CE 1.9 CONTACT HOURS Rx 0.5 PHARMACOLOGY

The practicalities and pitfalls of polypharmacy

By Tamara Zurakowski, RN, GNP-BC, PhD

Older adults typically present with several chronic illnesses in addition to acute problems and health promotion needs. The aging population is remarkably heterogeneous and a "one size fits all" prescribing pattern is ill-advised. Multiple research studies in the United States and abroad demonstrate that older adults are poorly served by pharmacotherapeutics. Safe and efficacious prescribing for this group is challenging and requires that the NP neither overprescribe nor underprescribe. A working knowledge of the pharmacokinetics of aging and basic pharmacodynamics of medications in the older adult is needed to appropriately care for elders.

Polypharmacy concerns

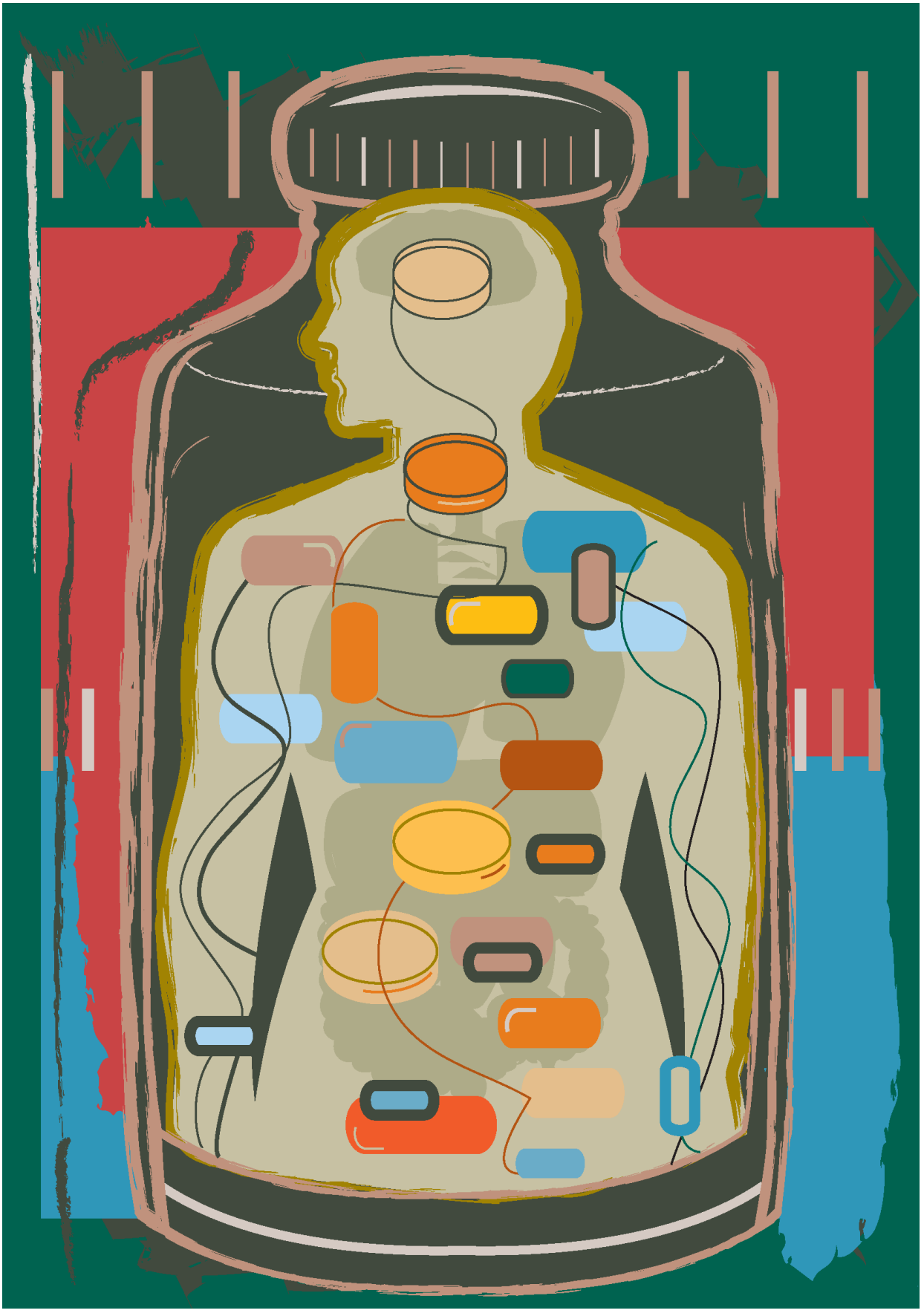
Most NPs have probably been cautioned about the dangers of polypharmacy, particularly in regard to older adults. It is a risk factor for many serious problems, including shortness of breath, hypertension, dependency in instrumental activities of daily living, poor self-reported health, decrease in lower extremity function, and tension between patient and provider.[1,2] Polypharmacy is typically defined as five or more prescribed medications, which sounds easy enough to avoid. The average older adult, however, has 6.5 chronic conditions,[3] and multidrug therapy is becoming an integral part of many treatment regimens.[4] All of a sudden, five medications can begin to sound like "oligopharmacy," or too few medications, not polypharmacy. Indeed, several studies have demonstrated that when older patients are prescribed more than five medications, they are likely to be missing an indicated medication, rather than taking unnecessary medications.[5–7] When these findings are combined, those that report the number of older adults who receive prescriptions for medications that are physiologically inappropriate for them, the landscape of prescribing for older adults looks treacherous for both patient and provider.[6,8-11]

