Neuropsychiatric Symptoms in Alzheimer's

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Review Article

Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms

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Abstract

Neuropsychiatric symptoms (NPSs) are hallmarks of Alzheimer's disease (AD), causing substantial distress for both people with dementia and their caregivers, and contributing to early institutionalization. They are among the earliest signs and symptoms of neurocognitive disorders and incipient cognitive decline, yet are under-recognized and often challenging to treat. With this in mind, the Alzheimer's Association convened a Research Roundtable in May 2016, bringing together experts from academia, industry, and regulatory agencies to discuss the latest understanding of NPSs and review the development of therapeutics and biomarkers of NPSs in AD. This review will explore the neurobiology of NPSs in AD and specific symptoms common in AD such as psychosis, agitation, apathy, depression, and sleep disturbances. In addition, clinical trial designs for NPSs in AD and regulatory considerations will be discussed.

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1. Introduction

Neuropsychiatric symptoms (NPSs) are hallmarks of Alzheimer's disease (AD), causing substantial distress for both people with dementia and their caregivers, and contributing to early institutionalization. They are among the earliest signs and symptoms of neurocognitive disorders and incipient cognitive decline, yet are under-recognized and often challenging to treat. The Alzheimer's Association's Research Roundtable, a consortium of experts from academia, industry, and regulatory agencies first addressed these challenges in 2010 [1].

Since then, there is renewed interest in mechanisms of NPSs and identification of effective treatments for these symptoms, in part through the efforts of the NPS professional interest area within the International Society to Advance Alzheimer's Research and Treatment [2]. In May 2016, the Research Roundtable revisited the topic, bringing together experts in the field to advance therapy development through a more comprehensive understanding of underlying mechanisms and application of novel clinical trial approaches.

2. History and overview

NPSs affect almost all individuals with dementia (97%) over the course of the disease [3], and although they fluctuate [4], they rarely disappear [5]. The effects on both patients and caregivers are severe: they are associated with impairment in activities of daily living [6], poor quality of life [7], earlier institutionalization [8], accelerated disease progression, increased mortality [9], caregiver stress [10], and increased cost of care [11].

Medical, environmental, and caregiver issues can impact the expression of NPSs, making the categorization of the symptoms challenging [12]. Each of these approaches has limitations because nosology does not always reflect pathophysiology. The top-down classification system of the Diagnostic and Statistical Manual, 5th edition, provides various syndrome categories, yet NPSs overlap substantially among these syndromes. For example, agitation may accompany depression, anxiety, or psychosis. The Research Domain Criteria project classifies NPSs based on neurobiological dimensions and behaviors rather than clinical syndromes, grouping them into five domains: (1) negative valence; (2) positive valence; (3) cognitive systems; (4) processes for social systems; and (5) arousal or regulatory systems [13]. Yet here, too, there is tremendous overlap. For example, impairment of cognitive systems may manifest in delusions, hallucinations, agitation, aggression, depression or dysphoria, anxiety, elation or euphoria, apathy, disinhibition, irritability, motor disturbance, sleep disorder, appetite disorder, aberrant vocalization, and ruminative, repetitive, and somatoform behaviors. Extensive overlap is also evident when NPSs are mapped to domains such as memory, visuospatial, executive function, or others.

The Neuropsychiatric Inventory (NPI) [14] is commonly used to assess NPSs in clinical trials. A meta-analysis of studies using this scale found that apathy was the most common NPS, followed by depression, aggression, anxiety, sleep disturbances, irritability, appetite disturbances, motor problems, delusions, disinhibition, hallucinations, and euphoria [15]. The NPI has some limitations: it multiplies severity and frequency scores resulting in noncontinuous and non-normal total scores [16], it fails to capture ruminative, repetitive, compulsive, and somatoform behaviors, and is dependent on caregiver report. The Clinician Rating of the NPI (NPI-C) expands the range of the symptoms assessed by the NPI [17].

NPSs can present in advance of dementia. Among cognitively normal individuals, symptoms of depression, irritability, agitation, and apathy predict more rapid cognitive decline [18–20]; some NPSs are more powerful predictors of incident mild cognitive impairment (MCI) than hippocampal atrophy [21]. One MCI study found NPSs in 59% of participants and were associated with poorer cognitive and psychosocial function [22]. Their presence predicted faster progression from MCI to dementia in two very large cohort studies [9,23].

