

Medications in Long-Term Care: When Less is More

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- Long-term care • Inappropriate prescribing • Polypharmacy
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HISTORY OF MEDICATION REDUCTION IN LONG-TERM CARE

The Nursing Home Reform Act (OBRA-87) enacted in 1987 called for sweeping changes in the standards of care in nursing homes in accordance with new, more demanding federal regulations. For example, OBRA-87 called for a new approach to the use of antipsychotics in persons with dementia. Because antipsychotics were regarded as frequently inappropriate chemical restraints in long-term care (LTC), OBRA-87 mandated dose reductions in antipsychotics in an effort to discontinue them whenever possible. OBRA-87 proposed that a safer, more supportive environment in LTC settings would facilitate such reductions in antipsychotic doses.¹

Overall rates of potentially inappropriate prescribing in older adults have ranged from 12% to 40%, depending on the setting, criteria, and population sampled.² Developing from burgeoning concerns for polypharmacy and potential iatrogenic toxicity of medication in older adults, expert consensus lists of potentially inappropriate pharmacotherapy in the elderly (PIPE) began to emerge. In general, drugs with activity in the central nervous system (CNS) were commonly placed on these PIPE lists, and hence our focus on such medications in this review.

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In 1991, Dr Mark Beers spearheaded a group of 12 experts in geriatrics to develop the first well-recognized PIPE list, intended specifically for older adults in LTC settings.³ This list was subsequently referred to as the Beers list and future iterations made this probably the most well-recognized PIPE list among practitioners in geriatrics. For example, in 1997, another PIPE list, updated and expanded to include community-dwelling older adults, was published.⁴ Much of the 1997 version of the Beers list was incorporated into the Centers for Medicare and Medicaid Services' Interpretive Guidelines for Long-Term Care Facilities to evaluate a nursing home's compliance with medication-related regulation. Most recently, in 2002, another iteration of the Beers list was issued, this time more explicitly explaining the process of arriving at the recommendations.⁵ A 5-step modified Delphi method of expert panel consensus was implemented to generate 2 categories for medications: (1) should generally be avoided in all elderly patients and (2) should generally be avoided in elderly patients with a specific illness/symptom.

Zhan and colleagues⁶ in 2001 published their own PIPE list specifically citing a criticism of previous Beers PIPE lists that they lacked the sufficient sensitivity and specificity of any explicit criteria. In an effort to overcome this limitation, they convened a 7-person panel of experts in geriatrics, pharmacoepidemiology, and pharmacy, who ultimately categorized PIPE into 3 categories: (1) always to be avoided, (2) rarely appropriate, and (3) some indications but often inappropriate. A more recent PIPE list has emerged from the Healthcare Effectiveness Data and Information Set (HEDIS) 2006.⁷ This list came about as only a small part of a large national program, the National Committee on Quality Assurance. The HEDIS 2006 PIPE list and subsequent updated iterations were developed using the Delphi method to examine and categorize drugs to avoid in older adults. Comparisons among the various PIPE lists are delineated in **Table 1**.

The concerns regarding antipsychotic use in older adults with dementia have been amplified substantially since OBRA-87 because of their recent black-box warnings. In 2003, a warning was issued for risperidone (Risperdal) regarding its increased risk of cerebrovascular adverse events including stroke. Soon thereafter similar black-box warnings for cerebrovascular adverse events were issued for olanzapine (Zyprexa) and aripiprazole (Abilify). Subsequent warnings advised that, as a class, antipsychotics increased the risk of mortality from 2.6% to 4.5% (vs placebo) over the course of 10 to 12 weeks.⁸ Never has the issue of the potential adverse events of CNS-acting agents among older adults been so front and center in geriatrics.

PREVALENCE OF NEUROPSYCHIATRIC ILLNESSES IN LTC

The use of psychotropic medications in LTC is common in part because neuropsychiatric illnesses are prevalent in this setting. Dementia affects 50% or more of LTC residents, with the most common causes being (in order) Alzheimer disease (AD), Lewy-body dementia, vascular dementia, and frontotemporal dementia.⁹ Dementia-associated neuropsychiatric symptoms, such as psychosis, aggression, and depression, occur in 80% to 100% of patients with dementia at some point in the illness course.¹⁰ Such neuropsychiatric symptoms remain one of the most challenging aspects of dementia to manage as they worsen patient and caregiver quality of life, often resulting in hastened placement of the patient outside the home. Furthermore, no treatments have been approved by the US Food and Drug Administration (FDA) for any dementia-related neuropsychiatric symptom. All commonly used off-label treatments carry the burden of substantial potential toxicity, lack of proven efficacy, or both. Also common in dementia, delirium was noted to have a 21.8% 1-month

Table 1 Psychotropic medications listed on some of the most prominent lists of potentially inappropriate medications for use in older adults					
Drug	Beers 1991	Beers 1997	Zhan 2001	Beers 2002	HEDIS 2009
{Barbiturates}	*	↑	1	↑	√
{Benzodiazepines}	•				
Diazepam	•	↑	2	↑	√
Flurazepam	•	↑	1	↑	√
Chlordiazepoxide	•	↑	2	↑	√
Quazepam				↑	
Halazepam				↑	
Chlorazepate				↑	
Meprobamate	•	↑	1	↑	√
Oxazepam	*	↓*		↑*	
Temazepam	*	↓*		↑*	
Triazolam	*	↓*		↑*	
Lorazepam		↓*		↑*	
Alprazolam		↓*		↑*	
Diphenhydramine	*	↓/↓*/↑*	3	↑	√
Hydroxyzine		↓/↓*/↑*	3	↑	√
Zolpidem		↓*			
{Sedatives}		↑*			
Amitriptyline	•	↑	3	↑	√
Doxepin		↑	3	↑	
Desipramine		↓*			
Fluoxetine				↑	
Bupropion				↑*	
{SSRIs}		↓*		↓*	
{MAOIs}		↓*		↑*	
{TCAs}		↑*/↑*/↑*		↑*/↑*/↑*/↓*	
Haloprediol	*	*			
Thiothixene				↑*	
Thioridazine	*	↓*		↑	√
Mesoridazine				↑	√
Chlorpromazine		↓*		↑*	
{Typical APs}				↑*	
Clozapine		↓*		↑*	
Olanzapine				↓*	
{Amphetamines}		↑*		↑	√
Tacrine				↑*	

Beers lists: •, avoid in general; *, avoid in certain situations or doses; ↑, high potential for adverse effect; ↓, low potential for adverse effects.

HEDIS 2009: √, included among high-risk medications to avoid in elderly patients.

