

Behavioral and Psychological Symptoms of Dementia (BPSD) Educational Pack



The BPSD Educational Pack was produced by the International Psychogeriatric Association (IPA) under an educational grant provided by Janssen-Cilag. The opinions expressed in the BPSD Educational Pack are those of the contributing authors and are not to be construed as the opinions or recommendations of the publishers or sponsors. Full prescribing information must be obtained for any of the drugs or procedures discussed herein.

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MODULE 6: Pharmacological management

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Key messages

- In general, non-pharmacological approaches are first-line treatment for behavioral and psychological symptoms of dementia (BPSD).
- For BPSD that are moderate to severe and which impact on the patient's or the caregiver's quality of life or functioning, medication is clearly indicated, often in conjunction with non-pharmacological interventions.
- In elderly patients with dementia, dosages of medication will generally be lower than those used in younger patients and in older non-demented people, although the elderly are a heterogeneous group requiring an individualized approach to dosing.
- Antipsychotic medication is most effective in the treatment of psychotic symptoms (hallucinations, delusions) and behavioral symptoms, such as physical aggression.
- Newer antipsychotic medications appear to be at least as effective as conventional neuroleptics, but have fewer side effects.
- Antidepressant medications are underused in people with dementia, despite the common occurrence of depression in dementia and the documented therapeutic value of these drugs.

General principles

The first step in the management of behavioral and psychological symptoms of dementia (BPSD) involves the careful assessment and correction of any physical, psychosocial or environmental triggers, or perpetuating factors, in the genesis of BPSD. The clinical presentation and diagnostic criteria for BPSD are presented in Module 2 and etiology is discussed in Module 3.

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- In general, non-pharmacological approaches are the first-line treatment for BPSD (see Module 5), but for symptoms that are moderate or severe, medication is indicated, often in conjunction with non-pharmacological interventions.
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When using drugs in a population with dementia, due consideration must be given to the age and disease-related changes in the pharmacokinetic and pharmacodynamic properties of the prescribed drug:

- Nutritional deficiencies in frail, elderly people can result in hypoalbuminemia leading to more of the active drug being available at the site of action
- Age-related changes in renal and hepatic function are associated with decreased drug metabolism and clearance and a greater chance of toxicity and side effects from drug-drug interactions
- The half-lives of psychotropics are further increased because most are lipophilic, and fat stores are increased in the elderly
- The brains of dementia patients are more sensitive than those of age-matched controls to the side effects of most drugs, particularly the sedating and cognitive-impairing effects of benzodiazepines, the central anticholinergic side effects of tricyclic antidepressants, and some neuroleptics.
- Many dementia patients, especially those with Lewy bodies, will demonstrate increased sensitivity to neuroleptic medication (conventional neuroleptics in particular), due to age and disease-related dopamine neuronal fallout.

Prescribing must be informed and judicious, utilizing low starting doses; slow and cautious dose titration, and careful monitoring for the emergence of side effects.

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- Before deciding whether to treat BPSD with medication, the following questions must be addressed:
 - Does the particular symptom or behavior warrant drug treatment, and why?
 - Is this symptom or behavior drug-responsive?
 - Which category of medication is most suitable for this symptom or behavior?
 - What are the predictable and potential side effects of a particular drug treatment?
 - How long should the treatment be continued?
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Drug treatment for BPSD should only be initiated after these symptoms have been found to:

- have no physical cause
- be unrelated to the effects of other medication
- not respond to or be appropriate for non-pharmacological interventions.

Drug classes and target symptoms

The issue of whether a particular drug is effective can be a difficult one. Pharmacological treatment is indicated, however, where there is evidence from practice that particular symptoms or behaviors respond to a drug intervention the use of different pharmacological agents in the management of BPSD is outlined in Table 1.

Table 1. Pharmacological therapy and BPSD.

Drug category	Target symptom
Antipsychotics	
Conventional neuroleptics	Psychosis (delusions, hallucinations), hostility, aggression, agitation, violent behavior, sleep-wake cycle disturbances
Newer antipsychotics	Psychosis (delusions, hallucinations), hostility, aggression, agitation, violent behavior, sleep-wake cycle disturbances
Antidepressants	
Trazodone	Sleep-wake cycle disturbances, agitation, aggression, anxiety, depressive syndromes
Selective serotonin reuptake inhibitors	Depressive syndromes, depression-associated agitation, emotionality, irritability
Tricyclic antidepressants	Depressive syndromes, depression-associated agitation, sleep disturbance, emotionality
Moclobemide	Depressive syndromes, depression-associated agitation
Benzodiazepines	Anxiety, agitation, tension, sleep disturbance
Anticonvulsants	Agitation, aggression, hostility, sleep-wake cycle disturbance, manic type behavior
Valproic acid, carbamazepine	

It is useful to identify the target symptoms or behaviors for a specific drug treatment because several symptoms can coexist in a single patient – a patient who is paranoid and aggressive may also be sleep disturbed and physically agitated. In this instance, a neuroleptic may be chosen to target the psychotic symptoms with secondary benefit for agitation and sleep disturbance.

As a matter of principle, drug treatment for BPSD should be time limited and, with the exception of antidepressant treatment for depression, should not exceed 12 weeks without a review of the treatment regimen. When medication is discontinued, however, it is possible that some patients will experience a recurrence of symptoms, in which case medication should be reinstated.

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- The outcome of a pharmacological treatment should be monitored on a routine basis for both its efficacy, i.e., effect on the frequency and severity of the symptom(s) and its side effects.
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Antipsychotics

There are two broad categories of neuroleptic medications available for use in dementia patients:

- Conventional neuroleptics are primarily dopamine D₂-blockers and are associated with the development of extrapyramidal side effects (EPS). Examples of such agents are haloperidol, thiothixene and loxapine
- The second category is newer and is often referred to as novel or atypical as this class of agent is not typically associated with EPS. These agents have weak D₂-blocking potential or, if they have D₂-antagonist properties, these are balanced by serotonergic antagonist action.

