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Relapse in Dementia-related Psychosis and Clinical Decisions

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Abstract: Patients with dementia can experience hallucinations and delusions because of their underlying neurodegenerative condition, a syndrome known as dementia-related psychosis. Dementia-related psychosis contributes to morbidity and mortality among patients with dementia and increases the burden on caregivers and the health care system. With no pharmacological treatment currently approved in the United States for this condition, patients are often treated off-label with antipsychotics. Though typical and atypical antipsychotics have demonstrated variable to modest efficacy in dementia-related psychosis, serious safety concerns arise with their use. Accordingly, clinical and Centers for Medicare & Medicaid Services guidelines recommend trying antipsychotics only when other therapies have failed and encourage treatment discontinuation of antipsychotics after 4 months to assess whether ongoing therapy is needed. Discontinuation of effective antipsychotic treatment, however, may increase the risk for relapse of symptoms and the associated morbidities that accompany relapse. A randomized medication withdrawal clinical trial design allows assessment of relapse risk after discontinuation and can provide initial information on longer-term safety of therapy for dementia-related psychosis. Given the substantial unmet need in this condition, new, well-tolerated therapies that offer acute and sustained reduction of symptoms while also preventing recurrence of symptoms of psychosis are critically needed.

Key Words: antipsychotic, delusions, dementia, hallucinations, psychosis, recurrence, relapse

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Dementia is a syndrome characterized by a significant decline in cognitive function that interferes with activities of daily living. This condition may be caused by a number of underlying neurodegenerative conditions, such as Alzheimer dementia (AD), dementia with Lewy bodies, frontotemporal dementia, Parkinson disease, and vascular dementia, which often overlap and occur simultaneously.[1] In addition to cognitive decline, patients with dementia often experience neuropsychiatric symptoms (NPS),[2,3] such as depression, psychosis (hallucinations and delusions), hyperactivity, agitation, and problems sleeping.[2–4] Occurrence of NPS is common, with most patients experiencing NPS at some point during the course of their dementing disease. These symptoms may occur before, during, or after the diagnosis of dementia.[4–6]

Dementia-related psychosis is defined by the presence of hallucinations and/or delusions that are the result of the underlying neurodegenerative dementia.[7–9] Psychosis is prevalent across all types of dementia, although prevalence rates and specific clinical presentations differ by underlying etiology.[7] One study reported an annual incidence of psychotic symptoms of 47% in patients with dementia followed up at monthly intervals.[10] Hallucinations and delusions may be persistent or episodic, but even when episodic, recurrence is common and frequent.[9–11]

Psychosis can result from a common underlying neurobiological mechanism in patients with dementia.[12,13] While the exact mechanism is unknown, an imbalance of dopaminergic, serotonergic, gamma-aminobutyric acid (GABA)ergic, and glutamatergic signaling within an identified cortical-limbic pathway may drive hallucinations and delusions, regardless of any specific dementia diagnosis.[13] Further, though dementia can be caused by distinct underlying neuropathologies, many dementia patients never receive a more specific diagnosis. Even in those with a specific diagnosis, co-occurrence of multiple dementia pathologies is common.[14] Autopsy studies have revealed that more than half of patients with dementia with psychosis have mixed dementia pathologies.[14,15] Because of the co-occurrence of dementia pathologies and high prevalence of mixed dementias among patients with psychosis, clinical practice guidelines and consensus statements approach dementia-related psychosis as a single diagnostic entity and do not make distinctions in treatment recommendations based on underlying dementia etiology, except for avoiding or reducing the use of antipsychotics in dementia with Lewy bodies and Parkinson disease dementia.[9,16,17]