Zhan criteria: 1, always avoid; 2, rarely appropriate; 3, sometimes indicated.

Abbreviations: AP, antipsychotic; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; {xxxx}, a class of medications in general.

prevalence in LTC settings in Iowa, although precise prevalence estimates are not well established.¹¹

The prevalence of major depressive disorder (MDD) in LTC seems to range from 10% to 15%, whereas that of subsyndromal depression (also associated with significant morbidity) has ranged from 33% to 61% in various LTC studies.¹² There have been few large-scale studies of antidepressants in LTC and/or among persons with comorbid dementia. Anxiety disorders may also affect older adults in LTC. One report diagnosed an anxiety disorder in 2.3% of older adults on admission to LTC.¹³ Data from studies in 1996 and 2005, respectively, provided similar estimates of the prevalence of anxiety disorders among older LTC residents, including, among the first sample, a 2.8% prevalence of generalized anxiety disorder (GAD) and 1.9% prevalence of panic disorder (total 4.7%),¹⁴ and a 5.7% prevalence of all *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)* anxiety disorders in the 2005 study.¹⁵

More serious and persistent mental illness is less prevalent in LTC settings. The reasons are likely multifactorial, including discriminatory exclusion of persons with such diagnoses from certain LTC facilities as well as early mortality of persons with illnesses such as bipolar disorder and schizophrenia. The data on the prevalence of bipolar disorder in LTC are scant, with only 1 article from 2005 reporting a prevalence of 0.5% on admission to LTC (lower than the 1%–2% rate reported among general adult populations).¹³ Similar prevalence estimates for schizophrenia (0.5%) were reported in the same study of persons undergoing LTC admission, again lower than the 1% prevalence widely quoted in younger adult populations.¹³ Few data also exist regarding the epidemiology of substance use diagnoses among older adults on admission to or during the course of stay in LTC.

MEDICATION REDUCTION: WHY, WHEN, HOW, AND WHAT?

Why?

There are several reasons why reducing medications among LTC residents should be a potential therapeutic goal for geriatricians. A typical LTC resident is on 7 or more prescription medications.¹⁶ Older adults are more susceptible to adverse medication side effects because of various age-related changes in the pharmacokinetic and pharmacodynamic effects of drugs; adverse reactions are almost 7 times more common in adults in their 70s than among those in their 20s. An example is the commonly unrecognized cumulative anticholinergic effects of several medications, which may lead to increased cognitive decline, delirium, constipation, and urinary retention, among other effects.¹⁷ This finding is particularly germane to older adults because, with age, the brain progressively loses cholinergic reserve, constipation commonly becomes an age-related symptom that decreases quality of life, and age-associated prostatic hypertrophy leaves older men vulnerable to iatrogenic urinary retention.

Polypharmacy (being on multiple simultaneous medications) is not de facto bad practice in the care of certain older adults, but there are high rates of older adults in LTC receiving probably inappropriate (harmful or of no clear benefit) medications.¹⁶ The increased morbidity, hospitalization rates, mortality, and health care expenditures associated with inappropriate prescribing patterns among older adults certainly warrant increased vigilance for PIPE.¹⁸

One often unspoken issue that promotes polypharmacy is physician discomfort when no specific therapy (usually expected in the form of a medication in the United States) can change the patient's course of illness. Prescribing a medication may give clinicians and patients/family members a false sense of reassurance that at least something tangible was done. Geriatricians in particular should gain a comfort level

permitting them to suggest no pharmacotherapy when it is not truly indicated. For instance, effects of long-term preventive medications may require more time to confer significant benefits than the patient's life expectancy (eg, statins for prevention of cardiovascular disease).

When?

It is good practice to establish a routine frequency (eg, twice yearly) for reviewing LTC residents' medication lists for inappropriate or unnecessary medications. Other important times to conduct such a review are during transitions of care (eg, admission to an LTC facility, discharge from a hospitalization). Patients with psychiatric disorders or disorders with persistent pain warrant even more vigilance. It is also important not to forget PRN (as needed) medications and to justify their ongoing use or discontinue them.

How?

Changes in medication therapy should involve discussions with patients and/or proxy decision makers regarding a medication's risk-benefit profile for that specific patient. Depending on the medication at hand, discontinuation may be achieved abruptly or may require a gradual taper (eg, with long-term use of benzodiazepines or opiates.) Successful systematic programs for reduction of certain potentially inappropriate medications are discussed in further detail later.

What?

The answer to this question is the core part of this review: describing which medications are common offenders in PIPE lists as well as potentially more appropriate alternatives. The discussion is organized according to medication classes commonly seen on PIPE lists. There are no absolutes in prohibitions against using most medications in older adults; nonetheless, avoiding or discontinuing many of the medications discussed later is more often more appropriate care for LTC residents than not doing so. Several CNS-acting medication classes are discussed in more detail.

Antipsychotics

As described in the history of medication reduction in LTC, antipsychotic medications have generally been at the forefront of medications targeted for reduction as a result of inappropriate use in LTC. The concerns have spanned from OBRA-87 to the more recent black-box warnings for antipsychotics as a class (typical and atypical) regarding about a 2% increased absolute risk of mortality in older persons with dementia (again, that includes $\geq 50\%$ of LTC residents). The cause of death in most cases was infection (eg, pneumonia) or sudden cardiac death. Although direct causal pathways are unknown, excessive sedation among persons commonly already compromised in swallowing function could easily lead to aspiration pneumonia.

Antipsychotics are also known to affect cardiac conduction, often prolonging the QT_c interval (the corrected QT interval on electrocardiogram), which may lead to fatal arrhythmias such as torsades de pointes. A postulated mechanism is antipsychotic interference with cardiac potassium channels leading to prolonged QT intervals.¹⁹ There are differences in the propensity to cause significant QT_c prolongation among various antipsychotics, prompting the inclusion of certain agents on various PIPE lists and/or withdrawal of some medications from the market (eg, thioridazine [Mellaril] and mesoridazine [Serentil]). A large study reported that persons aged 30 to 74 years with varied diagnoses taking antipsychotics (vs antipsychotic-naive persons) had a doubled incidence rate of sudden cardiac death, although it remained a rare event (absolute rates: nonusers, 0.143%; typical antipsychotic users, 0.294%; atypical

antipsychotic users, 0.28%).²⁰ Among atypical antipsychotics, ziprasidone (Geodon) has received the most attention for potential QT_c prolongation, with reports of average prolongations of 10 ms. This finding, combined with fewer studies among older adults, twice-daily dosing, and need for concomitant food intake to ensure adequate absorption, has made ziprasidone a rare choice for older adults prescribed an atypical antipsychotic.

