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ORIGINAL RESEARCH

Screening, Diagnosis, and Management of Parkinson's Disease Psychosis: Recommendations From an Expert Panel

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ABSTRACT

Introduction: Hallucinations and delusions present with psychosis are debilitating non-motor symptoms of Parkinson's disease, with a prevalence of up to 50–70% at some point during the course of the disease. Often patients and caregivers do not report the presence of hallucinations or delusions unless specifically questioned. A panel of experts in neurology and geriatric psychiatry convened to develop a simple screening tool and guidance on diagnosis and treatment of Parkinson's disease psychosis (PDP).

Methods: The working group reviewed literature for existing PDP guidelines on diagnosis and management and identified gaps in recommendations. The group discussed and developed a screening tool and treatment guidance that addressed the gaps in existing methodology based on their clinical experience.

Results: The proposed screening tool consists of two parts: (1) a brief pre-visit screening portion to be completed by the patient and caregiver, and (2) a clinician portion to be completed via clinical interview of the patient and caregiver. If psychotic symptoms are present, an appropriate treatment plan is developed for PDP based on evaluation.

Conclusions: This simple screening tool and treatment guidance offers a practical clinical approach for clinicians in the diagnosis and management of PDP.

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PLAIN LANGUAGE SUMMARY

Symptoms relating to psychosis are debilitating, progressive, and often emerge in patients with Parkinson's disease. Symptoms of Parkinson's disease psychosis include illusions, a false sense of presence, and hallucinations or delusions or both. While there are established consensus

criteria for the diagnosis of Parkinson's disease psychosis, there is currently a lack of simple and standardized criteria for the screening of Parkinson's disease psychosis. This can make it challenging to identify patients who may benefit from treatment for Parkinson's disease psychosis symptoms. A group of clinical experts met to discuss guidance for the screening, clinical diagnosis, and management of Parkinson's disease psychosis. The group identified a paucity of screening tools, weaknesses in existing criteria for diagnosing Parkinson's disease psychosis, and variability in treatment recommendations. The group proposed a screening tool that includes two parts: (1) a simple pre-visit screening to be completed by the patient and caregiver before an appointment, and (2) a clinician portion to be discussed with the patient and caregiver during the appointment. If a patient has hallucinations and/or delusions that require treatment, the proposed guidance includes potential interventions or medications, which were established by review of evidence-based literature and the US Food and Drug Administration guidelines. This provides a quick and relatively simple clinical tool for a patient and caregiver to report symptoms of Parkinson's disease psychosis, and for the clinician to formulate an accurate diagnosis and a decision tree to consider treatment options.

Keywords: Antipsychotics; Delusions; Hallucinations; Parkinson's disease; Parkinson's disease psychosis; Pimavanserin; Psychosis

Key Summary Points

Why carry out this expert panel?

Psychosis, with symptoms such as hallucinations and delusions, is a common and debilitating feature of Parkinson's disease.

The current lack of simple and standardized criteria for the screening of psychosis in Parkinson's disease limits the identification of patients who need treatment.

We present the findings and guidance developed from consensus meetings with a group of experts on psychosis in neurodegenerative disorders.

What was learned from the expert panel?

Untreated symptoms of psychosis in Parkinson's disease are associated with poor outcomes, poor quality of life, and significant distress to the caregiver and patient.

The proposed screening tool and treatment algorithm may provide guidance for improved management of Parkinson's disease psychosis.

