Behavioral disturbances in dementia

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Psychological symptoms and behavioral abnormalities are common and prominent characteristics of dementia. They include symptoms such as depression, anxiety, psychosis, agitation, aggression, disinhibition, and sleep disturbances. Approximately 80% to 90% of patients with dementia suffer from such behavioral disorders. There are complex interactions between cognitive deficits, psychological symptoms, and behavioral abnormalities. A large number of standardized, reliable, and well-validated instruments for assessing the behavioral and psychological symptoms of dementia have been developed in order to evaluate the efficacy of treatment. Neurodegenerative processes in various brain areas, particularly in the frontotemporal cortex and limbic regions, leading to cholinergic, serotonergic, and noradrenergic neurotransmitter dysfunctions constitute the biological matrix of behavioral symptoms, whereas psychological factors and personality traits play a modifying role. A large number of pharmacological, psychoeducational, psychotherapeutic, and social strategies have been developed to improve the quality of life of patients and their caregivers.

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Although cognitive decline and deficits in social competence are the hallmarks of progressive neurodegeneration, behavioral abnormalities are common and important characteristics of dementia. Alzheimer's disease (AD) is the principal cause of dementia in the elderly,[1] therefore the following review closely relates to this disorder. It affects almost 15 million people worldwide.[1] A wide range of behavioral disturbances afflict the majority of patients with dementia. Behavioral disturbances, such as verbal or physical aggression, urinary incontinence, and excessive wandering, are a major source of caregiver burden and an important contributor to the decision to admit AD patients to institutionalized long-term care.[2,3] The social and psychological skills and the compliance of the caregivers, as well as the presence and competence of the social networkers, determine to a large extent whether a demented patient with behavioral problems can live at home or needs nursing home admission. However, in the past, research in AD focussed primarily on the early detection and management of cognitive deficits, whereas behavioral disturbances have been neglected.[4]

Treatment of behavioral problems can improve the quality of life of the patient and the carer, and may help avoid premature institutionalization.

The relationship between these disturbances and the severity of dementia has not been clarified. There is some evidence that some symptoms such as depression and anxiety are more common during slight to moderate stages, whereas others, eg, behavioral problems like aggression, seem to occur more in advanced dementia. In severe stages, significant cognitive impairment becomes predominant and some behavioral dysfunctions get grad-

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Selected abbreviations and acronyms

AD	*Alzheimer's disease*
BEHAVE-AD	*Behavioral Pathology in Alzheimer's Disease Rating Scale*
BPSD	*behavioral and psychological symptoms of dementia*
BRSD	*Behavioral Rating Scale for Dementia*
CMAI	*Cohen-Mansfield Agitation Inventory*
EPS	*extrapyramidal side effects*
FTD	*frontotemporal dementia*
NPI	*Neuropsychiatric Inventory*
SSRI	*selective serotonin reuptake inhibitor*

ually less problematic.[3] However, many behavioral disturbances like physical violence, incontinence, hitting, accusatory behaviors, and suspiciousness do not appear to be closely related to cognitive deficits.[5]

There is also controversy about the prevalence of different behavioral abnormalities in patients with different types of dementia.[6] It has been suggested that depression is more common in vascular dementia than in AD.[6] In a recent study, only modest differences were found in the prevalence of mental or behavioral disturbances in different types of dementia or at different stages of illness.[7] The authors investigated a large community population of elderly people. Patients with AD were more likely to have delusions and less likely to have depression. Aberrant motor behavior and agitation/aggression were more common in patients with advanced dementia.

Epidemiology

The proportion of affected patients has varied among studies due to differing inclusion and assessment criteria. These studies suggest that approximately 80% to 90% of patients with dementia suffer from such behavioral disorders *(Table I)*[7-14] over the course of their illness. These rates are considerably higher than those reported in individuals aged 65 or older without dementia syndrome.

