GERINOTES

SECTION ON GERIATRICS, AMERICAN PHYSICAL THERAPY ASSOCIATION

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WANTED: ARTICLES FOR GERINOTES

TOPICS: Anything related to older adults

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Everyone loves to publish and it is easy!

Contact Melanie Sponholz, GeriNotes Editor
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PRESIDENT'S PERSPECTIVE: WE NEED TO REAFFIRM OUR COMMITMENT TO THE FOUNDATION

John O. Barr, PT, PhD

Established in 1979, the Foundation for Physical Therapy has awarded over $12 million in research grants, fellowships, and postprofessional doctoral scholarships to more than 500 researchers. Ultimately, Foundation award alumni have gone on to receive an estimated $61 million in funding from external sources, such as the National Institutes of Health, NFL Charities, and the Christopher Reeve Foundation.

Over the years, many of these awards have been associated with aging-related topics. Although not directly involved in the "Plymouth Rock" founding moment of the Foundation, the Section on Geriatrics (SOG) has contributed to maintaining a firm Foundation in a number of ways. In the early years, these included SOG leader Fran Kern, PT, PhD, being elected to serve on the Foundation Board of Trustees (1985); Foundation sponsorship of our "Project Focus '94: Physical Therapy Treatment Effectiveness for Older Persons" (1994); and our $50,000 endowment for geriatric research projects (1995).

Evidence of the Section's commitment to the Foundation in more recent years has been demonstrated as follows:

In 2009, Michael Lewek, PT, PhD, of the University of North Carolina at Chapel Hill received a $40,000 Geriatric Research Grant to fund his research project, "Biomechanical Influences on Motor Learning During Locomotor Retraining Post-Stroke." This grant was partially-funded by the Section on Geriatrics Fund and the Pittsburgh-Marquette Challenge.

In 2010, the Foundation awarded its largest funding opportunity since 2002, the Clagett Family Research Grant, to Laurie King, PT, PhD, of Oregon Health Sciences University. This $300,000 high-impact grant will be distributed over the next two years to fund Dr. King's research project titled, "Effectiveness of Physical Therapy in Chronic Neurologic Disease: The Role of Co-morbidities and Delivery of Physical Therapy Services." Dr. King will investigate the most beneficial mode of exercise intervention for older adults living with Parkinson disease and other co-morbidities associated with aging. Section on Geriatrics member, Katie Mangione, PT, PhD, was involved with the Foundation to formulate the request for proposals associated with this grant.

The Foundation awarded a 2011 Geriatric Research Grant to Daniel White, PT, ScD, MSPT, of Boston University for his project, "Factors Associated with Day-to-Day Walking in Older Adults with Knee Osteoarthritis," to study the pathology, impairment, and functional limitation associated with day-to-day walking. Dr. White's grant was funded in part by the Section on Geriatrics Fund, the Marilyn Moffat Endowment Fund for Geriatric Research, and the 2009-2010 Miami-Marquette Challenge.

For years the Section has struggled with the challenge of how to provide substantial funding for aging-related research projects. The examples cited above illustrate how we've been able to successfully partner with the Foundation and its other sources to underwrite modest grant funding, but this has been at the expense of building an endowment corpus from which interest can be used for future substantial grants. In 2010, we embarked on a new strategy to build this endowment by partnering the Foundation's Section on Geriatrics Fund with the Marilyn Moffat Endowment Fund for Geriatric Research. This involved transferring $91,000 from the "permanently restricted" portion of the Geriatrics Fund (ie, money not to be used for funding current research) to the correlate portion of the Moffat Fund. The outcome of this action is that as of the end of March, the total balance for the Moffat fund stood at $200,444, while the Geriatrics Fund totaled $11,043 ($10,993 "temporarily" and $50 "permanently" restricted).

Before the end of 2011, we need to substantially increase our "temporarily" restricted Section on Geriatrics Fund holdings, so that we can again help fund a contemporary Geriatric Research Grant in 2012. **This is why your active involvement in reaffirming our commitment to the Foundation is critical.** The SOG Board of Directors has authorized up to $50,000 to be matched dollar for dollar with member and friend donations through the end of 2011. Donations can be made online at Foundation4PT.org or via mail at: Foundation for Physical Therapy, 1111 N. Fairfax Street, Alexandria, VA, 22314. Make sure to direct your donation to the "Section on Geriatrics Fund." Your contribution is critical to assuring that both short- and long-term funding for aging-related research is available through the Foundation for Physical Therapy.

Dr. Barr is a Professor in the Physical Therapy Department at St. Ambrose University, Davenport, IA. He also serves on the Editorial Board for the *Journal of Geriatric Physical Therapy*.

EDITOR'S MESSAGE

Melanie Sponholz, MSPT, GCS

As I edited this year's Focus issue on pharmacology, I kept thinking of two articles that definitely reflect the way I practice: the November *GeriNotes* article by Brandy Whetten, DPT, and Mike Studer, MSPT, NCS, CEEAA, "Physical Therapists as the Pharmacists of Exercise,"[1] and "The Magic of Exercise," written by John E. Morely, MB, BCh, for the *Journal of the American Medical Directors Association*. Morely writes, "Exercise is a cornerstone in increasing strength and balance, and decreasing falls, improving functional decline and frailty, improving mobility in Parkinson patients, reducing injuries, improving glycemic regulation, slowing loss of bone mineral density, constipation, fear of falling, enhanced sleep, quality of life, and decreasing incontinence."[2] Think about that list! If your doctor told you there was a pill you could take that had all of those positive effects, would you take it? Absolutely! Well, exercise is that magic pill, and as Whetten and Studer point out, physical therapists are the pharmacists who can dispense it.

We live in a culture of pharma reps, direct-to-consumer pharmaceutical marketing campaigns, and big pharma lobbying interests. It is a culture in which patients believe, even expect, their physicians to write a script for whatever complaint presents. Chronic conditions, and the drugs that treat them, are rampant. We are bombarded by television commercials for drugs, many of which include the tag line, "when diet and exercise fail...ask your doctor if drug x is right for you." This begs the questions: Did anyone really try diet and exercise? Did they really fail? Would they fail if the "prescription" for exercise was appropriate and effective and issued by an exercise expert, by a PT? There are certainly many instances where a prescription drug is a lifesaver. However, when there are medications being prescribed to treat the side effects of other medications, it really is critical that we make a good and loud case for including our skills as pharmacists of exercise in the plan of care.

I attended a lecture by an Occupational Therapist colleague a few weeks ago, about defending our territory in the health care marketplace. She cautioned the clinicians in the audience not to sell themselves short, especially by dismissing our own expertise as "common sense." For example, how many times have you issued an off-the-cuff prescription for activity modification or exercises to avoid or alleviate knee or back pain? Such advice is second nature, back pocket information to us. It hardly seems like skill when you live and breathe the knowledge every day, but it is valuable intervention. And if it were just common sense, Advil sales would be way down!

In an ideal world, people would exercise more, lead healthier lifestyles, and need fewer medications. However, even in the best case scenario, prescription drugs will be part of a comprehensive intervention for many illnesses and conditions. That's why this issue is such a fantastic resource for therapists. Seldom do we see an older adult who is not taking multiple prescriptions, and it is critical that we understand how these medications affect our clients and interact with the exercise that we prescribe. The articles are a great review of everything from the pharmacodynamics and pharmacokinetics of commonly prescribed drugs to how physical therapists can help prevent polypharmacy. Understanding this information is essential for us to be able to write our exercise prescription. If we write it well, as outlined in the article by Whetten and Studer, we may be able to eliminate the need for some of the medications our clients are taking, and we will insure that we are not causing any adverse interactions ourselves. Further, we must also continue to publicize the "magic pill" called exercise, and our unique qualifications to dispense it!

REFERENCES

1. Whetten B, Studer M. Physical therapists as the pharmacists of exercise: determining the appropriate dosage (intensity) for your patient. *GeriNotes.* 2011;18: 27-30.
2. Morely JE. The magic of exercise. *J Am Med Dir Assoc.* 2008; 9:375-377.

Mark your Calendars for CSM 2012

CSM 2012 is fast approaching. Mark your calendars and be prepared for another year of fantastic programming! Hot topics for our Section include: "Walking Speed…A Vital Sign and Even More," Dr. Pameal Duncan, et al; "No Crashing, No Burning, Improving Function and Managing Pain in Clients with Neuropathy," Dr Brady Whetten, et a.; and "Exercise Adherence in Older Adults: Why Don't My Patients do Their Exercises and How Can I Improve This?," Dr. Anne Shumway-Cook, et al. This year, a gait track is being co-sponsored with the Acute Care and Neurology Sections, with clinical applications across settings and diagnoses. In addition, there are more great educational sessions and preconferences, platform presentations, SIG meetings, and members' meeting/receptions being planned. Plan to stay through Saturday so as not to miss a thing!

PHARMACOLOGY AND PHYSICAL THERAPY: CONSIDERATIONS WITH AGING POPULATIONS

CONTINUING EDUCATION MODULE

OVERVIEW

Physical therapists who work with the aging adult population must be versed in the ways that pharmacodynamics and pharmocokinetics effect patients and impact the planning of therapeutic interventions. The body and its physiological responses are impacted by medication, and this must be understood to treat patients safely and effectively. Increased knowledge in this subject matter will improve the quality of examination, assessment, and intervention, a prime goal of all physical therapists and assistants.

MODULE CHAPTERS

I. Pharmacology and the Aging Adult
II. Diabetes Medications: Considerations for Physical Therapy with Older Adults
III. Drug Management in the Elderly: Preventing Mismanagement, Avoiding Risky Prescriptions, and Diminishing the Adverse Effects of Polypharmacy
IV. Pharmacologic Profile as a Fall Risk Factor
V. Possible Interactions Between Exercise and the Pharmacocdynamics and Pharmacokinetics of Drugs
VI. Cardiac Medications: A Primer for Physical Therapists
VII. Pharmacology and Physical Therapy Intervention for Pain Management
VIII. Pharmacotherapy and Wound Healing in the Elderly Adult

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REFERENCE LIST

References can be found at the end of each chapter in the module.

OBJECTIVES

The reader will be able to:
1). Define polypharmacy.
2. Describe the ways that biological changes associated with aging effect the pharmacokinetics and pharmacodynamics of drugs.
3. Describe the stages of pharmacokinetics of drugs; absorption, distribution, metabolism and elimination.
4. Describe how drug therapy may influence exercise performance and how exercise may influence the pharmacokinetics and pharmacodynamics of a drug.
5. Identify which drug categories offer the greatest risk for adverse drug reactions.
6. Recognize when adjustments need to be made either to the dose of a drug, or the intensity or timing of exercise.
7. Define common pain management terms, common pain medications and their side effect profiles, and relate this information to the physical therapy management of patients with pain.
8. Understand the functional consequences of overmedicating the elderly.
9. Identify medication classes used to treat cardiovascular conditions.
10. Describe the medication intervention specific to the ACC/AHA Heart Stages.
11. Discuss available evidence and strategies for medication review as a component of fall risk assessment.
12. Discuss anti-hyperglycemic medications used in the treatment of diabetes as they relate to physical therapy interventions with older adults.
13. Recognize how pharmacotherapy may contribute to wound healing success or failure in the elderly adult.

TARGET AUDIENCE

Physical Therapists and Physical Therapist Assistants

CONTACT HOURS/CONTINUING EDUCATION UNITS

Completion of the CE Module is equivalent to 6 contact hours which converts to .6 Continuing Education Units

CONTINUING EDUCATION CERTIFICATE OF COMPLETION

A Continuing Education certificate will be provided to each participant after successful completion of the course requirements (post test and module evaluation) and payment of a processing fee. The Section on Geriatrics is a recognized component of the American Physical Therapy Association. The Section on Geriatrics has not applied to any state licensure agency for prior approval of this course. The module has all the components (content, objectives, qualified instructors, reference lists, and post test) that will

allow participants to submit the certificate of completion to meet CE requirements in most chapters. Please seek individual approval for this course from the states of Texas, Ohio, Oklahoma, and Nevada.

HOW TO SUBMIT CEUs

To obtain CEUs for this continuing education unit, participants must complete the post test as well as the evaluation form, which may be found on the Section on Geriatrics Web site, geriatricspt.org. A processing fee of $60.00 for SOG members and $120.00 for nonmembers is required. To apply for CEUs print and complete the post test and evaluation form and send them to the Section on Geriatrics along with payment. Applications must be postmarked no later than December 31, 2011. Upon submission of materials and a passing score of 80% or higher on the post test the Section will mail you a continuing education certificate for .6 CEUs. Those with incomplete submissions will be notified via e-mail and given the opportunity to re-take the exam.

Pharmacology Continuing Education Unit Post Test and CE Unit Evalution Form can be found on Section on Geriatrics Web site at www. Geriatricspt.org.

