Gradual Dose Reduction and Medication Tapering: A Clinical Perspective

Recent changes in the State Operations Manual put new emphasis on attempts to gradually reduce the dose of certain medications—namely psychotropic medications—as a component of medication management in nursing facilities. Applying these federal guidelines to caring for elderly patients is often highly complex. It requires an understanding of existing clinical evidence, the current standards of practice for using these medications, and the appropriate rationale for attempting to reduce drug dosages.

**Key Words:** Alzheimer’s disease, Antidepressant, Antipsychotic, Consultant pharmacist, Dementia, Depression, Elderly, Gradual dose reduction, Hypnotic, Nursing facility, Psychotropic, Sedative, State Operations Manual, Tapering.

**Abbreviations:** AD = Alzheimer’s disease, CATIE-AD Clinical Antipsychotic Trials in Intervention Effectiveness—Alzheimer’s Disease, CGIC = Clinical Global Impression of Change, NPI = Neuropsychiatric Inventory, MDD = Major depressive disorder, SOM = State Operations Manual, SSRI = Selective serotonin-reuptake inhibitor, STAR-D = Sequenced Treatment Alternatives to Relieve Depression.

New federal regulations are providing consultant pharmacists with a unique opportunity—to provide a newer, higher level of medication management to their patients. These regulatory changes are the results of recent revisions to the State Operations Manual (SOM), a publication of the Centers for Medicare & Medicaid Services (CMS) that provides guidance to surveyors who inspect long-term care facilities. The new rules more clearly define the role of pharmacists in long-term care, opening the way to greater responsibility for comprehensive medication management. Along with increased visibility, pharmacists also are experiencing an increased level of expectations—from facilities, patients, and families. For pharmacists who have become accustomed to, and comfortable with, previous regulatory requirements, this is an unprecedented opportunity. However, many pharmacists are asking questions, particularly about the new requirement to initiate gradual dose reduction (GDR) in psychotropic medications. This article, like the ones before it (see sidebar, page 640), attempts to address clinical issues in implementing the requirements of the SOM.

**Question 1: What is medication management?**

Medication management is more than just screening for drug interactions and adverse effects. The optimal management of an individual’s regimen has several goals, including to:
- Promote/maintain the highest practicable well-being
- Limit medications, doses, and duration to what is clinically indicated
- Consider nonpharmacologic interventions first and foremost
- Minimize adverse consequences
- Recognize changes in an individual’s condition, evaluate the role of medications, and modify regimen as needed on an ongoing basis

Much of medication management in the elderly centers around determining when a medication is no longer needed. According to the SOM, sometimes, the decision about
whether to continue a medication is clear. For example, someone with a history of multiple episodes of depression may need antidepressant medication indefinitely. Often, however, the only way to know whether a medication is needed indefinitely, and whether the dose remains appropriate, is to try reducing the dose and monitoring the resident closely for improvement, stabilization, or decline.

According to the SOM, tapering of any medication “may be indicated when the resident’s clinical condition has improved/stabilized, the underlying causes have resolved, and/or nonpharmacological interventions have been effective.” Many consultant pharmacists find, however, that prescribers often adopt an “if it isn’t broke, don’t fix it” philosophy and that convincing physicians to try tapering a medication can be a significant challenge.

**Manju T. Beier**, PharmD, FASCP, is senior partner, Geriatric Consultant Resources LLC, and clinical associate professor of pharmacy, School of Pharmacy, University of Michigan, Ann Arbor, Michigan. **Caren McHenry Martin**, PharmD, is a consultant pharmacist in Greensboro, North Carolina, and a contributing editor to *The Consultant Pharmacist*.

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Identifying Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening, adverse drug reaction that can result from therapeutic doses of proserotonergic agents. Some clinicians mistakenly think of serotonin syndrome as an idiopathic drug reaction, but it is actually a fairly predictable consequence of excess serotonergic agonism. The risk of serotonin syndrome, therefore, increases with the number and the doses of proserotonergic medications used. Signs of excess serotonin range from tremor and diarrhea in mild cases to delirium, neuromuscular rigidity, and hyperthermia in life-threatening cases. The true incidence of this syndrome is difficult to assess because more than 85% of physicians are unaware of the serotonin syndrome as a clinical diagnosis, and the symptoms of mild serotonin excess are often overlooked or misinterpreted by clinicians.

