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Review Article

# Recommendations for management and future investigation of psychosis in neurodegenerative disease: Findings from the International Psychogeriatric Association (IPA) working group

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ABSTRACT

*Introduction:* Psychosis is frequently observed in patients with neurodegenerative disease and may precede onset of cognitive symptoms. Additionally, the presence of psychosis in neurodegenerative disease is often associated with adverse effects including increased progression of cognitive decline and conversion to dementia, increased caregiver burden, and increased rates of placement in long-term care. Moreover, existing pharmacological treatments, which consist principally of off-label antipsychotic medications, may be associated with increased risk of harm, making management of symptoms challenging.

*Objective:* We review recent advances in the field of psychosis in neurodegenerative disease, including advances in clinical criteria, biomarkers (neuroimaging, pathology, and genomic and epigenomics), and treatments.

*Method:* Under the direction of the International Psychogeriatric Association (IPA), a task force comprised of experts in the field of psychosis in neurodegenerative disease was convened. An in-person meeting was organized in September 2024, coincident with the annual IPA Congress. The task force undertook a review of the literature

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in the areas of clinical care, biomarkers, and treatment, from which key recommendations for the management and future investigation of psychosis in neurodegenerative disease were derived.

*Results:* It was concluded that psychosis in neurodegenerative disease has a characteristic phenomenology that despite sharing some features with schizophrenia spectrum psychotic disorders, may differ in other clinically meaningful aspects. Etiopathogenesis based on biomarker, genomic, and treatment studies may differ to some extent among neurodegenerative diseases. There is emerging evidence supporting the use of prescriptive non-pharmacological (WHELD intervention) and novel pharmacological (pimavanserin, muscarinic agonists) approaches in the treatment of psychosis in neurodegenerative disease.

*Conclusion:* Future directions include the need for the implementation of evidence-based nonpharmacological treatments consistent with the aims of precision medicine, further investigation into novel pharmacological agents, mapping specific psychotic symptoms to specific biomarkers, and further exploration of the link between psychosis in neurodegenerative disease and other late-life psychoses.

## Background

In the context of neurodegenerative disease, cognitive decline is nearly always accompanied by neuropsychiatric symptoms (NPS), which are disturbances in emotional experience and behaviour [1]. Psychosis, consisting of delusions and hallucinations, is a common and consequential NPS. In addition to being distressing to people with neurodegenerative conditions, it is associated with greater caregiver distress, accelerated cognitive and functional decline, and higher rates of institutionalization and mortality [2]. Psychosis has been studied extensively in Alzheimer's disease (AD), in which its prevalence during the course of illness is at least 40 %, but it occurs at varying frequencies in dementia of all types [3]. Psychosis may also occur in advance of dementia at the preclinical (normal cognition) or prodromal (mild cognitive impairment [MCI]) stages of a neurodegenerative disease [3]. Importantly, the prevalence of delusions and hallucinations specifically can differ depending on dementia etiology [4].

Psychosis occurring within the context of neurodegenerative disease is sometimes referred to as dementia-related psychosis (DRP), a term of convenience to distinguish it from psychosis due to other causes, including early- or late-onset primary psychiatric disorders (e.g., schizophrenia and bipolar disorder). Some degree of shared etiopathology may exist between primary psychosis and DRP, but the existing research supports focusing on psychosis separately in each type of dementia, as there is evidence of potentially different mechanisms and treatment responses depending on dementia type [3]. In the context of AD, neurodegenerative disease biomarkers have advanced our ability to detect neurodegeneration early, more accurately determine dementia etiology, and more selectively administer disease-targeted therapies for patients [5]. The association between such biomarkers and psychosis in AD is as yet uncertain and represents an intriguing area for further research given that psychosis is often linked to accelerated cognitive decline [2].

Current strategies for treating psychosis in AD and other dementias are limited, though there is a promising pipeline of potential new therapies. Non-pharmacological interventions, while effective for other NPS such as agitation, lack evidence for treating psychosis specifically, highlighting a key research gap [6]. Pharmacological treatment has been influenced by the standardized treatment of psychosis in other psychiatric disorders, in particular patients with schizophrenia, with antipsychotics being the cornerstone of therapy. However, the use of medications originally developed for schizophrenia and bipolar disorder neglects the unique pathophysiology of psychosis in different dementias. Perhaps unsurprisingly, then, antipsychotics have demonstrated limited benefit in DRP while carrying considerable risks, with evidence of small treatment benefits coming from meta-analyses of clinical trials for the treatment of AD psychosis [7]. Despite this, antipsychotics are routinely prescribed, in part due to lack of other pharmacological or non-pharmacological treatment options.