NPSs typically emerge in three phases: (1) irritability, depression, and nighttime behavior changes; (2) anxiety, appetite changes, agitation, and apathy; and (3) elation, motor disturbances, hallucinations, delusions, and disinhibition [24]. This emergence of NPSs in later life is core to the construct of mild behavioral impairment (MBI), which describes later life acquired, sustained, and impactful NPS as an "at-risk" state for cognitive decline and dementia. Operationalized in the recently published Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) MBI criteria [25], NPSs can emerge in advance of, or in concert with MCI, must be of at least 6-month duration, and not better accounted for by conventional psychiatric nosology. MBI symptoms are categorized into five domains: decreased drive and motivation, affective and emotional dysregulation, impulsivity, social inappropriateness, and abnormal perceptions or thoughts (e.g., delusions and hallucinations). Many rating scales used in dementia do not differentiate between new symptoms and chronic psychiatric illness, and they have short reference times that may not allow time to rule out reactive states. The MBI checklist was developed to remedy these issues [26] (available at www.MBItest.org). The MBI criteria and MBI checklist will provide a screening method to capture neurodegenerative disease early, foster systematic research into the effect or predictive value of NPSs on cognitive and functional outcomes, and improve clinical trial enrollment and design [25,27].

Although the presence of NPSs in the early stages of dementia predict disease progression, it is not clear whether NPSs reflect a more aggressive form of disease [28]. In addition, there are few pharmacologic treatment options with proven efficacy and acceptable levels of risk that target NPSs. Only one medication is approved in AD for treatment of NPSs (Canada and Europe only): risperidone for short-term treatment of aggression. Nonpharmacologic interventions are considered by most clinicians to be first-line treatments, yet translation from clinical studies to the real world has been limited [29], in part because these interventions are not reimbursed, and caregivers are not trained to provide them. They are generally based on psychosocial models for understanding these conditions across the continuum of the disease and in the presence of comorbid conditions [30–33].

3. The neurobiology of NPSs in AD

Understanding the neurobiology of NPSs in the context of the AD brain could greatly advance the development of new therapies. Most efforts to map the progression of AD pathology have focused on the cortex (e.g. [34]). For NPSs, however, distinct syndromes have different neurobiological underpinnings, so understanding the dysfunction or dysregulation of subcortical forebrain, diencephalic, and brainstem nuclei that generate or mediate visceral, emotional, motivational, and other psychiatric symptoms will be required. Early studies recognized significant involvement of AD pathology in key components of the limbic system, including the amygdala, basal forebrain, hypothalamus, and brainstem. Neurofibrillary tangles, for example, are abundant in the amygdala of the Alzheimer's brain [35], as well as in the basal nucleus of Meynert [36], the locus coeruleus [37], substantia nigra [38], dorsal raphe nucleus [39], and hypothalamus [40]. Neuronal loss in the basal nucleus of Meynert and locus coeruleus also correlates with progression of AD dementia [41]. The hypothalamus is important for the regulation of appetite, sleep, and circadian rhythms, and mediates many aspects of emotional experience. However, the degree to which pathologic involvement of these structures correlates with NPSs has not been well studied. The relevance of neuropathology is fundamental to drug development, where currently approved treatments for mood and psychotic symptoms, such as antidepressants and antipsychotics, may not work because of lack of target engagement in a degenerating brain.

4. Neuropsychiatric symptoms

This section will review the neurobiology, epidemiology, and current treatments for psychosis, agitation, apathy, depression, and sleep disturbances.

4.1. Psychotic symptoms in AD

Both delusions and hallucinations are reported in AD [42]. In a study of 124 demented patients, 67% had psychotic symptoms. They occurred two to six times per week, persisted for 12 weeks among 32% and recurred in 50% within 12 months [43]. They were associated with accelerated cognitive and functional decline and increased mortality [44]. These frequencies were higher still among patients with dementia with Lewy bodies. Hallucinations occur less frequently than delusions in AD and rarely occur in isolation; the opposite is true for dementia with Lewy bodies and Parkinson's disease dementia. The hallucinations and delusions in AD are phenomenologically different to those in schizophrenia, psychotic depression, or mania. Hallucinations in AD are usually visual, less commonly auditory, and rarely tactile or olfactory [45]. Persecutory delusions occur earlier in AD than misidentification delusions; both kinds increase with dementia severity.