Clozapine was the first and prototypical novel antipsychotic but there are now a number of agents available including risperidone, olanzapine, quetiapine and ziprasidone.

Conventional neuroleptics

Traditionally, conventional neuroleptics are the most common psychotropic medication prescribed to agitated dementia patients in nursing homes and long-stay institutions (Ray et al., 1980; Gilleard et al., 1983). However, in spite of their widespread use only a modest evidence base exists to support such a trend. These drugs have been prescribed for a wide range of behavioral symptoms in dementia, sometimes without sufficient consideration given to which symptoms will respond to this class of medication and the impact of side effects.

Based on the evidence (Barnes et al., 1982; Petrie et al., 1982; Devanand et al., 1989; Finkel et al., 1995), the symptoms that appear to be most responsive to neuroleptic medications are:

- physical aggression and violent behaviors
- psychosis (hallucinations, delusions)
- hostility.

Individual patients with particular BPSD may show a beneficial response to neuroleptic medication and patients with distressing symptoms, other than these 'target symptoms or behaviors,' can benefit from an empirical trial of neuroleptic.

Efficacy of conventional neuroleptics

There have been several uncontrolled studies and a few reports of placebo-controlled trials of the efficacy of conventional neuroleptics in dementia (Finkel et al, 1995; Devanand et al, 1998).

The uncontrolled studies are generally of short duration, i.e., 3-8 weeks, and include elderly patients with schizophrenia who might be expected to respond to neuroleptic treatment (Tewfik et al., 1970; Tobin et al., 1970). The improvement rate in such studies is 25-75%, but very few critical outcome measures were used.

Of the randomized, placebo-controlled trials of conventional neuroleptics in dementia patients, most had small numbers of patients and were of short duration. The consistent findings in these studies (Sunderland and Silver, 1988; Devanand, 1995) were:

- frequent occurrence of side effects
- a large placebo effect
- variable efficacy.

It is important to note that the early placebo-controlled studies evaluating efficacy in BPSD were carried out with conventional neuroleptics at higher doses than those currently used. However, Finkel, in a 20-week placebo-controlled crossover study found the drug was statistically significant. This might account for the high frequency of side effects reported, an argument supported by the much lower side effect rates reported in recent trials of conventional neuroleptics (Finkel et al., 1995). From an efficacy standpoint, a meta-analysis of such studies showed that conventional neuroleptics improved BPSD overall, but only in 18-26% more of patients compared with placebo (Schneider et al., 1990; Lanctot et al 1998). A recent placebo controlled study with haloperidol over 6 weeks showed significant benefit for haloperidol for psychosis and psychomotor agitation at higher doses of 2-3mg/day but not at lower doses of 0.5-0.75mg/day. A subgroup of patients on the higher dose of haloperidol developed significant extra pyramidal side effects (Devanand, DP et al., 1998).

Side-effect profile of conventional neuroleptics

The most common side effects of conventional neuroleptics are:

- extrapyramidal side effects (e.g., drooling, rigidity, akinesia) with high-potency conventional agents such as haloperidol and thiothixene
- postural hypotension and anticholinergic side effects (e.g., dry mouth, constipation, blurred vision, urinary hesitancy and retention, increased confusion) with low-potency conventional agents such as thioridazine and chlorpromazine.

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- Dementia patients, because of their age and underlying degenerative brain disease are much more at risk of developing tardive dyskinesia.
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The estimated incidence of tardive dyskinesia in the elderly following conventional neuroleptic treatment is 30% per year. For this reason an 8-12 week (time-limited) exposure of dementia patients to neuroleptics is to be encouraged. When side effects occur, the dose of conventional neuroleptic should be reduced or discontinued depending on the severity of the adverse event, and an alternative agent considered. The use of anticholinergic agents to reverse the EPS of conventional neuroleptics should be avoided, as they are likely to increase cognitive impairment.

Effects of conventional neuroleptics on cognition and function

It is possible that long-term exposure to conventional neuroleptics, while improving behavioral disturbance, results in a more rapid deterioration in functional ability and a progression of the stage of dementia. Treatment with haloperidol over 6–8 weeks was associated with a decline in cognition

on the Mini-Mental State Examination (MMSE) (Devenand et al., 1989). A number of studies have reported an association between the presence of psychosis or psychiatric symptoms and a more rapid rate of progression (McShane et al. 1997).

The association between psychosis and a more rapid downhill course could also be explained by a worsening of cognition and functional abilities with conventional neuroleptics (Stern et al., 1987; Chui et al., 1994; McShane et al., 1997). It has also been suggested that the worsening of cognitive impairment in patients with Alzheimer's disease could result through central muscarinic blockade caused by the anticholinergic side effects of low-potency conventional neuroleptics.

Withdrawal of conventional neuroleptics

There are a number of studies to show that dementia patients' symptoms actually remain stable or improve when they are withdrawn from a conventional neuroleptic (Thapa et al., 1994; Horowitz et al., 1995; Bridges-Parlet et al., 1997). Thus, for some patients with disturbed behavior who are already on a conventional neuroleptic, withdrawing the medication may be a preferred option.

Reasons for limited efficacy of conventional neuroleptics in BPSD

The limited efficacy of conventional neuroleptics in treating BPSD (only 18-26% improvement vs. placebo in two meta-analyses; Schneider et al., 1990; Lanctot et al, 1998) may have several explanations:

- Psychosis in dementia may have a different neurobiological substrate from functional illness and therefore, may be less responsive to neuroleptics.
- Some psychotic symptoms in dementia (such as delusions of stealing and misidentifications) may be directly related to cognitive and perceptual abnormalities.
- People with dementia are elderly; therefore use of conventional neuroleptics is limited by the patient's sensitivity to side effects. Only low (and hence, less effective) doses can be used.

