Neurotherapeutics (2022) 19:99–116
https://doi.org/10.1007/s13311-021-01172-w

REVIEW

# Emotional and Neuropsychiatric Disorders Associated with Alzheimer's Disease

**Kenneth M. Heilman**[1,3,4] · **Stephen E. Nadeau**[2,3,4]

Accepted: 16 December 2021 / Published online: 10 January 2022


**Abstract**
Alzheimer's disease is associated with impairments in emotional communication including comprehension and production of facial emotional expressions, comprehension of affective prosody, and alexithymia. It is also associated with disorders of emotional experience including mood disorders (depression and anxiety), agitation/aggression, and psychosis. Agitation/aggression and psychosis are particularly disruptive, are associated with earlier institutionalization, and pose a major challenge to institutional management. Treatment of disorders of emotional experience has been primarily pharmacologic (reviewed here in detail) and has relied heavily on antipsychotic medications despite the small effect sizes demonstrated in a large number of randomized controlled trials and the prevalence of serious side effects associated with these drugs. Recent studies suggest that treatment with pimavanserin, an antipsychotic without activity at dopamine receptors, may represent an important advance for treatment of psychotic manifestations, even as the drug appears to pose significant risk. Dextromethorphan/quinidine may represent an important advance in the treatment of agitation/aggression. There is also compelling evidence that sleep disorders, which are common among patients with Alzheimer's disease and are readily treatable, may potentiate psychotic manifestations and agitation/aggression, but further studies are needed.

**Keywords** Alzheimer's disease · Emotional facial expression · Emotional prosody · Alexithymia · Agitation/aggression · Depression · Psychosis · Sleep disorders

## Introduction

An emotion corresponds physiologically to a pattern of neural activity in orbitofrontal cortex and linked limbic structures that represents the subjective value that defines that emotion [1]. Emotions may be elicited by salient environmental stimuli, e.g., the visual perception of a rose or a mutilated body, the sound of a nearby gunshot or a Brandenburg concerto, a bitter or sweet taste, or a painful stimulus, or by memories evoked by these stimuli. Patterns of neural activity in association cortices evoked by such stimuli in turn elicit patterns of activity in the orbitofrontal limbic system that define the corresponding emotion. In daily life, most often our emotions are evoked in the course of our interactions with other people, conveyed largely by their emotional facial expressions and their affective prosody. We in turn communicate our own emotions to others via our own facial expressions and affective prosody. The experience of emotions through such emotional communication depends upon the integrity of association cortices (predominantly in the right hemispheric convexity) and the integrity of the orbitofrontal limbic system, the substrate for emotional experience. Emotional experience can also be affected by endogenous dysfunction of orbitofrontal limbic systems associated with agitation/aggression, depression, anxiety, and psychosis.

Emotional manifestations of Alzheimer's disease (AD) thus can be logically divided into disorders of emotional

✉ Stephen E. Nadeau
snadeau@ufl.edu

1 Geriatric Research, Education, and Clinical Center, Malcom Randall VA Medical Center, 1601 SW Archer Road, Gainesville, FL 32608-1197, USA

2 Research Service, Malcom Randall VA Medical Center, 1601 SW Archer Road, Gainesville, FL 32608-1197, USA

3 The Brain Rehabilitation Research Center, Malcom Randall VA Medical Center, 1601 SW Archer Road, Gainesville, FL 32608-1197, USA

4 Malcom Randall VA Medical Center and the Department of Neurology, University of Florida College of Medicine, Gainesville, FL, USA

communication and disorders of emotional experience. Disorders of emotional communication include impaired comprehension of affective emotional speech prosody and emotional facial expression, impaired production of affective emotional prosody and facial emotional expression, and alexithymia. Disorders of emotional experience include mood disorders such as depression and anxiety, hallucinations and delusions (psychosis), and agitation and aggression. All these changes in emotion in patients with AD can lead to degradation of quality of life for patients and family members. Disorders of emotional experience tend to precipitate institutionalization and present the greatest challenges to institutional care.

Apathy, as typically operationally defined, is often included among neuropsychiatric features of AD. As will be discussed, it may best be viewed as predominantly a manifestation of impaired executive function.

## Disorders of Emotional Communication

There are several means by which emotions can be communicated: via facial expressions, via vocal emotional prosody, through words, and through body postures and movements.

### Comprehending Facial Emotional Expressions

During interpersonal communication, the recognition and production of facial emotional expressions are important means of communicating emotional experience. Hargrave, Maddock, and Stone [2] examined facial emotion matching, facial emotion labeling, and same-different emotion differentiation in patients with AD and healthy elderly volunteers. When compared with control participants, patients with AD were significantly impaired on all three measures. Patients with AD were also impaired on a facial identity matching task. When Hargrave et al. used facial identity matching scores as a covariate, they found that the facial emotion processing deficit may be independent of the impairment in non-emotional face processing. It has also been reported that patients with AD have the greatest difficulty recognizing sad faces [3]. Lavenu and Pasquier [4] found that as AD progressed, so did the impairment in recognizing emotional faces. They thought that this decline could be related to the progressive atrophy of the amygdala, the anterior temporal cortex, and the orbital frontal cortex. However, they provided no strong evidence to support this localization. Some investigators have not been able to detect an impairment in the understanding of emotional faces in patients with AD [5]. These disparate findings suggest that further research is needed.

Phillips et al. [6] reported that in patients with AD, impairments of facial emotion perception predicted quality of life, independent of variance related to cognitive functions and mood, suggesting the potential importance of emotion decoding skills in the well-being of older adults.

A failure to recognize emotional faces can also be caused by a visual attentional disorder. Bourgin et al. [7] investigated visual emotional processing in patients with AD by measuring performance on a task requiring saccades away from or toward emotional stimuli. Age-matched controls exhibited a bias toward negative stimuli, making more anti-saccade errors for negative stimuli and quicker saccades toward negative stimuli. In contrast, patients with AD exhibited no emotion-related differences. These results suggest that there is impairment in early emotional attention in patients with AD.

Güntekin et al. [8] performed EEG studies of patients with AD who had impairment in comprehension of emotional facial expressions and of matched healthy control participants. They found significant a hemispheric difference between these two groups. There was a right hemisphere alpha power dominance in healthy subjects but not in patients with AD.

Klein-Koerkamp et al. [9] wanted to learn whether abnormalities in emotional decoding in patients with AD were related to general cognitive decline or reflected an independent deficit. They performed a comprehensive meta-analysis of existing studies that compared patients with AD with age-matched healthy older adults on measures of emotional decoding. Their goals were to quantify the magnitude of the AD deficit and to identify the variables that may modulate the deficit. Their results indicated that patients with AD have significant impairment in emotional decoding regardless of the emotional task, the type of stimuli used, the type of emotion tested, or disease severity. Even after these investigators controlled for cognitive status, the emotional performance of patients with AD was still poorer than that of the healthy controls. These results suggest that impaired emotion processing in these patients cannot be solely explained by the cognitive deficit. They provide evidence that progressive neuropathological changes associated with AD can specifically impair emotional processing.

### Producing Facial Emotional Expressions

Facial emotional expressions can be either volitional, produced by means of the primary motor cortex via the corticobulbar tracks, or they can be spontaneous, elicited by patterns of neural activity in the orbitofrontal cortex and the limbic system [1]. Intentional (voluntary) emotional facial expressions are a highly complex and are a learned form of human communication [10]. These intentional expressions are often used to influence the behavior of others.

Smith [11] examined spontaneous facial expression in response to emotional stimuli and its relationship to subjective experience in patients with mild dementia of the Alzheimer type and in age-matched controls. Participants viewed a series of video clips depicting various emotions. The participants were videotaped while watching the vignettes, and their facial expressions were scored using the Facial Action Coding System [12]. Participants with AD showed more facial expression associated with negative emotion in reaction to the sad vignettes than did controls. However, self-ratings of emotional experiences were similar for both groups. Correlations between emotion ratings and intensity of facial expression were higher for healthy controls during happy vignettes.

Mograbi, Brown, and Morris [13] studied emotional reactivity in patients with mild to moderate AD and matched controls by using films with positive, neutral, or negative emotional content. Reactivity was measured through a self-report questionnaire and the filming of facial expressions during viewing. The patients with AD showed reduced self-reported reactivity to films with negative content but exhibited facial responses that were similar to those of controls for all films.

In summary, the limited studies on spontaneous emotional facial expression in patients with AD have yielded conflicting results.

## Comprehending Affective Prosody

Taler et al. [14] explored the emotional prosodic processing impairment associated with AD and in addition sought to learn if this disorder also impaired grammatic prosody. Patients with AD were impaired in comprehending both emotional prosody and grammatic prosody (discriminating between statements, questions, and commands). These results suggest that impairments in affective prosody processing in AD may be related to a more general prosodic processing impairment. It was also noted that the participants with AD had mild disease, suggesting that prosodic impairments occur early in this disease. Templier et al. [15] also tested comprehension of emotional prosody in patients with AD and found that these patients were impaired.

## Producing Affective Prosody

Horley, Reid, and Burnham [16] investigated the expression of emotional prosody in patients with moderate dementia of the Alzheimer's type, as well as control participants, investigating expression of happiness, anger, sadness, and surprise. In this expressive task, objective acoustic measurements revealed significantly less pitch modulation by the Alzheimer group. However, these measurements showed that the patients with AD retained their ability to vary pitch level, pitch modulation, and speaking rate as a function of emotion.

Martínez-Sánchez and co-workers [17] studied the production of speech prosody in patients with AD and healthy controls by measuring variation in fundamental frequency and amplitude of speech on a reading task. Their results revealed that pitch variations in speech and variations in syllable timing were reduced in the Alzheimer's group and that these impairments tended to produce a "flat" speech prosody in these patients.

## Alexithymia

The term alexithymia come from Greek and means "without words for emotions." However, it is presently defined by impaired awareness of one's feelings, reduced ability to explicitly identify and describe feelings, and limited differentiation of emotional states (see recent reviews by [1, 18]). Three scales are often used to assess patients for alexithymia: the Beth Israel Questionnaire, the Shalling Sifneos Psychosomatic Scale, and the Toronto Alexithymia Scale.

There have been only a few studies of alexithymia in patients with AD. Sturm and Levenson [19] reported that alexithymia scores were positively correlated with behavioral deficits in patients with dementia and were negatively correlated with the grey matter volume of the right pregenual anterior cingulate cortex. Yuruyen et al. [20] found significantly greater alexithymia (defined by scores on the Toronto Alexithymia Scale) in patients with AD and patients with mild cognitive impairment. However, they found no significant differences between these two groups of patients. Smirni et al. [21] also found higher total alexithymia scores in patients with AD or MCI than in healthy participants. In contrast, Arroyo-Aniló et al. [22] tested patients with mild AD and a matched group of healthy control participants for alexithymia using the Shalling Sifneos Psychosomatic Scale and found no differences. They also did not find any significant correlations between alexithymia scores and cognitive variables. The reason for the different result is not certain, but as this study used the Shalling Sifneos Psychosomatic Scale and other studies have use the Toronto Alexithymia Scale, it is possible that the difference is methodologic in origin.

## Treatment of Disorders of Emotional Communication

Treatment of disorders of emotional communication in general has recently been reviewed in detail elsewhere

[23]. We are not aware of any research on these treatments in patients with Alzheimer's disease.

