Neuropsychiatric Aspects of Alzheimer’s Disease

Clinically significant neuropsychiatric symptoms need evidence-based treatment.

By Zahinoor Ismail, MD, FRCPC and Zahra Goodarzi, BHSc (Hon), MD, MSc, FRCPC

**Introduction**

Neuropsychiatric symptoms (NPS) in dementia include apathy, mood and anxiety symptoms, agitation and aggression, social disinhibition, and psychotic symptoms. Historically described as behavioral and psychologic symptoms of dementia, modern nomenclature classifies them as NPS to better reflect increasing neurobiologic understanding of these symptoms. Sometimes NPS emerge before dementia, prognosticating incident cognitive decline and further supporting a neurobiologic etiology.

Up to 97% of people with dementia experience NPS, but the symptoms are often overlooked, especially when a cognocentric view of dementia is held. The NPS are associated with greater functional impairment and institutionalization, accelerated dementia progression, greater caregiver stress, poorer quality of life, increased risk of death, and more neuropathologic markers of dementia.

Research into biologic substrates of NPS is booming, but fundamental clinical questions of how to detect and manage NPS remain. We describe NPS and approaches to identification and measurement, review evidence for managing the most common NPS clusters (ie, agitation and psychosis, mood and anxiety symptoms, and apathy), and provide an algorithm to approach NPS in a neurologic clinical practice.

**Detection of Neuropsychiatric Symptoms**

When identifying NPS, general psychopathology tools encompass several symptoms, in addition to specific tools for agitation, apathy, depression, and anxiety. There are fewer specific questionnaires for certain symptoms (eg, nighttime or disinhibited behaviors), and these are diagnosed primarily based on history and observation.

A few tools are described in Figure 1, but these alone are not sufficient to understand all aspects of a behavior. Rather, these tools help identify symptoms that require further detailed assessment by elucidating frequency, severity, and type of symptoms present. However, most tools do not explain underlying causes or contributors to NPS. Many tools focus on evaluating care partners’ assessments, although some involve observation or interview of the person with dementia. Practitioners should focus on choosing the right tool for a clinical scenario. It is important to consider language and cultural differences when selecting a tool as both can affect accuracy.

Caution is suggested for use of tools not designed for people with dementia. There is some controversy regarding diagnostic criteria and definitions of individual NPS. There is also a sometimes poor distinction between symptoms and syndromes that furthers controversy and clouds prevalence estimates, contributing to heterogeneity in meta-analyses. For example, while apathy is a syndrome, a general scale can detect apathy as a symptom, which may or may not reflect presence of an underlying apathy syndrome. Similarly, depression can be a symptom or a syndrome that specific measurement tools may not always differentiate. These issues lead to potential misclassification, which has important implications for patient care. Nonetheless, tools are an essential part of dementia care, and monitoring NPS over time identifies those at higher risk. It is suggested that a global psychopathology measure like the brief questionnaire form of the Neuropsychiatric Inventory (NPI-Q) be completed at regular intervals as a minimum; persons with significant symptom burden can then be assessed further.

**General Nonpharmacologic Approaches**

Although not the focus of this review, nonpharmacologic measures must be considered in advance or in conjunction with pharmacotherapy. In milder cases, nonpharmacologic therapies are often sufficient. A particularly useful approach is the describe, investigate, create, evaluate (DICE) method. The first step is to describe and measure the NPS or behavior in detail and then investigate the causes. Investigation includes ensuring that medical (eg, infection or pain), drug
(eg, anticholinergics, antihistamines, opiates), or environmental factors (eg, poor light, excessive noise, disorientation) are not contributors to NPS, which can often be remedied without pharmacotherapy. Thereafter, a management plan is created and evaluated, as long as safety issues do not mandate urgent or emergent treatment with medications.5,13

**Dementia-Specific Treatments for Neuropsychiatric Symptoms**

Much of the evidence base supports the use of medications specific to dementia for NPS. The strongest evidence is for galantamine and donepezil, especially in mild-to-moderate stages of disease, and memantine, alone or in combination in the moderate-to-severe stages.13,14