Psychotic symptoms are correlated with increased neocortical neurofibrillary tangles [46], increased levels of intraneuronal hyperphosphorylated tau [47], disruption of serotoninergic signaling [48], decreased neuronal density, and increased myoinositol/creatinine ratio assessed using proton magnetic resonance spectroscopy [49]. Individuals with MCI who develop delusions also have greater gray-matter atrophy, particularly in the right frontal areas that regulate inhibitory control [50,51]. Some psychotic presentations are associated with distinct neuroanatomic substrates. For example, misidentifications, which might be understood as a disconnect between memory and familiarity, are associated with lower cell counts in the hippocampal CA1 region. Persecutory delusions are associated with cell loss in the dorsal raphe nucleus [52].

Genetics may play a role in AD psychosis: the serotonin 2A receptor single-nucleotide polymorphism 102 T allele is associated with the presence of delusions, whereas the C allele is protective [53]. The apolipoprotein E (*APOE*) ε4 allele is associated with an increased risk for AD, but the association between *APOE* ε4 and NPSs in AD is weak [54].

In recent years, atypical antipsychotics such as risperidone, olanzapine, quetiapine, and aripiprazole have largely replaced conventional antipsychotics such as haloperidol for the treatment of psychosis in dementia. They have minimal efficacy on psychotic symptoms [55] but are associated with many adverse effects, such as somnolence, cognitive decline, movement disorders, infections, edema, weight gain, metabolic syndrome, and hypotension, which leads to an increased risk of falls and stroke [55]. The major concern is their association with an increased risk of death [56]. Alternative treatments, such the 5-HT2A receptor antagonists/inverse agonists and 5-HT6 receptor antagonists, are undergoing clinical evaluation in AD psychosis. Part of the challenge in the development of new therapies is that psychosis in AD is difficult to define and clinically heterogeneous, and there is a paucity of clinically relevant outcome measures.

An alternative approach conceptualizes dementia psychosis as the combined impact of memory loss with other personal factors, such as post-traumatic stress disorder [57,58]. For example, a dementia sufferer might forget

where she placed her makeup and presume someone has stolen it, but will change this perception when the makeup is found. The core symptom is memory loss and not a psychotic episode. Thus, treatments targeting memory rather than psychosis would be more appropriate. Effective psychological interventions for functional psychosis might also be adapted for people with AD [59].

4.2. Agitation in AD

Agitation occurs frequently in AD. The prevalence varies greatly between studies due to the use of different definitions. The International Psychogeriatric Association consensus statement defines agitation as excessive motor activity, or verbal or physical aggression that associated with emotional distress: (1) severe enough to produce disability; (2) beyond what would be expected from cognitive impairment by itself; and (3) not solely attributable to another disorder, environmental conditions, or the physiological effects of a substance [60]. Agitation tends to persist; it increases as disease severity increases and is often associated with psychosis, anxiety, and disinhibition. Agitation and psychosis together are predictive of more rapid decline, increased institutionalization, and earlier death.

As recently reviewed, agitation in AD is associated with structural and functional abnormalities of the brain regions associated with emotional regulation and salience: the frontal, anterior cingulate, and posterior cingulate cortices, amygdala, and hippocampus [61]. Degeneration of these circuits may result in the overestimation of threat and/or affective dysregulation that induces hypervigilance. Agitation and aggression are associated with decreased cholinergic and serotoninergic markers, increased tau and phospho-tau, and regional decreases in the *N*-acetylaspartate/creatine ratio and increases in the myoinositol/creatine ratio [49,62].

Psychological theoretical frameworks provide alternative models with which to understand agitation in dementia [63]. The behavioral model focuses on triggers to the agitated behavior and reinforcements, which maintain the behavior. Interventions focus on eliminating the triggers and changing the relationship between behavior and reinforcement. The reduced stress threshold model posits that persons with dementia have a reduced threshold for stress, necessitating a very calm and quiet environment. The unmet needs model describes how people with dementia are unable to address their own needs or communicate them to others. These needs are unmet because their caregivers are unaware of the needs or of ways to meet them [64].