There have been three recent innovations in the field of DRP that warrant a re-evaluation of current clinical practices. First, revised criteria have been developed to acknowledge that DRP has some characteristic phenomenology and may occur in advance of cognitive decline. Second, new advances in biomarkers and genomics have prompted investigation into the pathophysiological overlap between late-life psychosis and neurodegeneration. Third, emerging treatments with novel mechanisms of action and more limited side effects have led to renewed optimism for therapeutic interventions for psychosis in AD and synuclein dementias.

In response to these innovations as well as new developments in other related NPS, the International Psychogeriatric Association (IPA) convened a task force to bring experts in the field of DRP together. This paper is the result of that effort and it outlines new clinical recommendations for the management of DRP based on the latest available evidence and consensus of experts in the field.

## Methods

A meeting was held with key opinion leaders in science and industry to identify important papers and findings that inform our current understanding of DRP. This meeting occurred in association with the IPA Congress in Buenos Aires on September 28th and 29th of 2024. The initiative was led by Drs. Mary Sano, Jeffrey Cummings, and Jacobo Mintzer, with co-chairs for the psychosis subgroup (Drs. Corinne Fischer and Clive Ballard) selected in June 2024. Similar groups were formed for agitation, apathy, and depression. The psychosis group comprised experts in neurobiology (Dr. Byron Creese), non-pharmacological interventions (Joanne McDermid), clinical features (Drs. Zahinoor Ismail, Dilip Jeste, and Manabu Ikeda), industry (Victor Abler and Dr. Sanjeev Pathak), and advocacy (Susan Peschin), along with trainees (Dr. Andrew Namasivayam and Kathryn Mills). There was an initial virtual meeting prior to the in-person meeting at which input was sought from members both within and outside of the group. The focus of day 1 was to summarize recent innovations in the field of DRP while day 2 focused on generating key recommendations.

## Results

### *Diagnosis – criteria and phenomenology*

Jeste and Finkel, focusing specifically on AD, originally published diagnostic criteria for DRP in 2000 [8]. The syndrome was defined as delusions and/or hallucinations that occur in the context of clinically diagnosed AD dementia and after the onset of dementia symptoms. The IPA recently led a revision of these criteria in 2020 to extend them to non-AD dementias, account for the association between DRP, depression and agitation, and reflect the emerging evidence that psychosis can occur in MCI [2].

Phenomenologically, DRP differs from psychotic symptoms seen in schizophrenia-spectrum psychotic disorders (SSPD) [5]. Misidentification delusions (e.g., mirror sign and TV sign) more frequently occur in DRP compared with SSPD, and persecutory delusions are typically less bizarre and complex. Delusions of theft and infidelity are seen more in DRP than in SSPD [3]. Additionally, there is a higher prevalence of visual hallucinations in DRP relative to SSPD, in which auditory hallucinations predominate. Evidence also suggests that hallucinations and

delusions in dementia are more transient than in SSPD, except in synuclein dementias where visual hallucinations are intense and persistent [9,10]. Moreover, psychotic symptoms in SSPD are often functionally debilitating, whereas in DRP, symptoms may be milder and less compromising in some individuals and may wane as cognitive decline progresses.

Along with other advances in the field, the recognition of phenomenological differences between DRP and psychosis in other psychiatric conditions spurred the formulation of new research criteria for psychosis in AD. The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) proposed these criteria, which complement the IPA clinical criteria, in 2020 [5]. In addition to including greater symptom specificity for psychosis in AD, the ISTAART framework suggests incorporating AD biomarkers, and accounts for psychosis occurring in the preclinical or prodromal stages of neurodegenerative disease as part of mild behavioural impairment (MBI). This is particularly important given the emerging literature showing that those with late-onset psychosis are at increased risk of subsequent cognitive impairment and incident dementia [11]. This at-risk population includes both those with MBI and those who have clinically defined psychiatric disorders (e.g., delusional disorder, very late-onset schizophrenia-like psychosis [VLOSLP], etc.). In addition to the ISTAART criteria for AD psychosis, research diagnostic criteria have been published for the prodromal phase of dementia with Lewy bodies (DLB), which recognizes a psychiatric-onset type often characterized by late-onset psychosis [12].