The discussion of potential toxicity of antipsychotics among LTC residents becomes even more germane in light of evidence questioning whether they are even effective for their most common (off-label) use in older adults: dementia-associated psychosis and agitation/aggression. The multisite CATIE-AD (Clinical Antipsychotic Trials in Intervention Effectiveness–Alzheimer Disease) trial compared risperidone, olanzapine, quetiapine (Seroquel), and placebo for psychosis and/or agitation in persons with AD.²¹ There was no difference in overall effectiveness (time to treatment discontinuation) between any of the active treatments or placebo. Superior efficacy in symptom reduction with risperidone and olanzapine was offset by early treatment discontinuation because of adverse events. Other evidence supports modest efficacy of atypical antipsychotics for psychosis and/or agitation in dementia; a 2006 review of 15 randomized controlled trials (RCTs) reported that, combining data for individual drugs, psychosis scores improved significantly with risperidone treatment (average dose 0.5–1.5 mg/d), and that global neuropsychiatric symptoms improved with aripiprazole (average dose 5–15 mg/d) and risperidone.²²

Despite the obvious limitations of antipsychotics when used for dementia-related neuropsychiatric symptoms, there is no FDA-approved medication for treating psychosis or aggression in dementia. Because these symptoms are common and produce a variety of potential adverse effects themselves, clinicians are now often left in a quandary. A proposed algorithm for the careful consideration of the off-label use of an atypical antipsychotic among older adults with dementia has been proposed (**Fig. 1**).⁸ No other pharmacotherapy has shown a better evidence-based risk-benefit profile for similar symptoms.

Psychosocial/behavioral treatments are underused in part because they are time-intensive and poorly reimbursed, but they are also generally more difficult to study empirically than medications. This finding leaves unanswered questions as to the efficacy of proposed psychosocial/behavioral therapies for dementia-associated psychosis/agitation. In a recent review, the best empirical evidence for RCTs using psychosocial/behavioral therapies was for: (1) caregiver psychoeducation/support, (2) music therapy, (3) cognitive stimulation therapy, (4) Snoezelen therapy, (5) behavioral management-based techniques, and (6) staff training/education.²³ There have also been systematic studies targeting reduction/cessation of antipsychotics in LTC, with effective results.^{24–26} This finding reinforces the notion that even if deemed appropriate for a given patient at a given time, trial tapers off antipsychotics should be considered every 3 to 6 months.

The clearest indications for antipsychotics in older adults are for schizophrenia or bipolar disorder. Quetiapine and aripiprazole have received recent FDA approval as adjunctive therapy for MDD, but data are limited in older adults. Extrapolating from RCTs and studies of real-world prescribing patterns, antipsychotic doses in older adults with these illnesses should be one-third to one-half those used in younger patients. A large study sponsored by the National Institutes of Health recently called into question the superiority of atypical over typical antipsychotics for schizophrenia,²⁷ but each class has its own potential side effect liabilities. The probable exception to this comparison is clozapine (Clozaril), which has shown superior efficacy to other antipsychotics in schizophrenia as well as protective benefits against suicide.

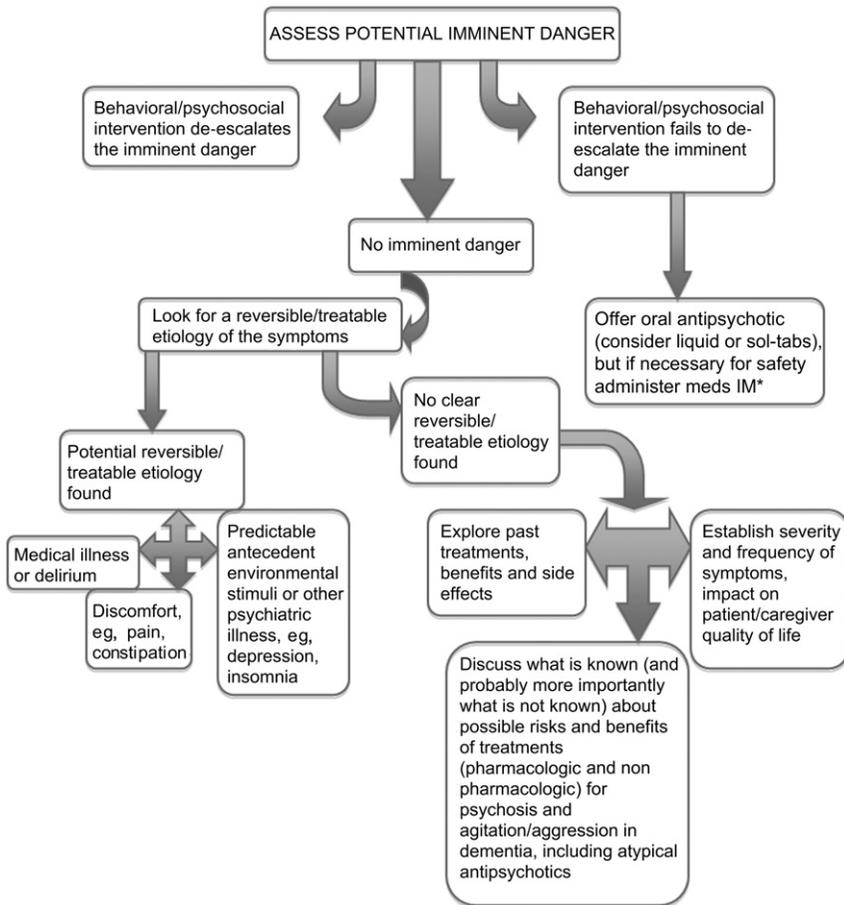


Fig. 1. A proposed algorithm for decision-making regarding the use of antipsychotics in older adults with dementia-related psychosis and/or agitation. (*) IM, intramuscularly. (Data from Meeks TW, Jeste DV. Beyond the black box: what is the role for antipsychotics in dementia? *Curr Psychiatr* 2008;7:50–65.)

However, its use in older adults is rare because of its strong anticholinergic properties, need for frequent laboratory tests (to monitor for agranulocytosis), and other unique side effects (eg, risk for seizures and cardiomyopathy).

