Pharmacologic Considerations in an Elderly Population

Wendy Ng, Meds 2009

Usually, elderly patients have more ongoing health concerns than younger patients. To date, there have been few reviews that examine the benefits and challenges to prescribing common medicines for a geriatric population. Overall, NSAIDs, anticholinergics, neuroleptics and benzodiazepines have serious side effects that are more often manifested in the elderly. Based upon the increased danger of pharmacologic adverse events in the older population, careful consideration of the benefits and risks of these medications is essential. It remains useful for clinicians to consider safer alternatives when writing prescriptions.

This article has been reviewed by Dr. John Greenaway.

In general, elderly patients have both chronic and multiple diseases. Consequently, polypharmacy is a major factor in the prevalence of adverse drug reactions, which increase in incidence with patient age. In addition, elderly patients have poorer homeostatic responses to physiologic challenges. A variable rate of declining organ and tissue function among different elderly individuals further complicates attempts at predicting patient responses to pharmacologic therapy. Finally, with poorer compliance to drug regimens, due to the complexities of timing doses of many drugs with different dosing schedules, sorting out pharmacology for elderly patients can be a challenge.

In both males and females, the proportion of total body weight as fat increases with age. Fat is localized to the middle and upper body regions as we age. In women, there is an additional postmenopausal acceleration of the fat distribution trend. Body fat tends to accumulate within organs. After a plateau in rising fat proportions at approximately the sixth decade of life, a reduction in the amount of body fat follows in even older ages.\(^1\)

Body water as a percentage of total body weight declines with increasing age. Furthermore, organ function tends to decrease with increasing age. Kidney glomerular filtration decreases, as measured by creatinine clearance. At the same time, serum creatinine concentration may not appear elevated, despite renal impairment, due to the decrease in serum creatinine concentration from lower levels of muscle mass as we age. In addition, liver size as a proportion of body weight decreases, leading to decreased total hepatic blood flow and poorer elimination of many drugs from the body, particularly lipophilic drugs that have a high hepatic extraction ratio. Cardiac output decreases, which may be due to a combination of sedentary lifestyle, progressive tissue degeneration with age, or disease. Blood perfusion of sites of body drug elimination can be inadequate in cardiac failure. With a decreased baroreceptor reflex, as well, older patients are at greater risk of orthostatic hypotension.\(^1\)

Based on these complex interactions and a multitude of factors, pharmacology for elderly patients requires extra consideration. The benefits and side effects of NSAIDs (non-steroidal anti-inflammatory drugs), anticholinergic drugs, neuroleptics and benzodiazepines merit discussion, as their uses have important implications in this population of older patients.

NSAIDs (Non-steroidal anti-inflammatory drugs)

NSAIDs (non-steroidal anti-inflammatory drugs) act by inhibiting the cyclooxygenase required for conversion of arachidonic acid to endoperoxide intermediates (PGG2 and PGH2). This leads to antipyretic, analgesic and platelet-inhibitory effects. There are also effects on rheumatic, inflammatory and immunological processes, as well as on acute gout. This cyclooxygenase inhibition is either readily or slowly reversible, unlike that of acetylsalicylic acid.\(^2\)

Side effects of NSAID use include agranulocytosis, which is not seen with salicylate use. As with salicylate use, NSAIDs cause gastric mucosal damage because they are weak organic acids, and inhibit prostaglandin synthesis and accumulate intracellularly due to the acidity of the gastric lumen. This is related to nonselective inhibition of both COX-1 and COX-2 isoenzymes involved in prostaglandin synthesis, where COX-1 generates prostanoids required for the maintenance of gastrointestinal mucosa and platelet aggregation, whereas COX-2 is required for
generating prostaglandins that modify inflammation and pain. Gastric bleeds, anemia, epigastric pain, hematemeses, dyspepsia, ulcerative esophagitis and ulceration and perforation of the gastrointestinal system have all been reported with NSAID use. Peptic ulcer disease is more significant in the elderly due to the higher prevalence of *Helicobacter pylori* and their more common use of NSAIDs, compared to their younger counterparts’ use of NSAIDs.4