## Apathy

Apathy has been defined as a neuropsychiatric symptom characterized by a loss of motivation, emotional reactivity, and initiative [24]. In 2021, the International Society for CNS Clinical Trials and Methodology (ISCTM) Apathy Work Group [25], in its refinement of diagnostic criteria for apathy, reached a consensus that manifestations in two of three dimensions must be present: B1, diminished initiative; B2, diminished interest; and B3, diminished emotional expression/responsiveness.

The word apathy derives from the Greek term for absence of feeling. The word abulia derives from a Latin-Greek construction meaning "without will." Apathy therefore relates to emotions and abulia to intention, an executive function. Widely used metrics for apathy (Apathy Evaluation Scale, Clinician Version [AES-C]) [26], the Apathy Scale [27], the Lille Apathy Rating Scale [LARS] [28], the Apathy-Motivation Index [29], the Dementia Apathy Interview and Rating [DAIR] [30], and the Neuropsychiatric Inventory Questionnaire (NPI)(1 item) [31]) conflate the two terms. Furthermore, a quick perusal of the items in these metrics reveals that they predominantly tap abulia (see also [32, 33]). This was made quite explicit in the 2018 consensus criteria for apathy: "a quantitative reduction of goal-directed activity in comparison to a patient's previous level of functioning" [34].

Research on apathy has faced a number of major challenges. One has been that the large number of more fundamental neural processing deficits implicated by the diagnostic criteria implicates multiple neural networks, each supporting a particular computational function. Diminished initiative (B1) and diminished interest (B2) are classic executive function deficits and, as such, suggest either abulia or akinesia. Deficits in emotional reactivity during person-to-person interactions (or person-to-pet interactions) could reflect impairment in perceptual processing (impairment in comprehension of facial expression or impairment in comprehension of affective prosody), impairment in emotional expression, or a disorder of orbitofrontal-limbic function that attenuates (as in 9) or distorts (as in 12) perceptions or memories potentially evocative of emotion and emotional expression. However, apathy, in operational terms, as noted above, is defined by the items included in 9 scales, which largely probe executive functions supported by dorsolateral prefrontal cortex. On the other hand, imaging studies (reviewed by 24) particularly point to pathology in the anterior cingulate cortex and medial prefrontal regions. This suggests that while apathy scale items load heavily on prefrontal functions associated with dorsolateral prefrontal cortex, the fundamental deficit may actually be best interpreted as a form of akinesia, as classically seen with midline frontal lesions [1, 35].

Apathy—absence of feeling—might best be viewed as a disorder of the magnitude of emotional feeling. This could be related to pathology in systems supporting emotional communication or in the orbitofrontal-limbic system. Because orbitofrontal neurofibrillary tangles do not typically develop until the most advanced stages of AD [36], disorders of emotional communication are likely to be the major factors in early and middle stages of the disease and would best be tested using the methods described in the forgoing. Orbitofrontal disease might best be tested using behavioral or autonomic responses to emotion-provoking stimulus sets such as the International Affective Pictures System (IAPS) [37, 38]. Joshi, Jimenez, and Mendez [39] presented pictures from the IAPS [37] to patients with early AD and matched controls. These pictures vary in valence (positive to negative) and their potential for eliciting arousal. These investigators measured their participants' initial heart rate deceleration, a measure of their orienting response, and their focusing of attention. Patients with early-onset AD had significantly larger orienting responses than did the normal controls across all conditions. The patients with early-onset AD, when compared to the controls, even showed orienting responses to less threatening stimuli, including pleasant stimuli. The orienting responses among the participants with AD significantly correlated with anxiety scores on the NPI.

The responses of some patients to SSRIs or SNRIs may provide a clue to the mechanisms of true apathy—absence of feeling related to orbitofrontal-limbic pathology. In the experience of one of us, a not particularly bright or introspective patient treated for migraine, neck pain, depression, and insomnia returned to clinic after his dose of venlafaxine had been increased and asked if it could be reduced, explaining "I'd rather feel sad than feel nothing at all." An SSRI/SNRI apathy syndrome is now well-reported in the psychiatric literature [40]. In one large study, emotional blunting, as assessed with the Oxford Questionnaire on the Emotional Side Effects of Antidepressants, was present in 46% of patients and was observed with SSRIs, SNRIs, and tricyclic antidepressants [41]. Emotional blunting correlates with severity of depression but clearly has a unique, antidepressant-associated component. Only about 50% of patients view it negatively. The apathy syndrome appears to be an extreme variant of antidepressant-associated emotional blunting.

Apathy as conventionally operationally defined—actually abulia—is very commonly observed in patients AD. It often starts even before the cognitive decline,

and it often progresses once this impairment becomes manifest. In neuroimaging studies, apathy in MCI and AD is associated with aberrant white matter integrity in widely distributed pathways [42].

Treatment with methylphenidate has been reported to significantly reduce abulia symptoms and improve global cognition [43] (see also recent Cochrane systematic review [44]). Open-label studies of cholinesterase inhibitors such as donepezil have also showed improvements in abulia [45].

## Disorders of Emotional Experience: Agitation/Aggression, Depression, and Psychosis

Agitation/aggression, depression, and psychosis (hallucinations or delusions) are the three most common behavioral and psychological endophenotypes of AD; each is observed in 30–40% of patients [46–49]. Anxiety symptoms have been observed in up to 70% of patients with AD and are strongly associated with other neuropsychiatric manifestations [50]. Anxiety is particularly likely to be a problem in patients who develop AD before the age of 65 [51, 52].

### Agitation/Aggression

Agitation in the context of dementia is defined as excessive motor activity and verbal or physical aggression that is associated with observed or inferred evidence of emotional distress; that is severe enough to produce excess disability; that, in the physician's opinion, is beyond that due to the cognitive impairment; and that cannot be attributed solely to another comorbid psychiatric or medical condition [53]. Agitated behavior is often preceded by interactions with institutional staff members involving either speaking or touching or by intrusion by staff members into the patient's own personal space, particularly in the context of bathing, toileting, grooming, or dressing, or during redirection of the patient. Physically aggressive behavior is often preceded by verbal aggression, acts of non-compliance, or defiance of requests [54]. Lower prevalence of agitation has been associated with favorable scores on measures of physical environment and staff treatment activities, such as general design, space, lighting, noise, maintenance, resident rooms, quality of the staff interaction with residents, and the proportion of residents engaged in planned activities [55] (but see also 56). Agitation is associated with incident anxiety, apathy (abulia), and delusions [57] but not depression [46]. Treatment-related reductions in agitation have been associated with treatment related reductions in psychotic manifestations [58]. A number of factors can predispose to the acute or subacute development of agitation. These include chronic or acute pain, sleep disturbances (including sundowning), changes in medications, acute medical illness, hospitalization, and delirium [59].

Agitation is often associated with more severe dementia, more rapid progression to severe dementia, reduced quality of life, earlier death, and worse relationships with family members and caregivers [56, 60]. It increases caregiver burden [61], risk of institutionalization, and costs associated with care of patients with AD [62].

### Depression

Olin et al. [63] defined provisional diagnostic criteria for depression in AD: clinically significant depressed mood; decreased positive affect or pleasure in response to social contact and usual activities; social isolation or withdrawal; disruption of appetite; disruption of sleep; psychomotor changes (e.g., agitation or retardation); irritability; fatigue or loss of energy; feelings of worthlessness, hopelessness, or excessive or inappropriate guilt; and recurrent thoughts of death, suicidal ideation, plan, or attempt.

Most depression scales have been validated in young participants. In contrast, the Geriatric Depression Scale [64] and the Cornell Scale for Depression in Dementia [65] were developed for use in geriatric patients. Patients with a cognitive impairment often fail to report or underreport symptoms of depression because of impairment in memory or ability to communicate, and thus, input from caregivers is important in diagnosing depression in patients with AD. Therefore, many clinicians use the Cornell Scale because it includes input from caregivers.

AD appears to frequently be associated with depression, and depressive manifestations are often quite persistent [66]. Reifler et al. [67] reported that of 102 patients satisfying DSM-III criteria for primary degenerative dementia, 26% had depression. Cummings et al. [68] found evidence of depressive symptoms in 17% of patients with AD; however, no patients with severe depression were identified. A relatively recent study reported a prevalence of up to 50% [69], and a meta-analysis of 57 studies of patients with MCI found a 32% prevalence of depression [70]. These differences in results may be related to differences in the diagnostic criteria used for depression in patients with AD.

MRI structural imaging studies of patients with late life depression and AD have demonstrated abnormalities in hippocampal volume and ventricular enlargement [71]. Some studies have suggested that depression may be related to degeneration of the dorsal raphe nucleus, which supplies serotonin to the brain, as well as the locus coeruleus, which supplies norepinephrine [72]. More severe loss of serotonin receptors and serotonin transporter binding has been reported in patients with AD and depression, findings that may have implications for treatment [73]. Other studies

suggest that the mechanisms may be more complex (1). In general, older adults with late-onset depression are more likely to have cerebrovascular disease, including white matter hyperintensities or leukoencephalopathy, especially when these white matter changes affect the frontal-striatal and frontal-limbic brain networks [73]. There are other factors that appear to be related to the development of depression in patients with AD. These include being female, having a previous history of depression, ApoE4 positivity, and a family history of depression. It has been reported that depression is less severe in the later stages of AD [74]. Some medications, such as centrally acting beta blockers (e.g., propranolol), can induce depression.

Zubenko et al. [75] compared depression in patients with AD to depression in aging participants without AD. They found that patients with AD and depression had more difficulties with concentration and indecisiveness, fewer sleep disturbances, and fewer reports of feelings of worthlessness or excessive guilt.

### Psychosis

In a retrospective study of 372 patients with autopsy-confirmed neurodegenerative disease [76], psychosis was by far most common in patients with Lewy body disease/AD and frontotemporal lobar degeneration with transactive response DNA binding protein-43 (TDP-43) inclusions. However, psychotic manifestations were documented in 22.5% of patients with AD, 6–41% with hallucinations (pooled prevalence of 16% in clinical series [77]), and 9–59% with delusions (pooled prevalence of 31% in clinical series [77]). Often psychotic manifestations are observed in the first 3 years of the disease. Auditory hallucinations are uncommon. Hallucinations tended to occur in association with sleep in 61.5%.

The nature of delusions differs among the major causes of dementia. In general, they are almost always conceivably possible [76]. Delusions in patients with AD are most often paranoid and infrequently are they persecutory, grandiose, erotic, reflect jealousy, or involve misidentification of people (Capgras syndrome) or places [76].

The precise toll taken by psychosis per se on families and the healthcare system is not certain. However, the additional burden posed by neuropsychiatric symptoms and usually measured using the NPI [31]) may be substantial. Neuropsychiatric manifestations in general and psychotic symptoms in particular are often associated with reduced caregiver ratings of health and quality of life [78]. They are also associated with much greater direct and indirect medical costs, even in patients with mild dementia [79]. Psychotic manifestations are associated with increased risk of cognitive and functional decline, institutionalization, and death [60, 80].

## Treatment

### Primary Treatment of Disorders of Emotional Experience

Although there is no substantially effective primary treatment for AD, there are several conditions susceptible to treatment that may contribute to behavioral and psychological features of AD. These conditions include depression, pain, and sleep disorders. Some of these conditions may be difficult to identify in patients with severe dementia, and in practice, they may go undetected and untreated, even as their treatment may be fairly benign (see below).