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Submission for Continuing Education Credits

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PHARMACOLOGY AND THE AGING ADULT

Jill Heitzman, PT, DPT, GCS, CWS, CEEAA, FACCWS

Physical therapists who work with the aging adult need to be aware of the variety of issues affecting this population, including pharmacology. Clinicians need to have an in depth awareness and knowledge of how drugs interact with various rehabilitation procedures. These interactions can affect outcomes and put this population at risk for falls and injury. The *Guide to Physical Therapist Practice* has identified pharmacology as part of the history taking for each of the 4 preferred practice patterns.[1] While this is an important area for any patient population seen by a physical therapist, the aging adult has biological changes that make them more sensitive to the adverse effects of drug therapy.[2] These biological changes, and resultant multiple comorbidities, mean that many elderly patients take multiple drugs, which means they also suffer from more adverse drug reactions.[3]

DEMOGRAPHICS

The basic age associated pharmacokinetic and pharmacodynamic changes were not identified until the 1980s. Since then, studies have attempted to identify efficacy, safety, and dosage of drugs, and how to monitor adverse drug reactions.[4] As with any studies of the aging population, the variety of aging physiological factors, functional and health status, and the need for longitudinal studies with a relatively low enrollment in the upper age group strata, make establishing exact dosing guidelines difficult. For practical purposes, the health professional has been advised to "start low and go slow" when prescribing any medication to this population.[5,6]

According to most studies, aging adults make up 13% of the population in the United States but take 34% of all drugs. By the year 2030, this population will make up 21% of the total population and take 40% of all drugs. A sampling of community dwellers has shown that 81% of those 57 to 85 years of age used at least one prescription, and 29% used 5 or more, with those in nursing homes tending to use more than 8 prescriptions each day.[2] Aging adults also purchase more than 40% of over-the-counter medications, adding to this polypharmacy.

The aging adult population also tends to have a greater number of co-morbidities. The average aging adult has two to three chronic conditions that require medication to control underlying pathology, decrease symptoms, and maintain functional capacity. The combination of the co-morbidites and the medications used to treat them leads to concerns regarding how medication therapy outcomes may be altered by the drug-drug interactions and the effect on functional status. This ultimately affects whether or not successful aging can be achieved.[4,6]

POLYPHARMACY

With the increased use of pharmaceuticals, prescription and over the counter, the aging adult is more often at risk for the development of polypharmacy and, ultimately, the risks that accompany this. A distinction must be made regarding what is polypharmacy and what is reasonable and appropriate use of pharmaceuticals. A definition for polypharmacy can be found on multiple Web sites and in medical dictionaries, and is usually defined as: The use of multiple medications/multiple pharmacies, administering many excessive medications.[7] When looking specifically at the aging adult and the comorbidities, use of multiple medications could seem reasonable. The *McGraw Hill Concise Dictionary of Modern Medicine* takes the definition of polypharmacy further to include "taking more drugs than are warranted by the disease/need, too many pills leading to pill burden, portion of the drug regime is not evidence based, increased adverse drug reactions and taking medications for these reactions, and unnecessary or multiple complex drug regimes."[7] In 2005, Fulton et al, did a literature review and found a definition more appropriate for clinical use with the aging adult: "the use of medications that are not clinically relevant."[8] Geriatric polypharmacy is defined as a situation in which an older adult is being prescribed or taking more medications than clinically appropriate.[9]

A literature review by Hajjar et al showed that unnecessary pharmaceutical usage is associated with negative health outcomes.[10] Factors contributing to the clinical picture of polypharmacy and the aging adult include use of medication for no apparent reason, duplication of medications, concurrent use of interacting medications, inappropriate dosage, use of drugs to treat adverse reactions of other drugs, use of contraindicated medications, and failure to stop use of a medication when an alternate drug is prescribed.[2] Problems associated with polypharmacy include (1) increased risk for drug interactions and adverse drug reactions, (2) unnecessary and/or inappropriate medication prescribing, (3) medication noncompliance, and (4) increased drug expenditures. Individuals who perceive that they are taking too many medications often have a lower quality of life and increased rates of depression. The physiologic process of aging makes patients more susceptible to adverse outcomes of medications and potential drug reactions.[9]

Polypharmacy is more often seen in the aging population as a result of prescribers choosing to treat problems with a drug rather than nonpharmalogical measures.[2] Due to the prevalence of multiple comorbidities, this population tends to see many physicians who may independently prescribe medications without communicating with other providers. Another cause of polypharmacy among aging adults is the sharing of medications between family and friends. Polypharmacy and/or adverse combinations of medications may also occur when aging adults' pharmacy purchases are influenced by the financial burden of purchasing drugs, for instance, using a medication because a coupon for the drug makes it less expensive. The average cost of one pill in August 2008

was $5.00, forcing some aging adults to choose between food and drugs. Aging adults also have easy access to over-the-counter medications, and may self medicate without understanding the interactions of these OTC medications with their prescription drugs, or even viewing the OTC medications as drugs.[4]

PHARMACOKINETICS, PHARMACODYNAMICS, AND AGING

The altered response to drugs in the aging adult can be attributed to how the biological changes associated with aging affect the pharmacokinetics and pharmacodynamics of the drug. These changes affect the therapeutic and toxic effects of the drugs and can often lead to significant health risk of morbidity and mortality. While a review of these biological changes is beyond the scope of this article, a discussion of the age related changes in pharmacokinetics will allow the physical therapist to understand the increased risk for adverse drug reactions and their effect on physical therapy outcomes.

There are 4 components to the pharmacokinetics of a drug: absorption, distribution, metabolism, and elimination. Each of these components is affected by the biological changes of the aging adult.

The changes to the GI tract with aging include decreased gastric acid production, decreased gastric emptying, decreased blood flow, diminished area of absorptive surface, and decreased motility.[2] Since most medications taken orally are absorbed through the small intestine, there may be a delay in absorption due to the slowing of the GI tract. However, since the drug is in the tract longer, there is still the ability for absorption. The overall result may be that the drug may take longer to reach the time of maximal concentration, thereby slowing the onset of action. This delayed action should be taken into account when assessing the effectiveness of pain medication for patients in this population, and when planning physical therapy sessions to coincide with optimal pain control.[4]

There is little evidence about the effect that aging changes in skin have on absorption of a medication through a transdermal patch. The decreased blood flow and thinning of the skin with age have not been shown to cause significant differences in absorption. Further, differences that do occur may also be attributed to the great variations in absorption through the skin across various demographics.[4] However, there is an awareness that elevated body temperature does increase absorption of some medications, so the cooler skin of the aging adult may be an inhibitor to absorption. As a result, the absorption of topical anesthetics could be inhibited as one ages.[4]

Physiological changes in the aging adult that affect medication distribution via the bloodstream include decreased total body water, decreased lean muscle, increased body fat, and decreased plasma protein concentrations. These changes can affect how the drug is distributed and how the body responds. Water soluble drugs (ie, lithium and morphine) will have less volume in which to dissolve, and so will have a greater concentration in the blood. Such medications should be prescribed at a smaller dose to attain the appropriate therapeutic response. Drugs that are distributed in lean muscle (ie, digoxin) will also have a smaller amount of volume of distribution, and smaller doses should be used in the aging population. Drugs that bind to protein (ie, aspirin, warfarin) will have less protein to bind to, and an increased concentration will reach the target tissue. This effect can increase with the more frail and malnourished adult, causing a greater risk for toxic effects. An increased percentage of body fat can act as a reservoir for lipid soluble drugs, and problems related to drug storage may occur.[2,4]

Metabolism of a drug makes the drug inactive and creates water soluble byproducts that can be eliminated by the kidneys. First pass metabolism through the liver is affected by the aging changes of decreased liver mass, decreased hepatic blood flow, and decreased action of metabolizing enzymes. This decrease in liver function during metabolism allows the drug to remain active for a longer period of time; increasing the risk for adverse reactions.[2,4]

The last component of pharmacokinetics is elimination (or excretion). The kidneys are the primary route for elimination of a drug. The aging adult has decreased renal mass and blood flow, with a correlated drop in the functioning glomeruli. This change in renal function extends the half life of many medications, such as Insulin, Valium, and Librium, each of which can have an effect on the function of the patient and need to be considered when planning a physical therapy intervention.[2,4]

Pharmacodynamics is the study of how the drug affects the body. With the physiological changes of the aging systems, the pharmacodynamics of a drug may be altered. The cardiovascular system is frequently associated with the pharmacodynamic changes, in part due to the increased medications taken by the aging adult for treatment of various cardiopulmonary conditions, especially blood pressure changes. The risk for orthostatic hypotension is increased as a result of the pharmacodyanmic changes in this system. The central nervous system is the second most common organ system with altered sensitivity to drugs in the aging adult, increasing the risk for associated cognitive dysfunction. To reduce the risk of adverse events as a result of altered pharmacodynamics, the prescribing practitioner should always start with low doses and titrate up, monitoring closely to achieve appropriate therapeutic dose. Adverse reactions should be monitored, as well as proper hydration and any signs of diarrhea, emesis, or GI hemorrhaging.[2,4,5,11]

THE ROLE OF PHYSICAL THERAPY

While a physical therapist doesn't prescribe medications, an understanding of the aging process and its effect on pharmacokinetics and pharmocodynamics will enable early recognition of adverse drug reactions. The therapist should be observant for conditions and situations that may occur as a result of polypharmacy. These conditions and situations include (1) arrhythmias, (2) balance disturbances resulting in falls and/or fractures, (3) cognitive changes, (4) confusion, (5) constipation or diarrhea, (6) depression, (7) gastric ulcers, (8) hyper-or hypotension, (9) pseudoparkinsonism, (10) rash, (11) hallucinations, (12) unexpected treatment failure, (13) medication errors, (14) increased risk of hospitalization, and (15) increased medication or treatment costs.[9]

Outcomes in physical therapy can also be interpreted in relation to the drug

(continued on page 14)

DIABETES MEDICATIONS: CONSIDERATIONS FOR PHYSICAL THERAPY WITH OLDER INDIVIDUALS

Kevin Neville, MS, PT, CCS
Karen Kemmis, PT, DPT, MS, CDE, CEEAA

Diabetes is a group of metabolic diseases marked by hyperglycemia, which is a result of defects in insulin production, insulin action, or both.[1] The Centers for Disease Control estimate that diabetes currently affects 25.8 million people in the United States, or 8.3% of the population. This includes 18.8 million people who have been diagnosed and 7.0 million people who are yet undiagnosed. Based on data from the National Health and Nutrition Examination Survey (NHANES), 10.9 million people ≥ 65 years have type 1 or type 2 diabetes, representing 26.9% of this population. About 25% of US adults have prediabetes, including 50% of those ≥ 65 years. In 2010, 390,000 people ≥ 65 years were newly diagnosed with diabetes based on data from the National Health Interview Survey (NHIS).[2]

Diabetes is the leading cause of kidney failure, new cases of blindness, and nontraumatic lower extremity amputations; a major cause of heart disease and stroke; and the seventh leading cause of death in the United States. The risk of death among those with diabetes is about twice that of the risk for those of similar age without diabetes.[2] Management of diabetes includes meal planning, physical activity, and medications. These interventions must constantly be balanced by the person with diabetes to promote good health and to avoid acute and chronic complications.[2]

There are two main types of diabetes, type 1 and type 2 diabetes. Type 1 diabetes (previously called juvenile-onset, insulin dependent, IDDM or type I diabetes) is characterized by an absolute deficiency in insulin production from the beta cells of the pancreas and accounts for about 5% of all diagnosed cases. People with type 1 diabetes must take exogenous insulin, via injection or an insulin pump, to survive. Type 2 diabetes (previously called adult-onset, non-insulin dependent, NIDDM, or type II diabetes), accounting for about 90% to 95% of all cases, is a result of relative insulin deficiency through lack of insulin production, resistance to insulin action at the cells, or a combination of both. People with type 2 diabetes may control blood glucose (BG) through meal planning and exercise, but most also take an oral agent and/or an injected medication. Based on data from the NHIS, 16% of adults with diagnosed diabetes are treated without medication, 58% receive treatment with oral medications only, 12% with insulin only, and 14% with a combination of oral medications and insulin.[2] This article will review medications used for BG management as they relate to physical therapy (PT) interventions for aging adults with diabetes.

Maintaining BG within goal ranges is encouraged to prevent or delay the onset, or delay progression, of long term complications of diabetes. Studies show that improved glycemic control can benefit those with diabetes, with every percentage point drop in A1c blood test reducing the risk of microvascular complications by 40%, including eye, kidney, and nerve diseases.[2] BG goals for those with diabetes are:

A1c	<7.0%
Preprandial capillary plasma glucose	70–130 mg/dl
Peak postprandial capillary plasma glucose*	<180 mg/dl

*Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, which is generally when BG is at peak level in people with diabetes.[1]

Goals should be individualized based on duration of diabetes, age/life expectancy, co-morbid conditions, known cardiovascular disease or advanced microvascular, complications, hypoglycemia unawareness, and individual patient considerations.[1]

When a person without diabetes increases activity, there is a concomitant decrease in insulin production to maintain glucose homeostasis. For those with diabetes, the protective mechanisms that would decrease insulin production may not be sufficient to create this balance, increasing the risk of hypoglycemia. To prevent hypoglycemia, extra BG checks may be required before, during, and after exercise. Some medications act in a way that risk of hypoglycemia is minimal. People taking these medications should do routine BG checks as directed by their health care provider, but they do not typically need to do additional checks with changes in activity. Since BG testing supplies are costly, and checking can be inconvenient and painful, it is important for PTs to know which medication(s) a person is taking and if there is a need for additional BG checks.