In addition, the synthesis of thromboxane A2 which is derived from cyclic endoperoxides PGG2 and PGH2 from arachidonic acid by cyclooxygenase is reversibly inhibited, such that platelets may fail to aggregate. Prostacyclin (PGI2), which opposes platelet aggregation, may be inhibited by NSAIDs due to the concentration of cyclooxygenase accumulating in endothelial cells. Interactions with warfarin can cause serious bleeding.2

In renal function, prostaglandins are important for increasing glomerular filtration rate, decreasing renal vascular resistance, increasing natriuresis and reducing water reabsorption in the loop of Henle. Prostaglandins may also prevent antidiuretic hormone action on tubular epithelium through negative feedback, to increase water elimination. However, NSAIDs inhibit prostaglandin synthesis, thus allowing excessive water retention and edema formation. The side effects of edema, fluid and electrolyte disturbances, sodium and chloride retention, and plasma dilution can be dangerous.2

Other side effects of NSAIDs related to cyclooxygenase inhibition include acute rhinitis, urticaria, bronchoconstriction and hypotension in patients suffering from asthma, chronic obstructive pulmonary disease or other lung ailments. Finally, adverse effects that are likely unrelated to cyclooxygenase inhibition can affect all body systems, ranging from headache, dizziness and rash to myalgia, tinnitus and flatulence.2

The long-term prescription of NSAIDs (non-steroidal anti-inflammatory drugs) to treat osteoarthritis for patients with a history of peptic ulcer may cause recurrence of peptic ulcer, due to gastric irritation.3 Non-drug therapy, or acetaminophen, or NSAID with gastroprotective agent is recommended instead. In patients with chronic renal failure, NSAIDs may worsen renal failure, causing salt and water retention. Again, non-drug therapy, followed by acetaminophen as necessary, is recommended as an alternative. In patients already receiving warfarin, NSAIDs may cause increased bleeding. In patients with a history of hypertension, NSAIDs may cause salt and water retention and exacerbation of hypertension. Thus, acetaminophen is preferable.4

**Anticholinergic Drugs**

Anticholinergics (muscarnic blockers) can be used to correct the dopamine/acetylcholine imbalance in Parkinson’s disease, by lowering the acetylcholine activity level. Atropine-like drugs such as benztropine and trihexyphenidyl can be used. However, unpleasant side effects of blurred vision, dry mouth, constipation, urinary retention and ataxia may occur. This is because salivary secretion is impaired, so swallowing also may become difficult. Gastric secretion is diminished, bronchial secretions are suppressed, and sweating is impaired. As such, anticholinergics have not been used as first line agents for Parkinson’s disease since the introduction of L-dopa.5

Alzheimer’s disease is the fourth largest cause of death in people over the age of 65, and is the most common form of dementia.6 Cholinesterase inhibitors are commonly used in the treatment of Alzheimer’s disease related dementia. Donepezil, galantamine or rivastigmine are often prescribed.7 While cholinesterase inhibitors have not been conclusively shown to reverse or slow down mild cognitive impairment, there are numerous randomized clinical trials that show that cholinesterase inhibitors slow the progression of Alzheimer’s dementia. This has been suggested to be due to the role of muscarinic receptors in neurotrophic regeneration, and acetylcholinesterase inhibitors’ role in restoration of nicotine receptor activity. It has also been shown that cholinesterase inhibitors can inhibit beta-amyloid plaque formation by impacting secretion of the amyloid precursor protein (APP).8 These drugs do not stop the process of neurodegeneration. Newer strategies of combating Alzheimer’s disease includes memantine, a NMDA-receptor antagonist that has been reported to be effective therapeutically in Alzheimer’s disease, and may be a better alternative.6

In contrast, due to its possible opposition of beneficial effects of cholinesterase inhibitors, anticholinergic medications are notorious for worsening cognitive function in susceptible patients. Patients with dementia and urge incontinence who might benefit from both an anticholinergic medication and a cholinesterase inhibitor present a challenge to the clinician, as it seems that the two drugs theoretically work against one another. While the drug combination is possible, it can be an imperfect means of treatment, but no randomized control trials for such cases have yet been reported.9

