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# Agitation and Irritability in Alzheimer's Disease: Evidenced-based Treatments and the Black Box Warning

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## Abstract

More than five million Americans suffer from Alzheimer's disease (AD), and this number is expected to triple by 2050. While impairments in cognition, particularly memory, are typically the defining features of the clinical syndrome, behavioral symptoms are extremely common, affecting up to 90% of patients. Behavioral symptoms in AD can be difficult to manage and may require a combination of non-pharmacological and pharmacological approaches. The latter is complicated by FDA "black-box warnings" for the medication classes most often used to target these symptoms, and currently there are initiatives in place to limit their use. In this review, we describe common behavioral symptoms of AD—with a particular focus on the challenging symptoms of "agitation" and "irritability"—and discuss evidence-based approaches to their management. Ultimately, multidimensional approaches tailored to the patient and their environment are recommended, and evidence-based practices should be used when available.

### Keywords

Alzheimer's disease; Neuropsychiatric symptoms; Pharmacological approaches; Non-pharmacological approaches; Black-box warning

## Introduction

More than five million Americans suffer from Alzheimer's Disease (AD), and by 2050 this number is expected to triple [1]. While impairments in cognition, particularly memory, are often the most prominent features of the disease, behavioral symptoms (also known as neuropsychiatric symptoms) are extremely common and estimated to affect up to 90% of

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patients [2]. Neuropsychiatric symptoms in AD constitute a heterogeneous group of non-cognitive symptoms and behaviors [2].

Borrowing from the taxonomic construct most often applied to delirium [3], behavioral symptoms of AD can be imperfectly categorized as “hyperactive” and “hypoactive,” and many of these symptoms are captured in commonly used frequency and severity measures [4, 5]. Broadly speaking, “hyperactive” symptoms of AD include verbal or physical agitation, irritability, anxious affect, disinhibited behavior such as aggression, behavioral responses to delusions and hallucinations, and disrupted sleep. “Hypoactive” symptoms, on the other hand, include apathy, abulia, disengagement from activities, poor oral intake, poor self-care, depression, and hypersomnia. “Hypoactive” symptoms are sometimes considered more difficult to detect in the clinical population, as patients presenting with them may be less “disruptive” than patients with hyperactive symptoms. However, both categories of symptoms are common, associated with greater morbidity and mortality, and may occur in the same individual at different points in time [13]. The current review will focus on the assessment and management of “hyperactive” behavioral symptoms of AD—particularly agitation and irritability—and the reader is referred elsewhere for a discussion of the management of “hypoactive” behavioral symptoms [6–9].

## Prevalence and Burden

Agitation and irritability are common in AD, and affect many patients at some point in their illness [13]. In a recent cross-sectional analysis, Van der Mussele and colleagues examined the prevalence of agitation in mild cognitive impairment (MCI)—often considered a “precursor” to AD—and AD itself, and found that agitation (rated by the Cohen-Mansfield Agitation Inventory [4]) was present in 76% and 60% of AD and MCI cases at initial evaluation, respectively [10]. In a recent cross-sectional study, Charernboon and Phanasathit observed high rates of agitation, aggression, aberrant motor behaviors, and sleep problems in patients with AD, and found that the frequency of symptoms increased with the severity of illness [11]. Moreover, over 60% of participants presented with a chief complaint of behavioral symptoms, which was more frequent than memory complaints [11]. In the primary care setting, Thyrian and colleagues found that behavioral symptoms are common in individuals screening positive for dementia, and identified aggression, anxiety, disinhibition, and delusions as “severely to extremely” distressing in more than 30% of cases identified [12].

Agitation and irritability in AD are associated with greater caregiver stress, increased morbidity and mortality, and earlier placement in long-term care facilities such as nursing homes [13]. Conde-Sala and colleagues examined the impact of behavioral symptoms and “lack of self-awareness” on perceived quality of life in AD patients and their caregivers, and found that these symptoms had a negative effect on perceived quality of life in both groups [14].

In a report focusing on sleep disturbances in caregivers, Lee and colleagues found that caregivers of individuals with MCI and dementia exhibited poorer sleep compared to non-

caregivers, with neuropsychiatric symptoms being predictive of poor sleep quality in caregivers [15].