Newer antipsychotics

There are open-label studies, case reports and recent reports from four placebo-controlled, double-blind studies to suggest that newer antipsychotics are effective in the treatment of BPSD and have improved side-effect profiles.

It has been suggested that newer antipsychotics, because of their lower propensity to cause EPS, may be less likely to cause tardive dyskinesia. However, a definitive statement to this effect will require long-term treatment studies.

Side-effect profile of newer antipsychotics

With the exception of clozapine (the utility of which is limited in BPSD by its side effects), the side-effect profile of newer antipsychotics is generally favorable.

Clozapine has significant anticholinergic and postural hypotensive effects, but it is associated with a risk of agranulocytosis and requires weekly white cell count monitoring. There is some evidence to suggest that olanzapine, like clozapine, has anticholinergic side effects. Risperidone can be associated with the emergence of EPS, postural hypotension, and sedation at higher doses. Specifically in the treatment of BPSD, there are no current data from controlled studies on the safety of neuroleptic agents other than risperidone and olanzapine. Studies with quetiapine are ongoing.

Efficacy of newer antipsychotics

Data are currently available for risperidone and olanzapine in dementia patients with BPSD. In one open-label study, 83% of patients with BPSD taking 0.5–1.0 mg/day risperidone showed an improvement in symptoms (Goldberg and Goldberg, 1995). This same study showed that

risperidone is able to produce an improvement in sleep quality--82% of patients reported better sleep quality and 63% reported that they were more awake during the day.

To date, three large multicenter trials of risperidone for BPSD have been conducted. Risperidone at a dose of approximately 1 mg/day has been found to be superior to placebo in the treatment of BPSD, particularly for aggressive behaviors in dementia patients and for psychotic symptoms. Risperidone at this dose is well tolerated and has an EPS profile similar to placebo (De Deyn, 1997; Katz, 1999, Brodaty et al, 2001, Alzheimer's Disease International Conference, Christchurch, October 2001).

A multicenter nursing home study of olanzapine in BPSD has shown that 5 and 10 mg/day doses of olanzapine was significantly superior to placebo and well tolerated in treating agitation/aggression. Curiously the 5mg dose showed greater efficacy than the 10mg dose (Street et al., 2000).

Dementia with Lewy bodies: considerations

Dementia with Lewy bodies can be a relatively common clinical problem. It has been observed in approximately 15% of dementia patients at autopsy. Patients often have prominent visual hallucinations and psychotic symptoms and are likely to be treated with neuroleptics. Severe and sometimes fatal sensitivity to conventional neuroleptics has been described in dementia with Lewy bodies (McKeith et al., 1995).

Evidence for the use of neuroleptics in dementia with Lewy bodies has generally come from retrospective chart reviews, and not from placebo-controlled clinical trials. The current recommendations are that patients who are suspected of having dementia with Lewy bodies should not be prescribed conventional neuroleptics.

Reports on the tolerance to novel antipsychotics such as risperidone in patients with dementia with Lewy bodies have been both positive and negative (Lee et al., 1994; Allen et al., 1995; McKeith et al., 1995). For severe BPSD, low doses of the newer antipsychotics, e.g., risperidone 0.25 mg, clozapine 6.25 mg, olanzapine 2.5 mg, or quetiapine 25mg could be used, but patients must be monitored very carefully in a day hospital or inpatient setting for treatment-emergent neuroleptic sensitivity.

Guidelines for prescribing

On the basis of evidence from the literature, the following clinical guidelines for the use of neuroleptics are recommended:

- Only treat moderate to severe BPSD.
- Try non-pharmacological methods first, then in conjunction with medication.
- Try to target specific symptoms: physical aggression, hallucinations and delusions.
- Check for a history of neuroleptic sensitivity and consider the diagnosis of dementia with Lewy bodies before prescribing any neuroleptic.
- Consider discontinuing neuroleptics in patients with BPSD before automatically switching to a different class of neuroleptic or increasing the dosage.
- Start with low dosages and go slowly when using neuroleptic medication. (See Table 2 for suggested dosage schedules.) A starting dose for a conventional neuroleptic would be 0.5 mg/day, and a maximum dose would be 2 mg/day haloperidol equivalents. The dosing range for risperidone is 0.5 mg/day to 2 mg/day with optimum dose of 1.0 mg/day (Brecher, 1997; De Deyn, 1999; Katz et al, 1999; Brodaty et al, 2001) allowing at least 2 days before the initial dose escalation. For olanzapine the dosage range would be 2.5mg-10mg, and for quetiapine 25-150 mg.

- Since newer antipsychotics are better tolerated than the older conventional agents the neuroleptic must be tailored to the individual patient. The choice of agents depends more on the likely side effects than differential efficacy.
- Watch closely for treatment-emergent side effects. Avoid or minimize side effects of EPS, postural hypotension, anticholinergic side effects, sedation, by slow titration and low doses.
- Set duration for treatment and monitor outcome. A time limit of 12 weeks' treatment is recommended and should be reviewed during and after. If a 4-6-week trial of one agent at an adequate dose fails to decrease the frequency, severity or impact of a target symptom, the trial of a second agent would be indicated.

Table 2. Clinical recommendations for dosing of conventional neuroleptics and newer antipsychotics in the treatment of BPSD.