#### Depression

The National Institute for Health and Care Excellence suggests that, for people with mild-to-moderate dementia, psychological treatments should be tried before antidepressants are initiated [73]. These behavioral and cognitive-behavioral modification programs include emotion-oriented therapies, psychotherapy, and sensory-stimulation therapies (e.g., music therapy, art therapy, pet therapy, aromatherapy, multisensory approaches, and structured activity programs).

The American Psychiatric Association [81] practice guidelines for pharmacologic treatment of patients with AD and other dementias who are depressed suggest that selective serotonin reuptake inhibitors (SSRIs) should be the first choice. However, this guideline is not powered by clinical trial data, and there is a paucity of adequately powered randomized controlled trials (RCTs) to test the value of these drugs in AD. Systematic reviews of published studies have failed to demonstrate a treatment effect [66, 82]. Furthermore, as with treatment studies of depression in any context, the conduct of RCTs that capture the flexibility of antidepressant treatment in clinical practice (with the opportunity for substantial titration and use of alternative or combined drug regimens), coupled with the magnitude of placebo effects, presents a major challenge.

#### Pain

Agitation/aggression can be related to a number of factors, including pain or discomfort related to an occult urinary tract infection, constipation, a broken bone, or degenerative joint disease; to headache or nausea; to frustration with inability to communicate; or it can be directly related to dementia pathology. Pain may be difficult to ascertain in patients with dementia, but Cohen-Mansfield and Lipson [83] have shown that it can be assessed even in a population of patients with an average MMSE of 6.3. In a

large cohort study [84], uncontrolled pain was associated with depression, psychotic manifestations, and disruptive behaviors including physical or verbal behaviors directed toward others and rejection of care.

Husebo et al. [85], in cluster randomized trial conducted at 18 nursing homes and involving 352 residents with dementia (mean MMSE 7.5), found that a very modest stepped analgesia regimen (initiated with scheduled acetaminophen, escalated as needed to a maximum opioid regimen of 24 mg morphine equivalent/day) reduced scores on the Cohen-Mansfield Agitation Inventory by a mean of 4.5 points (statistically significant at all time points; mean effect size 0.28) (see also [86]). In a secondary analysis, Husebo et al. [87] found that the greatest effect was on verbally agitated behavior (effect size 2 relative to placebo), followed by physically non-aggressive behavior (pacing, trying to get to a different place, general restlessness, inappropriate dressing or disrobing, handling things inappropriately, and performing repetitious mannerisms), and aggressive behavior (hitting, kicking, pushing, scratching, biting, grabbing, throwing things, cursing or verbal aggression, spitting, tearing things/destroying property, hurting self or others, and screaming) (all differences statistically significant).

### Sleep Disorders

In a systematic review and meta-analysis of 48 studies of patients with AD, sleep disorders were found in 14–69% (pooled prevalence 39%) [77]. These include prolonged latency, poorly sustained sleep, reduced sleep efficiency, sleep disordered breathing, restless leg syndrome (RLS)/periodic leg movements of sleep, circadian rhythm disturbances (often with sundowning), and excessive daytime sleepiness [88, 89]. Patients with mild or moderate AD exhibit sleep fragmentation (increase in the number and duration of awakenings) and reduced slow-wave sleep and rapid eye movement sleep. Between 40 and 70% of patients with AD exhibit > 5 apneas/hypopneas/hour [89], and 24% exhibit RLS [90]. Sleep disorders, irritability/lability, and anxiety are the three factors most strongly associated with NPI caregiver distress scores [91].

Sleep disorders are associated with and may contribute to behavioral and neuropsychiatric manifestations of AD, and to the extent that they do, they may represent a relatively easy means of treating these manifestations. A factor analysis of 362 patients with AD utilizing the NPI identified four endophenotypes: mood, hyperactivity, psychosis, and executive function. Nighttime behavioral disturbances loaded highly on psychosis, as did agitation (46). Agitation has been particularly associated with RLS [92].

**Treatment** Diurnally synchronized bright light therapy [89, 93, 94] and continuous positive airway pressure (CPAP) have been shown to improve sleep quality, daytime sleepiness, and cognitive function [88, 89, 95]. However, providing bright light therapy in an institutional setting is likely to be challenging. Compliance by demented patients with CPAP may be low.

RLS is readily treatable with dopaminergic drugs (levodopa/carbidopa continuous release, pramipexole, or ropinirole) or with alpha-2-delta voltage-gated calcium channel receptor blockers (gabapentin, pregabalin) in titrated dosage.

Trazodone, in doses ranging between 25 and 600 mg, has been tested in over 45 RCTs for its value in treating insomnia (primary, secondary, in the context of depression, and in patients with alcohol dependence) [96]. In all but two of these studies, it was judged to be highly effective and associated with minimal to no side effects beyond morning sedation in some individuals. Only one RCT of a fixed dose of 50 mg for treatment of insomnia in patients with AD (community dwelling) has been reported [97]. Results were comparable to those in other populations, and there was no excess of adverse effects relative to placebo. Dose response to trazodone is highly variable, and titration is essential.

In a 4-week placebo controlled RCT of suvorexant 10–20 mg (titrated) involving 285 participants with mild to moderate AD and insomnia, the drug was associated with a modest increase in sleep duration (28 min, as measured by polysomnography), mainly during latter parts of the night, and no side effects except somnolence insufficient in degree to lead to discontinuation of the drug [98].

In summary, sleep disorders are generally readily treatable with pharmacologic approaches using drugs with minimal side effects. To the extent that sleep disorders potentiate agitation/aggressiveness and psychosis (an under-studied subject), treatment of these disorders may be of substantial benefit for behavioral and psychological manifestations of AD.

## Symptomatic Treatment of Disorders of Emotional Experience

When factors that might be contributing to behavioral and psychological disorders of patients with AD cannot be identified or treated, symptomatic treatments are employed. Although current symptomatic treatments for neuropsychiatric disorders associated with AD have contributed to our ability to manage patients with this disease, the effectiveness of all drugs currently in use is, on average, modest and often insufficient, and many drugs, particularly the antipsychotics, carry with them substantial risk of serious side effects. A number of trials of new agents, some quite novel, are in progress [99].

### Anticonvulsants

Several adequately sized RCTs of carbamazepine and valproate suggest that these drugs do not have clinically significant effects on behavioral and psychological symptoms of dementia, most particularly agitation, and that they are often associated with adverse effects [100, 101]. However, one RCT of carbamazepine in 51 severely demented institutionalized patients [102] did report a significant benefit of the drug on the primary outcome measure, the Brief Psychiatric Rating Scale (BPRS), as well as several secondary measures, including a factor loading on agitation derived from a principal component analysis of the BPRS and tabulation of extra staff time required for care of the patient. There do not appear to have been any RCTs of pregabalin, gabapentin, lamotrigine, or topiramate.

### Acetylcholinesterase Inhibitors

Many studies have evaluated the impact of acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) on neuropsychiatric symptoms of AD [103] and have demonstrated significant but modest reductions in symptoms including delusions, agitation, depression, anxiety, apathy, disinhibition, and irritability. However, in a meta-analysis of 12 RCTs, Campbell et al. [104] found a weighted mean decline in NPI score of 1.38 points and a drug effect size of only 0.10. Other studies suggest that these results may reflect either the mildness of neuropsychiatric symptoms in participants typically recruited to trials of efficacy defined by measures of cognitive function [105] or heterogeneity in response to acetylcholinesterase inhibitors. In a randomized withdrawal study of donepezil administered to 96 participants with elevated NPI scores, Holmes et al. [106] reported a decline in NPI score of 2.9 points in those still on donepezil and an increase of 3.3 points in those on placebo 12 weeks after randomization. Mega et al. [107], in an open label trial of donepezil, found that 41% of participants (responders) demonstrated a $\geq$4-point decrease in NPI score, whereas 28% (non-responders) demonstrated a $\geq$4-point increase in NPI score. At baseline, responders had significantly worse delusions, agitation, depression, anxiety, and disinhibition (see also Cummings et al. [108]).

### Antidepressants

The use of antidepressants to treat depression in the context of AD was discussed above. We here consider other applications.

An RCT of citalopram 30 mg/day in 186 patients with AD with clinically consequential agitation demonstrated clinically significant reduction in agitation as defined by the two primary outcome measures, the Neurobehavioral Rating Scale-Agitation Subscale (NBRS-A) and the Clinical Global Impression of Change (GCIC), as well as the Cohen-Mansfield Agitation Inventory (CMAI) [109]. The citalopram-treated group experienced a significantly greater decline in NBRS-A score ($p=0.04$; effect size 0.29), CMAI ($p=0.008$; effect size 0.36), and a significantly better GCIC score ($p=0.007$). Major depressive disorder was an exclusionary criterion for this study but depression is common and may be particularly difficult to diagnose in patients with dementia. Citalopram treatment was associated with 1 point worsening in MMSE scores, prolongation of QT-interval, and an increase in fall risk. A secondary analysis of trial results revealed that citalopram treatment was also associated with reductions in delusions, hallucinations, anxiety, and irritability [110]. A recent RCT of mirtazapine, titrated to 45 mg, in 204 participants failed to demonstrate any benefit [111].

There is no logical reason to think that effects similar to those achieved with citalopram might not be achieved with other SSRIs, SNRIs, or bupropion, given the general comparability of the effects of these drugs. However, empirical evidence is lacking.

### Antipsychotics

Because of the prevalent use of antipsychotic medications for treatment of behavioral and psychological symptoms in AD, notwithstanding their serious side effect profile, we review this literature in somewhat more detail. A summary of results of RCTs of antipsychotic medications used to treat psychosis is reported in Table 1. Results of RCTs of trials targeting agitation are summarized in Table 2.

**Adverse Effects of Symptomatic Treatment** Even the newer, atypical antipsychotic drugs, which have largely replaced first generation drugs in clinical practice, are associated with a host of adverse effects, many serious [112] — hence FDA "black box" warnings. These include worsening of cognition [113], Parkinsonian manifestations, gait disturbances, drowsiness, and tardive dyskinesia; venous thromboembolic events (doubling of risk); peripheral edema; urinary tract infections; QT interval prolongation, torsade de pointes, and sudden cardiac death; metabolic syndrome; stroke (doubling of risk) [112]; and death (odds ratio 1.9–2.19) [114]. Mortality risk is highest in the first 6 months of use, it is dose related, and there is little difference in relative risk between atypical and typical antipsychotics [114].