In terms of financial burden, a recent study in the UK examined costs associated with agitation due to AD, and found that excess cost associated with each case of AD-associated agitation was £4091 (~$6000) a year, equating to £2 billion (~$3 billion) a year across all AD patients in the UK [16].

Finally, Peters and colleagues observed that the emergence of certain neuropsychiatric symptoms—including agitation, aggression, and psychosis—are associated with shorter survival time from diagnosis of mild disease to diagnosis of severe disease or death [17]. Overall, these studies suggest that behavioral symptoms in general, and agitation and irritability in particular, pose a threat to the health and quality of life of AD patients and their caregivers, and that effective treatments for these conditions have the potential to lower costs and perhaps even modify illness course [13].

## Describing, assessing, and understanding the patient's presentation

Prior to selecting a treatment for the agitated or irritable AD patient, the provider should work to uncover the etiology of the presenting behaviors. This requires careful attention to the patient's presentation, and involves describing, assessing, and understanding the distressing or troublesome symptoms.

### Describing

Agitation (anxious "stirring," restlessness, nervousness) and irritability (being easily "angered" or "frustrated," also described as a pervasive feeling of "unease") are common in all stages of AD and may be accompanied by inappropriate verbal, vocal, or motor activity [2]. The term "agitation" is often used interchangeably with abnormal motor behaviors (such as pacing [19]), and in some cases is extended to encompass behaviors such as repetitive movements, socially inappropriate disinhibition, and wandering [2]. Cohen-Mansfield, a leader in this area, has identified four distinct categories of agitation in AD, including (1) physically non-aggressive behaviors, (2) verbally non-aggressive behaviors, (3) physically aggressive behaviors, and (4) verbally aggressive behaviors [4]. While helpful from a nosological perspective, these labels are not consistently used in clinical settings or even in AD research [20]. For clinicians and researchers alike, however, it is critical to accurately describe the specific symptom or behavior of concern, as doing so may provide a framework for understanding its etiology, promote selection of an appropriate intervention, and offer a means for tracking its progression over time in terms of severity, frequency, and character.

The characterization of behavioral symptoms in AD is complicated by the fact that caregivers, rather than medical providers, are the most frequent observers of these symptoms. Their reports, as with all second-hand accounts, can be susceptible to bias [13]. Furthermore, caregivers are prone to depression, anxiety, and increased stress levels, which may influence their observations and reporting [19]. A recent study by Stella and colleagues found that the most common disagreements between caregiver reports and clinician impressions of behaviors in AD included ratings of agitation, irritability, and aberrant motor

behaviors, and these discrepancies were especially prevalent in patients with mild dementia [21]. Furthermore, caregiver communication styles, expectations, over- and underestimation of patient abilities, and cultural beliefs may all influence the very behaviors being observed [13].

To minimize ambiguity, agitation, irritability, and other challenging behaviors should be described in clear language that can be understood by all members of the care team. In fact, it is often helpful to avoid using ambiguous terms such as “agitation” and “irritability,” and instead describe the particular actions, responses, or emotional expressions observed in the patient. It is also important to identify the time course of the symptoms in question, including the context in which they first emerged, how frequently they occur, and if they have worsened, improved, or otherwise changed over time.

Recently reporting on the results of a three-year longitudinal study, Brodaty and colleagues observed that levels of agitation, disinhibition, irritability, and aberrant motor behavior, among others, increased over time in many subjects, and that severity of dementia and male gender were associated with greater levels of symptoms [22]. Interestingly, having received a diagnosis of AD (as opposed to another type of dementia, such as frontotemporal dementia) was associated with lower levels of neuropsychiatric symptoms [22]. Indeed, the presence of neuropsychiatric symptoms should remind the clinician to carefully consider their differential diagnosis (i.e. consider diagnoses other than AD, such as Dementia with Lewy Bodies [23] or Frontotemporal Dementia [24]), though the presence of neuropsychiatric symptoms by no means precludes the diagnosis of AD.