There is high-quality evidence of a small beneficial effect of memantine monotherapy for cognition, function, and behavior in AD, and memantine added to a cholinesterase inhibitor results in less deterioration compared with placebo augmentation.15 Real-life practice data demonstrate that memantine use stabilizes the trend of increasing psychotropic use in people with dementia prior to memantine initiation, increasing usefulness of memantine for safely

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**Figure 1. Tools to Detect Neuropsychiatric Symptoms.**

**Neuropsychiatric Inventory (all Versions)**

**Behavioural Pathology in Alzheimer’s disease**

**NPI – Questionnaire**

This is a short form version of the NPI. Consists of the same 12 areas, but focuses on if the behavior is present as well as frequency and caregiver distress. Given its range of items covered and brevity of questionnaire, allows for efficient use in clinical settings.

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References:
managing NPS while mitigating or minimizing exposure to psychiatric medications. Memantine tends to be better tolerated than the cholinesterase inhibitors, with dizziness being the most important side effect. For cholinesterase inhibitors, important concerns are bradycardia or heart block, which may limit or preclude cholinesterase use, as may gastrointestinal tolerability. If an agent is not tolerated, switching to another can be considered. Importantly, these agents were intended for the target population, and the side effect burden may be less than that of other psychiatric medications, developed for psychiatric conditions.

**Specific Neuropsychiatric Syndromes**

**Agitation and Psychosis**

Agitation is common in AD, increasing in frequency with disease severity. However, the study of agitation in AD and the absence of indicated treatments in the US has been hampered in part by the lack of an agreed-upon definition. Agitation is a nonspecific symptom, resulting in heterogeneity of the study population. More recently, the International Psychogeriatric Association (IPA) published a syndromic definition to facilitate clinical work and research, dividing agitation into excessive motor activity, verbal aggression, and physical aggression.17 Future studies can reassess treatments to determine if there are domain differences and appropriate approaches for different subtypes of agitation.

Agitation often accompanies psychosis18 and is a discrete syndrome; however, agitation and psychosis have historically been treated with a similar approach. Psychosis, consisting of delusions and hallucinations, generally worsens with disease stage. When assessing the evidence for treatments of agitation and psychosis in dementia, it is important to understand that different measures perform differently for capturing symptoms and response to treatment. Measurement is an important area for further refinement of the evidence base.19 For example, measurement tools often conflate persecutory (eg, theft) and misidentification delusions (eg, TV sign, mirror sign, phantom boarder), but these types of delusions have different natural histories and neural substrates,20 possibly suggesting different treatment approaches. Further work in this area is needed, and similar to agitation, a revised syndromic definition is under development by the IPA and the International Society to Advance Alzheimer’s Research and Treatment NPS Professional Interest Area.

**Antipsychotics.** As a carryover from use in people without dementia who have psychosis and agitation, antipsychotics have been used for these NPS in dementia. Although antipsychotics have modest efficacy for these NPS in persons with dementia,13 there is also an associated and significant risk of EPS, falls, cerebrovascular accidents, and all-cause mortality, in-part driven by arrhythmogenic potential. Black box warnings have been issued, informed by meta-analyses that show all-cause mortality of 3.5% for antipsychotic use vs 2.3% for placebo, or an odds ratio (OR) of 1.54.21 The distinction between absolute risk increase (1.2%) and relative increase (54%) is important to discuss with patients and decision-makers. The additional 1.2% increase in mortality should be assessed in the context of safety, quality of life, and utility of alternate approaches. Not all agents are equal in efficacy and risk. Older antipsychotics confer greater risk, and it is important to consider interdrug differences when making choices.13

