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This ACADEMIC HIGHLIGHTS section of *The Journal of Clinical Psychiatry* presents the highlights of the teleconference series “Dementia-Related Psychosis: Recognition and Treatment,” which was held in May and June 2020. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from ACADIA Pharmaceuticals Inc.

The teleconference was chaired by **Clive Ballard, MBChB, MMedSci, MRCPsych, MD**, University of Exeter College of Medicine and Health, UK. The faculty member was **Dag Aarsland, MD, PhD**, National Institute for Health Research Biomedical Research Centre at South London and Maudsley NHS Foundation and Institute of Psychiatry, Psychology & Neuroscience at King’s College London.

CME Objective

After studying this article, you should be able to:

- Provide evidence-based therapies to manage psychosis in patients with dementia

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Relieving Caregiver Burden Through Evidence-Based Treatment for Dementia-Related Psychosis

Clive Ballard, MBChB, MMedSci, MRCPsych, MD, and Dag Aarsland, MD, PhD

An estimated 50 million people worldwide are living with dementia.¹ The most common type of dementia is Alzheimer’s disease (AD), accounting for about 60%–70% of dementia cases,¹ followed by vascular dementia (VaD) with a prevalence of about 20%.² Other types of dementia include dementia with Lewy bodies (DLB), Parkinson disease (PD) dementia, and frontotemporal dementia (FTD).³ Along with cognitive decline, 90% of patients with dementia experience behavioral and psychological symptoms of dementia, such as psychosis, aggression, agitation, and depression.⁴ Dementia-related psychosis (DRP), which includes delusions and hallucinations, contributes to institutionalization, cognitive decline, and caregiver burden.⁵

In this Academic Highlights, Drs Ballard and Aarsland will address best practices for improving outcomes for people living with DRP and their care partners.

OVERVIEW OF DEMENTIA-RELATED PSYCHOSIS

A review⁶ of 55 studies showed that psychosis occurred in about 40% of patients with AD; delusions occurred more frequently (36%) than hallucinations (18%). Recurrent visual hallucinations are a core feature of DLB⁷ and are a common characteristic of PD dementia.⁸ Simple hallucinations are rare, with most patients experiencing complex hallucinations daily. The experiences often feature people or animals.^{8,9}

Dr Aarsland stated that delusions and hallucinations may increase in frequency over time and be persistent in some individuals.^{10,11} According to a study¹² of 83 patients with dementia and at least 1 psychotic symptom, most patients experienced psychotic symptoms at a frequency between daily and weekly. Thirty-seven patients (45%) were mildly distressed by their psychotic symptoms, and 14 (17%) were severely distressed.¹²

A complex interplay of factors can contribute to delusions and hallucinations in people with dementia (Figure 1).^{13–16}

According to Dr Aarsland, clinicians must probe factors that contribute to DRP in discussions with the

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Dr Ballard is a consultant for and has received honoraria from Acadia, Roche, Lundbeck, Exevia, AARP, Synexus, and Novo Nordisk; has received grant/research support from Synexus and Novo Nordisk; and is a member of the speakers/advisory boards for Acadia, Roche, AARP, Synexus, and Novo Nordisk.

Dr Aarsland has received research support and/or honoraria from AstraZeneca, Lundbeck, Novartis, Biogen, and GE Health and has served as a paid consultant for Lundbeck, Eisai, Heptares, and Mentis Cura.

Review Process

The faculty member(s) agreed to provide a balanced and evidence-based presentation and discussed the topic(s) and CME objective(s) during the planning sessions. The faculty's submitted content was validated by CME Institute staff, and the activity was evaluated for accuracy, use of evidence, and fair balance by the Chair and a peer reviewer who is without conflict of interest.

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patient (if possible) and the care partner. When talking to patients and carers, it is important to always explore both whether apparent delusions might in fact be true and whether there are factors before or after the occurrence that might initiate or maintain the behaviors. Based on Dr Aarsland's clinical experience, it is usually not helpful for clinicians or carers to argue with patients or try to convince them that these thoughts or sensory impressions are not real; it is more helpful to try to understand and acknowledge the patient's emotional reaction.

