Management of the behavioral and psychological symptoms of dementia

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Abstract: More than 50% of people with dementia experience behavioral and psychological symptoms of dementia (BPSD). BPSD are distressing for patients and their caregivers, and are often the reason for placement into residential care. The development of BPSD is associated with a more rapid rate of cognitive decline, greater impairment in activities of daily living, and diminished quality of life (QOL). Evaluation of BPSD includes a thorough diagnostic investigation, consideration of the etiology of the dementia, and the exclusion of other causes, such as drug-induced delirium, pain, or infection. Care of patients with BPSD involves psychosocial treatments for both the patient and family. BPSD may respond to those environmental and psychosocial interventions, however, drug therapy is often required for more severe presentations. There are multiple classes of drugs used for BPSD, including antipsychotics, anticonvulsants, antidepressants, anxiolytics, cholinesterase inhibitors and NMDA modulators, but the evidence base for pharmacological management is poor, there is no clear standard of care, and treatment is often based on local pharmacotherapy customs. Clinicians should discuss the potential risks and benefits of treatment with patients and their surrogate decision makers, and must ensure a balance between side effects and tolerability compared with clinical benefit and QOL.
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Typical behavioral and psychological symptoms of dementia

Eighty to 94% of residents of long term care facilities have a major psychiatric illness. Dementia is the most prevalent, observed in 47%–78% of residents (Rovner et al 1990; DeVane and Mintzer 2003). Regardless of its etiology, dementia is a clinical syndrome that expresses itself in three areas: cognitive deficits, psychiatric and behavioral disturbances, and difficulties in carrying out daily functions (De Dyn et al 2005). Alois Alzheimer, in his 1906 description of dementia, noted behavioral and psychological symptoms of dementia (BPSD) are prominent manifestations of the illness, including paranoia, delusions of sexual abuse, hallucinations and screaming (Kozman et al 2006). In 1996, the International Psychogeriatric Association convened a consensus conference on the behavioral disturbances in dementia. The consensus group made this statement: "The term behavioral disturbances should be replaced by the term BPSD, defined as symptoms of disturbed perception, thought content, mood or behavior that frequently occur in patients with dementia (Kozman et al 2006, p 1)." BPSD is not a diagnostic entity but is instead a term that describes a clinical dimension of dementia (Lawlor 2004). The multiple cognitive impairments of dementia are often associated with mood disorders and sleep disturbances. BPSD includes disinhibited behavior, delusions and hallucinations, verbal and physical aggression, agitation, anxiety and depression (Carson et al 2006). BPSD can cause tremendous distress for both the patient and the caregiver, and is often the trigger for referral of these patients to primary care and specialist services and placement in residential or nursing home

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care (Steele et al 1990; Ballard et al 2006). The development of BPSD is also associated with a poorer prognosis, a more rapid rate of cognitive decline, illness progression (Stern et al 1987; Paulsen et al 2000), greater impairment in activities of daily living (ADLs) (Lyketsos et al 1997) and diminished quality of life (QOL) (Gonzales-Salvador et al 2000), and it adds significantly to the direct and indirect costs of care (O'Brien and Caro 2001).

At least half of patients attending outpatient dementia clinics, and more than 75% of patients in nursing homes have some sort of BPSD (Zaudig 2000). The prevalence of BPSD in these 24 hour care settings has been reported to be as high as 90%, with individual behaviors including delusions (20%–73%), depression (up to 80%), and aggression and hostility (20%–50%). As many as 80% of Alzheimer's dementia (AD) patients will develop symptoms of BPSD during the course of their illness, often with the onset of cognitive impairment (Lyketsos et al 2002). Patients with mixed AD and vascular dementia have the highest level of psychiatric disturbances (Zaudig 2000; Kindermann et al 2002; Kozman et al 2006).

While the origin of BPSD remains unclear; it is presumed there are multiple etiologies for these symptoms. There are neurobiological, psychological (premorbid personality features and responses to stress), and social (environmental change and caregiver factors) aspects (Zaudig 2000). The neurobiology of behavioral disturbances involves correlations between memory deficits and decreasing cholinergic function, and between serotonin and noradrenaline depletion and a history of depression or aggression. Dysregulations in GABA (gamma-aminobutyrate)-ergic, serotonergic and noradrenergic neurotransmitter systems that have been associated with increased aggressiveness and disturbances are also found in dementia patients (Eichelman 1987; Stoppe et al 1999).

BPSD are now accepted as an important therapeutic target in dementia. Mild forms of BPSD may respond to simple environmental and psychosocial interventions. Although non-pharmacologic interventions should be the first line of treatment, drug therapy is often required for the more severe psychotic, aggressive, and agitated presentations (Lawlor 2004; Sink et al 2005).