The best evidence, at this stage, is for aripiprazole and risperidone. Aripiprazole dosing starts at 1 to 2 mg daily, with an upper limit of 10 mg. The major tolerability issue, early on, is akathisia or sedation; if sedation is problematic, aripiprazole can be taken at bedtime. For risperidone, which is available in different formulations, starting doses can be as low as 0.125 mg at bedtime or twice daily, with doses above 2 mg likely conferring no added benefit. Sedation and extrapyramidal syndrome (EPS) are the immediate side effects of concern. While quetiapine is used extensively for sleep at low doses of 12.5 to 50 mg, there is little evidence that these doses provide any antiagitation benefit beyond sedation, which is a side effect associated with risk. A network meta-analysis showed some utility for higher-dose quetiapine when using a schizophrenia rating scale as an outcome measure; it is important to consider the dosing of this agent if using for agitation or psychosis.22 Newer agents such as brexpiprazole are under investigation, leveraging the lower EPS burden of aripiprazole-like partial agonism, with novel receptor-binding and side-effect profiles. However, this medication is not yet approved, and like all the other antipsychotics remains an off-label choice with a black box warning.23 If antipsychotics are used, regular attempts at titration off should be considered, given that NPS are often transient, and mortality increases with chronic use.24 Deprescribing guidelines suggest titration off antipsychotics at 3 months, irrespective of whether or not medications were effective.25 There are fewer data on as-needed use vs regular use for both efficacy and safety, but it is the cumulative antipsychotic dose that is associated with mortality,26 so efforts to minimize cumulative dose may decrease risk. Clinical judgement is required to minimize antipsychotic exposure overall, balancing efficacy and safety, optimizing nonpharmacologic approaches, and considering the suitability of an individual’s environment or supports to manage or tolerate agitated and psychotic behaviors.

**Antidepressants.** Substantial background research supports use of serotonergic agents to decrease agitation in AD.27 The most rigorous trial showed efficacy of racemic citalopram to a target dose of 30 mg vs placebo in improving agitation and psychosis, as well as anxiety, irritability, and lability, but not without the side effect burden of prolonged QTc and a decreased Mini-Mental State Examination (MMSE) score.28
With evidence suggesting that the (R) enantiomer of citalopram confers more of the harm, and the (S) enantiomer more of the benefit, escitalopram is being investigated to determine if this agent is safer and/or more efficacious than the parent compound. In the meantime, some clinicians are using citalopram or sertraline, which have the best evidence, and others have switched to escitalopram or other antidepressants. Not all agents are equal, however, and some have substantial drug-drug interactions rendering them unsuitable for this patient population (eg, fluoxetine, paroxetine).

Anticonvulsants. Similar to antipsychotics, anticonvulsant use for agitation in dementia has been carried over from use in people without dementia, but use is decreasing with time. There is evidence that valproic acid causes harm, and use is no longer recommended. Despite drug interactions from induction of cytochrome P450 3A4, carbamazepine is a consideration, although not first line. Other anticonvulsant agents are even further down the decision tree due to a dearth of generalizable evidence.

Newer Agents. Several agents are under study for agitation and psychosis in AD. Dextromethorphan-quinidine has shown benefit for pseudobulbar affect and is being investigated for treatment of AD. Dextromethorphan is a sigma-1 and mu opioid receptor agonist that inhibits serotonin and norepinephrine transporters with antagonist properties at NMDA and nicotinic α3β4 receptors; it is combined with quinidine to prolong the half-life, which is otherwise too short. Pimavanserin, approved for treatment of psychosis in individuals with Parkinson’s disease, is also being investigated for use in AD. Like dextromethorphan-quinidine, pimavanserin is not indicated and would be an off-label consideration for management of agitation or psychosis, along with the attendant caveats and considerations for off-label use.

Depression and Anxiety

Depressive symptoms are very common in AD, and the prevalence of major depression is 14.8%. Anxiety symptoms occur frequently and are distressing to those with AD. There is debate as to the specificity and validity of the diagnostic constructs of major depression and anxiety disorders in neurodegenerative disease, as for some, the depressive and anxiety symptoms may be a result of the underlying dementia proteinopathy. Both the dorsal raphe nucleus (serotonin) and the locus ceruleus (norepinephrine) are among the first to be affected by tau protein abnormalities in the course of sporadic AD. This loss of diffuse systems can manifest as behavior changes, especially depression, anxiety, and agitation. Rigorous clinical trials have not demonstrated efficacy of antidepressants for depression in AD, possibly due to the challenges of applying psychiatric nosology to a population with neurodegenerative disease. Nonetheless, identification of depression and anxiety in AD is important. These symptoms are prognosticators for worse outcomes associated with a poor quality of life and serve as alert for a person who needs further attention, including a safety assessment for self-harm and suicidality. Because antidepressants improve serotonergic and noradrenergic transmission, these medications may temporarily improve symptoms resulting from monoaminergic dysfunction, in parallel to the putative mechanisms for treatment of major depression. Despite the failure of clinical trials, guidelines suggest offering depressed and anxious people with AD a trial of antidepressant treatment if severity, acuity, or safety issues warrant treatment. Systematic approaches to treatment have been published, which suggest first-line antidepressant choices include mirtazapine, sertraline, citalopram/escitalopram, venlafaxine/desvenlafaxine, duloxetine, bupropion, and vortioxetine. Of note is that clinical trials of duloxetine or vortioxetine for treatment of depression provide some evidence of improved cognition in adults over age 55. Whether this holds true for individuals with AD has not yet been studied. If safety issues persist, further intervention may be required, including medication augmentation, neurostimulation, or hospitalization, and further psychiatric support may be needed.

