REVIEW

CME CREDIT

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# A strategy to decrease the use of risky drugs in the elderly

## ABSTRACT

Many medications that are safe in most patients pose serious risks in older patients, including functional decline, delirium, falls, and poorer outcomes. We describe our institution's program of "academic detailing," designed to reduce the use of three high-risk drugs in elderly patients.

## KEY POINTS

Meperidine, diphenhydramine, and amitriptyline all pose a high risk of adverse reactions in older adults. Safer alternatives are available.

In our program, the pharmacy computer system generates a daily report of elderly patients who are prescribed any of these three agents. A pharmacist contacts the prescribing physician directly or leaves a preprinted note on the patient's chart, explaining the problems older patients often have with these medications and suggesting alternatives.

Although medications may contribute to delirium, dementia, constipation, or urinary retention, the contribution may be subtle or occur slowly, making it difficult to detect.

Meperidine has a long-acting, renally excreted metabolite that is toxic to the central nervous system; morphine is preferred.

Diphenhydramine and amitriptyline have powerful anticholinergic effects; alternatives depend on the indication.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

SOME MEDICATIONS that are safe in most patients are best avoided in elderly patients—and pharmacists can help physicians avoid them.

In this paper we discuss three medications, chosen on the basis of scientific evidence and our personal experience, that are associated with unacceptable risk in elderly patients and for which reasonable alternatives exist: meperidine, diphenhydramine, and amitriptyline.

We also describe our institution's program of "academic detailing" to reduce their use. Whenever a physician prescribes one of these high-risk drugs to an elderly patient at our institution, a computer alerts the pharmacist, who contacts the prescribing physician to explain the problems patients often have with these agents and to suggest alternatives. Under this program, use of these three drugs has fallen by one third to one half.

## SCOPE OF THE PROBLEM

Adverse drug reactions are a huge problem, especially in the elderly. Each year, at least 100,000 people are estimated to die of medication-related problems.[1] Adverse drug reactions are some of the most common complications in hospitalized elders and often lead to poorer outcomes.[2,3] An estimated $4 billion is spent on medication-related problems in acute care facilities each year.[4] Medications have been documented to be a significant factor in both delirium and falls.[5–7]

This is an important quality-improvement issue, since half of all adverse drug effects in older patients have been reported to be avoidable.[3]

## MEPERIDINE: RISK OF TOXICITY, DELIRIUM

Meperidine poses well-defined risks in older patients.[8]

Meperidine is metabolized by two hepatic pathways, one of which causes *N*-demethylation and the formation of the only active metabolite, normeperidine. Normeperidine is excreted renally and has a longer half-life than meperidine (15–40 hours vs 3–6 hours, respectively)[9]; it accumulates in patients who receive repeated high doses and in patients with renal dysfunction. Since renal function declines with age, normeperidine often accumulates in older adult patients, placing them at risk of toxicity.[10]

Kaiko et al[11] correlated high normeperidine levels with central nervous system toxicity, including anxiety, tremors, twitches, myoclonus, and seizures.

Meperidine has also been reported to cause delirium.[12,13] In a retrospective analysis of 92 elderly patients with hip fractures, Adunsky et al[14] found that patients receiving meperidine had a significantly higher incidence of delirium than did those receiving morphine.

**Meperidine's active metabolite accumulates in patients who have renal failure**

### Theoretical advantage of meperidine in gall bladder or pancreas disease

Despite its risks, meperidine is often prescribed to hospitalized older patients, perhaps because of its proposed advantage over morphine in patients with cholecystitis and pancreatitis.

Compared with morphine, meperidine has less effect on the motility of the sphincter of Oddi. However, no studies have been done to see if there is any difference in clinical outcome or pain control due to this effect.[15] Without these data, it is difficult to justify meperidine's use in patients at high risk of normeperidine accumulation and toxicity.

### Instead of meperidine, use morphine

Many organizations no longer recommend the use of meperidine. The American Pain Society recommends it only for brief courses (< 48 hours) in patients without renal or central nervous system disease, at doses lower than 600 mg/24 hours.[10] Neither the American Geriatrics Society's Panel on Persistent Pain nor its Panel for Assessing Care of Vulnerable Elders recommends meperidine use in the elderly.[16,17]

Meperidine is generally reserved for severe pain for which a parenteral narcotic is needed. The alternative agent in this situation is morphine.