Personality changes are most common in AD and affect approximately 70% of patients,[8] including disinterest in environment or inappropriate social behavior. Different aspects of personality traits may become more predominant depending on the patient's primary personality. Frontotemporal dementia (FTD), a syndrome first described by more than 100 years ago by Pick,[15] is particularly dominated by prominent and commonly disturbing behavior.[16] Early loss of personal and social awareness, early decline in social interpersonal conduct, early loss of insight, and emotional blunting are characteristic features of this dementia type.[16] Mychack and coworkers[16] assessed 41 patients with FTD and concluded from their findings that right-sided frontotemporal degeneration is associated with socially undesirable behavior. Symptoms like irritability, impulsiveness, bizarre alterations in dress, decreased facial expression, and limited and fixed ideas have been associated with predominantly right temporal dysfunction[16,17] in patients with FTD.

In addition to primary personality traits, environmental factors like unfamiliar surroundings may worsen the progression of AD.[18] In contrast to the negative impact of deficient social support, a positive atmosphere may affect the patient's physical and psychological well-being.[19] Relatives and caregivers often have difficulties in accepting the patient's loss of established roles and functions in partnerships or families.[20] The caregiver's skills handling these problems have a high impact on the development of psychopathology and behavioral disturbances.

	Prevalence (%)		
• ***Psychological symptomatology***			
Personality changes		70[8]	
Depression		24[9†]	24[13*]
Apathy	72[7]	41[9]	27[13*]
Mania		3.5[9]	
Anxiety	48[7]		17[13*]
Delusions	22[7]	16[10]	18.5[13*]
Hallucinations	10[7]	17[11]	13.5[13*]
Irritability	42[7]		20.4[13*]
Dysphoria	38[7]		
• ***Behavioral problems***			
Agitation	60[7]		24[13#]
Aggression		20[12]	
Wandering		19[12]	
Purposeless activity		40–80[§]	
Disinhibition	36[7]	7[12]	9.1[13*]
Binge eating		10[12]	
Hyperorality		6[12]	
Urinary incontinence		48[12]	
Aberrant motor behavior	38[7]		14.3[13*]
Sleep disorders		60–80[§]	

Table I. Psychological symptomatology and behavioral problems in dementia, particularly in Alzheimer's disease. *Dementia of any etiology; †major depression; #agitation/aggression; §depending on severity (F. Müller-Spahn, unpublished results).

Assessment of psychological and behavioral symptoms

The symptoms of dementia can be conceptualized in several ways.[18] The most popular dichotomic concept broadly distinguishes cognitive and noncognitive symptoms.[20] Other concepts differentiate between cognitive dysfunctions and behavioral or psychiatric disturbances. However, all of these concepts have limitations with respect to the complex interactions between cognitive deficits, psychological symptoms, and behavioral abnormalities. Recent studies indicate that several noncognitive symptoms are related to the level of cognitive dysfunction among patients with AD.[21,22] Most notably, aggression appears to increase with greater cognitive impairment.[22] Less consistent are data on the association of mood disorders, psychosis, and severity of cognitive dysfunctions. To date, the relationship of cognitive and functional status with disturbed/disturbing behaviors among dementia patients remains an understudied area.[21]
Alois Alzheimer stated in the case description of Auguste D. in 1906 that behavioral disturbances like screaming, paranoid ideations, hallucinations, and sexual disinhibition were prominent features of this dementia type.[23]
The basis of the diagnosis of behavioral and psychological symptoms of dementia (BPSD) comprises a clinical interview, direct observation of the patient with dementia, and/or a proxy report from a carer or other observers.[24]
Although more than 100 rating scales for the assessment of BPSD exist, neither the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) nor the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) provide detailed definitions of behavioral disturbances in dementia.[25] *ICD-10* dementia diagnosis include syndromes like predominantly depressive, delusional, hallucinatory, or mixed symptoms.
A large number of instruments for assessing BPSD have been developed, particularly in order to evaluate the efficacy of treatment of behavioral disturbances in patients with probable AD.
In this article, several standardized, reliable, well-validated, easily applicable, and internationally used rating scales will be briefly introduced *(Table II)*: the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD),[26] the Cohen-Mansfield Agitation Inventory (CMAI),[27,28] the Neuropsychiatric Inventory (NPI),[29] and the Behavioral Rating Scale for Dementia (BRSD).[30]