**Summary of Treatment Effects** A vast effort has been devoted to RCTs of antipsychotic agents for treatment of neuropsychiatric manifestations of AD. Unfortunately, they have been shown to yield modest benefits (small

**Table 1** Randomized controlled trials of antipsychotic drug treatment for psychotic manifestations in Alzheimer's disease

| Author | Patient Type | N | NPI/NPI-NH psychosis subscale change score (unless otherwise specified) | | | | CGI-S | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Drug | Placebo | *p* | ES | Drug | Placebo | *p* | ES |
| **Aripiprazole** | | | | | | | | | | |
| De Deyn et al. [148] 10 mg/day | Outpatient | 208 | −6.55 | −5.52 | .17 | - | −0.69 | −0.54 | .345 | - |
| Mintzer et al. [149] 10 mg/day | Institutionalized | 487 | −6.87 | −5.13 | .013 | - | −0.72 | −0.46 | .031 | - |
| Streim et al. [150] 10 mg/day | Institutionalized | 256 | −4.53 | −4.62 | .883 | .02 | −0.57 | −0.43 | .198 | .22 |
| **Olanzapine** | | | | | | | | | | |
| De Deyn et al. [151] 7.5 mg/day | Institutionalized | 257 | −6.2 | −5.0 | NS | .24 | 3.0* | 3.2* | NS | .22 |
| Debert et al. [152] 2.5–10 mg/day flexible | Outpatient | 284 | −4.0 | −4.7 | NS | .16 | 0.0 | 0.0 | NS | 0 |
| Street et al. [153] 5 mg/day | Institutionalized | 100 | −3.6 | −1.6 | .001 | .29 | - | - | - | - |
| 10 mg/day | | 94 | −2.2 | −1.6 | 0.04 | .09 | - | - | - | - |
| 15 mg/day | | 96 | −1.9 | −1.6 | 0.24 | .04 | - | - | - | - |
| Sultzer et al. [154] Adjusted dose: mean 5.5 mg/day | Outpatient and adult living facility | 238 | −0.3‡ | −0.2‡ | .199 | .067 | 3.9* | 4.2* | .057 | - |
| **Pimavanserin** | | | | | | | | | | |
| Ballard et al. [117] 34 mg/day | Institutionalized | 178 | −3.76 | −1.93 | .04 | .35 | - | - | NS | - |
| **Quetiapine** | | | | | | | | | | |
| Sultzer et al. [154] Adjusted dose, mean 56.5 mg/day | Outpatient and adult living facility | 233 | −0.4‡ | −0.2‡ | .352 | .137 | 3.8* | 4.2* | .031 | - |
| Tariot et al. [155] 100 mg/day | Institutionalized | 179 | −9.06¶ | −6.74¶ | NS | .23 | -0.60 | -0.47 | NS | .18 |
| Zhong et al. [156] 100 mg/day | Institutionalized | 216 | −1.8 | −2.5 | NS | .14 | 3.2* | 3.6* | NS | - |
| Zhong et al. [156] 200 mg/day | Institutionalized | 209 | −2.5 | −2.5 | NS | 0 | 3.0* | 3.6* | .017 | - |
| **Risperidone** | | | | | | | | | | |
| Brodaty et al. [157] adjusted: .5–2 mg/day, mean = 0.95 mg | Institutionalized | 301 | −2.0† | −0.7† | .004 | - | - | - | - | - |
| Debert et al. [152] 0.5–2 mg/day flexible | Outpatient | 281 | −4.2 | −4.7 | NS | .12 | 0.1 | 0.0 | NS | .125 |
| Katz et al. [158] 0.5 mg/day | Institutionalized | 307 | −2.2† | −1.9† | .316 | - | - | - | - | - |
| 1 mg/day | | 309 | −2.6† | −1.9† | .054 | - | −0.9 | −0.5 | .002 | - |
| 2 mg/day | | 323 | −3.2† | −1.9† | .002 | - | −1.0 | −0.5 | <.001 | - |
| Mintzer et al. [159] adjusted 0.5–1.5 mg/day; mean 1.03 mg | Institutionalized | 416 | −2.9† | −2.3† | .118 | .13 | - | - | - | - |
| Sultzer et al. [154] adjusted dose: mean 1.0 mg/day | Outpatient and adult living facility | 223 | −0.7‡ | −0.2‡ | .010 | .32 | 3.5* | 4.2* | <.001 | - |

*NPI* Neuropsychiatric Inventory; *NPI-NH* Neuropsychiatric Inventory-Nursing Home; *CGI-S* Clinical Global Impression-Severity of Illness; *ES* effect size (values provided when published data adequate)

*Global Clinical Impression of Change (lower is better)

†Behavioral pathology in Alzheimer's disease – psychosis subscale

‡Brief Psychiatric Rating Scale – psychosis factor score

¶Brief Psychiatric Rating Scale – total

**Table 2** Randomized controlled trials of antipsychotic drug treatment for agitation/aggression in Alzheimer's disease

| Author | Patient type | *N* | Various (see footnote) | | | | CGI-S | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Drug | Placebo | *p* | ES | Drug | Placebo | *p* | ES |
| **Brexpiprazole** | | | | | | | | | | |
| Grossberg et al. [160] 2 mg/day | Institutionalized | 276 | −21.6* | −17.8* | .040 | .22 | −1.27 | −1.11 | NS | .23 |
| **Olanzapine** | | | | | | | | | | |
| Debert et al. [152] 2.5–10 mg/day flexible | Outpatient | 298 | −1.3* | −0.9* | NS | - | 0.0 | 0.0 | NS | - |
| Street et al. [153] 5 mg/day | Institutionalized | 206 | −4.1† | −2.1† | .01 | - | - | - | - | - |
| 10 mg/day | | | −3.9† | −2.1† | .02 | - | - | - | - | - |
| 15 mg/day | | | −3.1† | −2.1† | NS | - | - | - | - | - |
| Sultzer et al. [154] adjusted dose: mean 5.5 mg/day | Outpatient and adult living facility | 238 | −0.4¶ | −0.1¶ | .021 | .26 | 3.9§ | 4.2§ | .057 | - |
| **Pimavanserin** | | | | | | | | | | |
| Ballard et al. [117] 34 mg/day | Institutionalized | 178 | −1.13† | −0.47† | .25 | - | - | - | NS | - |
| Ballard et al. [58]—post hoc analysis 34 mg/day | Institutionalized: patients in RCT: > (*N* = 44) vs < (*N* = 43) 50% decrease in psychotic symptoms | 44 | −2.85† (> 50% decrease) | 0.79† (< 50% decrease) | .0001 | - | - | - | - | - |
| **Quetiapine** | | | | | | | | | | |
| Ballard et al. [161]100 mg/day | Institutionalized | 56 | −4.0* | −6.2* | .30 | .13 | - | - | - | - |
| Sultzer et al. [154] Adjusted dose: mean 56.5 mg/day | Outpatient and adult living facility | 233 | −0.3¶ | −0.1¶ | .078 | .18 | 3.8§ | 4.2§ | .031 | - |
| Tariot et al. [155] 100 mg/day | Institutionalized | 179 | −2.63† | −1.49† | NS | .27 | −0.60 | −0.47 | NS | .18 |
| Zhong et al. [156] 100 mg/day | Institutionalized | 216 | −0.9† | −1.2† | NS | .10 | 3.2* | 3.6* | NS | - |
| Zhong et al. [156] 200 mg/day | Institutionalized | 209 | −1.1† | −1.2† | NS | .03 | 3.0* | 3.6* | .017 | - |
| **Risperidone** | | | | | | | | | | |
| Brodaty et al. [157] adjusted: .5–2 mg/day, mean = 0.95 mg | Institutionalized | 301 | −7.5** | −3.1** | < .001 | - | - | - | - | - |
| De Deyn et al. [162] adjusted 0.5–2 mg/day; mean 1.1 mg | Institutionalized | 229 | −3.9* | −1.6* | .01 | - | −0.7 | −0.4 | .05 | - |
| Debert et al. [152] adjusted: 0.5–2 mg/d | Outpatient | 281 | −1.5* | −0.9* | NS | .14 | 0.1 | 0.0 | NS | .125 |
| Katz et al. [158] 0.5 mg/day | Institutionalized | 307 | −1.9‡ | −1.2‡ | .02 | - | - | - | - | - |
| 1 mg/day | | 309 | −2.2‡ | −1.2‡ | .006 | - | −0.9 | −0.5 | .002 | - |
| 2 mg/day | | 323 | −3.0‡ | −1.2‡ | < 0.001 | - | −1.0 | −0.5 | < .001 | - |
| Sultzer et al. [154] adjusted dose: mean 1.0 mg/day | Outpatient and adult living facility | 233 | −0.2¶ | −0.1¶ | .082 | .08 | 3.5§ | 4.2§ | < .001 | - |

*CGI-S* Clinical Global Impression-Severity of Illness

**CMAI* Cohen-Mansfield Agitation Inventory

***CMAI* = Cohen-Mansfield Agitation Inventory – total aggression subscale

†Neuropsychiatric Inventory/NPI-NH – agitation/aggression

‡Behavioral pathology in Alzheimer's disease – aggressiveness subscale

¶Brief Psychiatric Rating Scale – agitation factor score

§Global Clinical Impression of Change (lower is better)

effect sizes) (Tables 1 and 2) and at the cost of onerous side effects, including an associated doubling of mortality (see also meta-analysis [115]). The advice proffered by Schneider et al. [116] 15 years ago still seems apropos: "if improvement is not seen [in 10 or 12 weeks] then the medication should be discontinued and other approaches…could be considered." Treatment in practice would undoubtedly benefit from the use of *N* of 1 trials in which a drug is instituted for 1 to 4 months, then discontinued for the same time period, and then re-instituted, thereby testing the value of a drug in an individual patient.

Pimavanserin, a 5-$HT_{2A}$ receptor inverse agonist and antagonist with little affinity for dopamine receptors, might prove to be a genuine innovation [117] (see also [118]). Its effect size (0.35, i.e., an average of 0.35 SD reduction in symptoms), though modest, compares favorably with that of traditional antipsychotics. The effect size was 0.73 in patients with more severe psychotic symptoms [117]. Patients treated with pimavanserin do not experience the clinical manifestations associated with dopamine D2 receptor blockers. However, a recent retrospective cohort study of 20,298 patients with Parkinson's disease residing in Medicare long-term care facilities (2186 of whom received pimavanserin), employing Medicare claims data and propensity score-based inverse probability of treatment weighting (24 baseline characteristics), revealed a 1-year absolute mortality rate of 38.5/100 person-years in the untreated group and a relative risk of death in pimavanserin users of 1.56 (95% CI 1.42–1.72) [119]. In retrospective studies, association can never be construed with absolute confidence as evidence of causation, and the reasons for prescribing pimavanserin could have predisposed its users to earlier death. Furthermore, patients with AD might not be susceptible to the risk observed in patients with Parkinson's disease. Nevertheless, this was an exceptionally well-controlled study, and the excess mortality associated with pimavanserin use (19/100 patient-years) was substantial.

The American Geriatrics Society has recommended avoidance of antipsychotics unless non-pharmacological options have failed or are not possible and the patient is threatening substantial harm to self or others [120]. Nevertheless 12–37.5% of patients with behavioral and psychological symptoms of dementia are treated with these drugs [121]. One can well ask why the use of these drugs continues to be so widespread. There are several possible answers:

- The enormous clinical challenge posed by psychosis and agitation and the paucity of options for meeting it.
- The absence of theoretically motivated and empirically tested alternatives favors perpetuation of old practices.
- The apparent similarity of psychotic manifestations of dementia and schizophrenia, coupled with the success of antipsychotic medications in 14 of schizophrenia, provides a strong theoretical appeal for their use in dementia.
- Human susceptibility to the effects of irregular reinforcement leads to generalization of favorable results in single patients to entire clinical populations.
- To the extent that psychotic manifestations and agitation wax and wane (a common observation [122, 123]), clinicians are most likely to prescribe medications during periods of maximal symptoms; improvement thereafter may reflect regression to the mean rather than drug effect, the conflation of which tends to convince clinicians of drug efficacy.
- The general absence in the practice of medicine of use of N of 1 trials — an effective means for testing efficacy in a given patient.