## Assessing

The first step in assessing new-onset agitation and irritability in a patient with AD is to determine the potential contributions of medical causes which may lead to the syndrome of “delirium superimposed on dementia” [25]. Delirium, or an acute/subacute worsening of cognition due to a medical condition or medication effect, is extremely common in individuals with AD, and itself may have a negative impact on the long-term cognitive and medical trajectory of affected individuals [26]. Common causes of delirium in AD include infections, dehydration, and pain, among others [19]. Medications—especially antihistamines, anticholinergics, opioid narcotics, corticosteroids, and sedative/hypnotic agents—are also frequent culprits. If no medical etiology is found, identifying factors in the physical or social environment that precipitate and exacerbate the patient’s agitation or irritability are critical steps in assessment [19]. An environment that is over- or under-stimulating, or lacking in predictable routines, may exacerbate these symptoms [13]. In addition, assessing the “safety” of a situation is paramount, including whether the patient or others are in danger as a consequence of the behaviors [13].

## Understanding

Underlying the patient’s agitation and irritability may be a host of cognitive and emotional experiences and behaviors [2] that stem from a variety of processes. The pathogenesis of behavioral symptoms in AD has not been clearly delineated, but is thought to result from a complex interplay of cognitive, psychological, social, and biological factors [2]. Recent

studies have emphasized the role of neurochemical, neuropathological, and genetic factors underlying the clinical manifestations of these symptoms [2], and symptoms may also be related, in part, to an individual's heightened vulnerability to environmental triggers as cognitive abilities decline [13]. AD patients have limited cognitive reserves for managing irritants presented by their internal or external environments, and this often causes or contributes to irritability and agitation.

In some AD patients, irritability or agitation may also be related to a preexisting or co-occurring mood or psychotic disorder. Both elated mood (ranging from hypomania to mania) and depression (from mild to severe) can be associated with irritable affect, and can be further aggravated by factors such as hunger, sleepiness, or pain [2]. Delusions are also seen in dementia, and can cause or contribute to irritability or agitation. Delusions can vary widely with respect to systematization, conviction, and the extent to which patients respond to them [2]. Delusions in AD are typically less complex and organized than those observed in non-demented psychotic patients. They often involve suspiciousness, fears of abandonment, and misidentification [2]. Memory deficits may lead to beliefs that misplaced objects have been stolen, and agnosia (or "the inability to recognize") or memory dysfunction (discordance between recognition and familiarity) may result in misidentification syndromes, such as believing that a person has been replaced by an imposter, or that the patient's house is not their home [19]. Understanding the drivers of irritability and agitation can inform approaches to the management of these symptoms.

## Non-pharmacological and pharmacological approaches to treatment

Treatment of agitation and irritability in AD generally begins with non-pharmacological approaches, with pharmacologic interventions added as necessary [19]. Although the FDA has not approved any medications for these indications, psychotropic medications are frequently used off-label to manage such symptoms, despite the risk of adverse drug effects [13].

For several non-pharmacological approaches, studies have demonstrated efficacy as well as minimal adverse effects, though their use is often hindered by practical challenges [13], including the need to provide training and support to caregivers for successful implementation. In cases of severe agitation that poses an acute risk of injury (to the patient or others), medications are often started along with behavioral interventions [19]. Ultimately, multidimensional treatment approaches that are flexible and patient-centered—i.e., tailored to the individual and their environment—tend to yield the best outcomes [19], though evidence-based practices remain an evolving and important area of study.

Finally, it is important for clinicians to be aware that challenging behaviors may diminish or remit spontaneously over time [27]. While it is not within the scope of this brief article to provide a comprehensive review of all interventions that have been studied for managing neuropsychiatric symptoms in AD, the sections that follow describe relevant studies and refer the reader to selected reviews, with a focus on those published in the past three years.

## Non-pharmacological interventions

Non-pharmacological approaches are considered first-line treatment for managing behavioral symptoms in AD. Staedtler and Nunez undertook a systematic review of studies examining non-pharmacological approaches, and found that they were generally safe and effective, had the potential to decrease agitation and improve patient outcomes, and appeared to improve overall caregiver satisfaction [28]. Such approaches, however, can be challenging to implement, even in long-term care settings [29], with barriers to use including limited time, lack of education regarding their efficacy, poor staff to resident ratios (in long-term care settings), and difficult-to-modify physical environments [28].

