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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, delusions, dementia, 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 in 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 each 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 the 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 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 mutation, 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 FTD-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 [^{18}F]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 (^{1}H-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- 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 Halvs 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 Halor Placebo in reducing psychotic symptoms

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 = 94	Qtp = 100 mg 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 will be the use of diagnostic criteria, and the use of mechanistically relevant biomarkers in carefully designed trials.

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DESCRIPTION OF AUTHOR'S ROLES

The different sections of this paper were initially drafted by authors expert in that particular fields as follows: Definitions of symptoms: Marie-Andrée Bruneau, Fabrizia d'Antonio, Sanjeev Kumar, Ramit Ravona-Springer; Prevalence and clinical relevance: Zahinoor Ismail, Fabricio Oliveira; Neurobiology and biomarkers: Byron Creese, Corinne Fisher, Jennifer Gatchel; Assessments instruments: Ganesh Babulal, William McGeown; Huali Wang;

Non-pharmacological interventions: Moyra Mortby, Arturo Pereiro, Hillary Rouse; Pharmacological treatment: Nicolas Núñez, Ramit Ravona-Springer. Luis Agüera-Ortiz and Krista Lanctôt drafted the introduction, general discussion, and conclusions and revised and coordinated the different drafts of the manuscript. All authors contributed to the revision and drafting of the final manuscript.

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