Both nonpharmacologic and pharmacologic approaches are used to manage agitation in patients with AD [12]. Nonpharmacologic approaches are based on psychosocial paradigms for NPSs and address them based on the specific model used. However, several general principles apply, including a detailed assessment of potential unmet needs and environmental or interpersonal stressors. The intervention is tailored to the NPS, the person with dementia's preferences and cognitive, motor, and sensory abilities. These approaches educate caregivers, make changes to the physical environment, increase social engagement, exercise and activities, and address sleep problems. They produce significant positive impacts on NPSs in randomized controlled trials [65,66]. The comprehensive assessment includes assessing pain, discomfort, and other medical conditions, as sometimes treating other medical conditions may relieve agitation. For example, many patients with dementia have pain, which may increase agitation and anxiety [67]. Indeed, treatment of pain has been shown to alleviate agitation in persons with dementia [68].

A range of medications—antipsychotics, benzodiazepines, cholinesterase inhibitors, memantine, anticonvulsants, and selective serotonin reuptake inhibitor (SSRI) antidepressants—have been used to treat agitation in patients with dementia but have shown minimal efficacy and/or substantial adverse effects. In a recent study, the SSRI citalopram was shown to reduce agitation and caregiver distress but was associated with cognitive decline and corrected QT interval prolongation [69]. A combination of dextromethorphan hydrobromide and quinidine sulfate, which is approved for the treatment of pseudobulbar affect in amyotrophic lateral sclerosis, is being investigated as a treatment for agitation in AD [70]. Several other drug development efforts targeting N-methyl-D-aspartate, dopamine D2, and serotonin receptors (5-HT1A and 5-HT2A), and cannabinoids are also being assessed.

4.3. Apathy in AD

Apathy, characterized by lack of motivation, decreased initiative, akinesia, and emotional indifference, is the most common NPS associated with AD and a primary cause of caregiver distress [71]. It is common in predementia states, increases in frequency as the disease progresses, and predicts conversion from normal cognition to MCI and MCI to dementia [72]. An international task force published diagnostic criteria for apathy in 2009, which require that two of three dimensions of diminished motivation must be present for at least 4 weeks with identifiable associated functional impairment [73]. The Apathy Evaluation Scale is commonly used to assess apathy across the AD continuum [72,74]. The NPI also includes an apathy subscale, but it has not yet been validated for use on its own. Apathy can occur alone or as a symptom of depression [75].

In neuroimaging studies of preclinical or prodromal AD, apathy is associated with cortical dysfunction in the posterior cingulate or inferior temporal cortex as well as atrophy, hypometabolism, and hypoperfusion in these regions. Abnormalities in cholinergic, GABAergic, and dopaminergic function have also been associated with apathy, as well as high levels of tau and phospho-tau in the cerebrospinal fluid (CSF) [76]. Dopaminergic circuits have been targeted in treatment trials using methylphenidate, with a significant reduction in apathy symptoms, improvement in global cognition, and minimal adverse events, for more than the

6-week study [77]. Interim results from another study also suggest that the combination of an acetylcholinesterase inhibitor (donepezil) with a cholinergic precursor (choline alphoscerate) decreased apathy and caregiver distress [78]. Open label studies of cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) showed improvement in apathy for all three medications [58].

4.4. Depression in AD

Depression is found in 16% in population-based AD studies, and 44.3% in hospital-based studies [79]. Depression is also common in MCI. A meta-analysis of 57 studies found an omnibus prevalence of 32%, but depressive symptoms more prevalent in clinical (40%) versus community-based (25%) samples [68] reflecting their clinical relevance in the cognitively impaired. Depression is also a predictor of progression from normal cognition to MCI and from MCI to dementia. However, whether depressive symptoms represent a risk factor or early manifestation of the AD brain disease or both is unclear. Supporting the latter notion, the presence of MCI in depression has been shown to predict later development of AD [80].

More severe neuropathology (tau, amyloid, and vascular disease) is seen in patients with AD with depression compared to those without. These patients also show severe loss of serotonin receptors and serotonin transporter binding, which may have implications for treatment [81].