Background

Pharmacodynamics represents the interactions between a drug and the target organ such that a therapeutic or adverse response is achieved.[12] Pharmacokinetics, on the other hand, is the process within the body that delivers the medication to the target.[12] The four major processes usually included in discussions of pharmacokinetics are absorption, distribution, metabolism, and elimination. Thus, these processes bring the drug to its intended objective, where pharmacodynamics takes over. There are many aging-related changes that affect pharmacokinetics, as well as a few that affect the dynamics of the drugs. Drug kinetics and dynamics are integrally related to polypharmacy in the elderly. It is important to remember that aging occurs in a very heterogeneous fashion, and no two people will experience change at the same rate or pattern. Also, frail elders generally experience more physiological changes of aging than their more fit counterparts.[12]

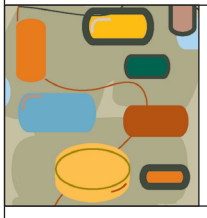
Absorption

Motility of the gastrointestinal (GI) tract slows and becomes less coordinated with age, increasing the length of time medications may remain in the tract and be absorbed as the nerves that supply the system change in function.[13] A decrease in the effectiveness of esophageal peristalsis, presbyesophagus, also increases the time medications remain in the GI tract.[12]



These changes may not necessarily lead to clinically important alterations in absorption, but are parts of a chain of events that may make a difference.

The stomach lining atrophies with age and produces less hydrochloric acid.[14] The intestines have an increased amount of collagen, and the villi become somewhat misshapen. The change in the shape of the villi makes less surface area available for transport of medications into the blood stream. This is compounded by a decrease in blood flow to the GI system, so that even when medications cross the tissue of the villi, there are fewer blood cells to pick them up.[12]



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Medications that are administered topically or parenterally may also be absorbed differently in older adults. Replacement of epidermal cells slows dramatically with age, yielding the typical "thin" skin of older adults.[15] Discolorations may result from decreased function of the melanocytes, and the dryness of older skin is a result of fewer sebaceous glands. There is less subdermal fat, the junction between the dermis and epidermis is flattened, and the small blood vessels in the skin become more fragile and more likely to rupture.[16] These changes combine to allow fewer medications to be passed from the epidermis into the underlying tissues, so topical and transdermal delivery systems may yield less absorption than expected.

Human aging is also marked by changes in muscle mass.[17] Lean muscle mass is replaced by intramuscular fat and connective tissue,[18] although elders who maintain higher levels of physical activity may lose less muscle mass.[19] Intramuscular injections may be absorbed faster because of the decreased muscle mass, but that is offset by decreased peripheral blood flow that may decrease absorption. The net result is that intramuscular medications may be poorly absorbed.[12]

Distribution

Once the medication has been absorbed, it must then be distributed throughout the body. As with absorption, age-related changes can affect this process. Cardiac output is decreased in many older adults, so tissues may not be well-perfused, hence medications may not reliably reach targeted organs.[12] Fat, protein, and water are all important in the distribution of drugs. The loss of lean muscle mass and increased body fat have already been noted above. Water makes up less of the total body composition in older adults than it does in younger people. The changes in body structure may increase the likelihood that drugs will be distributed in unexpected ways, and polypharmacy may compound the problem.[12]

Some drugs are water-soluble, others fat-soluble, and many may bind to protein. Because older adults generally have more overall body fat in comparison to lean muscle, fat-soluble medications such as diazepam may remain in the body longer, leading to possible overdose if adjustments in timing and dose are not made.[20] The lower percent of body water means that water-soluble medications, such as oxycodone, atenolol, captopril, and venlafaxine, may achieve higher serum concentrations.[21] Finally, drugs that bind to protein may be more active in people with low levels of body protein, as measured by albumin levels. Many older adults fall into that category, and protein-binding drugs such as phenytoin and warfarin must be monitored with extra care, as unexpectedly aggressive effects may be noted.[20] This is particularly worrisome when several protein-binding medications are used at the same time because they will compete for the available protein.