## *Biomarkers for DRP*

### *Neuroimaging*

Functional and structural imaging studies have been conducted to identify associations between specific neurocircuitry and DRP, again with most research done in AD [13]. Though a single neuroanatomical locus has yet to be identified, several single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies show reduced cerebral blood flow and metabolism in the right frontal and temporal lobes in people with AD and psychosis (AD + P) compared to those without psychotic symptoms (AD-P) [13]. Additionally, functional magnetic resonance imaging (fMRI) studies have investigated the potential etiological role of the default mode network (DMN) in AD psychosis. Two such studies, using a composite measure of psychosis, found no correlation with DMN activity [14,15]. In contrast, another study found that delusions specifically were associated with decreased DMN activity [16]. Relative to functional imaging studies, computerized tomography and MRI studies have yielded more varied results [13]. This may be because atrophy in different interconnected areas within a functional brain network might all lead to psychosis, or there may be a failure to account for overlapping NPS and genetic heterogeneity.

A small number of molecular imaging studies have provided insights into the biological mechanisms underlying DRP. One study compared the uptake of the PET ligand flortaucipir, which binds to aggregated tau filaments, between AD + P and AD-P cohorts [17]. Those with psychosis had increased ligand uptake in the frontal, medial temporal, and occipital cortices relative to those without psychosis. Other molecular imaging studies have revealed neurotransmitter systems involved in DRP. One showed increased striatal dopamine (D2/D3) receptor availability in AD patients with delusions versus those without delusions [18]. The cholinergic system has been implicated in DLB, with one SPECT study finding that relative to controls there was increased nicotinic α4β2 receptor binding in the occipital lobes of DLB subjects, especially in those with a recent history of visual hallucinations [19]. In PD, a study found increased serotonin 5-HT2A receptor binding in the visual processing areas of PD patients with visual hallucinations compared to those without [20], ultimately leading to the development of pimavanserin, which targets the 5-HT2A receptor and is effective for PD psychosis.

### *Pathology*

While the key role of pathological biomarkers in diagnosing AD has recently been established, relatively little is known about how such biomarkers might relate to DRP. Tau pathology has been most consistently implicated in AD psychosis, with several postmortem studies demonstrating an association with elevated phosphorylated tau (p-tau) in the dorsolateral prefrontal cortex (DLPFC) [21,22], and one in vivo study showing an association with increased cerebrospinal fluid (CSF) total tau [23]. There is evidence of a potential sex-based difference, with p-tau being a stronger predictor of psychosis among women and alpha-synuclein being a stronger predictor among men [22]. Most recently, a cohort study of patients with either MCI or AD dementia found that those with psychosis, whether present at baseline or developing later, exhibited higher plasma levels of p-tau than those without psychosis [24]. Aside from tau, studies have found associations between amyloid pathology and psychosis in individuals who are cognitively asymptomatic or have MCI [25,26]. Other studies have demonstrated links between DRP and both Lewy body and vascular pathology [27,28]. In the FTD-C9ORF72 genetic form of FTD, psychotic symptoms have been shown to be related to TAR DNA-binding protein 43 (TDP-43) pathology [29]. One retrospective study of patients with autopsy-confirmed frontotemporal lobar degeneration showed that delusions occurred more frequently in the those with TDP-43 compared to tau pathology [4].

Some studies have implicated frontotemporal muscarinic receptor density in AD psychosis [30], and reduced acetylcholinesterase activity has been reported as a specific association of hallucinations [31]. Similarly, there is evidence showing an association between the severity of cholinergic loss and visual hallucinations, and a relationship between altered muscarinic M2 and M4 receptors and delusions in people with DLB [32,33]. These findings suggest that cholinergic denervation and altered muscarinic binding are likely involved in psychosis in AD and DLB [30].

