Pharmacotherapy of Behavioral Disturbances in Dementia

Pharmacotherapy should not be considered a treatment of last resort for behavioral disturbances in dementia. Prescribing medications that balance effectiveness with the potential for adverse side effects can improve the quality of life for both patients and caregivers.

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Behavioral disorders in dementia (BDD) are serious, common problems that can affect the quality of life for both the patient and the caregiver. These disturbances include behaviors such as agitation, aggression, restlessness, insomnia, wandering, delusions, hallucinations, irritability, depression, apathy, anxiety, disinhibition and sexually inappropriate behaviors.

While the dementias have typically been characterized by their effects on cognition, it is these disturbances that caregivers find particularly difficult to deal with and that often lead to institutionalization. This article will focus on pharmacologic interventions.

Medications for the management of BDD should be considered as only one part of a multifaceted treatment plan that includes assessment and diagnosis, consideration of safety issues, choosing and monitoring target symptoms and instituting environmental and behavioral interventions. While medications need not be considered a treatment of last resort, there is some concern that pharmacotherapy is overused and prescribed for inappropriate indications. Studies in long-term care facilities have documented excessive dosages, use of poorly tolerated drugs and lack of monitoring for effectiveness and side effects.

The staff in these institutions often have little knowledge of how to administer drugs or their potential benefits and risks. It is essential for physicians to consider all aspects of treatment and include the staff in the design and monitoring of a comprehensive management plan.

Principles of Pharmacotherapy

Patients with BDD tend to be elderly with comorbid medical illness and concomitant medications. The age-associated changes that affect pharmacokinetics and pharmacodynamics of psychotropic medications may predispose this population to adverse drug effects and potential drug interactions.\(^1\)

As a result of the changes in the volume of distribution, many psychotropics will take longer to reach steady state. They have longer half-lives and they take longer to eliminate. These factors necessitate lower starting doses and slower titration. Frequently, a lower total daily dose compared to younger patients is needed.
Of specific concern in patients with dementia are the anticholinergic effects of many neuroleptics and antidepressants. Side effects caused by the blockade of muscarinic receptors include dry mouth, blurred vision, constipation and the more serious effects of tachycardia, urinary retention, increased cognitive impairment and the precipitation of delirium. Elderly patients with dementia already have a high risk of developing delirium, so drugs with strong anticholinergic properties should generally be avoided. It is also likely that these drugs will antagonize the effects of the cognitive-enhancer medications for Alzheimer’s disease like the cholinesterase inhibitors. Other potential concerns include orthostatic hypotension, excessive daytime sedation and drug interactions. Orthostatic hypotension is mediated by beta-adrenergic blockade. Medications with these side effects necessitate frequent blood-pressure monitoring during initiation and titration in order to avoid falls. Similarly, excessive daytime sedation caused by a histaminic blockade can also lead to unsteady gait and falls. Finally, the metabolism of many psychotropics, such as the selective serotonin reuptake inhibitors (SSRIs) may inhibit or be inhibited by many medications used for concomitant medical problems (e.g., beta-blockers, quinidine, codeine, erythromycin, ketoconazole and omeprazole).

After identifying appropriate target behaviors, a specific psychotropic is chosen based on evidence of its effectiveness in this population without the potential adverse effects described previously. Therapy is initiated at very low doses with increases every three to seven days, if necessary. Effectiveness is assessed while the target behaviors and adverse effects are carefully monitored. There are no agreed-upon times for the minimum length of a pharmacotherapeutic trial, but they usually range from two to four weeks for some medications to four to eight weeks for others. Periodic attempts to reduce or withdraw medications are recommended following improvements in behavior. Controlled trials of neuroleptic withdrawal in this population suggest that, for many patients, there is no exacerbation of problem behaviors and there is potential for improvement in mood, cognition and function.

Choosing target symptoms is not only important for the monitoring of effectiveness, but it helps guide the choice of medication. It is also important to avoid choosing target symptoms that are generally considered to be resistant to pharmacotherapeutic interventions. For example, there are no studies that have documented a pharmacotherapeutic approach to wandering. Conversely, many psychotropics will cause unsteady gait. Pharmacotherapy, therefore, has the potential to change a stable wanderer to a wanderer who is likely to fall.

**Pharmacotherapy Recommendations**

The following recommendations for pharmacotherapy will focus on the symptoms of agitation, aggression, sleep disturbances and depression. Detailed reviews of the pharmacotherapy for BDD can be found elsewhere.²,³

**Neuroleptics**. Neuroleptics are the best-studied medications for the treatment of agitation and aggression in patients with dementia. In very low doses, typical neuroleptics have well documented though modest efficacy. While all the typical neuroleptics appear to be equally effective, these agents will vary with respect to their potential for side effects (Table 1). For most patients with dementia, agitation and aggression, starting with low doses of perphenazine (2 mg to 4 mg) or loxapine (2.5 mg to 5 mg) offers the best balance between extrapyramidal, anticholinergic and sedative effects. Effective doses of all these medications are far less than indicated for treatment of young schizophrenics (Table 2).