While often thought of as a syndrome related mainly to selective serotonin-reuptake inhibitors (SSRIs), many drugs and drug combinations have been associated with serotonin syndrome. These include monoamine oxidase-inhibitors, tricyclic antidepressants, SSRIs, opioids, dextromethorphan, antibiotics, antiemetics, sumatriptan, lithium, drugs of abuse (“ecstasy” and LSD), and herbal products (ginseng, St. John’s wort, tryptophan). Additionally, drugs that inhibit cytochrome P450 2D6 and 3A4 isoenzymes (e.g., paroxetine and ketoconazole, respectively) may increase the serum concentrations of serotonergic drugs metabolized by these enzymes, consequently elevating the risk of serotonin syndrome.

While there are no laboratory tests to confirm the diagnosis of serotonin syndrome, presence of tremor, clonus, or akathisia without additional extrapyramidal signs should lead clinicians to consider this diagnosis. Management of serotonin syndrome involves removal of the precipitating drugs, supportive care, and, in moderate-to-severe cases, administration of 5-HT2A antagonists (cyproheptadine). Many cases of serotonin syndrome resolve within 24 hours after initiation of therapy and removal of the precipitating drugs, but some cases may persist in patients taking proserotonergic drugs with long-elimination half lives or active metabolites.

CMS is convinced that tapering medications is an important component of medication management, and it requires or suggests tapering of certain classes of medications, namely antipsychotics, sedative/hypnotics, and “psychopharmacological” (defined as “any medication used for managing behavior, stabilizing mood, or treating psychiatric disorders”) (see Table 1). However, trying to implement tapering can be complicated for clinicians treating patients in long-term care.

Consultant pharmacists need to be knowledgeable about the relevant, current standards of practice and clinical trials that address the rationale and need for these therapies to be continued—or tapered—to be able to appropriately guide therapy decisions.

Question 2: What evidence do we have for the use of antipsychotics to treat behavioral symptoms related to dementia?

Approximately 75% of patients who have Alzheimer’s disease (AD) experience psychotic symptoms such as hallucinations and behavioral symptoms like aggression and agitation. Antipsychotic medications are widely used to treat behavioral symptoms related to dementia, with an estimated 25% of Medicare beneficiaries in nursing homes receiving these medications. However, the Food and Drug Administration (FDA) has not approved the use of antipsycho-
tic medications for treating psychosis or agitation among AD patients.

Until recently, the extent to which specific atypical antipsychotics benefit dementia patients has been unclear because of an absence of well-designed, head-to-head trials. Moreover, the side effects and risks associated with these medications have stirred a continual risk-benefit debate by clinicians and policymakers. Since few other therapeutic alternatives exist, there has been a paucity of effectiveness data for atypical antipsychotics for this indication.

The recent release of phase I of the Clinical Antipsychotic Trials in Intervention Effectiveness—Alzheimer’s Disease (CATIE-AD) trial, however, has provided the first substantial set of real-world effectiveness data. This $16 million trial, sponsored by the National Institute of Mental Health (NIMH), is the first head-to-head comparison of the atypical antipsychotics used in treating patients with dementia. A multicenter, double-blind placebo-controlled trial, CATIE-AD studied 421 patients (average age of 78) in the ambulatory or assisted living community who were randomly assigned to one of four treatments:
Table 1. Tapering Guidelines: Old Version* of the State Operations Manual vs. New Versions**

