ABSTRACT
Aging affects the pharmacokinetics and pharmacodynamics of drugs, which has potentially important implications for the use of psychotropic medication in older adults. The absorption of orally administered drugs may be impaired or delayed, the volume of distribution of most drugs is decreased, and over time, the distribution shifts toward greater drug accumulation in fat stores. Decrease in renal function with age is especially important regarding the use of lithium but is also relevant for most drugs because they are eventually cleared through the kidneys after metabolism in the liver. Because pharmacodynamic changes associated with aging will make elderly patients more sensitive to the pharmacological effects of medication—especially adverse effects—nurses should be appropriately trained in pharmacology and therapeutics in older adults.
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Regulatory bodies usually consider older adults to be those older than age 65 (Hilmer, McLachlan, & Le Couteur, 2007). More than 90% of older adults take at least one medication, and the majority of them take two or more drugs (Qato et al., 2008). In the community, approximately 20% of older adults take psychotropic medication (Aparasu, Mort, & Brandt, 2003). The prevalence of psychotropic drug use is even higher in older adults who are hospitalized or who live in long-term care facilities. As people age, their bodies change, and this has potentially important implications for the use of psychotropic medication in this population. In this article, I will describe the effects of aging on the pharmacokinetics and pharmacodynamics of drugs. This information is crucial for understanding how the tolerability and safety of drugs change in older individuals and how medications should be prescribed for older patients, which will be covered in next month’s article.

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Pharmacokinetics refers to the absorption, distribution, metabolism, and excretion of drugs in the body. Changes can occur in these parameters with aging, which can affect how drugs are handled in older patients (Rudorfer, 1993; Turnheim, 1998). Because of reductions in gastric acid secretion and decreased gastrointestinal blood flow, the absorption of orally administered drugs may be impaired or delayed. As a result, the oral bioavailability of drugs might be decreased in older adults, although the clinical significance of this is not well established (ElDesoky, 2007; Greenblatt, Sellers, & Shader, 1982).

### Drug Pharmacokinetics and Older Adults

**Body Mass and Body Water**

The volume of distribution of a drug depends on total body mass (muscle and fat) and total body water, both of which are decreased in older adults (Borkan, Hults, Gerzof, Robbins, & Silbert, 1983; Hughes, Frontera, Roubenoff, Evans, & Singh, 2002; Ritz, 2000). In addition, the relative proportion of lean muscle mass to total body fat is reduced in older adults. With the exception of lithium, most psychotropic drugs are stored in fat tissue. For this reason, many drugs tend to accumulate with chronic dosing in older patients more so than in younger patients. The elimination of these drugs from fatty tissue tends to be slow, resulting in prolonged effects. Hence, the combined effects of ongoing administration together with the slow release from fat stores of already-administered drug can ultimately lead to higher and higher central nervous system (CNS) concentrations over time. This may lead to long-term “overdosing” in patients, resulting in potentially toxic effects.

This has been a particular concern with the long-term administration of benzodiazepine drugs in older adults. For drugs that are primarily distributed in water (e.g., lithium), higher drug concentrations will occur for a particular dosage as total body water decreases. Because total body water is normally decreased in older individuals, as well as because older adults are more susceptible to dehydration, the risk of adverse effects associated with lithium use (and other water-soluble drugs) is increased in elderly patients.

**Plasma Proteins**

Regardless of the route of administration, all drugs will enter the systemic circulation and most will reversibly bind to various plasma proteins. All psychotropic drugs, except for lithium, are highly protein bound. For protein-bound drugs, the higher bound fraction (i.e., the amount of drug binding to protein at any one time) exists in a reversible state of equilibrium with the smaller “free-floating” unbound fraction, called the free fraction. Only the free fraction of a drug exerts its pharmacological therapeutic and adverse effects, because it is able to cross the blood-brain barrier into the CNS or is able to bind to other organs throughout the body. Moreover, only the free fraction undergoes metabolism in the liver or clearance through the kidneys.

Plasma proteins tend to decrease with age, and even more...
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so in older patients who are debilitated or undernourished (Roberts & Tumer, 1998). As a result, a greater proportion of protein-bound drugs will exist as a free fraction in elderly patients. This may contribute to the increased risk of adverse effects in the CNS or other organ systems. Taking multiple drugs that bind to the same plasma protein can cause displacement of the protein-bound fraction, leading to higher concentrations of the free fraction. This can also result in more adverse effects in older adults. Laboratory tests can measure the amount of certain circulating plasma proteins (e.g., albumin). Many standard references, such as the Physicians Desk Reference, have information about the protein binding of various prescription medications.

