JJ, Marsh L. Depression in Parkinson's disease: identification and management. Pharmacotherapy. 2013;33(9):972–83.
49. Menza MA, Robertson-Hoffman DE, Bonapace AS. Parkinson's disease and anxiety: comorbidity with depression. Biol Psychiatry. 1993;34:465–70.
50. Benoit M, Robert PH. Imaging correlates of apathy and depression in Parkinson's disease. J Neurol Sci. 2011;310:58–60.
51. Marsh L, Williams JR, Rocco M, Grill S, Munro C, Dawson TM. Psychiatric comorbidities in patients with Parkinson disease and psychosis. Neurology. 2004;63:293–300.
52. Marsh L, McDonald WM, Cummings J, Ravina B, NINDS/NIMH Work Group on Depression and Parkinson's Disease. Provisional diagnostic criteria for depression in Parkinson's disease: report of an NINDS/NIMH Work Group. Mov Disord. 2006;21(2):148–58.
53. Armento MEA, Stanley MA, Marsh L, Kunik ME, York MK, Calleo JS. Cognitive behavioral therapy (CBT) for depression and anxiety in Parkinson's disease: a clinical review. J Parkinson's Dis. 2012;2:135–51.
54. Barone P, Scarzella L, Marconi R, Antonini A, Morgante L, Bracco F, Zappia M, Musch B, Depression/Parkinson Italian Study Group. Pramipexole versus sertraline in the treatment of depression in Parkinson's disease: a national multicenter parallel-group randomized study. J Neurol. 2006;253(5):601–7.
55. Rektorova I, Rektor I, Bares M, et al. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. Eur J Neurol. 2003;10:399–406.
56. Rektorova I, Balaz M, Svatova J, et al. Effects of ropinirole on nonmotor symptoms of Parkinson's disease: a prospective multicenter study. Clin Neuropharmacol. 2008;31:261–6.
57. Pae CU. Use of antidepressants for depression in patients with Parkinson's disease. Expert Opin Pharmacother. 2013;14(3):255–7.
58. Pact V, Giduz T. Mirtazapine treats resting tremor, essential tremor, and levodopa-induced dyskinesias. Neurology. 1999;53:1154.
59. Mahmoud F, Tampi RR. Valproic acid-induced parkinsonism in the elderly: a comprehensive review of the literature. Am J Geriatr Pharmacother. 2011;9:405–12.
60. Goetz CG, Fan W, Leurgans S. Antipsychotic medication treatment for mild hallucinations in Parkinson's disease: positive impact on long-term worsening. Mov Disord. 2008;23(11):1541–5.
61. Kuhl DE, Minoshima S, Fessler JA, et al. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. Ann Neurol. 1996;40(3):399–410.
62. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain. 2002;125(pt 2):391–403.
63. Goldman JG, Holden S. Treatment of psychosis and dementia in Parkinson's disease. Curr Treat Options Neurol. 2014;16(3):281.
64. Workman RH Jr, Orengo CA, Bakey AA, et al. The use of risperidone for psychosis and agitation in demented patients with Parkinson disease. J Neuropsychiatry Clin Neurosci. 1997;9:594–7.
65. Pollak P, Tison F, Rascol O, et al. Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. J Neurol Neurosurg Psychiatry. 2004;75(5):689–95.
66. Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH Work Group. Movement Disorders 2007;22(8):1061–1068