Review

Psychosis as a Treatment Target in Dementia: A Roadmap for Designing Interventions

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Abstract. Psychotic phenomena are among the most severe and disruptive symptoms of dementias and appear in 30% to 50% of patients. They are associated with a worse evolution and great suffering to patients and caregivers. Their current treatments obtain limited results and are not free of adverse effects, which are sometimes serious. It is therefore crucial to develop new treatments that can improve this situation. We review available data that could enlighten the future design of clinical trials with psychosis in dementia as main target. Along with an explanation of its prevalence in the common diseases that cause dementia, we present proposals aimed at improving the definition of symptoms and what should be included and excluded in clinical trials. A review of the available information regarding the neurobiological basis of symptoms, in terms of pathology, neuroimaging, and genomics, is provided as a guide towards new therapeutic targets. The correct evaluation of symptoms is transcendental in any therapeutic trial and these aspects are extensively addressed. Finally, a critical overview of existing pharmacological and non-pharmacological treatments is made, revealing the unmet needs, in terms of efficacy and safety. Our work emphasizes the need for better definition and measurement of psychotic symptoms in dementias in order to highlight their differences with symptoms that appear in non-dementing diseases such as schizophrenia. Advances in neurobiology should illuminate the development of new, more effective and safer molecules for which this review can serve as a roadmap in the design of future clinical trials.

Keywords: Clinical trials, dementia, delusions, hallucinations, investigational therapies, psychotic disorders

INTRODUCTION

The neuropsychiatric symptoms (NPS) of dementia were described by Alois Alzheimer in the initial report of the disease that now bears his name [1]. Their frequency is extraordinarily high throughout its evolution. For example, 75% of the patients with dementia in the Cardiovascular Health Study had NPS during the month prior to the evaluation [2], and in the Cache County Study, 97% of the patients had NPS over five years [3]. These symptoms are associated with a worse disease prognosis [4] and earlier death [5].

Of the NPS, psychosis and its associated phenomena are among the most severe and difficult to manage. Psychotic symptoms occur in one third to one half of patients with Alzheimer's disease (AD) [6], the most widely studied dementia, and also occur in other forms such as vascular dementia, Lewy body disease (LBD), or frontotemporal dementia (FTD) [7]. Due to their very nature and regardless of the etiology or age of the person, psychotic phenomena are generally severe, disruptive, persistent over time and with little tendency to spontaneously remit [8]. Therefore, they cause great suffering to the patient and those around them [9, 10]. They are also associated with poor general health [11], accelerated cognitive and functional decline [12, 13], higher risk of institutionalization [14], and increased mortality [15]. Better understanding of the natural history, prevalence, and presentation of these symptoms is essential to optimize care and decrease burden [16].

The definition and characterization of dementia-related psychosis (DRP) has evolved along time [8, 17]. The two most recent contributions from the International Psychogeriatric Association and the International Society to Advance Alzheimer's Research and Treatment (ISTAART) of the Alzheimer's Association can help research in the most appropriate treatments for DRP and the serious situations generated by them [17, 18].

The pharmacological treatment of the DRP with antipsychotics has a long tradition, but is not without controversy, regarding its efficacy [19, 20] and its safety [21]. In many countries, official initiatives

have been developed to control and regulate their use, through restrictions or notices such as *black box* warnings. However, although these measures had a short-term clinical impact by reducing the use of antipsychotics in this indication, in the longer term this effect has been highly variable depending on the different countries and clinical contexts, even increasing their use again in a number of cases [22–24]. These findings do not have a simple interpretation, but the explanation must take into account the relative efficacy of these drugs in the perception of those who prescribe them on a regular basis and the scarcity of real alternatives to them.

This paper is the fruit of a working group of experts in the field of NPS pertaining to ISTAART. The task was divided among the experts in each area, who selected the articles reviewed and wrote an initial draft of each part. The specific section(s) that each author contributed to, appears at the end of the paper. This work was shared, and all the authors collaborated in the further selection and review of the articles and in the final drafting of the article, after several rounds of sharing.

Our work aims to help define psychotic symptoms in dementia, their clinical relevance, the importance of their neurobiology and biomarkers in the investigation of possible treatments and the adequate selection of assessment instruments in clinical trials. Finally, the available non-pharmacological and pharmacological treatments are discussed, and the bases for the advancement of the much-needed future research in this field are proposed.

Although in-depth reviews of certain aspects of this topic already exist, we believe that none of those published so far are directly oriented to the conditions that must be met in the design of new treatments, both pharmacological and non-pharmacological, and make recommendations for conducting appropriate clinical trials. Thus, the goal of this review was to bring together in one article current knowledge to support the aim of highlighting recent advances pertinent to treatment of dementia-related psychosis. The potential for psychosis as a treatment target in patients with dementia is also emphasized.

DEFINITION OF SYMPTOMS

Psychotic symptoms are frequent in neurodegenerative disorders with the prevalence and phenomenology differing depending on the pathological context. Jeste et al. proposed criteria for psychosis in dementia

and defined it as the emergence of psychosis after the onset of dementia, with a predominance of visual hallucinations (VH), and a relative absence of complex delusions and thought disorder [6, 25]. DSM 5 also acknowledges differences in phenomenology of psychosis of neurodegenerative disorders from primary psychotic spectrum disorders such as schizophrenia [26]. In the recent revised criteria for psychosis in AD and related disorders [18], psychotic symptoms have been restricted to delusions and hallucinations, and are treated as separated entities. These criteria emphasize that characteristic VH are more common in psychosis of cognitive disorders. Further, these criteria expand the definition of cognitive disorders by including mild cognitive impairment (MCI) [18]. The research criteria framework proposed by ISTAART for psychosis in cognitive disorders takes this expansion one step further by allowing the presymptomatic cases where psychosis may be the first clinical manifestation of the cognitive disorder [17]. In this framework, the preclinical stage of the illness should be verified by biomarker positivity. This framework also further characterizes delusions into persecutory or misidentification or other type and hallucinations need to be coded based on modality [17]. The evidence supports both a shared mechanism and differentiated neural correlates for delusions and hallucinations [17]. Accordingly, psychosis phenomenology in neurodegenerative disorders varies across disorders such as AD or dementia with Lewy bodies (DLB) [7, 27].

In AD, delusions have been divided into two subtypes, paranoid and misidentification, on the basis of a cluster and factor analyses [28]. The paranoid subtype includes persecutory delusions, such as delusion of theft, abandonment, and jealousy. The misidentification subtype includes phenomena such as a failure to recognize one's own home (reduplicative paramnesia), beliefs that someone is living in the house (phantom boarder syndrome); misinterpretations that one's loved ones are imposters or that they change appearances (Capgras and Fregoli syndromes) [29, 30], beliefs that characters on the television are real (the television sign), and failure to recognize oneself in the mirror (the mirror sign) [29, 30]. Although misidentifications tend to manifest in advanced disease stages, when cognitive impairment is more severe [31], evidence also supports its presence to be indicative of a more aggressive phenotype of the illness [29, 32, 33].

VH in AD may consist of the vision of alive or dead people, objects, and animals. It has been

hypothesized that some of the VH in AD might be due to the alteration of the inhibitory control mechanism that suppresses the intrusion of personal memories from long-term memory into awareness or a compensatory mechanism to fill the vacancy of loneliness [34, 35]. Visual hallucination features in AD often overlap with misidentification delusion contents [36] and there is a high degree of comorbidity between delusions and hallucinations in AD. However, around 10–20% of people with dementia experience hallucinations without delusions and the two symptoms may be associated with different clinical outcomes [9]. Auditory hallucinations (AH) are less frequently reported than VH in AD. Typical Schneiderian symptoms, such as those seen in schizophrenia are extremely rare.

In vascular cognitive impairment (VCI), psychotic symptoms are less well characterized as compared to AD. While estimates in the prevalence of different symptoms varied, studies generally found similar prevalence of psychotic symptoms in AD and VCI [2]. Nonetheless, there may be differences in mechanisms of psychosis in AD and VCI and the risks and benefits of treatment interventions may also be different [37].

In LBD, including both Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), VH have a high prevalence and heterogeneous phenomenology. Thus, visual experiences in LBD can be grouped into minor hallucinations, illusions, passage and presence hallucinations, and complex hallucinations [38, 39]. Illusions are perceptions of something objectively existing in such a way as to cause misinterpretation of its actual nature. One type of illusion, pareidolia, is defined as the tendency to perceive a specific, often meaningful image in a random or ambiguous visual pattern (like seeing faces in clouds). The passage hallucinations are referred to as unformed shadows of something or someone passing fast in the periphery of the eye field. The presence hallucinations consist of the sensation/vision that someone is behind oneself. Minor hallucinations may also arise as precursors of motor symptoms in Parkinson's disease (PD) and may appear even in the absence of dopaminergic treatment. Complex VH in LBD consist of well-formed recurrent and stereotyped visions of insects, people (familiar or unfamiliar, alive or dead), animals or animated figures (often children) [40]. They can move but rarely talk, are mostly annoying or amusing before becoming threatening, and predominantly appear in low stimuli environments, usually crepuscular or at night.

The phenomenology of these visual experiences may be linked with LBD disease progression according to Braak stages [41, 42]. Indeed, minor hallucinations occur when alterations mainly involve the brainstem and can be due to an alteration in the interaction between subcortical and cortical regions, including areas part of the dorsal visual stream, involved in visuospatial elaboration leading to passage [43] and presence phenomena [44]. Then as the disease progresses, alterations involve high brain stem loci and forebrain, leading to a deafferentation from subcortical regions to ventral visual stream and limbic areas, which may account for complex VH. When the neuropathological process affects cortical regions, the complex hallucinations become recurrent, insight is lost, and delusions can also appear [42]. This hypothesis suggests that VH phenomenology may represent a clue of the different mechanisms involved in producing these disorders. With increasing severity of PD, hallucinations in other modalities—auditory, tactile, and olfactory—are more common [45]. Though less well studied, AH have been reported in up to 20% of people with PD [46] and in more than one third of people with LBD [47]. The most commonly reported AH in this context have been described as sounds of a doorbell ringing, music, human voices, or footsteps [47–50]. AH seldom appear in the absence of VH, and are sometimes perceived as a soundtrack to the scene [47]. They are associated with a higher co-occurrence of other NPS [47]. Patients with hearing impairment are at a higher risk for AH [47], potentially suggesting uninhibited spontaneous activity as observed in VH in the context of Charles Bonnet syndrome [51].

Naasan and colleagues have recently proposed that the phenomenology of psychosis can suggest what is the underlying neuropathology [52]. Thus, in their neuropathological study, they showed that visual misperceptions, and hallucinations shapeless, peripheral, images that moved, and feeling of presence in addition to complex hallucinations were more frequent in patients with LBD/AD pathology. Delusions of misidentification were instead more frequent in patients with LBD/AD and patients with Frontotemporal Lobar Degeneration with TDP-43 inclusions (FTLD-TDP). Moreover, they found that PD Braak 5–6 stages and FTLD-TDP pathology were predictive of misidentification delusions. Paranoia, especially in early disease stage, was associated with FTLD-TDP or LBD pathology [52].

Until recently, FTD was not thought to be commonly associated with psychotic symptoms except in certain genetic forms, such as C9Orf72, GRN muta-

tion, or argyrophilic grain disease (AGD). However, the 2021 paper by Nassan et al. [52] showed that FTLD-TDP inclusions pathology is associated with a 31.6–52.9% rate of psychotic symptoms (mostly paranoid delusions), as opposed to FTLD-tau pathology. In FTD-C9Orf72, which is associated with FTLD-TDP pathology, a late psychotic presentation is found in 21–56%, with delusions or bizarre somatic obsessions and hallucinations in all modalities. Delusions in C9orf72 expansion carriers were shown to mainly correlate with left frontal cortical atrophy in a paper by Sellami et al. [53].

Usually, these patients do not have a psychiatric history, but in their families, cases of schizophrenia, late-onset schizophrenia, autism spectrum disorder, and suicide are found. Unfortunately, responses to antipsychotics are limited [54]. AGD is a limbic tauopathy (preferential involvement of the hippocampus and amygdala) associated with slowly progressive amnestic minor cognitive impairment, personality changes, and disturbances in emotional control (irritability, restlessness, anxiety, depression). Cases of late psychosis presentation are also reported in this AGD [55].

Delusions and hallucinations in dementia are often associated with other behavioral symptoms such as depression, agitation, and apathy. Differences have been shown in patients who have psychosis and agitation, whose occurrence might be a marker of severity [56, 57]. Moreover, hallucinations are frequent in people with AD who also have depression [35]. It is still not clear whether the latent cluster association of the behavioral disorders represents a different phenotype in dementia [57]. Co-occurrence of different behavioral disorders may influence the individual responses to the pharmacological treatments.

It is important to carefully consider phenomenology of psychotic symptoms in later life to make appropriate treatment plans. First, as discussed above, psychosis related to cognitive disorders presents differently than primary psychotic disorders [6, 25]. Secondly, psychosis in late life may be a harbinger of the cognitive disorder even in the absence of other overt symptoms. This consideration could help the clinician in considering diagnosis of cognitive disorder at an early stage and inform treatment planning. Third, many times the psychotic symptoms in cognitive disorders may not always need antipsychotic treatment. In many instances the psychotic symptoms may be harmless and not distressing to the patient, and treatment with an antipsychotic may present more risks than benefits, thus antipsychotics should only be considered when the symptoms themselves are distressing to the patient or lead to other problems such as agitation or aggression.

In summary, current data suggest dementia subtypes may have an important influence on the clinical expression of DRP. This highlights the need for customized treatments when considering potential therapies given some symptoms (such as hallucinations and misidentifications) have shown a much inferior response to antipsychotic medication relative to other symptoms (such as delusions).

PREVALENCE AND CLINICAL RELEVANCE

Psychotic symptoms in dementia are important for patients, caregivers, and health systems, and are associated with cognitive and functional decline, higher rates of institutionalization, greater mortality, caregiver burden, and likelihood of pharmacological intervention [13–15, 58, 59]. A better understanding of the natural history, prevalence, and presentation of these symptoms is essential to optimize care and decrease burden [60].

The prevalence of psychotic symptoms in dementia depends upon the dementia syndrome, stage of the neurodegenerative disease (preclinical or prodromal disease, and mild, moderate, or severe dementia), and the diagnostic criteria. Exclusions are other conditions associated with psychosis (schizophrenia, autism spectrum disorders, mood disorders, personality disorders, post-traumatic stress disorder, delirium, epilepsy, hearing or visual impairments, systemic lupus erythematosus), and substance abuse and psychosis-inducing drugs (monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants or other anticholinergic drugs, opiates, benzodiazepines, methylphenidate, modafinil, memantine, dopamine agonists, levodopa, beta-blockers, clonidine, anti-histaminergic drugs, anti-migrainous drugs, proton pump inhibitors, baclofen and disulfiram among others) [17]. Use of selective serotonin reuptake inhibitors, cholinesterase inhibitors and antipsychotics may result in the underestimation of the actual prevalence of psychosis [17] while those without psychotic symptoms may develop them, highlighting differences based on point versus period prevalence. Overall, the true prevalence of psychosis is challenging to measure. Factors affecting prevalence and relevance of psychotic symptoms in different neurocognitive disorders will be discussed below.