### *Omics*

Genetic factors are likely to contribute to the development of DRP, and this has already been demonstrated in AD psychosis specifically [34]. Early familial studies suggested AD psychosis has a heritability of 61 % [34], while a 2021 genome-wide association study (GWAS) estimated heritability attributable to common single nucleotide polymorphisms (SNPs) to be 18–31 % (depending on the method used), which is similar to the estimate for schizophrenia [35]. The same GWAS identified the first two risk loci for psychosis in AD; one, located in *ENPP6*, was associated with an increased risk, while the other, located in *SUMF1*, was associated with a decreased risk [35], though replication and functional characterisation are needed to establish whether these point towards druggable targets. A subsequent GWAS—using a subset of participants from the prior GWAS—highlighted that psychosis and affective symptoms (depression, anxiety, and/or irritability) in AD may be twice as common as psychosis alone [36]. This genetic support for a link between psychosis and affective symptoms is corroborated by clinical data and suggests a possible distinct treatment target [37]. Additionally, the apolipoprotein E ε4 (*APOE4)* gene has been associated with increased risk of psychosis in AD [35]. Evidence suggests that the risk conferred by this allele may be stronger in females, though this finding was limited to a pathological cohort [38]. In terms of molecular mechanisms, an epigenome-wide association study (EWAS) comparing methylation in AD + P and AD-P groups found that two differentially methylated genes (*TBX15* and *WT1*) were linked to AD pathophysiology [39]. In the largest EWAS to date, a network of co-methylated genes in the DLPFC enriched for synaptic pathways and in excitatory and inhibitory neurons was linked to AD psychosis in two independent cohorts [40]. Consistent with clinical observations suggesting a degree of overlapping phenomenology, there is evidence from GWAS and molecular genetic studies of mechanistic overlap between psychosis in AD, depression, and schizophrenia. In the aforementioned GWAS, there was

a genetic correlation between psychosis in AD and depressive symptoms [35]. While there was no evidence of genetic correlation with schizophrenia, other studies have reported links. One study showed that the polygenic risk score for schizophrenia (a calculated value reflecting the number and effect sizes of schizophrenia risk alleles carried) was higher in AD + P subjects than AD-P ones [41]. Moreover, the aforementioned EWAS found that SNPs influencing the methylation of genes linked to AD psychosis overlapped with SNPs associated with schizophrenia, providing evidence of shared biological mechanisms [40].

Transcriptomic and proteomic studies have also offered molecular insights into psychosis in AD. A transcriptome-wide analysis of the anterior cingulate cortex of AD subjects found a unique signature of gene expression for psychosis compared to other NPS domains, though with high overlap with agitation [42]. In another transcriptome analysis focused on the DLPFC, there was a 9 % reduction in excitatory neurons in AD + P patients relative to AD-P [43]. The DLPFC was also evaluated in a proteomic study that compared the post-synaptic density proteome among an AD + P cohort, an AD-P cohort, and cognitively normal controls [44]. There was a significant global reduction in protein levels in the AD + P group relative to the other two groups, particularly for proteins involved in maintaining dendritic spine structure, and the reduction could be reversed with an existing drug. Though promising, most of the omics studies have been conducted in bulk tissues; future spatial or single-cell omics analyses are warranted as they may yield more specific insights. The DLPFC is likely to be a key region of focus for AD psychosis since it has been shown etiological relevance across imaging, pathological, and omics studies.

## Treatment

### Non-pharmacological

Guidelines routinely recommend non-pharmacological interventions for DRP [45], and the relatively high rate of placebo responses in trials of antipsychotic medications for the treatment of AD-related psychosis suggests that non-pharmacological interventions may be effective [46]. However, there is a dearth of research examining which specific interventions have efficacy. A 2019 international Delphi consensus highlighted this gap [6], and since then two randomized controlled trials (RCTs) in patients with dementia have been conducted to address this question. In the first, published in 2018, 847 participants were randomized to receive either treatment as usual or the Well-being and Health for People with Dementia (WHELD) intervention, which combines person-centred care training for staff, antipsychotic review, and Brief Psychosocial Therapy [47]. Those receiving WHELD demonstrated a significant reduction in agitation compared to those receiving treatment as usual, but no improvements in psychotic symptoms specifically. A secondary analysis of patients with psychosis at baseline (n = 163) also found no improvement in psychosis from the WHELD intervention, though it did improve agitation, apathy, and quality of life [48].