When choosing amongst the other available antipsychotics, the side effect profile takes precedence. Typical antipsychotics appear on certain PIPE lists because of older adults' sensitivity to developing parkinsonism and tardive dyskinesia (TD). The risk of TD is 4 to 5 times higher in older versus younger patients with schizophrenia.²⁸ This risk is likely diminished by use of atypical versus typical antipsychotics.²⁹ However, atypical antipsychotics seem more likely to cause metabolic abnormalities such as hyperglycemia, dyslipidemia, and abdominal weight gain. Clinical experience along with published data such as the American Psychiatric Association/American Diabetes Association guidelines suggest that metabolic risks are highest for clozapine and olanzapine, intermediate for quetiapine and risperidone, and lowest for aripiprazole and ziprasidone.³⁰ Olanzapine was included in the Beers 2002 PIPE list because

of its relative propensity to cause metabolic side effects⁵; it is also the most anticholinergic of atypical antipsychotics, especially at doses greater than 10 mg/d. All atypical antipsychotics may cause akathisia, a motor/psychological restlessness that may be misinterpreted as increased agitation, as well as extrapyramidal symptoms (most prominent with risperidone) and orthostasis (most notable with quetiapine).

Benzodiazepines

An unanticipated and unproductive outcome of OBRA-87's focus on reducing antipsychotic usage in LTC was an increase in the use of other potentially inappropriate medications (eg, the benzodiazepine clonazepam [Klonopin]).³¹ Benzodiazepines are sometimes indicated for LTC residents diagnosed with a specific anxiety or sleep disorder, such as restless leg syndrome. Benzodiazepines on more rare occasions are used as antiepileptics, muscle relaxants, or premedication for invasive procedures. However, these medications are often also prescribed to residents without an appropriate indication. Even although benzodiazepines should generally be avoided in the older population, 30% of LTC residents are still prescribed this medication class despite the availability of safer alternatives.³²

Benzodiazepines, for example, may be used to sedate agitated patients, which may provide a transient band-aid for the problem but also may cause a paradoxical reaction in persons with dementia, worsening confusion and agitation and causing a cycle of escalating inappropriate pharmacotherapy for an ill-defined target symptom. Even when used in a more appropriate circumstance such as for anxiety or insomnia, benzodiazepine side effects are problematic for older adults (some agents more than others, see later discussion), and their use should generally be short-term (often not the case once initiated).

Overall, among older adults in LTC, the use of benzodiazepines often carries risks that outweigh any benefits. They may result in excessive sedation, leading to falls, and cognitive confusion.^{33,34} The results of a recent meta-analysis by Woolcott and colleagues³⁵ showed that benzodiazepines increase the risk of falling in patients aged 60 years or older (odds ratio 1.41). Another study showed that older adult drivers using benzodiazepines with a long half-life had an increased risk of motor vehicle collisions.³⁶ Furthermore, benzodiazepines cause physical (if not psychological) tolerance and dependence even if they are not misused, and withdrawal can be difficult. Several studies have shown effective methods of decreasing sedative and antipsychotic use through multidisciplinary teams. One Swedish study showed that regularly occurring multidisciplinary team meetings aiming to improve health care provider teamwork decreased the usage of psychotropics by 19%, and benzodiazepines by 37%.²⁶ Another study by Westbury and colleagues²⁵ used an interdisciplinary, multifaceted strategy to decrease antipsychotic and benzodiazepine use by using prescription audits, feedback, and educational sessions.

Recommendations to avoid certain benzodiazepines have been present since 1991 because there are significant inherent pharmacokinetic differences among various agents in this class as well as age-related differences in their metabolism. Meaningful pharmacokinetic differences include those related to half-lives and hepatic metabolism; for instance, temazepam (Restoril) and lorazepam (Ativan) require only hepatic glucuronidation but not cytochrome P450 activity, and are thus less susceptible to age-related alterations in metabolism or medication interactions. On the other hand, diazepam (Valium) has a problematically long half-life in older adults, especially because it stores in and is slowly released from adipose tissue, which increases relative to muscle mass with age. The Beers criteria 1991 recommended avoiding all long-acting benzodiazepines such as diazepam in older

adults.³ In 1997, the Beers criteria expanded the list of benzodiazepines one should avoid to include short-acting benzodiazepines, beyond a specified dose range.⁴ In 2002, the Beers criteria were once again updated, emphasizing the need to prescribe smaller doses of benzodiazepines, if at all, particularly among persons with chronic obstructive pulmonary disease or those with a history of syncope and/or falls. The long-acting benzodiazepines are included on the HEDIS PIPE list as medications to be avoided.³⁷

Benzodiazepines may be appropriate for short-term use in select psychiatric disorders (eg, panic disorder). Benzodiazepine use in palliative care is a distinct issue beyond the scope of discussion of this article, but there is generally more laxity in their use in that scenario. However, most older adults are receiving these medications without an appropriate indication. This situation is particularly concerning in a population at risk for adverse side effects with such potential risk for morbidity and mortality, such as gait impairment, respiratory suppression (eg, with comorbid obstructive sleep apnea), cognitive impairment/delirium, and falls with subsequent fractures.

Other sedatives/hypnotics

Problematic toxicity with barbiturates or related drugs such as meprobamate consistently landed them on virtually all PIPE lists, and prompted initial hope for benzodiazepines as an alternative. Given the problematic issues discussed earlier with benzodiazepines, there has been a search for a safer sedative medication. Nonbenzodiazepine sedatives have emerged as possible alternatives, such as the Z drugs zolpidem (Ambien/Ambien CR), zaleplon (Sonata), and eszopiclone (Lunesta); however, these drugs do act on benzodiazepine type 1 receptors but without the muscle relaxant or antiepileptic effects of benzodiazepines, and with some evidence for less physiologic dependence/withdrawal. However, they also significantly affect postural stability and thus risk for falling during their hours of peak onset.³⁸ There have also been reports of hallucinations and amnesic episodes, including sleepwalking and sleep-eating, with these Z drugs.^{39,40} Although some such medications have been FDA-approved for long-term treatment of insomnia (eg, eszopiclone), their use is generally best limited in older adults in LTC settings, with particular attention to other possible causes of sleep disruption (eg, restless legs syndrome, obstructive sleep apnea, poor sleep hygiene, nocturia).