The DICE approach (*D*escribe, *I*nvestigate, *C*reate, *E*valuate), described in detail by Kales and colleagues [13], is an important starting point for any discussion of non-pharmacological interventions. The DICE approach assumes that a "problem behavior has been identified and brought to the provider's attention," and begins by asking the caregiver to "*D*escribe" the behavior to the provider, including the context in which it occurs [13]. A basic problem-solving approach identifies antecedents and consequences, and caregivers are encouraged to record behaviors in a diary (to help identify underlying patterns). Once described, the behaviors are "*I*nvestigated" to identify modifiable causes, which may include a medical work-up involving laboratory testing or a review of medications. Next, the provider and caregiver (and the patient, if possible) are asked to "*C*reate" and implement a treatment plan. This may include actions such as discontinuing offending medications or removing noxious stimuli (such as turning down the volume of a loud radio), but more often "requires creativity on the part of the provider and caregiver to address the active problem, model problem-solving, and obtain buy-in for recommendations" [13]. Finally, the provider is asked to "*E*valuate" whether recommended strategies were attempted and, if so, effective [13]. If an intervention is not implemented, it is important for the provider (and caregiver) to understand why this is so. Likewise, it is important to evaluate if there are any untoward consequences of the intervention [13].

Embracing similar principles, the U.S. Veterans Health Administration has, in recent years, implemented the "Staff Training in Assisted Living Residences" or "STAR-VA" program, an interdisciplinary behavioral approach for managing challenging dementia-related behaviors in VA nursing homes [29], as well as the "Tailored Activity Program - Veterans Administration" or "TAP-VA" for managing dementia-related behaviors in the outpatient setting [30]. Both programs have been designed to improve the quality of life of veterans with dementia and reduce the burden on caregivers, with activities and behavioral interventions tailored to the veteran's preserved capabilities, and avoiding stimuli and activities that challenge the patient in areas of cognition that are most impaired.

Non-pharmacological approaches to managing behavioral disturbances in AD that have gained favor in recent years include light therapy [31], aroma therapy [32], and music therapy [33], among others. Figueiro and colleagues investigated the effectiveness of a tailored lighting intervention for individuals with AD, and found that this intervention significantly increased total sleep time and sleep efficiency, as well as reduced depression and agitation scores [31]. They concluded that timed light exposure can alleviate evening agitation, reduce nocturnal wandering, and improve nighttime sleep efficiency in AD

patients. Burns and colleagues conducted a double-blind placebo-controlled randomized trial of *Melissa officinalis* (lemon balm) aromatherapy and donepezil for the treatment of agitation in AD, and found that both aromatherapy and donepezil were effective and well tolerated, but neither demonstrated effects that differed significantly from placebo [32]. Despite this, the authors note that sizable improvement in the control group emphasizes the non-specific benefits of touch and interaction in the treatment of agitation in AD patients (since the control group in this study received placebo lotion, which required elements of touch and social interaction with members of care staff). Ambient music therapy and other environment-based interventions have also been examined for the management of agitation in AD, with the goal of providing an environment that helps to reduce noxious stimuli that may promote problem behaviors [33, 34]. While these interventions are generally safe and well-tolerated, studies of their effectiveness have been limited by methodological problems including small sample size and reliance on self-reported outcome measures, among others [35].