The BEHAVE-AD scale can be completed in a short period of time (20 min). Reisberg et al[26] identified 25 symptoms in 7 major categories or clusters of psychological and behavioral disturbances. The second part of the BEHAVE-AD comprises a global rating of the severity of the BPSD. There is a large variability of the different symptoms at the different stages of AD.[31] Most of the behavioral symptoms occur at later stages of the disease.
The NPI is a relatively brief assessment instrument that evaluates a wide range of psychopathologies, and their severity and frequency of symptoms. It helps to differentiate between dementias. It requires 10 min to perform.
The BRSD from the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) considers a wide variety of symptoms in 8 areas. The BRSD was developed for the assessment of AD patients with mild to moderate cognitive impairment.[30] It takes 20 to 30 min to administer.
The CMAI[27,28] is a 7-point rating scale that assesses the frequency with which patients manifest up to 29 agitated behaviors and takes 10 to 15 min to perform. The behavioral symptoms assessed by the CMAI are listed in *Table II*.
The comprehensive assessment of the effects of drug treatment on behavior should include not only those instruments designed to assess behavioral abnormalities in dementia, but also rating scales that measure cognitive changes and health-related quality of life.[3] For example, the use of antipsychotics, benzodiazepines, or anticonvulsants may substantially reduce an undesirable behavior, but may cause sedation and impair cognitive performance and the ability to perform activities of daily living. Therefore, a proper assessment should include cognitive, behavioral, and quality of life domains.[3] Many of the psychological symptoms and behavioral problems are likely to be responsive to pharmacological interventions or nonpharmacological management.

Etiology

The behavioral symptoms seen in dementia *(Table II)* are not due to an uniform etiology.[18] They are often multifactorial and related to the severity of the disease. Loss of neurons has been considered as a major pathophysiological hallmark in AD. These include not only nerve cells of association cortices, but also neurons of certain nuclei like cholinergic cells of the dorsal raphe. In addition to the decrease in cholinergic and serotonergic activity, alterations in the noradrenergic systems occur; these are reflected by a decrease in the norepinephrine level and an

increase in the level of its major metabolite 3-methoxy-4-hydroxyphenylglycol.[32] The extent of deficits in serotonergic, cholinergic, and noradrenergic neurotransmission varies depending on the progression of the neurodegeneration and the functional integrity of other neurotransmitter systems.[18] Neuropathological alterations and changes in brain metabolism in the mesotemporal and frontal brain areas appear to be related to psychotic symptoms *(Table III)*.[33-37]

Primary personality, behavior of the caregiver, and social environment largely influence the pattern of behavioral disturbances.

In conclusion, neurodegenerative processes in various brain areas, including neurotransmitter dysfunctions, constitute the biological substrate of behavioral symptoms, whereas psychological factors and personality play a modifying role.

Psychosis

Delusions and hallucinations are common and prominent features of dementia, and were even described by Alzheimer.[23] They are usually manifest for the first time in patients with moderate cognitive decline and tend to disappear in severe stages of dementia probably due to the inability to articulate psychotic experience. They tend to recur or persist for several years in the majority of patients.[38] Delusions and hallucinations may be associ-

Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)
• Paranoid and delusional symptoms
• Hallucinations
• Activity disturbances
• Aggressiveness
• Diurnal rhythm disturbances
• Affective disturbances
• Anxieties and phobias
Neuropsychiatric Inventory (NPI)
• Delusions
• Hallucinations
• Agitation, dysphoria
• Anxiety
• Apathy
• Irritability
• Euphoria
• Disinhibition
• Aberrant motor behavior
• Nighttime behavior disturbances
• Appetite and eating abnormalities
CERAD Behavioral Rating Scale for Dementia (BRSD)
• Depressive features
• Psychotic features
• Defective self-regulation
• Irritability and agitation
• Vegetative features
• Apathy
• Aggression
• Affective lability