People with diabetes frequently take many other medications for co-morbidities including hypertension and dyslipidemia, as well as for complications of diabetes (including neuropathy, nephropathy and end-stage renal disease, retinopathy, and cardiovascular disease). Controlling blood pressure, blood lipids, and other preventative care measures can reduce the risk and progression of micro- and macrovascular complications in those with diabetes. Though these medications are beyond the scope of this article, they must be considered when working with a person with diabetes. Also, many medications may effect the action of diabetes medications. Physical therapists should be aware of changes in symptoms following initiation or adjustment of other medications.

ORAL MEDICATIONS

There are several oral medications approved for the treatment of type 2 diabetes. It is important for PTs to understand the mechanism of action for these medications. Of greatest immediate concern are those that increase insulin production, since they have the greatest potential to cause hypoglycemia. All oral

medications have a risk of other adverse effects that will be briefly reviewed. Oral medications are summarized in Table 1.

Insulin Secretagogues

Sulfonylureas

The sulfonylureas stimulate insulin release from the pancreas. When a person takes a sulfonylurea, there is a risk of hypoglycemia; therefore, BG should be monitored before, possibly during, and after exercise. This is especially important if a person has had episodes of hypoglycemia or the increase in activity is novel. The sulfonylureas are classified as first-generation and second-generation. Due to increased potency and decreased side effects of second-generation sulfonylureas, first-generation sulfonylureas are rarely used. The sulfonylureas are listed in Table 1. Some sulfonylureas are available in combination with other medications (listed in Table 2). Another possible adverse effect of sulfonylurea use is weight gain.[3-5] When exploring options for BG management, this is an important consideration, since many people with type 2 diabetes are overweight, and weight loss can improve long term control of diabetes and the person's overall health.

Meglitinides

The meglitinide analogues, also called nonsulfonylurea-secretagogues, also stimulate insulin secretion. They have a more rapid onset and shorter duration of action than the sulfonylureas. Though there is a risk of hypoglycemia with these medications, it is less than with sulfonylurea use.[6] Repaglinide and nateglinide are the currently available meglitinides. They are taken just prior to meals and are particularly useful for those individuals with an irregular mealtime schedule. A person taking meglitinides can choose to decrease or eliminate a dose prior to a meal if they plan to exercise shortly after the meal, decreasing the risk of activity-related hypoglycemia.

Insulin Sensitizers

There are oral agents available, including biguanides and thiazolidinediones, that have a main effect of increasing the sensitivity of target organs to insulin.

Biguanides

Metformin hydrochloride is the only drug in this class available for prescription in the United States. Metformin inhibits the production of glucose by the liver and improves glucose uptake by other tissues, notably skeletal muscle.[7] Metformin is also commonly prescribed for individuals with prediabetes, because it has been shown to reduce the onset in those at high risk of developing type 2 diabetes by 31%.[8] A very rare, but potentially fatal, adverse effect of metformin is lactic acidosis.[9] Patients who have renal impairment are at increased risk for lactic acidosis and should not be using metformin for BG management.[10] Physical therapists should be aware that lactic acidosis is often preceded by abdominal discomfort and diarrhea producing dehydration.[11] Cardiac failure, chronic hepatic dysfunction, and pulmonary disease are also considered contraindications to metformin use.[11]

Thiazolidinediones

The thiazolidinediones (TZDs), also called glitazones, increase insulin sensitivity and glucose uptake in the tissues.[3] A secondary effect of the TZDs is a reduction in hepatic glucose production.[4] There are two drugs currently available in this class, rosiglitazone maleate and pioglitazone hydrochloride. Troglitazone, which is also in this class, was withdrawn from the market in the United States after it was found to be associated with an increased rate of hepatotoxicity.[12] The US Food and Drug Administration (FDA) is placing restrictions on prescribing and availability of rosiglitazone due to evidence of elevated risk of myocardial infarction in patients treated with this medication. Patients will need to be enrolled in a special program to receive the drug, and health care providers are only to prescribe to patients who are already being successfully treated with rosiglitizone and whose BG cannot be controlled with other medications and do not want to be on pioglitazone.[13] The incidence of hypoglycemia with these drugs is negligible.[14] The most common adverse effects with TZD use are weight gain, fluid retention, pedal edema, and new-onset or worsening heart failure.[7] Another possible adverse effect that has been reported is an increase in fractures in older men and women.[15,16] Use of TZDs should be taken into account when evaluating a person's risk of osteoporosis or fracture.

Alpha-Glucosidase Inhibitors

There are two oral medications available in the alpha-glucosidase inhibitor category; miglitol and acarbose. These medications decrease the normal elevation in post-prandial BG by inhibiting the break down of complex carbohydrates into simple carbohydrates that can be absorbed into the blood.[12] Common side effects include diarrhea, flatulence, and abdominal pain. Since these medications act in the gastrointestinal tract, risk of hypoglycemia is negligible. If a person is also taking a sulfonylurea and experiences hypoglycemia, treatment should consist of ingestion of dextrose or glucose, since absorption of other carbohydrates will be delayed by the alpha-glucosidase inhibitor.[17]

Peptide Analogs

There are 2 categories of peptide analogs, amylin analogs and incretin mimetics, including glucagon-like peptide-1 (GLP-1) and dipeptidyl peptidase-4 (DPP-4) inhibitors. The DPP-4 inhibitors, which are oral medications, will be described in this section. Amylin and GLP-1 will be discussed in the section on injectable medications.

Dipeptidyl-peptidase 4 inhibitors

The DPP-4 inhibitors are approved for the treatment for those with type 2 diabetes. There are currently 3 drugs in the United States in this class; sitagliptin, saxagliptin, and linagliptin. The DPP-4 enzyme degrades hormones in the small intestine in response to the ingestion of carbohydrates. The action of these drugs is to inhibit the effects of the DPP-4 enzyme.[18]

Combination Therapy

Many people with type 2 diabetes require more than one medication to meet BG goals. Multiple medications, or one of several combination medications, may be prescribed.[3] This must be considered during rehabilitation of a person with diabetes. Oral medications which are currently available in the United States as a combination medication are presented in Table 2.

INJECTED AGENTS

Since type 2 diabetes is a progressive disease, many people require insulin for BG control. Insulin may be used alone

Table 1. Oral Glucose-Lowering Agents

Drug Class	Action	Generic name	Trade name(s), generic	Comments
Sulfonylureas	Stimulate insulin release from beta cells	Tolbutamide	Orinase*, generics	Risk of hypoglycemia, gastric distress, and weight gain; is a first-generation, short half-life, kidney impairment may require a decreased dose; can be taken in divided doses to improve GI tolerance
		Tolazamide	Tolinase*, generics	Risk of hypoglycemia, gastric distress, and weight gain; is a first-generation, absorbed more slowly than other sulfonylureas, kidney impairment may require a decreased dose; doses over 500 mg/day should be given in divided doses
		Chlorpropamide	Diabinese*, generics	Risk of hypoglycemia, nausea, and weight gain; is a first-generation, longest duration of action of first-generation sulfonylureas; to be avoided in older adults; kidney impairment may require a decreased dose
		Glyburide	Diaβeta*, Micronase*, Glynase Prestabs*, generics	Risk of hypoglycemia and weight gain; is a second-generation; kidney impairment may require a decreased dose
		Glipizide	Glucotrol*, Glucotrol XL*, generics	Risk of hypoglycemia and weight gain; is a second-generation with the shortest half-life; kidney impairment may require a decreased dose; taken 30 minutes before meals
		Glimepiride	Amaryl*, generics	Risk of hypoglycemia and weight gain; is a second-generation; kidney impairment may require a decreased dose
Meglitinides (Nonsulfonylurea-secretagogues)	Stimulate insulin release from beta cells	Repaglinide	Prandin*	Risk of hypoglycemia and weight gain; precaution with poor kidney and hepatic function
		Nateglinide	Starlix*	
Biguanides	Inhibit hepatic glucose output and increases glucose uptake	Metformin	Glucophage*, generics	Contraindicated in those with poor kidney function; caution with congestive heart failure, liver disease, and alcohol abuse; side effects of diarrhea during first 7-10 days of use and nausea; risk of lactic acidosis (rare)
		Metformin extended release	Glucophage XR*	
Thiazolidinediones (Glitazones, TZDs)	Enhance insulin sensitivity at skeletal muscle, adipose tissue, and liver	Pioglitizone	Actos*	Risk of edema and weight gain; precaution with hepatic impairment, may cause or exacerbate heart failure; monitor for symptoms of heart failure (rapid weight gain, dyspnea, edema, etc.) and liver function tests; increased risk of fracture
		Rosiglitazone	Avandia*	Risk of edema and weight gain; precaution with hepatic impairment, may cause or exacerbate heart failure; monitor for symptoms of heart failure (rapid weight gain, dyspnea, edema, etc.) and liver function tests; increased risk of fracture; will have restricted availability due to increased risk of myocardial infarction
Alpha-glucosidase Inhibitors	Delay carbohydrate absorption from the intestines	Acarbose	Precose*	Dose-related diarrhea, abdominal pain, flatulence; must use oral glucose if hypoglycemia occurs since carbohydrate absorption is delayed
		Miglitol	Glyset*	
Incretins	Similar effects to glucagon-like peptide (GLP-1)	Exenatide	Byetta*	Precautions with gastroparesis and hypoglycemic unawareness; weight-friendly
		Liraglutide	Victoza*	
Amylin analog	Similar to amylin	Pramlintide	Symlin*	Approved for treatment of type 1 and type 2 diabetes; precautions with gastroparesis and hypoglycemic unawareness; weight-friendly
Dipeptidyl peptidase IV (DPP-IV) inhibitors	Restore GLP-1 levels; inhibition of enzymatic degradation of glucagon-like peptide-1 (GLP-1)	Sitagliptin	Januvia*	Side effects may not yet be known
		Saxagliptin	Onglyza™	
		Linagliptin	Tradjenta*	

Table 2. Combination Oral Glucose-Lowering Agents

Trade Name	Individual Medications	Relative Risk of Hypoglycemia
Glucovance*	glyburide-metformin	High
Metaglip*	glipizide-metformin	High
*Avandaryl**	rosiglitazone-glimepiride	High
*Avandamet***	rosiglitazone-metformin	Low
Actoplus Met™	pioglitazone-metformin	Low
Janumet™	sitagliptin-metformin	Low
Kombiglyze™ XR	saxagliptin-metformin	Low

*See note on prescribing restrictions for rosiglitazone which also apply to these combination medications.

or in combination with oral medications. People with type 1 diabetes must take insulin to survive. There are also other injectable medications, in the peptide analog category, that are approved for the treatment of diabetes.

Insulin

Insulin is secreted from the beta cells of the pancreas. There is a continuous low level of insulin secretion, the basal level, and an increase in secretion, as a bolus, in response to various stimuli. The increase in secretion may be due to an increase in BG level following ingestion of carbohydrate, from some amino acids, the incretin hormones, and vagal stimulation.[12] Insulin acts at the liver, muscle, and adipose cells to allow storage of glucose or fat.

Insulin, to be taken exogenously, is produced through recombinant DNA, and is currently available in 4 types in the United States, categorized by timing of activity onset (listed in Table 3). Rapid-acting is used just prior to a meal to manage the carbohydrates of that meal, typically resulting in a response most similar to physiological insulin. This is the most common insulin used in insulin pumps, or continuous subcutaneous insulin infusion (CSII). Short-acting, or regular, insulin has a slower onset than rapid-acting, and does not as closely match physiological insulin activity, resulting in an increased frequency of hypoglycemia.[12] There is one available form of intermediate-acting insulin, neutral protamine Hagedorn (NPH) insulin. It is highly variable in its onset and duration of action. It is most often given in combination with a rapid- or short-acting insulin. There are two long-acting insulin preparations, insulin glargine and insulin detemir, both without a notable peak in their activity.[12] Long-acting insulin, injected 1 or 2 times per day, acts most similarly to physiological basal insulin. Insulin is also available in pre-mixed combinations (also listed in Table 3).

The goal of insulin therapy is to mimic the insulin production of the healthy pancreas--a low, basal level of insulin secretion, with periodic spikes in response to certain stimuli. This is commonly achieved through one to two injections of long-acting insulin and a bolus injection of rapid-acting insulin just prior to ingestion of a meal. A person may initiate insulin as part of their treatment regime with an intermediate-acting or long-acting insulin at night or a dose of long-acting insulin in the morning.[3] If further changes are required to achieve BG goals, injections of rapid-acting insulin can be added prior to the meal(s) after which blood glucose is elevated.[3] Combination insulins may be more convenient to individuals, since they decrease the required number of injections; however, there may be an increased risk of hypoglycemia if a meal is not ingested when NPH insulin action begins.

Insulin can be administered with a syringe, an insulin "pen," or an insulin pump. Insulin treatment is most likely to cause hypoglycemia in those with type 2 diabetes. Up to 25% of patients with type 2 diabetes treated with insulin for more than 5 years have experienced at least one episode of severe hypoglycemia.[14] Milder episodes of hypoglycemia can cause overeating, resulting in weight gain.