## Pharmacological interventions

**Antipsychotic medications—**Over the past decade, the management of agitation and irritability in AD has been complicated by concerns pertaining to the safety and efficacy of the major classes of psychotropic medications—particularly second-generation antipsychotic medications—that are frequently prescribed to control these symptoms. Through the early 2000s, atypical antipsychotics were widely used “off-label” to treat elderly dementia patients with behavioral disturbances [18]. However, safety concerns related to increased risk for cerebrovascular events, metabolic disturbances, and mortality led the FDA to issue a black box warning for their use in 2005 [18]. These concerns, compounded by questions regarding their effectiveness, has led to a number of policy initiatives seeking to limit the scope of their use, and has left treatment providers in a challenging position. However, medications remain an important option for treatment, especially if behaviors are frequent, aggressive, or have the potential to injure the patient or caregiver [19], and many clinicians continue to turn to second generation antipsychotic medications as first-line pharmacotherapy. A decade ago, the seminal CATIE-AD (Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer’s Disease) trial raised doubts about the benefit of treating AD-related agitation with atypical agents [36]. CATIE-AD was a 42-site, double-blinded, placebo-controlled trial of 421 outpatients with AD and psychosis, aggression, or agitation, and randomized patients to receive olanzapine, quetiapine, risperidone, or placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. No statistically significant differences were noted with regard to improvement on the Clinical Global Impression of Change (CGIC) scale with any medication. There were, however, non-significant improvements in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, and 29% of patients assigned to risperidone, compared to improvement in 21% of patients assigned to placebo ($p=0.22$). In addition, time to discontinuation of treatment due to adverse events or intolerability favored placebo, highlighting the very real side effect burden of atypical agents.

During the same period, Schneider and colleagues (2005) performed a meta-analysis to assess risk for mortality from atypical antipsychotics in individuals with dementia, and

found that death occurred more often among patients randomized to active drug (3.5%, compared to 2.3% with placebo), with an odds ratio of 1.54 [37]. They concluded that atypical antipsychotics may be associated with a small but significantly increased risk of death compared with placebo, and that the risk of using these agents should be considered within the context of medical need, medical comorbidity, and the efficacy and safety of alternatives [37]. Similar findings by the FDA of increased risk of both cerebrovascular adverse events and death, based on retrospective analyses of pooled safety data from several efficacy studies, resulted in the issuance of the FDA's "black box" warning in 2005 that "patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death" (now primarily attributed to cardiovascular and infectious etiologies). The mortality risk warning was extended in 2008 to include "conventional" antipsychotics as well [38]. Within a month of the original warning, use of these agents reportedly dropped by 50% in the elderly [18], though a recent analysis by Dorsey et al [39] suggests only a small decline in their use, with similar findings by Singh and Nayak [40].

The aforementioned safety concerns regarding antipsychotic agents have been confirmed by subsequent analyses, including a recent study by Maust and colleagues that examined the mortality risk and number needed to harm (i.e. number of patients receiving treatment that would be associated with one death) of antipsychotics, valproate, and antidepressants in patients with dementia [41]. This retrospective case-control study included over 90,000 older patients with a diagnosis of dementia who received a new prescription for an antipsychotic (haloperidol, olanzapine, quetiapine, or risperidone), valproate, or an antidepressant. As a group, the atypical antipsychotics (olanzapine, quetiapine, and risperidone) showed a dose-response increase in mortality risk, with 3.5% greater mortality in the high-dose subgroup relative to the low-dose group. When compared directly with quetiapine, dose-adjusted mortality risk was increased with both risperidone and olanzapine. The authors concluded that the absolute effect of antipsychotics on mortality in elderly patients with dementia may be higher than previously reported, and appears to increase with dose.

While safety concerns have been consistently replicated, the efficacy of atypical agents for the treatment of agitation and irritability in AD has been less clear. A recent meta-analysis by Ma and colleagues, for example, found significant efficacy of atypical antipsychotics for behavioral symptoms of dementia compared to placebo, with a lower rate of agitation (OR = 0.80) [42]. The authors also confirmed significantly higher risks of somnolence (OR = 2.95), extrapyramidal symptoms (1.74), cerebrovascular adverse events (2.50), gait abnormality (3.35), and death (1.52), and concluded that efficacy, safety, and tolerability should be carefully weighed against clinical need [42]. Similarly, a recent meta-analysis by the US Agency for Healthcare Research and Quality (AHRQ) examined the efficacy and safety of atypical antipsychotics for use in conditions lacking FDA approval, and examined controlled trials comparing atypical antipsychotics to either placebo, another atypical antipsychotic drug, or other pharmacotherapy [43]. Among placebo-controlled trials of elderly patients with dementia reporting a total/global outcome score that included symptoms such as psychosis, mood alterations, and aggression, small but statistically-significant effect sizes ranging from 0.12 and 0.20 were observed for aripiprazole, olanzapine, and risperidone, with more mixed but still marginally positive effects for quetiapine. This analysis also

confirmed adverse events including an increased risk of death, stroke, and extrapyramidal symptoms, among others [43].