The prescription of anticholinergic drugs to treat irritable bowel syndrome for patients with dementia may worsen cognitive and behavioural function. Instead, nondrug and diet therapy, and a calcium channel blocker to treat diarrhea, are recommended. The prescription of anticholinergic drugs to prevent extrapyramidal effects of
antipsychotic drugs may cause agitation, delirium, and impaired cognition. Instead, decreased dosages of antipsychotic drugs or the reassessment of need for these drugs is recommended.4

**Neuroleptic Drugs (Antipsychotic Drugs)**

Neuroleptics are types of antipsychotic medications. Antipsychotics can be used to treat psychosis that may be encountered in patients with severe dementia, depression or severe metabolic disturbances from liver failure or kidney failure. When given to patients, these drugs produce decreases in bizarre behaviour, delusions, and hallucinations. They also decrease anxiety, and promote sleepiness or sedation. In the early 1950’s, Laborit, a surgeon in Paris, noted that various antihistamine drugs such as promethazine had a calming effect on postoperative patients. In 1950, Charpentier synthesized chlorpromazine, a related compound, which reduced both the need for surgical anaesthetic and patients’ anxiety. As such, psychiatrists began to use the drug for treating psychosis.10

Most antipsychotics act selectively on dopamine receptors, blocking dopamine receptors due to their similar structures to the dopamine molecule, such as chlorpromazine (a phenothiazine) and haloperidol (a butyrophenone). Antipsychotic action seems to be more closely linked to D2 than to D1 antagonism. Antipsychotics can also block the actions of L-dopa, apomorphine, and bromocriptine, which are all dopamine agonists. In addition, the chemoreceptor trigger zone outside of the blood-brain barrier in the reticular formation of the medulla oblongata, which stimulates nausea and vomiting, is rich in D2 receptors. Thus, antipsychotics also have an effect of reducing nausea. As such, antipsychotics can reduce nausea produced by other drugs, pregnancy, radiation sickness, and cancer.10

Most side effects of antipsychotics arise from their cholinergic, adrenergic and histaminergic receptor actions, because their antipsychotic effects originate from their antidopaminergic actions. Peripheral side effects include hypotension, constipation and tachycardia.10 Other side effects include antipsychotic-induced parkinsonism from effects on the nigrostriatal pathways, dyskinesias and dystonias, and akathisia, and later tardive dyskinesia over months or years. In a study of 56 older psychiatric patients, even after controlling for spontaneous extrapyramidal signs at baseline and for natural fluctuations, there was a substantial risk of neuroleptic-induced parkinsonism in patients treated with very low doses of neuroleptics.11 In another group of over 3500 patients aged 65 to 99 enrolled in a Medicaid program in Massachusetts, patients were found to be 5.4 times more likely to require antiparkinsonian medication if they were taking neuroleptics, as compared to non-users. Neuroleptic use is well-known and common cause of extrapyramidal dysfunction in the elderly.12

Neuroleptic malignant syndrome is a rare but severe side effect, which includes extreme rigidity, fever, marked autonomic disturbances and muscle destruction. Unwanted sedation can be due to a complex interaction of antihistaminergic, antiadrenergic and anticholinergic actions. Orthostatic hypotension occurs because antipsychotics depress blood pressure by dilating the arterioles through directly acting on alpha-adrenoceptors responsible for vasoconstriction. There may also be a direct effect on the vasomotor centre, contributing further to hypotension. Anticholinergic effects can lead to mydriasis and weakened ciliary muscles, causing mydriasis. Decreased tear secretion can lead to dry eyes, and mydriasis may decrease aqueous humor outflow and precipitate glaucoma in certain patients. Dry mouth, constipation, and urinary hesitancy may also result from anticholinergic effects. Pseudopregnancy, due to dopamine’s actions on the pituitary to inhibit mammotroph cell prolactin release, and blockade of follicle stimulating hormone and luteinizing hormone may lead to anovulation, lack of menstruation and hyperprolactinemia, swollen breasts and galactorrhea. In patients predisposed to seizures, antipsychotics can produce seizures, most prominently with low-potency agents. More rarely, phenothiazine-induced jaundice and dermatitis and photosensitivity may occur with antipsychotics.10