An increase in exercise or physical activity can increase the risk of hypoglycemia. People using insulin for BG management may need to do extra BG checks prior to, during, or after performing exercise.[19] If a person is at risk of exercise-related hypoglycemia, they may decrease the dose of insulin that is taken prior to a planned exercise session. If exercise or physical activity is planned and BG is below 100 mg/dl (variable based on individual experience), extra fast-acting carbohydrate should be ingested. Fast-acting glucose (ie, orange juice, sugar packets, skim milk, glucose tablets) should always be available during exercise.[19]

Incretin Mimetics

Exenatide and Liraglutide are synthetic analogs of the incretin hormone GLP-1, administered by subcutaneous injection, for treatment of type 2 diabetes. They slow gastric emptying, stimulate insulin secretion, inhibit glucagon release, and decrease appetite. These medications may produce weight loss, a possible benefit to an individual with type 2 diabetes. Exenatide is typically used in addition to metformin, a sulfonylurea, or a TZD, when satisfactory BG control is not achieved with one of these agents. The risk of mild to moderate hypoglycemia with these medications is low, but increases when exenatide is added to a sulfonylurea.[20]

Amylin Analog
Pramlintide

Pramlintide is an analog of the pancreatic hormone amylin, produced from the beta cells. Amylin, has effects similar to those of the incretin hormones, slowing gastric emptying, decreasing post-prandial glucagon secretion, and promoting satiety.[21] It is administered by subcutaneous injection before a meal and is approved for use as an adjunct to insulin to lower post-prandial glucose in individuals with either type 1 or type 2 diabetes.[12] Pramlintide does not promote weight gain or produces a small weight loss.[3] Use of pramlintide combined with insulin can increase the risk of hypoglycemia.[20]

In summary, there are many treatment options for individuals with diabe-

Table 3. Insulins with Timing of Actions

Category of Insulin by Timing of Action	Brand name (generic)	Timing of Onset	Timing of Peak Action	Duration of Action	Comments
Rapid-acting	Humalog® (lispro)	5-15 min	30-90 min	<5 hr	Little variability in absorption; used in continuous subcutaneous insulin infusion
	Novolog® (aspart)				
	Apidra® (glulisine)				
Short-acting	Humulin® R (regular)	30-60 min	2-3 hr	5-8 hr	Duration and intensity of action are dose-dependent; IV administration
	Novolin® R (regular)				
Intermediate-acting	Humulin® N (NPH)	2-4 hr	4-10 hr	10-16 hr	Duration and intensity are dose-dependent; highly variable absorption
	Novolin® N (NPH)				
Long-acting	Lantus® (glargine)	2-4 hr	No peak	20-24 hr	"Peakless;" should not be mixed in the syringe with other insulins
	Levemir® (detemir)	3-8 hr	No peak	5.7-23.2 hr	Dose-dependent onset
Fixed Combinations	Humulin®70/30	30-60 min	Dual	10-16 hr	70% NPH and 30% regular
	Novolin® 70/30	30-60 min	Dual	10-16 hr	70% NPH and 30% regular
	Humulin® 50/50	5-15 min	Dual	10-16 hr	50% NPH and 50% regular
	Humalog® Mix 75/25	5-15 min	Dual	10-16 hr	75% NPL and 25% lispro
	Novolog® Mix 70/30	5-15 min	Dual	10-16 hr	70% NPA and 30% aspart

NPL=NPH combined with lispro, NPA=NPH combined with aspart

tes. Exercise and a healthy diet, along with medications and blood glucose checks, remain the cornerstone of treatment, likely with the goal of weight control for those with type 2 diabetes. Older individuals have special needs; therefore, treatment goals and interventions should be individualized. When working with a person with diabetes, general health, minimizing acute and chronic complications and the impact of co-morbidities, and safety with regard to medications should be considered throughout PT interventions.

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Pharmacology & the Aging Adult
(continued from page 8)

therapy, since polypharmacy may hinder progress towards the goals of PT intervention. For example, a patient who is lethargic due to his or her medications will be unable to exercise optimally, and therefore will not get strong enough to live a life of independence. By working as part of the interdisciplinary health team, the physical therapist can help recognize the need for changes in medication to achieve more successful outcomes for patients.

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DRUG MANAGEMENT IN THE ELDERLY: PREVENTING MISMANAGEMENT, AVOIDING RISKY PRESCRIPTIONS, AND DIMINISHING THE ADVERSE EFFECTS OF POLYPHARMACY

Jennifer M. Bottomley, PT, MS, PhD

Last Wednesday, on a home visit, the Physical Therapist observed that her 82-year-old female patient seemed disoriented and showed signs of dehydration and respiratory distress. Her respiratory rate was rapid, shallow, and laborious. The Physical Therapist called the physician to discuss her assessment and… This 82-year-old Massachusetts woman wound up in the hospital after a particularly bad asthma attack. She'd quit using her inhaler, since it made her nauseated. While in the hospital she was given powerful steroids to treat her asthma. These raised her blood pressure. So she was given an antihypertensive drug. It made her dizzy. When her ankles swelled, she was prescribed a diuretic to reduce water retention. But that dropped her potassium level. Naturally, potassium supplements were added. She was also given an osteoporosis drug. This made her stomach bleed…

The geriatric specialist in physical therapy, who understands the functional, cognitive, physical, and neuromuscular influences of the many medications our elderly patients are prescribed or purchase over-the-counter, should play an active role in drug management. Communication with the physician, pharmacist, nurse practitioner, or other case manager could potentially prevent drug mismanagement, alert the "non-geriatric" clinician to the prescription of risky drugs, and diminish the preventable complications of adverse effects of drug-to-drug interactions. Additionally, the physical therapist can play a role in patient education in the proper management and dosage schedule that may eliminate undesirable complications experienced by patients like the 82-year-old Massachusetts grandmother described above. Team management could lead to a new trend. That is, rather than overmedicating older adults---working to reduce the number of prescription and over the counter drugs that our patients take to the very minimum necessary to manage conditions that can't be managed through diet, hydration, and exercise.

Ten to 20% of adults over the age of 65 who go to the hospital do so because of prescription medicines that have been taken improperly. One in 3 elderly hospital patients becomes sicker during hospitalization because of prescription drugs. Drugs prescribed are often considered risky drugs for older individuals due to the adverse effects created by poorer or slower metabolism, utilization and elimination of drugs in an aged system. Over-the-counter medications and herbal substances used for self-management of pain and other symptoms frequently create unfavorable reactions when taken concomitantly with prescribed drugs. Thirty to 50% of prescriptions written for older adults are taken improperly. Up to 140,000 seniors die each year because of problems with medications.[1] This is not only financially costly, but costly in terms of morbidity and mortality in our older patients.

If we are trying the buffer and protect Medicare's solvency for future generations, wouldn't it seem wise to look towards a preventative approach in drug management of elderly people in the U.S. – including the elimination of harmful drugs that affect functional independence and mar the quality of life? Pointless expenses are incurred by overmedicating the elderly and then paying for further medications to counteract the ill-effects of the drugs needed to treat the side effects of the initial drugs. This can get very expensive. News of this kind of needless expenditure should make people sit up and take notice. So the fact that *$200 billion is spent every year to pay for complications resulting from prescribed medicines*[2] should bring us to full consciousness. It is important to increase awareness that prescriptions for the elderly often do more harm than good, and that less, not more, should be our goal.

POLYPHARMACY

Medicines save lives, but few are completely free of risks or side effects. The more drugs that are taken together, the greater the risk for side effects and interactions. The Massachusetts grandmother's troubled relationship with her medications is far from unique. In fact, it's common enough that experts have even given the phenomenon the requisite medical label that confers official status in the medical world: *polypharmacy*.

Polypharmacy, traditionally defined as the use of two or more drugs, is now more frequently described as the use of a medication for which no clear indication exists.[3] There is a distinction between *rational polypharmacy* (drug prescription following clinical indications and best practice) and *irrational polypharmacy* (inappropriate drug prescribing, using more than one drug from the same class, prescribing drugs with similar pharmacologic action to treat different conditions, involvement of multiple providers, and self medication). The term describes cases in which patients are prescribed many different medications, often by different doctors, for a succession of conditions or for side effects created by other medications. Polypharmacy exists when the conditions can be effectively treated with fewer medications or through diet, hydration, and/or exercise. One third of polypharmacy involves self-medication with over-the-counter and herbal drugs, most commonly acetaminophen, ibuprofen, and aspirin.[4] Fifty-four percent of older patients add medications like

laxatives or tranquilizers to their prescribing regimen without health provider consultation.[5] Polypharmacy is more commonly seen in older people, who tend to have more chronic conditions that call for drug treatment.

RISKY DRUGS

Many Americans over the age of 65 hold prescriptions for drugs considered potentially risky for elderly patients, according to a new study by Duke University Medical Center researchers. The finding emphasizes a need for greater awareness among physicians and other health care providers, about the risks presented by commonly prescribed medications as people age and for additional measures to monitor prescription drug use. The Duke researchers found that over the course of a year, one in 5 elderly Americans, whose benefits were processed by one of the largest pharmaceutical benefits managers in the U.S., filled a prescription for at least one drug classified as a "drug of concern" by the established criteria known as the Beers list. Of those claims, half were for drugs with potential for severe adverse effects in older people, including the anti-depressant amitriptyline (Elavil®, Endep®, Vanatrip®) and anti-anxiety drug diazepam (Valium®).[6]

Older individuals, in general, have a higher disease burden compared with younger adults and are the major users of prescription medications, yet premarketing drug clinical trials---even for drugs that have high utility in this age group---have often excluded them. Extrapolation of clinical results from younger to older individuals does not provide adequate benefit-risk estimation, and the frequent need for dose adjustment in older patients from initially approved doses exemplifies the lack of adequate clinical data about older adults. We need to be aware of this information gap and the need for a better understanding of the effect of aging on drug responses. We also should encourage alternatives for future research and development, urging the implementation of improved clinical trial designs that employ new and emerging pharmacokinetic and pharmacodynamic methods to provide evidence-based and unique treatment to this high drug use group.

The list of criteria for determining the appropriate use of medication in elderly living in nursing homes was developed in 1991 by a team led by Mark Beers at the University of California, Los Angeles, culled from the opinions of a panel of experts. In 1997, Beers updated the original list, initially intended primarily for institutional use, for use in any setting. The list named 48 medications or classes of medications considered inappropriate for use in elderly patients. The panel deemed those medications to have potentially severe adverse outcomes when taken by older people.[5]

Many drugs widely used by elderly people may present special concerns. For instance, diuretics are commonly prescribed to reduce the amount of water in the body, an effect that ultimately reduces the workload of the heart and arteries. These "water pills" increase the flow of urine and are used to treat hypertension, heart failure, and other ailments common to older people, but they can also cause a loss of potassium and other minerals from the body. A potassium deficiency will produce symptoms that range from weakness, listlessness, and a loss of appetite to an irregular heartbeat. Such a deficiency can be resolved by changing the diuretic or reducing the dosage, or by taking a potassium supplement. Although many foods contain potassium, it is difficult to correct a deficiency by diet alone.

Other examples of common classes of drugs that cause adverse effects in elderly adults include anti-hypertensive medications, sedatives, and tranquilizers. Anti-hypertensives often cause the older people who take them to feel depressed, drowsy, or suddenly faint, especially upon standing. Among sedatives, barbiturates are particularly risky, because they can cause severe mental confusion or even psychosis if taken to excess. Benzodiazepine tranquilizers, taken to ease the nervousness and stress of everyday life, may also cause drowsiness, shakiness, and confusion in older people. If it is necessary for an older person to take a tranquilizer, the physician needs to choose the drug carefully and probably prescribe a dosage that is lower than what is normally indicated for a younger person.

Another drug class that is commonly prescribed to older adults, with known adverse effects, is digitalis. These drugs, prescribed to improve the strength and efficiency of the heart, can also result in toxicity, causing excessive fatigue, loss of appetite, vision problems, and psychological disturbances. These symptoms occur in the elderly because they are commonly given digitalis for long periods, and they do not eliminate the drug as readily as younger persons. To avoid toxicity, older people may need to take lower doses of digitalis.

ADVERSE DRUG REACTIONS

Adverse reactions to medications represent one of the number one health problems facing the elderly today, and are a problem that we can help address. Older adults often see multiple physicians and other health care professionals who prescribe drugs without comparing notes with each other. The older adult may also go to several different pharmacies to fill prescriptions. The result of this situation is that there is no one health care provider, physician, or pharmacist who can serve as a gatekeeper for all prescriptions. A pharmacy computer will flag many potential prescription drug interactions, but it can't catch all potential problems if the patient fills prescriptions at different drugstores or has an unusual reaction. Moreover, computers can't address the complexity of interactions among 6 or more different drugs.

Physical therapists in all settings can assess for polypharmacy and help prevent adverse drug reactions. A PT or other coordinating health care provider can conduct an annual "brown bag visit," to which a patient brings all of his or her prescriptions, over-the-counter medications, vitamins, and herbal supplements for itemization. The health care provider can then identify any expired medications, look for potential drug interactions and non-compatible drugs, and determine if an individual is taking the medications as prescribed and/or if he or she is receiving unnecessary drugs. A "brown bag visit" offers an important opportunity to provide the referring physician with a complete list of all drugs a patient takes, so that polypharmacy may be evaluated, addressed, and prevented.[7]

Overmedication problems can't be blamed solely on physicians. Patients often think that they haven't received treatment for a condition if they haven't received a prescription. This is a cultural issue. Every culture has healers. There are expectations of those healers. We expect a healing magic that takes physical form. In our culture the magic takes the form

of prescription drugs, rather than diet or exercise, which could potentially eliminate the need for many drugs.