Alzheimer's disease

In AD, the prevalence of DRP ranges from 10%–75%, with a median of 41%. Recurrent hallucinations are typically present in 5%–15%, usually later in the disease course, while persistent delusions range from 15%–30% [17] but may reach 50% in severely impaired patients, particularly in those who are *APOE* ε4 carriers [61]. In addition, it has been suggested that participants with AD who do not carry *APOE* ε4 alleles may have greater cognitive and functional impairment from second-generation antipsychotics and antiepileptic drugs compared to *APOE* ε4 carriers [62].

Concerning minor hallucinations, one study found prevalences of 13% in amnestic MCI and 21% in untreated mild and moderate AD, with higher frequency of presence hallucinations followed by passage hallucinations and visual illusions [63]. Of note, the frequency and severity of psychosis are usually higher for those bearing amyloid pathology [64]. People with AD and co-existent Lewy body pathology have been found to have a higher prevalence of psychosis relative to people with pure AD [52].

Vascular dementia

In cortical vascular dementia (large-vessel), one study showed that psychosis was less frequent than that in AD. However, psychosis increased in association with worsening dementia from mild to moderate to severe, for both delusions (12% to 35% to 55%) and hallucinations (12% to 33% to 52%). In subcortical vascular dementia (small-vessel), however, both delusions (23% to 47% to 42%) and hallucinations (11% to 44% to 37%) increased in frequency from mild to moderate dementia, and then declined in severe dementia [65].

Lewy body disease

In LBD syndromes, psychosis is usually more intense than in AD [66]. Hallucinations may be present in more than 80% of all patients, while systematized delusions might affect up to 55%, though dopaminergic therapy may increase these numbers particularly regarding delusional jealousy [67]. The prevalences of delusions and hallucinations tends to be dissociated, considering that in AD delusions are more common than hallucinations, whereas in LBD hallucinations are more common [68]. While pareidolia is not unusual in LBD syndromes, one study

showed that multimodal hallucinations are infrequent: little more than 20% of those who presented VH also had tactile and verbal auditory hallucinations, while less than 6% had olfactory or gustatory hallucinations [69]. Persistent musical hallucinations, often religious and patriotic, are more common in LBD than in other dementia syndromes [48].

In LBD syndromes, patients with delusions and agitation usually have a higher frequency of VH [67]. Complex VH are the most distinguishing NPS for DLB in mildly impaired patients, whereas one cross-sectional study showed point prevalence of 96% in comparison with 71% in PDD and 28% in late-onset *APOE* ε3/ε3 AD [66]. Additionally, psychosis is more prevalent in association with REM sleep behavior disorder [14].

Capgras delusions may occur in up to 10% of patients with DLB, but have not been described in PDD [67]. However, paranoid delusions (delusions of theft and persecution) are more frequent than Capgras delusions in DLB, while fluctuating cognition and excessive daytime somnolence tend to cluster with hallucinations probably due to central cholinergic deficiency [70]. Delusional misidentification is more characteristic of DLB than AD, also for less frequent manifestations such as the mirror sign (5% of DLB, 3% of AD) and the television sign (4% of DLB, 2% of AD) [71].

Frontotemporal dementia

In FTD, psychosis is thought to occur in less than 10% of patients, but may be present in as much as 52% in FTD-TDP pathological forms (mostly paranoid delusions) and in 20%-60% of *C9orf72* expansion carriers who may have prevalent bizarre somatic delusions and multimodal hallucinations [17]. In fact, as stated before, recent clinicopathological studies suggest patients with FTD-TDP may have a frequency of psychotic symptoms that is comparable to that seen in patients with combined AD/Lewy body pathology and that persecutory delusions make up the predominant phenotype [52].

MCI and normal cognition (NC)

Overall, the frequency of psychotic symptoms is lower in MCI versus dementia. In MCI, delusions range from 3%–9%, and hallucinations are prevalent in less than 3% of patients [2]. In MCI, most studies have demonstrated that psychotic symptoms are associated with a greater risk of dementia [72–76].

Assessing psychosis as part of the neurodegenerative disease continuum is challenging in older adults with NC, as traditional psychiatric nosology might apply (e.g., delusional disorder, very late onset schizophrenia like psychosis). Further, these symptoms are of very low frequency, not detectable in sufficient numbers in population-based cohorts of older adults to provide reliable estimates [77]. An analysis of 12,452 NC older adults in National Alzheimer's Coordination Center data determined that delusions were present in 0.8% and hallucinations in 0.3%. Of all NPS, psychotic symptoms had the highest hazard ratio for incident dementia (3.6) [78].

Psychosis in MCI and NC are described in the neurobehavioral syndrome mild behavioral impairment (MBI) [79]. MBI is characterized by new onset NPS in later life as an at-risk state for incident cognitive decline and dementia and is the initial manifestation of dementia for some. Psychosis is the least frequent of the 5 MBI domains but is associated with substantial risk. Using the MBI checklist for case ascertainment [80], psychosis was prevalent in 3–6% of NC older adults in a community sample [81], and in 5.4% of subjective cognitive decline and 17.2% of people with MCI in a memory clinic [82]. A study of MBI in those with MCI determined psychosis prevalence of 3%, with a HR for incident dementia of 2.9 [76]. More research is required in MBI psychosis to better characterize symptoms and determine if they represent valid treatment targets for either symptom reduction or dementia prevention.

In summary, psychotic symptoms are seen in a significant percentage of patients across the dementia spectrum and thus may serve as an important target for intervention.

NEUROBIOLOGY AND BIOMARKERS

Psychosis in dementia is currently understood to represent a group of phenomena, likely with different underlying physiological, anatomical, and biological substrates. Thus, in order for psychosis to be a viable treatment target, it is imperative that we understand the underlying pathophysiology of DRP. Newly established research criteria for DRP [17] now incorporate biomarkers, thus making this even more crucial. Studies of DRP in relation to pathology, neuroimaging and genetics have together provided insight into neurobiology and potential treatment strategies. Recent studies suggest analyses of cerebrospinal fluid (CSF) neurodegenerative biomarkers such as amyloid and tau may differentiate psychosis associated with neurodegenerative conditions from that associated with psychiatric disorders [83].

Pathology

Emerging studies have traditionally favored tau over amyloid as a marker of DRP [84–87] with postmortem and CSF studies having identified tau and phosphorylated tau as playing an important role [84–87]. Moreover, there has been a link of psychosis with emerging tauopathies such as AGD, a 4-repeat tauopathy associated with the aging process [55]. Conversely, amyloid pathology has been recently linked to psychosis in prodromal dementia [88], to delusions in MCI [64] and to illusions and well-formed VH among people with PD [89]. Low levels of alpha-synuclein in the CSF have been found to correlate with hallucinations and executive dysfunction among healthy controls and people with MCI and AD [90]. Synaptic proteins may also play a role in conferring resilience to DRP according to a recent paper, a finding observed to be independent of neuropathological burden [91].

Other studies have confirmed the already established link of DRP with Lewy body pathology and demonstrated a relationship with vascular pathology and vascular risk factors, specifically subcortical ischemic vascular pathology [92, 93], amyloid angiopathy [93], and microinfarcts [94], though whether vascular risk factors mediate increased vascular pathology among patients with psychosis is not clear [95]. Recent studies have suggested the emergence of TAR DNA-binding protein 43 (TDP-43) as a protein that accumulates in patients with amyotrophic lateral sclerosis and the behavioral variant of FTD which may be associated with psychosis among patients with C9orf72 expansions [96, 97].

Retrospective studies conducted in neuropathologically-verified cohorts of patients with different neurodegenerative conditions have demonstrated pathology may affect the nature of psychotic symptoms expressed. As cited before, Nassan and colleagues [52] noted that patients with co-existent AD and DLB pathology were more likely to have multiple subtypes of hallucinations, while patients with Lewy body pathology/PD had a higher prevalence of misperceptions and misidentification delusions and patients with FTLD-TDP were more likely to have delusions. Moreover, contrary to previous findings, prevalence of psychosis and specifically delusions was comparable or greater in patients with FTLD-TDP relative to pure AD.

Neuroimaging

Neuroimaging studies across several modalities —including CT, MRI, SPECT, PET, and magnetic resonance spectroscopy (MRS)—have provided some convergent evidence of brain regions and circuits associated with DRP [98, 99]. These studies have also provided insight into differential regional patterns of structural and functional change associated with subtypes of psychotic symptoms.

Some of the more consistent neuroimaging biomarker findings of DRP have emerged from studies of cerebral blood flow (CBF) and metabolism using SPECT and [18F]fluorodeoxyglucose (FDG) PET, respectively. These convergent findings suggest an association between psychotic symptoms in AD and decreased CBF or metabolism of frontal and temporal lobes; with the right hemisphere more severely affected than the left [100–104]. Findings from structural imaging studies of DRP have been more variable. CT and some MRI studies have shown associations between psychotic symptoms and atrophy, right hemisphere greater than left [105–108]. Other MRI studies have reported either no association between psychotic symptoms and atrophy [109] or evidence of regional and sex-specific vulnerability. For example, VH have been associated with occipital atrophy [110] and delusions with decreased frontotemporal cortical thickness in females rather than males [111]. Findings both support and refute white matter changes (as measured from CT or MRI scans) as biomarkers of DRP [100, 112].

The pathophysiology of DRP has been further dissected using molecular imaging. Though studies in this modality have been limited, a proton MRS (1H-MRS) study showed an association between delusions and a decreased N-acetyl-aspartate-to-creatine (NAA/Cr) ratio—a marker of neuronal function—in the frontal cingulate cortex [113]. Another study using a dopamine receptor PET probe found evidence for increased dopamine D2/D3 receptor availability in the striatum in individuals with AD dementia and psychosis compared to those without psychosis [114]. Future imaging studies using PET probes for neurotransmitter systems, synaptic activity, and AD pathology have the potential to provide further insight into pathophysiology and intervention strategies for DRP, including identification of candidate treatment targets.

Longitudinal neuroimaging studies have provided additional insights, particularly into pathophysiology and predictors of psychotic symptom emergence.

Fischer and colleagues carried out voxel-based morphometry to identify regional gray matter differences pre- and post-onset of delusions in patients with MCI and early AD dementia [115]. They found significant gray matter atrophy post-symptom emergence in several brain regions including the cerebellum and left posterior hemisphere [115]. Meanwhile, D'Antonio and colleagues observed greater gray matter atrophy over time in the right anterior-inferior temporal pole (part of the ventral visual system) and the insula (part of the salience network) in AD subjects with psychosis compared to those without psychosis [116]. These findings suggest that aberrations in salience and visual perception (misattribution and misperception) may underlie the pathogenesis of DRP [116].

In summary, neuroimaging biomarkers across several modalities have provided some degree of convergence of brain regions and networks (frontal and temporal lobes; insula; salience network and ventral visual stream, to name a few) that may be affected in DRP.

Genomics

Recently, the first risk loci were recently reported in a genome-wide association study (GWAS) of 12,317 AD cases with or without psychosis; these were located in *ENPP6* and *SUMF1* [117]. The identification of these loci is an important development, but the findings require replication and functional characterization is also required. It is notable that *APOE* ε4 was associated with psychosis in this study. Being by far the largest genetic study to date, this brings greater clarity to the inconsistencies in previous literature, where small sample sizes and possible effect modification by sex may have masked associations [118, 119]. This study, and others, have also examined shared genetic liability between psychosis and other neurological and psychiatric conditions, which can give insight into common mechanisms across diagnostic boundaries. In the aforementioned GWAS, depressive symptoms were positively genetically correlated with psychosis, while bipolar disorder was negatively correlated. No genetic correlation was found with schizophrenia, but previous studies using schizophrenia polygenic risk scores to evaluate shared genetic liability have reported associations with psychosis in AD and in Huntington's disease, and with psychotic experiences in the general population [120–123].

Study of the epigenome, and DNA methylation in particular, may offer new insights. Encouragingly, the

only epigenome-wide association study (EWAS) of psychosis in AD conducted to date identified two differentially methylated regions of the genome, located in *TBX15* and *WT1* which are both implicated in the pathophysiology of AD [124]. Interestingly the top-ranked differentially methylated positions were enriched in known schizophrenia-associated genetic and epigenetic variants, supporting a common mechanism of psychosis.

The genomics of psychosis in other dementias is a nascent field. In PD, mutations in the *GBA* gene, which codes for the lysosomal storage enzyme glucocerebrosidase, are associated with psychotic symptoms [125], and potentially implicated in DLB as well [126].

While current treatments in DRP involve antipsychotic medications, these medications primarily target serotonin and dopamine receptors and have no effect on underlying neurodegenerative disease pathology or other putative pathogenic mechanisms. There are also serious safety concerns, so the search for novel agents is essential. Drug discovery rooted in GWAS and other association studies (e.g., EWAS) could have the potential to bring about efficiencies to development pipelines [127] so the identification of the first genome-wide and epigenome-wide significant loci implicated in psychosis in AD are important milestones. Further research into the molecular-level mechanisms underlying DRP, which is becoming increasingly common, will likely lead to further identification of novel targets. However, target validation is essential to establish whether modulation of these targets may bring about therapeutic benefits to DRP. As well as the identification of novel targets, the repurposing of existing agents developed for other psychiatric conditions is also worth exploring. This avenue should proceed with caution given the lessons learned from the use of typical and atypical antipsychotics, and exploration of preclinical methods to examine mechanisms of harm of licensed psychotropic drugs in AD before they enter human trials may be warranted [128].

Evolving treatments that target amyloid-beta and tau have the potential to reduce psychotic symptoms given the overlap with neurodegeneration and studies done suggesting linkages with amyloid-beta and tau. Other potential therapeutic targets include inflammatory markers, vascular risk factors and TDP-43, all of which have been demonstrated to play a role in DRP.

Overall, ongoing work to establish and refine biomarkers of DRP across pathology, neuroimaging and genetic studies is critical to advance psychosis as a treatment target. Together, biomarker profiles that integrate these modalities may provide insight into disease mechanisms, treatment targets, and therapeutic response patterns, thus ultimately paving the way for personalized intervention strategies. Different biomarkers may have distinct contributions in this regard: molecular and functional imaging—in identifying treatment targets and monitoring target engagement; structural imaging—in providing predictors of symptom onset and treatment response; and structural and functional connectivity—in tracking treatment response for a given therapeutic intervention.

ASSESSMENT INSTRUMENTS

The primary criterion for assessing treatment efficacy is the extent psychotic symptoms are experienced. Efficacy may be determined by reduction or elimination of symptoms over time, with consideration of caregiver burden/distress and risk of harm. Instruments used to assess symptomatology may rely on patient self-report, informant report (e.g., a caregiver), or assessment by a healthcare professional. With this in mind, it is essential to consider the possibility of anosognosia, poor insight, or diminished awareness on self-report of psychotic symptoms. As discussed, biomarkers of psychotic symptoms may also be used as clinical trial outcome measures; however, these measures are typically first developed/identified by utilizing clinical assessments (e.g., for classification purposes). Choice of assessment is therefore of vital importance, both for accurately capturing the symptoms (e.g., frequency or severity) for clinical trials (participant screening/selection, outcome measures, safety profiling), and for the process of developing alternative outcome measures (biomarkers).