Methods of measuring BPSD and the associated challenges

It is important to remember that behavior is merely a form of communication (Kozman et al 2006). BPSD can be difficult to diagnose, given the variety of symptoms. Evaluation of BPSD includes a thorough diagnostic investigation, careful consideration of the etiology of the dementia, and the exclusion of other causes, such as drug-induced delirium or adverse effects of treatments for comorbid conditions (Finkel et al 1996; Zaudig 2000). Undiagnosed medical problems such as pain, depression, dehydration, sleeping difficulty, anxiety and delirium can all lead to agitation.

Pain is often underdiagnosed in patients with dementia, and can manifest itself by behavior changes (such as agitation and increased confusion) and decreased mobility (Pautex et al 2006). Language difficulties associated with dementia interfere with the patient's ability to express pain. In addition, the autonomic activation in response to pain may be blunted in AD patients. A number of pain scales have been developed to evaluate pain in patients with dementia. Some are self-report (for milder dementia); others, such as the PAIN-AD-Pain Assessment in Advanced Dementia (Lane 2003), measure non-verbal signs such as breathing, vocalization, facial expression, and body language. A small study (Douzjian 1998) found that empiric pain medication reduced troublesome behaviors, and allowed for a reduction in psychoactive medication. Positioning and physical therapy may able be helpful.

Sleep disturbances may be associated with and part of BPSD. Circadian rhythms may be altered in AD. Patients with Lewy Body dementia have a high incidence of REM sleep disorders, acting out their dreams. Clinicians should evaluate medications that may disrupt sleep. Other common medical causes of confusion and agitation in the elderly include infections, endocrine disorders, fluid and electrolyte imbalances, and constipation (Daniel 2000). Emotional and interpersonal issues (such as dislike for certain foods or reactions of other people to the patient's behavior) can be a significant factor in agitation. Environmental factors, such as enclosed spaces, isolation, and visual and auditory sensory deprivation may all contribute to or cause a problem.

The diagnostic evaluation and treatment of BPSD require special considerations. Institutionalized, demented and acutely ill elders, particularly those taking multiple medications, are at risk for BPSD. The aging brain provides a different substrate for both the therapeutic and potentially toxic effects of medications. In elderly patients with degenerative brain disorders, the normal redundancy, interdependence, and checks and balances of neuronal networks and neurotransmitters may be disturbed or deficient. For example, delirium may be reversible if the underlying medical causes are addressed promptly, or fatal if overlooked or untreated. A careful medication review should be performed, paying particular attention to any recently introduced medications.

Elderly patients may be more vulnerable to the cognitive effects of drug interactions or to what may be considered therapeutic blood drug levels in younger patients (Stoppe et al 1999; Daniel 2000). Many medications can cause delirium or dementia-like symptoms (Tariot, Profenno et al 2004). While drugs with anticholinergic properties are often associated with delirium or behavior changes, many others such as psychoactive and cardiovascular drugs may also be implicated.

More than 30 scales are available for measuring the behavioral manifestations of dementia (Weiner et al 1996; Stoppe 1999). A number of instruments have been developed to assess the range and severity of BPSD (see Table 1). The most useful, in terms of outcomes assessment, are the Cohen-Mansfield Agitation Inventory (CMAI), neuropsychiatric inventory: nursing home version (NPI-NH), and behavioral pathology in AD (BEHAVE-AD) scales. They are particularly useful because of their specificity, reliability and validity in BPSD (Zaudig 2000; De Deyn et al 2001). It is not clear how much of a percentage change in each assessment tool represents a clinically significant response, however (Lee et al 2004).

Table 1 Common scales used for measuring the behavioral manifestations of dementia

Test name	Test description
Cohen-Mansfield Agitation Inventory (CMAI)	Developed in 1986. It examines 29 types of agitated behavior, including pacing, verbal or physical aggression, repetitious mannerisms, screaming and general restlessness.[a]
Neuropsychiatric Inventory: Nursing Home version (NPI-NH)	Assesses 12 behavioral disturbances: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances and appetite and eating abnormalities.[b]
Behavioral Pathology in AD (BEHAVE-AD)	Developed in 1987. It is a structured psychiatric interview, assessing 25 behaviors in 7 areas: paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance and anxieties and phobia.[c]
Clinical Global Impression of Change (CGI-C)	Establishes a global rating of all aspects of the patient's condition.
Functional Assessment Staging scale (FAST)	Measures the levels of basic activities such as bathing and toileting, and rates patients from independent to totally dependent.