The fact that most clinical research is conducted on subjects under the age of 65, and such research provides limited evidence for what is or is not beneficial to older people, also creates a problem, as previously noted. The most accepted treatments for older adults are based on past practice, rather than on scientific findings.

"Natural" medications, such as herbal and dietary supplements, are not solutions to the problems created by too many medications and pills. These natural remedies are not regulated by the FDA. The good news is that there are typically fewer side effects from herbal treatments. The bad news is that many herbal supplements will interact negatively with prescription drugs by interfering with absorption, accelerating the effects of a prescription drug, or decreasing a drugs' effectiveness. For instance, combining ginkgo biloba, an herbal product promoted to improve memory, with blood-thinning drugs like aspirin or warfarin, can lead to severe bleeding. Further, many natural pharmaceuticals have not been tested to determine whether they actually do what they say they do. Dietary supplements are often considered "safe" and "natural." However these supplements can also impact the effectiveness of prescription medications. Conversely, prescription drugs may interfere with the absorption, metabolism, and excretion of nutrient supplements.

Some of the most dangerous drug-drug reactions occur when patients take over-the-counter medicines along with their prescription drugs. For instance, nonsteroidal anti-inflammatory agents like ibuprofen can cause bleeding ulcers when taken with more powerful prescription painkillers. As with herbal and dietary supplements, people often assume that over-the-counter and drugs and supplements are safe, and forget to tell their physicians about them.

Of course, prescription drugs also interact with each other. The antibiotic erythromycin, for example, can lead to a toxic reaction when combined with certain cholesterol-lowering drugs, potentially leading to kidney failure. According to some estimates, as many as one-fourth of all nursing home admissions, and an even higher percentage of hospitalizations among older adults, may be due to "preventable drug therapy failures," resulting from adverse reactions or interactions, noncompliance, or use of medications inappropriate to the patient's condition.[1]

"DRUG FREE" MANAGEMENT

Drug free management doesn't mean omitting ALL drugs in the management of an elderly person. Rather, this concept is directed at treating an older adult with the fewest number of drugs possible, eliminating drugs that impact function and cognition, and looking at more holistic interventions, such as exercise, hydration, and diet.

By looking carefully at what medicines older adults are taking, and for what conditions, it may be determined that there are better alternatives. Sometimes a newer drug with multiple actions can be substituted for two or more older drugs. Or a medicine that causes a bad side effect can be exchanged for one that doesn't, so the patient no longer needs another drug to treat the side effect.

Research on "drug-free" management in the elderly estimates that the number of drugs could be cut by 50% and result in fewer drug-related complications. The therapeutic effectiveness of drugs changes as time goes on. A person may continue to take medication at a dosage that seems to be effective, when titration may reveal that they continue to feel fine at a lower dosage, or even when eliminating the drug entirely.[6]

COST OVERDOSE

Prescription drugs are the fastest growing component of health care spending for Medicare. In fact, prescription drug expenditures are increasing faster than any other health care service under Medicare. The burden of these rising costs falls most heavily on the elders, who do not have Part D or other insurance coverage for prescription drugs, particularly Medicare beneficiaries, who rely more heavily on drugs. Here are the most recent financial facts[8]:

- By 2010, annual per person spending on drugs for the elderly was $2,810/year, an increase of 133% over spending in 2000.
- A 76% increase in overall health care spending in the elderly occurred between 2000 and 2010.
- Over an 18-year period, 1992 to 2010, prescription drug spending per older adult grew 403%.
- The portion of senior health spending devoted to prescription drugs has grown from 7.4% in 1992 to 13.3% in 2010.

THE STATISTICAL IMPERATIVE

Persons aged 65 and older constitute approximately 13% of the US population, but they take about one-third of all prescribed drugs. The typical senior citizen regularly takes 6 to 9 prescription drugs, plus a couple of over-the-counter preparations. Nursing home residents typically take more. The number of drugs prescribed to older adults continues to increase worldwide.[9] Medication prescription is the most frequent therapeutic intervention offered, with 75% of older adults leaving a physician's office with an order for a medication.[10]

Prescription drug usage by Medicare beneficiaries has drastically changed.[11] The latest facts reveal:

- The average number of prescriptions per elderly person grew from 19.6 in 1992 to 28.5 in 2010 (an increase of 45%).[8]
- The average number of prescriptions per elderly person grew to 38.5 in 2010, an annual increase of 10 prescriptions over the course of a year, or 35% per senior since 2000.
- The average number of prescriptions per senior grew by 96% from 1992 to 2010.[8]
- Overall total number of prescriptions for seniors grew from 648 million in 1992 to over 1 billion in 2000 to 1.6 billion in 2010.[8,11]

Statistically, a person taking 6 different drugs has an 80% chance of at least one drug-drug interaction. With 8 drugs, the chance is 100%. There is no magic number of pills that constitutes polypharmacy, but if a patient senses a decline in functional ability since the addition of a medication, the drug regimen should be evaluated. Advocates of reducing medications are not suggesting that people abruptly stop taking prescribed medications or attempt to adjust drug regimens themselves. Proper adjustments require the efforts of a physician and pharmacist working together.

THE PHARMACIST AS A GATE KEEPER

The solution may lie in a group of professionals who specialize in drug therapy: pharmacists. In a new program in geriatric

pharmaco-therapy at Harvard University in Boston, pharmacists are trained to work with older patients to improve their drug regimens by prescribing the least number of medications possible for adequate medical management. Clinically, these efforts reflect a movement toward positioning pharmacology as a cost-effective player in today's health care market. At least two organizations representing pharmacists--the American Pharmaceutical Association and the American Society of Consultant Pharmacists--have been lobbying for the inclusion of medication management services by pharmacists in any outpatient drug benefit that is part of a new Medicare reform package. Pharmacists can provide an important service. Clinical pharmacists certainly do have many skills to bring to the table. The Medicare reimbursement is so low that doctors don't have the incentive to work with the elderly on the management of their drug regimes. Pharmacists could alert the physician about potential problems and make recommendations. The pharmacist could become an elder's drug advocate.

The universal adoption of such services by pharmacists nationwide would not only dramatically improve quality of life among seniors, but would save billions of dollars in health care costs. The positive outcomes could save more than the total costs of the drugs themselves. When you look at the whole picture of an individual's health care costs, in terms of unscheduled doctor visits, emergency room visits, and hospitalizations, the costs are much lower with pharmaceutical therapy management than without it.

The policy problem is that, with a few exceptions, pharmacists don't get paid anything extra for such services. Insurance companies typically reimburse pharmacies for dispensing, but not for clinical or administrative services. Although pharmacists routinely answer customers' questions about medications as part of their jobs, in-depth consultations may be difficult to schedule in busy drugstores where the dispensing volume is high.

Assessment of drug prescribing practices has been on-going at the Peter Lamy Center on Drug Therapy and Aging at the University of Massachusetts School of Pharmacy in Boston. The findings of these studies note that very little research has been done on the financial impact of programs aimed at improving drug therapy in the elderly, and that it is impossible to eliminate all drug reaction and interaction problems. Moreover, the savings from eliminating inappropriate drugs must be balanced against the cost of therapies that replace them.[12]

For the Massachusetts grandmother, the cost savings were obvious. Her monthly drug bill dropped from about $250 to $60, after the pharmacist helped pare her daily regimen to just two asthma inhalers, a diuretic, and a new blood pressure drug that doesn't make her dizzy. Instead of taking potassium pills, "Now I just eat bananas." But that extra $190 a month is minuscule compared with what was saved by keeping her out of a nursing home. Now she is self-sufficient. "I clean, I shop, I do everything," she says. "I feel as well as before the hospital, maybe better." This is the ideal in drug management.

CONCLUSION

What is important in every case is for both the elder and the health care professional to be vigilant so that the cure doesn't become worse than the disease. It was the physical therapist who alerted the physician to problems observed in our 82-year-old Massachusetts grandmother. Her initial problem was due to the mismanagement of her medication, and subsequent problems were from side effects of drugs prescribed to treat acute conditions. In this case, thanks to the physical therapist, this woman's mismanagement of her prescription and subsequent overmedication and adverse effects were addressed properly, reducing the number of drugs to the very minimum, saving money, and improving overall quality of life in an 82 year old who may have otherwise required nursing home placement. Physical therapists working with older people are in an ideal spot for determining whether medications are impacting function or cognition, or creating negative side effects that lead to safety issues and affect the quality of life.

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PHARMACOLOGIC PROFILE AS A FALL RISK FACTOR

Rebecca Galloway, PT, MPT, GCS

INTRODUCTION

An estimated one out of three community-dwelling older adults falls each year. In a US survey, 16% of persons aged 65 years and older reported at least one fall in the previous 3 months.[1] Fall-related injury, defined as subsequent limitation of regular activity or a visit to a doctor, occurred for 31% of fallers.[1] Clinical guidelines for fall prevention include screening all older adults for acute or recurrent fall history and difficulty with walking or balance. A positive fall risk screen indicates the need for further multifactorial fall risk assessment and interventions to address identified risk factors.[2] Fall risk assessment and prevention is often complicated by co-existence of risk factors in various categories: gait/mobility/balance, strength, footwear, environment, medications, vision, orthostatic hypotension, cardiac or neurological impairments.[2,3] Given the high prevalence (84% – 90%) of prescription drug use among older adults,[4] consideration of a patient's pharmacological profile is an essential component of every fall risk assessment. The purpose of this review is to examine available evidence and strategies for medication review as a component of fall risk assessment.

Variations in response to medications are common among older adults,[5] which is a challenge for appropriate medication administration. In general, physiological changes with aging are associated with slower drug absorption, metabolism, and excretion.[5-8] Thus activity of drug metabolites and adverse effects are prolonged in older adults. Medication-related fall risk is higher for drugs with half-lives greater than 24 hours.[6] Polypharmacy is also a significant consideration with this population, with more medications causing an increased risk of drug-drug interactions and poor adherence to the medication regimen.

MEDICATIONS ASSOCIATED WITH FALL RISK

Certain medications can be directly linked to falls or interact with other factors to increase overall fall risk. Appendix 1 shows estimated fall risks for medication classes included in meta-analyses and large sample multi-site studies.[9-13] Any medication that causes an adverse effect of impaired mobility or balance, drowsiness, delirium, dizziness, orthostatic hypotension, incontinence, or weakness amplifies fall risk.[6] Medications that act on the central nervous system have adverse effects including unsteadiness, dizziness, sedation, increased postural sway, and overall impaired functional ability.[6,14] Cardiovascular drugs may cause orthostatic hypotension, vasovagal syndrome, carotid sinus hypersensitivity, or arrhythmias resulting in lightheadedness and/or unsteadiness.[7]

Other drug classes not directly linked to falls may have an important impact on overall fall risk for an individual. For example, prolonged use of glucocorticoids is associated with catabolic effects on the musculoskeletal system,[5] which may contribute to higher risk of falls and related injuries. Muscle relaxants have adverse effects of weakness and sedation with questionable benefit versus risk in many older adults.[15] Vestibular suppressants such as meclizine can exacerbate balance problems when inappropriately prescribed for benign paroxysmal positional vertigo.[16]

Medication Quantities, Dosages, and Timing

The association between falls and specific central nervous system (CNS) drug regimens is an emerging area of investigation. A longitudinal study of 3,055 community-dwelling older adults found an increased risk of recurrent (≥ 2) falls associated CNS medications.[14] The CNS medication classes included opioid analgesics, antidepressants, antipsychotics, and benzodiazepines.[14] Risk of recurrent falls was higher for use of two or more CNS drugs (adjusted OR = 1.95; 95% CI 1.35 – 2.81) compared to use of only one CNS drug (adjusted OR = 1.55; 95% CI 1.22 – 1.97).[14] Recurrent fall risk also progressively increased for low, moderate, and high categories of standard daily doses.[14] Thus quantity and dosage of CNS medications exhibited dose-response relationships with fall risk. Change in CNS medications (ie, start new medication, discontinue medication, dose change) has also been associated with elevated fall risk (OR = 3.4; 95% CI 1.2 – 9.5) for the timeframe of one to 3 days from the change among a sample of nursing home residents.[17]

Confounding Risk Factors

Indications for taking new medications may conflict with their potential adverse effects on fall risk. This concept of "confounding by indication" applied to falls occurs with administration of "a medication for a specific illness that itself can increase the risk of falls."[18] For example, a study of 34,163 nursing home residents found a significant association between insomnia and falls (adjusted OR = 1.52; 95% CI 1.38 – 1.66), but not between hypnotics and falls (adjusted OR = 1.13; 95% CI 0.98 – 1.30).[12]

Complementary and Alternative Medications

Standards for "dietary supplements," defined in the Dietary Supplement Health and Education Act (DSHEA), are not as stringent as the requirements for prescription or over-the-counter medications.[19-21] "Dietary supplements," commonly refers to vitamins, minerals, herbs/botanicals, or amino acids.[19] Although studies have not been conducted to investigate direct relationships between various supplements and falls, several products have the potential to indirectly influence known fall risk factors. Appendix 2 includes dietary supplements that may warrant special

consideration for persons at risk for falls.[20,22,23]

Research Limitations

Most studies examining medications and fall risk have an observational design and inconsistent adjustment for confounding fall risk factors. Additional limitations include disparities between self-report medication use and physician-prescribed medication lists, diverse combinations of medications, and inconsistent operational definitions for falls.[11] Fall risk publications have described at least 30 definitions of falls.[24] The definition of a fall is "an unexpected event in which the participants come to rest on the ground, floor, or lower level" is supported by an international expert consensus panel and the benefit of common use, clarity, and perceived ability of elderly patients to comprehend the vocabulary.[25] Syncope is an adverse effect of certain medications (ie, cardiac drugs) and is inconsistently addressed by inclusion/exclusion criteria for falls definitions. The distinction between presyncope and syncope may not be clear for patient-reported fall scenarios.[7]

PHARMACOLOGICAL INTERVENTIONS

Assessment of fall circumstances (symptoms, frequency, location, activity, time) in the context of a patient's medication regimen (schedule, adherence, dosage, duration of medication use) may reveal pertinent associations. Clinical guidelines for the prevention of falls associated with medication use include:

- The reduction or withdrawal of medications for older adults as medically appropriate.[2,3]
- Conducting trials to determine the lowest effective dose of new medications and discontinuation of any drug that is not clinically effective.[6]
- Tapered (gradual) reduction of medications that cause physical dependence or tolerance, such as benzodiazepines,[5] to minimize withdrawal symptoms.
- Avoiding the misuse of psychotropic medications as chemical restraints for behavior, which negatively impacts functional ability.[6]

Fall risk assessment pre- and post-medication administration, with consideration of peak effect and half-life, and analysis of nonpharmacological interventions, are important determinants of medication appropriateness.