Currently, there are several assessment instruments to measure psychotic symptoms. The psychosis subscale of the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) instrument [129] has been utilized in a variety of clinical/regulatory trials (e.g., for risperidone) [130–132]. The BEHAVE-AD comprises 25 informant-queried items assessing severity of NPS (seven items measuring delusions and five hallucinations). Delusional items include assessment of suspiciousness/paranoia, and misidentification, whereas hallucination items cover visual, auditory, olfactory, and haptic modalities. The BEHAVE-AD, as a whole, has good reliability (see e.g., [133] for

details), and has many translations (e.g., Spanish [134]; French [135]). The Empirical BEHAVE-AD Rating Scale (E-BEHAVE-AD) [136] enables direct observation instead of informant-queried rating. The frequency-weighted BEHAVE-AD (BEHAVE-AD-FW) [137] includes frequency assessment, in addition to severity, as in the original. Increased sensitivity afforded by assessment of frequency [137] may be of use in clinical trials.

Versions of the Neuropsychiatric Inventory (NPI) [138, 139] have been used in many clinical pharmacological trials, for screening or as outcome measures, for example, for pimavanserin [140], olanzapine [141], and aripiprazole [142, 143]. Depending on the version, 10 or 12 neuropsychiatric symptoms are rated for severity and frequency by an informant, and caregiver burden may be recorded. Alternative versions exist for completion by a clinician (NPI-C), an informant (shortened-format: NPI-Q), or for use in a nursing home environment (NPI-NH), and the scales are available in many different languages (see [144] for an overview). Inter-rater reliability is good [138], with recommendations to enforce this [145]. A criticism is that typical scoring requires the frequency and severity ratings to be multiplied, meaning some scores on a linear scale will not be achievable; however, these could be treated separately, with a decrease in either likely to benefit both patient and caregiver [146], or summed as in the clinician version. One consideration is that although separate sub-scale scores are provided for both delusions and hallucinations, the different types of delusions/hallucinations are not rated separately. This may be relevant for certain clinical trials, as different timelines and neurobiological underpinnings may exist, for example, for delusions of paranoia versus misidentification [147].

Another potentially useful instrument is the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD) [148]. With 11 distinct items, the CUSPAD provides the most detailed assessment of delusions (and 5 items cover hallucinations). Comparing scales assessing delusions and hallucinations (including the NPI-NH, BEHAVE-AD, CUSPAD), Cohen-Mansfield & Golander [149] demonstrated the CUSPAD recorded the highest prevalence of delusions, with prevalence of hallucinations comparable to the BEHAVE-AD and NPI-NH. For clinical trials requiring sensitivity and separation between delusions, the CUSPAD could therefore be a strong contender.

The Mild Behavioral Impairment Checklist (MBI-C) [80] was designed to assess adults in the prodromal or preclinical stages of neurodegenerative disease. The checklist, completed by an informant, comprises 34 items, 5 of which relate to abnormal perception and thought content (hallucinations and delusions). Assessment items include delusions relating to suspiciousness/paranoia, grandiosity, and hallucinations in the visual and auditory domains. The MBI-C was mainly designed for case identification for prodromal dementia [80]. It already has several translated versions, for example, Spanish and Chinese [150, 151]. Given that symptom presence is assessed over the previous 6 months, it probably has high utility as a screening instrument. As an outcome measure, the MBI-C would only be relevant for long-term interventions, and depending on the intervention, other instruments may be more desirable.

Other instruments exist, such as the Consortium to Establish a Registry for Alzheimer's Disease Behavior Rating Scale for Dementia (CERAD-BRSD) [152] and the Neurobehavioral Rating Scale [153]. What is critical is an appropriate instrument be chosen to optimally capture the specific set of psychotic symptomologies thought to be prevalent in the sample (based on etiology) and at the particular disease stage. For example, delusions of misidentification appear to be more prevalent in DLB than AD, particularly in the early stages [154], whereas delusions of paranoia occur in both patient groupings. Considerations like this highlight that to select the most appropriate instrument for recruitment or assessing treatment response, the clinical trial team should be familiar with the range of psychotic symptomatology exhibited in the sample.

In relation to areas for future development, evaluations of the currently available instruments could be made to assess whether they adequately capture the full range of psychotic phenomena and at an appropriate level of detail, given our current state of knowledge. Considerations of the scoring methods of the scales can be made and whether these reflect symptomology optimally for clinical trials. Another area for future consideration is on the timescales over which symptomology is measured on the instruments and whether these enable phenomenology to be captured in the most accurate way. Also of note, many assessments have been developed in relatively homogenous samples, thus limiting generalizability. Relevant to this, group differences have been noted in the manifestation and representation of symptoms across race and ethnicity [155–157]. Future instruments must be culturally sensitive, beginning with

the inclusion of diverse racial and ethnic groups in the development, testing, and validation stages.

In summary, the availability of a broad array of assessment tools to detect DRP emphasize its utility as a possible treatment target.

NON-PHARMACOLOGICAL INTERVENTIONS

The first line of treatment for NPS in people with dementia are non-pharmacological interventions. The goal of these interventions is to prevent or reduce the severity of NPS, avoid side effects of psychoactive drugs, promote a higher quality of life, and delay placement into a long-term care setting [158, 159]. Non-pharmacological interventions encompass a range of behavioral, psychosocial, sensory, and environmental approaches [160]. However, to date there is very little evidence on the efficacy of these interventions in DRP, and when it exists, the effects usually focus on clusters of NPS. Therefore, when investigating the effectiveness of non-pharmacological interventions for people with dementia and psychosis, specific conclusions about the usefulness of these interventions are difficult to estimate [161, 162].

There is scarce evidence to support the use of behavioral and psychosocial interventions for treating psychosis in dementia. In a single-blind, block-randomized cross-over controlled study, Brunelle-Hamann et al. [163] implemented a four-week home-based cognitive rehabilitation program to train instrumental activities of daily living and reported that delusional symptoms decreased when compared to the control group. Further, Chen et al. [164] carried out a multi-component intervention study in a small sample, non-randomized without-contact control group that included cognitive and orientation training among others (e. g., sensorial and physical activities). Favorable differences to the experimental group were reported for hallucinations and delusions, but there was no significant change in the use of psychotropic medications at the end of the trial with regards to the baseline levels. A final intervention called the tailored activity program-outpatient version was recently assessed in a randomized, controlled, double-blind pilot study [165]. This tailored activity program is delivered by an occupational therapist who implements three individualized activities based on cognitive and functional capabilities, that can also be generalized to strategies used for activities of daily living. A significant reduction in multiple

NPS, including hallucinations, was observed after intervention. Delusions were also reduced comparing to pre-test assessment, although this change did not reach significance [165].

An alternative approach to treating delusions and hallucinations in dementia is validation therapy and reminiscence therapy. Each of these therapies can be easily implemented, but there is currently no evidence to suggest that they reduce the presence of delusions and hallucinations [166]. Rather, the general consensus for these therapies is that they may improve cognition, mood, or general behavior [166], which could indirectly reduce the presence of delusions and hallucinations. Additional evidence for the use of these therapies was found in a study that simulated presence by family-generated videotape recordings. In this study, Cohen-Mansfield & Werner [167] reported specific efficacy in reducing hallucinations regarding those observed in the pre-intervention period.

The environment, which incorporates sensory approaches, plays a critical role in the development and treatment of DRP. A study by Zeisel et al. [168] systematically analyzed the relationship between the environmental design of nursing homes and the presence of various NPS among residents with dementia. This study found a significant association between these variables, including the presence of psychosis. In particular, they found that higher privacy-personalization (i.e., individual privacy and personalization of one's room) and sensory comprehension (i.e., staff control and understandable sensory input) resulted in lower levels of psychosis among these residents [168]. Personalization of the environment to ensure it is more home-like has been found to be especially important in reducing psychotic symptoms associated with dementia [169].

There are multiple sensorial approaches that can help with reducing the levels of psychosis among patients with dementia. These include utilizing music and ambient noise, improving lighting, and providing walkways for exercise [170]. Music has been found to reduce both hallucinations [167, 171] and delusions in dementia [172]. One study in particular that utilized a randomized controlled trial (RCT) across three nursing homes found nonverbal music therapy (i.e., rhythmical and melodic instruments) significantly decreased delusions over a 16-week intervention period [173]. Lighting is found to be one of the most important environmental factors as it plays a critical role in sleep patterns, interpretation of visual stimuli, and the risk of falls [169, 174]. Adequate

lighting has also been found to improve behavior, including delusions and hallucinations, among long-term care residents [175]. However, efficacy of bright light therapy [174] in reducing paranoid delusions and hallucinations still remains unclear [176].

Providing hearing aids and correcting for visual disability (glasses, cataract surgery) could also decrease psychotic symptoms such as paranoia [177, 178]. Additional environmental interventions that have been found to reduce delusions and hallucinations in dementia include incorporating routine activities, removing the person from environmental triggers, providing cues for orientation, and redirection [170].

Although there is limited evidence to support the efficacy of non-pharmacological interventions for DRP, some results suggest that the interventions are effective if implemented in a person-centered manner [179]. This approach takes into consideration the person and ensures that the intervention is tailored to them based on their previous experiences, previous and current interests, and current needs and disease stage [179]. Non-pharmacological interventions should continue to be utilized for DRP, and further research should be conducted across all approaches to better understand their ability to treat these symptoms. In particular, more RCTs should be performed on larger samples, including an active control group, and specifically targeting DRP. Since psychotic symptoms can occur intermittently, pre-post comparison of measurements collected at a single time should be avoided. Specific reliable and valid instruments to assess psychotic symptoms should be used, contrasting the reports of the patient and the partner and taking into account the stages of dementia. Neuroimaging correlates could also be useful to determine possible differences in the efficacy of the intervention. In addition, measuring external outcomes such as changes in psychotropic prescription or caregiver burden is also convenient. Finally, a tentative dynamic consensus on dose (i.e., frequency, duration, and/or intensity) and standardization of procedures for each of the non-pharmacological interventions is desirable to avoid excessive heterogeneity in RCT studies, and therefore, prevent future complications in the results comparison.

PHARMACOLOGICAL TREATMENT

The need for pharmacological interventions to treat all psychotic symptoms in dementia is a matter of debate. Currently, antipsychotic medications in patients with dementia are recommended only in cases in which there is substantial risk for harm to self or others, and after all non-pharmacological measures have failed [180]. This approach is apparently justifiable in the case of minor hallucinations in PDD or DLB, to which patients are usually insightful, and which rarely lead to patient suffering or to behavioral changes. Nevertheless, early treatment of minor psychotic symptoms in PD has been suggested by some authors to attenuate psychiatric deterioration [181].

Despite the modest effect of pharmacological interventions [19] and the increased risk for side effects, morbidity, and mortality [20, 182–188], in practice, psychoactive medications are commonly used for the treatment of patients with dementia and psychosis, especially if clinical presentations are accompanied by additional behavioral disturbances such as agitation or aggression. For example, between 37.5–60% of patients with dementia in residential care facilities are usually prescribed antipsychotic medications, not only for genuine psychotic symptoms but also to control agitation, aggression, or severe sleep disturbances [189, 190]. Most notable is the use of typical (haloperidol, thioridazine) or atypical (risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone) antipsychotics with the latter being the preferred pharmacological treatment option [191].

Clozapine [192] is also used, but the adverse effects of this drug are often too problematic for elderly patients. The recently introduced drug pimavanserin [193], an inverse agonist and antagonist of the serotonin 5-HT2A receptor which lacks the dopamine receptor blocking effects of other antipsychotics [194], is progressively being used, based on its beneficial effect on ameliorating psychotic symptoms PD and AD-related psychosis [195] and its acceptable safety profile.

Psychotic symptoms in PD and LBD are specifically challenging for pharmacological treatment; in addition to the increased risk for morbidity and mortality [196], the dopaminergic blockade induced by most antipsychotic medications leads to worsening of motor symptoms, with LBD patients being particularly sensitive to this effect [197, 198]. Despite limited evidence for its efficacy in delusions and hallucinations, quetiapine, a mixed dopaminergic and serotonergic antagonist, is a widely used antipsychotic medication in patients with PD and LBD [199]. As mentioned before, pimavanserin has been proven effective and well-tolerated for psychosis symptoms in PD [140, 195] and LBD [199], being approved by

the FDA for this indication. Nevertheless, its advantages over quetiapine are yet to be studied [199]. Clozapine showed efficacy for the treatment of PD [200] and, although less consistently for LBD-related psychosis [201]. Importantly, its use is not associated with an exacerbation of motor symptoms such as tremor; conversely, these may be ameliorated [202]. However, the risk for life-threatening agranulocytosis and the resulting need for frequent blood draws limits the practicality of its use.

In Table 1, we summarize the most relevant evidence from clinical trials which examined the efficacy of atypical antipsychotic medications on ameliorating psychotic symptoms in patients with dementia.

In 2005, the Food and Drug Administration (FDA) issued a black box warning regarding safety concerns associated with the treatment of patients with dementia treated with atypical antipsychotic medications. The use of these medications in dementia is associated with an increased risk for side effects, namely cerebrovascular events [182], extrapyramidal symptoms, hypotension, sedation, anticholinergic effects [183], and mortality [203]. These concerns resulted in a reduction in the use of these medications in dementia in the US [22, 204, 205] though reports on the extent of this decline are inconsistent. Atypical antipsychotic medications still comprised 9% of the drugs prescribed to patients with dementia in 2008. The use of typical antipsychotic medications in patients with dementia is associated with at least as much risk for morbidity and mortality as atypical antipsychotics [206], and the FDA has extended its warning to include haloperidol [207], one of the most widely used typical antipsychotics used to treat psychotic and behavioral symptoms in dementia. A survey among health care providers specialized in geriatrics demonstrated that the most commonly reported barriers for the adoption of the FDA's warnings were lack of alternative treatments, lack of guidance, lack of evidence regarding pharmacological treatments, and poor availability of data [208]. Similar problems have been found in other clinical settings [209]. Despite these obstacles, the potential to change antipsychotic-prescribing habits exists, as reflected in the vast differences observed between nursing homes in the United States concerning the use of antipsychotic medications [210, 211]. The rates and doses of antipsychotics prescriptions were related to factors such as staff quantity and training, facility size, and the existence of optional facilities; smaller facilities, with less competition, less registered nurses' staffing, and those providing acute care, were more likely than others to prescribe antipsychotic medications. Interventions aimed at deprescribing (cessation or dose reduction) of antipsychotic medications in long-term care facilities' residents with dementia have recently been successfully implemented without exacerbation of behavioral disorders and without increases in prescription rates of benzodiazepine or antidepressants [210, 212].

Most of the current evidence for the use of atypical antipsychotics shows a heterogeneity based on numerous factors such as: study population (institutionalized [132, 141, 143, 213–215] versus non-institutionalized [142, 216] or mixed patient populations [217]); type of dementia (any dementia [218]; probable AD [143, 213, 214, 219, 220]; dementia with parkinsonism [221]); or type of behavioral abnormality (psychosis [142, 143, 213, 217, 222] versus psychosis and/or other behavioral abnormalities—agitation or aggression [220, 221, 223], or merely behavioral and psychological symptoms of dementia such as agitation [216, 218, 224]). These differences are also reflected in the primary outcome measures used to quantify improvement in most of the studies.