Drug	Start (mg)	Dose range (mg)	Schedule
Haloperidol	0.5	0.5–2	Once daily
Thiothixene	1	1–10	Once daily
Risperidone	0.5	0.5–2	Once daily
Clozapine*	6.25	10–100	Twice or once daily
Olanzapine.	2.5	5–10	Once daily
Quetiapine*	25	25-150	Divided dose

*No double blind, placebo-controlled data available

Anxiolytics

Benzodiazepines

After neuroleptics, benzodiazepines are the second most frequently used agents in the treatment of BPSD. Benzodiazepines are used clinically primarily for 'agitated behaviors' and sleep disturbance in dementia patients. A number of controlled studies have shown that benzodiazepines decrease agitated behaviors compared with placebo to the same extent as conventional neuroleptics (Chesrow et al., 1965; Kirven and Montero, 1973; Covington, 1975; Coccaro et al., 1990).

BPSD that respond best to benzodiazepines include:

- anxiety
- tension
- irritability
- insomnia

Side effects are common and most often include excessive sedation (drowsiness), ataxia, amnesia, and confusion. In addition, the risk of falls in dementia patients is increased with benzodiazepines, particularly the long-acting agents that accumulate over time (Grad, 1995).

Short-acting benzodiazepines such as oxazepam or lorazepam that do not accumulate are preferred, and are most effective if used for short periods, i.e., a few weeks (Sanders, 1965). Low doses, e.g., lorazepam 0.5–2.0 benzodiazepine equivalents mg/day should be used for a time-limited period. Lorazepam may be especially useful as a premedication for episodic disturbance or where agitation or distress can be anticipated (e.g., minor surgical procedures or dental visits).

After patients have been maintained on benzodiazepines for over 4–6 weeks, a gradual taper is advised prior to discontinuation.

Buspirone

Buspirone is a serotonin 5-HT_{1a} partial agonist, that in case reports, and open studies have been found to be helpful in agitated dementia patients. However, in a placebo-controlled study (at doses of 30 mg/day), buspirone was very well tolerated, but had no beneficial effect on agitation (Lawlor et al., 1994). In a multicenter study performed in the USA, no positive results have been reported.

On the basis of the available data, buspirone cannot be recommended routinely for moderate to severe BPSD, but may have a role in the management of mild anxiety in dementia patients at doses of 20-60 mg/day.

Anticonvulsants

Both open-label and controlled evidence is accumulating for the efficacy of anticonvulsants for agitated behaviors in dementia. In general, anticonvulsants are well tolerated and produce little toxicity compared with conventional neuroleptics. They are being used increasingly in the treatment of some BPSD.

Carbamazepine

Carbamazepine (usual dose range 300–800 mg/day) has been used in patients with agitation secondary to brain damage and is increasingly being prescribed to patients with BPSD. Several case reports, open trials (Essa, 1986; Leibovici and Tariot, 1988; Patterson, 1988; Gleason and Schneider, 1990; Lemke and Stuhlmann, 1994) and double-blind trials (Tariot et al., 1994; 1998) support the efficacy of carbamazepine to treat agitation in BPSD.

In two of the controlled trials, doses of up to 300 mg/day were well tolerated by frail elderly patients. Small, placebo-controlled studies of doses up to 600 mg/day have also shown positive effects (Cooney et al., 1996). Another open study suggested that carbamazepine augmentation of a conventional neuroleptic was helpful in agitated dementia patients (Lemke, 1995).

The side effects of carbamazepine include sedation, skin rash, headache, leucopenia and mild elevation of liver function tests.

Valproic acid

Valproic acid is available in several forms, including the well-tolerated divalproex sodium formulation that minimizes gastrointestinal distress. The results from clinical trials for bipolar disorder, open trials in patients with dementia (Mellow et al., 1993; Lott et al., 1995), and a single placebo controlled study show that valproate demonstrates similar efficacy to carbamazepine; however, data from further controlled trials are awaited. The usual dose range for valproic acid is 400–1000 mg/day (Porsteinsson et al., 2001).

Compared with carbamazepine, valproic acid has a significantly reduced potential for drug-drug interactions and side effects. But, it has been associated with sedation, diarrhea, tremor, nausea, weight gain, hair loss and abnormal liver function.

Antidepressants

Trazodone

In keeping with the serotonin hypothesis for AD (Lawlor, 1990), open studies and some controlled trials support the use of trazodone for agitation in patients with BPSD (Pinner and Rich, 1988; Aisen et al., 1993; Lawlor et al., 1994; Sultzer et al., 1997). Trazodone has sedative properties and thus may also be useful in treating sleep disturbance in dementia.

Doses varying from 50–600 mg/day have been used, although the recommended dose range for patients with severe BPSD would generally not exceed 200–300 mg/day. The main side effects of trazodone are:

- somnolence
- postural hypotension.

Tricyclic antidepressants

There is much anecdotal evidence supporting the use of tricyclic antidepressants in depressed dementia patients (Reynolds et al., 1987). There is, however, only one placebo-controlled trial evaluating the beneficial effects of a tricyclic antidepressant in depressed dementia patients and this study found a significant benefit for both drug and placebo (Reifler et al., 1986).

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- Tricyclic antidepressants are associated with problematic and frequent side effects in dementia patients and must be used with caution.
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The most common side effects associated with tricyclic antidepressants are postural hypotension, blurred vision, urinary hesitancy and intracardiac conduction defects. If tricyclic antidepressants are to be used in depressed dementia patients, secondary (e.g., nortriptyline, desipramine, lofepramine) rather than tertiary amines (e.g., amitriptyline, dothiepin) are preferred, due to better tolerability.

Selective serotonin reuptake inhibitors

There is mainly open experience with selective serotonin reuptake inhibitors in depressed demented patients with the suggestion that they improve depressed mood and are well tolerated (Burke et al., 1994).

There have been some indications that dementia patients, particularly those with associated extrapyramidal syndromes, may be more likely to develop EPS (Gormley et al., 1997). Two placebo-controlled trials of selective serotonin reuptake inhibitors (citalopram 10–30 mg/day) in elderly patients, with and without dementia, who had depression requiring treatment found significant improvements in depression, emotionality, anxiety, agitation and social interaction on citalopram compared with placebo (Nyth and Gottfries, 1990; Gottfries et al., 1992).