Because insomnia itself has such subjective and objective detriments for older adults, and when no primary cause of insomnia can be established, geriatricians often search for alternatives to the aforementioned treatments to alleviate this symptom. Trials of melatonin among older adults have produced mixed results,⁴¹ but a specific melatonin receptor agonist, ramelteon (Rozerem), has produced some benefits in insomnia, primarily in reduced sleep latency. Although limited in effects on measures such as total sleep time, ramelteon use in older adults does not seem to cause the postural instability or amnesia associated with medications such as zolpidem.⁴² Another commonly used drug for insomnia is trazodone (Desyrel/Oleptro). Originally developed as an antidepressant that proved too sedating at therapeutic doses, its off-label use (dosed at 50–150 mg at bedtime) for insomnia has gained popularity because of its potential to augment other antidepressants, its lack of addictive qualities, and its low cost. However, long-term data on its efficacy are lacking, and it does carry some risks such as orthostasis, residual fatigue, and priapism.⁴³ One option for insomnia treatment that is clearly a poor choice is a sedating antihistamine (eg, diphenhydramine [Benadryl] or hydroxyzine [Vistaril]). These medications are common on PIPE lists, because of both lack of proven efficacy for insomnia and strong anticholinergic effects among older adults. If outside medications are allowed in an LTC

setting, careful scrutiny for use of over-the-counter sleep aids should be conducted. Many older adults inadvertently take such sedating antihistamines as part of PM formulations of medications such as acetaminophen.

Antidepressants

Antidepressants have not received as much attention on PIPE lists as the psychotropics discussed earlier, although MDD affects 10% to 15% of LTC residents and anxiety disorders affect about 5% of LTC residents. Many studies have documented the underdiagnosis and undertreatment of these disorders in LTC,⁴⁴ as well as, less commonly, undocumented reasons for the use of and successful discontinuation of unnecessary antidepressants.⁴⁵ The use of even newer-generation antidepressants has recently attracted attention as not being as completely benign as once believed. For instance, antidepressants as a class have received a black-box warning for increased risk of suicidality (not usually suicide attempts or completed suicides; more often ideation or any other self-harm), but this risk was significant only up to age 24 years; antidepressants seem increasingly protective of suicidality with increasing age.⁴⁶ Other potential risks to be considered in prescribing antidepressants to older adults include reports of increased rates of hyponatremia caused by syndrome of inappropriate antidiuretic hormone (SIADH), osteoporosis, falls, and gastrointestinal (GI) bleeding (especially when on concomitant nonsteroidal antiinflammatory drugs [NSAIDs]), in particular with selective serotonin reuptake inhibitors (SSRIs).⁴⁷

In addition to these safety concerns, there are limited and mixed data on the efficacy of antidepressants among the oldest old adults, those in institutional settings, and among older adults with comorbid dementia.^{48–53} **Box 1** summarizes the suggestions for choosing antidepressants in treating MDD (or anxiety disorders) among LTC residents. Antidepressants may be used off-label in nonmajor or subthreshold depression, which may affect up to 30% to 60% of LTC residents, but their efficacy is not well established in this condition.¹² SSRIs are usually used as a first-line treatment of late-life MDD as well as most anxiety disorders, including GAD, panic disorder, social anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder, with GAD being the most common presentation of clinically significant anxiety in late life. It is important when assuming care of a patient admitted on an antidepressant that the indication be clearly established, that the time course of treatment and past treatment history be obtained, and that some subjective (if possible objective) measure of symptomatic and functional response to the medication be assessed over time.

Analgesics

Pain is one of the most common symptoms among LTC residents. Optimal assessment and treatment of pain is complicated by the: (1) broad variety of causes causing pain, (2) diagnostic uncertainty and frequently fluctuating course of symptoms and response to treatment, (3) availability of multiple treatment options, and (4) presence of regulatory and administrative guidelines.⁵⁵ The challenge to LTC providers is to identify the most efficacious treatments for pain and minimize medication toxicities and interactions. Most residents identified as receiving polypharmacy are receiving analgesic medications that may have significant toxicities and adverse drug interactions.⁵⁶

Expert recommendations for treating pain in LTC have been described in detail by the American Geriatrics Society Panel on Pharmacologic Management of Persistent Pain in Older Persons (AGS Panel).⁵⁷ Although analgesic medications can reduce pain intensity/frequency and enhance older adults' quality of life, the identification and treatment of an underlying cause of the pain may permit pain management with

fewer analgesics, lower doses, or medications with a lower risk of serious adverse consequences. Optimization of medication management requires an accurate assessment of the level of pain. A pain scale that combines descriptive and behavioral measurements and is valid across the range of cognitive and communicative abilities encountered in LTC ensures more accurate assessment of pain and the efficacy of interventions. In each case, the provider must consider the level of discomfort acceptable to the resident.⁵⁸

Although the general principles of pain management apply to both acute and chronic pain, each provides its own challenge in LTC. Persistent pain is often more difficult to treat than acute pain, and requires a combination of drug and nonpharmacologic approaches to reduce the requirement for analgesic medications. Patient and staff education, frequent reassessment, and goal setting can lower expectations of the complete elimination of pain in favor of achieving tolerable pain control. The interdisciplinary team and the LTC resident collaborate to arrive at pertinent, realistic, and measurable goals for treatment, such as reducing pain sufficiently to allow the resident to ambulate comfortably to the dining room for each meal or to participate in 30 minutes of physical therapy.⁵⁹

Often, the perception of control of pain is improved through the use of regularly scheduled dosing as opposed to as-needed orders. Patients who require frequent as-needed doses should be encouraged to consider taking their analgesic medication on a regular schedule. Pain that has become severe requires higher doses of medications to achieve satisfactory control.⁵⁹ Long-acting preparations minimize fluctuations in efficacy caused by pharmacokinetics and often result in more effective pain control at lower overall doses. The use of multiple medications is justified if the dose requirements, and therefore side effects and toxicities, are reduced. Often, several trials must be attempted before determining the optimal combination for a particular resident.⁵⁷ Careful assessment of efficacy permits the practitioner to eliminate all analgesic medications that are not contributing to dynamic pain control.

An interdisciplinary care plan that includes physical therapy modalities such as cold compresses, heat, ultrasound, and kinesiotherapy is an indispensable part of effective pain management. Increasing flexibility of muscles can improve their range of motion, and strengthening can improve support and stabilization around the joint. Treatment with heat and cold compresses increases circulation and reduces inflammation. This strategy may result in less pain with functional movement. Physical and occupational therapists may be able to suggest specific modifications of existing equipment or provide assistive devices to provide support during functional activity, which reduces the pain of movement.⁶⁰ Although evidence regarding the benefits of massage therapy, chiropractic manipulation, or acupuncture is mixed, these techniques decrease overall medication requirements for many LTC residents.⁵⁹