In some studies, the improvement in behavioral outcomes observed at follow-up was attributed to the beneficial effect of antipsychotic medications over placebo [218, 223]. However, in others, a significant improvement was observed in both groups with no differences between the active treatment and the placebo groups [142, 213, 217, 221, 222]. These results may suggest that treatment of behavioral symptoms in dementia may be prone to a significant placebo effect, thus potentially resulting from non-specific benefits such as the enrollment in a clinical trial, the natural course of illness, and symptomatic decline over time [225]. A significant placebo effect has been recognized in patients with antidepressants and agitation who have been randomized to citalopram or placebo [226]. The most significant improvement was recorded in patients who were most symptomatic at baseline, suggesting that a placebo effect may also result from regression towards the mean [225].

Other types of medications prescribed for patients with dementia-related severe behavioral disturbances include antidepressants, anticonvulsants, and cholinesterase inhibitors, though clinical trials examining their efficacy and safety specifically on psychosis are scarce. Citalopram for example, may have a beneficial impact on agitation with or without

Table 1
Characteristics of the randomized controlled trials examining the use of four major atypical antipsychotics

Author, Year	Intervention	Setting	Sample size	Mean dose	Female (%)	Mean age (years)	Trial duration (weeks)	Outcome Measure	Results
Aripiprazole									
Mintzer et al. 2007 [213]	Ari vs Placebo	Inpatients	487	Ari = 2 mg, 5 mg, 10 mg	79	82.5	10	NPI-NH CGI-S BPRS	**Positive.** Ari 10 mg showed significantly greater improvements.
De Deyn et al. 2005 [142]	Ari vs Placebo	Outpatients	208	Ari = 10 mg range (2–15 mg)	72	81.5	10	NPI-NH	**Negative.** Ari did not show significant differences compared to placebo.
Streim et al. 2008 [143]	Ari vs Placebo	Nursing homes	256	Ari = 8.6 mg	76.1	83	10	NPI-NH CGI-S BPRS	**Negative.** Ari did not show a significant difference in psychotic symptoms
Olanzapine									
Deberdt et al. 2005 [217]	Olz vs Placebo vs Ris	Outpatients	494 Olzp = 204 Ris = 196 Placebo = 94	Olz = 5.2 mg Ris = 1 mg	65.2	78.3	10	NPI-NH	**Negative.** Olz was not significantly more effective than Ris or placebo.
De Deyn et al. 2004 [214]	Olz vs Placebo	Nursing homes	652	Olanzapine = 7.5 mg	75	76.6	10	NPI-NH	**Positive.** Olz was superior to placebo
Schneider et al. 2006 [220] Sultzer et al. 2008 [243] CATIE-AD trial Phase 1	Olz vs Ris, Qtp vs Placebo	Outpatients	421 Olz = 100 Ris = 85 Placebo = 142 Qtp = 94	Olz = 5.5 mg Qtp = 56.5 mg Ris = 1 mg	56	77.9	12	NPI-NH	**Positive.** Olz was significantly more effective than placebo or Qtp
Street et al. 2000 [223]	Olz vs Placebo	Nursing homes	206	Olz = 15 mg	61.2	82.8	6	NPI-NH	**Positive.** Olz low dose effective in reducing agitation/aggression and psychosis compared to placebo
Quetiapine									
Ballard et al. 2005 [215]	Qtp vs Placebo	Nursing homes	93	Hal = 1.9 mg Qtp = 96.9 mg	79.6	83.8	26	NPI-NH	**Negative.** Qtp not significant in reducing psychotic symptoms
Schneider et al. 2006 [220] Sultzer et al. 2008 [243] CATIE-AD trial Phase 1	Olz vs Ris, Qtp vs Placebo	Outpatients or Nursing homes	421 Olz = 100 Ris = 85 Placebo = 142 Qtp = 94	Olz = 5.5 mg Qtp = 56.5 mg Ris = 1 mg	56	77.9	12	NPI-NH	**Negative.** Qtp did not show significant differences compared to placebo in reducing psychotic symptoms
Tariot et al. 2006 [222]	Qtp vs Hal vs Placebo	Nursing homes	180	Hal = 1.9 mg Qtp = 96.9 mg	73	83.2	10	NPI-NH	**Negative.** Qtp was not more effective than Hal or Placebo in reducing psychotic symptoms

Study	Comparison	Setting	N	Dose	%	Age	Wks	Scale	Outcome
Rainer et al. 2007 [216]	Qtp vs Ris	Nursing homes	72	Qtp = 77 mg Ris = 0.9 mg	58	77.8	8	NPI CGI-I	Qtp and Ris equally effective and well tolerated.
Kurlan et al. 2007 [221]	Qtp vs Placebo	Nursing homes or outpatients	40	Qtp = 120 mg	37.5	73.8	10	BPRS	**Negative.** Qtp did not show significant decrease in psychotic symptoms. Well tolerated.
Paleacu et al. 2008 [244]	Qtp vs Placebo	Nursing homes	40	Qtp = 200 mg	65	82.2	6	NPI CGI-I	**Negative**. Qtp did not significantly reduce psychosis symptoms compared to placebo.
Zhong et al. 2007 [218]	Qtp vs Placebo	Nursing homes	333	Qtp = 100 mg Qtp = 94 Qtp = 200 mg	74	83	10	PANSS NPI-NH CGI-C	**Positive.** Qtp 200 mg was associated with clinically greater improvements
Risperidone									
Brodaty et al. 2003 [245]	Ris vs Placebo	Nursing homes	345 Ris = 173 Placebo = 172	Ris = 0.95 mg	71.9	83	12	BEHAVE-AD CMAI CGI-S	**Positive.** Ris significantly improved aggression, agitation, and psychosis.
Brodaty et al. 2005 [130]	Ris vs Placebo	Nursing homes	93 Ris = 46 Placebo = 47	Ris = 1.03 mg	85	83.5	12	BEHAVE-AD CGI-S	**Positive**. Ris significantly separated from placebo reducing psychotic symptoms.
Deberdt et al. 2005 [246]	Olz vs Placebo vs Ris	Nursing homes	494 Olz = 204 Ris = 196 Placebo = 94	Ris = 1 mg	65.2	78.3	10	NPI	**Negative.** Ris was not more effective than olanzapine or placebo
De Deyn et al. 1999 [247]	Ris vs Hal vs Placebo	Nursing homes	344 Hal = 81 Ris = 68 Placebo = 74	Ris = 1.1 mg	58	81	12	BEHAVE-AD CGI-S	**Positive.** Ris was more effective than Hal or placebo
Katz et al. 1999 [131]	Ris vs Placebo	Nursing homes	625	Ris = 2 mg	67.8	82.7	12	BEHAVE-AD CGI-S	**Positive.** Ris was more effective than placebo.
Mintzer et al. 2006 [132]	Ris vs Placebo	Nursing homes	473 Risp = 235 Placebo = 238	Ris = 1.03 mg	77	83.3	8	BEHAVE-AD CGI-S	**Negative.** Ris was not more effective than placebo.
Schneider et al. 2006 [220] Sultzer et al. 2008 [243] CATIE-AD trial Phase 1	Olz vs Ris, Qtp vs Placebo	Nursing homes	421 Olz = 100 Ris = 85 Placebo = 142 Qtp = 94	Ris = 1.03 mg	56	77.9	8	NPI CGI-I BPRS	**Positive.** Ris effective in reducing psychotic symptoms compared to placebo or Qtp.

Ari, Aripiprazole; Olz, Olanzapine; Ris, Risperidone; Qtp, Quetiapine; BEHAVE-AD, Behavioral Symptoms in Alzheimer's Disease; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impression – Improvement scale; NPI, Neuropsychiatric Inventory–Questionnaire; NPI-NH, Neuropsychiatric Inventory–Questionnaire Nursing Home version.

psychosis [226–228]; however, it is still not clear whether this treatment is advantageous over other atypical antipsychotics such as risperidone [227, 228]. However, antidepressants may be used as first-line treatment to decrease the use of antipsychotic medication. The use of anticonvulsants for this indication is even more controversial in light of their low tolerability and inconclusive evidence on their efficacy [191, 222, 229]. The primary outcomes of clinical trials examining the efficacy of cholinesterase inhibitors and memantine were mostly targeted to evaluate a sum of behavioral symptoms rather than psychosis per se [230–233]. In most of these studies, these medications did not show a substantial beneficial effect on behavior.

The course of psychosis and resulting behavioral disturbances is an additional important consideration. The frequency and severity of these symptoms' change over time [234], with some patients even experiencing resolution of their psychotic symptoms within several months [235]. Therefore, treatment discontinuation should be considered within a specific time frame after remission of symptoms. A recent Cochrane review demonstrated that in most studies, treatment discontinuation was not associated with a significant behavioral worsening [236]. Nevertheless, some patient subgroups [131], for example, those with more severe behavioral symptoms at baseline [237], with specific types of psychotic symptoms [238], or those that have responded well to antipsychotic medications [239], may benefit from continued treatment.

To examine the effect of pharmacological interventions specifically in DRP, future clinical trials, should probably be designed for more homogeneous patient populations (i.e., include patients with specific types of dementia and of psychotic symptoms, and exclude patients with behavioral disorders in the absence of psychosis). As previously discussed, the mechanisms underlying psychosis subtypes may differ by dementia type and severity. Additionally, disruptive behavioral symptoms of dementia, such as agitation or aggression, may appear in the absence of psychosis, and inclusion of patients with these symptoms but without psychosis in clinical trials, may affect the results. A deeper understanding of the biology underlying specific psychosis subtypes will enable optimal patients' selection in future studies.

Since psychosis per se is not necessarily associated with disruptive behavior and in light of the general goal to refrain from pharmacological treatment if possible, the primary outcomes in future clinical trials should not necessarily be only the amelioration of psychosis per se, but also the amelioration of the resulting behavior, as reflected in objective measurements. This also reflects on the outcomes' measurement method. Up to date, the outcomes of most clinical trials aimed to treat psychosis in dementia were based on caregivers' reports and clinicians' impressions—both potentially affected by subjectivity [240]. Thus, routine inclusion of markers of motor behavior and sleep (e.g., actigraphs) [241] may contribute to more realistically reflect the efficacy of treatment interventions.

Similarly, we should acknowledge that trial design characteristics for most atypical antipsychotics have been tailored for schizophrenia rather than dementia [242] and that studies differed in the tools applied for response measurement, potentially contributing to negative results. The definitions of response or partial response of DRP to treatment require further adjustment for dementia [140]. An important consideration for future clinical trial design should be the use of placebo control arms versus head-to-head drug comparisons and adjusting analyses for concomitant medications, dosage modifications-adjustments, and the presence of adverse events which may influence the overall results and effect sizes. Finally, future studies should examine the efficacy of medications targeting the neuropathology underlying psychotic symptoms in dementia. For example, psychosis in AD is associated with increased neurofibrillary tangle density and concentrations of phosphorylated tau in the neocortex, frontal cortex, and CSF [57]. Thus, anti-tau medications may potentially affect psychotic symptoms. Gaining knowledge of the mechanisms underlying psychosis in dementia may enable the development of better pharmacological approaches for these symptoms. The latter may differ by dementia type and psychosis phenotype.

LIMITATIONS

Our goal was to qualitatively summarize evidence on a broad topic and thus we used informal or subjective methods to collect and interpret studies. However, it is not a systematic review, and this should be understood as a limitation of our work. As a next step, systematic reviews that identify, select, synthesize, and appraise all high quality research evidence relevant to single focused clinical questions should be performed.

CONCLUSIONS

This paper offers a critical evaluation of recent advances in key areas of research focusing on DRP as a treatment target, such as symptom definition, prevalence and clinical relevance, neurobiology, and biomarkers and assessment instruments. Suggestions oriented to the design of clinical trials are indicated for each of the topics included. Likewise, areas of research warranting future attention are identified.

As highlighted above, DRP symptoms are typically severe, disruptive, and persistent. While many existing treatments have limited efficacy and concerning side-effects, recent success with pimavanserin suggests that DRP can be drug-responsive. Several advances provide encouragement for improving the treatment of DRP. The definition and characterization of DRP has recently been updated [8, 17], providing a framework for a consistent definition across neurocognitive disorders. Efforts in understanding the neuropathology of DRP have made clear that there is likely some common neurocircuitry combined with disease-specific pathologies. Evolving treatments that target amyloid-beta and tau have the potential to reduce psychotic symptoms given suggesting linkages with amyloid-beta and tau. Next steps in improving treatment require the identification of new targets. As reviewed above, various studies support a relationship between DRP and inflammatory markers, vascular risk factors and TDP-43 and GWAS studies have the potential to identify novel mechanisms. Key to advancing DRP research will be the use of diagnostic criteria, and the use of mechanistically relevant biomarkers in carefully designed trials.

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REFERENCES

[1] Alzheimer A (1907) Uber eine eigenartige erkrankung der hirnrinde. *Allgemeine Z Psychiatr Psychisch Gerichtliche Med* **64**, 146-148.

[2] Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S (2002) Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *JAMA* **288**, 1475-1483.

[3] Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, Breitner JC, Steffens DC, Tschanz JT, Cache County Investigators (2008) Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: The Cache County Study. *Int J Geriatr Psychiatry* **23**, 170-177.

[4] Lyketsos CG, Colenda CC, Beck C, Blank K, Doraiswamy MP, Kalunian DA, Yaffe K; Task Force of American Association for Geriatric Psychiatry (2006) Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer disease. *Am J Geriatr Psychiatry* **14**, 561-572.

[5] Peters ME, Schwartz S, Han D, Rabins PV, Steinberg M, Tschanz JT, Lyketsos CG (2015) Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: The Cache County Dementia Progression Study. *Am J Psychiatry* **172**, 460-465.

[6] Ropacki SA, Jeste DV (2005) Epidemiology of and risk factors for psychosis of Alzheimer's disease: A review of 55 studies published from 1990 to 2003. *Am J Psychiatry* **162**, 2022-2030.

[7] Murray PS, Kumar S, Demichele-Sweet MA, Sweet RA (2014) Psychosis in Alzheimer's disease. *Biol Psychiatry* **75**, 542-552.

[8] Fischer CE, Agüera-Ortiz L (2018) Psychosis and dementia: Risk factor, prodrome, or cause? *Int Psychogeriatr* **30**, 209-219.

[9] Connors MH, Ames D, Woodward M, Brodaty H (2018) Psychosis and clinical outcomes in Alzheimer disease: A longitudinal study. *Am J Geriatr Psychiatry* **26**, 304-313.

[10] Brandt T, Frangiosa T, Biggar V, Taylor A, Valentine J, Keller B, Price M, DeMuro C, Abler V (2022) Symptoms and treatment needs of people with dementia-related psychosis: A mixed-methods study of the patient experience. *Clin Gerontol* **45**, 681-695.

[11] Bassiony MM, Steinberg MS, Warren A, Rosenblatt A, Baker AS, Lyketsos CG (2000) Delusions and hallucinations in Alzheimer's disease: Prevalence and clinical correlates. *Int J Geriatr Psychiatry* **15**, 99-107.

[12] Emanuel JE, Lopez OL, Houck PR, Becker JT, Weamer EA, Demichele-Sweet MA, Kuller L, Sweet RA (2011) Trajectory of cognitive decline as a predictor of psychosis in early Alzheimer disease in the cardiovascular health study. *Am J Geriatr Psychiatry* **19**, 160-168.

[13] Fischer CE, Ismail Z, Schweizer TA (2012) Delusions increase functional impairment in Alzheimer's disease. *Dement Geriatr Cogn Disord* **33**, 393-399.

[14] Scarmeas N, Brandt J, Albert M, Hadjigeorgiou G, Papadimitriou A, Dubois B, Sarazin M, Devanand D, Honig L, Marder K, Bell K, Wegesin D, Blacker D, Stern Y (2005) Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol* **62**, 1601-1608.