Psychosis in patients with dementia is associated with negative outcomes for the patient and a greater burden of disease than dementia without psychotic symptoms.[18–23] Longitudinal studies of patients with AD have demonstrated that hallucinations and/or delusions are associated with greater cognitive and functional decline,[23–26] institutionalization,[23] and mortality.[18,23] In patients with mild AD, the presence of certain symptoms of psychosis is associated with a shorter time to progression to severe AD and/or death.[18] Moreover, in patients with mild cognitive impairment, the presence of delusions is associated with a higher risk of progression to dementia because of AD.[27] Dementia-related psychosis also has negative consequences for the caregiver related to health, quality of life, and finances.[28]

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Currently, no pharmacological treatments are approved by the US Food and Drug Administration (FDA) to treat dementia-related psychosis. Typical and atypical antipsychotics are often used off label, usually at a low dose, to manage the symptoms of psychosis in dementia, but these medications come with significant risk-benefit concerns. In meta-analyses of the efficacy of second-generation antipsychotics in treating patients with dementia-related psychosis, minimal to modest efficacy was seen.[29,30] Most studies have examined the effects of antipsychotic treatment in patients with dementia-related psychosis over a relatively short period of 6 to 12 weeks,[29,31,32] and it is not clear whether the variable reduction in hallucinations and delusions observed shortly after treatment initiation is maintained over longer periods. In addition to the modest efficacy results, off-label antipsychotics are associated with substantial safety concerns in patients, including increased mortality, development and/or worsening of extrapyramidal symptoms, somnolence, falls, orthostatic hypotension, and metabolic syndrome.[30,33] Atypical and conventional antipsychotics are also associated with significant accelerations in cognitive decline in patients with dementia, which are believed to be associated with their potent antagonist activities at dopamine and acetylcholine receptors.[34–38] The significant risk of increased mortality in elderly patients with dementia-related psychosis is communicated in the prescribing information for all antipsychotics as a Boxed Warning.[39]

The American Psychiatric Association (APA) has provided guidelines that recommend limiting the nonemergency use of off-label antipsychotics in treating psychosis or agitation in patients with dementia.[16] These guidelines recommend addressing modifiable environmental and psychological factors first and implementing a comprehensive treatment plan that incorporates nonpharmacological alternatives. Because of the significant safety concerns associated with antipsychotic use in dementia patients, initiation of these medications is advised only in patients with symptoms that are severe, dangerous, and/or causing substantial distress, and should occur after reviewing the patient's response to nonpharmacological treatments. The medication should be tapered and withdrawn in patients whose symptoms do not respond after a 4-week trial. In patients whose symptoms do respond to an antipsychotic, to reduce the risk of associated adverse events, an attempt to taper and withdraw the medication should be made within 4 months of initiation unless the patient had experienced symptom relapse during prior attempts to taper their antipsychotic treatment. Patients should be monitored for signs of relapse during the tapering period on at least a monthly basis and for at least 4 months after medication discontinuation. The guidelines note that decisions related to tapering an antipsychotic and monitoring for recurrent symptoms will require clinical judgement. Use of quantitative measures, such as the Neuropsychiatric Inventory (NPI) and Brief Psychiatric Rating Scale (BPRS), and other structured approaches like keeping a log of target behaviors are recommended when monitoring patients tapering off antipsychotic treatment; however, specific criteria regarding recognition of relapse are not provided.

Here, we summarize the literature that underscores the importance of monitoring patients for signs of a relapse or impending relapse and the need for therapeutic options that both address initial symptoms and provide long-term maintenance to reduce the likelihood of recurrence. This review will address the concerns surrounding relapse after improvement of psychotic symptoms for patients with dementia-related psychosis and will establish the importance of long-term maintenance of efficacy with avoidance of relapse when treating dementia-related psychosis as an area of clinical focus for health care providers.