Medication Review

Routine review of the patient's complete medication list is essential to the prevention of adverse polypharmacy sequelae,[5,8] and appropriate adjustments can potentially reduce falls.[2,26] Medication lists should include all prescriptions, over-the-counter drugs, vitamins, minerals, herbs, and any other complementary or alternative products.[21,22] More than half of older adults use 5 or more medications/supplements when all categories are included.[4] Use of alcohol, cigarettes, and caffeine are also important to consider in the pharmacological profile. Patients may need guidance with the definition of a "drug" or "medication" when completing a self-report form.

With a comprehensive medication list and evaluation, a physician can discontinue unnecessary drugs and modify necessary prescriptions to address adverse effects. Clinical tools, such as Beers Criteria, address medication classes of particular concern for older adults.[15] Appendix 1 includes some examples of medications in Beers Criteria.

Vitamin D and falls

Medication review should also include identification of protective factors. One meta-analysis estimated a 22% reduction in risk of falls for older adults randomized to Vitamin D.[27] A Cochrane review only found significant fall rate reduction for a subgroup of participants with lower Vitamin D levels,[26] indicating a need for further studies. Current best practice guidelines include Vitamin D (800 IU) daily supplement "for all older adults at risk for falls."[2]

PT role in medication-related fall risk

Physical therapists (PTs) need to recognize adverse drug effects and be able to distinguish them from disease symptoms. They can help patients understand the importance of adherence to a medication regimen, and empower them to discuss medication concerns. Physical therapists can also provide valuable insight into interdisciplinary fall risk assessment. Examples of fall risk assessment/reassessment strategies with medication-related factors include:

- Observing functional performance and postural reactions before and after a change in central nervous system medications.
- Evaluating vital signs and orthostatic hypotension before and after a change in cardiac medications.
- Using outcome measures before and after nonpharmacological approaches to behavioral management and pain control.

Physical therapists may intuitively schedule intervention sessions when adverse drug effects medications are minimized. However, a comprehensive fall risk assessment should also include a time period during peak effect for medications that influence balance. If observed changes are potentially related to adverse drug effects, then documentation may warrant reference to the medication schedule and discussion with the physician.

Clinical Query: Medications & Fall Risk

1. What symptoms and circumstances are most likely associated with the patient's fall(s)?
2. Are the fall scenarios explained by known risk factors?
3. Is the patient's medication list comprehensive and current?
4. How recently has the patient's medication list been reviewed by a physician?
5. Do the patient and/or caregiver(s) have strategies for documenting falls and medication regimens?

"FALLS FREE" INITIATIVE

The National Action Plan for "Falls Free," developed by the National Council on the Aging, Archston Foundation and Home Safety Council, includes two medication management goals[28]:

"**Goal A**: All older adults will become aware that falling is a common adverse effect of some prescription and nonprescription medications and discuss these effects with their health care provider."[28]

"**Goal B**: Health care providers will be aware that falling is a common adverse effect of some prescription and nonprescription medications, and therefore will adopt a standard of care that balances the benefits and harms of older adult medication use."[28]

Physical therapists who interact with older adults in any clinical setting should address these goals with an interdisciplinary health care team.

Appendix 1. Medication Classes and Associated Fall Risk Estimates

Medication Group **or** ***Class***	**Examples: Generic**	**Odds Ratios (OR)** (95% confidence intervals) *Adjusted for fall risk factors
Psychotropics: • anti-depressants • sedative/hypnotics • neuroleptics/antipsychotics		**1.73 (1.52 – 1.97)[9]** ***1.69 (1.25 – 2.27)[9]**
Anti-depressants	amitriptyline[B] fluoxetine[B]	***1.36 (1.13 – 1.76)[11]** ***1.85 (1.20 – 2.85)[9]** ***2.23 (2.09 – 2.39)[13]**
Sedative-Hypnotics	flurazepam[B] Phenobarbital	**1.47 (1.35 – 1.62)[11]** **1.54 (1.40 – 1.70)[9]** *1.13 (0.98 – 1.30)[12]
Benzodiazepines	diazepam[B] lorazepam[B] oxazepam[B]	**1.57 (1.43 – 1.72)[11]** ***1.41 (1.20 – 1.71)[11]** **1.48 (1.23 – 1.77)[9]**
Neuroleptics/ Antipsychotics	risperidone haloperidol	**+1.66 (1.38 – 2.00)[9]** **1.59 (1.37 – 1.83)[11]** *1.39 (0.94 – 2.00)[11]
Antihypertensives		**1.24 (1.01 – 1.50)[11]**
Diuretics *(Thiazides)*	furosemide (hydrochlorothiazide)	**1.07 (1.01 – 1.14)[11]** *0.99 (0.78 – 1.25)[11] **1.08 (1.02 – 1.16)[10]** ***1.28 (1.16 – 1.42)[13]**
Beta-blockers	metoprolol atenolol	1.01 (0.86 – 1.17)[11] 0.93 (0.77 – 1.11)[10] 0.90 (0.85 – 0.96)[13]
ACE inhibitors	Lisinopril	1.20 (0.92 – 1.58)[10] **1.07 (1.01 – 1.14)[13]**
Calcium Channel Blockers	Amlodipine	0.94 (0.77 – 1.14)[10] 0.98 (0.92 – 1.04)[13]
Nitrates	Nitroglycerin	1.13 (0.95 – 1.36)[10]
Antiarrhythmics (class Ia)	disopyramide[B]	**1.59 (1.02 – 2.48)[10]**
Digoxin	digoxin[B]	**1.22 (1.05 – 1.42)[10]**
Opioid analgesics	propoxyphene[B] *(no longer FDA approved)* meperidine[B]	0.96 (0.78 – 1.18)[11] 0.97 (0.78 – 1.20)[10]
NSAIDs	aspirin indomethacin[B] naproxen[B]	**1.21 (1.01 – 1.44)[11]** 1.16 (0.97 – 1.38)[10]

[B]Indicates a medication included in Beer's Criteria[15], NSAIDs = nonsteroidal anti-inflammatory drugs; ACE = angiotensin-converting enzyme, + Pooled OR for excludes psychiatric inpatients (OR = 0.41, 95% CI = 0.21 – 0.82)

Appendix 2. Dietary Supplements with Special Considerations for Fall Risk

Fall Risk Factors	**Special Considerations**	**Dietary Supplement Examples**
Dizziness	Persons at risk for falls who report dizziness	St. John's wort[20], ginkgo biloba[20], cat's claw[20], grape seed extract[20], hawthorn[20],valerian[20]
Drowsiness	Persons at risk for falls who report drowsiness; can exacerbate effect of sedative medications	kava[20;21], lavender[20],valerian[20-23]
Hypoglycemia	Persons with diabetes who use medications to lower blood sugar	ginseng[20-22], garlic[21;22], ginger[22], milk thistle[20], aloe vera[20]
Digoxin	Digitalis toxicity has fall risk side effects of delirium, weakness, and arrhythmias (*light-headedness/syncope*); drug interactions may interfere with narrow therapeutic range	St. John's wort[20;22], ginseng[22], ephedra[22], calcium[23],hawthorn[22]
Anticoagulants	Persons who take aspirin, heparin, coumadin (Warfarin) or other anticoagulants could be at risk for excessive/prolonged bleeding after falls	garlic[20-22], ginkgo biloba[20-22], ginseng[21;22], vitamin E[21-23]

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POSSIBLE INTERACTIONS BETWEEN EXERCISE AND THE PHARMACODYNAMICS AND PHARMACOKINETICS OF DRUGS

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INTRODUCTION

Exercise and its use in promoting health and well-being is a value deep seated in our profession. Both single bouts of exercise and regular exercise for fitness produce changes in physiological parameters that may interfere with the effectiveness of some drugs. In addition, several drugs are known to affect exercise performance.

Over the past several years, individuals in this country have been prescribed a greater number of prescription drugs. The National Association of Chain Drug Stores (NACDS) reported that in 2006 there were 3.42 billion scripts dispensed totaling $249.8 billion in prescription sales up from $220.1 billion in 2004.[1] Reasons for the rise in sales include an aging population, direct to consumer marketing influencing prescribing patterns, increased drug discovery, and the consumption of a poor diet and sedentary lifestyle leading to greater illness and the need for polypharmacy.[2-4]

With the increase in prescription drug use, it is not surprising to see a jump in adverse drug reactions (ADRs).[5] From 1998 to 2005 the number of serious adverse drug events reported to the FDA increased approximately 2.6 times to 89,842 cases and the number of fatal adverse drug events was reported to be 15,107.[6] Note that these were "reported" cases and probably under represent the true actual number. Additionally, from 2004 to 2008 there was a 52% increase in adverse reactions in the inpatient setting, largely due to use of steroids, anticoagulants, and sedatives.[7] In 2008 alone there were approximately 1.9 million drug related events among inpatients and 838,000 among patients who visited the emergency department and were released. Individuals consuming "High–Alert Medications" such as anticoagulants, sedatives, narcotics, and insulin are at greatest risk for developing serious complications.[8] Whether you treat patients with multiple co-morbidities who maintain a large pill burden, or you invest your time in treating presumably healthy individuals, the statistics cited above highlight the need for therapists to be knowledgeable in pharmacology, particularly drug-exercise interactions. This article will address potential interactions between exercise and pharmacotherapeutics. We stress the term potential since the research in this area is rather sparse. A Pubmed query using the search terms: exercise, pharmacokinetics, absorption, metabolism, excretion, interaction, and exercise performance, for the years between 1978 and May 2011, revealed few studies. Comparisons between articles were difficult to make since some studies used healthy volunteers and others used patients. The mode of exercise was also inconsistent; some reports used resistance exercise and others used aerobic activities. If aerobic exercise was chosen, the intensity and duration varied. Another noted inconsistency was an assumption by the authors that data collected after a single dose study could be equivalent to data sampled at the end of a 6 week training period or after repeated dosing. In addition, we were not always convinced that serum drug testing was performed at a steady state drug level in every study. However despite these limitations in the literature, there are certain assumptions that may be discussed based on the mechanism of action of the drug and its pharmacokinetic properties, and our knowledge of physiologic responses to exercise.

EFFECT OF EXERCISE ON PHARMACOKINETICS

Pharmacokinetics refers to the rate at which a drug is absorbed into the body, how it is distributed, and how quickly it is eliminated either through metabolism or through excretion.[9] Pharmacokinetic principles are used to determine the onset of drug action and the duration of effect, and therefore provide a means to determine a dosing schedule. Thus, any change in pharmacokinetics should result in a corresponding change in either dosing schedule or dose.

There are 4 phases of pharmacokinetics; absorption, distribution, metabolism, and elimination.[10] Each phase may be influenced by a number of factors including dosage form and mode of administration, blood flow to the site of absorption, degree of ionization of the drug compared to the pH of the body compartment, competition for metabolizing enzymes, and the general health of the liver and kidney, which are the prime organs for drug elimination. In addition, exercise and ambient temperature are known to alter the pharmacokinetics of drugs.

Absorption and Exercise

Depending on a drug's mode of administration, absorption into the systemic circulation can take place through the gastrointestinal tract, through subcutaneous or intramuscular tissue, through the dermis, or across the alveolar surface of the lungs.[10] Oral agents are primarily absorbed through the small intestine although there are some exceptions. Some drugs, such as aspirin, are primarily absorbed in the stomach due to their pH and ionization properties. However given the intestine's enormous surface area for drug absorption, drugs that are primarily absorbed in the stomach are still likely to enter the portal circulation from this area as well. Exercise influences oral absorption of drugs, and it has been shown that maximum aerobic exercise

for more than 30 minutes lowers the pH of blood and of the gastric mucosa.[11] For acidic drugs this means a greater proportion of the dose will remain non-ionized, and drug absorption might be increased. The opposite would occur for drugs that are basic in nature.