In the second RCT, published in 2019 and involving 21 participants, an intervention called the tailored activity program-outpatient (TAP-O) was compared to psychoeducation [49]. TAP-O involved an occupational therapist assessing patients' abilities and interests, prescribing tailored activities, and educating caregivers about dementia, NPS, and how to implement meaningful activities in the daily routine. Over the three-month study period, TAP-O was found to significantly reduce hallucinations, but not delusions, compared to psychoeducation. TAP-O was also superior for reducing several other NPS such as agitation and aggression, plus caregiver burden. The main limitations of the study were its small sample size and lack of control for multiple outcomes, but its findings suggest that personalized activities and family intervention for DRP are promising treatments. A prospective cohort study and a pilot RCT on these types of interventions also support the importance of personalized interventions [50,51]. Accordingly, in 2024, a second Delphi study that integrated a review of existing literature and international expert consensus resulted in three nominated non-pharmacological treatment options for DRP: 1) cognitive behavioural therapy (CBT); 2) family intervention/education; and 3) personalized activities/environmental/sensory interventions [52]. CBT was chosen due to its potential to modify the distorted thought patterns that lead to psychosis, but in practice would need to be tailored to a patient's cognitive ability.

Other important non-pharmacological treatment strategies for DRP include correcting hearing and vision impairment, optimizing and personalizing the environment, identifying and minimizing triggers for psychosis, music therapy [53], and targeting accompanying symptoms (e.g., anxiety, low mood).

### Pharmacological

*Antidepressants.* Citalopram has shown efficacy for psychosis in AD that is equivalent to that of risperidone, while producing fewer side effects [54]. A secondary analysis of the CitAD trial found that citalopram 30 mg daily significantly reduced delusions and hallucinations compared to placebo [55]. Notably, citalopram above 20 mg daily is not generally recommended in older adults due to concerns about QTc prolongation.

*Atypical antipsychotics.* Atypical antipsychotics are the most widely studied and prescribed class of medications for psychosis in AD. One analysis of Medicare claims from 2008 to 2016 showed that roughly 65 % of patients with DRP received an antipsychotic, most often an atypical one [56]. Despite their frequent use, evidence indicates that their risk-benefit profile is marginal. Most individual studies have not identified a significant advantage of antipsychotics compared to placebo [7], although a secondary analysis in the CATIE-AD study did suggest a small but significant improvement on the BPRS psychosis score for risperidone but not other antipsychotics, and there was no change in the clinical global impression of change at 12 weeks [57]. A recent Cochrane review found that typical antipsychotics may have a slight effect on psychosis while atypical antipsychotics have a negligible one, with both posing substantial risks [7]. Potential adverse events related to antipsychotics include sedation, hypotension, anticholinergic effects, extrapyramidal symptoms, falls, cerebrovascular adverse events, and death. In 2005 the US FDA issued a boxed warning that atypical antipsychotic use for behavioural disturbances in older patients with dementia increased the risk of death by 1.6–1.7 times [58]. The warning was later extended to include typical antipsychotics, which were noted to carry comparable or higher mortality risk [59]. This warning was based on short-term trials spanning 8–12 weeks, and a subsequent study showed increased mortality risk with antipsychotic use after 12 months [60]. In December 2024, the FDA and the Duke-Margolis Institute for Health Policy convened a public workshop to review the existing data and hear additional perspectives on the association between antipsychotics and mortality in dementia [61]. While this association was again demonstrated in a revised meta-analysis presented at the workshop, concerns were raised about the lack of specificity of the FDA's boxed warning, which does not consider variables such as the type of dementia, severity of dementia, type of NPS, presence of comorbidities, or specific antipsychotic drug used. The FDA proposed potential next steps, including obtaining patient-level data from existing studies to conduct an updated analysis that includes these additional variables. These considerations notwithstanding, the efficacy and safety concerns of atypical antipsychotics in DRP highlight the importance of investigating medications with alternative mechanisms of action.

*Pimavanserin.* Recent research has supported pimavanserin as an effective antipsychotic for treating psychosis in PD and potentially other dementias. Pimavanserin has a novel mechanism of action involving inverse agonism and antagonism at the 5-HT2A receptor without dopamine receptor blockade. In 2016 it was approved by the

FDA for psychosis in PD after demonstrating efficacy in a phase III clinical trial [62]. It was then studied in AD psychosis, with a phase II trial demonstrating its efficacy in treating psychosis at the 6-week primary endpoint, but not at the 12-week secondary one [63]. This led to a phase III, 6-month relapse prevention trial for the broader indication of DRP [64]. In this trial, 351 patients received open-label pimavanserin for 12 weeks, with 217 showing a positive response at the 8-week and 12-week time points. These positive responders were then randomized to either continue pimavanserin or be switched to placebo. During the 6-month double-blind phase, relapse of psychosis was significantly reduced in the pimavanserin group relative to placebo, and the trial was stopped early for efficacy. However, there was a differential treatment response, with individuals with PD dementia and psychosis having the most favourable outcome [65,66]. The results of the subgroup analyses are difficult to interpret as they were underpowered, but they have generated uncertainty about the benefits specifically in the AD group. A differential treatment response in PD versus AD psychosis suggests that pathophysiological drivers of DRP may differ based on the underlying neurodegenerative disease.