The prescription of chlorpromazine to treat psychosis for patients with a history of postural hypotension may worsen postural hypotension and cause falls. Alternatively, high-potency neuroleptic such as haloperidol with blood pressure monitoring is recommended.4

**Benzodiazepines**

Chlordiazepoxide was the first benzodiazepine marketed in 1960, followed by diazepam in 1963 and oxazepam in 1965. All benzodiazepines are variations upon the 5-aryl-1,4-benzodiazepine nucleus. Diazepam and many other benzodiazepines are metabolized to the active metabolite N-desmethyldiazepam, also known as nordiazepam. In 1977, specific receptors for benzodiazepines were discovered in the nervous system. Type I receptors are abundant in the cerebellum, cerebral cortical layer IV, and the substantia nigra. In contrast, Type II receptors are located in the hippocampus, superior colliculus and cerebral cortical layers I-III. It is believed that both
anxiolytic and sedative effects are mediated through the Type I receptors, whereas anticonvulsant and muscle relaxation effects are mediated through the Type II receptors. The benzodiazepine receptors may also be linked cooperatively with GABA receptors, since GABA and GABA agonists have been shown to enhance benzodiazepine receptor binding abilities.\(^{13}\)

Benzodiazepines have an antianxiety action. Most benzodiazepines have been approved for use in acute anxiety disorders. Since efficacy decreases a bit after a few weeks, the drugs are less useful in the treatment of chronic anxiety. Benzodiazepines also have anticonvulsant activity, but tolerance to the anticonvulsant effect can develop with long-term use. Most benzodiazepines are useful in alcohol withdrawal syndrome treatment. Benzodiazepines are also useful for their muscle relaxant effects, such as in treating neuromuscular disorders like cerebral palsy and tetanus. Furthermore, benzodiazepines are useful for achieving amnesia with sedation. Finally, benzodiazepines can treat the symptom of insomnia. Since elderly patients are more sensitive to the effects of such drugs, initial doses in patients over age 60 should be 50% of the listed dose requirements for insomnia. The most common side effect is a feeling of sedation or mental “fuzziness” in the morning. Patients must also be reminded that no hypnotic drugs should be taken with alcohol, which can be a fatal combination.\(^{13}\)

Common side effects of drowsiness, ataxia, lethargy and rarely coma occur in less than 10% of hospitalized patients that receive oral benzodiazepines.\(^{13}\) Delirium, oversedation, and hypotension are other major side effects. Lorazepam has been found to be associated with the more serious side effects of ataxia and delirium, which could result in potentially debilitating accidents, including falls and fractures.\(^{14}\) Other side effects include: interference with memory and recall, and anterograde amnesia. With intravenous administration of benzodiazepines, important but uncommon side effects include: respiratory or cardiac arrest, hypotension, and phlebitis at the injection site.\(^{13}\)

The long-term prescription of long half-life benzodiazepines to treat insomnia or anxiety may cause falls, fractures, confusion, dependence and withdrawal. Alternatives include non-drug therapy or the usage of short half-life benzodiazepines. Similarly, the long-term prescription of a long half-life benzodiazepine to treat agitation in dementia may be replaced by loxapine or haloperidol, or a short half-life benzodiazepine.\(^{4}\)

**Summary**

Overall, NSAIDs, anticholinergics, neuroleptics and benzodiazepines have both important and serious side effects that are more pronounced in the elderly. Based on the susceptibility of older patients to adverse events from pharmacologic effects, careful consideration of the advantages and disadvantages of these medications remains valuable. Before prescribing these medications, it is useful for clinicians to first consider safer alternatives for their elderly patients.

**References**