Exercise affects the rate of absorption of drug through the gastrointestinal tract, and also affects the drug's rate of passage or transit from mouth to rectum. The sympathetic nervous system, which is active during exercise, reduces GI contractility thus delaying transit time.[12] Mild to moderate exercise may hasten gastric emptying compared to rest, but emptying slows during high intensity exercise performed at or above 75% of VO_2max.[13,14] Emptying rate is also diminished with exercise in a heated environment versus exercise at a neutral temperature of 18 °C.[15] A delay in emptying increases time for drug absorption, especially of acidic drugs, but also increases drug exposure to the catabolic digestive enzymes. For example, penicillin is degraded in an acidic environment, so lower serum levels would be expected when a patient is dosed prior to intense exercise. Depending on the health of a patient's immune system and the type of infection, exercising shortly after drug dosing might compromise the efficacy of treatment. However there are some medications, like the anti-HIV drug saquinavir, that undergo increased absorption with prolonged gastric residence time. Research has demonstrated that orocaecal transit time (time from mouth to rectum) was slowed, while intestinal permeability and intestinal glucose absorption were all increased during periods of high intensity cycling and running.[16] Perhaps then drug absorption through the intestinal wall might also increase with intense exercise. However, absorption of certain drugs, such as levodopa, which undergo some metabolism by mucosa enzymes of the small intestine, would be adversely affected. Clearly there are many factors to consider when determining the effects of exercise on drug absorption through the GI tract. The rate of drug absorption, as well as the actual amount of drug absorbed, is likely to be different depending on the drug ingested and the mode and intensity of the exercise. A general and conservative recommendation is to hold the drug administration until after exercise is completed, or to schedule the exercise several hours after dosing.

Transdermal absorption of drugs during exercise

Research has confirmed that exercise increases the absorption of drugs applied transdermally. Increased blood flow to the skin, increased skin temperature and hydration from sweat, are contributing factors. Specifically nicotine, nitroglycerin, fentanyl, and birth control patches have been studied. A study of the Otho/Evra/Evra® contraceptive patch found that physical activity and exposure to heat and humidity resulted in increased drug delivery, although the amount of drug delivered remained within the therapeutic reference range.[17,18] While increased absorption of a contraceptive during exercise may not be clinically relevant or have immediate consequences, increased absorption of nitroglycerin and fentanyl can produce immediate negative consequences. Nitroglycerin is a powerful arterial and venous vasodilator used to treat angina. Cycling at a workload adjusted to maintain a heart rate of 110 beats/min, alternating with a workload that increases heart rate to 150 beats/min (sustained for one minute every 10 minutes), for a total of one hour of exercise, produced a 93% increase in plasma level of the drug.[19] In another study conducted on 12 healthy individuals, a 20-minute sauna treatment, resulting in peak skin temperature of 39 °C., significantly increased plasma concentration of nitroglycerin compared with a control group at room temperature. Nine of the 12 subjects experienced a significant drop in diastolic blood pressure as well as a significant reflex tachycardia.[20,21] This demonstrates that the increased absorption of transdermal drug applications is in part due to an increase in skin temperature. Similar results have been obtained by others.[20,22] It is important to mention that these studies were performed on healthy volunteers, which does not always translate to our patient population.

Transdermal fentanyl is an opioid given for chronic pain and pain related to cancer. It offers significant pain relief, but also can produce significant side effects. Nausea and vomiting are common with initial administration, and respiratory depression, which can be fatal, occurs when the amount of absorption is greater than what the patient can tolerate. Ashburn and colleagues used "controlled heat," delivering approximately 42 °C for a duration of up to 240 minutes, to determine if reaching a serum therapeutic level could be hastened.[23] The heat source was placed over a portion of a 25 ug/h patch. Higher fentanyl concentrations were obtained during the heating periods but the overall "area under the concentration curve" was similar to the sessions without heat. The authors concluded that the controlled application of heat to the patch is one method to hasten the onset of the drug's effect. However out of the 10 subjects participating in this study, 5 developed respiratory depression and needed to be treated with verbal stimulation and nasal oxygen. Several deaths and cases of severe toxicity have been reported with this patch, including a case in which a patient was exposed to activity in high ambient heat. In 2005, the FDA issued a Public Health Advisory on the fentanyl patch, when a woman who was prescribed a 50 mcg patch for sciatic pain, which was placed on her buttocks, along with a heating pad, was found deceased.[24]

There are at least 16 different transdermal patch drug preparations available, and several are available under different trade names.[25] Given the widespread use of these drugs and favorable acceptance by patients, it is imperative that patients receive instruction on their safe use either from the provider or pharmacist. Drugs should be initially used with caution until possible adverse reactions for that patient are known. In addition, exercise should be performed at a lower intensity until the serum drug concentration reaches steady state and the patient can be evaluated for side effects. Since ambient temperature affects absorption, the patient should refrain from exercising during periods of high heat and humidity. Lastly the patient should be familiar with the side effects and signs of toxicity.

Subcutaneous/intramuscular absorption of drugs with exercise

Insulin is the prototypic example of a drug injected subcutaneously that is affected by exercise. Insulin is typically injected into the subcutaneous tissues of the abdomen, upper outer arms, upper

outer legs, or buttocks and is used to help maintain serum glucose level between 80 and 110 mg. The fastest absorption is from the abdomen. The slowest absorption results from injection to the buttocks area or when the drug is injected into areas of lipohypertrophy.[26] Exercise increases subcutaneous absorption of insulin by enhancing transcription of the Glut-4 gene in skeletal muscle which codes for the glucose transporter and enhanced movement of glucose into the working muscle.[27,28]

Exercise increases drug absorption for both subcutaneous and intramuscular injected drugs when the site of administration is into the tissues actively engaged in activity, while drug absorption from inactive tissues is reduced.[29] One hour of intermittent moderate cycling has been shown to increase regular insulin absorption from the thigh but not when the insulin is injected into the arm.[30] The question then arises, how much glucose supplementation should be given to a patient on insulin to avoid hypoglycemia during or after exercise; or, how much should the pre-exercise insulin dose be reduced. A few studies have attempted to answer these questions. Nine subjects with type I disease who were maintained on a regimen of Humulin N (intermediate acting insulin) and Lispro (short acting insulin) prior to breakfast, were given 0g, 15g, or 30 g, of glucose supplementation 15 minutes before one hour of cycling performed at 50% VO_2max.[31] In addition the subjects received a dextrose infusion during exercise when their blood glucose level fell below 5 mmol/L. The amount of dextrose infused was then compared to the amount of glucose supplementation received prior to the exercise. It was then determined that 40 g of a glucose supplement ingested 15 min prior to exercise would maintain a safe blood glucose level during the 60 minutes of exercise. It is also significant to note that the exercise was performed 180 minutes after breakfast when the insulin was at its peak effect, and the insulin was injected into the abdomen. The American Diabetes Association recommends ingesting 15 g of carbohydrates for each hour of exercise, which is below what was recommended in this study. They also recommended giving 15-20 g of glucose to any conscious individual experiencing hypoglycemia.(26, 32) In another study, 8 subjects with type 1 disease performed various intensities of exercise (ranging from 25% VO_2max to 75% VO_2 max) for 30 and 60 minutes after a premeal dose of lispro (an ultrashort acting insulin), plus a 600 Kcal, 75 g carbohydrate breakfast.[33] The premeal dose of lispro also varied and each subject served as his own control. Exercise at all the stated intensities and durations produced a drop in glucose level, but more than two-thirds of subjects receiving the full lispro dose experienced hypoglycemia, including 3 who required a dextrose infusion for recovery. It was also observed that even at the lowest exercise intensity of 25%VO_2max, there was a significant drop in glucose level. The authors conclude that a reduction in premeal insulin is necessary when planning postmeal exercise. However, the exact reduction can only be determined on an individual basis, and depends on Kcal consumed and energy expended. As a guideline, Schiffrin and Parikh recommend a 30% to 50% reduction in premeal regular insulin prior to exercising moderately for 45 minutes.[34]

An additional variable to consider when exercising a patient on insulin is the type of insulin used. When glargine (long acting, basal insulin) was injected into the thigh there was no increased absorption during intense exercise (65% of VO_2 max for 30 minutes) compared to rest.[35] However, exercise does increase absorption of both regular and ultra short acting insulin.[30,31] Another variable is the type of exercise.[36] It has been shown that the drop in blood glucose level is less when the patient is performing intermittent high-intensity exercise compared with moderate continuous exercise. In this study, moderate exercise referred to continuous exercise performed for 30 minutes at 40% VO_2 max, and the intermittent intense exercise was the same except a 4 second maximal sprint was added every 2 minutes.

Since there are so many variables associated with injection of insulin and exercise, it is best to have patients routinely check their blood glucose level before, during, and after exercise, and to eat and exercise at the same time every day. A regular routine plus a consistent caloric intake will help patients avoid hypoglycemia associated with exercise and insulin.

Inhalation of drugs and exercise

The extensive surface area of the lung, ample vascularization, and the thin, highly permeable alveolar surface, produce a rapid systemic absorption of inhaled drugs. It is the primary route of administration for gaseous agents such as general anesthetics, and delivers beta$_2$ agonists (bronchodilators for asthma) directly to the target tissue. Other drugs administered in this manner include ipratropium (an anticholinergic drug) and corticosteroids, also for asthma and chronic obstructive lung disease, and amphotericin B and tobramycin, antimicrobial agents, for lung infections.

Exercise increases ventilation and produces changes in perfusion of the lung, favoring increased absorption of drugs. In addition, moderate exercise as well as deep breathing has been shown to produce a faster absorption and an increased plasma concentration of both terbutaline (beta2 agonist) and nedocromil sodium (mast cell stabilizer).[37,38] While these effects may prove to be beneficial in preventing exercise induced asthma, a similar use of inhaled insulin may result in a detrimental or hazardous state of hypoglycemia.

Drug Distribution

Distribution of the drug is the second phase of pharmacokinetics. Distribution generally refers to where the drug goes following absorption into the systemic circulation. Tissues and organs that have generous perfusion will receive a larger proportion of the dose compared with those that are poorly perfused. This means that a substantial portion of the drug dose travels to the liver and kidneys, and less to the skin and subcutaneous tissues. However during exercise there is a drop of 10% to 15% in plasma volume as the plasma leaves the vascular compartment and enters extravascular space. Drug therefore is also re-distributed to the working muscles, skin, and heart. This distribution holds true for a trained individual as it does for an untrained person.

Drugs are described as either having a high volume of distribution (Vd), meaning that the drug leaves the circulation and distributes widely into the tissues, or has a low Vd, ie, stays predominantly within the vascular compartment. It is

reasonable to assume that the drugs with a high Vd will be less influenced by a drop in plasma volume. However for drugs with a low Vd, a change in plasma volume may have significant influence over the drugs' effectiveness and safety profile. It is reasonable to assume again that the volume of distribution for some drugs will change with the changing distribution of the blood that occurs with exercise. Warfarin, an anticoagulant, has a low Vd and has been shown to be less effective with exercise, although this may also be due to a change in protein binding as described below. [39]

Some drugs have a strong binding affinity for the plasma protein albumin. When this occurs there is a reduced concentration of free drug available to travel to the site of action. During exercise the relative concentration of albumin increases due to redistribution of the plasma volume and results in a subsequent increase in drug-plasma protein binding. Warfarin binding to plasma proteins has been shown to increase with physical activity.[40] In addition there have been reports demonstrating that doubling the number of steps walked in a day, as determined by a pedometer, was correlated with a drop in the international normalized ratio (INR) in a direction that promotes clotting.[39] The number of steps walked/day ranged from 11,460 to 12,570, which is a little more than 5 miles. There were no changes in food choices or drug dose, which means that the change in INR was due to exercise.

Metabolism and Elimination

Hepatic elimination

After nutrients and drugs are absorbed through the gastrointestinal tract they enter the liver through the venous portal system. Research has shown that high intensity exercise can reduce portal blood circulation by as much as 50% to 80%.[16] This in turn reduces drug delivery to the liver, which also alters metabolism since the amount of drug that can be metabolized is limited by the amount that is delivered. Metabolism (also known as biotransformation) is the process whereby the liver transforms an active drug compound into an inactive agent that can be easily excreted by the body. The ability of the liver to extract drug from the portal circulation for purposes of metabolism is referred to as "first-pass effect."[41] Some drugs undergo high hepatic extraction, meaning that the liver metabolizing enzymes inactivate a large amount of the drug before it enters the systemic circulation, and less drug is available to reach the target tissue. In this case the drug is said to have low bioavailability. Other drugs have a low first-pass effect, indicating low hepatic extraction, and therefore high bioavailability. Drugs that are given intravenously are 100% bioavailable, meaning that 100% of the drug given to the patient enters the systemic circulation. Drugs administered orally are less than 100% bioavailable, since some drug is lost in the feces or metabolized by mucosal enzymes, and other amounts undergo first-pass effect. It is the high hepatic extraction ratio drugs that are sensitive to changes in portal circulation and liver blood flow.[42] Exercise may reduce extraction rate and therefore lead to higher than expected serum drug levels. Incorporating the research cited above one may conclude that oral medications with a high first pass effect should be held until after exercise to avoid interfering with the amount and rate of drug advancement to the liver. See Table 1 for a list of high hepatic extraction ratio drugs.