The initial trial leading to the approval of pimavanserin for PD psychosis included a subgroup of 46 patients with PD dementia who had a larger benefit than was seen in the trial overall [67]. This study and the results of the relapse prevention study provided strong evidence of pimavanserin's effectiveness for treating psychosis in PD dementia. The FDA subsequently expanded pimavanserin's approved indication to include psychosis in PD patients with (or without) dementia [68]. In clinical trials, pimavanserin has demonstrated a favourable safety profile relative to other antipsychotics, as it does not worsen parkinsonism or stroke risk, and only modestly prolongs QTc (~9 ms) [3,69]. As with other antipsychotics, the FDA issued a boxed warning for mortality risk with pimavanserin [3]. However, no significant excess mortality was reported in the two trials focusing on dementia [62,63], and the FDA completed a postmarketing review of adverse events that did not find any new safety concerns [3]. Notably, a long-term safety study in patients with PD psychosis showed that use of pimavanserin in combination with another atypical antipsychotic resulted in a threefold rise in serious adverse effects and a fourfold rise in deaths [70]. Therefore, atypical antipsychotics should be avoided in people taking pimavanserin.

*Muscarinic receptor agonists*. Xanomeline, an M1 and M4 receptor agonist, has potential therapeutic value in AD [71] and other dementias. In a 1997 study, it produced dose-dependent reductions in delusions and hallucinations, among other behavioural symptoms, in patients with AD [72]. When xanomeline is combined with trospium chloride, a nonselective muscarinic receptor antagonist that does not cross the blood-brain barrier, the peripheral cholinergic activity of xanomeline is neutralized. This has been shown to reduce the incidence and severity of adverse cholinergic effects from xanomeline [71]. In patients with schizophrenia, xanomeline-trospium was found to improve psychosis while being well tolerated over a 5-week clinical trial [73], leading to FDA approval for its use in this disorder. The FDA did not impose a boxed warning on the agent for mortality risk in older adults with DRP, suggesting that safety concerns are lower compared to atypical antipsychotics. There are three phase III clinical trials currently underway testing xanomeline-trospium in AD-related psychosis, two of which are expected to be completed in 2025 and the third in 2026 [71]. This agent may be a therapeutic option for patients with DRP, especially given its observed beneficial effects on cognition [73].

*Cholinesterase inhibitors*. A recent meta-analysis assessed the use of cholinesterase inhibitors in managing psychosis across 5 PD and 12 AD trials in which NPS were measured [74]. It found that cholinesterase inhibitors improved delusions and hallucinations, though the effect size was small. There are no RCTs evaluating the effect of cholinesterase inhibitors on DRP as a primary outcome. However, one study found that for AD patients who were not on psychotropics at the time of diagnosis, use of cholinesterase inhibitors was associated with lower rates of antipsychotic initiation [75].

## Discussion

Our enhanced understanding of the distinct phenomenology of psychosis in AD and other dementias has significant clinical implications. First, higher symptom specificity can lead to more accurate diagnosis and appropriate choice of treatment. This is particularly important as late-onset psychotic symptoms may portend cognitive or functional decline. Clinicians are encouraged to use the IPA clinical criteria and be attentive to characteristic symptoms (e.g., delusions of theft or visual hallucinations) that suggest a neurodegenerative etiology. Second, it is crucial to explain the phenomenology of DRP to patients and caregivers, who may associate psychosis with severe mental illness such as schizophrenia. Communicating that DRP follows a highly individual course, ranges in severity, and is often transient can alleviate undue distress about prognosis. Finally, providing more precise information about the phenomenology of DRP to other healthcare providers, such as family physicians, can improve the care of their patients. For instance, if healthcare providers are aware that DRP often does not persist, they may be more likely to re-evaluate the continual use of burdensome medications like antipsychotics.