Cohen-Mansfield Agitation Inventory (CMAI)—Long Form
• Pace, aimless wandering
• Inappropriate dress or disrobing
• Spitting (including at meals)
• Cursing or verbal aggression
• Constant unwarranted request for attention or help
• Repetitive sentences or questions
• Hitting (including self)
• Kicking
• Grabbing onto people
• Pushing
• Throwing things
• Strange noises (weird laughter or crying)
• Screaming
• Biting
• Scratching
• Trying to get to a different place (eg, out of room or building)
• Intentional falling
• Complaining
• Negativism
• Eating/drinking inappropriate substances
• Hurt self or others (cigarette, hot water, etc)
• Handling things inappropriately
• Hiding things
• Hoarding things
• Tearing things or destroying property
• Performing repetitious mannerisms
• Making verbal sexual advances
• Making physical sexual advances
• General restlessness

Table II. Clusters assessed by the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD),[26] the Cohen-Mansfield Agitation Inventory (CMAI),[27,28] the Neuropsychiatric Inventory (NPI),[29] and the Behavioral Rating Scale for Dementia (BRSD).[30] CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

ated with agitation and aggression in AD patients.[39] Misidentification phenomena are frequent; delusions are typically paranoid type and noncomplex.[40]

Schneiderian first-rank symptoms are extremely rare in AD patients.[40] Jeste and Finkel[40] compared clinical features of psychosis in AD with schizophrenia in elderly patients. In contrast to AD patients, elderly patients with schizophrenia have a past history of psychotic episodes, their long-term course is generally stable, and delusions are frequently bizarre or complex. These authors believe that psychosis in AD is a distinct syndrome that is markedly different from schizophrenia in the elderly. Approximately 30% to 50% of AD patients show psychotic symptoms.[41] Delusions appear to be more frequent than hallucinations in AD patients (10% to 70% of patients have delusions while only 3% to 33% have hallucinations).[42] Hallucinations in AD are more commonly visual than auditory.[40]

The cumulative 4-year incidence of new-onset psychosis in AD patients has been calculated to be 51% *(Figure 1)*.[43] There is some evidence of clinical and neurobiological differences between AD patients with and without psychotic symptoms.[40] Those with psychosis had greater impairment on neuropsychological tests preferentially testing frontal lobe functions.[44] Psychosis in AD patients was associated with a higher prevalence of extrapyramidal signs.[45] On the basis of neurochemical and neuropathological investigations, those with psychotic symptoms had increased neurodegenerative alterations in the cortex and reduced cortical and subcortical serotonin.[46]

Lopez et al[47] reported of a more rapid rate of cognitive decline as measured by the Mini-Mental State Examination (MMSE)[48] and a specific deficiency in respective language in AD patients with delusions and hallucinations than in patients without such symptoms. Analysis of electroencephalograms (EEGs) showed a significantly greater proportion of moderately abnormal EEGs with an increased amount of delta and theta activity. These findings suggest that AD patients with psychotic symptoms have a greater degree of cerebral dysfunction and more focal neuropsychological defects.[47] Cummings[34] suggested that lesions in the right temporal cortex might cause abnormal perceptual input to the limbic system thus leading to, or facilitating the development of, psychotic symptoms. In conclusion, these studies suggest a neuropathological basis for psychosis in AD.

Although antipsychotics have been found to be the treatment of choice for behavioral disturbances, particularly in nursing facilities,[49] a meta-analysis of 33 controlled trials comparing conventional antipsychotics with placebo in elderly, severely demented patients with agitation showed only moderate superiority to placebo.[50] Despite the extensive use of traditional neuroleptics, such as haloperidol, the risks may overweigh clinical benefits.

There is much evidence suggesting a high incidence rate of extrapyramidal side effects (EPS) in patients with dementia exposed to traditional antipsychotics. Even at

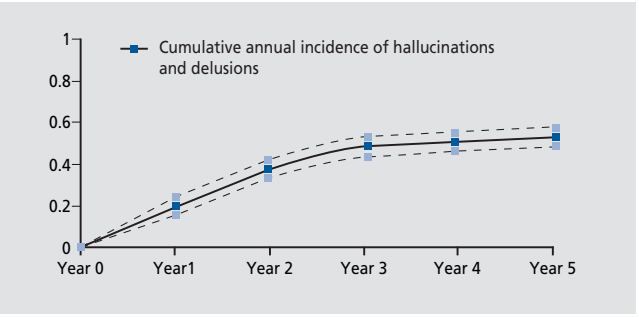

Figure 1. Cumulative incidence of new-onset psychosis of Alzheimer's disease (with 95% confidence interval) at 1, 2, 3, 4, and 5 years after baseline evulation.