### Benzodiazepines

Benzodiazepines would seem to be logical candidates for treatment of certain neuropsychiatric manifestations of dementia, for example, agitation or psychotic manifestations occurring at night in patients with insomnia or, during the day, in patients with high anxiety. However, research on this subject has been at a standstill for over 20 years. The use in elderly patients of benzodiazepines and other drugs acting on the central nervous system has long been guided by the Beers criteria, which were most recently updated in 2003 [124]. The Beers criteria are based on an expert consensus developed through an extensive literature review with a bibliography and questionnaire evaluated by nationally recognized experts in geriatric care, clinical pharmacology, and psychopharmacology using a modified Delphi technique to reach consensus. Our impression is that the Beers criteria have been widely taken as an absolute contraindication to use of any dose of a benzodiazepine in the elderly. However, the specific recommendation of the 2003 updated version of the Beers criteria on benzodiazepines is the following: potentially inappropriate use, "short-acting benzodiazepines: doses greater than lorazepam, 3 mg; oxazepam, 60 mg; alprazolam, 2 mg; temazepam, 15 mg; and triazolam, 0.25 mg", and concern, "Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the suggested maximums" [124]. Even now, 18 years later, we find little to disagree with. Nevertheless, we felt it worth reconsidering this literature, if for no other reason than to emphasize the need for further studies.

Most of the case against benzodiazepines derives from cohort or case–control studies [125]. In such studies, patients in the drug group are assumed to differ from those in the control group only in that they are taking the drug. Quite obviously, patients in the drug group differ in another important

respect: they suffered symptoms that led physicians to prescribe the drug, symptoms that might be having a major detrimental impact on the patient's life and that might be associated with intrinsic hazard, as well as additional comorbidities. Cohort studies can only establish statistical association, but all too often, causality is inferred. For example, it is often assumed that benzodiazepines cause worsening of cognitive function or more rapid cognitive decline when it is actually the case that they were prescribed because such patients are more likely to experience symptoms that might lead physicians to prescribe benzodiazepines. It is unlikely that prescribing rationale can be adequately captured in retrospective studies by using propensity score matching. By the very nature of cohort studies, risk is reported as relative risk. A relative risk of 3 might sound impressive until one is told that the baseline risk of the adverse effect in question is 0.01%/year. Clinical decision making is based upon the weighing of absolute likelihood of benefit against absolute risk of harm. It might be perfectly appropriate to incur a certain risk of harm to achieve an important benefit (as we do, e.g., in the use of antipsychotic medications and in the use of anticoagulants to mitigate stroke risk in patients with atrial fibrillation). Many studies seem to assume that the risk is homogeneous, experienced equally by all patients treated with the drug. The possibility that risk is predominantly associated with excessive dosing is seldom considered. Any drug acting on the central nervous system, particularly when prescribed in excessive dosage, might have deleterious effects on cognition, the more so in patients with already compromised cognitive function. Absolute dosage may be a poor guide because optimal dosage, probably influenced in part by genetics, likely varies substantially between different patients. The possibility that certain side effects may be associated predominantly with certain risk factors, e.g., loss of postural reflexes, or idiosyncratic in nature (likely also because of genetic variants), is seldom considered. When guidelines proscribe the use of certain drugs, the absence of suitable alternatives is seldom considered. Finally, many patients with insomnia, left to their own devices, will resort to use of over-the-counter hypnotics, which almost universally contain diphenhydramine, a drug with potent anticholinergic effects, which may impair cognition.

The origins of the concept of high risk of dependency are not so clear [126]. The most likely explanation appears to be conflation of persistent disorder symptoms with dependency symptoms. Although benzodiazepines have generally been FDA approved on the basis of data from short trials (which are less expensive to perform), they are commonly used to treat chronic conditions. If a benzodiazepine is initiated for treatment of generalized anxiety disorder and symptoms recur 10 years later when the drug is discontinued, this likely constitutes evidence that the original condition persists, rather than that the patient has become dependent on the drug. Symptoms of over-rapid reduction in dosage/sudden termination might also be interpreted as evidence of psychological dependence when they actually reflect physical dependence and can easily be avoided.

Well-designed RCTs can address many, albeit not all, of the problems that plague cohort and case–control studies. RCTs of benzodiazepines for neuropsychiatric manifestations of dementia were conducted decades ago [125]. None would remotely meet today's standards: they were vastly underpowered, there was inadequate attention to dose titration, and experimental control was lacking. Testing the effects of drugs that require titration constitutes a particular challenge for RCT design. It is by no means certain that the risk/benefit ratio of benzodiazepines when used in patients with AD will justify their risks, but given the data bearing on antipsychotics discussed in the foregoing, the pursuit of further RCTs would seem to be warranted.

The possibility that the use of benzodiazepines might increase the risk of developing dementia has been raised by a number of studies [127, 128]. Because most of these studies have involved retrospective cohort designs, they are susceptible to the same methodologic weaknesses as studies reporting the clinical adverse effects were associated with benzodiazepine use, as discussed above. Only prospective studies (and preferably RCTs) can definitively determine whether a cause-effect relationship exists. Prospective cohort studies have not shown an association between short-acting benzodiazepine use and incident dementia [129, 130].

### Cannabinoids

A recent systematic review [131] and a meta-analysis [132] of nine small clinical trials of cannabinoids (tetrahydrocannabinol, dronabinol, and nabilone; six RCTs and three quasi-randomized trials) in the treatment of behavioral and psychological symptoms of dementia, primarily agitation and aggression, suggested a sufficient possibility of benefit to motivate the conduct of larger trials. A number of RCTs are in progress [133].

### Dextromethorphan + quinidine

Dextromethorphan is a low-affinity, uncompetitive *N*-methyl-D-aspartate receptor antagonist, $\sigma_1$ receptor agonist, serotonin and norepinephrine reuptake inhibitor, and neuronal nicotinic $\alpha_3\beta_4$ receptor antagonist. The combination with low-dose quinidine inhibits the metabolism of dextromethorphan, thereby achieving higher central nervous system concentrations of the drug. The combination has been approved by the Food and Drug Administration for the treatment of pseudobulbar affect. In an RCT of 218 patients with AD, treatment with dextromethorphan 30 mg + quinidine 10 mg twice daily reduced scores on the

NPI agitation/aggression domain by 1.5 points relative to placebo ($p < 0.001$; effect size 0.60) [134]. The mean Clinical Global Impression of Change was 3.0 in the drug group and 3.6 in the placebo group ($p < 0.01$; lower is better). Major adverse effects included falls (8.6% versus 3.9%), diarrhea (5.9% versus 3.1%), and urinary tract infections (5.3 versus 3.9%).

#### Memantine

A number of RCTs have shown that memantine has a statistically and clinically significant beneficial effect in reducing scores on the NPI symptom cluster of agitation/aggression, delusions, hallucinations, and irritability/lability in patients with moderate to severe AD [135, 136]. However, more recent RCTs have failed to show any benefit for agitation/aggression [137, 138].

#### Propranolol

There has been a single small trial of propranolol [139]. Thirty-one patients with persistent disruptive behaviors (NPI domains: agitation/aggression, irritability/lability, and/or aberrant motor behavior) were titrated to a mean dose of propranolol 106 mg/day or placebo, maintained for 6 weeks. The drug group experienced a mean decrease in total NPI score that was 7.5 points greater than in the placebo group ($p < 0.01$; effect size 0.49). Clinical Global Impression of Change was 3 in the drug group and 4.5 in the placebo group ($p < 0.005$; lower is better). Although there was a high drop-out rate in the placebo group and the small number of patients in this trial limits generalizability, the medium effect size that was achieved suggests that further trials are warranted.

#### Non-pharmacologic Interventions

An RCT of various combinations of antipsychotic drug review, a very modest social intervention program, and a very modest exercise program [140], conducted in patients with dementia in 16 nursing homes, demonstrated that antipsychotic drug review reduced the use of these drugs by 50%, and the combination of antipsychotic drug review and the social interaction program reduced mortality from 35 to 19%. Antipsychotic drug review worsened neuropsychiatric symptoms (NPI score), but this effect was rendered negligible when this review was combined with the social intervention. Exercise significantly improved neuropsychiatric symptoms overall but not depression. The modest nature of the interventions employed in this study means that they would likely be feasible in most institutional settings. In an older study, Fossey [141] demonstrated, in a cluster randomized trial of a psychosocial intervention combined with efforts to reduce neuroleptic use conducted in 12 nursing homes, that neuroleptic use could be reduced by 19% without any associated increase in agitation and aggression.

There have been a large number of studies of interventions to ameliorate agitation [142] (see also [143] for comprensive review). Some have demonstrated very large effect sizes (> 2), particularly those that involve various methods of training institutional staff. However, results have varied enormously from trial to trial, suggesting that specific attributes of a particular intervention pursued in a particular trial are very important. These also tend to be more intensive and therefore more costly interventions.

Studies testing the effect of non-pharmacological approaches on activities of daily living and depression in patients with moderate to severe dementia have reported effects sizes in the small (ADL 0.28) to medium range (depression 0.44) [144] but no impact on other behavioral and psychological symptoms, including anxiety.

Finally, a comprehensive management guideline, "Describe, Investigate, Create, and Evaluate" (DICE), has been formulated by a multidisciplinary panel of experts [145, 146] for management of behavioral and psychological symptoms of AD. The approach was recommended in a recent international consensus evaluation that employed a modified Delphi approach [147]. Insofar as we can determine, DICE has not been subject to empirical testing.

## Conclusion

There is now strong evidence that patients with AD have lost their ability to comprehend and express affective prosody, impaired ability to comprehend emotional facial expressions and affective body gestures, and impaired ability to express affect by these same means. These symptoms are typically not particularly disruptive, but they are associated with impoverishment of the emotional life of affected patients and degradation of close emotional relationships. Patients with AD also experience disorders of emotional experience, mood (including depression and anxiety), agitation/belligerence, and psychosis. These disorders reduce quality of life and are often very disruptive to families. They are frequently the precipitant of institutionalization. Some disorders, particularly agitation/belligerence, which become more severe with advancing disease, pose major challenges to institutional management of patients with AD.

Research on primary treatment of disorders of emotional communication is in earliest stages, and so far, no treatment has demonstrated sufficient efficacy to justify translation to clinical practice [1]. The mechanisms underlying disorders of emotional experience are generally too poorly understood to enable the development of a primary treatment. However, the treatment of depression, pain, and sleep disorders may

have substantial benefits on daytime quality of life. Treatment of sleep disorders, using CPAP for obstructive sleep apnea, dopaminergic treatment or gabapentin/pregabalin for RLS/periodic leg movements of sleep, or trazodone in titrated dosage for idiopathic insomnia, shows the greatest promise for management of the most disruptive manifestations, agitation/belligerence, and psychosis; unfortunately, there have not been sufficient studies in this area. Treatment of depression in AD reflects inference from success in the use of SSRIs and SNRIs for treatment of idiopathic depression as there have been no sufficiently powered and adequately designed RCTs to prove their benefit in patients with AD who have depression.