INTRODUCTION

Psychotic symptoms present with Parkinson's disease (PD) are common and debilitating [1], occurring in up to 50–70% of patients at some point during the course of their illness [2–5]. Symptoms of psychosis, such as hallucinations and delusions, may lead to increased disability, hospitalization, long-term care placement, morbidity and mortality, and significant distress to patients and caregivers [4, 6, 7]. Risk factors for Parkinson's disease psychosis (PDP) include older age, longer PD duration, comorbidity with depression or sleep disorders, and

the presence of dementia. Around 70% of patients with both PD and dementia report visual hallucinations [6]. Existing screening tools and rating scales for PDP that were developed for clinical trials are too lengthy for routine clinical use or do not clearly define psychotic symptoms enough to inform treatment decisions. Details of such currently available tools are described in a recently published review article [8]. This lack of a simple, straightforward, and standardized screening and diagnostic approach limits the identification of patients suffering from PDP, thus lowering the likelihood of earlier and effective treatment [4].

Antipsychotic drugs are often prescribed to treat patients with PDP; however, currently available antipsychotics may worsen motor parkinsonism, except pimavanserin, clozapine, and quetiapine [9–11]. Pimavanserin is the only US Food and Drug Administration (FDA)–approved treatment for hallucinations and delusions associated with PDP, based on a pivotal 6-week trial [12, 13]. Efficacy has been demonstrated at 10 weeks and maintained long term in an open-label safety study, without emergence of safety concerns [14, 15]. Clozapine has demonstrated antipsychotic benefit in two 4-week clinical trials for PDP, but its use is limited due to the requirement of frequent blood monitoring for agranulocytosis [16, 17]. Quetiapine has not demonstrated efficacy in several small trials, and a systematic review of randomized controlled trials assessing quetiapine in the treatment of psychosis in patients with neurodegenerative parkinsonian disorders (PD, Lewy body dementia [LBD], or other neurodegenerative parkinsonian disorders) showed that quetiapine did not result in motor deterioration but also did not significantly reduce psychotic symptoms compared to placebo, and dosing can be limited by somnolence and orthostatic hypotension [18, 19]. All other available antipsychotics that were evaluated to treat PDP worsened underlying PD motor symptoms due to their post-synaptic dopamine receptor blockade, and their use is cautioned against by the Movement Disorder Society (MDS) guidelines and the American Geriatrics Society Updated Beers Criteria [9, 11, 19].

There is an unmet need for a brief screening tool to facilitate the diagnosis and treatment of patients with PDP [8]. Identifying and classifying the frequency and severity of psychotic symptoms can have significant implications for disease management and prognosis, highlighting the importance of a standardized set of diagnostic and treatment criteria. A working group of experts on psychosis in neurodegenerative disorders convened to discuss the current guidance on the screening, diagnosis, and management of PDP. They concluded that an ideal screening tool would allow a patient and/or caregiver to easily report symptoms of PDP and allow a clinician to probe into the nature of these symptoms prior to making treatment decisions. Associated treatment guidance would be helpful for clinicians to develop treatment strategies for PDP. Here, we present the findings of this working group to develop a screening tool for psychosis and guidance on management approaches for PDP.

METHODS

Working Group Methods

A multidisciplinary expert panel of neurologists and psychiatrists assembled to generate a diagnostic screening tool and treatment guidelines for PDP. The panel met via video teleconference platform due to COVID-19 pandemic–related travel restrictions. Two meetings (April 24, 2020 and June 24, 2020) of 4 h each were held, with all members of the working group in attendance at both sessions. Professional medical writers also attended both meetings to record feedback from working group participants.

The working group guidance was developed through discussion of existing recommendations, clinical experience, and review of evidence-based literature. Evidence supporting a clinical unmet need for standardized diagnostic tools and treatment guidelines for PDP was derived from the literature search of existing movement disorder–focused guidelines developed by professional societies. The working group of advisors discussed and provided feedback regarding gaps in the existing clinical research measures and guidelines concerning the diagnosis and management of

PDP, which were identified via PubMed searches and clinical experience. Among the movement disorder–focused clinical research screening tools discussed were the MDS–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [20], the MDS–Non-Motor Rating Scale [21], MDS Non-Motor Symptoms Scale (NMSS) [22], the Non-Motor Symptoms Questionnaire (NMSQ) [23], and the Scale for Assessment of Positive Symptoms Adapted for Parkinson's Disease (SAPS-PD) [24, 25]. Society guidelines included in the review were the National Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Mental Health (NIMH) Diagnostic Criteria for Psychosis in Parkinson's Disease; MDS Guidelines for the Treatment of Non-Motor Symptoms in Parkinson's Disease (Psychosis) [9]; the American Academy of Neurology (ANN) Guidelines for Evaluation and Treatment of Depression, Psychosis, and Dementia in Parkinson Disease and for the Management of Dementia [26]; and the American Geriatrics Society Updated Beers Criteria [11].