There is a need for future studies to elaborate the relationship between neurodegenerative disease biomarkers and psychosis in specific dementias. Given that both pathological and molecular imaging studies have demonstrated a link between AD psychosis and tau pathology, further research is warranted to elucidate this link and its potential to produce a clinically useful biomarker. Co-pathology with alpha-synuclein and TDP-43 occurs commonly in AD and may contribute to differential phenomenology and treatment responsiveness within AD psychosis [76]. Likewise, different neurodegenerative subtypes may present with unique disease-associated phenomenology and therapeutic substrates. The *APOE4* gene, which has been shown in some studies to be an important risk factor for psychosis in people with AD, and whose effects may be accentuated among women [77], merits further research. The association between late-onset psychosis—whether related to clinically defined psychiatric disorders or MBI —and hastened conversion to dementia suggests the importance of further biomarker studies of these subgroups. VLOSLP, which likely has overlap with MBI psychosis [3], is of particular interest as it is associated with substantially increased risk of dementia, especially shortly after its diagnosis [78]. Future research illuminating the relationship between late-onset psychosis and neurodegeneration can potentially improve early detection of dementia. Lastly, the conceptualization of psychosis as a unitary construct spanning early-onset, late-onset, and neurodegenerative time courses warrants exploration.

Management of psychosis in AD, synuclein dementias, and other dementias should begin by determining whether treatment is necessary. This will be based on how much distress and/or impairment the symptoms cause for the patient, as well as safety concerns (danger to self or others). Obtaining caregiver input at this stage is essential. Treatment can be considered even for mild psychosis given that symptoms may progress in severity over time [79]. If treatment is deemed necessary and symptoms are mild, evidence-based non-pharmacological interventions are recommended as first-line treatment, though our review revealed scant literature on the subject. Our current recommendations are adopted from the aforementioned 2024 Delphi consensus paper that highlighted cognitive-behavioural therapy (CBT) and the WHELD/Brief Psychosocial Therapy program as promising evidence-based interventions. CBT requires tailoring to the patient's cognitive level and may be challenging to implement if there is a lack of access to therapists. One strength of the WHELD/Brief Psychosocial Therapy program is that it is structured and manualized, allowing for

replicability. High fidelity to current and future evidence-based programs is essential to maximize efficacy. This in turn will lead to decreased need for psychotropic medications which often have adverse effects.

However, when symptoms are severe or if there are safety concerns, pharmacological treatment is recommended. Ideally, a combination of non-pharmacological and pharmacological interventions would be deployed, particularly because the effect sizes for existing medications are modest. Given the potential adverse effects of antipsychotics, prescribers are advised to use these medications judiciously, assess for emergence of adverse effects within one week of initiation and at every follow-up appointment, and re-evaluate the need for continued use of the medication every three months. Where possible, deprescribing (either discontinuing or reducing the dose of) antipsychotics is recommended and has been shown to be feasible without worsening NPS or increasing prescriptions of other psychotropics [80]. Extra caution should be taken in patients with PD dementia and DLB who have exquisite sensitivity to antipsychotics. Fortunately, medications with novel mechanisms of action have recently shown promise in treating DRP while having fewer risks. Pimavanserin has been shown to be effective and relatively safe in treating psychosis in PD dementia, and studies on novel therapies such as muscarinic agonists (e.g., xanomeline-trospium) are underway. Notably, however, there is little high-quality evidence for the pharmacological treatment of psychosis in FTD, vascular dementia, and MCI. These represent emerging avenues of exploration.

## Conclusion and future directions

Based on the discussion above, we propose the following recommendations:

1. **Operationalizing Evidence-Based Practices**
   There is a need to implement evidence-based and operationalized non-pharmacological interventions as first-line treatments in clinical practice. These interventions should be tailored to individual patient needs and the unique characteristics of each dementia subtype.
2. **Advancing Clinical Trials**
   Robust clinical trials should focus on:
   - Novel targeted non-pharmacological therapies, such as cognitive behavioural therapy specifically adapted for psychosis in dementia.
   - Promising pharmacological treatments, including 5-HT2A inverse agonists/antagonists and muscarinic agonists.
3. **Linking Phenomenology to Biomarkers**
   Efforts should aim to map specific psychotic symptoms, such as delusions and hallucinations, to distinct biomarkers and underlying biological mechanisms. Applied across the cognitive continuum, this approach can expand understanding of late-life psychosis and facilitate personalized treatment strategies.
4. **Exploring the Prodromal Phase**
   The link between very late-onset schizophrenia-like psychosis (VLOSLP) and dementia progression underscores the importance of studying psychosis as a potential prodromal feature of neurodegenerative disease. Research should explore the role psychosis might play in early detection and intervention of neurodegeneration [11].
5. **Targeting Phosphorylated Tau**

Emerging evidence highlights phosphorylated tau as a critical biomarker and therapeutic target for psychosis in dementia. Preclinical studies should investigate its role in symptom onset and progression.