<table>
<thead>
<tr>
<th>Category</th>
<th>Old</th>
<th>New for Dementia-Related Behaviors</th>
<th>New for Psychiatric Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Twice a year, only for organic mental syndrome</td>
<td>Twice in first year, and annually thereafter</td>
<td>Twice in first year, and annually thereafter</td>
</tr>
<tr>
<td>Clinically contraindicated</td>
<td>Two failed GDRs OR documentation of clinical rationale or psychiatric diagnosis</td>
<td>Failed GDR with documentation</td>
<td>Failed GDR with documentation OR documentation of clinical rationale</td>
</tr>
<tr>
<td><strong>Sedative/Hypnotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Three times within six months, after ten days of continuous use</td>
<td>Quarterly for medications used beyond manufacturer’s recommendation for duration of use</td>
<td></td>
</tr>
<tr>
<td>Clinically contraindicated</td>
<td>Three failed taper attempts</td>
<td>Failed taper with documentation OR documentation of clinical rationale</td>
<td></td>
</tr>
<tr>
<td><strong>Psychopharmacological Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications included</td>
<td>Benzodiazepines and miscellaneous anxiolytics</td>
<td>Any medication used to manage behaviors, stabilize mood, or treat psychiatric conditions</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Twice a year</td>
<td>Twice in first year, then annually thereafter</td>
<td></td>
</tr>
<tr>
<td>Clinically contraindicated</td>
<td>Two failed taper attempts</td>
<td>Failed taper with documentation OR documentation of clinical rationale</td>
<td></td>
</tr>
</tbody>
</table>

*Revised, 1999.
**Revised, December 2006.

Abbreviation: GDR = Gradual dose reduction.
olanzapine, risperidone, quetiapine, or placebo. These patients, who presented with symptoms of psychosis, agitation, or aggression, were followed for 36 weeks. The main outcomes were time from initial treatment to discontinuation for any reason (either lack of efficacy or intolerable side effects), and the number of patients with at least a minimal improvement on the Clinical Global Impression of Change Scale (CGIC), at 12 weeks.

There were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks) ($P = 0.52$). The median time to the discontinuation of treatment because of a lack of efficacy favored olanzapine (22.1 weeks) and risperidone (26.7 weeks) compared with quetiapine (9.1 weeks) and placebo (9.0 weeks) ($P = 0.002$). The time to the discontinuation of treatment because of adverse events or intolerability favored the placebo. No significant differences were noted among the groups with regard to improvement on the CGIC scale. (Improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo [$P = 0.22$]).

Thus, the CATIE-AD trial has provided data corroborating what many clinicians have observed in their patients: that there is a modest treatment effect with antipsychotic medications for behavioral symptoms related to dementia, and one must carefully evaluate the risk-benefit ratio before instituting therapy. These medications may, however, benefit patients under the following circumstances: when the relief of severe, persistent symptoms would be beneficial, alternate therapies have failed, there is an identifiable risk of harm, and/or distress is significant.

Question 3: What are the considerations for medications used for sleep?

The revised SOM (Tag F329) states:

- The continued use is in accordance with relevant current standards of practice, and the physician has documented the clinical rationale for why any attempted dose reduction would be likely to impair the resident’s function.

While the old guidelines focused primarily on benzodiazepines used for sleep, the new guidelines apply to all medications being used for insomnia.
or cause psychiatric instability by exacerbating an underlying medical or psychiatric disorder.

or

- The resident’s target symptoms returned or worsened after the most recent attempt at tapering the dose within the facility, and the physician has documented the clinical rationale for why any additional attempted dose reduction at that time would be likely to impair the resident’s function or cause psychiatric instability by exacerbating an underlying medical or psychiatric disorder.  

While the old guidelines focused primarily on benzodiazepines used for sleep, the new guidelines apply to all medications being used for insomnia, including sedating antihistamines (hydroxyzine, diphenhydramine), antidepressants (trazodone, mirtazapine, etc.) and the newer, nonbenzodiazepine sleep agents (zaleplon, ramelteon, etc.). Additionally, Table 1 of F329 states that before initiating medications to treat insomnia, other factors potentially causing insomnia should be evaluated, including environment, lack of physical activity, and facility routines.

The revised F329 focuses on nonpharmacologic interventions to improve sleep, stating that:

- Initiation of medications to induce or maintain sleep should be preceded or accompanied by other interventions to try to improve sleep, and that all sleep medications should be used in accordance with approved product labeling, for example the timing and frequency of administration relative to anticipated waking time.  