[a]Ballard et al 2006; Kozman et al 2006.
[b]Carson et al 2006.
[c]Carson et al 2006; Kozman et al 2006.

Recognition of BPSD is the first step in developing a management plan, and care must be taken to establish its presence. The goal of treatment should be to detect and manage BPSD before caregiver burnout and irreversible damage to the support environment occurs. The plan should consider the severity and intrusiveness of the behavior and whether non-pharmacologic intervention is sufficient or the behavior is significant enough to require both pharmacologic and psychological interventions (Lawlor 2004). Identifying target syndromes (such as psychotic syndrome versus psychomotor agitation or a sleep disturbance) is useful in development of the management plan. Useful clinical outcomes such as nursing home placement, QOL, and caregiver burden improve a clinician's ability to interpret test results and inform patients and families about the risks and benefits of treatment (Sink et al 2005).

Non-pharmacologic therapy and its evidence

Care of patients with BPSD involves a broad range of psychosocial treatments for both the patient and family. Caregiver education, support and behavioral training are integral parts of the intervention for these patients (Lawlor 2004; Sink et al 2005). Interventions need to be approached in a systematic manner that includes management of the patient's physical health, psychiatric symptoms, and environmental factors (Kozman et al 2006). In a study by Palmer et al (1999), the use of hearing aids improved scores on the BEHAVE-AD. Environmental adjustments, such as lifestyle support are generally first line interventions; however, many cases of aggression, agitation and psychotic symptoms may require pharmacotherapy (Zaudig 2000).

Individualized music therapy, bright light treatment (BLT) and aromatherapy have been found to improve certain problematic behavioral symptoms (Lawlor 2004), as has pet therapy (Sink et al 2005). In a randomized controlled trial (RCT) by Smallwood et al (2000), a combination of aromatherapy and massage mid-afternoon resulted in a reduction in the frequency of behavioral disturbances. In a larger, double-blind, placebo-controlled trial, aromatherapy was found to be a safe and effective treatment for clinically significant agitation in patients with severe dementia (Ballard et al 2002). Lovell et al (1995) studied the effect of BLT on levels of agitation in moderately to severely demented persons. Agitation scores were significantly reduced during therapy compared with controls (Lovell et al 1995). Good sleep hygiene, avoidance of

caffeine and alcohol, and adequate daytime physical activity can be beneficial, particularly for patients who have sleep disturbances and depression. In a randomized controlled trial by Teri et al (2003), a combination of exercise training and caregiver education on behavioral management techniques resulted in improvements in depression and a trend toward less institutionalization. Teaching caregivers techniques to minimize behavior problems can make the home environment less stressful for both the family and the patient (see Table 2). Sloane et al (2004) performed an RCT which measured agitation and aggression, comparing usual hygiene with person-centered showering and towel baths. Results showed that the latter techniques were effective methods of reducing BPSD during bathing persons with dementia. Finally, physical restraints should be avoided, for they are associated with injury, not protection, of confused or demented patients (Miles et al 1992; Sink et al 2005).

Pharmacologic management and its evidence

The evidence base for drug treatment of the behavioral and psychological symptoms of dementia is poor, considering the size of the problem and the distress these symptoms cause. Over the years, drug prescribing for BPSD has evolved in a haphazard and anecdotal way. Although there are multiple classes of drugs in use for neuropsychological symptoms, including antipsychotics, anticonvulsants, antidepressants, anxiolytics, cholinesterase inhibitors and NMDA modulators, there is no consensus nor clear standard of care, and treatment is often based on local pharmacotherapy customs (Sink et al 2005). A balance needs to be made between side effects and tolerability and safety issues compared with clinical benefit and QOL (Kozman et al 2006). In elderly patients, it is possible that any medication could help and/or harm, and the safety of a drug must be considered in the context of its known efficacy (Schneider et al 2005).

Table 2 Behavioral management interventions

Activity associated with potential BPSD	Intervention
Bathing	Make a safe bathroom. Be prepared, don't rush. Ensure room and water temperature are comfortable. Wash hair last. A recent study found benefit of person-centered bathing and towel bath in decreasing agitation and discomfort.[a]
Dressing	Limit choices. Prepare clothing. Give specific cues. Provider larger clothing and soft stretchy fabrics. Provide duplicate outfits and comfortable shoes with Velcro. Give positive reinforcement.
Eating	Maintain a regular mealtime. Avoid distraction at meals. Check the food temperature. Honor preferences when possible, and offer finger foods.
Wandering	Provide adequate daily physical activity. Create a safe environment and safe wandering paths. Remove reminders of leaving (coats, umbrella). Have alarms or bells at exit doors. ID bracelet and "Safe Return" programs are available.
Incontinence	Scheduled voiding. Be attentive to nonverbal cues (such as pacing). Simplify clothing and clear obstacles. Put signs (including pictures) at the bathroom door. Give positive reinforcement.