IMPACT OF DEMENTIA-RELATED PSYCHOSIS ON PATIENTS AND CAREGIVERS

Delusions and hallucinations may directly impact the patient's ability to perform cognitive and functional tasks,¹⁷ which can contribute to carer distress.^{18,19} Further adding to carer distress, Dr Aarsland explained, patients experiencing hallucinations, such as seeing a person in the house who should not be there, may run after "the person" or even call the police for help.

Additionally, although some psychotic symptoms might not be dramatic, they are often accompanied by troublesome affective and behavioral symptoms that can be stressful for the carer. For instance, sleep disturbances associated with psychotic symptoms may not only lead to increased agitation and reduced daytime functioning in patients, which are challenging for carers to address, but also may cause lack of sleep for carers.²⁰ Psychotic symptoms can also adversely impact the emotional connection between the care partner and the patient.²¹

**Family Perspectives**

Here, a relative describes her ongoing stress:

*"My mother was diagnosed with vascular dementia almost 2 years ago . . . She is very bitter towards me since she blames me for losing her independence. I'm her power of attorney and she barely understands what that is and thinks I just go shopping with her money. She is always asking about her money and where it is. She also wants to know how much there is. She has financial scammers that are still in regular contact with her. She tells them everything. I even found out that [a scammer] tried getting in a lawyer to see her to do a new will. The only reason they didn't succeed is because of COVID. I'm in a constant state of panic and it's affecting my health."*²²

Dr Aarsland recommended several scales to measure the impact of DRP on care partners, including the Zarit Burden Interview,²³ the Relatives' Stress Scale (RSS),²⁴ and the Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D).²⁵ Cognitive-behavioral therapy^{26,27} or emotion-based and problem-focused interventions²⁶ may help care partners cope with DRP.

Although psychotic symptoms can have an immense negative impact on carers,^{28,29} the symptoms do not necessarily cause distress to patients.¹² Patients' degree of insight appears to affect whether they consider hallucinations to be threatening.³⁰ One study³¹ found that 40% of delusions did not cause discomfort to the patients. Dr Ballard said that discussing this perspective with caregivers may help to relieve some of their own distress.

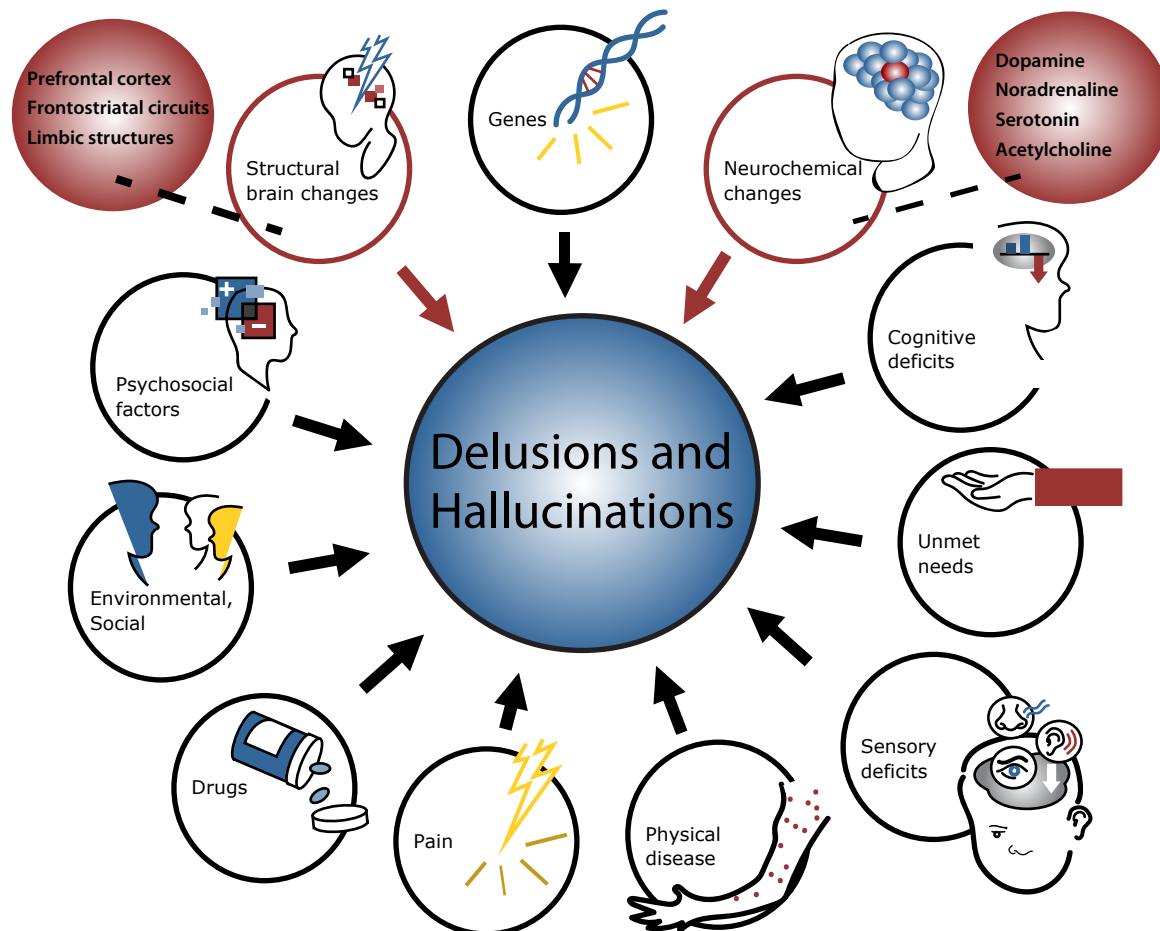
Another point that may help care partners is that psychotic symptoms are not persistent in every patient³²⁻³⁴; they can last for less than 3 months.³⁵