This means that, generally speaking, sedative/hypnotics should be used short-term (7 to 10 days) for the management of insomnia characterized by difficulty falling asleep or frequent nocturnal awakenings.

Chronic insomnia has varying definitions in the literature, but the recent NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults defined it as lack or poor quality of sleep for 30 days or more.  

Some of the newer agents (eszopiclone, ramelteon) are indicated by FDA for the treatment of chronic insomnia and have studies that include the elderly in their package labeling. It is important for consultant pharmacists and prescribers to be familiar with what the product manufacturers are saying in their product literature to see if these drugs are being used appropriately. In general, these medications should be taken on a relatively empty stomach, as food can retard the absorption and delay the onset of sleep.

The timeline for the GDR of any medication is patient-specific and based on numerous variables.
Question 4: What evidence do we have concerning the duration of use for antidepressants and the risk of relapse, recovery, and recurrence for use of multiple agents for depression?

Depression in the elderly patient is prevalent, and antidepressant use is commonly seen in this population. In the previous version of the SOM, antidepressants were not included in the classes of medications that required ongoing tapering and evaluation. The revised SOM, however, includes antidepressants as one of several classes of medications considered “psychopharmacologic,” and therefore under greater scrutiny.

Management of depression generally focuses on Response, Remission, Relapse, Recovery, and Recurrence (sometimes referred to as the “5 Rs”). Remission of depression (symptoms resolved and reverting to baseline) and preventing its recurrence are the primary treatment goals. Consensus guidelines from the NIMH state that when the first onset of depression occurs later in life, treatment should be continued for more than six months.¹¹ For those with recurrent illness, these guidelines suggest that therapy should continue for more than 12 months, and prophylactic treatment should be of the same type and at the same dose. Additionally, these guidelines say that the treatment response and long-term outcomes for elderly patients are similar to those observed in younger patients, but the temporal course is slower and the risk of relapse greater, which may prompt some clinicians to maintain patients on antidepressants for a longer duration.

Another set of guidelines published in 2003 by Baldwin and colleagues also suggest that antidepressant therapy for an elderly patient with a first onset depressive episode should be continued for a minimum of 12 months on the same dosage that led to remission of symptoms.¹² For recurrent depression, treatment should be continued for 12 to 36 months at the same dose that led to remission. High-risk patients should be continued for a minimum of three years.

Recently, results from the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial have been published.¹³ This trial, the largest and longest study ever conducted to evaluate depression treatment, assessed the comparative efficacy, effectiveness, and harms of 12 second-generation antidepressants—bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine—in treating patients with major depressive disorder (MDD).

Cholinesterase inhibitors have been shown to produce significant improvements in behavioral symptoms in patients with both mild-to-moderate and moderate-to-severe AD.
Each of the four levels of the study tested a different medication or medication combination. The primary goal of each level was to determine if the treatment used during that level could adequately treat participants’ MDD. Those who did not become symptom-free could proceed to the next level of treatment. Over a seven-year period, the study enrolled 4,041 outpatients diagnosed with MDD, ages 18 to 75 years, from 41 clinical sites around the country, which included both specialty care settings and primary medical care settings. (For a detailed analysis of the various medication levels in this trial and the corresponding remission rates see: www.nimh.nih.gov/healthinformation/stard-qa-overall.cfm.)

This study provides clinical evidence for the use of more than one antidepressant for some patients whose depression does not fully respond to the use of a single agent. However, an important consideration when managing antidepressants—especially multiple antidepressants—is the potential additive side effects, such as serotonin syndrome (see sidebar, page 630).