A recent retrospective review of studies evaluating selective serotonin reuptake inhibitors in patients with depression and psychosis complicating dementia showed a significant effect on both psychosis and depression, suggesting that these agents could have antipsychotic potential in dementia patients (Burke et al., 1997). However, this preliminary finding must be tested further in double-blind controlled studies.

Side effects of selective serotonin reuptake inhibitors are generally less common and severe than those of tricyclic antidepressants but include:

- gastrointestinal symptoms (e.g., nausea, vomiting)
- akathisia
- restlessness
- insomnia
- weight loss
- hyponatremia.

Other antidepressants used in depressed dementia patients

When an antidepressant is selected, overall tolerability as well as favorable effects on anxiety, sleep disturbance and agitation should also be considered. Two recently introduced antidepressants, mirtazepine and nefazodone, share these properties and can be considered promising candidates for use in depressed patients with dementia. Both are proven to be effective and safe in elderly patients.

A number of placebo-controlled trials carried out with antidepressants that are not available in the USA and some European countries, namely, maprotiline and minaprine have indicated that depressed dementia patients respond to antidepressants (Passeri et al., 1987; Fuchs et al., 1993).

Other agents such as moclobemide, a reversible inhibitor of monoamine oxidase A, at doses of 150–600 mg/day have a proven favorable side-effect profile in elderly dementia patients and can be useful in the treatment of depression. One study demonstrated it was effective in the treatment of depression in dementia (Roth M et al., 1996).

Antidepressant dosing recommendations

If an antidepressant is to be prescribed, selective serotonin reuptake inhibitors or secondary amine tricyclic antidepressants should be used. Doses should start low and be increased gradually. A dosing schedule for selected antidepressants is shown in Table 3. Patients should be treated for a time-limited period of 6 months at a time and do not need to be maintained on antidepressants indefinitely, since many of the depressions remit within a 12-month period (Brodaty and Luscombe, 1996).

Table 3. Dosing schedule for selected antidepressants in patients with dementia.

Drug	Initial dose (mg/day)	Target dose (mg/day)
Paroxetine	10	20–30
Fluoxetine	10	20–30
Sertraline	25	50–100
Nortriptyline	10	20–60
Moclobemide	150	150–600
Mirtazepine	15	15–45

Miscellaneous drug classes

Cholinesterase inhibitors

Cholinesterase inhibitors (such as tetrahydroaminoacridine or tacrine, donepezil hydrochloride, rivastigmine and galantamine) are only licensed for the treatment of cognitive symptoms in Alzheimer's disease. There is some evidence, however, that cholinergic drugs may have beneficial effects on BPSD, particularly apathy, hallucinations and delusions, anxiety and depression (Kaufer et al., 1996; Feldman 2001; Blesa R. 2000; Scott and Goa, 2000).

Cholinergic drugs may even decrease the emergence of BPSD (Tariot et al 2000). A placebo-controlled study in DLB has demonstrated efficacy for rivastigmine in the treatment of hallucinations, delusions, apathy and anxiety. Not all studies have demonstrated a benefit on BPSD with cholinesterase inhibitors (Fillit et al, 2000), and not all BPSD benefit from their use. The use of this class of drugs may depend on the nature of the behavioral disturbance and the stage of the dementia.

Lithium

Published data on the use of lithium in BPSD are limited and there are no controlled studies of its use. One open study (Williams and Goldstein, 1979) reported decreased agitation in six out of eight patients with mixed chronic brain syndromes, but another reported little benefit and prominent toxicity (Randels et al., 1984). Thus, there seems to be no reason to use lithium to treat BPSD given its toxicity in this patient group and the lack of data showing any therapeutic effect.

β -Blockers

There have been only two reports, both uncontrolled, of β -blockers in dementia, which found some benefit (Petrie and Ban, 1981; Weiler et al., 1986). The only controlled studies with propranolol (40–400 mg) and pindolol (10–40 mg) have been in brain injury patients (Greendyke et al., 1989). Thus, there is no evidence on which to base a recommendation for the use of β -blockers in BPSD.

Selegiline

Selegiline is an irreversible inhibitor of monoamine oxidase B at low doses. It has been suggested that decreasing or normalizing monoamine oxidase B activity in Alzheimer's disease might result in asymptomatic improvement in this illness (Tariot et al., 1987).

The results to date with selegiline in the treatment of BPSD in Alzheimer's disease have been mixed. Some small, open-label studies have shown beneficial effects on BPSD (Goad et al., 1991; Schneider et al., 1991), but the largest and most recent placebo-controlled study showed no effect of selegiline treatment (Burke et al., 1993). The dementia patients in this last study did not exhibit BPSD; therefore, it was unlikely that a treatment effect would be seen. In a study of Alzheimer's disease patients with depression and agitation, selegiline has been shown to improve BPSD, although the effect size was small (Lawlor et al., 1997).

The evidence for selegiline in BPSD is generally positive for minor depressive symptoms associated with withdrawn behavior or agitation. Side effects are infrequent with the usual dose of 10 mg/day and include postural hypotension. There are no dietary restrictions while the dose is maintained at 10 mg/day.

Sedative hypnotics

There are no specific studies of pharmacological treatment of sleep disturbance in dementia patients and there is therefore little evidence to guide practice.

In general, agents with short-to-intermediate half-lives and few active metabolites are to be favored (e.g., zopiclone 3.75–7.5 mg, zolpidem 5–10 mg, lorazepam 0.5–1.0 mg, oxazepam 7.5–15 mg, temazepam 10 mg). Sedative hypnotics should only be used for the short-term management of sleep disturbance in BPSD. When long-term treatment is necessary, an alternative agent with sleep-enhancing properties such as trazodone (50–150 mg nocte) may be useful.

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- Where sleep disturbance is part of depression or psychotic behavior, an antidepressant or antipsychotic should be the drug of choice.
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Electroconvulsive therapy for depression in dementia

In the management of depression in patients with dementia, electroconvulsive therapy (ECT) may be an option in the management of severe depression complicating dementia. There are three important issues to be addressed when considering whether ECT should be given:

- making the diagnosis of depression in the face of dementia
- excluding medical causes of depression (e.g., UTI)
- the efficacy of ECT in depressed dementia patients
- potential side effects of ECT in the depressed patient with pre-existing cognitive impairment.

The obvious concern when using ECT with dementia patients is the risk of increased cognitive impairment after ECT. Increasing the time interval between treatments can reduce this risk. Less cognitive impairment would be expected if unilateral treatment were used, but balanced against this is the need for more sessions with unilateral treatment compared with bilateral.

The issue of competency to give informed consent for ECT in a dementia patient is a difficult one. Even in patients with mild dementia it is advisable to obtain the consent of the next of kin. Patients should be taken off all psychotropics during the course of ECT to decrease the likelihood of post-ECT confusion. After the course of ECT (usually 6–8 treatments), patients should receive prophylactic treatment with antidepressants for 6–9 months, and possibly longer if there is a history of previous episodes.

References and recommended reading

ANTIPSYCHOTICS

Allen RL, Walker Z, D'Ath PJ, Katona CL. Risperidone for psychotic and behavioral symptoms in Lewy body dementia. *Lancet* 1995; 346: 185.

Barnes R, Veith R, Okimoto J, et al. Efficacy of antipsychotic medications in behaviorally disturbed dementia patients. *Am J Psychiatry* 1982; 139: 1170–1174.

Brecher M. Risperidone in the treatment of psychosis and aggressive behavior in patients with dementia. Presented at the Congress of the International Psychogeriatric Association (IPA), Jerusalem, Israel. 17–22 August 1997.

Bridges-Parlet S, Knopman D, Steffes S. Withdrawal of neuroleptic medications from institutionalized dementia patients: results of a double blind, baseline-treatment-controlled pilot study. *J Geriatr Psychiatry Neurol* 1997; 10: 119–126.

Brodsky H, Grossman F, Bruynseels J, Lyons B. Risperidone in the treatment of agitation and psychosis of dementia. Paper presented at the Alzheimer's Disease International Conference. Christchurch, New Zealand. October 2001.

Chui HC, Lyness SA, Sobel E, et al. Extrapyramidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer's disease. *Arch Neurol* 1994; 51:676–681.

Devanand DP, Marder K, Michaels KS, Sackeim HA, Bell K, Sullivan MA, Cooper TB, Pelton GH, Mayeux R. 20 A randomized, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in Alzheimer's disease. *Am J Psychiatry* 1998 Nov; 155(11): 1512-20.

De Deyn P. Risperidone in the treatment of behavioral disturbances in dementia. Presented at the Congress of the International Psychogeriatric Association (IPA), Jerusalem, Israel. 17–22 August 1997.

Devanand DP. Role of neuroleptics in treatment of behavioral complications. In: Behavioral complications in Alzheimer's disease. Lawlor BA (ed). Washington DC: APA Press Inc., 1995.

Devanand D, Sackheim HA, Brown R, et al. A pilot study of haloperidol treatment of psychosis and behavioral disturbance in Alzheimer's disease. *Arch Neurol* 1989; 46: 854–857.

Finkel SI, Lyons JS, Anderson RL, et al. A randomized, placebo-controlled trial of thiothixene in agitated, demented nursing home elderly. *Int J Geriatr Psychiatry* 1995; 10: 129–136.

Gilleard CJ, Morgan K, Wade BE. Patterns of neuroleptic use among the institutionalized elderly. *Acta Psychiatr Scand* 1983; 68: 419–425.

Goldberg RJ, Goldberg JS. Low dose risperidone for dementia related disturbed behavior in nursing homes. *J Am Psychoanal Assoc* 1995; (Suppl): 126.

Horwitz GJ, Tariot PN, Mead K, et al. Discontinuation of antipsychotics in nursing home patients with dementia. *Am J Geriatr Psychiatry* 1995; 394: 290–299.

Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J, et al. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group: *J Clin Psychiatry* 1999; 60(2): 107-15.

Lanctot KL, Best TS, Mittmann N, Liu BA, Oh PI, Einarson TR, Naranjo CA. Efficacy and safety of neuroleptics in behavioral disorders associated with dementia *J Clin Psychiatry* 1998 Oct; 59(10): 550-61.

Lee H, Cooney JM, Lawlor BA. The use of risperidone, an atypical neuroleptic, in Lewy body disease. *Int J Geriatr Psychiatry* 1994; 9: 415 -417.

McKeith IG, Ballard CG, Harrison RW. Neuroleptic sensitivity to risperidone in Lewy body dementia. *Lancet* 1995; 346: 699.

McShane R, Keene J, Gedling K, Fairburn C, Jacoby R., et al. Do neuroleptic drugs hasten cognitive decline in dementia? A prospective study with necropsy follow up. *BMJ* 1997, 314:266-270.

McShane R, Keene J, Fairburn C, et al. Issues in drug treatment for Alzheimer's disease (letter). *Lancet* 1997; 350: 886–887.

Petrie WM, Lawson EN, Hollender MH. Violence in geriatric patients. *JAMA* 1982; 248: 443–444.

Ray WA, Federspeil CF, Schaffner WA. A study of antipsychotic drug use in nursing homes: epidemiological evidence suggesting misuse. *Am J Public Health* 1980; 70: 485–491.

Schneider LS, Pollock VE, Lyness SA. A meta-analysis of controlled trials of neuroleptic treatment in dementia. *J Am Geriatr Soc* 1990; 38: 553-563.

Stern Y, Sano M, Hauser WA. Predictors of disease course in patients with probable Alzheimer's disease. *Neurology* 1987; 37: 1649-1653.

Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatry*. 2000 57(10): 968-76.

Sunderland T, Silver M. Neuroleptics in the treatment of dementia. *Int J Geriatr Psychiatry* 1988; 3: 79–88.

Tewfik GI, Jain VK, Harcup M, et al. Effectiveness of various tranquilizers in the management of senile restlessness. *Gerontol Clin* 1970; 12: 351–359.

Thapa PB, Meador KG, Gideon P, et al. Effects of antipsychotic withdrawal in elderly nursing home residents. *J Am Geriatr Soc* 1994; 42: 280–286.

Tobin JM, Brousseau ER, Lorenz AA. Clinical evaluation of haloperidol in geriatric patients. *Geriatrics* 1970; 25: 119–122.

Devanand DP, Marder K, Michaels KS, Sackeim HA, Bell K, Sullivan MA, Cooper TB, Pelton GH, Mayeur R. A randomized, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in Alzheimer's disease. *Am J Psychiatry* 1998;155(11):1512-20.

Lancot KL, Best TS, Mittmann N, Liu BA, Oh PI, et al. Efficacy and safety of neuroleptics in behavioral disorders associated with dementia. *J Clin Psychiatry* 1998 Oct; 59(10): 550-61; quiz 562-3.

Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatry*, 2000; 57(10): 968-76.

ANXIOLYTICS

Chesrow EJ, Kaplitz SE, Vetra H, et al. Double-blind study of oxazepam in the management of geriatric patients with behavioral problems. *Clin Med* 1965; 72: 1001–1005.

Coccaro EF, Kramer E, Zemishlany Z, et al. Pharmacological treatment of non-cognitive behavioral disturbances in elderly demented patients. *Am J Psychiatry* 1990; 147: 1640–1645.

Covington JS. Alleviating agitation, apprehension and related symptoms in geriatric patients: a double-blind comparison of phenothiazine and benzodiazepine. *South Med J* 1975; 68: 719 -724.

Grad R. Benzodiazepines for insomnia in community dwelling elderly: a review of benefit and risk. *J Fam Pract* 1995; 41: 473–481.

Kirven LE, Montero EF. Comparison of thioridazine and diazepam in the control of non-psychotic symptoms associated with senility: double-blind study. *J Am Geriatr Soc* 1973; 21: 546–551.

Lawlor BA, Radcliffe J, Molchan SE, et al. A pilot placebo-controlled study of trazodone and buspirone in Alzheimer's disease. *Int J Geriatr Psychiatry* 1994; 9: 55–59.

Sanders JF. Evaluation of oxazepam and placebo in emotionally disturbed aged patients. *Geriatrics* 1965; 20: 739 -749.

ANTICONVULSANTS

Cooney C, Mortimer A, Smith A, et al. Carbamazepine in aggressive behavior associated with senile dementia. *Int J Geriatric Psychiatry* 1996; 11: 901–905.

Essa M. Carbamazepine in dementia. *J Clin Psychopharmacol* 1986; 6: 234–236.

Gleason RP, Schneider LS. Carbamazepine treatment of agitation in Alzheimer's outpatients refractory to neuroleptics. *J Clin Psychiatry* 1990; 51: 115–118.

Leibovici A, Tariot PN. Carbamazepine treatment of agitation associated with dementia. *J Geriatr Psychiatry Neurol* 1988; 1: 110–112.

Lemke MR. Effect of carbamazepine on agitation in Alzheimer's inpatients refractory to neuroleptics. *J Clin Psychiatry* 1995; 56: 354–357.

Lemke MR, Stuhlmann W. Therapeutic use of carbamazepine for treatment of agitation and affective disorders in geriatric psychiatry patients. *Psychiatr Prax* 1994; 21: 147–150.

Lott AD, McElroy SL, Keys MA. Valproate in the treatment of behavioral agitation in elderly patients with dementia. *J Neuropsychiatry Clin Neurosci* 1995; 7: 314–319.

Mellow AM, Solano-Lopez C, Davis S. Sodium valproate in the treatment of behavioral disturbance in dementia. *J Geriatr Psychiatry Neurol* 1993; 6: 205–209.

Patterson JF. A preliminary study of carbamazepine in the treatment of assaultive patients with dementia. *J Geriatr Psychiatry Neurol* 1988; 1: 21–23.

Porsteinsson, AP, Tariot PN, Erb R, Cox C, Smith E et al. Placebo-controlled study of divalproex sodium for agitation in dementia. *Am J Geriatr Psychiatry*. 2001 Winter; 9(1): 58-66.

Tariot PN, Erb R, Leibovici A, et al. Carbamazepine treatment of agitation in nursing home patients with dementia: a preliminary study. *J Am Geriatr Soc* 1994; 42: 1160–1166.

Tariot PN, Erb R, Podgorski CA, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry* 1998; 155: 54–61.

Porsteinsson AP, Tariot PN, Erb R, Cox C, Smith E, Jakimovich L, Noviasky J, Kowalski N, Hold CJ, Irvine C. Placebo-controlled study of divalproex sodium for agitation in dementia. *Am J Geriatr Psychiatry*. 2001 Winter; 9(1): 58-66.

ANTIDEPRESSANTS

Aisen PS, Johannsen DJ, Marin DB. Trazodone for behavioral disturbance in dementia. *Am J Geriatr Psychiatry* 1993; 1: 349–350.

Brodsky H, Luscombe G. Depression in persons with dementia. *Int Psychogeriatr* 1996; 8(4): 609–622.