[a]Sloane et al 2004.

Since the neurobiology of BPSD is still unclear, it seems likely that the symptoms may involve different neurotransmitter systems and may therefore respond to different therapies (Kozman et al 2006). Drug-responsive symptoms include anxiety, verbal and physical agitation, hallucinations, delusions, and hostility, whereas wandering, hoarding, unsociability, poor self-care, screaming and other stereotypical behavior seem to be unresponsive to all drugs (Maletta 1990; Stoppe et al 1999). Pharmacologic intervention is often necessary and includes use of antidepressants for mood disorders, anticonvulsants for nonpsychotic agitation and antipsychotics for aggression, agitation and psychotic symptoms. Antidepressants, anxiolytics and hypnotics should only be used in patients with marked and persistent symptoms and drug treatment should be targeted to specific syndromes that are clinically significant because of their frequency, pervasiveness, or impact (Lawlor 2004).

If drug therapy is to be instituted, Sink et al (2005) recommend two approaches to the management. One is to identify the target symptom and choose a drug that is known to treat symptoms most closely related to the one the patient is exhibiting (as mentioned above). An alternative approach is one guided by current evidence in combination with the goal of minimizing side effects. They recommend beginning with a cholinesterase inhibitor if the patient is not already on one, because they are well tolerated and may benefit cognition and function. It is important to remember that titration speed and target dosage of psychoactive drugs are substantially reduced in the elderly (Daniel 2000). Benzodiazepines should be avoided, especially for long term management, as their use can lead to increased confusion, falls and may paradoxically increase agitation in patients with dementia. No psychoactive medication prescribed to treat neuropsychiatric symptoms of dementia should be continued indefinitely and attempts at

drug withdrawal should be made regularly. Because of the instability of the symptoms of BPSD, many patients who are prescribed antipsychotics for neuropsychiatric symptoms will no longer need them when the drug is later discontinued (Stoppe et al 1999).

Medications commonly used to treat BPSD

In psychotic, behaviorally disturbed elders, an ideal medication should have rapid onset, sustained action and minimal somatic and cognitive side effects (Daniel 2000). Conventional antipsychotics, such as haloperidol, have been used effectively to control the behavioral and psychological symptoms of dementia. Other drugs, such as valproate and carbamazepine, have shown some efficacy in controlling behavioral symptoms in elderly patients (Mellow et al 1993; Tariot et al 1994; DeVane and Mintzer 2003). However, only the atypical antipsychotics risperidone and olanzapine currently have the best evidence of efficacy in treating neuropsychiatric symptoms. Trials of cholinesterase inhibitors have had consistent yet small positive effects as well (Sink et al 2005).

Antipsychotics

Antipsychotic medications have been the mainstay of psychopharmacological treatment for BPSD during the last several decades despite their overuse in the 1980s and the federal regulations implemented in the early 1990s (Schneider et al 2005). Up until the mid 1990s, conventional neuroleptics such as haloperidol were the primary pharmacologic treatments for BPSD. Antipsychotics are the drugs of choice in the treatment of intrusive delusions and hallucinations. Coexisting nonpsychotic symptoms including sleeplessness, excitability, hostility, belligerence, emotional liability, restlessness, agitation, aggression and irritability may also show improvement with antipsychotics. Other symptoms such as hypersexuality, apathy and withdrawal do not generally improve. Since antipsychotics have such a narrow therapeutic window, they should be prescribed and dosage adjusted with the expectation of clinical improvement within a certain timeframe (Kindermann et al 2002). If improvement is not observed, the medication could be discontinued or switched after two to four weeks (Schneider et al 2005; Schneider, Tariot et al 2006). Low dosages and careful dose titration are needed when prescribing them to the elderly with dementia. However, these low dosages may also lead to limited efficacy (Stoppe et al 1999).

In the past, antipsychotic use in dementia has been excessive, possibly inappropriate, and poorly monitored. The goal of antipsychotic therapy must be the improvement in a specific target behavioral syndrome without impairing other aspect of dementia such as cognition, function, and quality of life (Lawlor 2004). Antipsychotics are more effective than placebo, but the effect is modest and they are frequently associated with adverse effects, including increased risk of falls and drowsiness, parkinsonism, akathisia, tardive dyskinesa (TD), social withdrawal, accelerated cognitive decline, QT prolongation, stroke, and sensitivity reactions (Ballard et al 2006). Both conventional antipsychotics and just the presence of psychosis have been associated with more rapid cognitive decline in dementia patients (Schneider, Dagerman et al 2006). Patients with Lewy Body dementia have been reported to have marked sensitivity, including neuroleptic malignant syndrome, to typical and atypical antipsychotics, especially risperidone (Ballard et al 1998; Sink et al 2005).