The reduced potential for extrapyramidal symptoms in this highly vulnerable population means that the atypical neuroleptics (e.g., risperidone, olanzapine and quetiapine) may be particularly useful. Several large series with risperidone have shown that this medication is both effective and well tolerated for treating agitation, aggression and psychotic symptoms in patients with dementia. Treatment should be initiated at 0.25 mg to 0.5 mg per day, with slow titration to a maximum of 1 mg to 1.5 mg per day.

### Table 1

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<th>Neuroleptic Side Effects</th>
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<td><strong>Type (Potency)</strong></td>
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<td>Low (e.g., thioridazine, chlorpromazine)</td>
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<tr>
<td>Middle (e.g., loxapine, perphenazine)</td>
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<tr>
<td>High (e.g., haloperidol)</td>
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<td>Atypical (e.g., risperidone)</td>
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EPS: Extrapyramidal symptoms
Non-Neuroleptics. The problems caused by neuroleptic side effects led to the investigation of other classes of medications for the treatment of agitation and aggression. There is mounting evidence that low-dose carbamazepine is both effective and surprisingly well tolerated. Oral therapy is initiated at 100 mg daily and increased to three times daily. Dosages must be individualized, but serum concentrations should be kept low (4 mg/L to 8 mg/L) in order to avoid toxicity. Side effects include drowsiness, hypersensitivity reactions, blood dyscrasias and the potential for drug interactions.

Trazodone, a serotonergic antidepressant, has also been shown to reduce agitation and aggression in dementia. Treatment can be initiated with dosages of 25 mg to 50 mg, with slow titration up to 50 mg three times daily or higher, if necessary. The most common side effects of trazodone are excessive daytime sedation and orthostatic hypotension. The SSRIs may also be effective in those cases.

Pharmacotherapy of Sleep Disturbances
There are few studies that have specifically examined the pharmacotherapy of sleep disturbances in dementia. This is surprising, given their frequency and the toll they exact on caregivers. For this target symptom, it is absolutely essential to exhaust the nonpharmacologic alternatives before resorting to medications. The avoidance of stimulants, attention to sleep hygiene and simply insuring there is no daytime napping can frequently improve nighttime sleep.

When pharmacotherapy is necessary, physicians commonly consider benzodiazepines. While potentially effective for some patients, they have well-documented adverse effects, including increasing cognitive impairment. Other side effects include excessive daytime sedation, tolerance and withdrawal reactions. If benzodiazepines are prescribed for this indication, low doses of the short-acting medications (e.g., lorazepam 0.5 mg to 1 mg, oxazepam 15 mg) should be chosen with frequent attempts to reduce or discontinue them after a regular sleeping pattern is induced. The non-benzodiazepine hypnotic zopiclone may be a slightly safer alternative, though no data is available for use in this population. An alternative approach that should be considered prior to benzodiazepines is a trial of trazodone. Trazodone can be initiated at 25 mg to 50 mg at bedtime and increased to 50 mg to 100 mg for sedative effects. Doses above this are unlikely to improve effectiveness.

Pharmacotherapy of Depression
There is a variety of effective choices for the pharmacotherapeutic management of depression in dementia. While tricyclic antidepressants have demonstrated effectiveness in this population, their anticholinergic effects may worsen cognition. They can also be lethal in overdose. The SSRIs are effective, do not impair cognition, and they have fewer anticholinergic, beta-adrenergic and antihistaminic effects. Therapy can be initiated with sertraline 25 mg to 50 mg or fluvoxamine 50 mg at bedtime with a maximum of one or two dose increases at two to four weeks, if necessary. Potential side effects include gastrointestinal problems (nausea, vomiting, loose stools), headaches, sedation or insomnia and gait instability.

Another alternative is the reversible inhibitor of monoamine oxidase, type A, moclobemide. Therapy can be initiated at 150 mg once or twice daily and increased to 150 mg, three times daily, within one to two weeks. This medication is very well tolerated. The most common side effects are nausea, insomnia and restlessness.

Summary
The pharmacotherapy of BDD is an important component of the comprehensive treatment plan for BDD patients. Even small improvements in these disturbing behaviors will improve the quality of life for both the patient and the caregivers. It is the physician’s responsibility to ensure that all aspects of management, including pharmacotherapy, are considered and that the medications chosen provide the best balance of effectiveness with the lowest potential for adverse reactions. With careful monitoring, these drugs, along with the emerging class of cognitive enhancer medications, provide new hope for a devastating illness.

References: