INTRODUCTION

Approximately 5 million Americans have dementia, a number that is rapidly growing and may eventually reach 16 million or more.1 Many of these patients also suffer from psychiatric or behavioral problems, some with psychotic symptoms. This group of problems is sometimes referred to as BPSD (behavioral and psychological problems of dementia) or NPS (neuropsychiatric symptoms of dementia). Such problems contribute greatly to reduced quality of life for patients, their families, and the community. They are also significant drivers of hospitalization and nursing-home placement, adding to the costs of care.

Many nursing-home residents with dementia receive psychiatric medications for management of behavior. The management of NPS is complex and controversial. No medication has proven to be uniquely effective, many patients do not respond to medication trials, responses are sometimes idiosyncratic, and the risks associated with treatment are considerable. In this context, the ethics of care present significant dilemmas.2–4 In recent years, it has become apparent that there is no safe harbor for clinicians—all potential pharmacological therapies present risks.

SYMPTOMATOLOGY OF NPS

Virtually any psychiatric symptom or syndrome may occur as part of NPS. Complex combinations of symptoms are common, evolving over time. Anxiety, depression, apathy, and other mood disturbances are common in early or mild dementia. In moderate dementia, agitation, combative ness, wandering, vocalization syndromes, and sleep disturbances may occur. Disturbances of vocalization include yelling, repeatedly asking the same question, chanting the same word or phrase, or constantly asking for help without a discernible cause. Catastrophic reactions may occur: panic-like responses to changes in the environment (such as an alteration in routines). In moderate dementia, psychotic symptoms may first be observed. Paranoid delusions may serve a self-protective psychological function by allowing the individual to focus on external explanations for memory lapses, such as misplacing items. Psychosis can be difficult to diagnose in demented patients. Delusions and confabulation may overlap, and determining whether an individual suffers from hallucinations can be surprisingly difficult. Loss of inhibition (including inappropriate sexual behaviors) may also take place. In late-stage dementia, all the aforementioned problems may persist or intensify. However, eventually problems of disengagement take hold, such as severe apathy, refusal of care, and loss of appetite. The re-emergence of childlike or infantlike regressive behaviors, such as wandering or shadowing the caregiver, may mark the later stages of dementia. Physical violence, such as pushing or striking others, may also occur.2,5

The etiology of NPS is not well understood and likely involves a variety of factors. These may include pre-existing psychiatric illness, cognitive loss, neurodegeneration, changes in neurotransmitters and neuroreceptors, reactions to the stress of living with dementia, and changes in the environment. Interaction with others, especially caregivers, may play a part in NPS. Delirium and pain are also important contributors to NPS. Medications (especially anticholinergic drugs) and polypharmacy may also be a factor.3

ASSESSMENT AND MANAGEMENT

The assessment of NPS involves a characterization of the symptoms (preferably with some way to quantify them). Understanding the social and environmental context of NPS is necessary to develop a comprehensive plan of management, and pharmacological options are always to be considered in the management of NPS, preferably before medications. Patients’ medical status must also be carefully evaluated, especially since they may be unable to articulate their physical complaints. Possible medical conditions should be considered as a source of delirium or pain.5,6

The possible role of polypharmacy and anticholinergic effects of medications must also be heeded. Caregivers have differing levels of tolerance for problem behaviors, which must be considered during the evaluation process—particularly since clinicians must usually rely on caregiver observations. Similar patient behaviors may be experienced and reported in very different ways by different caregivers, or by the same caregiver at different times. Likewise, a single episode of problematic behavior may be described in different ways by different observers. The caregiver’s level of distress, coping skills, and expectations are all important factors. Clinicians reacting to these observations may propose widely divergent treatments based on such reports. Caregiver support and education may help them objectively manage the behavior in a better fashion, and also cope with the behaviors in a way that lessens their requests for medications.5

The management of NPS involves goal setting. When there is controversy about the conceptualization of NPS and its treatment, it is helpful to establish a consensus among the patient’s family members, physicians, and nursing personnel. Treatment goals should be realistic. It is often useful to identify a primary target symptom for treatment. Preferably, such a target is measurable, can be monitored over time, and relates to the patient’s quality of life. Attempting to treat each symptom separately may lead to overmedication. The Food and Drug Administration (FDA) does not indicate any psychiatric medication specifically for dementia-related behavioral problems. Therefore, such

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Prescriptions are “off-label.” This requires special attention to the risk–benefit ratio, documentation of the therapy and its rationale, and ongoing monitoring for benefits and side effects. More explicit attention is also required for informed consent, typically from a surrogate rather than the patient.

Medication effects are often nonspecific and are highly variable among patients. Therefore, the treatment is essentially empirical and has a significant trial-and-error component. However, some general principles of pharmacotherapy should be observed. An effort should be made to logically select a drug that addresses a target symptom. It is not advisable to prescribe a different drug for each symptom, particularly since there may be a plethora of symptoms. Polypharmacy should be minimized. Frequent reassessment is recommended. The full effects of a medication change may take weeks to emerge. Drugs should be used at the lowest effective dose and for the shortest time period that is clinically feasible. There should be a high index of suspicion for treatment-induced side effects, including increased confusion, agitation, delirium, sedation, falls, swallowing problems, and parkinsonism. Overly rapid dose titration, multiple medications, frequent changes of approach, or multiple simultaneous medication changes may increase the likelihood of problems. The goals of treatment include an acceptable quality of life for both caregivers and patients, rather than simply the eradication of a particular symptom. Reduction in agitation rather than sedation is a goal of treatment in most cases. Undue sedation is associated with side effects and poor outcomes. Behavioral symptoms change and evolve over the course of dementia. Medication requirements also evolve over time. Frequent monitoring after initiation or change of treatment is required. Regular monitoring at intervals of at least three months is recommended. Consideration should be given to tapering and discontinuing medication when symptoms abate.

Cholinesterase inhibitors as well as memantine have been shown to have a modest impact on dementia-related behavioral symptoms, in addition to cognition. However, in cases of significant behavioral symptoms, these medications are usually not sufficient. In recent decades the atypical antipsychotics have probably been the most widely utilized medications in NPS. Many studies, some of limited scope, have shown modest efficacy with reasonable tolerability for atypical antipsychotics in dementia. The large-scale CATIE-AD study showed modest efficacy for risperidone and olanzapine in NPS. However, these effects were counterbalanced by side effects, leading the authors to conclude that there was no evidence of net benefit. In this study, time to discontinuation was an important measure of effectiveness and tolerability. The atypical antipsychotics studied did not show a significant difference from placebo on this measure. In addition, the FDA added boxed warnings concerning the use of atypical antipsychotics, beginning in 2004 with risperidone and olanzapine but ultimately expanded to include the entire classes of both typical and atypical antipsychotics. These warnings cite an elevated overall mortality rate and an elevated risk of cerebrovascular adverse events for risperidone and olanzapine.

These observations continue to be controversial, but there is now a widespread belief that significant health risks are associated with the use of antipsychotics in dementia. This presents a challenge in establishing consensus on how best to care for NPS, as well as contributing to the medicolegal risk of caring for such patients. Following the initial FDA warnings concerning the atypical antipsychotics, some physicians shifted to conventional (typical) antipsychotics such as haloperidol or perphenazine. However, these medications have proven to have as much or more of a side-effect burden, and this trend seems to have faded. Largely owing to these warnings, the rate of prescriptions for antipsychotics in nursing homes has fallen significantly since 2004. Antipsychotic use has become a focus of scrutiny in the nursing home industry.

The presence of boxed warnings for antipsychotics, rather than other categories of medication used in the treatment of NPS, has led to an assumption that other medications must be safer and more appropriate. However, several recent studies have complicated this picture. A 2012 study by Devanand et al. revealed that a relapse of agitation and psychosis may occur in some Alzheimer’s disease patients who are taken off risperidone. In this study, patients maintained on risperidone (mean dose, 0.97 mg daily) who showed a response to treatment were randomized to receive continuing risperidone versus placebo. Over the first 16 weeks of the study, the risk of relapse was 60% in the placebo group versus 33% in the risperidone group. In the following 16 weeks, the group that was switched from risperidone to placebo had a 48% relapse versus 15% in the group that continued to receive risperidone. The rates of adverse events and death did not differ among groups, although comparisons were based on small groups. In a 2013 study by Lopez et al., mortality in dementia patients was found to be correlated with the presence of psychiatric symptoms themselves rather than with antipsychotic medication use per se. The results of this study suggested that high degrees of agitation in dementia are a marker (or perhaps a risk factor) for increased mortality. This underlying agitation, rather than solely the medications used to treat it, may be an important factor in mortality. One study revealed an advantage in safety for quetiapine.