The newer atypical antipsychotics are associated with fewer extrapyramidal symptoms (EPS) (Jeste et al 1999; De Dyn et al 2005). The perceived safety advantages of the atypicals include less of the following: sedation, cardiovascular (CV) adverse effects, postural instability, falls and movement disorders. The FDA added warnings of increased CV adverse events to the US prescribing information for some atypical antipsychotics in April 2003, January 2004 and February 2005. In April 2005, the FDA issued a health advisory for increased risk for death with use of atypicals in patients with dementia (Kozman 2006; Schneider, Dagerman et al 2006).

Atypical antipsychotics

The American Academy of Neurology recommends the use of antipsychotics to treat agitation and psychosis in patients with dementia where environmental manipulation fails, and guidelines state that atypical antipsychotics may be better tolerated than older conventional antipsychotics (Doody et al 2001; Carson et al 2006). Clozapine, the prototypical atypical antipsychotic, was approved in 1989. Since then, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole have been introduced (Carson et al 2006). Risperidone was the first agent to be proven effective for the behavioral and psychological diagnoses of dementia, and it has the largest database of double-blind controlled trials to support its efficacy (De Dyn et al 2005). It is effective in controlling aggression, agitation and psychotic symptoms in patients with many different forms of dementia. It is well tolerated and does not further impair the daily function of elderly patients with dementia (Zaudig 2000). Atypical antipsychotic drugs in general are widely used to treat psychosis, aggression and

agitation in patients with AD, however, their benefits are uncertain and concerns about safety have emerged.

In a double-blind, placebo-controlled trial (Schneider, Tariot et al 2006), 421 outpatients with AD and psychosis, aggression or agitation were randomly assigned to receive risperidone, olanzapine, quetiapine, or placebo. No significant differences were noted with regard to improvement on the CGIC scale. Adverse effects offset advantages in the efficacy of atypicals for the treatment of BPSD (Schneider, Tariot et al 2006). A 2006 Cochrane Review (Ballard et al 2006) evaluated 16 placebo-controlled studies with atypicals. Only 9 had sufficient data for a meta-analysis. The review looked at outpatients or people living in care facilities and found (Ballard et al 2006, p 5):

1. A significant improvement in aggression with risperidone and olanzapine compared to placebo.
2. A significant improvement in psychosis with risperidone.
3. Risperidone and olanzapine patients had a significantly higher incidence of serious adverse CV events and EPS (especially with risperidone doses greater than 1 milligram).
4. A significant increase in drop-outs with risperidone and olanzapine.
5. Data was insufficient to comment on cognitive function.

These reviewers and numerous other studies throughout the literature have come to similar conclusions that, overall, the evidence for olanzapine and risperidone supports their efficacy compared with placebo, but their potential for increased risk of CV events and mortality is a serious concern and limits their overall effectiveness (Ballard et al 2006; Carson et al 2006; Schneider, Tariot et al 2006). Likewise, the Committee on the Safety of Medications reported a three-fold increase in the risk of CV adverse events with the atypicals, compared with placebo. Both olanzapine and risperidone have good evidence base and they appear to be well tolerated otherwise. Considering the consistency of the risks among the various studies reviewed, it is likely that there is increased risk from any of the atypicals and not from a particular one (Schneider et al 2005). The modest efficacy and uncertain response rates combined with the risks detailed suggest that antipsychotics should be used within the context of medical need and the efficacy and safety of alternatives (Schneider, Dagerman et al 2006). Their use should be targeted towards the treatment of those patients in whom BPSD are prominent and associated with significant distress, functional impairment or danger to the patient (De Dyn et al 2005). The use of lower doses might be prudent and effective (Schneider, Dagerman et al 2006).

The adverse effects associated with atypical antipsychotics seem to be dose related, supporting the practice of starting with a low dose and increasing slowly as the drug is tolerated. In addition to the adverse CV effects discussed above, there is increasing evidence that the treatment with antipsychotics may be associated with metabolic disturbances such as impaired glucose metabolism, hyperlipidemia, and weight gain, all of which may adversely affect QOL (Lee et al 2004; Jones et al 2006). Neutropenia and agranulocytosis may also occur with olanzapine (Benedetti et al 1999; Zaudig 2000). There were no clinically relevant changes in blood pressure or heart rate in phase III studies with risperidone, nor were there any occurrences of EKG abnormalities (Katz et al 1999; Zaudig 2000). There has been no evidence for increased injury, fall or syncope; however the risks of somnolence and urinary tract infections (or incontinence) are increased with the atypicals (Schneider, Dagerman et al 2006). Sedation is particularly likely with olanzapine, which can also be associated with increased confusion (Schneider, Tariot et al 2006).