The working group members participated in a session to propose a screening tool and treatment guidance for PDP, using a screening tool and treatment guidance developed at a prior working group meeting as the basis of discussion. The proposed tool was divided into three components for review: (1) a pre-visit screener, (2) a clinician assessment, and (3) treatment guidance. The meeting output was refined in an iterative process into a single, harmonized diagnostic screening tool with treatment guidance for PDP; drafts of the meeting output were circulated to all working group participants, and further feedback/comments were received and incorporated. This article is based on previously conducted studies and does not contain any studies with human participants or animals that were performed by any of the authors.

RESULTS

Diagnostic Screening Tool: Pre-visit Screening

The proposed criteria for the screening of patients for PDP are shown in Fig. 1A, B. The recommended framework incorporates the strengths of current methodology (e.g., some existing clinical research tools had useful language or methodologies but were too lengthy for use in clinical practice) and addresses the weaknesses (e.g., variability in definitions of psychosis and psychotic symptoms, lack of distinction between psychotic symptoms and overlapping related symptoms) identified by the working group [8]. The working group guidance also incorporates clinical experience and more recent advances in the understanding of psychosis in PDP. The screening tool was divided into a pre-visit screening portion and a clinician assessment portion. Questions are addressed to both the patient and caregiver, while noting that their answers may differ.

The pre-visit screener is to be administered in the waiting room prior to the clinician visit or at a long-term care institution in either a digital or paper-based format. This way, the clinician can efficiently review the results and can determine if they would like to assess further (using the clinician assessment) before determining appropriate therapeutic intervention. The pre-visit screening tool includes two broad questions to assess the presence of hallucinations and delusions, respectively: (1) "Does the patient see, hear, or otherwise sense things that others do not?" and (2) "Does the patient believe things others do not believe to be true?" (Fig. 1A). This portion of the screening tool is intended for completion by the patient and/or caregiver, and the two questions are not specific to every possible type of hallucination or delusion. It was noted that diagnostic tools could be more robust if they included more specific differentiation between hallucinations and delusions and served to clarify the overlap of related symptoms (e.g., illusions, agitation). To achieve this, the working group included examples of common hallucinations ("seeing people or animals that are not there, hearing music, or misidentifying objects") and delusions ("that their spouse is cheating, others are causing them harm or deceiving them, or others are conspiring against them") to help caregivers accurately identify symptoms (Fig. 1A). The language "*otherwise sense things*" was included to acknowledge other sensory modalities for