Metabolism

The liver becomes less effective with increased age, affecting medication metabolism, but standard liver function tests, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), do not accurately reflect pharmacokinetic ability. In general, Phase I, or "first pass" metabolism is significantly decreased in older adults, particularly older men.[12] When the rate of metabolism is slowed, bioavailability is prolonged.[12] Again, it is important to monitor the older adult for evidence that medications may be longer-acting than anticipated.

Excretion

Perhaps the most significant effects of aging on pharmacokinetics are on excretion. Multiple organs are involved in excretion, including the kidneys, intestines, lungs, and sweat and salivary glands, and all have age-related decrements in function. Both vital capacity and tidal volume decrease, but residual volume may increase by as much as 50% from late adolescence.[22,23] The alveoli lose surface area and fewer waste products are diffused from the pulmonary capillaries.[24] Chronic kidney disease is caused by irreversible age-related and disease-related damage to the kidney and affects nearly 30% of elders.[25] The skin loses sweat glands over time and the salivary glands produce less saliva. As discussed above, there is less exchange across the membranes of the intestines, and in terms of excreting medications, metabolites are not as effectively transported from blood into the intestine.[13,14]

Of all these mechanisms for drug excretion, only kidney function may be reliably measured. A reasonably accurate estimate of the glomerular filtration rate (GFR) in older adults may be made using the Cockcroft-Gault equation. The modification of diet in renal disease (MDRD) equation tends to significantly overestimate kidney function in older adults.[26]

Pharmacodynamics

Even after all the potential problems in moving medications into, around, and out of the body are taken into account, pharmacodynamics is still an important aspect to consider. The loss of physiological reserve that accompanies aging predisposes older adults to unexpected effects from medications. Postural hypotension is one such effect. This occurs when the baroreceptors and peripheral vasculature do not respond as quickly to drops in BP in older adults.[12] When an older adult stands up, for example, the baroreceptors are slow to recognize the drop in BP and to initiate compensatory action. In a related concern, older adults have fewer beta-receptors and those receptors are not as likely to bind to adrenergic particles. Hence, beta-adrenergic blocking and beta-agonist medications are not likely to be effective. Any medication that affects the central nervous system (CNS) is likely to have amplified therapeutic and adverse effects, because the CNS of older adults has less ability to withstand any assault. Dopamine reserves, in particular, decrease with advancing age, and medications that may affect dopamine pathways are likely to trigger extrapyramidal effects.[12]

Changes in the elderly's immune system are of particular concern when infection sets in. The natural killer cells become less functional with increased age, although they become more numerous.[27,28] T-lymphocytes are similarly affected, with a decreased ability to recognize and attack the antigens for which they were produced. New T-lymphocytes are essentially not produced in older adults, severely impairing the elder's ability to combat a previously unencountered antigen.[27] B-lymphocytes continue to be produced, but they become less effective in producing antibodies to pathogens. Coupled with changes in pharmacokinetics, as discussed above, anti-infectives may achieve subtherapeutic levels in older adults.[20] Macrolides do not concentrate well in elders, but acidic anti-infectives (penicillin, ceftriaxone, sulfonamides, and clindamycin) may achieve concentrations higher than in younger adults. Longer courses of anti-infectives may be needed to adequately treat infections in the elderly, but decreased immunity of the GI tract in older adults predisposes them to *Clostridium difficile* infection.[14]

Potentially inappropriate medications

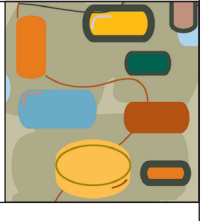
The pharmacokinetic and pharmacodynamic changes in older people are the bases for identifying potentially inappropriate medications (PIMs) for older adults. The most well-known listing of these medications is the "Beers Criteria," a consensus report on PIMs that is updated periodically.[29] An easily accessible list of these medications and medication-disease combinations to avoid may be found on the Hartford Institute for Geriatric Nursing's Web site, ConsultGeriRN.org (http://www.consultgerirn.org/).[30] The list is a valuable resource for NPs who work with older adults.