Reproduced from reference 43: Paulsen JS, Salmon DP, Thal LJ, et al. Incidence of and risk factors for hallucinations and delusions in patients with probable AD. *Neurology*. 2000;54:1965-1971. Copyright © 2000, American Academy of Neurology.

Symptomatology	Neurobiological basis
Psychosis	Degeneration in mesotemporal and frontal brain areas[33,34]
Depression	Degeneration of the brain stem aminergic nuclei (especially the locus ceruleus)[35]; decrease in serotonergic neurotransmission[35]
Apathy, communication failure	Degeneration in the parahippocampal gyrus, frontal and parietal neocortex, hippocampus, and basal nucleus of Meynert[36]
Klüver-Bucy syndrome	Degeneration in the parahippocampal gyrus and parietal neocortex[36]
Agitation, aggression	Hypofunction of the serotonin and cholinergic systems, relative hyperfunction of dopaminergic and noradrenergic systems resulting from neuropathological changes[36,37]

Table III. Neuropathological basis of behavioral disturbances in dementia.

low doses of haloperidol (2 to 3 mg/day), 20% of AD patients with psychosis and disruptive behaviors developed moderate to severe EPS.[51] The new generation of antipsychotics has a considerably lower potential for EPS and is therefore generally recommended for treatment of psychosis in the elderly, particularly in patients with dementia *(Table IV)*.[52-55] However, only a few placebo-controlled studies have been published to date.[52,53] Low starting doses are recommended *(Table IV)*.

Agitation and aggression

The term agitation is poorly defined and applied to a heterogeneous group. Behavioral disturbances in dementia are often globally described as "agitation" including verbal and physical aggression, wandering, and hoarding.[56] These symptoms create patient and caregiver distress, and lead to nursing home placement. Agitation is a very common phenomenon in dementia with various causes, such as undiagnosed medical problems or pain, environmental or social factors (eg, overstimulation, unwanted care), drug side effects, sleep disturbances, delirium, and depression.[57] Wandering is a frequent behavioral problem in patients with an advanced stage of dementia. Nineteen of the 107 patients with AD studied by Burns et al[12] exhibited excessive walking behavior. This disturbance appears to be closely linked to the severity of dementia.

Physical aggressiveness is one of the most serious and challenging behavioral disturbances in dementia with a number of adverse consequences, including injury, chronic distress, and patient abuse.[22,58] It is probably the main reason why physicians are called in to treat.[8] Most studies have shown that 15% to 20% of patients with dementia develop violent behavior.[22,59] Interestingly, several studies suggested a relationship between gender, mood disturbances, psychosis, and the development of aggression. Male gender,[60] delusions and hallucinations,[2,39] more severe dementia,[60,61] moderate to severe depression,[22] caregiver depression, greater impairment in activities of daily living,[22] sleep disturbances,[62] and limited space to live in[63] have all been described as risk factors for physically aggressive behavior. On the neurochemical level, many of the behavioral disturbances and psychological symptoms may be linked to a serotonergic deficit in the brain.

Treatment of agitation in dementia requires a correct identification of the underlying physical, environmental, and psychiatric conditions. Common symptomatic pharmacological interventions—this is the next step when nonpharmacological treatment approaches including behavioral management, environmental modifications, interventions using sound and light, and social interaction groups[3] fail—include antipsychotics, selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, β-blockers, and anticonvulsants, such as carbamazepine and valproate. Citalopram and perphenazine were found to be more efficacious than placebo in the treatment of agitation/aggression and psychosis in demented patients.[64] Neuroleptics, particularly the conventional ones, are often poorly tolerated by patients with dementia. Patients with severe dementia are at an especially high risk of adverse effects like EPS, drowsiness, and accelerated cognitive decline.

If benzodiazepines are used, the application of substances with a relatively short half-life and without active metabolites is recommended (eg, lorazepam and oxazepam). Sedation, risk of falls, a negative impact on cognitive abilities, and in some cases paradox effects restrict the clinical use of these compounds.