Conventional antipsychotics

Conventional (or typical) antipsychotics have been extensively studied in elderly demented patients with disappointing results. Effect size and response rates have been modest, with no consistent evidence that any conventional antipsychotic is more effective than another. Potentially serious adverse effects occur frequently, especially motor side effects, sedation, cognitive impairment, orthostatic hypotension, constipation, and urinary hesitancy (Daniel 2000; Lee et al 2004). In the US, concerns about overuse of antipsychotics led to the introduction of legislation (the Omnibus Budget Reconciliation Act of 1987) that attempted to restrict prescribing of antipsychotics to residents of nursing homes (Streim 1995; Stoppe et al 1999). Before the introduction of this act, up to 55% of nursing home residents were treated with antipsychotics (Lee et al 2004).

Haloperidol is the most widely studied typical antipsychotic and modest improvement in psychosis and agitation has been reported in investigations with it (Kindermann et al 2002). A Cochrane review of haloperidol compared with placebo concluded that haloperidol had no effect on agitation, behavioral symptoms as a whole, or CGIC scores, but appeared to reduce aggression (Sink et al 2005; Kozman et al 2006). In two other meta-analyses there was no difference in efficacy among the different typical antipsychotics on neuropsychiatric symptoms (these studies included haloperidol, thioridazine, thiothixene,

chlorpromazine, trifluoperazine and acetophenazine). There is no evidence that any one typical antipsychotic is more effective than another (Sink et al 2005). In addition, conventional antipsychotics were associated with a significantly higher adjusted risk of death than were atypicals in all subgroups defined according to the presence or absence of dementia or nursing home residency (Wang et al 2005). The greatest increases in risk occurred soon after therapy was initiated and with higher dosages. Conventional antipsychotics are at least as likely as atypicals to increase the risk of death among elderly persons and should not be used to replace the atypicals that were discontinued in response to the 2005 FDA warning (Wang et al 2005).

Elderly patients are sensitive to EPS, especially parkinsonism, akathisia, and TD. Only one third of patients with dementia show behavioral improvement with conventional antipsychotic treatment, while the majority of patients treated with these will experience side effects, especially the anticholinergic effects (Tariot, Profenno et al 2004). The presence of EPS can lead to medication intolerance, falls and other adverse effects. In addition, typical antipsychotics have serious, potentially fatal, consequences in patients with Lewy Body dementia (Ballard et al 1998; Zaudig 2000). In one study, patients started on very low dosages of haloperidol or thioridazine developed parkinsonism within nine months of antipsychotic therapy (Kindermann et al 2002). The lower incidence of EPS and TD seen with atypicals represents a significant benefit to patients. Choosing antipsychotic agents with fewer anticholinergic properties is an important consideration in elderly patients.

Anticonvulsants

Anecdotal reports have suggested that anticonvulsants such as carbamazepine, valproic acid and gabapentin may be effective in the treatment of BPSD. Gabapentin has shown some benefit when treating aggressive behavior in patients with dementia, but it has not been well studied (Hawkins et al 2000; Kozman et al 2006). Carbamazepine has been investigated in several trials and was found to reduce agitation, restlessness and anxiety (Tariot et al 1994; Stoppe et al 1999), however the efficacy and tolerability of long term use of this drug is yet to be established (Kozman et al 2006). Ataxia can occur in elderly patients treated with carbamazepine (Kindermann et al 2002) and in the United States there is an FDA "black box" warning for hematologic toxicity and the potential for drug-drug interaction with its use (Sink et al 2005). Valproic acid had been reported to show some positive effects, with a benign adverse effect profile (Mellow et al 1993; Stoppe et al 1999); however, in more recent studies it does not appear to be effective for the treatment of neuropsychiatric symptoms of dementia, whether in short or long acting preparations. It also caused significantly more adverse effects than placebo, especially sedation. Therefore, valproic acid is not routinely recommended for the treatment of BPSD (Sink et al 2005).