Transcutaneous electrical nerve stimulation is a noninvasive method intended to reduce both intermittent and persistent pain. Although controversy exists as to its effectiveness, several systematic reviews have confirmed its effectiveness for chronic musculoskeletal pain.⁶¹ Practitioners who are unfamiliar or uncomfortable with the use of this device can obtain consultation with pain management specialists. These practitioners can also perform a variety of temporary or permanent nerve blocks and present novel options for pain control in an older adult with particularly challenging pain management issues. Specialized surgical intervention is an effective option in some circumstances.⁶² Spinal decompression, vertebroplasty, or surgical fixation of a severely damaged joint may provide a significant reduction in pain in select patients. In addition, a variety of braces and prosthetic devices may be customized for individual resident's needs by a trained prosthetist.⁶⁰

Box 1**Guidelines for choosing antidepressants when indicated and removing potentially inappropriate antidepressants in LTC***First-line Medications*

SSRIs

- Best overall risk-benefit profile and best evidence base for efficacy (typical side effects may be transient GI upset, headache, anxiety/insomnia, and more persistent sexual side effects)
- New concern for accelerating bone loss and increasing fall risk thus far has not changed their status as first-line medications (other antidepressants are not clearly absent of these risks)

Increased vigilance for patients after recommended screening for osteoporosis

Monitor vitamin D levels and discuss calcium/vitamin D supplements with primary care

Gait assessments such as simple timed get-up-and-go test⁵⁴

- Avoid SSRIs with long-term NSAID use or a history of significant GI bleeding
- For new-onset altered mental status or general lethargy, consider SSRI-induced hyponatremia caused by SIADH
- Among SSRIs, favored medications are recommended based on moderate half-lives and decreased potential for medication interactions through hepatic CYP450 (cytochrome P450, a hepatic enzyme system) inhibition:

- Citalopram (Celexa)

Few CYP450 inhibition/medication interactions; itself metabolized primarily by CYP450 2C19 and 3A4

A racemic mixture of *s*-citalopram and *r*-citalopram, with possibly more antihistamine (sedating) effects than pure *s*-citalopram; available as inexpensive generic (eg, \$4/mo at major retailers)

In older adults, typical starting dose is 10 mg/d titrated over weeks to a target dose of 20 to 40 mg/d, with a maximum dose being 60 mg/d

- Escitalopram (Lexapro)

Virtually no CYP450 inhibition/medication interactions; itself metabolized primarily by CYP450 2C19

Expensive (>\$100/mo), no generic available

In older adults, typical starting dose is 5 to 10 mg/d titrated over weeks to a target dose of 10 to 20 mg/d

- Sertraline (Zoloft)

Minimal CYP450 inhibition/medication interactions (modest inhibition at 2B6, 2C19, and 2D6); itself metabolized primarily by CYP450 2B6 and 2C19

Available as inexpensive (<\$10/mo) generic

In older adults, typical starting dose is 25 mg/d titrated over weeks to a target dose of 50 to 150 mg/d, with a maximum dose being 200 mg/d

Potential First-line or Second-line Medications

SSRIs

- Fluoxetine (Prozac)

On the Beers 2002 list primarily because of its long half-life (and that of its metabolite norfluoxetine), which can be problematic if discontinuation because of side effects is necessary, as well as its inhibition of CYP450 1A2, 2B6, 2C19, 2D6, and 3A4

Dose of 20 to 40 mg/d, with a maximum dose being 60 mg/d; available as inexpensive generic (eg, \$4/mo at major retailers)

- Paroxetine (Paxil)

The most anticholinergic SSRI, which cumulatively with other medications may cause many negative effects; among shortest half-lives of the SSRIs, which increase risk for discontinuation symptoms; also strong inhibitor of CYP450 2B6 and 2D6

If used, typical starting dose is 10 mg/d titrated over weeks to a target dose of 20 to 40 mg/d, with a maximum dose being 60 mg/d; available as inexpensive generic (eg, \$10–15/mo)

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- As a class, probably have some of the same risks as SSRIs re: osteoporosis, GI bleeding, fall risk, SIADH
- Also the noradrenergic reuptake inhibition seems to carry some potential for increasing heart rate and blood pressure
- The dual SNRI action seems to confer some analgesic effects (especially in neuropathic pain disorders) as a result of altered serotonin/norepinephrine transmission in the spinal cord

- Venlafaxine (Effexor XR)

Serotonin reuptake inhibition primarily at initial doses; norepinephrine reuptake inhibition begins generally at doses 150 mg/d or greater

Minimal CYP450 inhibition/drug interactions and itself metabolized primarily by CYP450 2D6; mostly renal excretion; shorter half-life increases risk for discontinuation symptoms

If used, typical starting dose is 37.5 mg/d titrated over weeks to a target dose of 75 to 225 mg/d, with a maximum dose being 300 mg/d

- Desvenlafaxine (Pristiq)

Active hepatic metabolite of venlafaxine with more balanced serotonin and norepinephrine reuptake inhibition at starting dose

New medication with minimal experience in older adults

Starting dose (50 mg/d) is also maximum dose shown to have benefit

- Duloxetine (Cymbalta)

More balanced serotonin and norepinephrine reuptake inhibition at starting doses

Moderate CYP450 2D6 inhibition; possible increased risk for hepatotoxicity, so best avoided in persons with compromised liver function (eg, heavy alcohol users)

FDA-approved for treatment of fibromyalgia and diabetic neuropathy pain

If used, typical starting dose is 30 mg/d titrated over weeks to a target dose of 60 mg/d, with a maximum dose being 120 mg/d

Other Atypical Antidepressants

- Mirtazapine (Remeron)

Complex mechanism of action: α_2 -adrenergic receptor antagonist (which disinhibits norepinephrine release at presynaptic receptors and disinhibits serotonin release at postsynaptic receptors); 5-HT_{2A}/5-HT_C serotonin receptor blockade seems to facilitate dopamine and norepinephrine release in the prefrontal cortex; 5-HT₃ blockade prevents nausea/GI upset as a side effect; increased serotonin levels are targeted toward 5-HT_{1A} receptors, believed to be the key receptors for anxiolytic/antidepressant effects

Side effects include sedation (caused by antihistamine effects and 5-HT_A receptor blockade) and weight gain (caused by antihistamine effects and 5-HT_C receptor

Box 1
(continued)

blockade); may be useful for older adults with anorexia and insomnia as part of major depression; sedation may increase fall risk; decreased sexual side effects versus SSRIs

Minimal CYP450 inhibition; itself metabolized by CYP450 1A2, 2D6, and 3A4

If used, typical starting dose is 7.5 to 15 mg at bedtime titrated over weeks to a target dose of 15 to 45 mg at bedtime; available as generic (eg, \$15–20/mo)

- Bupropion (Wellbutrin)

Described as an inhibitor of norepinephrine and dopamine reuptake, although these effects are weak, leaving its mechanism of action controversial