Low-potency neuroleptics with low anticholinergic properties may be beneficial (eg, 10 to 150 mg/day melperone) *(Table V)*; low-dose new antipsychotics (eg, 1 mg/day risperidone[52] and 5 mg/day olanzapine[53]) have been reported efficacious against violent behavior. Alternatively anticonvulsants, in particular carbamazepine[65] and divalproex sodium,[66] have been investigated as antiaggressivity compounds in controlled trials in demented patients with violent behavior.

Compound	Average dose (mg/day)	Starting dose (mg)	Comments
Haloperidol	1–3	0.5	Risk of extrapyramidal side effects
Melperone	50–200	25	Low risk of extrapyramidal side effects
Pipamperone	20–80	10	Low risk of extrapyramidal side effects
Risperidone[52]	0.5–2	0.5	(Low) risk of orthostatic hypotension
Olanzapine[53]	5–10	2.5	Sedation
Quetiapine[54]	50–150	25	Sedation
Clozapine[55]	12.5–50	12.5	Risk of confusion, sedation, and agranulocytosis

Table IV. Examples for drug treatment of psychosis in patients with dementia.

Tariot et al[65] assessed the efficacy, safety, and tolerability of carbamazepine in the treatment of agitation and aggression associated with severe dementia in a placebo-controlled trial. Clinical Global Impression (CGI) ratings showed global improvement in 77% of the patients taking carbamazepine and 21% of those taking placebo. The mean daily dose of carbamazapine at week 6 was 304 mg/day (SD=119) with a mean serum level of 5.3 µg/mL. The drug was generally well tolerated.

Divalproex sodium with an average dose at week 6 of 826 mg/day (375–1.375 mg/day with an average level of 45 µg/mL) has been shown superior to placebo (reduced agitation on the CGI in 68% of patients on valproate vs 52% on placebo; *P*=0.06). Side effects were generally rated as mild.

These data suggest that anticonvulsants might be a helpful strategy in the treatment of agitation and aggression in dementia. However, further placebo-controlled trials are required to explore the clinical efficacy and tolerability of these compounds, particularly of the new generation of anticonvulsants. Because aggressive patients do not always respond to medication (single drug or in combination), one-to-one nursing in a quiet room is sometimes indicated.

Sleep disturbances

Sleep disturbances in AD patients are characterized by fragmented sleep or disruption in the day–night sleep cycle.[8] They appear to become progressively worse as the disease progresses, although the severity of this disturbance varies considerably among individual patients. Apart from the neurodegenerative disease process itself, various other factors may influence the quality of sleep including physical or environmental conditions and drug side effects. Pharmacological conditions and drug side effects. Pharmacologically, chloralhydrate (250–1000 mg/24 hours), new nonbenzodiazepine hypnotics, such as zolpidem (5–10 mg at night), an imidazopyridine derivative, zopiclone (3.75–7.5 mg at night), a cyclopyrrolone-derivative, and low-potency neuroleptics (eg, melperone 25–75 mg at night) have been found effective.[20] Trazodone, a sedative antidepressant agent with anxiolytic properties and minor anticholinergic effects improves sleep disorders (25–75 mg). However, some patients may develop hypotension.

Anxiety

Anxiety occurs in 50% to 80% of patients with AD.[7,9,13] However, in contrast to agitation, aggression, psychosis, and depression, anxiety has been less well studied in patients with dementia. Anxiety and depression coexist and overlap with various symptoms, such as agitation and the awareness of the cognitive deficiencies with resulting helplessness.

The etiology and pathophysiology of anxiety in AD is not well understood. There is evidence that anxiety is associated with loss of serotonergic neurons in AD. Antidepressants enhancing serotonergic activity, particularly SSRIs, may improve depression and anxiety.

Benzodiazepines should be used with caution in dementia with anxiety because of the risk of worsening cognitive abilities, oversedation, gait disturbances, daytime sleepiness, and paradoxical effects.

The serotonin (5-hydroxytryptamine) 5-HT_{1A} receptor agonist buspirone, a nonbenzodiazepine that is generally well tolerated, may be beneficial in the treatment of anxiety in dementia. It is used at dosages of 10 to 45 mg/day.