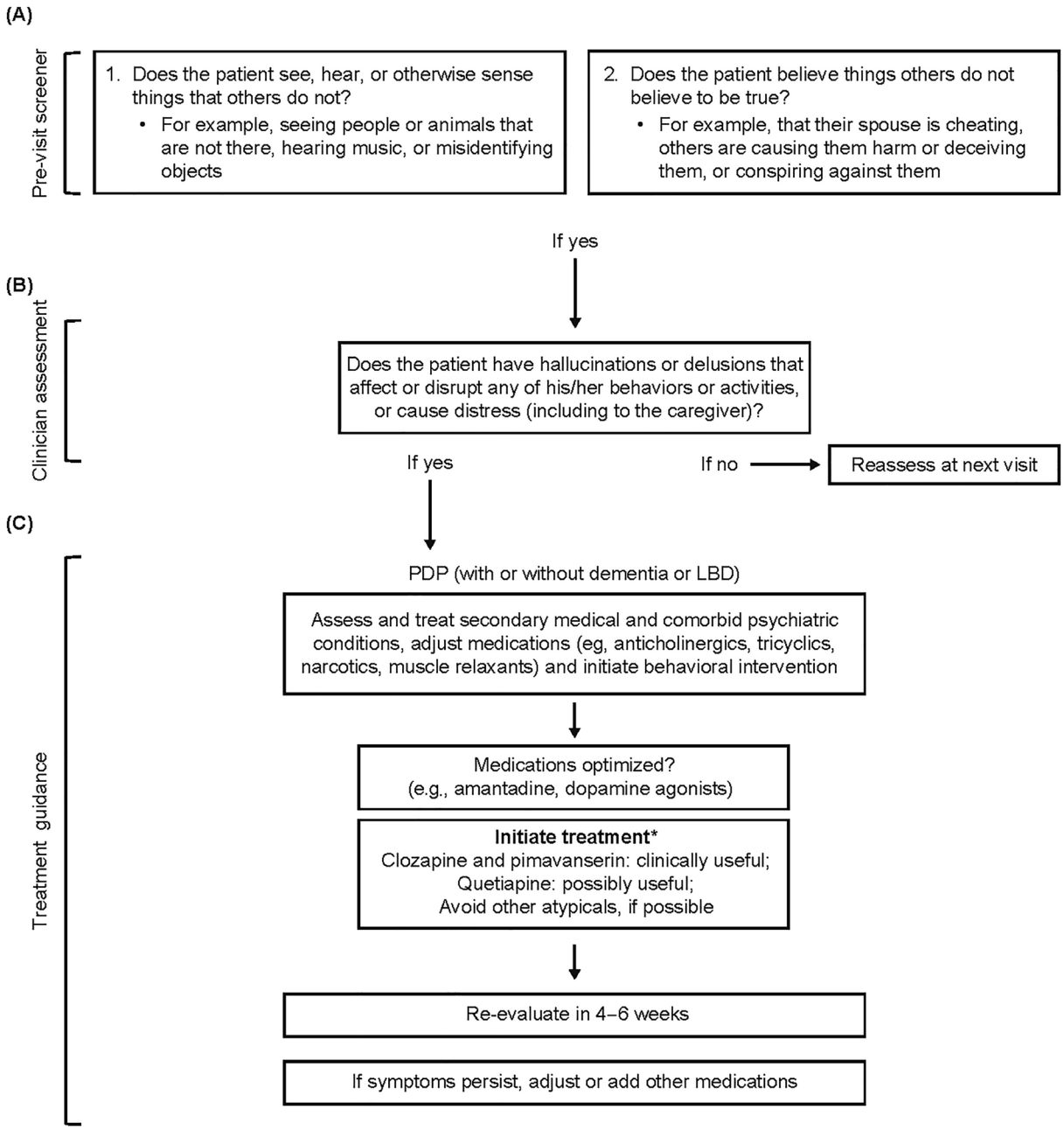

Fig. 1 Screening tool and treatment algorithm for diagnosis and management of PDP. *PDP* Parkinson's disease psychosis, *LBD* Lewy body dementia, *MDS* Movement Disorder Society, *FDA* US Food and Drug Administration. *Based on MDS guidelines; only pimavanserin is FDA approved for the treatment of hallucinations and delusions associated with PDP. The use of pimavanserin for LBD is off-label. Note: The proposed screening tool should guide clinicians to investigate deeper into the issue of psychosis. The clinician should make the assessments and final treatment decisions

hallucinations beyond sight and sound. The possibility of including additional questions sensitive enough to capture illusions (e.g., "do you ever look outside and mistake a tree for a person?" or "have you ever thought a belt on the floor looks like a snake?") was discussed, but

it was ultimately decided that this would introduce unnecessary complexity into a screening tool intended for clinical practice.