Medications used as alternatives to antipsychotic drug therapy may also be problematic. Anticonvulsant mood stabilizers have long been used to treat agitation, mood lability, aggression, disinhibition, and manic-like symptoms in dementia patients. Of these, valproic acid formulations (such as divalproex) are by far the most widely utilized; they have shown promise in several small trials. However, a large-scale nursing-home trial of divalproex showed no benefit versus placebo as well as significant adverse effects. A 2011 study of valproate in agitation associated with Alzheimer’s disease also failed to show efficacy, and revealed sedation even at low doses. In addition, a 2009 Cochrane review failed to demonstrate efficacy for valproate in NPS in dementia and found greater adverse effects than placebo. Other mood stabilizers such as carbamazepine, oxcarbazepine, topirimate, gabapentin, levetiracetam, and lamotrigine have also been utilized. Carbamazepine has shown promise in reducing symptoms but carries a high side-effect burden. Low-dose topiramate was found to be equal in efficacy to risperidone in one small, prospective, randomized study. A randomized, prospective trial of oxcarbazepine failed to show any benefit. Several case studies and open trials have shown some limited promise for gabapentin, lamotrigine, and levetiracetam, but these require further study.

Antidepressants, particularly the selective serotonin reuptake
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inhibitors (SSRIs) and some serotonin–norepinephrine reuptake inhibitors (SNRIs), are widely used in dementia for depressed mood, anxiety, agitation, and apathy. Unfortunately, several recent studies failed to show a benefit for SSRIs in the treatment of depressive symptoms in demented patients. In 2011, a study by Banerjee et al. failed to show clinical value in treating depression with either sertraline or mirtazapine in patients with dementia, including Alzheimer’s disease. Compared with placebo, patients treated with the antidepressants suffered more adverse events.26 A 2014 study by Porsteinsson et al. showed that the SSRI citapram reduced agitation and caregiver distress but worsened cognition and caused QT-interval prolongation, believed to be a risk for arrhythmia. The QT prolongation seen in this study was at the 30-mg daily dose. Currently, the FDA recommends no more than 20 mg daily in the elderly due to the risk of QT-interval prolongation and torsades de pointes.27 Trazodone, an older antidepressant with primarily serotonergic effects, is used mainly as a sleep aid. It has shown modest effects in reducing agitation in some studies but not others. One trial comparing trazodone to haloperidol showed similar efficacy,28,29 while another trial comparing trazodone to haloperidol did not show a difference from placebo.30 SNRIs such as venlafaxine are widely used although they have not been studied extensively. Mirtazapine is sometimes used to aid sleep, increase appetite, and address weight loss, in addition to reducing depressive symptoms, and may have some benefits for other dementia-related symptoms. One 12-week, open-label study of mirtazapine showed reduced agitation,31 but there are no placebo-controlled trials. Tricyclic antidepressants are not recommended for elderly dementia patients for a number of reasons, including anticholinergic effects, cardiac issues, and orthostatic hypotension.32,33

Benzodiazepines are widely utilized despite admonitions against their use in the elderly. Indications include anxiety, agitation, and sleep. Potential problems include sedation, ataxia, falls, cognitive clouding, and paradoxical reactions.34 Very little systematic study has actually been done in the area of benzodiazepines in NPS. Their use has probably increased as a result of the boxed warnings with antipsychotic medications. In 2014, a large case-control study revealed a strong association between use of benzodiazepines in the elderly and the risk of developing Alzheimer’s disease.35 However, the question of cause and effect was not settled.

In 2011, a study of NPS treatment using opioids revealed a significant response rate and good tolerance, at least over the short term. The possible role of undiagnosed pain in these subjects was not resolved.36 However, this observation remains controversial and is not supported by several other studies.37

CONCLUSION

The use of psychiatric medications, especially antipsychotics, in dementia always involves ethical issues. The patient is usually unable to participate fully in the decision-making process. The interests of patients may not always be identical to those of caregivers. For example, the caregiver may favor a medication that will promote sleep so that the caregiver may also rest, despite possible risks. Families and caregivers may be in conflict over diagnosis, goals, and means of treatment. The boxed warnings and off-label nature of therapy, in addition to the potential for harm as well as benefit, should be weighed against the lack of good alternatives.

There is no single ideal treatment for NPS. The treatment flows from assessment but is nonetheless empirical. It is prudent to maximize nonpharmacological treatments. Consideration of the possibility of pain or delirium as a possible factor in NPS is important. The target symptom may help in selecting and monitoring therapy. The use of cholinesterase inhibitors and/or memantine may help minimize agitation. Close monitoring and frequent re-evaluations are required. Informed consent from proxies is necessary. Responses to medications are individual and widely variable. Patients may respond or fail to respond in unique ways or have unusual adverse reactions.

Antipsychotics have become extremely controversial. There is no clear current consensus concerning their use. Nevertheless, given the lack of alternatives, they will probably continue to be necessary for the foreseeable future. Limiting the use of antipsychotics to management of treatment-resistant cases, psychosis, or severe agitation or aggression may be a prudent stance. The available alternatives to antipsychotics, including valproate, also have limited efficacy and the potential for adverse reactions, and the assumption that they are better alternatives needs to be viewed cautiously.

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