Apathy

Apathy is marked by loss of interest, initiative, or emotional reactivity. With prevalence of 49%, apathy is the most common NPS in AD, associated with functional impairment, and emergence is a treatment target. Distinguishing apathy from depression, however, can be challenging. Although apathy may be comorbid with depression, or sometimes confused with depression, antidepressants have not proven effective for apathy, and may even worsen it. Unfortunately, the evidence from treatment studies is of low quality, and most studies are significantly hampered by the variability of measurement tools used. Secondary analyses demonstrated efficacy with cholinesterase inhibitors, but not memantine, but prospective studies are few. From a recent Cochrane review, the best evidence so far is with methylphenidate 20 mg daily, which is thus recommended as the first-line agent if cholinesterase inhibitors are not used. Further studies are ongoing, and the evidence base will grow in this active field of research.

Applying the Evidence for Pharmacotherapy

Once a decision has been made to treat pharmaco logically, the approach depends on the acuity and safety issues associated with the NPS syndrome, and the timeframe required for symptom improvement (Figure 2). For example, if the behavior syndrome is less severe and the individual is not on a dementia medication, then a cholinesterase inhibitor and/or memantine might be an approach, in order to decrease the likelihood of exposure to psychiatric medications. Similarly, if
Figure 2. Stepwise Approach to Pharmacotherapy for Neuropsychiatric Symptoms in People With Alzheimer’s Dementia.
choosing between different medication classes such as antidepressant versus antipsychotic, the time to symptom improvement is a consideration, as antipsychotics act more quickly. The need to manage physical aggression may be more urgent than the need to manage verbal aggression or excessive motor activity and can be taken into consideration. These questions influence the informed consent discussion around pharmacotherapy. For example, in a milder, but clinically significant case of agitation in AD, the first step might be to offer a cholinesterase inhibitor and/or memantine or an antidepressant depending on patient and care partner preferences. However, if the agitation domain of physical aggression is present and puts self or others at risk of harm, temporary antipsychotic use may be considered. Systematic and algorithmic approaches to management of psychiatric syndromes may offer better outcomes than ad hoc trials of individual medications, and an algorithm for agitation management has been developed and is in the process of validation. The clinician should use all information available and frame the treatment in the context of the individual needs of people with dementia, their families, and caregivers, and the public at large, using informed consent principles. Outcomes should be continually assessed, and treatments regularly reevaluated.

Conclusion

Almost ubiquitous in AD, NPS are associated with poor outcomes and impaired quality of life for both the person with NPS and her or his care partner. Clinically significant NPS require judicious, evidence-based treatment. Measurement tools are suggested for routine use in dementia care, at baseline and at regular intervals. Whether for global NPS burden, or for specific neuropsychiatric syndromes, measurement is necessary to assess burden and risk, and to guide and monitor response to treatment. Based on current evidence, we have suggested an approach to the most common NPS manifesting in AD, but this is a rapidly expanding field, and the evidence base is evolving.


Zahinoor Ismail, MD, FRCP C
Hotchkiss Brain Institute
University of Calgary
Calgary, Alberta, Canada

Zahra Goodarzi, BHS (Hon), MD, MSc, FRCP C
Assistant Professor
Department of Geriatrics
Cuming School of Medicine
University of Calgary
Calgary, Alberta, Canada

Disclosures
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