Dr Ballard explained that he has found it important to talk with patients and caregivers about the impact of DRP on well-being, their level of distress (and patients' insight), the potential course of DRP, and the potential risks of medications used to treat DRP. Then, it is possible for people to knowledgeably discuss treatment options.

Terminology is important when discussing DRP with patients and caregivers. Dr Ballard noted that the lay understanding of *psychosis* is usually associated with schizophrenia. Individuals may be more comfortable if providers avoid terms such as *psychotic* and instead describe symptoms according to their presentations.

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Figure 1. Factors Contributing to Psychotic Symptoms in Patients With Dementia



Based on Cerejeira et al,¹³ El Haj et al,¹⁴ Cohen-Mansfield et al,¹⁵ and Targum.¹⁶

EVIDENCE-BASED TREATMENT

Dr Ballard explained that pharmacologic treatment is probably not necessary if symptoms are not severe and are not causing aggressive behavior that puts the patient and others in danger.³⁶⁻³⁸ Although atypical antipsychotics may play a limited role in the short-term management of psychosis in patients with dementia,^{39,40} any benefit has to be balanced against the risk of significant harms (Figure 2^{41,42}).³⁸ Dr Ballard noted that the US Food and Drug Administration (FDA) requires a “black box” warning⁴³ on atypical antipsychotic labels indicating an increased risk of mortality, other known harms, and limited efficacy in patients with dementia,⁴ and European agencies have similar warnings.⁴⁴ Cholinesterase inhibitors may provide a pharmacologic treatment alternative for psychosis in people with DLB,⁴⁵ but benefits are less clear in people with other dementias.