[15] Wilson RS, Tang Y, Aggarwal NT, Gilley DW, McCann JJ, Bienias JL, Evans DA (2006) Hallucinations, cognitive decline, and death in Alzheimer's disease. *Neuroepidemiology* **26**, 68-75.

[16] Poirier A, Voyer P, Legare F, Morin M, Witteman HO, Kroger E, Martineau B, Rodriguez C, Giguere AM (2018) Caring for seniors living with dementia means caring for their caregivers too. *Can J Public Health* **108**, e639-e642.

[17] Fischer CE, Ismail Z, Youakim JM, Creese B, Kumar S, Nunez N, Ryan Darby R, Di Vita A, D'Antonio F, de Lena C, McGeown WJ, Ramit R, Rasmussen J, Bell J, Wang H, Bruneau MA, Panegyres PK, Lanctot KL, Aguera-Ortiz L, Lyketsos C, Cummings J, Jeste DV, Sano M, Devanand DP, Sweet RA, Ballard C (2020) Revisiting criteria for psychosis in Alzheimer's disease and related dementias: Toward better phenotypic classification and biomarker research. *J Alzheimers Dis* **73**, 1143-1156.

[18] Cummings J, Pinto LC, Cruz M, Fischer CE, Gerritsen DL, Grossberg GT, Hwang TJ, Ismail Z, Jeste DV, Koopmans R, Lanctot KL, Mateos R, Peschin S, Sampaio C, Tsuang D, Wang H, Zhong K, Bain LJ, Sano M (2020) Criteria for psychosis in major and mild neurocognitive disorders: International Psychogeriatric Association (IPA) consensus clinical and research definition. *Am J Geriatr Psychiatry* **28**, 1256-1269.

[19] Jin B, Liu H (2019) Comparative efficacy and safety of therapy for the behavioral and psychological symptoms of dementia: A systemic review and Bayesian network meta-analysis. *J Neurol* **266**, 2363-2375.

[20] Ballard C, Howard R (2006) Neuroleptic drugs in dementia: Benefits and harm. *Nat Rev Neurosci* **7**, 492-500.

[21] Schneider LS, Dagerman KS, Insel P (2005) Risk of death with atypical antipsychotic drug treatment for dementia: Meta-analysis of randomized placebo-controlled trials. *JAMA* **294**, 1934-1943.

[22] Desai VC, Heaton PC, Kelton CM (2012) Impact of the Food and Drug Administration's antipsychotic black box warning on psychotropic drug prescribing in elderly patients with dementia in outpatient and office-based settings. *Alzheimers Dement* **8**, 453-457.

[23] Kim HM, Chiang C, Kales HC (2011) After the black box warning: Predictors of psychotropic treatment choices for older patients with dementia. *Psychiatr Serv* **62**, 1207-1214.

[24] Sultana J, Fontana A, Giorgianni F, Pasqua A, Cricelli C, Spina E, Gambassi G, Ivanovic J, Ferrajolo C, Molokhia M, Ballard C, Sharp S, Sturkenboom M, Trifiro G (2016) The effect of safety warnings on antipsychotic drug prescribing in elderly persons with dementia in the United Kingdom and Italy: A population-based study. *CNS Drugs* **30**, 1097-1109.

[25] Jeste DV, Finkel SI (2000) Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. *Am J Geriatr Psychiatry* **8**, 29-34.

[26] American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders*. 5th ed, American Psychiatric Publishing, Washington, DC.

[27] Van Assche L, Van Aubel E, Van de Ven L, Bouckaert F, Luyten P, Vandenbulcke M (2019) The neuropsychological profile and phenomenology of late onset psychosis: A cross-sectional study on the differential diagnosis of very-late-onset schizophrenia-like psychosis, dementia with Lewy bodies and Alzheimer's type dementia with psychosis. *Arch Clin Neuropsychol* **34**, 183-199.

[28] Cook SE, Miyahara S, Bacanu S-A, Perez-Madriñan G, Lopez OL, Kaufer DI, Nimgaonkar VL, Wisniewski SR, DeKosky ST, Sweet RA (2003) Psychotic symptoms in Alzheimer disease: Evidence for subtypes. *Am J Geriatr Psychiatry* **11**, 406-413.

[29] Forstl H, Almeida OP, Owen AM, Burns A, Howard R (1991) Psychiatric, neurological and medical aspects of misidentification syndromes: A review of 260 cases. *Psychol Med* **21**, 905-910.

[30] Mojtabai R (1994) Fregoli syndrome. *Aust N Z J Psychiatry* **28**, 458-462.

[31] Perez-Madrinan G, Cook SE, Saxton JA, Miyahara S, Lopez OL, Kaufer DI, Aizenstein HJ, DeKosky ST, Sweet RA (2004) Alzheimer disease with psychosis: Excess cognitive impairment is restricted to the misidentification subtype. *Am J Geriatr Psychiatry* **12**, 449-456.

[32] D'Antonio F, Reeves S, Sheng Y, McLachlan E, de Lena C, Howard R, Bertrand J (2019) Misidentification subtype of Alzheimer's disease psychosis predicts a faster cognitive decline. *CPT Pharmacometrics Syst Pharmacol* **8**, 308-315.

[33] Ferman TJ, Arvanitakis Z, Fujishiro H, Duara R, Parfitt F, Purdy M, Waters C, Barker W, Graff-Radford NR, Dickson DW (2013) Pathology and temporal onset of visual hallucinations, misperceptions and family misidentification distinguishes dementia with Lewy bodies from Alzheimer's disease. *Parkinsonism Relat Disord* **19**, 227-231.

[34] El Haj M, Roche J, Gallouj K, Gandolphe MC (2017) Autobiographical memory compromise in Alzheimer's disease: A cognitive and clinical overview. *Geriatr Psychol Neuropsychiatr Vieil* **15**, 443-451.

[35] El Haj M, Jardri R, Laroi F, Antoine P (2016) Hallucinations, loneliness, and social isolation in Alzheimer's disease. *Cogn Neuropsychiatry* **21**, 1-13.

[36] Onofrj M, Thomas A, Martinotti G, Anzellotti F, Giannantonio MD, Ciccocioppo F, Bonanni L (2015) The clinical associations of visual hallucinations. In *The Neuroscience of Visual Hallucinations*, Collerton D, Perry E, Mosimann UP, eds. Wiley-Blackwell, pp. 91-117.

[37] Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR (2013) Risk of incident stroke in patients with Alzheimer disease or vascular dementia. *Neurology* **81**, 910-919.

[38] Lenka A, Pagonabarraga J, Pal PK, Bejr-Kasem H, Kulisvesky J (2019) Minor hallucinations in Parkinson disease: A subtle symptom with major clinical implications. *Neurology* **93**, 259-266.

[39] Lenka A, Kamat A, Mittal SO (2019) Spectrum of movement disorders in patients with neuroinvasive West Nile Virus infection. *Mov Disord Clin Pract* **6**, 426-433.

[40] Onofrj M, Taylor JP, Monaco D, Franciotti R, Anzellotti F, Bonanni L, Onofrj V, Thomas A (2013) Visual hallucinations in PD and Lewy body dementias: Old and new hypotheses. *Behav Neurol* **27**, 479-493.

[41] Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* **24**, 197-211.

[42] Ffytche DH, Pereira JB, Ballard C, Chaudhuri KR, Weintraub D, Aarsland D (2017) Risk factors for early psychosis in PD: Insights from the Parkinson's Progression Markers Initiative. *J Neurol Neurosurg Psychiatry* **88**, 325-331.

[43] Pagonabarraga J, Soriano-Mas C, Llebaria G, Lopez-Sola M, Pujol J, Kulisevsky J (2014) Neural correlates of minor hallucinations in non-demented patients with Parkinson's disease. *Parkinsonism Relat Disord* **20**, 290-296.

[44] Fenelon G, Soulas T, Cleret de Langavant L, Trinkler I, Bachoud-Levi AC (2011) Feeling of presence in Parkinson's disease. *J Neurol Neurosurg Psychiatry* **82**, 1219-1224.

[45] Ffytche DH, Aarsland D (2017) Psychosis in Parkinson's disease. *Int Rev Neurobiol* **133**, 585-622.

[46] Fenelon G, Alves G (2010) Epidemiology of psychosis in Parkinson's disease. *J Neurol Sci* **289**, 12-17.

[47] Tsunoda N, Hashimoto M, Ishikawa T, Fukuhara R, Yuki S, Tanaka H, Hatada Y, Miyagawa Y, Ikeda M (2018) Clinical features of auditory hallucinations in patients with dementia with lewy bodies: A soundtrack of visual hallucinations. *J Clin Psychiatry* **79**, 17m11623.

[48] Golden EC, Josephs KA (2015) Minds on replay: Musical hallucinations and their relationship to neurological disease. *Brain* **138**, 3793-3802.

[49] Bjoerke-Bertheussen J, Ehrt U, Rongve A, Ballard C, Aarsland D (2012) Neuropsychiatric symptoms in mild dementia with Lewy bodies and Alzheimer's disease. *Dement Geriatr Cogn Disord* **34**, 1-6.

[50] Suarez-Gonzalez A, Serrano-Pozo A, Arroyo-Anllo EM, Franco-Macias E, Polo J, Garcia-Solis D, Gil-Neciga E (2014) Utility of neuropsychiatric tools in the differential diagnosis of dementia with Lewy bodies and Alzheimer's disease: Quantitative and qualitative findings. *Int Psychogeriatr* **26**, 453-461.

[51] Ffytche DH (2005) Visual hallucinations and the Charles Bonnet syndrome. *Curr Psychiatry Rep* **7**, 168-179.

[52] Naasan G, Shdo SM, Rodriguez EM, Spina S, Grinberg L, Lopez L, Karydas A, Seeley WW, Miller BL, Rankin KP (2021) Psychosis in neurodegenerative disease: Differential patterns of hallucination and delusion symptoms. *Brain* **144**, 999-1012.

[53] Sellami L, Bocchetta M, Masellis M, Cash DM, Dick KM, van Swieten J, Borroni B, Galimberti D, Tartaglia MC, Rowe JB, Graff C, Tagliavini F, Frisoni G, Finger E, de Mendonca A, Sorbi S, Warren JD, Rohrer JD, Laforce R; Genetic FTD Initiative, GENFI (2018) Distinct neuroanatomical correlates of neuropsychiatric symptoms in the three main forms of genetic frontotemporal dementia in the GENFI Cohort. *J Alzheimers Dis* **65**, 147-163.

[54] Devenney EM, Ahmed RM, Halliday G, Piguet O, Kiernan MC, Hodges JR (2018) Psychiatric disorders in C9orf72 kindreds: Study of 1,414 family members. *Neurology* **91**, e1498-e1507.

[55] Yokota O, Miki T, Ikeda C, Nagao S, Takenoshita S, Ishizu H, Haraguchi T, Kuroda S, Terada S, Yamada N (2018) Neuropathological comorbidity associated with argyrophilic grain disease. *Neuropathology* **38**, 82-97.

[56] Lyketsos CG, Sheppard JM, Steinberg M, Tschanz JA, Norton MC, Steffens DC, Breitner JC (2001) Neuropsychiatric disturbance in Alzheimer's disease clusters into

three groups: The Cache County study. *Int J Geriatr Psychiatry* **16**, 1043-1053.

[57] Ballard C, Kales HC, Lyketsos C, Aarsland D, Creese B, Mills R, Williams H, Sweet RA (2020) Psychosis in Alzheimer's Disease. *Curr Neurol Neurosci Rep* **20**, 57.

[58] Fischer CE, Ismail Z, Schweizer TA (2012) Impact of neuropsychiatric symptoms on caregiver burden in patients with Alzheimer's disease. *Neurodegener Dis Manag* **2**, 269-277.

[59] Zahodne LB, Ornstein K, Cosentino S, Devanand DP, Stern Y (2015) Longitudinal relationships between Alzheimer disease progression and psychosis, depressed mood, and agitation/aggression. *Am J Geriatr Psychiatry* **23**, 130-140.

[60] Ismail Z, Creese B, Aarsland D, Kales HC, Lyketsos CG, Sweet RA, Ballard C (2022) Psychosis in Alzheimer disease - mechanisms, genetics and therapeutic opportunities. *Nat Rev Neurol* **18**, 131-144.

[61] Oliveira FFd, de Almeida SS, Smith MC, Bertolucci PHF (2021) Behavioural effects of the ACE insertion/deletion polymorphism in Alzheimer's disease depend upon stratification according to APOE-ϵ4 carrier status. *Cogn Neuropsychiatry* **26**, 293-305.

[62] de Oliveira FF, de Almeida SS, Chen ES, Smith MC, Bertolucci PHF (2022) APOE epsilon4 carrier status as mediator of effects of psychotropic drugs on clinical changes in patients with Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. doi: 10.1176/appi.neuropsych.21060160.

[63] Ruiz M, Arias A, Sánchez-Llanos E, Gil MP, López-Ortega R, Dakterzada F, Purroy F, Piñol-Ripoll G (2018) Minor hallucinations in Alzheimer's disease. *J Alzheimers Dis* **64**, 543-549.

[64] Goukasian N, Hwang KS, Romero T, Grotts J, Do TM, Groh JR, Bateman DR, Apostolova LG (2019) Association of brain amyloidosis with the incidence and frequency of neuropsychiatric symptoms in ADNI: A multisite observational cohort study. *BMJ Open* **9**, e031947.

[65] Manso-Calderón R, Cacabelos-Pérez P, Sevillano-García MD, Herrero-Prieto ME, González-Sarmiento R (2020) The impact of vascular burden on behavioural and psychological symptoms in older adults with dementia: The BEVASDE study. *Neurol Sci* **41**, 165-174.

[66] Oliveira FF, Machado FC, Sampaio G, Marin SM, Chen ES, Smith MC, Bertolucci PH (2015) Contrasts between patients with Lewy body dementia syndromes and APOE-ε3/ε3 patients with late-onset Alzheimer disease dementia. *Neurologist* **20**, 35-41.

[67] de Oliveira FF, Machado FC, Sampaio G, Marin SdMC, da Graça Naffah-Mazzacoratti M, Bertolucci PHF (2020) Neuropsychiatric feature profiles of patients with Lewy body dementia. *Clin Neurol Neurosurg* **194**, 105832.

[68] Oliveira FF, Chen ES, Smith MC, Bertolucci PH (2017) Associations of cerebrovascular metabolism genotypes with neuropsychiatric symptoms and age at onset of Alzheimer's disease dementia. *Braz J Psychiatry* **39**, 95-103.

[69] Dudley R, Aynsworth C, Mosimann U, Taylor J, Smailes D, Collerton D, McCarthy-Jones S, Urwyler P (2019) A comparison of visual hallucinations across disorders. *Psychiatry Res* **272**, 86-92.

[70] Matar E, Martens KAE, Halliday GM, Lewis SJ (2020) Clinical features of Lewy body dementia: Insights into diagnosis and pathophysiology. *J Neurol* **267**, 380-389.

[71] Nagahama Y, Fukui T, Akutagawa H, Ohtaki H, Okabe M, Ito T, Suga H, Fujishiro H (2020) Prevalence and clinical implications of the mirror and TV signs in advanced Alzheimer's disease and dementia with Lewy bodies. *Dement Geriatr Cogn Dis Extra* **10**, 56-62.