Often used for fatigue, amotivation, apathy (alone or as an augmentation to other antidepressants); dosed in the morning because activating and later dosing can cause insomnia; not approved to treat any anxiety disorder; may worsen anxiety in some persons; tends to be weight neutral or even decrease appetite; seems devoid of sexual side effects; slight increased risk of seizures compared with other antidepressants

Significant inhibition of CYP450 2D6; itself metabolized primarily by 2B6 and 2D6

If used, typical starting dose is 100 mg/d in the morning titrated over weeks to a target dose of 150 to 300 mg/d; maximum dose 450 mg/d (available in immediate release, sustained release, and extended release formulations)

Less Preferred, Possibly Appropriate at Times

Secondary Tricyclic Antidepressants (TCAs)

- TCAs were a class that preceded SSRIs and have largely been supplanted in modern psychiatry by newer antidepressants because newer medications have shown equivalent efficacy, a lower side effect burden, and lower toxicity in overdose
- They generally work by dual reuptake inhibition of serotonin and norepinephrine, although each agent has different degrees of relative serotonin versus norepinephrine effects; secondary TCAs tend to have more norepinephrine than serotonin reuptake inhibition; this dual reuptake effect makes them effective in certain pain disorders, similar to newer SNRIs
- TCAs are on most PIPE lists because of effects on nontherapeutic receptors (eg, anticholinergic effects such as cognitive impairment and constipation; α_1 -adrenergic receptor blockade, causing orthostasis and fall risk; and sodium channel blockade in the cardiac conduction system, increasing risk for arrhythmias and sudden cardiac death); tend to prolong QT_c intervals

- Nortriptyline (Pamelor)

For TCAs, has low potential for causing orthostasis (and falls) and anticholinergic effects in older adults

Primarily metabolized by CYP450 2D6; is a metabolite of the tertiary TCA amitriptyline

If used, typical starting dose is 10 to 25 mg at bedtime titrated over weeks to a target dose of 50 to 150 mg/d; dosing guided by target blood levels of 50 to 150 ng/mL

- Desipramine (Norpramin)

For TCAs, has low potential for causing orthostasis (and falls) and anticholinergic effects in older adults

Primarily metabolized by CYP450 2D6; is a metabolite of the tertiary TCA imipramine

If used, typical starting dose is 10 to 25 mg daily (often norepinephrine effects can be activating, requiring morning dosing) titrated over weeks to a target dose of 100 to 200 mg/d; dosing guided by target blood levels of 150 to 300 ng/mL

Almost Always Inappropriate

Tertiary TCAs

- These medications are common on PIPE lists in particular (eg, amitriptyline [Elavil], doxepin [Sinequan]) because of the reasons discussed earlier. Tertiary TCAs tend to have more balanced serotonin-to-norepinephrine reuptake inhibition, but they also tend to have more potent blockade at the nontherapeutic receptor sites mentioned earlier that produce unwanted side effects

Monoamine Oxidase Inhibitors (MAOIs)

- The first antidepressant drugs discovered, MAOIs work by inhibiting the breakdown of all 3 monoamines dopamine, serotonin, and norepinephrine. Although they may prove effective in persons with treatment refractory major depression, especially atypical depression, they have several major limitations. They must be taken with a strict tyramine-free diet to avoid a potentially lethal hypertensive reaction. When taken as directed, the opposite problem is often limiting in older adults: orthostatic hypotension. They also have multiple potential drug interactions that require close vigilance by the patient to avoid reactions such as serotonin syndrome
- Older examples include phenelzine (Nardil) and tranylcypromine (Parnate). A newer patch for selegiline (Emsam), more selective for MAO type B (more responsible for dopamine metabolism), has been approved for major depression, but the only advantage seems to be lack of need for dietary restriction at the starting and lowest dose (only 6 mg/d). Doses of 9 mg and 12 mg/d also exist and carry the same restrictions as older MAOIs. The role of Emsam in geriatric depression is poorly established

Cognitive-behavioral therapy performed by a psychologist or informally by a provider or staff can also benefit the resident by providing a feeling of greater control over their pain, and provide nonpharmaceutical alternatives to increase increasing quality of life. Relaxation techniques, reminiscing, diversions, activities, music therapy, and coping techniques can be effective alternative means to achieve pain relief.⁶²

Despite the frequent use of analgesic medication, there is considerable evidence that physicians fail to adequately control chronic pain in geriatric patients. Studies of Minimum Data Set information have found that 25% to 49% of nursing home residents have persistent pain, and that persons suffering daily pain were more likely to have severe impairment of activities of daily living, depressive symptoms, and less frequent involvement in activities. One-quarter received no analgesics, and the most commonly prescribed analgesic was acetaminophen, which was given as needed. Male residents, racial minorities, and cognitively impaired individuals were at increased risk.⁶³

Topical Analgesics and Local Injections

Some causes of chronic pain may be treated effectively with topical agents, intra-articular injections of steroid or hyaluronic acid, and trigger-point intramuscular steroid injections. This strategy may potentially lower the systemic analgesic dose required to achieve adequate pain control. Capsaicin, topical lidocaine 5% patches, and topical NSAIDs may provide relief for patients with musculoskeletal and neuropathic pain.⁵⁹

Acetaminophen

The low toxicity and risk of drug interactions of acetaminophen make this agent an excellent choice for mild to moderate pain; however, the short half-life provides less than optimal dosing if analgesia is required for persistent pain. The potential

for hepatotoxicity at doses greater than 4 g/d can limit the optimal use of combination drugs containing acetaminophen. For these reasons, acetaminophen and acetaminophen-containing compounds are most effective for acute intermittent pain control.⁶²

NSAIDs

The risk of GI bleeding, renal dysfunction, and cardiovascular complications requires careful consideration before initiating therapy with NSAIDs. These agents have a variety of half-lives, and once-daily or twice-daily dosing represents a major advantage. The AGS Panel recommends that nonselective and cyclooxygenase 2 selective inhibitor NSAIDs be considered rarely, and used with extreme caution in highly selected individuals.⁵⁷ Long-term use of full-dosage, longer half-life NSAIDs is considered potentially inappropriate in older adults according to the Beers criteria.⁵ Generally, representatives of this drug class are best used sporadically for acute intermittent pain at doses on the low end of the dosage recommendations.⁵⁹