Morphine, like meperidine, has an active metabolite. Although this metabolite may also become elevated in patients with renal insufficiency, it has a much shorter half-life (2.4–6.7 hours); therefore, it is less likely to accumulate. This metabolite is not associated with excitatory effects on the central nervous system.[15]

## DIPHENHYDRAMINE: ANTICHOLINERGIC EFFECTS

Diphenhydramine poses a risk in older adults owing to its powerful anticholinergic effects.

With age, acetylcholine production decreases, leading to increased sensitivity of cholinergic receptors and eventual destruction of cholinergic neurons. In demented patients, the rate and extent of this process is accelerated.[18] This places older adults, and especially demented patients, at a greater risk of adverse reactions from anticholinergic agents.

The anticholinergic actions of medications can cause or worsen confusion, sedation, blurred vision, urinary retention, and constipation.[3] These drugs also oppose the action of the acetylcholinesterase inhibitors (ie, donepezil, galantamine, and rivastigmine) in patients being treated for dementia.

Many studies have documented the deleterious effects of medications with anticholinergic effects.

Han et al,[19] in a prospective observational study, found that the greater the anticholinergic "load" (defined as the sum of the anticholinergic activity of medications that a patient received), the greater the severity of delirium symptoms.

Gustafson et al,[20] in a prospective study of 111 patients treated for femoral neck fractures, found that the incidence of an acute confusional state was significantly greater in patients receiving drugs with anticholinergic

properties than in patients not receiving them.

Agostini et al,[21] in a prospective cohort study of 426 patients, found that diphenhydramine use in patients older than 70 years was associated with an increased risk of delirium.

Older patients face a significantly higher risk of illness and death if they develop delirium in the hospital. Moreover, delirium is often not recognized or treated appropriately and is often associated with a prolonged hospital stay, functional decline, and postdischarge institutionalization.

Other cognitive adverse reactions have been associated with anticholinergic agents. Lu and Tune[22] found that in 69 patients with Alzheimer disease receiving donepezil 10 mg/day, Mini-Mental State Exam scores at 2 years were significantly worse for those who received anticholinergic medications compared with those who did not receive these medications.

Weiler et al,[23] in a randomized placebo-controlled study of 40 young people, found that driving was significantly more impaired in patients who received diphenhydramine 50 mg compared with fexofenadine 60 mg or an alcoholic drink to achieve an approximate blood alcohol level of 0.1%.

### Many alternatives to diphenhydramine

Of the available antihistamines, diphenhydramine has the greatest anticholinergic effect.[24] Although patients, family members, nurses, and physicians perceive it as benign, diphenhydramine should not be used in older adults except in acute allergic reactions. Since safer alternatives are available, the risks of this medication clearly outweigh the benefits in older patients.

**For environmental allergies,** a second-generation antihistamine is preferred.[8] The second-generation agents cetirizine, loratadine, and fexofenadine all have fewer anticholinergic effects and less penetration into the central nervous system than first-generation agents.[24,25]

Studies comparing these agents in elderly patients are lacking, however. Simon et al[26] performed a small, randomized, double-blind study in elderly patients, comparing cetirizine and loratadine to chlorpheniramine and diphenhydramine. Although they concluded that cetirizine and loratadine were less likely to cause central nervous system effects than diphenhydramine and chlorpheniramine, variances in measurements did not allow parametric statistical tests in this study.

Studies in younger patients have demonstrated a lower incidence of central nervous system effects with the second-generation antihistamines, although cetirizine has been associated with a higher incidence of somnolence than the other second-generation agents.[27–29] Loratadine or fexofenadine are preferred for this reason.

**For insomnia,** sleep hygiene protocols are preferred to medications.[21,30] If sleep hygiene protocols fail or cannot be used, low doses of trazodone (25–50 mg) may be an option, although trazodone is not approved by the US Food and Drug Administration (FDA) for this indication. Trazodone has little anticholinergic activity, and low doses are widely used for depression-associated insomnia.[31–33]

## AMITRIPTYLINE: ALSO ANTICHOLINERGIC

Amitriptyline is another anticholinergic medication that should be avoided in older adults.[8] Amitriptyline has the most potent anticholinergic profile of all tricyclic antidepressants. Like diphenhydramine, it may also be prescribed for a variety of uses, including as a sedative, neuropathic pain reliever, and antidepressant. Again, because there are newer, lower-risk agents, alternatives should be used for these conditions.