DEFINING RELAPSE

Although not well described in the context of dementia-related psychosis, the concept of relapse is familiar to clinicians working in other disease states. Relapse is a commonly used concept in oncology, where trials assessing drug impact on recurrence of disease (often represented by Kaplan–Meier curves) are prominent. In the central nervous system realm, other relapsing-remitting conditions commonly lead to a focus on relapse prevention. Relapse in patients with schizophrenia is defined as an acute psychotic exacerbation and is often associated with treatment discontinuation.[40] In this patient population, there is concern that relapse and the associated psychotic episodes may have negative neurobiological effects, leading to progression of the underlying disease and making treatment more challenging.[40] Thus, the goal of antipsychotic treatment in these patients is to treat acute symptoms and subsequently maintain long-term efficacy through prevention of additional relapses.[40] The European Medicines Agency guidelines for the treatment of schizophrenia now include the proportion of patients who relapse as a primary efficacy endpoint for long-term studies,[41] highlighting the importance of monitoring disease relapse rates when considering the most appropriate treatment plan to support long-term efficacy. In multiple sclerosis (MS), relapse has long been a critical clinical outcome measure for assessing treatment effectiveness. MS relapse is defined as an incidence of new neurological symptoms or worsening of old symptoms that follows a period of remission[42] and can occur on or off MS therapy. Although MS relapses are acute, patients may not completely recover, leading to disability accumulation over time.[43] A number of therapies are now available for treatment optimization in MS, and achieving a state free from relapse, as well as maintaining improvement with long-term treatment have become attainable goals for patients.[44]

Despite the common consideration of relapse in other disease states and the increased burden that hallucinations and delusions place on patients with dementia-related psychosis as well as on their caregivers, relapse in the context of dementia-related psychosis has not been consistently defined or investigated. To be considered a relapse, the recurrence of delusions and/or hallucinations in patients with dementia-related psychosis must be clinically meaningful and require further intervention, even if symptom severity does not reach the initial pretreatment level. The definition of "clinically meaningful" is subjective, and clinical trials often use a predetermined rate of change in psychosis score to define relapse, defined according to various scales, such as the NPI, Scale for the Assessment of Positive Symptoms (SAPS), and the Clinical Global Impression (CGI) Scale.[7] However, in real-world settings, the clinical significance of relapse may be determined primarily by the need for treatment with off-label therapies with significant liabilities and/or the extent to which hallucinations and delusions impact daily function and cause distress for the patient or caregiver.[22] For example, relief of distressing anxiety or suspiciousness related to a persistent hallucination might allow a patient to

remain at home.[16] Alternatively, a delusion about food being poisoned that leads a patient to avoid eating might not distress the patient but does impact care.

CURRENT CLINICAL CONSIDERATIONS

As there are no clinical practice guidelines defining relapse in dementia-related psychosis and criteria from clinical trials vary across studies,[45,46] clinicians currently largely rely on clinical judgment to evaluate patients and develop treatment plans. In chronic schizophrenia, more than half of patients and their caregivers reported that an onset of noticeable symptoms occurred at least 1 week before relapse,[45] including changes in thoughts, feelings, or behaviors noted even 2 to 3 weeks before relapse of psychosis.[47] Combining patient reports and observer interviews led to identification of 79% of impending relapse cases in the sample with schizophrenia.[48] Experiences such as anxiety, dysphoria, insomnia, poor concentration, and attenuated psychotic symptoms have been reported as early signs of relapse.[48,49] Studies offer variable conclusions about the value of these observations[40,47]; however, such early signs appear to be moderately effective as early indicators of relapse in schizophrenia, and researchers continue to pursue options for tracking such symptoms in clinical practice.[49] While the equivalent is not yet available for dementia-related psychosis, with more concrete clinical markers, clinicians could identify patients with impending relapse and initiate earlier treatment, thereby reducing the impact of adverse outcomes often associated with exacerbation of psychotic symptoms in patients with dementia-related psychosis.

Although a standardized assessment of relapse in patients with dementia-related psychosis is needed, identification of relapse will have subjective elements. As symptoms increase, they may not immediately require treatment or cause distress, or equivalent psychotic symptoms may be distressing to one patient or caregiver but not to another. Clinicians are generally dependent on patients and caregivers to report the emergence of hallucinations or delusions in a previously well-controlled patient. Awareness and close follow-up among clinicians are ultimately crucial for ensuring that relapse is identified and managed promptly; this is essential in facilities where patients may reside with infrequent ongoing evaluation by physicians.