Burke WJ, Folks DG, Roccaforte WH, et al. Serotonin reuptake inhibitors for the treatment of coexisting depression and psychosis in dementia of the Alzheimer type. *Am J Geriatr Psychiatry* 1994; 2: 352–354.

Burke WJ, Wengel SP, Roccaforte WH, et al. The use of selective serotonin reuptake inhibitors for depression and psychosis complicating dementia. *Int J Geriatr Psychiatry* 1997; 12: 519–525.

Fuchs A, Henke U, Erhart DH, et al. Video rating analysis of effect of maprotiline in patients with dementia and depression. *Pharmacopsychiatry* 1993; 26: 37–41.

Gormley N, Watters L, Lawlor BA. Extrapyramidal side effects in elderly patients exposed to selective serotonin reuptake inhibitors. *Hum Psychopharmacol* 1997; 12: 139–143.

Gottfries CG, Karlsson I, Nyth AI. Treatment of depression in elderly patients with and without dementia disorders. *Int Clin Psychopharmacol* 1992; 6 (Suppl 5): 55–64.

Lawlor BA. Serotonin and Alzheimer's disease. *Psychiat Ann* 1990; 20: 567–570.

Lawlor BA, Radcliffe J, Molchan SE, et al. A pilot placebo-controlled study of trazodone and buspirone in Alzheimer's disease. *Int J Geriatr Psychiatry* 1994; 9: 55–59.

Nyth AL, Gottfries CG. The clinical efficacy of citalopram in treatment of emotional disturbance in dementia disorders. A Nordic Multicentre study. *Br J Psychiatry* 1990; 157: 894–901.

Passeri M, Cucinotta D, DeMello M, et al. Comparison of minaprine and placebo in the treatment of Alzheimer's disease and multi-infarct dementia. *Int J Geriatr Psychiatry* 1987; 2: 97–103.

Pinner E, Rich CL. Effects of trazodone on aggressive behavior in seven patients with organic mental disorders. *Am J Psychiatry* 1988; 145: 1295–1296.

Reifler BV, Larson E, Teri L, et al. Dementia of the Alzheimer's type and depression. *J Am Geriatr Soc* 1986; 34: 855–859.

Reynolds CF III, Perel JM, Kupfer DJ, et al. Open trial response to antidepressant treatment in elderly patients with mixed depression and cognitive impairment. *Psychiatry Res* 1987; 21: 111–122.

Roth M, Mountjoy CQ, Amrein R. Moclobemide in elderly patients with cognitive decline and depression: an international double-blind, placebo-controlled trial. *Br J Psychiatry*. 1996 168(2):149-57.

Sultzer D, Gray KF, Gunay I, et al. A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. *Am J Geriatr Psychiatry* 1997; 5: 60–69.

MISCELLANEOUS DRUG CLASSES

Blesa R. Galantamine: therapeutic effects beyond cognition. *Dementia and geriatric cognitive disorders*, 2000, 11(suppl 1) 28-34.

Burke WJ, Ranno AE, Roccaforte WH, et al. L-deprenyl in the treatment of mild dementia of the Alzheimer type: preliminary results. *J Am Geriatr Soc* 1993; 41: 367–370.

Feldman H, Gauthier S., Hecker J, Vellas B, Subbiah P, et al. A 24-week, randomized, double blind study of donepezil in moderate to severe Alzheimer's disease. *Neurol.* 2001. 57(4): 613-20.

Fillit HM, Brooks RL. Impact of donepezil on caregiving burden for patients with Alzheimer's disease. *Int Psychogeriatr.* 12(3):2000; 389-401.

Goad DL, Davis CM, Liem P, et al. The use of selegiline in Alzheimer patients with behavioral problems. *J Clin Psychiatry* 1991; 52: 342–345.

Greendyke RM, Berkner JP, Webster JC, et al. Treatment of behavioral problems with pindolol. *Psychosomatics* 1989; 30: 161–165.

Kaufer DI, Cummings JL, Christine D. Effect of tacrine on behavioral symptoms in Alzheimer's disease: an open label study. *J Psychiat Neurol* 1996; 9: 1–6.

Lawlor BA, Aisen PS, Greene C, et al. Selegiline in the treatment of behavioral disturbance in Alzheimer's disease. *Int J Geriatr Psychiatry* 1997; 12: 319–322.

Petrie WM, Ban TA. Propranolol in organic agitation (letter). *Lancet* 1981; 1: 324.

McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, et al., Efficacy of rivastigmine in dementia with Lewy bodies: a randomized, double blind, placebo-controlled international study. *Lancet* 2000; 356(9247): 2031-6

Randels PM, Marco LA, Ford DI, et al. Lithium and lecithin treatment in Alzheimer's disease. *Hillside J Clin Psychiatry* 1984; 6: 139–147.

Schneider LS, Pollock VE, Zemansky MF, et al. A pilot study of low-dose L-deprenyl in Alzheimer's disease. *J Geriatr Psychiatry Neurol* 1991; 4: 143–148.

Scott, LJ.; Goa, KL. Galantamine: A Review of its Use in Alzheimer's Disease *Drugs.* 60(5):1095-1122, 2000.

Tariot PN, Solomon PR, Morris JC, Kershaw P, Lillienfeld S, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurol* 2000; 54(12): 2269-76.

Tariot PN, Cohen RM, Sunderland T, et al. L-Deprenyl in Alzheimer's disease. *Arch Gen Psychiatry* 1987; 44: 427–433. Weiler PG, Mungas D, Bernick C. Propranolol for the control of disruptive behavior in senile dementia. *J Geriatr Psychiatry Neurol* 1986; 1: 226–230.

Williams KH, Goldstein G. Cognitive and affective responses to lithium in patients with organic brain syndrome. *Am J Psychiatry* 1979; 136: 800–803.