**Question 5: What evidence do we have for cholinesterase inhibitors and memantine for treating behavioral symptoms related to dementia?**

While not included in the SOM list of medications requiring attempts to taper the drug, cholinesterase inhibitors and memantine are increasingly being evaluated and used to manage mild behavioral symptoms related to dementia. To date, there have been a few controlled trials using behavioral tools as secondary outcome measures to evaluate the efficacy of these medications in nursing facilities and community-based settings. In 2003, a meta-analysis of cholinesterase-inhibitor trials demonstrated a modest beneficial impact on neuropsychiatric and functional outcomes for patients with AD. A recent comprehensive review of placebo-controlled trials, which used the Neuropsychiatric Inventory (NPI) to assess behavioral symptoms of AD, also found evidence that suggests that when cholinesterase inhibitors and memantine are optimized for the various stages of AD, they can prevent the emergence of neuropsychiatric symptoms. This review also found that, although results from the literature are not uniformly positive, cholinesterase inhibitors have been shown to produce significant improvements in behavioral symptoms in patients with both mild-to-moderate and moderate-to-severe AD. Evidence also indicates that memantine might be of benefit as an adjunct to long-term donepezil treatment in patients with moderate-to-severe AD.

When nonpharmacologic strategies are deemed insufficient to ease problem behaviors in patients with AD, treatment with cholinesterase inhibitors, alone or in combination with memantine as appropriate for the stage of disease, may be considered as a first-line option in the early pharmacologic management of AD-related behavioral symptoms.

**Question 6: How slow should dose reductions be?**

GDR is defined by the SOM as:

*The stepwise tapering of a dose to determine if symptoms, conditions, or risks can be managed by a lower dose or if the dose or medication can be discontinued.*

Some clinicians question how gradual the dose reductions should be. According to the SOM:

*The time frames and duration of attempts to taper any medication depend on factors including the coexisting medication regimen, the underlying causes of symptoms, individual risk factors, and pharmacologic characteristics of the medications. Some medications (e.g., antidepressants, sedative/hypnotics, opioids) require more gradual tapering so as to minimize or prevent withdrawal symptoms or other adverse consequences.*

The tapering of psychopharmacologic medications over several weeks
to months permits detection of returning symptoms that require reinsti-
tution of the original medication dose for another three to six months. It also minimizes the risk of discontin-
uation syndrome, which is known to be especially relevant to the selective serotonin-reuptake inhibitors (SSRIs).
SSRI discontinuation syndrome (sometimes referred to as withdrawal syndrome, which erroneously implies drug dependence), is a constellation of symptoms that can occur as a result of intermittent noncompliance, abrupt cessation of treatment and, less often, tapering of the SSRI dose.

Physical symptoms of imbalance; gastrointestinal and influenza-like symptoms; sensory and sleep disturbances; psychological symptoms such as anxiety, agitation, crying spells, and irritability, can occur within 24 to 72 hours after abrupt discontinuation of an SSRI. While these symptoms are not dangerous, they can be uncomfortable and distressing to patients, and they may lead to the initiation of additional medications and the prescribing cascade. A recent Agency for Healthcare Quality and Research review also cautions about the discontinuation syndrome, especially with venlafaxine and paroxetine.

While the time line for the GDR of any medication is patient-specific and based on numerous variables such as the patient’s age, comorbid conditions, and presence of side effects, consultant pharmacists may consider the following conservative guidelines for attempting a slow GDR when it has been decided that the agent in question should be discontinued.

- Begin with a 25% reduction in total dose from the original dose, and monitor for changes in target symptoms including side-effect burden. This can be accomplished over a period of two to three months, depending on the severity of the target symptoms, the kinetics of the drug, and other interacting agents.

- This 25% reduction may be accomplished weekly or every other week, or less frequently based on the patient’s individual need.

**Conclusion**
GDR of medications can play an important role in the management of medications for all patients, particularly the frail elderly patient who may be taking multiple medications and who may be more prone to medication side effects. While the recent revisions to the SOM focus on the importance of performing GDRs for certain classes of medica-
tions, practitioners should be attuned to the continual need to assess the patient and the medication regimen for opportunities to modify all medications, based on the current clinical evidence as well as the current needs of the patient.
Gradual Dose Reduction and Medication Tapering: A Clinical Perspective

Understanding the State Operations Manual

This article is the third in a series about changes in the State Operations Manual to help consultant pharmacists understand the changes that affect drug therapy in nursing facilities. These guidelines, implemented in December 2006, were issued by the Centers for Medicare & Medicaid Services and are used by surveyors to evaluate nursing facilities.

Previous articles were published in:


References

23. Beier MT. The serotonin syndrome revisit.