[72] Liew TM (2019) Symptom clusters of neuropsychiatric symptoms in mild cognitive impairment and their comparative risks of dementia: A cohort study of 8530 older persons. *J Am Med Dir Assoc* **20**, 1054.e1-1054. e9.

[73] Peters ME, Rosenberg PB, Steinberg M, Norton MC, Welsh-Bohmer KA, Hayden KM, Breitner J, Tschanz JT, Lyketsos CG, Cache County Investigators (2013) Neuropsychiatric symptoms as risk factors for progression from CIND to dementia: The Cache County Study. *Am J Geriatr Psychiatry* **21**, 1116-1124.

[74] Pink A, Stokin GB, Bartley MM, Roberts RO, Sochor O, Machulda MM, Krell-Roesch J, Knopman DS, Acosta JI, Christianson TJ, Pankratz VS, Mielke MM, Petersen RC, Geda YE (2015) Neuropsychiatric symptoms, APOE epsilon4, and the risk of incident dementia: A population-based study. *Neurology* **84**, 935-943.

[75] Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG (2013) The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. *Am J Geriatr Psychiatry* **21**, 685-695.

[76] Yokoi Y, Takano H, Sakata M, Maruo K, Nakagome K, Matsuda H (2019) Discrete effect of each mild behavioural impairment category on dementia conversion or cognitive decline in patients with mild cognitive impairment. *Psychogeriatrics* **19**, 591-600.

[77] Geda YE, Roberts RO, Mielke MM, Knopman DS, Christianson TJ, Pankratz VS, Boeve BF, Sochor O, Tangalos EG, Petersen RC, Rocca WA (2014) Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: A population-based study. *Am J Psychiatry* **171**, 572-581.

[78] Liew TM (2020) Neuropsychiatric symptoms in cognitively normal older persons, and the association with Alzheimer's and non-Alzheimer's dementia. *Alzheimers Res Ther* **12**, 35.

[79] Ismail Z, Smith EE, Geda Y, Sultzer D, Brodaty H, Smith G, Aguera-Ortiz L, Sweet R, Miller D, Lyketsos CG, Area INSPI (2016) Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement* **12**, 195-202.

[80] Ismail Z, Aguera-Ortiz L, Brodaty H, Cieslak A, Cummings J, Fischer CE, Gauthier S, Geda YE, Herrmann N, Kanji J, Lanctot KL, Miller DS, Mortby ME, Onyike CU, Rosenberg PB, Smith EE, Smith GS, Sultzer DL, Lyketsos C; NPS Professional Interest Area of the International Society of to Advance Alzheimer's Research and Treatment (NPS-PIA of ISTAART) (2017) The Mild Behavioral Impairment Checklist (MBI-C): A rating scale for neuropsychiatric symptoms in pre-dementia populations. *J Alzheimers Dis* **56**, 929-938.

[81] Creese B, Griffiths A, Brooker H, Corbett A, Aarsland D, Ballard C, Ismail Z (2020) Profile of mild behavioral impairment and factor structure of the mild behavioral impairment checklist in cognitively normal older adults. *Int Psychogeriatr* **32**, 705-717.

[82] Hu S, Patten S, Charlton A, Fischer K, Fick G, Smith EE, Ismail Z (2022) Validating the mild behavioral impairment checklist in a cognitive clinic: Comparisons with

the neuropsychiatric inventory questionnaire. *J Geriatr Psychiatry Neurol*. doi: 10.1177/08919887221093353.

[83] Paquet C, Magnin E, Wallon D, Troussiere AC, Dumurgier J, Jager A, Bellivier F, Bouaziz-Amar E, Blanc F, Beaufils E, Miguet-Alfonsi C, Quillard M, Schraen S, Pasquier F, Hannequin D, Robert P, Hugon J, Mouton-Liger F; For ePLM network and collaborators (2016) Utility of CSF biomarkers in psychiatric disorders: A national multicentre prospective study. *Alzheimers Res Ther* **8**, 27.

[84] Murray PS, Kirkwood CM, Gray MC, Fish KN, Ikonomovic MD, Hamilton RL, Kofler JK, Klunk WE, Lopez OL, Sweet RA (2014) Hyperphosphorylated tau is elevated in Alzheimer's disease with psychosis. *J Alzheimers Dis* **39**, 759-773.

[85] Koppel J, Sunday S, Buthorn J, Goldberg T, Davies P, Greenwald B; Alzheimer's Disease Neuroimaging Initiative (2013) Elevated CSF Tau is associated with psychosis in Alzheimer's disease. *Am J Psychiatry* **170**, 1212-1213.

[86] Ehrenberg AJ, Suemoto CK, França Resende EP, Petersen C, Leite REP, Rodriguez RD, Ferretti-Rebustini REL, You M, Oh J, Nitrini R, Pasqualucci CA, Jacob-Filho W, Kramer JH, Gatchel JR, Grinberg LT (2018) Neuropathologic correlates of psychiatric symptoms in Alzheimer's disease. *J Alzheimers Dis* **66**, 115-126.

[87] Whitfield DR FP, Ballard C, Williams G (2018) Associations between ZnT3, tau pathology, agitation, and delusions in dementia. *Int J Geriatr Psychiatry* **33**, 1146-1152.

[88] Kim J, Schweizer TA, Fischer CE, Munoz DG (2018) Psychosis in "cognitively asymptomatic" elderly subjects is associated with neuritic plaque load, not neurofibrillary tangles. *Alzheimer Dis Assoc Disord* **32**, 185-189.

[89] Ffytche DH, Creese B, Politis M, Chaudhuri KR, Weintraub D, Ballard C, Aarsland D (2017) The psychosis spectrum in Parkinson disease. *Nat Rev Neurol* **13**, 81-95.

[90] Mackin RS, Insel P, Zhang J, Mohlenhoff B, Galasko D, Weiner M, Mattsson N (2015) Cerebrospinal fluid alpha-synuclein and Lewy body-like symptoms in normal controls, mild cognitive impairment, and Alzheimer's disease. *J Alzheimers Dis* **43**, 1007-1016.

[91] Krivinko JM, Erickson SL, Ding Y, Sun Z, Penzes P, MacDonald ML, Yates NA, Ikonomovic MD, Lopez OL, Sweet RA, Kofler J (2018) Synaptic proteome compensation and resilience to psychosis in Alzheimer's disease. *Am J Psychiatry* **175**, 999-1009.

[92] Fischer CE, Qian W, Schweizer TA, Millikin CP, Ismail Z, Smith EE, Lix LM, Shelton P, Munoz DG (2016) Lewy bodies, vascular risk factors, and subcortical arteriosclerotic leukoencephalopathy, but not Alzheimer pathology, are associated with development of psychosis in Alzheimer's disease. *J Alzheimers Dis* **50**, 283-295.

[93] Vik-Mo AO, Bencze J, Ballard C, Hortobágyi T, Aarsland D (2019) Advanced cerebral amyloid angiopathy and small vessel disease are associated with psychosis in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **90**, 728-730.

[94] Ting SK, Hao Y, Chia PS, Tan EK, Hameed S (2016) Clinicopathological correlation of psychosis and brain vascular changes in Alzheimer's disease. *Sci Rep* **6**, 20858.

[95] Kim J, Schweizer TA, Fischer CE, Munoz DG (2017) The role of cerebrovascular disease on cognitive and functional status and psychosis in severe Alzheimer's disease. *J Alzheimers Dis* **55**, 381-389.

[96] Dobson-Stone C, Hallupp M, Bartley L, Shepherd CE, Halliday GM, Schofield PR, Hodges JR, Kwok JB (2012) C9ORF72 repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts. *Neurology* **79**, 995-1001.

[97] Scarioni M, Gami-Patel P, Timar Y, Seelaar H, van Swieten JC, Rozemuller AJM, Dols A, Scarpini E, Galimberti D, Netherlands Brain B, Hoozemans JJM, Pijnenburg YAL, Dijkstra AA (2020) Frontotemporal dementia: Correlations between psychiatric symptoms and pathology. *Ann Neurol* **87**, 950-961.

[98] Victoroff J, Lin FV, Coburn KL, Shillcutt SD, Voon V, Ducharme S (2018) Noncognitive behavioral changes associated with Alzheimer's disease: Implications of neuroimaging findings. *J Neuropsychiatry Clin Neurosci* **30**, 14-21.

[99] Rosenberg PB, Nowrangi MA, Lyketsos CG (2015) Neuropsychiatric symptoms in Alzheimer's disease: What might be associated brain circuits? *Mol Aspects Med* **43**, 25-37.

[100] Starkstein SE, Sabe L, Vazquez S, Di Lorenzo G, Martinez A, Petracca G, Teson A, Chemerinski E, Leiguarda R (1997) Neuropsychological, psychiatric, and cerebral perfusion correlates of leukoaraiosis in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **63**, 66-73.

[101] Fukuhara R, Ikeda M, Nebu A, Kikuchi T, Maki N, Hokoishi K, Shigenobu K, Komori K, Tanabe H (2001) Alteration of rCBF in Alzheimer's disease patients with delusions of theft. *Neuroreport* **12**, 2473-2476.

[102] Nakano S, Yamashita F, Matsuda H, Kodama C, Yamada T (2006) Relationship between delusions and regional cerebral blood flow in Alzheimer's disease. *Dement Geriatr Cogn Disord* **21**, 16-21.

[103] Mentis MJ, Weinstein EA, Horwitz B, McIntosh AR, Pietrini P, Alexander GE, Furey M, Murphy DG (1995) Abnormal brain glucose metabolism in the delusional misidentification syndromes: A positron emission tomography study in Alzheimer disease. *Biol Psychiatry* **38**, 438-449.

[104] Sultzer DL, Mahler ME, Mandelkern MA, Cummings JL, Van Gorp WG, Hinkin CH, Berisford MA (1995) The relationship between psychiatric symptoms and regional cortical metabolism in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* **7**, 476-484.

[105] Forstl H, Burns A, Jacoby R, Levy R (1991) Neuroanatomical correlates of clinical misidentification and misperception in senile dementia of the Alzheimer type. *J Clin Psychiatry* **52**, 268-271.

[106] Geroldi C, Akkawi NM, Galluzzi S, Ubezio M, Binetti G, Zanetti O, Trabucchi M, Frisoni GB (2000) Temporal lobe asymmetry in patients with Alzheimer's disease with delusions. *J Neurol Neurosurg Psychiatry* **69**, 187-191.

[107] Geroldi C, Bresciani L, Zanetti O, Frisoni GB (2002) Regional brain atrophy in patients with mild Alzheimer's disease and delusions. *Int Psychogeriatr* **14**, 365-378.

[108] Serra L, Perri R, Cercignani M, Spano B, Fadda L, Marra C, Carlesimo GA, Caltagirone C, Bozzali M (2010) Are the behavioral symptoms of Alzheimer's disease directly associated with neurodegeneration? *J Alzheimers Dis* **21**, 627-639.

[109] Barber R, McKeith IG, Ballard C, Gholkar A, O'Brien JT (2001) A comparison of medial and lateral temporal lobe atrophy in dementia with Lewy bodies and Alzheimer's disease: Magnetic resonance imaging volumetric study. *Dement Geriatr Cogn Disord* **12**, 198-205.

[110] Holroyd S, Shepherd ML, Downs JH 3rd (2000) Occipital atrophy is associated with visual hallucinations in

Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* **12**, 25-28.

[111] Whitehead D, Tunnard C, Hurt C, Wahlund LO, Mecocci P, Tsolaki M, Vellas B, Spenger C, Kloszewska I, Soininen H, Cromb D, Lovestone S, Simmons A; AddNeuroMed Consortium (2012) Frontotemporal atrophy associated with paranoid delusions in women with Alzheimer's disease. *Int Psychogeriatr* **24**, 99-107.

[112] Ogawa Y, Hashimoto M, Yatabe Y, Kaneda K, Honda K, Yuuki S, Hirai T, Ikeda M (2013) Association of cerebral small vessel disease with delusions in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* **28**, 18-25.

[113] Shinno H, Inagaki T, Miyaoka T, Okazaki S, Kawamukai T, Utani E, Inami Y, Horiguchi J (2007) A decrease in N-acetylaspartate and an increase in myoinositol in the anterior cingulate gyrus are associated with behavioral and psychological symptoms in Alzheimer's disease. *J Neurol Sci* **260**, 132-138.

[114] Reeves S, Brown R, Howard R, Grasby P (2009) Increased striatal dopamine (D2/D3) receptor availability and delusions in Alzheimer disease. *Neurology* **72**, 528-534.

[115] Fischer CE, Ting WK, Millikin CP, Ismail Z, Schweizer TA; Alzheimer Disease Neuroimaging Initiative (2016) Gray matter atrophy in patients with mild cognitive impairment/Alzheimer's disease over the course of developing delusions. *Int J Geriatr Psychiatry* **31**, 76-82.

[116] D'Antonio F, Di Vita A, Zazzaro G, Brusa E, Trebbastoni A, Campanelli A, Ferracuti S, de Lena C, Guariglia C, Boccia M (2019) Psychosis of Alzheimer's disease: Neuropsychological and neuroimaging longitudinal study. *Int J Geriatr Psychiatry* **34**, 1689-1697.

[117] DeMichele-Sweet MAA, Klei L, Creese B, Harwood JC, Weamer EA, McClain L, Sims R, Hernandez I, Moreno-Grau S, Tárraga L, Boada M, Alarcón-Martín E, Valero S; NIA-LOAD Family Based Study Consortium, Alzheimer's Disease Genetics Consortium (ADGC), Liu Y, Hooli B, Aarsland D, Selbaek G, Bergh S, Rongve A, Saltvedt I, Skjellegrind HK, Engdahl B, Stordal E, Andreassen OA, Djurovic S, Athanasiu L, Seripa D, Borroni B, Albani D, Forloni G, Mecocci P, Serretti A, De Ronchi D, Politis A, Williams J, Mayeux R, Foroud T, Ruiz A, Ballard C, Holmans P, Lopez OL, Kamboh MI, Devlin B, Sweet RA (2021) Genome-wide association identifies the first risk loci for psychosis in Alzheimer disease. *Mol Psychiatry* **26**, 5797-5811.

[118] Shah C, DeMichele-Sweet MAA, Sweet RA (2017) Genetics of psychosis of Alzheimer disease. *Am J Med Genet B Neuropsychiatr Genet* **174**, 27-35.

[119] Kim JE, Fischer CA, Schweizer TG, Munoz D (2017) Gender and pathology-specific effect of Apolipoprotein E genotype on psychosis in Alzheimer's disease. *Curr Alzheimer Res* **14**, 834-840.

[120] Creese B, Vassos E, Bergh S, Athanasiu L, Johar I, Rongve A, Medbøen IT, Vasconcelos Da Silva M, Aakhus E, Andersen F, Bettella F, Braekhus A, Djurovic S, Paroni G, Proitsi P, Saltvedt I, Seripa D, Stordal E, Fladby T, Aarsland D, Andreassen OA, Ballard C, Selbaek G; AddNeuroMed consortium and the Alzheimer's Disease Neuroimaging Initiative (2019) Examining the association between genetic liability for schizophrenia and psychotic symptoms in Alzheimer's disease. *Transl Psychiatry* **9**, 273.

[121] Ellis N, Tee A, McAllister B, Massey T, McLauchlan D, Stone T, Correia K, Loupe J, Kim K-H, Barker D, Hong EP, Chao MJ, Long JD, Lucente D, Vonsattel JPG, Pinto RM, Elneel KA, Ramos EM, Mysore JS, Gillis T, Wheeler VC, Medway C, Hall L, Kwak S, Sampaio C, Ciosi M, Maxwell A, Chatzi A, Monckton DG, Orth M, Landwehrmeyer GB, Paulsen JS, Shoulson I, Myers RH, van Duijn E, Rickards H, MacDonald ME, Lee J-m, Gusella JF, Jones L, Holmans P (2020) Genetic risk underlying psychiatric and cognitive symptoms in Huntington's disease. *Biol Psychiatry* **87**, 857-865.

[122] Legge SE, Jones HJ, Kendall KM, Pardiñas AF, Menzies G, Bracher-Smith M, Escott-Price V, Rees E, Davis KAS, Hotopf M, Savage JE, Posthuma D, Holmans P, Kirov G, Owen MJ, O'Donovan MC, Zammit S, Walters JTR (2019) Association of genetic liability to psychotic experiences with neuropsychotic disorders and traits. *JAMA Psychiatry* **76**, 1256-1265.

[123] Pain O, Dudbridge F, Cardno AG, Freeman D, Lu Y, Lundstrom S, Lichtenstein P, Ronald A (2018) Genome-wide analysis of adolescent psychotic-like experiences shows genetic overlap with psychiatric disorders. *Am J Med Genet B Neuropsychiatr Genet* **177**, 416-425.

[124] Pishva E, Creese B, Smith AR, Viechtbauer W, Proitsi P, van den Hove DLA, Ballard C, Mill J, Lunnon K (2020) Psychosis-associated DNA methylomic variation in Alzheimer's disease cortex. *Neurobiol Aging* **89**, 83-88.

[125] Creese B, Bell E, Johar I, Francis P, Ballard C, Aarsland D (2018) Glucocerebrosidase mutations and neuropsychiatric phenotypes in Parkinson's disease and Lewy body dementias: Review and meta-analyses. *Am J Med Genet B Neuropsychiatr Genet* **177**, 232-241.

[126] Shiner T, Mirelman A, Gana Weisz M, Bar-Shira A, Ash E, Cialic R, Nevler N, Gurevich T, Bregman N, Orr-Urtreger A, Giladi N (2016) High frequency of GBA gene mutations in dementia with Lewy bodies among Ashkenazi Jews. *JAMA Neurol* **73**, 1448-1453.

[127] Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, Floratos A, Sham PC, Li MJ, Wang J, Cardon LR, Whittaker JC, Sanseau P (2015) The support of human genetic evidence for approved drug indications. *Nat Genet* **47**, 856-860.

[128] Malekizadeh Y, Williams G, Kelson M, Whitfield D, Mill J, Collier DA, Ballard C, Jeffries AR, Creese B (2020) Whole transcriptome in silico screening implicates cardiovascular and infectious disease in the mechanism of action underlying atypical antipsychotic side effects. *Alzheimers Dement (N Y)* **6**, e12078.

[129] Reisberg B, Borenstein J, Franssen E, Salob S, Steinberg G, Shulman E, Ferris SH, Georgotas A (1987) BEHAVE-AD: A clinical rating scale for the assessment of pharmacologically remediable behavioral symptomatology in Alzheimer's disease. In *Alzheimer's disease: Problems, Prospects and Perspectives*, Altman HJ, ed. Springer, Boston, pp. 1-16.

[130] Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, Lee E, Greenspan A (2005) Risperidone for psychosis of Alzheimer's disease and mixed dementia: Results of a double-blind, placebo-controlled trial. *Int J Geriatr Psychiatry* **20**, 1153-1157.

[131] Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, Brecher M (1999) Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: A randomized, double-blind trial. Risperidone Study Group. *J Clin Psychiatry* **60**, 107-115.

[132] Mintzer J, Greenspan A, Caers I, Van HI, Kushner S, Weiner M, Gharabawi G, Schneider LS (2006) Risperidone in the treatment of psychosis of Alzheimer disease:

Results from a prospective clinical trial. *Am J Geriatr Psychiatry* **14**, 280-291.

[133] Reisberg B, Monteiro I, Torossian C, Auer S, Shulman MB, Ghimire S, Boksay I, Guillo BenArous F, Osorio R, Vengassery A, Imran S, Shaker H, Noor S, Naqvi S, Kenowsky S, Xu J (2014) The BEHAVE-AD assessment system: A perspective, a commentary on new findings, and a historical review. *Dement Geriatr Cogn Disord* **38**, 89-146.

[134] Boada M, Tarraga L, Modinos G, Diego S, Reisberg B (2006) Behavioral pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD): Spanish validation. *Neurologia* **21**, 19-25.

[135] Sclan SG, Saillon A, Franssen E, Hugonot-Diener L, Saillon A, Reisberg B (1996) The Behavior Pathology In Alzheimer's Disease Rating Scale (BEHAVE-AD): Reliability and analysis of symptom category scores. *Int J Geriatr Psychiatry* **11**, 819-830.

[136] Auer SR, Monteiro IM, Reisberg B (1996) The empirical behavioral pathology in Alzheimer's disease (E-BEHAVE-AD) rating scale. *Int Psychogeriatr* **8**, 247-266.

[137] Monteiro IM, Boksay I, Auer SR, Torossian C, Ferris SH, Reisberg B (2001) Addition of a frequency-weighted score to the behavioral pathology in Alzheimer's Disease Rating Scale: The BEHAVE-AD-FW: Methodology and reliability. *Eur Psychiatry* **16**, 5s-24s.

[138] Cummings JL (1997) The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology* **48**, S10-S16.

[139] Cummings JL, Mega M, Gray K, Rosemberg-Thompson S, Carus DA, Gornbein J (1994) The Neuropsychiatric Inventory- comprehensive assessment of psychopathology in dementia. *Neurology* **44**, 2308-2314.

[140] Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, Dhall R, Ballard C (2014) Pimavanserin for patients with Parkinson's disease psychosis: A randomised, placebo-controlled phase 3 trial. *Lancet* **383**, 533-540.

[141] Street J, Tollefson GD, Tohen M (2000) Olanzapine for psychotic conditions in the elderly. *Psychiatr Ann* **30**, 191-196.

[142] De Deyn P, Jeste DV, Swanink R, Kostic D, Breder C, Carson WH, Iwamoto T (2005) Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease: A randomized, placebo-controlled study. *J Clin Psychopharmacol* **25**, 463-467.

[143] Streim JE, Porsteinsson AP, Breder CD, Swanink R, Marcus R, McQuade R, Carson WH (2008) 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* **16**, 537-550.

[144] Cummings J (2020) The Neuropsychiatric Inventory: Development and applications. *J Geriatr Psychiatry Neurol* **33**, 73-84.

[145] Connor DJ, Sabbagh MN, Cummings JL (2008) Comment on administration and scoring of the Neuropsychiatric Inventory in clinical trials. *Alzheimers Dement* **4**, 390-394.

[146] Robert P, Verhey FR, Aalten P, Cortes F, Byrne EJ (2007) Neuropsychiatric outcome for clinical trials. *J Nutr Health Aging* **11**, 345-347.

[147] Reeves SJ, Gould RL, Powell JF, Howard RJ (2012) Origins of delusions in Alzheimer's disease. *Neurosci Biobehav Rev* **36**, 2274-2287.

[148] Devanand DP, Miller L, Richards M, Marder K, Bell K, Mayeux R, Stern Y (1992) The Columbia University scale for psychopathology in Alzheimer's disease. *Arch Neurol* **49**, 371-376.

[149] Cohen-Mansfield J, Golander H (2011) The measurement of psychosis in dementia: A comparison of assessment tools. *Alzheimer Dis Assoc Disord* **25**, 101-108.

[150] Aguera-Ortiz LF, Lopez-Alvarez J, Del Nido-Varo L, Soria Garcia-Rosel E, Perez-Martinez DA, Ismail Z (2017) Mild behavioural impairment as an antecedent of dementia: Presentation of the diagnostic criteria and the Spanish version of the MBI-C scale for its evaluation. *Rev Neurol* **65**, 327-334.

[151] Xu L, Li T, Xiong L, Wang X, Ismail Z, Fukuda M, Sun Z, Wang J, Gauthier S, Yu X, Wang H (2021) Reliability and validity of the Chinese version of mild behavioral impairment checklist in mild cognitive impairment and mild Alzheimer's disease. *J Alzheimers Dis* **81**, 1141-1149.

[152] Tariot PN (1996) CERAD behavior rating scale for dementia. *Int Psychogeriatr* **8**(Suppl 3), 317-320.

[153] Levin HS, High WM, Goethe KE, Sisson RA, Overall JE, Rhoades HM, Eisenberg HM, Kalisky Z, Gary HE (1987) The neurobehavioural rating scale: Assessment of the behavioural sequelae of head injury by the clinician. *J Neurol Neurosurg Psychiatry* **50**, 183-193.

[154] Ballard C, Holmes C, McKeith I, Neill D, O'Brien J, Cairns N, Lantos P, Perry E, Ince P, Perry R (1999) Psychiatric morbidity in dementia with Lewy bodies: A prospective clinical and neuropathological study with Alzheimer's disease. *Am J Psychiatry* **156,** 1039-1045.

[155] Gara MA, Vega WA, Arndt S, Escamilla M, Fleck DE, Lawson WB, Lesser I, Neighbors HW, Wilson DR, Arnold LM, Strakowski SM (2012) Influence of patient race and ethnicity on clinical assessment in patients with affective disorders. *Arch Gen Psychiatry* **69**, 593-600.

[156] Strakowski SM, Flaum M, Amador X, Bracha HS, Pandurangi AK, Robinson D, Tohen M (1996) Racial differences in the diagnosis of psychosis. *Schizophr Res* **21**, 117-124.

[157] Tortelli A, Nakamura A, Suprani F, Schurhoff F, Van der Waerden J, Szoke A, Tarricone I, Pignon B (2018) Subclinical psychosis in adult migrants and ethnic minorities: Systematic review and meta-analysis. *BJPsych Open* **4**, 510-518.

[158] Cohen-Mansfield J (2005) Nonpharmacological interventions for persons with dementia. *Alzheimers Care Today* **6**, 129-145.

[159] Opie J, Rosewarne R, O'Connor DW (1999) The efficacy of psychosocial approaches to behaviour disorders in dementia: A systematic literature review. *Aust N Z J Psychiatry* **33**, 789-799.

[160] Zucchella C, Sinforiani E, Tamburin S, Federico A, Mantovani E, Bernini S, Casale R, Bartolo M (2018) The multidisciplinary approach to Alzheimer's disease and dementia. A narrative review of non-pharmacological treatment. *Front Neurol* **9**, 1058.

[161] Ballard C, O'Brien J (1999) Treating behavioural and psychological signs in Alzheimer's disease. *BMJ* **319**, 138-139.

[162] Cohen-Mansfield J (2003) Nonpharmacologic interventions for psychotic symptoms in dementia. *J Geriatr Psychiatry Neurol* **16**, 219-224.

[163] Brunelle-Hamann L, Thivierge S, Simard M (2015) Impact of a cognitive rehabilitation intervention on neuropsychiatric symptoms in mild to moderate Alzheimer's disease. *Neuropsychol Rehabil* **25**, 677-707.

[164] Chen RC, Liu CL, Lin MH, Peng LN, Chen LY, Liu LK, Chen LK (2014) Non-pharmacological treatment reducing not only behavioral symptoms, but also psychotic symptoms of older adults with dementia: A prospective cohort study in Taiwan. *Geriatr Gerontol Int* **14**, 440-446.

[165] de Oliveira AM, Radanovic M, Homem de Mello PC, Buchain PC, Dias Vizzotto A, Harder J, Stella F, Piersol CV, Gitlin LN, Forlenza OV (2019) An intervention to reduce neuropsychiatric symptoms and caregiver burden in dementia: Preliminary results from a randomized trial of the tailored activity program-outpatient version. *Int J Geriatr Psychiatry* **34**, 1301-1307.

[166] Reese TR, Thiel DJ, Cocker KE (2016) Behavioral disorders in dementia: Appropriate nondrug interventions and antipsychotic use. *Am Fam Physician* **94**, 276-282.

[167] Cohen-Mansfield J, Werner P (1997) Management of verbally disruptive behaviors in nursing home residents. *J Gerontol A Biol Sci Med Sci* **52**, M369-M377.

[168] Zeisel J, Silverstein NM, Hyde J, Levkoff S, Lawton MP, Holmes W (2003) Environmental correlates to behavioral health outcomes in Alzheimer's special care units. *Gerontologist* **43**, 697-711.

[169] Marquardt G, Bueter K, Motzek T (2014) Impact of the design of the built environment on people with dementia: An evidence-based review. *HERD* **8**, 127-157.

[170] Small GW (2020) Managing the burden of dementia related delusions and hallucinations. *J Fam Pract* **69**, S39-S44.

[171] Gómez Gallego M, Gómez García J (2017) Music therapy and Alzheimer's disease: Cognitive, psychological, and behavioural effects. *Neurologia* **32**, 300-308.

[172] Raglio A, Bellandi D, Baiardi P, Gianotti M, Ubezio MC, Zanacchi E, Granieri E, Imbriani M, Stramba-Badiale M (2015) Effect of active music therapy and individualized listening to music on dementia: A multicenter randomized controlled trial. *J Am Geriatr Soc* **63**, 1534-1539.

[173] Raglio A, Bellelli G, Traficante D, Gianotti M, Ubezio MC, Villani D, Trabucchi M (2008) Efficacy of music therapy in the treatment of behavioral and psychiatric symptoms of dementia. *Alzheimer Dis Assoc Disord* **22**, 158-162.

[174] van Hoof J, Kort HS, van Waarde H, Blom MM (2010) Environmental interventions and the design of homes for older adults with dementia: An overview. *Am J Alzheimers Dis Other Demen* **25**, 202-232.

[175] Wong JK, Skitmore M, Buys L, Wang K (2014) The effects of the indoor environment on residential care homes on dementia suffers in Hong Kong: A critical incident technique approach. *Build Environ* **73**, 32-39.

[176] Schindler SD, Graf A, Fischer P, Tölk A, Kasper S (2002) Paranoid delusions and hallucinations and bright light therapy in Alzheimer's disease. *Int J Geriatr Psychiatry* **17**, 1071-1072.

[177] Blazer DG, Tucci DL (2019) Hearing loss and psychiatric disorders: A review. *Psychol Med* **49**, 891-897.

[178] Chapman FM, Dickinson J, McKeith I, Ballard C (1999) Association among visual hallucinations, visual acuity, and specific eye pathologies in Alzheimer's disease: Treatment implications. *Am J Psychiatry* **156**, 1983-1985.

[179] Camp C, Cohen-Mansfield J, Capezuti E (2002) Mental health services in nursing homes: Use of nonpharmacologic interventions among nursing home residents with dementia. *Psychiatr Serv* **53**, 1397-1401.

[180] Reus VI, Fochtmann LJ, Eyler AE, Hilty DM, Horvitz-Lennon M, Jibson MD, Lopez OL, Mahoney J, Pasic J, Tan

ZS (2016) The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. *Am J Psychiatry* **173**, 543-546.

[181] Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Mov Disord* **23**, 2129-2170.

[182] Yunusa I, Alsumali A, Garba AE, Regestein QR, Eguale T (2019) Assessment of reported comparative effectiveness and safety of atypical antipsychotics in the treatment of behavioral and psychological symptoms of dementia: A network meta-analysis. *JAMA Netw Open* **2**, e190828.

[183] Parker C, Coupland C, Hippisley-Cox J (2010) Antipsychotic drugs and risk of venous thromboembolism: Nested case-control study. *BMJ* **341**, c4245.

[184] Tampi RR, Tampi DJ, Balachandran S, Srinivasan S (2016) Antipsychotic use in dementia: A systematic review of benefits and risks from meta-analyses. *Ther Adv Chronic Dis* **7**, 229-245.

[185] Rossom RC, Rector TS, Lederle FA, Dysken MW (2010) Are all commonly prescribed antipsychotics associated with greater mortality in elderly male veterans with dementia? *J Am Geriatri Soc* **58**, 1027-1034.

[186] Douglas IJ, Smeeth L (2008) Exposure to antipsychotics and risk of stroke: Self controlled case series study. *BMJ* **337**, a1227.

[187] Gill SS, Bronskill SE, Normand S-LT, Anderson GM, Sykora K, Lam K, Bell CM, Lee PE, Fischer HD, Herrmann N (2007) Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* **146**, 775-786.

[188] Wooltorton E (2004) Olanzapine (Zyprexa): Increased incidence of cerebrovascular events in dementia trials. *CMAJ* **170**, 1395-1395.

[189] Kirkham J, Sherman C, Velkers C, Maxwell C, Gill S, Rochon P, Seitz D (2017) Antipsychotic use in dementia: Is there a problem and are there solutions? *Can J Psychiatry* **62**, 170-181.

[190] Bell JS, Taipale HT, Soini H, Pitkälä KH (2010) Sedative load among long-term care facility residents with and without dementia. *Clin Drug Investig* **30**, 63-70.

[191] Sink KM, Holden KF, Yaffe K (2005) Pharmacological treatment of neuropsychiatric symptoms of dementia: A review of the evidence. *JAMA* **293**, 596-608.

[192] Morgante L, Epifanio A, Spina E, Di Rosa A, Zappia M, Basile G, La Spina P, Quattrone A (2002) Quetiapine versus clozapine: A preliminary report of comparative effects on dopaminergic psychosis in patients with Parkinson's disease. *Neurol Sci* **23**, S89-S90.

[193] Yunusa I, El Helou ML, Alsahali S (2020) Pimavanserin: A novel antipsychotic with potentials to address an unmet need of older adults with dementia-related psychosis. *Front Pharmacol* **11**, 87.

[194] Friedman JH (2013) Pimavanserin for the treatment of Parkinson's disease psychosis. *Expert Opin Pharmacother* **14**, 1969-1975.

[195] Ballard C, Youakim J, Coate B, Stankovic S (2019) Pimavanserin in Alzheimer's Disease psychosis: Efficacy in patients with more pronounced psychotic symptoms. *J Prev Alzheimers Dis* **6**, 27-33.

[196] Weintraub D, Chiang C, Kim HM, Wilkinson J, Marras C, Stanislawski B, Mamikonyan E, Kales HC (2016)

Association of antipsychotic use with mortality risk in patients with Parkinson disease. *JAMA Neurol* **73**, 535-541.

[197] Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D, Sampaio C; the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine Committee (2019) Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. *Mov Disord* **34**, 180-198.

[198] Bergman RN, Ader M (2005) Atypical antipsychotics and glucose homeostasis. *J Clin Psychiatry* **66**, 504-514.

[199] Horn S, Richardson H, Xie SX, Weintraub D, Dahodwala N (2019) Pimavanserin versus quetiapine for the treatment of psychosis in Parkinson's disease and dementia with Lewy bodies. *Parkinsonism Related Disord* **69**, 119-124.

[200] Group PS (1999) Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Eng J Med* **340**, 757-763.

[201] Kyle K, Bronstein JM (2020) Treatment of psychosis in Parkinson's disease and dementia with Lewy Bodies: A review. *Parkinsonism Relat Disord* **75**, 55-62.

[202] Yaw TK, Fox SH, Lang AE (2016) Clozapine in parkinsonian rest tremor: A review of outcomes, adverse reactions, and possible mechanisms of action. *Mov Disord Clin Pract* **3**, 116-124.

[203] Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, Kales HC (2015) Antipsychotics, other psychotropics, and the risk of death in patients with dementia: Number needed to harm. *JAMA Psychiatry* **72**, 438-445.

[204] Kales HC, Zivin K, Kim HM, Valenstein M, Chiang C, Ignacio RV, Ganoczy D, Cunningham F, Schneider LS, Blow FC (2011) Trends in antipsychotic use in dementia 1999-2007. *Arch Gen Psychiatry* **68**, 190-197.

[205] Dorsey ER, Rabbani A, Gallagher SA, Conti RM, Alexander GC (2010) Impact of FDA black box advisory on antipsychotic medication use. *Arch Int Med* **170**, 96-103.

[206] Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS (2007) Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ* **176**, 627-632.

[207] Kirshner HS (2008) Controversies in behavioral neurology: The use of atypical antipsychotic drugs to treat neurobehavioral symptoms in dementia. *Curr Neurol Neurosci Rep* **8**, 471-474.

[208] Saad M, Cassagnol M, Ahmed E (2010) The impact of FDA's warning on the use of antipsychotics in clinical practice: A survey. *Consult Pharm* **25**, 739-744.

[209] Manzano-Palomo S, Aguera-Ortiz LF, Garcia-Caballero A, Martinez-Raga J, Ojea-Ortega T, Sanchez-Valle R, Anton-Jimenez M, Monge-Argiles JA, Ramos-Garcia I (2020) Use of antipsychotics in patients with behavioral and psychological symptoms of dementia: Results of a Spanish Delphi consensus. *Dement Geriatr Cogn Disord* **49**, 573-582.

[210] Cossette B, Bruneau MA, Couturier Y, Gilbert S, Boyer D, Ricard J, McDonald T, Labarre K, Déry V, Arcand M (2020) Optimizing Practices, Use, Care and Services–Antipsychotics (OPUS-AP) in long-term care centers in Québec, Canada: A strategy for best practices. *J Am Med Dir Assoc* **21**, 212-219.

[211] Cioltan H, Alshehri S, Howe C, Lee J, Fain M, Eng H, Schachter K, Mohler J (2017) Variation in use of antipsychotic medications in nursing homes in the United States: A systematic review. *BMC Geriatr* **17**, 32.

[212] Muniz R, Perez-Wehbe AI, Couto F, Perez M, Ramirez N, Lopez A, Rodriguez J, Usieto T, Lavin L, Rigueira A, Aguera-Ortiz L, Lopez-Alvarez J, Martin-Carrasco M, Olazaran J (2020) The "CHROME criteria": Tool to optimize and audit prescription quality of psychotropic medications in institutionalized people with dementia. *Int Psychogeriatr* **32**, 315-324.

[213] Mintzer JE, Tune LE, Breder CD, Swanink R, Marcus RN, McQuade RD, Forbes A (2007) 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* **15**, 918-931.

[214] De Deyn P, Carrasco MM, Deberdt W; Jeandel C, Hay DP, Feldman PD, Young CA, Lehman DL, Breier A (2004) Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* **19**, 115-126.

[215] Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A, O'Brien J, Everratt A, Sadler S, Maddison C, Lee L, Bannister C, Elvish R, Jacoby R (2005) Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: Randomised double blind placebo controlled trial. *BMJ* **330**, 874.

[216] Rainer M, Haushofer M, Pfolz H, Struhal C, Wick W (2007) Quetiapine versus risperidone in elderly patients with behavioural and psychological symptoms of dementia: Efficacy, safety and cognitive function. *Eur Psychiatry* **22**, 395-403.

[217] Deberdt W, Lipkovich I, Heinloth AN, Liu L, Kollack-Walker S, Edwards SE, Hoffmann VP, Hardy TA (2008) Double-blind, randomized trial comparing efficacy and safety of continuing olanzapine versus switching to quetiapine in overweight or obese patients with schizophrenia or schizoaffective disorder. *Ther Clin Risk Manag* **4**, 713-720.

[218] Zhong KX, Tariot P, Mintzer J, Minkwitz M, Devine N (2007) Quetiapine to treat agitation in dementia: A randomized, double-blind, placebo-controlled study. *Curr Alzheimer Res* **4**, 81-93.

[219] De Deyn PP, Katz IR, Brodaty H, Lyons B, Greenspan A, Burns A (2005) Management of agitation, aggression, and psychosis associated with dementia: A pooled analysis including three randomized, placebo-controlled double-blind trials in nursing home residents treated with risperidone. *Clin Neurol Neurosurg* **107**, 497-508.

[220] Schneider LS, Dagerman K, Insel PS (2006) Efficacy and adverse effects of atypical antipsychotics for dementia: Meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry* **14**, 191-210.

[221] Kurlan R, Cummings J, Raman R, Thal L (2007) Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. *Neurology* **68**, 1356-1363.

[222] Tariot PN, Schneider LS, Cummings J, Thomas RG, Raman R, Jakimovich LJ, Loy R, Bartocci B, Fleisher A, Ismail MS (2011) Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. *Arch Gen Psychiatry* **68**, 853-861.

[223] Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN, Mitan SJ, Kadam DL, Sanger TM, Feldman PD (2000) Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease

in nursing care facilities: A double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* **57**, 968-976.

[224] Ballard C, Cream J (2005) Drugs used to relieve behavioral symptoms in people with dementia or an unacceptable chemical cosh? Argument. *Int Psychogeriatr* **17**, 4-12.

[225] Rosenberg PB, Drye LT, Porsteinsson AP, Pollock BG, Devanand DP, Frangakis C, Ismail Z, Marano C, Meinert CL, Mintzer JE, Munro CA, Pelton G, Rabins PV, Schneider LS, Shade DM, Weintraub D, Newell J, Yesavage J, Lyketsos CG; CitAD Research Group (2015) Change in agitation in Alzheimer's disease in the placebo arm of a 9-week controlled trial. *Int Psychogeriatr* **27**, 2059-2067.

[226] Porsteinsson AP, Keltz MA, Smith JS (2014) Role of citalopram in the treatment of agitation in Alzheimer's disease. *Neurodegener Dis Manag* **4**, 345-349.

[227] Pollock BG, Mulsant BH, Rosen J, Mazumdar S, Blakesley RE, Houck PR, Huber KA (2007) A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. *Am J Geriatr Psychiatry* **15**, 942-952.

[228] Pollock BG, Mulsant BH, Rosen J, Sweet RA, Mazumdar S, Bharucha A, Marin R, Jacob N, Huber KA, Kastango KB (2002) Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. *Am J Psychiatry* **159**, 460-465.

[229] Olin JT, Fox LS, Pawluczyk S, Taggart NA, Schneider LS (2001) A pilot randomized trial of carbamazepine for behavioral symptoms in treatment-resistant outpatients with Alzheimer disease. *Am J Geriatr Psychiatry* **9**, 400-405.

[230] Maidment ID, Fox CG, Boustani M, Rodriguez J, Brown RC, Katona CL (2008) Efficacy of memantine on behavioral and psychological symptoms related to dementia: A systematic meta-analysis. *Ann Pharmacother* **42**, 32-38.

[231] Wang HF, Yu JT, Tang SW, Jiang T, Tan CC, Meng XF, Wang C, Tan MS, Tan L (2015) Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: Systematic review with meta-analysis and trial sequential analysis. *J Neurol Neurosurg Psychiatry* **86**, 135-143.

[232] Fox C, Crugel M, Maidment I, Auestad BH, Coulton S, Treloar A, Ballard C, Boustani M, Katona C, Livingston G (2012) Efficacy of memantine for agitation in Alzheimer's dementia: A randomised double-blind placebo controlled trial. *PLoS One* **7**, e35185.

[233] Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, Burns A, Dening T, Findlay D, Holmes C (2012) Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Eng J Med* **366**, 893-903.

[234] Garre-Olmo J, López-Pousa S, Vilalta-Franch J, de Gracia Blanco M, Vilarrasa AB (2010) Grouping and trajectories of neuropsychiatric symptoms in patients with Alzheimer's disease. Part II: Two-year patient trajectories. *J Alzheimers Dis* **22**, 1169-1180.

[235] Ballard C, O'Brien J, Coope B, Fairbairn A, Abid F, Wilcock G (1997) A prospective study of psychotic symptoms in dementia sufferers: Psychosis in dementia. *Int Psychogeriatr* **9**, 57-64.

[236] Van Leeuwen E, Petrovic M, van Driel ML, De Sutter AI, Vander Stichele R, Declercq T, Christiaens T (2018) Discontinuation of long-term antipsychotic drug use for behavioral and psychological symptoms in older adults aged 65 years and older with dementia. *J Am Med Dir Assoc* **19**, 1009-1014.

[237] Declercq T, Petrovic M, Azermai M, Vander Stichele R, De Sutter AI, van Driel ML, Christiaens T (2013) Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia. *Cochrane Database Syst Rev* **28**, CD007726.

[238] Patel SN, Lau-Cam CA (2017) The Effect of taurine and its immediate homologs on diabetes-induced oxidative stress in the brain and spinal cord of rats. *Adv Exp Med Biol* **975**, 337-351.

[239] Devanand D, Mintzer J, Schultz SK, Andrews HF, Sultzer DL, de la Pena D, Gupta S, Colon S, Schimming C, Pelton GH (2012) Relapse risk after discontinuation of risperidone in Alzheimer's disease. *N Eur J Med* **367**, 1497-1507.

[240] McCurry SM, Vitiello MV, Gibbons LE, Logsdon RG, Teri L (2006) Factors associated with caregiver reports of sleep disturbances in persons with dementia. *Am J Geriatr Psychiatry* **14**, 112-120.

[241] Valembois L, Oasi C, Pariel S, Jarzebowski W, Lafuente-Lafuente C, Belmin J (2015) Wrist actigraphy: A simple way to record motor activity in elderly patients with dementia and apathy or aberrant motor behavior. *J Nutr Health Aging* **19**, 759-764.

[242] Cummings J (2021) New approaches to symptomatic treatments for Alzheimer's disease. *Mol Neurodegener* **16**, 2.

[243] Sultzer DL, Davis SM, Tariot PN, Dagerman KS, Lebowitz BD, Lyketsos CG, Rosenheck RA, Hsiao JK, Lieberman JA, Schneider LS (2008) Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: Phase 1 outcomes from the CATIE-AD effectiveness trial. *Am J Psychiatry* **165**, 844-854.

[244] Paleacu D, Barak Y, Mirecky I, Mazeh D (2008) Quetiapine treatment for behavioural and psychological symptoms of dementia in Alzheimer's disease patients: A 6-week, double-blind, placebo-controlled study. *Int J Geriatr Psychiatry* **23**, 393-400.

[245] Brodaty H, Ames D, Snowdon J (2003) A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry* **64**, 134-143.

[246] Deberdt WG, Dysken MW, Rappaport SA, Feldman PD, Young CA, Hay DP, Lehman DL, Dossenbach M, Degenhardt EK, Breier A (2005) Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. *Am J Geriatr Psychiatry* **13**, 722-730.

[247] De Deyn P, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PL, Eriksson S, Lawlor B (1999) A randomized trial of risperidone, placebo, and haloperidol in behavioral symptoms of dementia. *Neurology* **53**, 946-955.