Working group members emphasized the wide variation in assessment scoring criteria (ratings of frequency, severity, impact, and caregiver distress) among the existing diagnostic tools and symptom definitions. The ultimate consensus of the working group was that a simple answer of "yes" to either question on the pre-visit screener would indicate symptoms that required further assessment. It is anticipated that this pre-visit questionnaire will assist the clinician in deciding if further assessment is needed for the possible diagnosis of psychosis, with subsequent assessment for the type, frequency, severity, and impact of hallucinations or delusions in the clinician assessment portion.

Table 1 Diagnostic criteria for psychosis in Parkinson's disease (based on an NIH-sponsored NINDS, NIMH Working Group)

PDP diagnostic criteria [30]	
Characteristic symptoms	**Associated features**
At least one symptom of illusions, false sense of presence, hallucinations, or delusions	Note symptoms as occurring with or without insight, dementia, or PD treatment
Primary diagnosis	**Exclusion of other causes**
Per UK brain bank criteria for PD	Symptoms are not better accounted for by another cause of parkinsonism
Chronology of symptoms	**Duration of symptoms**
Psychosis symptoms occur after PD onset	Symptoms recur or are continuous for 1 month

Adapted from Ravina et al. [30] ©2007 Movement Disorder Society, with permission from Wiley
NIH National Institutes of Health, *NINDS* National Institute of Neurological Disorders and Stroke, *NIMH* National Institute of Mental Health, *PDP* Parkinson's disease psychosis, *PD* Parkinson's disease

Screening Tool: Clinician Assessment

The clinician screener is intended to allow for further investigation into hallucinations and delusions in order to inform a decision on treatment. The diagnosis of PDP is based on the National Institutes of Health criteria (Table 1). In addition to distress to the patient caused by psychotic symptoms, caregiver distress and the burden of PDP is an important factor to be considered. The decision to treat should be a shared decision among the clinician, patient, and caregiver based on the frequency, severity, impact, and degree to which psychotic symptoms cause patient and/or caregiver distress. This decision can be challenging when patients suffering from psychosis do not discuss symptoms with their clinicians or caregivers. It is not uncommon for patients to avoid mentioning the presence of hallucinations or delusions unless specifically questioned; therefore, a simple and effective tool is imperative to detect these symptoms.

To simplify the clinician assessment, specific examples of hallucinations or delusions that would need to be treated were not included. A single question for the clinician assessment portion of the tool was developed: "Does the patient have hallucinations or delusions that affect or disrupt any of his/her behaviors or activities, or cause distress (including to the caregiver)?" (Fig. 1B). This allows the clinician to evaluate and discuss with the patient and caregiver how often hallucinations and delusions occur and how disruptive they are in order to make a decision regarding treatment. The wording "affect or disrupt" indicates negative impact on patient activity or behavior in any way.

Treatment Guidance

Once a clinician has evaluated the presence of PDP and determined if the PDP symptoms cause distress or disruption to the patient/caregiver or to the treatment of PD motor symptoms, the next step is to consider any underlying medical reasons contributing to psychotic symptoms (Fig. 1C). Adjustments to existing medications

that can cause or exacerbate psychosis should be made. As patients with PDP who are optimized on PD motor treatments may not tolerate dose reductions or discontinuations of PD medications, adjustments to other offending agents (e.g., anticholinergics, tricyclics, narcotics, muscle relaxants) should be attempted first. In the case that adjustments to non-PD medications are not viable, use of PD medications should also be evaluated and adjusted as needed, especially dopamine agonists (e.g., pramipexole, ropinirole), amantadine, or monoamine oxidase B inhibitors (e.g., rasagiline, selegiline). For example, in patients who experience an acute increase in psychosis, temporary lowering of dopamine agonists can be considered based on severity of PDP symptoms. Furthermore, secondary medical (e.g., presence of urinary tract infection) and comorbid psychiatric conditions (e.g., depression, insomnia, dementia) should be assessed and treated. For example, dementia assessments containing blood test (serology or thyroid test) and neuropsychiatric exams (Mini Mental State Exam [MMSE], CDR Sum of Boxes, or Montréal Cognitive Assessment [MoCA]) can be considered. In addition to treating for these medical conditions, consideration should also be given for psychotherapy and behavioral therapy.