**Of the antihistamines, diphenhydramine has the greatest anticholinergic effect**

### Alternatives to amitriptyline

**For insomnia,** sleep hygiene protocols or a low dose of trazodone are alternatives.[21,30–33]

**For neuropathic pain,** gabapentin is as effective as amitriptyline and has fewer adverse effects.[34,35] No studies of gabapentin for this indication have been done specifically in elderly patients. Even so, it is recommended as a preferred medication in elderly patients.[36]

Nortriptyline and desipramine are tricyclic antidepressants with fewer anticholin-

TABLE 1



ergic effects. Desipramine has been found to be as effective as amitriptyline against neuropathic pain.[37] Again, although geriatric-specific studies have not been done and these drugs are not approved by the FDA for this use, they are rational alternatives for the treatment of neuropathic pain in older adults.[36–38]

**For zoster nerve pain,** topical lidocaine or capsaicin are also effective alternatives without systemic adverse effects.[39]

**For depression** in older adults, there are many alternatives with fewer adverse effects. These include venlafaxine, mirtazapine, buproprion, and selective serotonin reuptake inhibitors such as sertraline, escitalopram, and citalopram.[40–42]

## OUR STRATEGY FOR REDUCING USE OF HIGH-RISK DRUGS

Our institution, a 1,000-bed health system with beds on three campuses, contains an Acute Care of Elders (ACE) unit that has been in place for 10 years. The ACE unit is an interdisciplinary model of care designed to prevent functional decline in hospitalized elderly patients by integrating the principles of geriatric assessment and continuous quality improvement. The ACE intervention consists of a prepared environment, interdisciplinary patient-centered care, comprehensive discharge planning, and medical care review.[43]

The ACE staff developed a list of high-risk medications (TABLE 1), using the best avail-

TABLE 1 continued



able scientific evidence. This list discusses the risks that these medications pose to older patients and offers alternatives.

### The 'Elder Monitor' program

A continuous quality improvement (CQI) team, composed of members of this hospital's ACE unit, developed what we informally call the "Elder Monitor" program. Approved by the Pharmacy and Therapeutics Committee, the program targets meperidine, amitriptyline, and diphenhydramine, with the intent of decreasing their use in our elderly hospitalized patients. We chose these three particular drugs because of our personal experience with frequent problems with them in our older patients in the ACE unit.

Every day, the pharmacy computer system generates a report of all patients age 65 or older who are prescribed one of these three agents. The pharmacist then contacts the prescribing physician directly or leaves a preprinted note (FIGURE 1) on the patient's chart, explaining the problems older patients often have with these medications and suggesting alternatives. Reference materials supporting the recommendations are available upon request. This method, known as "academic detailing," has been shown to be effective for changing or improving prescribing patterns.[44,45]

We implemented the program in March 2001. Baseline use of these medications was established by tabulating usage for the same

## Sample note from the pharmacist

Patient name:_____ Date_____

PHARMACY NOTES

Dear Doctor: Please consider whether the following suggestion(s) would be appropriate as part of your patient's medication regimen.

**Meperidine**

_____ has been on meperidine for more than 48 hours. His/her calculated creatinine clearance is _____ mL/minute. Meperidine is not recommended to be used in patients with reduced renal function. A toxic metabolite, normeperidine, can accumulate in patients with decreased renal function. Normeperidine causes central nervous system toxicity, including agitation and seizures. The American Pain Society recommends that meperidine not be used for more than 48 hours. The Pharmacy and Therapeutics Committee has recommended that the Pharmacy screen and intervene on all meperidine used in elderly patients for more than 48 hours. Can an alternative agent be used?

**Diphenhydramine**

_____ has an order for diphenhydramine. Diphenhydramine is no longer recommended for use in elderly patients (Beers MH. Arch Intern Med 1997; 157:1531–1536). The anticholinergic effects of diphenhydramine can cause or worsen confusion, unsteadiness, urinary retention, and constipation. The Pharmacy and Therapeutics Committee does not recommend its use in elderly patients except in the therapy of acute allergic reactions. Can an alternative agent be used? If using as a hypnotic, trazodone 25–50 mg or temazepam 7.5–15 mg is recommended as an alternative.