A single, quite impressive study of a non-pharmacologic treatment of psychosis in patients institutionalized for AD has shown a clinically important benefit [140]. However, the general approach to psychosis and agitation/aggression in this population has been overwhelmingly pharmacologic, predominantly relying on antipsychotic medications, notwithstanding the small effect sizes demonstrated in the very large number of adequately powered RCTs and their potentially serious side effects. These data suggest that antipsychotic medications should be used only as a last resort and then only for limited periods of time because psychosis and agitation/aggression tend to wax and wane. Newer approaches, for example, using pimavanserin, a 5-$HT_{2A}$ receptor inverse agonist and antagonist with little affinity for dopamine receptors, for psychosis, and dextromethorphan + quinidine for agitation/aggression, show considerable promise, but data are not yet adequate to support on-label use of these drugs for these indications. Unfortunately, the substantial excess mortality associated with pimavanserin use in patients with Parkinson's disease strikes a strong cautionary note. Physicians are perfectly free to prescribe these drugs off-label, but this prescription will likely be strongly resisted by insurance companies.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s13311-021-01172-w.

**Acknowledgements** This work was supported by resources provided by the North Florida/South Georgia Veterans Health System, Gainesville, FL. It was not supported by a specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The contents of this manuscript do not represent the views of the US Department of Veterans Affairs, the US Government, or the University of Florida.

**Required Author Forms** 34 provided by the authors are available with the online version of this article.

## References

1. Nadeau SE. Neural mechanisms of emotions, alexithymia, and depression. Handbook of Clinical Neurology: Disorders of Emotion in Neurologic Disease. 2021;183:299–314.
2. Hargrave R, Maddock RJ, Stone V. Impaired recognition of facial expressions of emotion in Alzheimer's disease. J Psychiatry Clin Neurosci. 2002;14(1):64–71.
3. McLellan T, Johnston L, Dalrymple-Alford J, Porter R. The recognition of facial expressions of emotions in Alzheimer's disease: a review of findings. Acta Neuropsychiatr. 2008;20(5):236–50.
4. Lavenu I, Pasquier F. Perception of emotion on faces in frontotemporal dementia and Alzheimer's disease: a longitudinal study. Dement Geriatr Cogn Disord. 2005;19(1):37–41.
5. Bucks RS, Radford SA. Emotion processing in Alzheimer's disease. Aging Ment Health. 2004;8(3):222–32.
6. Phillips LH, Scott C, Henry JD, Mowat D, Bell JS. Emotion perception in Alzheimer's disease and mood disorder in old age. Psychol Aging. 2010;25(1):38–47.
7. Bourgin J, Guyader N, Chauvin A, Juphard A, Sauvée M, Moreaud O, et al. Early emotional attention is impacted in Alzheimer's disease: an eye-tracking study. J Alzheimers Dis. 2018;63(4):1445–58.
8. Güntekin B, Hanoğlu L, Aktürk T, Fide E, Emek-Savaş Dd, Ruşen E, et al. Impairments in recognition of emotional facial expressions in Alzheimer's disease is represented by EEG theta and alpha responses. Psychophysiology. 2019;56(1):e13434.
9. Klein-Koerkamp Y, Beaudoin M, Baciu M, Hot P. Emotional decoding abilities in Alzheimer's disease: a meta-analysis. JAlzheimers Dis. 2012;32(1):109–25.
10. Niedenthal PM, Brauer M. Social functionality of human emotion. Annu Rev Psychol. 2012;63:259–85.
11. Smith MC. Facial expression in mild dementia of the Alzheimer type. Behav Neurol. 1995;8(3–4):149–56.
12. Ekman P, Friesen W. Facial action coding system: a technique for the measurement of facial movement. Palo Alto, California: Consulting Psychologists Press; 1978.
13. Mograbi DC, Brown RG, Morris RG. Emotional reactivity to film material in Alzheimer's disease. Dement Geriatr Cogn Disord. 2012;34(5–6):351–9.
14. Taler V, Baum SR, Chertkow H, Saumier D. Comprehension of grammatical and emotional prosody is impaired in Alzheimer's disease. Neuropsychology. 2008;22(2):188–95.
15. Templier L, Chetouani M, Plaza M, Belot Z, Bocquet P, Chaby L. Altered identification with relative preservation of emotional prosody production in patients with Alzheimer's disease. Geriatrie at psychologie neuropsychiatrie du vieillissement. 2015;13(1):106–15.
16. Horley K, Reid A, Burnham D. Emotional prosody perception and production in dementia of the Alzheimer's type. J Speech Lang Hear Res. 2010;53(5):1132–46.
17. Martínez-Sánchez F, Garcia Meilán JJ, Pérez E, Carro J, Arana JM. Expressive prosodic patterns in individuals with Alzheimer's disease. Psicothema. 2012;24(1):16–21.
18. Hogeveen J, Grafman J. Alexithymia. Handb Clin Neurol. 2021;183:47–62.
19. Sturm VE, Levenson RW. Alexithymia in neurodegenerative disease. Neurocase. 2011;17(3):242–50.
20. Yuruyen M, Akcan FE, Batun GC, Gultekin G, Toprak M, Yavuzer H, et al. Alexithymia in people with subjective cognitive decline, mild cognitive impairment, and mild Alzheimer's disease. Aging Clin Exp Res. 2017;29(6):1105–11.
21. Smirni D, Beadle JN, Paradiso S. An initial study of alexithymia and its relationship with cognitive abilities among mild cognitive impairment, mild Alzheimer's disease, and healthy volunteers. J Nerv Ment Dis. 2018;206(8):628–36.
22. Arroyo-Aniló EM, Souchaud C, Ingrand P, Chamorro Sánchez J, Melero Ventola A, Gil R. Alexithymia in Alzheimer's disease. J Clin Med. 2020;10(1):44.
23. Nadeau SE. Treatment of disorders of emotional comprehension, expression, and emotional semantics. Handbook of

Clinical Neurology: Emotional Disorders Associated with Neurological Diseases. 2021;183:283–97.
24. Mortby ME, Adler L, Agüera-Ortiz L, Bateman DR, Broidaty H, Cantillon M, et al. Apathy as a treatmet target in Alzheimer's disease: implications for clinical trials. Arch Gen Psychiatry. 2021.
25. Miller DS, Robert P, Ereshefsky L, Adler L, Bateman D, Cummings J, et al. Diagnostic criteria for apathy in neurocognitive disorders. Alzheimer's Dement. 2021:1–13.
26. Marin RS. Apathy: concept, syndrome, neural mechanisms, and treatment. Semin Clin Neuropsychiatry. 1996;1:304–14.
27. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Psychiatry Clin Neurosci. 1992;4:134–9.
28. Sockeel P, Dujardine K, Devos D, Deneve C, Destée A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. J Neurol, Neurosurg Psychiatry. 2006;77:579–84.
29. Ang Y-S, Lockwood P, Apps MAJ, Muhammed K, Husain M. Dinstinct subtypes of apathy revealed by the apathy motivation index. PLoS ONE. 2017;12(e0169938).
30. Strauss ME, Sperry SD. An informant-based assessment of apathy in Alzheimer disease. Neuropsychiatry Neuropsychol Behav Neurol. 2002;17:176–83.
31. Cummings JL. The Neuropsychiatric Inventory Questionnaire. 1994. https://www.NPItest.net.
32. Clarke DE, Ko JY, Kuhl EA, van Reekum R, Salvador R, Marin RS. Are the available apathy measures reliable and valid? A review of the psychometric evidence. J Psychosom Res. 2011;70:73–97.
33. Mohammad D, Ellis C, Rau A, Rosenberg PB, Mintzer J, Ruthirakuhan M, et al. Psychometric properties of apathy scales in dementia: a systematic review. J Alzheimers Dis. 2018;66:1065–82.
34. Robert P, Lanctot KL, Agüera-Ortiz L, Aalten P, Bremond F, D'efrancesco M, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. Eur Psychiatry. 2018;54:71–6.
35. Arnts H, van Erp WS, Lavrijsen JCM, van Gaal S, Gorenewegen HJ, van den Mnckhof P. On the pathophysiology and treatment of akinetic mutism. Neurosci Biobehav Rev. 2020;112:270–8.
36. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol. 1991;82:239–59.
37. Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): instruction manual and affective ratings. Gainesville, Florida: Center of Research in Psychophysiology, University of Florida; 1999.
38. Bradley MM, Lang PJ. Fearfulness and affective evaluations of pictures. Motiv Emot. 1999;23:1–13.
39. Joshi A, Jimenez E, Mendez MF. Initial heart rate reactivity to socioemotional pictures in early-onset Alzheimer's disease. J Alzheimers Dis. 2017;60(4):1325–32.
40. Barnhart WJ, Makela EH, Latocha MJ. SSRI-induced apathy syndrome: a clinical review. J Psychiatric Pract. 2004;10:196–9.
41. Goodwin GM, Price J, De Bodinat C, Laredo J. Emotional blunting with antidepressant treatments: a survey among depressed patients. J Affect Disord. 2017;221:31–5.
42. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. Psychiatry Res. 1991;38(2):143–62.
43. van Dyck CH, Arnsten AFT, Padala PR, Brawnman-Mintzer O, Lerner AJ, Portsteinsson AP, et al. Neurobiologic rationale for treatment of apathy in Alzheimer's disease with methylphenidate. Am J Geriatr Psychiatry. 2021;29(1):51–62.
44. Ruthirakuhan MT, Herrmann N, Abraham EH, Lanctot KL. Pharmacological interventions for apathy in Alzheimer's disease (Review). Cochrane Database Syst Rev. 2018 (5. Art. No.:CD012197).
45. Rea R, Carotenuto A, Traini E, Fasanaro AM, Manzo V, Amenta F. Apathy treatment in Alzheimer's disease: interim results of the ASCOMALVA Trial. J Alzheimers Dis. 2015;48(2):377–83.
46. Scassellati C, Ciani M, Maj C, Geroldi C, Zanetti O, Gennarelli M, et al. Behavioral and psychological symptoms of dementia (BPSD): clinical characterization and genetic correlates in an Italian Alzheimer's disease cohort. J Person Med. 2020;10:90.
47. Deardorff WJ, Grossberg GT. Behavioral and psychological symptoms in Alzheimer's dementia and vascular dementia. Handb Clin Neurol. 2019;165:5–32.
48. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. Front Neurol. 2012;3:73.
49. van der Linde RM, Dening T, Matthews FE, Brayne C. Grouping of behavioral and psychological symptoms of dementia. Int J Geriatr Psychiatry. 2014;29:562–8.
50. Teri L, Ferretti LE, Gibbons LE, Logsdon RG, McCurry SM, Kukull WA, et al. Anxiety in Alzheimer's disease: prevalence and comorbidity. J Gerontol: Med Sci. 1999;54A(7):M348–52.
51. Joshi A, Jimenez E, Mendez MF. Initial heart rate reactivity to socioemotional pictures in early-onset Alzheimer's disease. J Alzheimer's Dis. 2017;60(4):1325–32.
52. Kaiser NC, Liang LJ, Melrose SS, Wilkins SS, Sultzer DL, Mendez MF. Differences in anxiety among patients with early- versus late-onsert Alzheimer's disease. J Psychiatry Clin Neurosci. 2014;26(1):73–80.
53. Cummings J, Mintzer J, Brodaty H, Sano M, Banerjee S, Devanand DP, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. Int Psychogeriatr. 2015;27:7–17.
54. Zuidema S, Koopmans R, Verhey F. Prevalence and predictors of neuropsychiatric symptoms in cognitively impaired nursing home patients. J Geriatr Psychiatry Neurol. 2007;20:41–9.
55. Sloane PD, Mitchell CM, Preisser JS, Phillips C, Commander C, Burker E. Environmental correlates of resident agitation in Alzheimer's disease special care units. J Am Geriatr Soc. 1998;46:862–9.
56. Livingston G, Marston L, Rapaport P, Livingston D, Cousins S, Robertson S, et al. Prevalence of and associations with agitation in residents with dementia living in care homes: MARQUE cross-sectional study. Brit J Psychiatry Open. 2017;3:171–8.
57. Liu KY, Costello H, Reeves S, Howard R, for the Alzheimer's Disease Neuroimaging Initiative. The relationship between anxiety and incident agitation in Alzheimer's disease. J Alzheimer's Dis. 2020;78:1119–27.
58. Ballard CG, Coate B, Abler V, Stankovic S, Foff E. Evaluation of the efficacy of pimavanserin in the treatment of agitation and aggression in patients with Alzheimer's disease psychosis: a post hoc analysis. Int J Geriatr Psychiatry. 2020;35:1402–8.
59. Carrarini C, Russo M, Dono F, Barbone F, Rispoli MG, Ferri L, et al. Agitation and dementia; prevention and treatment strategies in acute and chronic conditions. Front Neurol. 2021;12:644317.
60. Peters ME, Schwartz S, Han D, Rabins PV, Steinberg M, Tschanz JT, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County dementia progression study. Am J Psychiatry. 2015;172:460–5.
61. Gaugler JE, Wall MM, Kane RL, Menk JS, Sarsour K, Johnston JA, et al. The effects of incident and persistent behavioral problems on change in caregiver burden and nursing home admission of persons with dementia. Med Care. 2010;48:875–83.
62. Cloutier M, Gauthier-Loiselle M, Gagnon-Sanschagrin P, Guerin A, Hartry A, Baker RA, et al. institutionalization risk and costs associated with agitation in Alzheimer's disease. Alzheimers Dem: Transl Res Clin Intervent. 2019;5:851–61.