If treatment with an antipsychotic agent is undertaken, atypical antipsychotics are generally preferred over first-generation agents [44] due to the former's more favorable side effect profile and tolerability [19]. It is also important to be aware of the separate but related issue of psychosis in AD. As noted by Murray and colleagues, psychosis in AD indicates a more severe phenotype, often with more rapid cognitive decline [45]. Atypical antipsychotics are used to treat psychosis in AD, especially when associated with agitated or aggressive behavior. As noted above, however, these agents are not approved for this indication by the FDA and their use in this context is considered "off-label" [46].

**Medication alternatives to antipsychotic medications—**Unfortunately, there are no other drugs that have been approved by the FDA as safe and effective for the treatment of irritability or agitation in AD. Benzodiazepines, used in the general adult population to treat restlessness, anxiety, and irritability, are a relatively poor choice in the older population given their risk for worsening confusion [47], gait steadiness, and falls [48]. Typically, we recommend reserving benzodiazepines for severe cases in which symptoms are distressing, disabling, disruptive (e.g., interfere with delivery of essential care), or dangerous, and when alternatives have been unsuccessful [42]. Anticholinergic medications, such as diphenhydramine and hydroxyzine, are not recommended in older patients due to similar safety and tolerability concerns [49], and both are included on the "Beers Criteria" list for potentially inappropriate medication use in older adults [50]. Beta-adrenergic antagonists such as propranolol have, in older case-based literature, been suggested for treatment of agitation in AD [51], though their efficacy has not been consistently replicated [52] and we have found them to be of limited utility for this indication.

Antidepressant and mood-stabilizing agents have shown some promise for alleviating agitation and irritability in AD. The antidepressant citalopram was evaluated in the CitAD study, an NIMH-funded placebo-controlled, double-blind, parallel group trial that enrolled 186 patients with probable AD and clinically significant agitation. Subjects were randomized to receive a psychosocial intervention for agitation plus either citalopram or placebo over nine weeks [53]. Among patients with AD and agitation who were receiving psychosocial intervention, the addition of citalopram compared with placebo significantly reduced agitation and caregiver distress [53]. However, QTc prolongation and cognitive worsening were observed in the citalopram group.

In another study, Suzuki and Gen investigated the clinical efficacy of lamotrigine for AD with behavioral symptoms. This 16-week, open-label trial measured behavioral and cognitive symptoms in 40 inpatients, with behavioral symptoms assessed using the Neuropsychiatric Inventory (NPI) [54]. Although mean change from baseline global NPI and two NPI subscales (anxiety and irritability) were significantly improved in the lamotrigine group, the differences were not significantly different as compared to the control group. However, concomitant use of psychotropics was also measured (calculated in terms of risperidone or diazepam equivalents), and it was found that the mean decrease from baseline in diazepam-equivalent doses of benzodiazepines was significantly greater in the

lamotrigine group than in the control group, suggesting that the administration of lamotrigine to patients with AD-related behavioral disturbances may facilitate reduction in doses of other psychotropic medications being prescribed [54]. As with other classes of medications, the clinical utility of these mood-stabilizing agents must be weighed against their potential side effects [55].

The NMDA receptor antagonist memantine has also been studied for its potential prophylactic effect on behavioral symptoms in AD [56]. MAIN-AD was a randomized, placebo-controlled, double-blind withdrawal trial comparing memantine with antipsychotics for the treatment of neuropsychiatric symptoms over 24 weeks, in which 199 individuals with AD who were already receiving an antipsychotic medication were randomized to either switch to memantine or continue their antipsychotic. Primary outcomes were function and agitation, and secondary outcomes were cognition and mortality. While the study showed no benefits from memantine for prophylaxis of clinically significant behavioral symptoms, the results did indicate some benefits for antipsychotic medications in reducing the rate of relapse of behavioral symptoms [56].