Guidance on Atypical Antipsychotics in DRP

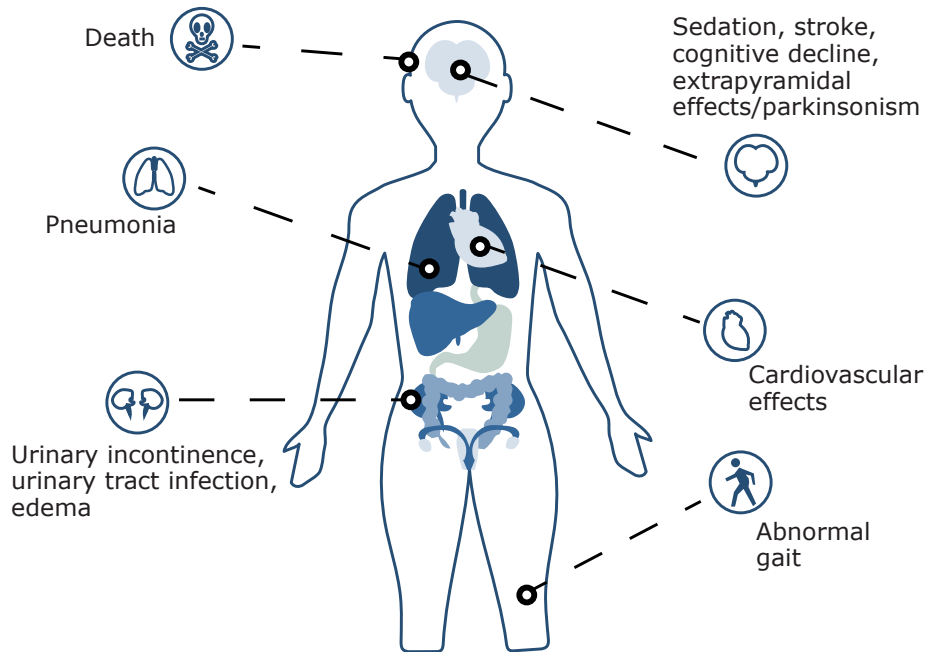
According to the American Psychiatric Association (APA) practice guideline⁴⁶ on the use of antipsychotics for agitation or psychosis in individuals with dementia,

antipsychotic medication should be used only when symptoms are severe, are dangerous, and/or cause significant distress to the patient. The APA recommends that, before nonemergency treatment with an antipsychotic is initiated, the potential risks and benefits must be assessed by the clinician and discussed with the patient (if feasible), family, and/or the surrogate decision maker. If the risk-benefit assessment favors the use of an antipsychotic, the treatment should be initiated at a low dose and titrated up to the minimum effective dose as tolerated.^{41,46} (The first-generation antipsychotic haloperidol should not be used in the absence of delirium.) Response should be assessed with a quantitative measure. Dr Ballard recommended the Neuropsychiatric Inventory (NPI)⁴⁷⁻⁴⁹ for assessment and monitoring.

If no response is evident after 4 weeks, the medication should be tapered and withdrawn.⁴⁶ Among those who respond adequately, an attempt to taper and withdraw the medication should be made within 16 weeks unless previous attempts at tapering were associated with recurrence of symptoms. A long-acting injectable antipsychotic agent should not be used.

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Figure 2. Potential Serious Adverse Effects With Atypical Antipsychotics in Patients With Dementia



Based on Tampi et al⁴¹ and Yunusa et al.⁴²

Dr Ballard explained that since the 2016 publication of the APA guidelines,⁴⁶ evidence has become available on pimavanserin, a selective 5-HT_{2A} inverse agonist, which is FDA-approved for the treatment of hallucinations and delusions associated with PD.⁵⁰ A meta-analysis by Zhang et al⁵¹ concluded that pimavanserin is effective in the treatment of PD psychosis. Unlike other atypical antipsychotics, pimavanserin has no clinically significant antagonism of dopaminergic, muscarinic, or histaminergic receptors.⁵² Evidence⁵³ indicates that pimavanserin may decrease hallucinations and delusions in patients with AD, PD dementia, VaD, DLB, and FTD (including among nursing home residents with severe psychotic symptoms⁵⁴), but it is not FDA-approved for this indication.

Dr Ballard summarized that a patient treated with an antipsychotic for DRP may have marginal benefits in the context of many potential harms; however, for patients with severe symptoms, the risks may be worthwhile with short-term treatment. Atypical antipsychotics are not a widespread, long-term treatment solution.⁵⁵



Family Perspectives

Here, a family member describes the struggle to find therapy for a patient with PD-related psychosis:

"My father-in-law is very sensitive to certain medications. [One antipsychotic] made him hallucinate more. . . . He goes through phases. He's generally happy, then has a few days of constant hallucinations and gets aggressive when the sun goes down."⁵⁶



Case Practice Question

Discussion of the best response can be found at the end of the activity.