Opiate Analgesics

Opiates are essential to providing safe, effective pain control in the LTC setting. Despite the wide variety of individual agents and delivery systems available, many practitioners limit their prescribing options, and thus miss an opportunity to discover an optimal combination for a particular resident.⁶³ Low potency agents such as codeine or tramadol are often combined with acetaminophen and therefore provide a reasonable progression, particularly in moderate intermittent pain. Drug interactions and the presence of baseline cognitive impairment may increase the bolus effect that occurs with the initial doses of analgesics with activity at opioid receptors. The presence of pain may also increase the likelihood of delirium. Impairment often subsides as tolerance develops after the initial few doses. Side effects such as constipation require prophylactic use of laxatives and stool softeners.⁵⁷

Hydrocodone, hydromorphone, and oxycodone are commonly considered for severe pain. These opiates require frequent dosing and are not optimal for persistent pain management. Long-acting morphine sulfate (MS Contin) is dosed twice daily and therefore has the pharmacokinetic advantage of more stable blood levels. This treatment often provides greater efficacy and permits the development of tolerance to sedative and cognitive side effects of opiates. Transdermal delivery systems enable the opiate fentanyl to be applied as a single patch every 2 to 3 days. This strategy eliminates the need for residents, practitioners, and staff to focus on the clock in anticipation of the return of pain symptoms. With appropriate titration of dose in opiate-tolerant patients, it is not uncommon for adequate pain control to be achieved with a single agent.⁶² Once stable pain control is achieved, the need for frequent dosing should be limited, although an order for a short-acting opiate is usually appropriate in the event of breakthrough pain. Education of residents, families, and staff often determines the success of this care plan.⁵⁹

Fear of abuse or diversion is a major barrier to long-term opiate treatment in chronic nonmalignant pain. Residents, family members, and staff may confuse physical dependence, a natural consequence of appropriate chronic opiate analgesia at appropriate and effective doses, with abuse. It is common for prescribing practitioners to misinterpret drug seeking by patients with poorly managed chronic pain as a symptom of abuse.⁶⁴ Several studies have shown minimal risk of abuse or drug-seeking behavior in patients treated with long-term opiate therapy who do not have a previous history of substance abuse. Although individuals with a history of alcohol-use disorders are at increased risk to abuse opiates, even in this small group of LTC residents,

opiates are essential for providing safe, effective pain control.⁶⁵ The prescription of schedule II agents is subject to specific state law and administrative regulations. The medical director of each facility can assist with the establishment of a clear protocol to review and continue the prescription of these agents based on clinical assessment.⁵⁸ The Federation of State Medical Boards provides guidelines for the prescription of opiate analgesics in the treatment of persistent nonmalignant pain.⁶⁶

Antidepressants and Anticonvulsants

The presence of chronic pain is almost universally accompanied by symptoms of depression, and all residents with persistent pain syndromes should be routinely screened for depression. Once identified, the depression should be adequately treated with standard therapies. Successful treatment of depression permits an accurate assessment of resident pain and can reduce the need for analgesic medications.⁵⁹ TCAs have been found to reduce pain associated with postherpetic neuralgia and diabetic neuropathy; however, their adverse effect profile often prohibits the use of these medications in older residents. SSRIs are not so effective in the treatment of pain as mixed serotonin and norepinephrine reuptake inhibitors such as duloxetine and venlafaxine. Anticonvulsants such as gabapentin and pregabalin have been shown to reduce neuropathic pain from a variety of conditions and have low side effect profiles.⁵⁷ These pain-modulating medications are long-acting, and careful titration to maximal tolerated dosages with frequent monitoring is essential before determining the need for additional medications.

Other Common Adjuvant Medications

The use of systemic steroids for acute musculoskeletal pain with an inflammatory component is well established. A short course (≤ 2 weeks) averts significant adrenal suppression; symptoms often return after cessation of treatment. Optimal use of physical therapy modalities may decrease the likelihood that additional medication is necessary. Longer courses of steroid should be reserved for chronic inflammatory disorders such as rheumatoid arthritis or malignant bone pain. Osteoarthritis should not be treated with chronic systemic steroid therapy.⁵⁷ Serious side effects caused by long-term use (eg, insulin resistance, osteoporosis, central obesity, neuropsychiatric effects) makes it essential to use the lowest possible steroid dose and consider the use of additional agents and modalities to provide effective pain management.

Persistent pain associated with osteoporosis and vertebral compression fractures has been shown anecdotally to improve with calcitonin. Because this agent also has efficacy in increasing bone mass, it may be an attractive option for some LTC residents.⁵⁹ Bisphosphonates may reduce persistent pain for patients with bone metastases and reduce the need for other analgesics. Cyclobenzaprine, carisoprodol, and other skeletal muscle relaxants are considered to be potentially inappropriate in older adults because their efficacy is insufficient to outweigh their adverse effect profile (sedation, addictive qualities, anticholinergic effects).⁵ Although these agents may relieve skeletal muscle pain, their effects are largely unrelated to muscle relaxation. Baclofen has documented skeletal muscle relaxant efficacy in patients with severe spasticity caused by CNS or neuromuscular disorders and is useful in reducing the need for other analgesic medications.⁵⁷ Benzodiazepines should not be used for pain management in older individuals unless there is a significant general anxiety component, and even then with caution and usually not indefinitely.

Factors that can be modified in pursuit of optimal pain control in LTC settings include: (1) knowledge about pain and management through direct education of patient, family,

staff, and administration, (2) algorithm development and implementation of pain management pathways, (3) treatment modifications that involve the full spectrum of pharmacologic and nonpharmacologic tools, and (4) system modifications to measure and provide feedback for continuous improvement.⁶⁷

SUMMARY

The reduction of psychotropic drugs in the LTC setting requires a process of systematic review and cultural change beyond that of federal regulation and warnings. Each member of the interdisciplinary team must consider behavioral modification and environmental change to be an essential part of the health care plan for each resident. Practitioners, nursing staff, family members, and residents must come to see medication as a complementary or secondary treatment of behavioral problems and pain. Anxiety, depression, and pain are frequent antecedents and/or consequences of chronic illness and functional decline. The LTC environment can be developed to include opportunities for positive interaction and alternative activities that may significantly decrease the necessity of medications affecting the CNS.

Some residents continue to require psychotropic medications to maximize their quality of life and/or to maintain a safe environment in the LTC community. Careful assessment of the clinical condition of each resident and their specific response to a chosen regimen of medication must be accompanied by a willingness to modify that regimen over time. A routine of periodic chart reviews for potentially unnecessary medications could greatly reduce the burden of iatrogenic illness. Although it is often difficult to predict clinical response, the consequences of excessive medication are significant; the LTC practitioner can take the lead to involve the entire interdisciplinary team in reducing these medications whenever possible.

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