In addition to choosing the medication itself, the provider must also consider the medication's dosing schedule. "Pro re nata" (PRN) dosing of psychotropics, for example, has been used in patients with behavioral symptoms of dementia [57], but may be a potential source of inappropriate medication administration [58]. A recent study employing a retrospective chart review examined 170 inpatients with dementia, and found that individuals were more likely to receive a psychotropic medication dose PRN if they were younger, or required medication shortly after nursing shift change, in the evening, or during the weekend. Furthermore, if a range of the dose of the antipsychotic was prescribed, patients were more likely to receive the higher dose than if they were receiving a regularly scheduled medication from the same class [58]. Whenever possible, using "standing" dosing of medications rather than PRN dosing is recommended, with regular dose reduction trials attempted as appropriate.

## Treatment considerations and the black box warning

Based on the published literature as well as our clinical experiences, a non-pharmacologic intervention (e.g. the DICE approach) for the treatment of agitation and irritability in AD is generally recommended, with pharmacologic interventions added as necessary (i.e., when symptoms remain distressing, disabling, disruptive, or dangerous). In cases of severe symptoms in which the risk of injury is high, the patient should be started on medication along with behavioral interventions, with drug class and selection of a specific agent based on symptom targets and medication side effect profiles [19]. Psychotropic "polypharmacy" should be avoided whenever possible.

The FDA's black box warning for antipsychotic medications in elders with dementia warrants special discussion, particularly given media portrayals [59] and regulatory initiatives [60] that have focused on this frequently prescribed class of medications. As Stevens and colleagues (2014) write in their excellent review of the topic, an FDA "black box warning" indicates that a medication "has serious or potentially life-threatening side

effects" but remains "FDA-approved and may have critically important therapeutic roles" [18]. In other words, the black box warning "is a way to urge physicians to carefully consider the risks and benefits, before prescribing a drug that has a potentially disabling or fatal reaction" [18]. They note that a physician who tries to prescribe "around" these warnings (i.e. avoids prescribing these medications at "all costs") ultimately works from a limited armamentarium that may hinder, rather than promote, the best patient-centered care [18]. Beyond the FDA's black box warning, federal and state initiatives to reduce the prescription of psychotropic medications (and antipsychotic medications in particular) to individuals with dementia may discourage health care providers from prescribing medications for irritability and agitation associated with AD, even when clinically appropriate (i.e., in carefully selected cases in which the benefit to the patient substantially outweighs the risk) [61].

In 2014, The Centers for Medicare & Medicaid Services' "National Partnership to Improve Dementia Care" announced having met its initial goal of reducing the national prevalence of antipsychotic use in long-stay nursing home residents by 15.1 percent, and proposed an even higher goal of 25% reduction by the end of 2015 [60]. While these reductions are likely to include large numbers of patients for whom antipsychotics were prescribed inappropriately (e.g., in the absence of appropriate target symptoms, or in patients with gait instability who have a high risk of falling), it is not known to what extent these reductions also leave, untreated, some patients who fail to respond to non-pharmacological approaches and may derive symptom relief from drug treatment (and without experiencing significant harm).

As with all medications, physicians must exercise professional judgment when recommending a drug with a black box warning [18], and must document the basis for their clinical decisions, including that they have obtained informed consent. Informed consent is based on the principle that all individuals have the right to make decisions that affect their well-being, and requires disclosing, discussing, and weighing the risks and benefits of an intervention [62]. All patients—including those suffering from AD—are presumed competent to make their own decisions unless an evaluation determines otherwise. Informed consent is best approached as an open discussion between the patient, their caregivers (if incapacity necessitates), and the physician, and may be facilitated by beginning with a discussion of the patient's (and family's) "goals of care" [63]. In the case of AD, this may require an acknowledgement that AD is a disease for which there is currently no cure, and that many of the treatments that we provide—particularly for the management of neuropsychiatric symptoms—are prescribed to palliate (i.e., lessen the burden of the disease) without necessarily correcting the underlying cause. Discussing "goals of care" involves, among other topics, identifying the patient's (and family's) tolerance for risk, including risks associated with treatment and with deferring treatment. Regardless of whether a treatment is implemented or deferred, it is critical for the physician to document that informed consent has been provided. In Table I, we have provided a framework for documenting the critical components of such a discussion.