Antidepressants

Depression is common in patients with dementia. As many as 40% of patients with dementia have significant depressive symptoms at some stage. Reducing symptoms such as irritability may aid in the treatment of BPSD (Kozman et al 2006). Biochemical data have suggested that serotonergic deficits in AD contribute to aggressive verbal and physical outbursts, sleep disturbance, depression and psychosis (Polluck et al 2002). Some antidepressants have significant side effects, and not all studies have shown efficacy in treatment of neuropsychiatric symptoms of dementia other than depression (Sink et al 2005; Kozman et al 2006).

Selective serotonin reuptake inhibitors (SSRI's) may have "neuroleptic" effects by reducing dopaminergic outflow, and dysregulation in serotonergic neurotransmission may play an important role in the psychotic symptoms of dementia patients (Polluck et al 2002). Citalopram is the most selective, with moderate potency and high bioavailability. An open pilot study using citalopram demonstrated that it was well tolerated and the patients experienced a significant reduction in agitation, hostility and suspicion (Polluck et al 1997). One review found that citalopram significantly improved emotional bluntness, confusion, irritability, anxiety, fear, depressed mood, and restlessness (Nyth et al 1990; Kozman et al 2006). In AD patients, psychotic and nonpsychotic behavioral disturbances improved acutely with both citalopram and perphenazine. However, only citalopram demonstrated acute efficacy superior to placebo (Polluck et al 2002). Sertraline, in conjunction with donepezil, showed statistically significant improvement in CGIC scores (Finkel et al 2004; Kozman et al 2006), but in another trial, there was no significant benefit of sertraline on neuropsychiatric symptoms other than depression (Lyketsos et al 2003; Sink et al 2005). Trazodone is widely used for agitation, sleep disorders, and disruptive behavior because of its sedative effect and negligible anticholinergic activity. A comparison of trazodone with haloperidol for treatment of agitation in 28 patients with dementia showed similar overall efficacy of both drugs and a lower rate of adverse effects in the trazodone group (Sultzer et al 1997; Stoppe et al 1999).

Cholinesterase inhibitors

Cholinesterase inhibitors are licensed for the treatment of mild to moderate AD (Kozman et al 2006). In some studies, donepezil had no effect on neuropsychiatric symptoms while in one study, anxiety, depression/dysphoria and apathy were significantly improved compared with placebo (Feldman et al 2001; Kozman et al 2006). In Lewy Body dementia, donepezil has shown significant improvement over time in behavioral symptoms (Lanctot and Herrmann 2000; Kozman et al 2006). Galantamine has demonstrated effectiveness, and has shown a significant reduction in behavioral disturbances and improvement in the total NPI caregiver burden. A study using rivastigmine showed that long term therapy with it can slow the progression of BPSD symptoms, including aggressiveness and activity disturbances (Rosler et al 1999; Kozman et al 2006). In another study, rivastigmine significantly improved neuropsychiatric and behavioral symptoms compared with baseline (Aupperle et al 2004; Kozman et al 2006). Although some of these trials have shown statistically significant differences, most data reporting the benefits on behavioral and psychological disturbances are from secondary outcome measures and the magnitude of effect has been small and of questionable clinical significance (Sink et al 2005). Further research is needed.

Other medications

Medications such as memantine, buspirone, beta blockers, benzodiazepines, and thiothixene (Finkel et al 1995) have been evaluated for their use in treating BPSD. Adding memantine to donepezil resulted in better outcomes (than placebo) for dementia patients on measures of cognition, ADLs, global outcome, and behavior. It showed a significantly beneficial effect compared with placebo in relation to agitation and aggression (Tariot, Farlow et al 2004; Kozman et al 2006). However, there does not appear to be a clinically significant benefit using memantine in the treatment of neuropsychiatric symptoms of patients with moderate to severe AD (Sink et al 2005). A case report noted the addition of buspirone to antidepressants and olanzapine after 2 weeks resulted in significant improvements (Cooper 2003; Kozman et al 2006). Its benign adverse effect profile also makes buspirone a useful alternative in mild agitation. However, it showed less effect on agitation compared with trazodone or placebo (Lawlor et al 1994; Stoppe et al 1999). Low dose propranolol was effective in reducing disruptive, aggressive behavior in the majority of outpatients in one study; however, there are no controlled trials on use of beta blockers in BPSD (Shankle et al 1995; Kozman et al 2006). Benzodiazepines show significantly more improvement in BPSD symptoms when compared with placebo; however, they should be used with caution because of their adverse effects (Stoppe et al 1999; Zaudig 2000; Kindermann et al 2002).