Identifying risk factors for relapse in dementia-related psychosis may be a useful supplement to clinical judgment. The severity and nature of a patient's initial presentation of psychosis may predict the likelihood of relapse.[50,51] For example, patients with dementia-related psychosis who exhibit severe NPS may be at a greater risk for relapse than those with less severe symptoms.[50,51] Likewise, one study that compared continuing to stopping neuroleptics in patients with dementia found that patients who began the trial with a greater initial NPI score benefited more from continuing treatment than those with a lower initial score.[51] In a secondary analysis of a trial conducted to evaluate relapse after withdrawal from risperidone,[52] relapse was predicted by severe versus mild hallucinations at baseline, particularly auditory hallucinations.[50] Considering these clinical characteristics may help identify patients likely to relapse, allowing for targeted monitoring and planning for treatment options.

Once either impending or acute relapse has been identified in a patient with dementia-related psychosis, clinicians must determine an appropriate course of action. A new risk-benefit analysis should determine whether retreatment is necessary for the patient. If newer therapies demonstrate long-term efficacy and safety, prompt initiation and long-term maintenance of therapy may be appropriate, reducing risk of relapse.

CLINICAL STUDIES OF RELAPSE IN DEMENTIA-RELATED PSYCHOSIS

Clinical trials testing the long-term efficacy of antipsychotics in patients with dementia-related psychosis have used randomized withdrawal study designs in which the primary endpoint is the time to relapse (often represented as a hazard ratio).[46,52–54] These trials involve an initial phase during which the ability of the drug to reduce a patient's symptoms is evaluated. Patients who demonstrated a response to treatment in the initial phase are then randomized to continue taking the study drug or to be switched to placebo, which allows for enrichment of the treatment responsive sample leading into the subsequent maintenance phase and minimizes exposure to drug for patients who have not demonstrated benefit.

During the maintenance phase, patients are carefully followed to assess for recurrence or relapse of psychosis symptoms. It is important to note that not all psychosis in dementia is recurrence of the original symptoms, as patients with dementia also experience hallucinations and/or delusions in the setting of delirium. Trial design that addresses adequate distinction between delirium and true recurrence of dementia-related psychosis is critical.

For patients who experience a relapse of dementia-related psychosis, discontinuation of the study medication to seek alternative treatment options is common, primarily for clinical and ethical reasons, and must be accounted for when analyzing relapse outcomes. Randomized withdrawal studies are event driven, and typically use Kaplan–Meier survival analyses to examine time to relapse (from the point of double-blind randomization). With a Kaplan–Meier curve, patients who discontinue early without relapse or who complete the study without having experienced a relapse event are censored at the time of the last assessment.[54] In this type of analysis, hazard ratios are frequently used to represent the likelihood of an event over the examined period.[55] Together, the graphical representation of risk with Kaplan–Meier curves and the use of hazard ratios to estimate risk of dementia-related psychosis relapse over time are less subject to bias than simple rates of relapse and thus allow for more accurate consideration of risks and benefits over time. Randomized withdrawal trials are often longer in duration than other trials, and thus are able to evaluate efficacy and safety of long-term treatment in patients who show initial response. The ability of such designs to evaluate the long-term maintenance of efficacy and sustained benefit of treatment over time is also an important advantage that translates well into clinical decision-making paradigms regarding the benefits of ongoing pharmacologic therapy.

Two studies used a prospective design to assess the role of antipsychotics in preventing relapse after medication withdrawal in patients with AD who manifested agitation and/or psychosis.[52,54] In both studies, patients with an initial response to treatment were randomized to either continue medication or switch to placebo in a blinded manner. This randomized withdrawal study design was used to examine NPS relapse, specifically, combined score of delusions, hallucinations, and agitation/aggression, in patients with AD.