Polypharmacy and safe prescribing

Many NPs become discouraged by the difficulties encountered in managing the medication needs of older adults, especially given the sheer volume of prescriptions many older adults take. The coalescence of people who survive into old age with many health problems, and the success of managing those problems with medications, has made polypharmacy a fact of life.

One study of older adults found an average of 3.8 different therapeutic categories per patient, with cardiovascular, CNS, and hormone (for example, thyroid) the most common.[31] Individual patients were prescribed an average of 6.1 medications across those categories, with women averaging both more prescriptions and more therapeutic categories. Elders between the ages of 80 and 84 had the highest mean number of prescriptions. The study did not document unnecessary prescriptions or frivolous prescribing patterns. Indeed, according to a study completed by Kuijpers et al., 43% of those taking at least five medications were underprescribed by an average of 1.4 indicated medications.[5]

Drugs that bind to protein may be more active in people with low levels of body protein as measured by albumin levels.



The goal is not to simply avoid polypharmacy, but to practice rational drug therapy or rational polypharmacy instead of indiscriminate polypharmacy.[4,32] Some experts have advised defining polypharmacy as nine or more medications, rather than the more usual five or more.[7] Even by this more lenient definition, a significant number of older adults still experience polypharmacy.[6,7]

One of the major concerns of polypharmacy is the increased likelihood of drug interactions.[33,34] It is true that more drug-related problems are noted in patients taking multiple drug combinations, but there is no apparent cutoff point in

Safe prescribing for older adults[4,20,34,35]

Polypharmacy should be considered as one factor of safe prescribing practice, along with assessment of PIMs, monitoring for drug-related problems, and underutilization of indicated medications. The following suggestions may be useful to NPs who prescribe medications for older adults:

- Review medications with the older patient at every visit. Strongly encourage the older adult to bring all medications (not just a list) to the appointment. Inadvertent duplication caused by multiple providers, or generic versus brand names, is most easily detected in this manner.
- Evaluate the older adult's medication-taking success. Consider financial constraints, poor understanding, and alternate explanatory models instead of "noncompliance."
- Consider every new symptom or complaint as a possible drug-related problem and investigate it as such.
- Review your patient's medications in light of the current problem list and ensure that each medication is still indicated.
- Use the Beers Criteria as an initial filter when considering a new medication. If an alternative is available for a PIM, use it.
- Assess current medications against the Beers Criteria. Consider changing PIMs for a safer alternative.
- Explicitly ask about over-the-counter medications, herbal preparations, and home remedies. These substances can have a significant effect on the action of a prescribed medication.
- When considering dosages, remember to start low and go slow.
- When prescribing anti-infectives, obtain culture and sensitivity data whenever possible. Ignore the usual rule of starting at a lower dose in most cases. Rather, use the usual adult dose. Be aware of anti-infectives, such as the quinolones, that must be dose-adjusted for decreased GFR. Follow treatment with a test of cure, if possible.
- Consult with another healthcare professional, preferably a pharmacist, on a regular basis. Review the charts of your older patients and make sure every medication has a concomitant diagnosis.

the number of medications at which drug-related problems rise exponentially.[6,33] Rather, the relationship between the number of medications and the number of drug-related problems is linear, and each additional medication increases the risk of an adverse reaction.[33] Defining polypharmacy as a certain number of medications and attempting to stay below that number may lead the prescriber into a false sense of security. A safer practice is to be alert for any evidence of a drug-related problem and deal with it promptly rather than avoiding polypharmacy for its own sake.

Another concern with polypharmacy is PIMs. A disturbing number of older adults are prescribed medications that should be avoided for their population. In one study, nearly one-third of older adults presenting to an ED were taking a medication in contradiction to the Beers Criteria.[11] A similar percent (37%) of Veterans Affairs outpatients with more than five prescription medications were also on medications that should have been avoided.[6] The more medications they were on, the more likely the veterans were to be taking PIMs. The most common PIMs in the ED setting were propoxyphene (Darvon), muscle relaxants, and antihistamines.[11] Even more disconcerting, 13% of ED patients left with a new prescription for a PIM, again with propoxyphene leading the list.[11] Prescribers in all areas of practice must become more aware of medication safety for older adults.

Safe prescribing practice

It is not always possible to adhere to every guideline when working with older patients. Clinical judgment must be exercised at every juncture, and the risks and benefits of a medication should be evaluated in the context of the individual older adult's situation (see *Safe prescribing for older adults*).

Improving quality of care

Working with older adult patients is both rewarding and challenging. The changes that aging brings to pharmacokinetics and pharmacodynamics add an increased responsibility to the NP who prescribes for this population. An awareness of the physiological needs of older patients and the resources available to the NP can help improve the quality of care for these patients.

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