63. Olin JT, Schneider LS, Katz IR, Meyers BS, Alexopoulos GS, Breitner JC, et al. Provisional diagnostic criteria for depression of Alzheimer disease. Am J Geriatr Psychiatry. 2002;10:125–8.
64. Sheikh JI, Yesavage JA. Geriatric depression scale (GDS): recent evidence and development of a shorter version. Clin Gerontol. 1986;5:165–73.
65. Alexopolous GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. Biol Psychiatry. 1988;23(3):271–84.
66. Orgeta V, Tabet N, Nilforooshan R, Howard R. Efficacy of antidepressants for depression in Alzheimer's disase: systematic review and meta-analysis. J Alzheimers Dis. 2017;58:725–33.
67. Reifler BV, Larson E, Hanley R. Coexistence of cognitive impairment and depression in geriatric outpatients. Am J Psychiatry. 1982;139(5):623–6.
68. Cummings JL, Miller B, Hill MA, Neshkes R. Neuropsychiatric aspects of multi-infarct dementia and dementia of the Alzheimer type. Arch Neurol. 1987;44(4):389–93.
69. Chi S, Yu J-T, Tan M-S, Tan L. Depression in Alzheimer's disease: epidemiology, mechanisms, and management. J Alzheimers Dis. 2014;42(3):739–55.
70. Ismail Z, Elbayoumi H, Fischer CE, Hogan DB, Millikin CP, Schweizer T, et al. Prevalence of depression in patients with mild cognitive impairment: a systematic review and meta-analysis. JAMA Psychiat. 2017;74(1):58–67.
71. Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S, et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry. 2011;68(7):675–90.
72. Zweig RM, Ross CA, Hedreen JC, Steele C, Cardillo ER, Whitehouse PJ, et al. Neuropathology of aminergic nuclei in Alzheimer's diseease. Progr Clin Biol Res. 1989;317:353–65.
73. Burke AD, Goldfarb D, Bollam P, Khokher S. Diagnosing and treating depression in patients with Alzheimer's disease. Neurol Ther. 2019;8(2):325–50.
74. Starkstein SE, Jorge RE, Mizrahi S, Robinson RG. The construct of minor and major depression in Alzheimer's disease. Am J Psychiatry. 2005;162(11):2086–93.
75. Zubenko GS, Zubenko WN, McPherson S, Spoor E, Marin DB, Farlow MR, et al. A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. Am J Psychiatry. 2003;160(5):857–66.
76. Naasan G, Shdo SM, Rodriguez EM, Spina S, Grinberg L, Lopez L, et al. Psychosis in neurodegenerative disease: differential patterns of hallucination and delusion symptoms. Brain. 2021;144:999–1012.
77. Zhao Q-F, Tan L, Wang H-F, Jiang T, Tan M-S, Tan L, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and meta-analysis. J Affect Disord. 2016;190:264–71.
78. Karttunen K, Karppi P, Hiltunenm A, Vanhanen M, Välimäki T, Martikainen J, et al. Neuropsychiatric symptoms and quality of life in patients with very mild and mild Alzheimer's disease. Int J Geriatr Psychiatry. 2011;26:473–82.
79. Herrmann N, Lanctot KL, Sambrook R, Lesnikova N, Hébert R, McCracken P, et al. The contribution of neuropsychiatric symptoms to the cost of dementia care. Int J Geriatr Psychiatry. 2006;21:972–6.
80. Scarmeas N, Brandt J, Albert M, Hadjigeorgiou G, Papadimitriou A, Dubois B, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. Arch Neurol. 2005;62(10):1601–8.
81. American Psychiatric Association Work Group on Alzheimer's Disease and Other Dementias. Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias. Second Ed: American Psychiatric Association; 2007.
82. Dudas R, Malouf R, McCleery J, Dening T. Antidepressants for treating depression in dementia (review). Cochrane Database Syst Rev. 2018(8):CD003944.
83. Cohen-Mansfield J, Lipson S. The utility of pain assessment for analgesic use in persons with dementia. Pain. 2008;134:16–23.
84. Wei Y-JJ, Chen C, Fillingim RB, DeKosky ST, Schmidt S, Pahor M, et al. Uncontrolled pain and risk for depression and behavioral sykmptoms in residents with dementia. J Am Med Dir Assoc. 2021;05.010.
85. Husebo BS, Ballard C, Sandvik R, Nilsen OB, Aarsland D. Efficacy of treating pain to reduce behavioral disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. BMJ. 2011;343:d4065.
86. Habiger TF, Flo E, Achterberg WP, Husebo BS. The interactiver relationship between pain, psychosis, and agitation in people with dementia: results from a cluster-randomized clinical trial. Behav Neurol. 2016;2016(Article ID 7036415).
87. Husebo BS, Ballard C, Cohen-Mansfield J, Seifert R, Aarsland D. The response of agitated behavior to pain management in persons with dementia. Am J Geriatr Psychiatry. 2014;22:708–17.
88. Cordone S, Scarpelli S, Alfonsi V, De Gennaro L, Gorgoni M. Sleep-based interventions in Alzheimer's disease: promising approaches from prevention to treatment along the disease trajectory. Pharmaceuticals. 2021;14(383).
89. Peter-Derex L, Yammine P, Bastuji H, Croisile B. Sleep and Alzheimer's disease. Sleep Med Rev. 2015;19:29–38.
90. Rose KM, Beck C, Tsai PF, Liem PH, Davila DG, Kleban M, et al. Sleep disturbances and nocturnal agitation behaviors in older adults with dementia. Sleep. 2011;34:779–86.
91. Terum TM, Andersen JR, Rongve A, Aarsland D, Svendsboe EJ, Testad I. The relationship of specific items on the neuropsychiatric inventory to caregiver burden in dementia: a systematic review. Int J Geriatr Psychiatry. 2017;32:703–17.
92. Richards KC, Allen RP, Morrison J, Kovach CR, Rangel A, Loera A, et al. Nighttime agitation in persons with dementia as a manifestation of restless legs syndrome. J Am Med Dir Assoc. 2020. https://doi.org/10.1016/j.jamda.2020.11.026.
93. Figueiro MG, Plitnick B, Roohan C, Sahin L, Kalsher M, Rea MS. Effects of a tailored lightning intervention on sleep quality, rest-activity, mood, and behavior in older adults with Alzheimer disease and related dementias: a randomized clinical trial. J Clin Sleep Med. 2019;15(12):1757–67.
94. Mitolo M, Tonon C, La Morgia C, Testa C, Carelli V, Lodi R. Effects of light treatment on sleep, cognition, mood, and behavior in Alzheimer's disease: a systematic review. Dement Geriatr Cogn Disord. 2018;46:371–84.
95. Mullins AE, Kam K, Parekh A, Bubu OM, Osorio RS, Varga AW. Obstructive sleep apnea and its treatment in aging: effects on Alzheimer's disease biomarkers, cognition, brain structure, and neurophysiology. Neurobiol Dis. 2020;145(105054).
96. Jaffer KY, Chang T, Vanle B, Dang J, Steiner AJ, Loea N, et al. Trazodone for insomnia: a systematic review. Innov Clin Neurosci. 2017;14:24–34.
97. Camargos EG, Lousada LL, Quintas JL, Naves JOS, Lousada FM, Nóbrega OT. Trazodone improves sleep parameters in Alzheimer disease patients: a randomized, double-blind, and placebo-controlled study. Am J Geriatr Psychiatry. 2014;22:1565–74.
98. Herring WJ, Ceesay P, Synder E, Bliwise D, Budd K, Hutzelmann J, et al. Polysomnographic assessment of suvorexant in patients with probable Alzheimer's disease dementia and insomnia: a randomized trial. Alzheimer's Dem. 2019;16:641–551.
99. Cummings J. New approaches to symptomatic treatments for Alzheimer's disease. Molecular Degen. 2021;16(2).
100. Konovalov S, Muralee S, Tampi RR. Anticonvulsants for the treatment of behavioral and psychological symptoms of dementia: a literature review. Int Psychogeriatr. 2008;20:293–308.