In a single-site study, 22 of 44 patients with AD psychosis and/or AD with agitation or aggression responded to treatment after receiving 20 weeks of haloperidol in the first open-label phase of the trial. Over the next 24 weeks of double-blind treatment, 4 of 10 patients who continued to receive haloperidol experienced a relapse in symptoms compared with 8 of 10 patients who were switched to placebo and experienced a relapse.[54]

Subsequently, withdrawal of risperidone was examined in a multicenter study of 180 patients with AD psychosis and/or AD with agitation or aggression.[52] During the initial 16-week open-label phase of the trial, patients experienced reduction of NPS but a mild increase in extrapyramidal signs. In this phase, 112 patients (62%) met the criteria for response to treatment, and 110 were then randomized to 1 of 3 treatment groups in the next phase of the trial: (i) 32 weeks of risperidone (n = 32); (ii) 16 additional weeks of risperidone followed by 16 weeks of placebo (n = 38); or (iii) 32 weeks of placebo alone (n = 40). Compared with the group remaining on risperidone, the group switching to placebo experienced a 1.94-fold increase in risk of relapse during the first 16 weeks and a 4.88-fold increase in risk of relapse in the second 16 weeks. Although continuation of risperidone decreased the risk of relapse, the safety profile of continuing risperidone remained of concern. The authors concluded that patients with a sustained response to risperidone have a significantly increased risk of relapse upon withdrawal, but that the benefit needed to be carefully weighed against the risk of adverse events associated with continued treatment.[52]

Recently, a phase 3 study utilizing a randomized withdrawal trial design investigated the efficacy of pimavanserin, a serotonin receptor-modulating agent with inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors and to a lesser extent at serotonin 5-HT_{2C} receptors, in preventing relapse of hallucinations and delusions associated with dementia-related psychosis.[56] This randomized, double-blind, placebo-controlled basket trial included patients who satisfied criteria for all-cause dementia because of one or more of the most common causes of neurodegenerative and/or vascular dementia. Eligible patients received 12 weeks of open-label pimavanserin treatment, and the subset of patients who had a sustained response to pimavanserin at both 8 and 12 weeks was randomized to receive pimavanserin or placebo for 26 weeks. The primary outcome of this trial was time to relapse of psychosis from randomization in the double-blind phase. The trial enrolled 392 patients. Total of 62% of patients in the open-label phase showed a sustained response to pimavanserin and were randomized into the double-blind period. The trial was stopped early after patients on pimavanserin demonstrated a statistically significant longer time to relapse compared with placebo.[56] Patients with a response to pimavanserin had a >2.8X lower risk of relapse with continuation of pimavanserin compared with placebo (hazard ratio, 0.35; 95% confidence interval, 0.17 to 0.73; $P = 0.005$).[56]

Taken together, available clinical evidence for the long-term maintenance of efficacy for current antipsychotics used to treat dementia-related psychosis is limited and affected by concerns of persistent side effects among commonly used antipsychotics. In prospective, controlled studies in which antipsychotic use was associated with prevention of relapse of psychosis symptoms, significant safety concerns were also demonstrated.[52,54] Further results from rigorously designed studies are needed to determine therapies that can provide a balance of long-term efficacy with a tolerable safety profile.

CONCLUSIONS

If untreated, dementia-related hallucinations and delusions can be persistent, frequent, and recurring.[57] In treated patients with dementia-related psychosis, relapse may occur either while taking an initially effective or partially effective antipsychotic treatment or during withdrawal of the drug in the context of current treatment recommendations to reduce antipsychotic exposure because of safety concerns. Randomized discontinuation study designs can establish maintenance of efficacy data that provide essential information for prescribers about the long-term effectiveness of therapies for enduring conditions. Thus, as more therapies with favorable benefit to risk profiles for long-term treatment of dementia-related psychosis become available, early drug tapering may become less clinically relevant and sustained efficacy during long-term treatment will be an increasingly important consideration.

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