**Amitriptyline**

_____ has an order for amitriptyline. Amitriptyline is no longer recommended for use in elderly patients (Beers MH. Arch Intern Med 1997; 157:1531–1536). The anticholinergic effects of amitriptyline can cause or worsen confusion, unsteadiness, urinary retention, and constipation. The Pharmacy and Therapeutics Committee does not recommend its use in elderly patients. Can an alternative agent be used? If using as an antidepressant, consider a selective serotonin reuptake inhibitor, such as paroxetine, citalopram, or sertraline. If using for neuropathic pain, consider desipramine or nortriptyline. If using as a hypnotic, consider trazodone 25–50 mg or temazepam 7.5–15 mg.

Thank you— _____, RPh

PHYSICIAN RESPONSE

Please note: Physicians must write all necessary orders to implement changes in therapy.

Comment/response_____

**FIGURE 1**

**For insomnia, sleep-hygiene programs are preferable to drugs**

month in the 2 years before the program was implemented. Postintervention use was measured 1 year later.

Use of all three medications decreased in the year after the program was implemented—meperidine by 33%, diphenhydramine by 52%, and amitriptyline by 50% (although there was a trend toward a decrease in the use of amitriptyline in the year before the intervention (TABLE 2).

### Does medication reduction save money?

We believe that reducing the use of these three medications should decrease the incidence of delirium in hospitalized older patients, and therefore should decrease length of stay and costs.

Unfortunately, gathering these hard data is beyond the scope of the current project. To document any effect of the program on the incidence of delirium would require an

**TABLE 2**

**Reducing prescriptions for risky medications in elderly hospitalized patients**

| | BEFORE THE PROGRAM | | AFTER THE PROGRAM | |
|---|---|---|---|---|
| | FEBRUARY 2000 | FEBRUARY 2001 | FEBRUARY 2002 | % DECREASE 2001-2002 |
| **Monthly census** | 3,582 | 3,395 | 3,536 | |
| **Prescriptions** | | | | |
| Amitriptyline | 20 | 10 | 5 | 50% |
| Meperidine | 133 | 126 | 84 | 33% |
| Diphenhydramine | 170 | 177 | 84 | 52% |

extensive chart review, which would be difficult to justify since the medications that were chosen have already been proved to cause delirium. Moreover, our institution's medical records department implemented its own program in 2001 to increase the documentation of various diagnoses, including delirium. Therefore, any comparison of the incidence of delirium with the historical record may not be valid.

We did, however, estimate the impact that our program would have on hospital costs on the basis of reducing the use of diphenhydramine, using conservative data from other studies.

Delirium has been reported to occur in 14% to over 50% of hospitalized elderly patients[5]; we took the lower figure as the baseline incidence. Agostini et al[21] found that delirium symptoms increased with diphenhydramine use by a factor of 1.7 to 5.6, depending on the symptom. Using the lower figure, we calculated that the incidence of delirium in patients receiving diphenhydramine would be 14% × 1.7, or approximately 24%.

At our hospital, the average additional length of stay due to delirium is 3 days, and the cost of a patient remaining in the hospital for an additional test-free day is $300. Using the data for February 2001 and February 2002 (TABLE 2), an estimated 66 fewer patient days would occur in February 2002 compared with February 2001 due to a decreased usage of diphenhydramine. Using these figures, this would translate into a cost savings of $105,589 per year.

## OVERCOMING BARRIERS

Barriers still exist when trying to switch elderly patients' medications to lower-risk alternatives. A common reason for not changing medications is that the patient is currently tolerating the agent.

However, physicians should still exercise caution when prescribing high-risk medications, for two reasons. First, the contribution of high-risk medications to other disease states (delirium, dementia, constipation, urinary retention) may occur slowly and subtly, therefore making it difficult to relate the medication's contribution to the patient's current problem. Second, if these medications are used chronically, as the patient ages, adverse effects will become less tolerable.

We found that the use of three high-risk medications in older adult patients was substantially reduced in our hospital by using a structured protocol developed by members of an interdisciplinary geriatric team. This protocol encourages pharmacists to directly communicate with physicians and provide academic detailing concerning specific alternatives for these medications.

**Under our program, use of three risky drugs in elderly patients fell by one third to one half**

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