Depression

Symptoms of depression are common in Alzheimer's disease, ranging from 20% to 60% in most epidemiological

Compound	Average dose (mg/day)	Starting dose (mg)	Comments
Lorazepam	0.5–1.5	0.5	Risk of falls
Melperone	25–100	25	Weak or no extrapyramidal side effects
Pipamperone	10–80	10	(Low) risk of extrapyramidal side effects
Chlorprothixene	15–75	15	Sedation, minor extrapyramidal side effects
Risperidone	0.5–1	0.5	(Low) risk of orthostatic hypotension
Olanzapine	5–10	2.5	Sedation
Carbamazepine	100–200	20	Slow dose titration, drug–drug interactions, risk of sedation
Divalproex sodium	125–1000	125	Risk of sedation, nausea, ataxia

Table V. Examples for drug treatment of aggressive behavior in patients with dementia.

Class	Compound	Average dose (mg/day)	Starting dose (mg)	Comments
SSRI	Citalopram[77]	20–40	10	
SSRI	Sertraline[78]	50–150	25	
RIMA	Moclobemide	75–450	75	
SNRI	Venlafaxine	37.5–150	37.5	Linear dose–response curve
NaSSA	Mirtazepine	15–45	15	Sedative properties
NRI	Reboxetine	2–6	2	

Table VI. Examples for drug treatment of depression in patients with dementia. SSRI, selective serotonin reuptake inhibitor; RIMA, reversible inhibitor of monoamine oxidase A; SNRI, serotonin and noradrenergic reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; NRI, norepinephrine reuptake inhibitor.

studies,[9,41] and 10% to 30% meet criteria for a major depressive disorder. Common manifestations include depressed mood, apathy, lack of interest, agitation, loss of emotional control (easily upset, tearful, or irritable), and worries about the future and finances. Depression is often the first symptom/syndrome of AD.[67] However, it remains unclear whether depressed mood is an early manifestation of AD or increases susceptibility through another mechanism.[68] The presence of dementia symptoms may impair reporting and recognition of depression. Depression may result from the patient's recognition of the severity of his or her cognitive impairment or from neurotransmitter dysfunctions associated with the underlying disease process.[68] The discussion on the psychological impact of insight into having AD is controversial. For many investigators, depression in most patients with AD is not "reactive" to the awareness of having AD or the disability associated with it.[67,69,70] Major depression tends to first manifest in AD patients with mild to moderate cognitive deficiencies, whereas in the advanced stages of dementia there might be insufficient brain tissue to maintain any depressive affect.[71]

All patients with cognitive decline and depressive symptoms should undergo a comprehensive evaluation to specify the type and cause of depression.[7,72,73] Particular attention should be paid to the differential diagnosis of primary dementia with secondary depressive symptoms from a primary major depressive episode with cognitive dysfunctions (depressive dementia), an adjustment disturbance, or minor depressive syndrome.[73] Insidious mode of onset, fluctuations in mood (irritability, loss of emotional control), objective deficits on neuropsychological tests, normal self-image, and progression of cognitive deficits point to primary dementia.[73,74]

Treatment of depression in dementia comprises pharmacotherapy and nonpharmacological strategies, such as psychological interventions to enhance quality of life (eg, emotion-oriented psychotherapy and stimulation-oriented treatment, including art or social therapies, exercise, and dance).[75] Developing a daily routine and the institution of pleasant activities are considered first step.[67] Simultaneously, the problem-solving skills of caregivers should be enhanced and psychoeducational programs conducted. Sometimes psychotherapeutic interventions with family members are indicated. Pharmacological treatment in aged patients with traditional antidepressants may evoke difficult clinical situations. Altered pharmacokinetics and pharmacodynamics associated with aging, accompanying physical disorders, as well as polypharmacy in the elderly, must

Side effects	TCAs	SSRIs	MAOIs	Venlafaxine	Mirtazepine	Nefazodone	Reboxetine
Anticholinergic	+++	+	0	+	+	(+)	+
Orthostatic hypotension	+++	0	+	0	+	+(+)	+
Hypertension	0	0	+(+)	+(+)	0	0	+
Weight gain	+++	+	+	+	++	+	+
Gastrointestinal symptoms	+	++	+	++	+	+	+
Sexual dysfunction	+(+)	++	+	++	+	+	+
Toxicity in overdose	+++	+	+++	+	+	+	+

Table VII. Common side effects of antidepressants. +, mild; ++, moderate; +++, strong; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.

all be considered.[75] The recommendation "start low, go slow" should be strictly followed.