Risks associated with pharmacologic treatment of BPSD

The elderly are at particular risk for drug-related adverse events. Older patients in general, and patients with dementia in particular, are more sensitive to medication adverse effects, including anticholinergic effects, orthostatic hypotension, sedation, parkinsonism, tardive dyskinesia (TD) and cognitive impairment than younger patients with dementia or individuals without dementia. They are also especially prone to falls, and drugs that cause sedation, postural hypotension or extrapyramidal symptoms (EPS) have been found to cause an increased incidence of falls (Zaudig 2000).

The aging body undergoes physiological changes that affect both pharmacokinetics and pharmacodynamics (DeVane and Mintzer 2003). Aging is characterized by a progressive loss of the functional capacities of all the vital organs, including the brain. There is an alteration in the body's composition of lean and fat body mass and a decrease in the excretory capacity of the kidney, causing many drugs to be eliminated from the body more slowly. Changes in drug distribution are also important. Age related reductions in liver mass, hepatic blood flow and hepatocyte function result in delayed clearance of drugs that are metabolized in the liver. Lower starting doses, smaller dose increments and longer dose escalation periods must be used to avoid potentially toxic drug accumulation. Concurrent illnesses and associated polypharmacy are extremely common in elderly patients. Potential drug-drug interactions must be considered (Zaudig 2000).

Central and peripheral anticholinergic adverse effects, such as constipation, urinary retention, dry mouth, blurred vision and cognitive deficits, are particularly troublesome for elderly patients (Kindermann et al 2002). Peripheral effects include urinary retention, constipation, blurred vision, and dry mouth. Central anticholinergic effects include sedation, confusion, delirium, and cognitive decline. Elders are also more sensitive to the adverse effects related to blockade of adrenergic and histaminic receptors. Histaminic blockade causes sedation and adrenergic receptor blockade can lead to orthostatic hypotension, dizziness and syncope (which can contribute to falls) (DeVane and Mintzer 2003). Evidence also suggests that the relative affinity at muscarinic and adrenergic receptors may affect multiple aspects of cognition, including memory and executive functions (Daniel 2000).

An approach to management of BPSD

The initial approach to the management of BPSD should always include the non-pharmacologic therapies discussed earlier. Often, pharmacologic intervention is needed. As mentioned previously, there is no consensus nor clear standard of care when it comes to pharmacologic management of BPSD. We would like to offer, instead, general guidance for first and second line treatment of some of the behavioral and psychological symptoms associated with dementia. Most patients with dementia present with more than one of these symptoms, and a single medication may be able to treat multiple symptoms. First, when the diagnosis of AD has been made, a cholinesterase inhibitor could be initiated, with or without memantine (in mild to moderate AD). For second line therapies, providers should use target symptoms to guide their treatment. The SSRI antidepressants citalopram and sertraline have the best evidence for their use in reducing symptoms such as irritability, sleep disturbances, and some aggression. Trazodone may also be helpful, particularly with sleep disturbances and agitation. Benzodiazepines can be effective but must be used with caution in the elderly. Finally, the atypical antipsychotics such as risperidone and olanzapine may be used for controlling aggression, agitation and psychotic symptoms in many different forms of dementia. We caution, however, that close monitoring be undertaken, and the medications be carefully titrated for effect. If they are not effective in controlling target symptoms, then the medications should be discontinued.

Conclusion

The increasing life expectancy in most Western societies along with other factors such as improved detection of dementia, administration of disease modifying agents, and improved healthcare techniques, has led to a rapidly growing number of elderly people with dementia and longer survival of these patients. Behavioral and psychological disorders occur in most dementing conditions, usually in later stages. One half of these patients experience psychotic symptoms, such as delusions and hallucinations, which in turn makes them more vulnerable to severe agitation. Treatment of these disorders in dementia should reduce the patients' and the caregivers' burden, resulting in lower rates of institutionalization and less psychophysical morbidity in the family (Stoppe et al 1999; Kindermann et al 2002).

Caregiver education, support and behavioral training, and environmental modifications are important components of the management of BPSD, and should be the first step in approaching the dementia patient with these symptoms. However, pharmacologic management is often needed. There are many classes of medications to choose from for treating these neuropsychiatric symptoms, but the evidence behind treatment is varied and confusing. Clinicians considering pharmacologic therapy, especially the antipsychotics, should discuss the potential risks and benefits of such therapy with patients and their surrogate decision makers, noting any risk factors those patients may have (for CV disease, for example). Good clinical practice dictates that patients receive individualized pharmacotherapeutic dosing regimens initiated and modified relative to clinical efficacy and tolerability and targeted to specific neuropsychiatric symptoms (Tariot, Profenno et al 2004). "The art of drug treatment is to use the right drug for the right symptoms at the proper stage of the disease starting low and going slow (Gauthier 2005, p 857)."

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