Experts who participated in the working group reviewed the available evidence on the safety and efficacy of treatments used for PDP. Nonpharmacologic approaches, such as behavioral therapy, improved overnight sleep, lighting, and reassurance, may improve psychotic symptoms. Behavioral intervention (independently or with concurrent therapeutic intervention) should be initiated early in treatment once adjustments for secondary medical and comorbid psychiatric conditions have been made. The consensus was that if PDP persists despite nonpharmacologic therapies, then a combination of behavioral and pharmaceutical intervention would provide a more comprehensive approach to PDP treatment.

The working group collectively discussed making treatment recommendations for specific antipsychotics. Guidelines for PDP are available from the MDS "Treatment of Non-Motor Symptoms in Parkinson's Disease." These guidelines recommend pimavanserin and clozapine as "clinically useful." However, clozapine requires frequent blood monitoring due to risk of agranulocytosis, and therefore it is rarely used. Since the FDA approval of pimavanserin for hallucinations and delusions PDP, the working group came to a consensus that pimavanserin should be considered as the first-line medication for the treatment of PDP. Quetiapine is recognized as "possibly useful" by MDS guidelines due to the lack of established efficacy [9]. Since it does not worsen motor symptoms at the low doses used in PDP, the working group consensus was that quetiapine may be considered for patients when pimavanserin is either not tolerated or is unavailable, with monitoring for off-target receptor adverse effects of somnolence and orthostatic hypotension [19]. Guidelines recommend, and experts agree, to avoid all other typical and atypical antipsychotics (e.g., olanzapine, risperidone, aripiprazole) due to their likelihood of worsening motor parkinsonism caused by dopamine receptor blockade [11, 19]. As LBD often has parkinsonian features, and most of these patients are on anti-parkinsonian medications, these patients should also follow the PDP pathway and similar guidance should be considered. However, no antipsychotics have been approved for the treatment of psychosis associated with LBD.

Reassessment after initiating antipsychotics should be based on the clinical scenario. Over time, patients may require ongoing nonpharmacologic treatments, adjustment of PD motor therapies, or treatment with an additional antipsychotic. Safety data are lacking regarding the use of a combination of two antipsychotics, and the management of this should be based on clinician experience and judgment. One study indicated significant risk of mortality and severe adverse reactions in patients with PD receiving atypical antipsychotics [27]. Based on their collective experience, the working group suggested a follow-up after approximately 4–6 weeks after initiation of treatment to evaluate tolerability and onset of response, and then continuing to evaluate for treatment benefit for up to 8 weeks and adjusting medications as needed. Pimavanserin may take 6 weeks to observe benefit, and if the patient reports no benefit after 8 weeks it may be discontinued.

Importantly, symptoms of psychosis may be severe and require multiple interventions, which should be considered upon reassessment.

DISCUSSION

PDP is common and progressive, yet often not diagnosed or treated until symptoms become severe. Previous research has proposed guidance for screening PDP in specific situations or populations. The 20-item Psychosis and Hallucinations Questionnaire (PsycH-Q) is a self-completed tool that was found to reliably identify hallucinations and psychosis in patients with PD [28]. The Parkinson Psychosis Questionnaire (PPQ) is an instrument that was found to be suitable in diagnosing patients with drug-induced psychosis in routine PD care [29]. However, there is still an unmet need for standardized diagnostic tools and treatment guidelines for PDP in general. A simple screening questionnaire to identify patients with psychosis in a clinical practice setting would help remedy the underrecognition of PDP in the clinic. This working group suggests a screening tool that can be used by a patient and/or caregiver, with further evaluation by clinicians to confirm diagnosis and initiate a treatment plan. Development of the tool was based on existing recommendations and literature, as well as the group's clinical experience and expertise. Compared to existing screening guidelines, the proposed tool allows for a quick and relatively simple assessment in the clinical setting.