## CRediT authorship contribution statement

**Andrew A. Namasivayam:** Writing – review & editing, Writing – original draft, Conceptualization. **Corinne Fischer:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Victor Abler:** Writing – review & editing, Conceptualization. **Byron Creese:** Writing – review & editing, Conceptualization. **Maria Paula Gastiazoro:** Writing – review & editing, Conceptualization. **Adriana P. Hermida:** Writing – review & editing, Conceptualization. **Manabu Ikeda:** Writing – review & editing, Conceptualization. **Zahinoor Ismail:** Writing – review & editing, Conceptualization. **Dilip V. Jeste:** Writing – review & editing, Conceptualization. **Joanne McDermid:** Writing – review & editing, Conceptualization. **Kathryn Mills:** Writing – review & editing, Conceptualization. **Sanjeev Pathak:** Writing – review & editing, Conceptualization.**Susan Peschin:** Writing – review & editing, Conceptualization. **Anne Margriet Pot:** Writing – review & editing, Conceptualization. **Jacobo Mintzer:** Writing – review & editing, Conceptualization. **Mary Sano:** Writing – review & editing, Conceptualization. **Jeffrey Cummings:** Writing – review & editing, Conceptualization. **Clive Ballard:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

## Declaration of Competing Interest

The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article. This applies to Dilip Jeste and Corinne Fischer. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andrew Namasivayam has no competing interests to report. Corinne Fischer reports receiving grant funding from the following organizations over the last five years: NIH, NIA, CIHR, CCNA, the Hilary and Galen Weston Foundation, ADDF, Brain Canada, Cortexyme, Vielight Inc, Genetech, Hoffman La Roche, Novo Nordisk. Clive Ballard reports receiving personal fees from Acadia, Johnson & Johnson, Janssen, Bristol-Myers Squibb, Eli Lilly, TauRx, Novo Nordisk, BioXcel Therapeutics, Orion, Addex, AARP, GW Pharmaceuticals, Roche, Sunovion, Suven, and Biogen and grants from Novo Nordisk and ReMYND. Jacobo Mintzer reports financial support was provided by International Psychogeriatric Association. Jacobo Mintzer reports a relationship with Axsome Therapeutics Inc that includes: board membership. Jacobo Mintzer reports a relationship with National Institute on Aging that includes: funding grants. Jacobo Mintzer reports a relationship with AARP Global Council on Brain Health that includes: board membership and travel reimbursement. Jacobo Mintzer reports a relationship with Acadia Pharmaceuticals Inc that includes: consulting or advisory and travel reimbursement. Jacobo Mintzer reports a relationship with Alliance for Aging Research that includes: board membership. Jacobo Mintzer reports a relationship with Alzheimer's Association that includes: funding grants. Jacobo Mintzer reports a relationship with ACTC that includes: board membership and funding grants. Jacobo Mintzer reports a relationship with Alzheimer's Therapeutic Research Institute that includes: board membership and funding grants. Jacobo Mintzer reports a relationship with BioPharma Connex that includes: board membership and equity or stocks. Jacobo Mintzer reports a relationship with Exciva that includes: consulting or advisory. Jacobo Mintzer reports a relationship with Genetec Inc that includes: consulting or advisory. Jacobo Mintzer reports a relationship with Lunbeck LLC that includes: consulting or advisory. Jacobo Mintzer reports a relationship with NeuroQuest Ltd. that includes: board membership and equity or stocks. Jacobo Mintzer reports a relationship with Otsuka America Pharmaceutical Inc that includes: consulting or advisory. Jacobo Mintzer reports a relationship with Praxis Bioresearch that includes: consulting or advisory. Jacobo Mintzer reports a relationship with Recruitment Partners that includes: board membership and equity or stocks. Jacobo Mintzer reports a relationship with Sunnybrook Research Institute that includes: consulting or advisory. Jacobo Mintzer reports a relationship with Suven Life Sciences Limited that includes: funding grants. Jacobo Mintzer reports a relationship with Technology Accelerator Company that includes: consulting or

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