Several studies have examined antidepressant efficacy in the context of AD. The Depression in Alzheimer's Disease Study (DIADS) demonstrated improvement with sertraline compared with placebo in patients with AD with major depression for more than 12 weeks [82]. A follow-up study, DIADS-2, included patients meeting criteria for "depression of AD," but found no differences in depression outcomes for more than 12 weeks of treatment with sertraline or placebo [83]. There were no differences in outcome in a 13-week trial comparing sertraline, mirtazapine, or placebo [84]. A meta-analysis of SSRI and serotonin-norepinephrine reuptake inhibitors (SRNI) treatment for depression in AD found "small to null"effect sizes [85], with small responses in those with subsyndromal levels of depression. Standardized psychosocial interventions were given to caregivers concomitantly in both DIADS and DIADS-2. There is some evidence that psychosocial interventions such as these, as well as exercise, increasing social contact, reminiscent therapy, and others can be efficacious (reviewed in [64,86]). For example, cognitive rehabilitation may decrease depression among women with AD and mild dementia [87].

4.5. Sleep disturbances and AD

A bidirectional relationship between sleep disturbances and dementia has been demonstrated in both humans and animals. For example, sleep problems and sleep disruption are associated with increased risk of cognitive decline [88,89] and higher risk for developing dementia [90]. Cognitively normal people with biomarkers of AD have slightly decreased sleep efficiency [91]. A similar relationship is seen between the presence of sleep apnea and dementia: those with sleep apnea are more likely to develop MCI and dementia [92,93] and those with more severe dementia have more severe sleep apnea [94]. In addition, sleep apnea has been associated with a younger age of decline to MCI or AD [95]. Circadian rhythm disruption has also been linked to a greater risk of MCI and dementia [96], as well as neuroinflammation and synaptic loss in mice [97].

The link between disrupted sleep and dementia may be the accumulation of amyloid β (Aβ) in the brain, according to studies in mice [98] and humans [99]. Aβ dynamics in the brain and CSF are strongly influenced by the sleep-wake cycle, and sleep deprivation accelerates Aβ plaque deposition in mice [68,69]. Orexin, a hypothalamic neurotransmitter implicated in sleep homeostasis, may play a role in Aβ regulation as genetic or pharmacologic inhibition of orexin function suppresses Aβ pathology in mice [100,101]. The glymphatic system—an astrocyte-driven system of perivascular fluid flow through which the brain removes toxic waste products—may also play an important role because slow-wave sleep (SWS) dramatically increases glymphatic influx and efflux [102]. SWS is also the stage of sleep where there is a greater reduction in corticocortical connectivity [103–107] and cerebral blood flow [108,109], indicating that it may also play a role in decreasing Aβ production (which is closely associated with neuronal activity [110]) as shown by two recent human studies in which slow-wave activity was associated with decreased CSF Aβ40 and Aβ42 levels in healthy control subjects [111].

These data suggest that behavioral and pharmacologic interventions targeting SWS enhancement, sleep disorders, and circadian disturbances may improve cognitive function or slow deterioration. These include both nonpharmacologic approaches such as bright-light therapy [112,113] and pharmacologic approaches using cholinesterase inhibitors, trazodone, melatonin or melatonin agonists, and orexin antagonists. However, a recent meta-analysis of drug treatment versus placebo for sleep disorders in patients with AD found insufficient evidence to help guide drug treatment of sleep problems in AD [114], and there is some uncertainty about the balance of benefits and risks associated with these common treatments. Continuous positive airway pressure for sleep apnea may also delay the progression of cognitive impairment in patients with sleep apnea [95,115,116]. Given the growing evidence of the link between sleep and dementia, and the high prevalence of sleep disorders in patients with AD, objective sleep measures should be included in all AD studies and NPS measures should be included in all sleep research in AD.

5. Design for NPS trials

Only two drugs are indicated for NPSs in dementia: pimavanserin for hallucinations and delusions associated with PD psychosis (USA), and risperidone for short-term treatment of persistent aggression in moderate-to-severe AD (only in Canada and Europe). There are 16 ongoing trials, mostly for agitation and aggression. This low productivity raises several questions: are the drugs ineffective or the trials inappropriately designed? Are syndromes phenomenologically similar but neurobiologically diverse? Are diagnostic criteria and assessment tools for behavioral syndromes capturing study populations that will enable detection of a positive signal? Do nonpharmacologic paradigms and treatments show more promise than pharmacologic ones? Has an effective dose range been established and are sufficient dose arms used? If titration is used, has enough time been allowed to reach the optimal treatment effect? Which outcome measures should be used? What is a clinically significant effect size?