Annette, aged 85 years, has Parkinson disease dementia of moderate severity. Annette lives at home with her husband. She has become increasingly suspicious over the last 5 days. According to guidelines provided by the American Psychiatric Association, which of the following statements is accurate?

- a. This is a clear presentation of dementia-related psychosis.
- b. Given the severity of Annette's symptoms, an atypical antipsychotic should be started as soon as possible.
- c. The first step should be investigation of possible causes of delirium.
- d. A nonpharmacologic intervention is the top priority.

Alternatives to Antipsychotics

Nonpharmacologic interventions. Dr Ballard stated that, although practice guidelines³⁸ for the treatment of BPSD recommend first-line use of non-pharmacologic interventions,^{38,57,58} these strategies are more effective for the treatment of agitation than psychosis.

Medications. Both delusions and hallucinations were reduced with citalopram compared with placebo⁵⁹; however, adverse effects may limit its practical application at the 30 mg/d dose.⁶⁰ Masupirdine is a potentially beneficial treatment for BPSD in patients with AD.⁶¹ Trials^{45,62,63} assessing cholinesterase inhibitors in people with LBD have shown significant efficacy in reducing psychotic symptoms, particularly visual hallucinations,⁶⁴

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but quetiapine⁶⁵ has not demonstrated benefit. Finally, tau-directed therapies could be a potential treatment for DRP.⁶⁶

CONCLUSION

Mechanisms behind DRP include neurobiological, environmental, social, and psychological factors. Clinicians must be prepared to offer strategies and educational support to relieve the burden of DRP on patients and their care partners. Depending on the levels of distress and danger to patients or others, short-term medication may be needed.



Clinical Points

- Consider environmental, social, and psychological factors behind DRP.
- Assess the distress and burden of DRP in both patients and care partners using appropriate rating scales.
- Talk with caregivers about whether the psychotic symptoms are causing distress to patients; if not, caregivers may be able to feel less distressed themselves.
- Explain to care partners that antipsychotics have a limited role as short-term treatment for DRP; long-term efficacy is marginal, and the risk of serious adverse effects is considerable.



Discussion of Case Practice Question

Preferred response is c.

Given the acute presentation associated with increased confusion, investigation of delirium should be the first step. Guidelines provided by the American Psychiatric Association⁴⁶ recommend that antipsychotic medication should be used only when symptoms are severe, are dangerous, and/or cause significant distress to the patient.

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Disclosure of off-label usage: Dr Ballard has determined that, to the best of his knowledge, no therapies are approved by the US Food and Drug Administration for the treatment of dementia-related psychosis.

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POSTTEST

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1. You have an 85-year-old patient, Bonnie, who presented with mild dementia in primary care. Because of hearing loss, Bonnie finds it difficult to communicate and is often isolated. Bonnie's daughter Julia, who accompanies her to appointments, mentions that sometimes her mother speaks to a dog that Julia cannot see. Julia says that Bonnie seems comforted by the "dog," so she ignores it. As you relay information about dementia-related psychosis (DRP), which statement would accurately explain the potential cause of DRP to Julia?
 - a. Sensory deficits, including Bonnie's hearing loss, may contribute to the risk of DRP
 - b. Neurochemical mechanisms are likely to be an important cause of DRP
 - c. Bonnie's social environment may contribute to the risk of DRP
 - d. All of the above
2. Several appointments later, Julia tells you that Bonnie is now frequently experiencing hallucinations and delusions. Bonnie also has difficulty sleeping, and Julia is exhausted by around-the-clock care. Which statement accurately reflects an evidence-based treatment option that you should advise for Bonnie at this time?
 - a. You advise the prescription of an atypical antipsychotic, which is approved for the treatment of DRP
 - b. You tell Julia that if her mother responds well to an atypical antipsychotic, the treatment should be continued for as long as possible
 - c. You explain to Julia that increased mortality, stroke, and accelerated cognitive decline are well established adverse events associated with the use of atypical antipsychotics in people like Bonnie
 - d. You advise that cholinesterase inhibitors provide an evidence-based treatment alternative to atypical antipsychotics for DRP in people with all dementias