Compounds, such as tricyclic antidepressants (TCAs) are characterized by a high potential for anticholinergic side effects, including memory impairments, delirium, behavioral toxicity, and cardiovascular dysfunctions. Demented patients appear particularly prone to these effects probably due to diminished capacities in central regulatory systems.[76] The new generation of antidepressants, particularly the SSRIs, the reverse inhibitors of monoamine oxidase A (RIMAs), tianeptine, venlafaxine, and mirtazepine have been demonstrated to be as efficient as traditional TCAs with a better tolerability[67,77] and appear appropriate for treatment of depression in dementia *(Tables VI and VII)*.[78,79] The choice of an antidepressant should be based on the patient's general medical and psychiatric status and the drug's profile of adverse effects.[75]

Conclusion

BPSDs are a major component of dementia. Neuropathological and biochemical studies have clearly demonstrated multiple neurotransmitter dysfunctions in patients with AD involving cholinergic, serotonergic, and noradrenergic pathways. These alterations have been associated with different psychopathological states including cognitive decline, depression, anxiety, agitation, aggression, sleep disturbances, and psychosis. There are a number of pharmacological and nonpharmacological treatments available that can enhance quality of life. ❑

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Trastornos de conducta en la demencia

Los síntomas psicológicos y los trastornos de conducta son características comunes y prominentes de la demencia. Ellos incluyen síntomas como depresión, ansiedad, psicosis, agitación, agresividad, desinhibición y trastornos del sueño. Aproximadamente un 80% a 90% de los pacientes con demencia sufren de tales trastornos de conducta. Existen interacciones complejas entre los déficits cognitivos, los síntomas psicológicos y los trastornos de conducta. Se ha desarrollado un gran número de instrumentos estandarizados, confiables y bien validados para cuantificar los síntomas conductuales y psicológicos de la demencia, y así poder evaluar la eficacia del tratamiento. Los procesos neurodegenerativos que ocurren en diversas áreas cerebrales, especialmente en la corteza fronto-temporal y en las regiones límbicas, llevan a disfunciones de los neurotransmisores colinérgicos, serotoninérgicos y noradrenérgicos, y de ese modo constituyen la base biológica de los síntomas conductuales; en cambio, los factores psicológicos y los rasgos de personalidad tienen un rol modificador. Se ha desarrollado un gran número de estrategias farmacológicas, psicoeducacionales, psicoterapéuticas y sociales para mejorar la calidad de vida de los pacientes y de sus cuidadores.

Troubles comportementaux de la démence

Les symptômes psychologiques et les anomalies comportementales constituent des caractéristiques à la fois courantes et importantes de la démence. Ils incluent des symptômes tels que la dépression, l'anxiété, la psychose, l'agitation, l'agressivité, la désinhibition et les troubles du sommeil. Environ 80 à 90 % des patients atteints de démence souffrent de tels troubles comportementaux. Des interactions complexes existent entre les déficits cognitifs, les symptômes psychologiques et les anomalies du comportement. Un grand nombre d'outils standardisés, fiables, et bien validés pour explorer les symptômes comportementaux et psychologiques de la démence ont été développés afin d'évaluer l'efficacité du traitement. Les processus neurodégénératifs dans différentes aires du cerveau, particulièrement dans le cortex frontotemporal et les régions limbiques, entraînant des dysfonctionnements des neurotransmetteurs cholinergiques, sérotoninergiques et noradrénergiques, forment la base biologique des symptômes comportementaux, alors que les facteurs psychologiques et les traits de personnalité jouent un rôle modificateur. Un grand nombre de stratégies pharmacologiques, psychoéducationnelles, psychothérapeutiques et sociales ont été développées pour améliorer la qualité de vie des patients et de leurs soignants.

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