101. Tariot PN, Schneider LS, Cummings J, Thomas RG, Raman R, Jakimovich LJ, et al. Chronic divalproex sodium to attentuate agitation and clinical progression of Alzheimer disease. Arch Gen Psychiatry. 2012;68:853–61.
102. Tariot PN, Erb R, Podgorski CA, Cox C, Patel S, Jakimovich L, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. Am J Psychiatry. 1998;155:54–61.
103. Cummings J, Lai T-J, Hemrungrojn S, Mohandas E, Kim SY, Nair G, et al. Role of donepezil in the management of neuropsychiatric symptoms in Alzheimer's disease and dementia with Lewy bodies. CNS Neurosci Ther. 2016;22:159–66.
104. Campbell N, Ayub A, Boustani MA, Fox C, Farlow M, Maidment I, et al. Impact of cholinesterase inhibitors on behavioral and psychological symptoms of Alzheimer's disease: a meta-analysis. Clin Interv Aging. 2008;3:719–28.
105. Rodda J, Morgan S, Walker Z. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. Int Psychogeriatr. 2009;21(5):813–24.
106. Holmes C, Wilkinson D, Dean C, Vethanayagam S, Olivieri S, Langley A, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. Neurology. 2004;63:214–9.
107. Mega MS, Masterman DM, O'Connor SM, Barclay TR, Cummings JL. The spectrum of behavioral responses to cholinesterase inhibitor therapy in Alzheimer disease. Arch Neurol. 1999;56:1388–93.
108. Cummings J, McRae T, Zhang R, The Donepezil-Sertraline Study Group. Symptoms in patients with dementia and severe behavioral disorders. Arch Geriatr Psychiatry. 2006;14:605–12.
109. Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, et al. Effect of citalopram on agitation in Alzheimer disease. The CitAD randomized clinical trial JAMA. 2014;311:682–91.
110. Leonpacher AK, Peters ME, Drye LT, Makino KM, Newell JA, Devanand DP, et al. Effects of citalopram on neuropsychiatric symptoms in Alzheimer's dementia: evidence from the CitAD study. Am J Psychiatry. 2016;173:473–80.
111. Banerjee S, High J, Stirling S, Shepstone L, Swart AM, Telling T, et al. Stufy of mirtazapine for agitated behaviours in dementia (SYMBAD): a randomised, double-blind, placebo-controlled trial. Lancet. 2021;398:1487–97.
112. Calsolaro V, Antognoli R, O'Koye C, Monzani F. The use of antipsychotic drugs for treating behavioral symptoms in Alzheimer's disease. Front Pharmacol. 2019;10(1465).
113. Vigen CLP, Mack WJ, Keefe R, Sano M, Sultzer D, Stroup S, et al. Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. Am J Psychiatry. 2011;168:831–9.
114. Ralph SJ, Espinet AJ. Increased all-cause mortality by antipsychotic drugs: updated review and meta-analysis in dementia and general mental health care. J Alzheimers Dis Rep. 2018;2:1–26.
115. Farlow MR, Shamliyan TA. Benefits and harms of atypical antipsychotics for agitation in adults with dementia. Eur Neuropsychopharmacol. 2017;27:217–31.
116. Schneider LS, Dagerman KS, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006;14:191–210.
117. Ballard C, Khan Z, Cummings J, Demos G, Coate B, Youakim JM, et al. Evaluation of the safety, tolerability, and efficacy of pimavanserin versus placebo in patients with Alzheimer's disease psychosis: a phase 2, randomised, placebo-controlled double-blind study. Lancet Neurol. 2018;17:213–22.
118. Tariot PN, Cummings JL, Soto-Martin ME, Ballard C, Erten-Lyons D, Sultzer DL, et al. Trial of pimavanserin in dementia-related psychosis. N Engl J Med. 2021;385:309–19.
119. Hwang YJ, Alexander GC, An H, Moore TJ, Mehta HB. Risk of hospitalization and death associated with pimavanserin use in older adults with Parkinson disease. Neurology. 2021;97:e1266–75.
120. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society. updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;2015(63):2227–46.
121. Kirkham J, Sherman C, Velkers C, Maxwell C, Gill S, Rochon P, et al. Antipsychotic use in dementia. Can J Psychiatry. 2017;62:170–81.
122. Ballard CG, Saad K, Patel A, Gahir M, Solis M, Coope B, et al. The prevalence and phenomenology of psychotic symptoms in dementia sufferers. Int J Geriatr Psychiatry. 1995;10:477–85.
123. Ballard C, O'Brien J, Coope B, Fairbairn A, Abid F, Wilcock G. A prospective study of psychotic symptoms in dementia sufferers: psychosis in dementia. Int Psychogeriatr. 1997;9:57–64.
124. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappopriate medication use in older adults. Arch Intern Med. 2003;163:2716–24.
125. Defrancesco M, Marksteiner J, Fleischhacker WW, Blasko I. Use of benzodiazepines in Alzheimer's disease: a systematic review of the literature. Int J Neuropsychopharmacol. 2015:1–11.
126. Bandelow B, Reitt M, Röver C, Michaelis S, Görlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol. 2015;30:183–92.
127. Tseng L-Y, Huang S-T, Peng L-N, Hsiao F-Y. Benzodiazepines, z-hypnotics, and risk of dementia: special considerations of helflives and concomitant use. Neurotherapeutics. 2020;17:156–64.
128. DeKosky ST, Williamson JB. The long and the short of benzodiazepines and sleep medications: short-term benefits, long-term harms? Neurotherapeutics. 2020;17:153–5.
129. Shash D, Kurth T, Bertrand M, Dufouil C, Barberger-Gateau P, Berr C, et al. Benzodiazepine, psychotrophic medication, and dementia. A population-based cohort study Alzheimers Dement. 2016;112:604–13.
130. Grossi CM, Richardson K, Fox C, Maidment I, Steel N, Loke YK, et al. Anticholinergic and benzodiazepine medication use and risk of incident dementia: a UK cohort study. BMC Geriatr. 2019;19:276.
131. Paunescu H, Dima L, Ghita I, Coman L, Ifteni PI, Fulga I, et al. A systematic review of clinical studies on the effect of psychoactive cannabinoids in psychiatric conditions in Alzheimer dementia. Am J Ther. 2020;27:e249–69.
132. Bahji A, Meyyappan AC, Hawken ER. Cannabinoids for the neuropsychiatric symptoms of dementia: a systematic review and meta-analysis. Can J Psychiatry. 2019;65(6):365–76.
133. Liu KY, Borissova A, Mahmood J, Elliott T, Knowles M, Bentham P, et al. Pharmacological treatment trials of agitation in Alzheimer's disease: a systematic review of ClinicalTrials.gove registered trials. Alzheimers Dement. 2021;2021(e12157).
134. Cummings JL, Lyketsos CG, Peskind ER, Porsteinsson AP, Mintzer JE, Scharre DW, et al. Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia. A randomized clinical trial JAMA. 2015;314(12):1242–54.
135. 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;69:341–8.
136. Gauthier S, Loft H, Cummings J. Improvement in behavioral symptoms in patients with moderate to severe Alzheimer's

disease by memantine: a pooled data analysis. Int J Geriatr Psychiatry. 2008;23:537–45.
137. Fox C, Crugel M, Maidment I, Auestad BH, Coulton S, Treloar A, et al. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. PLoS ONE. 2012;7(5:e35185).
138. Herrmann N, Gauthier S, Boneva N, Lemming OM, 10158 Investigators. A randomized, double-blind, placebo-controlled trial of memantine in a behaviorally enriched sample of patients with moderate-to-severe Alzheimer's disease. Int Psychogeriatr. 2013;25(6):919–27.
139. Peskind ER, Tsuang DW, Bonner LT, Pascualy M, Riekse RG, Snowden MB, et al. Propranolol for disruptive behaviors in nursing home residents with probable or possible Alzheimer disease. A plecebo-controlled study. Alzheimer Dis Assoc Disord. 2008;19:23–8.
140. Ballard C, Orrell M, YongZhong S, Moniz-Cook E, Staffort J, Whittaker R, et al. Impact of antipsychotic review and nonpharmacological intervention on antipsychotic use, neuropsychiatric symptoms, and mortality in people with dementia living in nursing homes: a factorial cluster-randomized controlled trial by the Well-Being and Health for People with Dementia (WHELD) Program. Am J Psychiatry. 2016;173:252–62.
141. Fossey J, Ballard C, Juszczak E, James I, Alder N, Jacoby R, et al. Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. BMJ. 2006. https://doi.org/10.1136/bmj.38782.575868.7C.
142. Livingston G, Kelly L, Lewis-Holms E, Baio G, Morris S, Patel N, et al. Non-pharmacological interventions for agitation in dementia: systematic review of randomised controlled trials. Br J Psychiatry. 2014;205:436–42.
143. Abraha I, Rimland JM, Trotta FM, Dell'Aquila G, Cruz-Jentoft C, Petrofic M, et al. Systematic review of systematic reviews of non-pharrmacological interventions to treat behabioural disturbances in older patients with dementia. The SENATOR-OnTop series. BMJ Open. 2017;7:e012759.
144. Na R, Yeom Y, Kim YJ, Byun S, Kim K, Kim KW. A systematic review and meta-analysis of nonpharmacological interventions for moderate to severe dementia. Psychiatry Invest. 2019;16:325–35.
145. Kales HC, Gitlin LN, Lyketsos CG. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. J Am Geriatr Soc. 2014;62:762–9.
146. Kales HC, Gitlin LN, Kyketsos CG. State of the art review: assessment and management of behavioral and psychological symptoms of dementia. BMJ. 2015;350.
147. Kales HC, Lyketsos CG, Miller EM, Ballard C. Management of behavioral and psychological symptoms in people with Alzheimer's disease: an international Delphi consensus. Int Psychogeriatr. 2019;31(1):83–90.
148. De Deyn P, Jeste DP, Swanink R, Kostic D, Breder C, Carson WH, et al. Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease. A randomized, placebo-controlled trial. J Clin Psychopharmacol. 2005;25:463–7.
149. Mintzer JE, Tune LE, Breder CD, Swanink R, Marcus RN, McQuade RD, et al. 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;15:918–31.
150. Streim JE, Porsteinsson AP, Breder CD, Swanink R, Marcus R, McQuade R, et al. A randomized, double-blind, placebo-controlled study of aripiprazole for the treatment of psychosis in nursing home patients with Alzheimer disease. Am J Geriatr Psychiatry. 2008;16:537–50.
151. De Deyn PP, Carrasco MM, Debert W, Jeandel C, Hay DP, Feldman PD, et al. Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 2004;19:115–26.
152. Debert WG, Dysken MW, Rappaport SA, Feldman PD, Young CA, Hay DP, et al. Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. Am J Geriatr Psychiatry. 2005;13:722–30.
153. Street JS, Clark WS, Gannon KS, Cummings J, Bymaster FP, Tamura RN, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities. Arch Gen Psychiatry. 2000;57:968–76.
154. Sultzer DL, Davis SM, Tariot PN, Dagerman KS, Lebowitc BD, Lyketsos CG, et al. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. Am J Psychiatry. 2008;165:844–54.
155. Tariot PN, Schneider L, Katz IR, Mintzer JE, Street JS, Copenhaver M, et al. Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial. Am J Geriatr Psychiatry. 2006;14:767–76.
156. Zhong KX, Tariot PN, Mintzer J, Minkwitz MC, Devine NA. Quetiapine to treat agitation in dementia: a randomized, double-blind, placebo-controlled study. Cur Alz Res. 2007;4:81–93.
157. Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry. 2003;64:134–43.
158. Katz IR, Jeste DP, Mintzer JE, Clyde C, Napolitano J, Brecher M, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry. 1999;60:107–15.
159. Mintzer J, Greenspan A, Caers I, Van Hove I, Kushner S, Weiner M, et al. Risperidone in the treatment of psychosis of Alzheimer disease: results from a prospective clinical trial. Am J Geriatr Psychiatry. 2006;14:280–91.
160. Grossberg GT, Kohegyi E, Mergel V, Josiassen MK, Meulien D, Hobart M, et al. Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized double-blind, placebo-controlled trials. Am J Geriatr Psychiatry. 2020;28(4):383–400.
161. Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ. 2005;330(7496).
162. De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PLJ, Eriksson S, et al. A randomized trial of risperidone, placebo, and haloperidol for behiavoral symptoms of dementia. Neurology. 1999;53(5):946–55.