The underreporting of symptoms in clinics results in a challenge for the effective and timely treatment of psychosis. Patients may not discuss all symptoms with clinicians, as they are often not aware of psychosis-specific symptoms and may attribute their experiences to concomitant diseases or medications. In addition, previous data have shown that clinicians also commonly miss symptoms and identification of psychosis; the proposed screening tool incentivizes clinicians to investigate further and deeper into the presenting symptoms, thus increasing the likelihood of diagnosis. This screening tool provides specific differentiation between various types of hallucinations and delusions. The presence of hallucinations and delusions with related behavioral symptoms (e.g., agitation) and other false perceptions (e.g., illusions) can have confounding implications on the diagnosis and treatment of PDP. The working group noted that simplicity and time are critical for implementing a screening tool and treatment algorithm suitable for routine clinical practice and considered the future possibility of developing multiple versions of varying complexity to maximize its utility in different settings. As frequency and severity are highly correlated, the proposed screening tool was not designed to include a frequency rating scale, and the presence of any symptoms would require further assessment and possible treatment.

The group discussed currently used therapy options for PDP and provided potential treatment recommendations. Nonpharmacologic approaches include medication survey, restoration of daytime lighting and nighttime sleep, behavioral intervention, and education of caregivers. Timely education of caregivers to perform necessary behavioral interventions might not be feasible in cases where patients require urgent treatment; therefore, the working group participants thought that behavioral intervention should be recommended early in the treatment algorithm, followed by (or in conjunction with) pharmaceutical recommendations, as needed.

In terms of pharmacologic treatment recommendations, pimavanserin is suggested as the first-line treatment for patients with PDP based on its established efficacy, safety, and tolerability, which led to FDA approval [12, 13]. Clozapine can also be suggested for PDP, although its use would be off-label and require intensive blood monitoring [16, 17]. As use of pimavanserin is limited in countries where it is not yet approved, clozapine is a useful and reasonable option in these countries. Quetiapine may be considered for patients but lacks established efficacy and can lead to daytime somnolence, orthostatic hypotension, and other adverse effects [19]. Other atypical antipsychotics, such as olanzapine, risperidone, and aripiprazole, should be avoided, as they all block dopamine receptors and will worsen PD

motor symptoms [9, 19]. Overall, the working group suggested reassessment of a patient after initiation of antipsychotic treatment. Symptoms of PDP are progressive and may be severe, requiring multiple interventions, which should be considered upon reevaluation.

The awareness of screening tools can sometimes be limited in anyone outside those working in the specific disease state for which the research tool was developed. The working group also discussed goals of providing standardized recommendations to a wide group of clinicians across different specialties and care settings. Beyond specialists, physicians and staff in outpatient clinics and long-term care facilities (such as assisted living or nursing homes) may also benefit from additional guidance in identifying symptoms. The proposed screening tool and treatment algorithm are intended for outreach to a broad group of health care professionals, which is critical for the standardization of a clinically focused tool.

However, the proposed screening tool is not intended to direct specific treatment decisions, but rather to provide guidance for clinicians to investigate deeper into the presenting symptoms. Further research and study are needed to assess the usefulness, practicality, test–retest reliability, and validity of this tool in clinical practice. Utility among clinicians, patients, and caregivers also requires further investigation.

CONCLUSIONS

Untreated symptoms of psychosis in PD are associated with progressive PDP symptoms, poorer outcomes, impaired quality of life, and significant distress to the caregiver and patient. The proposed screening tool and treatment algorithm can provide optimized guidance for the management of PDP.

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