It is important to note that informed consent must be obtained voluntarily and without coercion (i.e., without external forces that limit the autonomy of the patient) [64]. The assessment of "voluntariness" is complex, and includes attention to pressures that may be

introduced by family members, staff, and physicians, among others. Of course, patients at any stage of AD may lack (a) awareness of both their cognitive deficits and non-cognitive behavioral symptoms, (b) ability to comprehend the available treatment options, and (c) appreciation of the risks and benefits of accepting or declining treatment, including palliative treatments. When awareness, comprehension, or appreciation of treatment issues are limited, it may indicate that cognitive impairment from AD has progressed to the point of impeding the patient's capacity to make treatment decisions on their own behalf. In such cases, which are very common, a surrogate decision-maker must be identified.

## Conclusions

Agitation and irritability in AD can be difficult to manage, and may require the combination of non-pharmacological and pharmacological approaches. Generally, the treatment of these symptoms in AD begins with a non-pharmacological approach, with pharmacologic interventions added as necessary. Although the FDA has not approved any medications for the treatment of agitation and irritability in AD, psychotropic medications are frequently used off-label to manage these symptoms, and must be done so judiciously, with careful documentation of informed consent in the medical record. Ultimately, a multidimensional treatment approach that is flexible and patient-centered—i.e., tailored to the individual and their environment, and incorporating the wishes of family and caregivers—tend to yield the most favorable outcomes.

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**Table I:**

Documenting informed consent

| Step* | Description* | Example |
|---|---|---|
| 1 | Nature of the condition being treated, and the proposed treatment | Mr. Jones has been diagnosed with AD, and insists to nursing home staff that he “has to go to work” each morning (despite having been retired for 15 years). Furthermore, he appears frustrated when gently redirected by his nurse, and becomes insistent and intrusive (entering into the personal space of others) when his request to leave for work is denied. On a few occasions, this intrusiveness has excited other patients, and yesterday another patient attempted to push Mr. Jones in an act of self-defense. Given that Mr. Jones has not responded to non-pharmacological interventions, as well as concern for his safety and the safety of peers and staff, we recommend a one-week trial of Drug A, to be administered each morning for the next 7 days. |
| 2 | Reasonably expected benefits from the proposed treatment | Drug A has been shown to improve symptoms of agitation and irritability in some but not all patients with AD. We expect that the frequency and severity of Mr. Jones’ intrusiveness will decline after treatment is started. |
| 3 | Nature and likelihood of the risks of the proposed treatment | Drug A is a second-generation antipsychotic agent. The FDA has determined that patients with dementia who are treated with antipsychotic medications are at an increased risk of death. In addition, Drug A is known to cause a number of side effects, the most common of which are {list}. Mr. Jones’s wife, who is his surrogate decision-maker, demonstrates her awareness and expresses her acceptance of these risks. |
| 4 | Inability to precisely predict results of the proposed treatment | Mr. Jones and his wife have been advised that we cannot predict the results of any particular treatment trial, and that Mr. Jones’ symptoms may improve, worsen, or remain unchanged after treatment has been started. We have advised Mr. and Mrs. Jones that we will continually review the patient’s response to this medication, and will recommend adjustments as appropriate. |
| 5 | Potential irreversibility of the proposed treatment or its side-effects | When given to older adults with dementia, Drug A has been associated with an increased risk for death, most often due to cardiovascular or infectious events. Mr. Jones had a recent electrocardiogram and complete blood count, which were normal. Despite these reassuring results, Mr. Jones’ wife is aware of the potential for the aforementioned irreversible effects of treatment with Drug A, and indicates that, as his proxy, she accept these risks. |
| 6 | The expected risks, benefits, and results of alternative, or no, treatment. | Mr. Jones’ intrusiveness may also be treated with other classes of medications, as well as non-pharmacological approaches such as {list}. In addition, the patient and his wife could elect to take no therapeutic action at this time. However, we have counseled Mr. and Mrs. Jones that we recommend a trial of Drug A over the next week to help diminish Mr. Jones’ distress related to these symptoms, and to mitigate the significant danger of physical retaliation by peers on the unit. |

*Adapted from Brendel et al. 2010 [64], and used with permission from Elsevier Limited (Oxford, UK)