NPS treatment studies are particularly affected by large placebo effects. Sequential parallel comparison designs [117] use a two-stage approach to mitigate these effects: placebo nonresponders from the first randomization are rerandomized to receive active treatment or placebo. Studies using historical data, run-in designs, or multiple clinical and biomarker variables might enroll more homogeneous populations and more accurately predict effect sizes.

Several tools are available for assessing NPSs. Each has its pros and cons. The appropriate tool depends on the clinical condition and trial design. Informant-based measures such as the NPI-Q, Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), and Cohen-Mansfield Agitation Inventory are low cost and clinically relevant but reflect the biases of the informant. Their validity depends on the extent of contact the informant has with the person with dementia and caregiver depression and cognitive status [118]. Of the informant-based tools, only the NPI prescribes the minimum contact the caregiver must have with the patient: 4 hours per day at least 4 days per week, and knowledge of daytime and nighttime behaviors. Sponsors set lower standards: all seven current trials have less stringent NPI criteria.

Clinician ratings such as with NPI-C are relatively free from this "caregiver filter." They have higher inter-rater reliability but cost more. Video recordings are more objective but are not appropriate for low-frequency behaviors. They are intrusive, costly, and can have questionable clinical relevance. Wearable sensors are good for low-frequency behaviors but may introduce noise and have questionable clinical relevance [33].

The commonly used rating scales (e.g., BEHAVE-AD, Neurobehavioral Rating Scale, and NPI) characterize symptoms similarly, but they assess severity differently. For example, BEHAVE-AD uses an impact scale, NPI-Q assesses frequency and severity, and NPI-C produces symptom-specific severity ratings. They may therefore differ in detecting response to treatment, so researchers should select the scale that maximizes sensitivity in their population and indication.

Psychosocial interventions and concomitant medications, if introduced during a trial, increase variability and affect the placebo response. Ideally, both should be in place (and their benefit assessed) before trials begin. Standardized psychosocial interventions such as those used in DIADS [82], DIADS-2 [83], and the Citalopram for agitation in Alzheimer's Disease (CitAD) study [119]) enhance recruitment and retention, and minimize variability by standardizing procedures across sites.

6. Regulatory considerations

US Food and Drug Administration and Health Canada representatives at the Roundtable were asked whether composite end points for NPSs in AD might be accepted. They noted that composite end points are approved when validated and when accepted as clinically meaningful by academics, physicians, patients, and caregivers. Also, trials may be required to use a primary end point and a coprimary global end point. To obtain approval for therapies to prevent the emergence of symptoms, the key for regulators is that a meaningful outcome is measurable and can be interpreted.

Pimavanserin was recently approved to treat hallucinations and delusions associated with psychosis in Parkinson's disease. The sponsor was granted breakthrough therapy designation by the Food and Drug Administration, allowing approval based on a single small study rather than the usual requirement for two pivotal studies. Would NPS therapies in AD qualify for breakthrough designation? Regulators emphasized that breakthrough status and priority review are for potentially transformative therapies that address unmet medical needs.

7. Conclusions

There is renewed enthusiasm among industry, academic, regulatory, and patient and family advocacy groups to accelerate the development of new treatments for NPSs in AD. Major challenges for clinical trials include the need to (1) allocate sufficient funds to develop nonpharmacologic interventions and implement them in routine clinical practice, these funds are crucial as nonpharmacologic intervention studies generally do not have a sponsor; (2) better define entry criteria (e.g., diagnosis and severity of patients and the presence of comorbidities); (3) develop, validate, and standardize outcome measures that are clinically meaningful to patients and caregivers; (4) continue to seek biomarkers of NPSs; (5) standardize issues related to caregiver, informant involvement and care setting (outpatient vs. nursing home) in clinical trials; (6) incorporate designs that account for increased placebo responses; and (7) reach consensus on the use of psychosocial interventions as background therapy in trials.

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