**Metabolic Pathways**

With a few exceptions (i.e., lithium, gabapentin [Neurontin®]), most psychotropic drugs are metabolized as they pass through the liver. Age-related decreases in hepatic blood flow and the activity of some liver enzymes may result in decreased metabolism of many drugs in older patients. The two main metabolic pathways in the liver involve oxidative processes and conjugation processes. Conjugation processes are not strongly affected by aging, but some oxidative processes decline with age.

Most oxidative processes are mediated by cytochrome P-450 (CYP-450) enzymes. The CYP-450 system is a group of different enzymes that are responsible for the metabolism of approximately 60% of commonly prescribed medications. Multiple CYP-450 enzymes exist in the liver. The major drug-metabolizing CYP-450 enzymes relevant in clinical psychopharmacology are CYP-1A2, CYP-2B6, CYP-2C9, CYP-2C19, CYP-2D6, and CYP-3A4. Aging effects have not been well studied or well established for all of these enzymes. The effect of aging on enzyme activity also is not uniform across all enzymes. For example, CYP-2D6 activity does not change with age, whereas CYP-2C19 and CYP-3A4 appear to decline with age (Pollack, Forsyth, & Bies, 2009). Therefore, age-related changes in the metabolism of a drug will depend on the particular enzymes involved.

In addition, drugs binding to various CYP-450 enzymes can inhibit or induce the activity of the enzyme. Because older patients typically take multiple medications, more adverse effects would be expected, based on not only age-related metabolic enzyme changes but also multiple potential drug-drug interactions. The kinds of blood tests that are usually ordered for “liver function” or “liver enzymes” are not useful for measuring or predicting the metabolism of medications.

**Renal Function**

Most psychotropic drugs, as well as their metabolites, are excreted through the kidneys. Renal function decreases with age, which is especially important for the use of lithium in older patients (Rudorfer, 1993). Renal function is relevant for most drugs because they are eventually cleared through the kidneys after metabolism in the liver. Decreased renal clearance can result in higher concentrations of the parent drug and any active metabolites, increasing the risk of adverse or toxic effects. In contrast to liver function tests, renal function tests provide clinically useful information about the patient’s capacity to excrete drugs through the kidneys.

**Drug Pharmacodynamics and Older Adults**

After a drug is administered, it is eventually distributed to its site of action, where it interacts with its particular targets, undergoes metabolism, and is then excreted. Pharmacodynamics refers to the pharmacological mechanism of action of a drug at its particular targets, which includes its therapeutic effects as well as any adverse effects. Psychotropic drug targets are typically various enzymes, transporters, and receptors that regulate the synthesis, transmission, and degradation of different chemical neurotransmitters in the CNS. How a drug will affect patient function overall depends on the net effect of its intended therapeutic use, together with any unintended effect on other organ systems throughout the body.
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The functional consequences of taking a psychotropic medication may result from its pharmacodynamic effects on mood (e.g., depression, mania), perception (e.g., hallucinations, delusions), arousal (e.g., sedation, anxiety, agitation), cognition (e.g., memory, concentration, attention), the neuromusculoskeletal system (e.g., gait, balance, motor coordination), vision, speech articulation, and bowel, bladder, and sexual function. Pharmacodynamic changes that are associated with aging will make older patients more sensitive to the pharmacological effects of medication. Although this might influence the therapeudic efficacy of a medication in older patients compared with younger patients, this phenomenon has not been clearly established (Hilmer et al., 2007). By contrast, the relationship between adverse medication effects and pharmacodynamic changes has been better demonstrated (Roberts & Tumer, 1998). Indeed, the known adverse effects of a drug are much more likely to occur in older patients than in younger patients, and older patients are much more likely to have serious consequences such as falls and delirium.

**CONCLUSION**

Nursing staff should be sufficiently trained in pharmacology and therapeutics in older patients, especially because altered pharmacokinetic and pharmacodynamic processes influence the sensitivity of older people to medication effects (Banning, 2005). Understanding how the tolerability and safety of drugs is different in older adults and how medications should be prescribed for this population will be discussed further next month. This information is important for nurses for clinical monitoring and patient education.

**REFERENCES**


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