Renal excretion

Drug clearance from the body primarily occurs via the kidneys and depends on glomerular filtration, and tubular secretion and reabsorption. Other factors include the degree of protein binding and ionization of the drug as well as renal blood flow. As discussed earlier, exercise reduces blood flow to the kidneys by as much as 53% with exercise to exhaustion.[43] However, for drugs that are primarily metabolized to inactive compounds, reduced renal perfusion will not alter serum drug levels. But for drugs that are excreted unchanged by the kidney, a drop in renal blood flow can produce a significant increase in drug concentration. Moderate to strenuous exercise has been shown to increase the plasma concentration of both atenolol (a $beta_1$ blocker) and procainamide (an antiarrhythmic drug).[44-46] It is important to add that the resultant increase in drug concentration only occurred during exercise and at 30 minutes and one hour post exercise. Although the authors report that the clinical significance of the increased plasma concentration is unknown, we speculate that the changes occurring with exercise are beneficial for the patient with these conditions. The beta blocker will minimize the exercise induced increase in heart rate, and procainamide is helpful toward reducing arrhythmias that are likely to be caused by elevated levels of circulating epinephrine.

Table 1. High Hepatic Extraction Ratio Drugs Whose Clearance is Limited by Blood Flow103

Generic Name	Trade Name	Indication
Amitriptyline	Elavil	Tricyclic Antidepressant
Imipramine	Tofranil	Tricyclic Antidepressant
Isoniazid	generic	Tuberulosis
Labetalol	Normodyne	Congestive Heart Failure/ Hypertension
Lidocaine	Xylocaine	Local Anesthetic
Lisinopril	Zestril	Hypertension
Losartan	Cozaar	Hypertension
Meperidine	Demerol	Opioid Analgesic
Morphine	MS-Contin	Opioid Analgesic
Propranolol	Inderal	Hypertension
Verapamil	Calan	Arrhythmia

The above discussion illustrates some changes that occur in drug pharmacokinetics with exercise. Although based on sound principles of pharmacokinetics, these relationships cannot always be predicted, and the clinical significance of these changes is not always known. The remainder of this article will focus on some specific exercise-drug interactions seen in physical therapy practice that have known clinical significance either from a pharmacokinetic or pharmacodynamic perspective.

DRUGS AFFECTING THE MUSCULOSKELETAL SYSTEM

Fluoroquinolones

There are a number of drugs that appear to affect connective tissue and tendon strength. The fluoroquinolone drugs are a group of antibiotics widely used to treat urinary, bronchopulmonary, and intestinal infections, as well

as septic arthritis and osteomyelitis. Perhaps the best known of these drugs by the lay public is ciprofloxacin. Side effects of this drug include gastrointestinal effects, dizziness, and headache, although arthralgias, myalgias, tendinitis, and tendon ruptures have been reported.[47] The most common site affected is the Achilles tendon, although tendonitis has also been reported in the rotator cuff and patellar and quadriceps tendons. The estimated incidence is 3.2 cases per 1000 patient years and predominantly affects individuals aged 60 or over and those who are also taking corticosteroids.[48] It appears that patients are more susceptible to injury within the first 30 days following drug withdrawal. It is speculated that consistent overloading of the tendon during activities are to blame. Studies on the canine Achilles tendon have shown a decrease in fibroblast metabolism along with increased degrading activity when tendon specimens are incubated with ciprofloxacin.[48]

One case study of bilateral Achilles tendon pain associated with levofloxacin use has been reported in the physical therapy literature.[47] The author reported on a two-phase program that first aimed to reduce the loading stress on the tendon with crutches and an orthotic. Phase I continued for the first 6 weeks post medication withdrawal and was followed by Phase II consisting of progressive loading of the tendon over an additional 3-month period. Care was taken to protect the tendon from rupture while it was still susceptible to the degrading effects of the drug.

Statin Therapy

The statin drugs are used to lower LDL cholesterol levels for primary and secondary prevention of cardiovascular disease. They block the action of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is involved in the first step of cholesterol synthesis in the liver. Safety concerns about these drugs surfaced when cerivastatin was withdrawn from the market after reports of fatal rhabdomyolysis. Statins have been associated with muscle complaints ranging from mild weakness to myalgia and myopathy, with or without elevated creatine kinase (CK). Rhabdomyolysis is a more severe form, resulting from sarcolemmal injury that causes release of myocyte contents (myoglobin, CK, uric acid, and electrolytes) into the circulation. The patient experiences marked muscle damage and pain, dark or brown urine, and a CK level 40 times greater than normal (compared to 10X upper limit of normal for myositis) leading to acute renal failure.[49] Symptoms develop within a few months of either starting therapy, increasing the dose, or when adding an interacting drug.[50] The condition is also more likely to occur with advanced age, female gender, renal or hepatic dysfunction, or hypothyroidism.[51] Note that joint pain, nocturnal leg cramps, and localized pain are not considered symptoms of myopathy. It is important to note that the incidence of myopathy is extremely small. In a recent meta-analysis there were 9 mypopathy cases out of 39,884 patients reported in the treatment arm compared to 6 cases out of 39,817 patients in the placebo arm.[52,53] Another consideration is that many middle aged and elderly individuals suffer from muscle pain, but a diagnosis of myopathy or the more severe, rhabdomyolysis should not be given unless the CK value is elevated. There are reports of statin related muscle pain, with or without elevated CK occurring in 10% of the population.[54]

Determining the exact incidence of statin related muscle complaints has been difficult, since there are inconsistencies in how myopathy is defined. Even the US Food and Drug Administration (FDA) differs in their definition from the National Cholesterol Education Program (NCEP) Advisory Panel.[55]The statins are metabolized in the liver by a group of enzymes known as the CYP isoenzymes (CYP 3A4 enzyme).[56] The activity of these enzymes can be either induced or inhibited by other drugs. If the enzyme is inhibited, patients will have higher plasma statin levels leading to toxicity. So if a patient develops unexplained muscle pain, a statin related myopathy may be considered if the patient is also consuming a CYP 3A4 inhibitor drug such as a macrolide antibiotic, a calcium channel blocker (diltiazem or nifedipine), or a protease inhibitors.

If a patient is elderly, experiences renal failure, or has several co-morbidities, statin related myopathy should be considered. See Tables 2 and 3 for additional risk factors for statin associated muscle syndromes. If any of these conditions exist, referral to the MD is necessary for further evaluation, particularly blood tests to measure CK. Most likely the statin dose would be lowered or switched to every other day dosing, and the patient observed for a reduction in symptoms.[57]

In addition to myopathy, there have been reports of tendonitis and tendon rupture and peripheral neuropathy with the use of statins.[58,59] During a 15-year period from 1990 to 2005 there were 96 reports of tendon complications in France. The average age of the patient was 56 years old, with a median time to onset after initiating statin therapy of 243 days. Many of those patients reporting symptoms had diabetes, hyperuricemia, or participated in sports. As of March 2006, there were 247 reports of tendon rupture associated with statin therapy in the Food and Drug Administration adverse event data base.

Since myopathy and tendon lesions secondary to statin use are not commonly seen in physical therapy practice, there are no clear guidance documents for the treating therapist. Currently the prevailing thought is that there is no reason to withhold strengthening exercises for patients on these drugs, except if they are reporting muscle pain. The decision to stop therapy and refer the patient for CK testing is complicated by the fact that intense exercise can also lead to elevated CK levels. Bilateral pain, pain unrelated to physical activity, or pain lasting longer than 48 to72 hours or proximal muscle involvements are red flags that warrant a referral. Therapists should also be alert to an unexplained change in functional abilities, such as difficulty moving from sit to stand or climbing stairs. Muscle biopsies may be helpful in the diagnosis, and the presence of cytochrome oxidase negative fibers, accumulating lipids, and "ragged red fibers" suggest statin related myopathy.[54]

There are many reports addressing the general topic of statin-related myopathy, but only a few focus on the development of myopathy in response to exercise in patients on these drugs. Examination of these studies may provide the therapist with some dos and don'ts regarding which modes of exercise should be avoided in patients prescribed statins. In one study, subjects received either lovastatin or placebo for 5 weeks along with a

Table 2. Drugs that Increase Statin Associated Muscle Syndromes

Generic Name	Brand Name	Indication
Clarithromycin	Biaxin	Antimicrobial Agent
Cyclosporine	Sandimmune	Immunosuppressant
Diltiazem	Cardizem	Calcium Channel Blocker/hypertension
Ketoconazole	Nizoral	Antifungal Agent
Midazolam	Versed	Short-acting hypnotic
Nifedipine	Procardia	Calcium Channel Blocker/hypertension
Protease inhibitors	Crixivan Invirase Norvir	HIV Disease
Verapamil	Calan	Calcium Channel Blocker/antiarrhythmic
Sildenafil	Viagra	Erectile Dysfunction
Warfarin	Coumadin	Anticoagulant

single session of exercise in week 4 and 5.[60] In the fourth week of treatment, subjects received downhill walking exercise, and then subsequently a biceps curl exercise in the following week. Results of the study showed that CK levels were elevated following the eccentric treadmill exercise but not after the biceps resistance exercise. This indicates that mode of exercise and type of muscle fiber recruited influences the interaction between statin related myopathy and exercise. However this assumption is complicated by the fact that eccentric exercise alone may produce higher CK levels and greater muscle damage than other types of exercise.[61] In a more recent study, serum CK levels were determined following downhill treadmill exercise in patients receiving 10 mg of atorvastatin compared with those receiving an 80 mg dose.[61] No difference in CK levels were seen implying that perhaps the elevated enzyme levels were due to exercise and not statin dosing. Clearly more work needs to be performed in this area before definitive recommendations can be made to the treating therapist.

Nonsteroidal Anti-inflammatory Drugs

Perhaps the most widely used category of drugs in the world is the nonsteroidal anti-inflammatory drugs (NSAIDs).[62] They are prescribed by physicians and also self-administered by patients, to reduce pain, fever, minimize inflammation following injury, and to bridge a gap between onset of symptoms and time to onset of the disease modifying agents in rheumatoid diseases. They act by blocking the cyclooxygenase enzyme (COX), and hence prevent arachidonic acid metabolites from being released from injured tissue.[63] These metabolites, prostaglandins and thromboxanes, assist in creating the inflammatory response to injury by increasing capillary permeability and mediating pain responses.

Three isoforms of the Cox enzyme have been identified. COX-1 is found in platelets, kidneys, and in the stomach.[64] The enzyme actually has a protective role by facilitating release of prostaglandins to protect the mucosal lining of the stomach and to help dilate the renal artery. COX-2 is induced by injury and then found in synoviocytes, endothelial cells, and macrophages, and it is involved with the inflammatory reaction that occurs with injury. Cox-3 is located in the brain and may be inhibited by acetaminophen.[65] There are nonselective NSAIDs available including ibuprofen and indomethacin, that block both COX-1 and COX-2, and there are NSAIDs that are selective for inhibiting just the COX-2 enzyme such as celecoxib (Celebrex). Inhibition particularly of the COX-2 enzyme reduces pain and inflammation from injury or arthritis.

Unfortunately both selective and nonselective COX inhibitors have been shown to suppress muscle regeneration and repair in both an animal and human model, with inhibition of COX-2

Table 3. Conditions that Increase the Risk of Statin-Related Myopathy

- Elevated liver transaminases prior to statin therapy
- Dehydration and/or renal compromise
- Acute illness
- Patient taking more than one lipid-lowering agent
- Patient taking a CYP 3A4 inhibitor
- Hypothyroidism
- Age>65
- Co-morbidities
- Diabetes

producing a greater impairment in function of the satellite cells.[66-68] The clinical implication of these studies is huge for our patients and suggests that these anti-inflammatory agents impair muscle healing as well as the normal hypertrophy that occurs with resistive exercise training. However at the present time the research does not offer guidelines regarding which NSAID produces the least deleterious effect, and at what time if any would it be safe to consume the drugs during the healing process. It may be that NSAIDs could be administered safely after 48 hours (after the initial stages of inflammation), but should be avoided in the chronic stages of healing.[69] It is important to note however that in the human studies cited above, the NSAIDs were administered via a local infusion to the treatment leg and not given orally and systemically in a manner consistent with normal dosing, nor does this match the long term dosing often seen in our patients with arthritic conditions. Further study on this topic is definitely necessary.

An addendum to the NSAID story is the growing evidence that Cox-2 inhibitors and NSAIDs increase hypertension, kidney failure, cardiac events, and mortality after a previous myocardial infarction, and decrease the lung function of patients with asthma. At least in the case of the Cox-2 inhibitors, it is thought that the drug reduces levels of prostacylin that is needed to offset the prothrombotic action of thromboxane A2. The net effect is that these selective NSAIDs promote thrombosis.[70,71] In addition selective and nonselective agents have been shown to reduce glomerular filtration and increase blood pressure, producing hypertension and/or exacerbating congestive heart failure. Also, NSAIDS will diminish blood circulation to the kidneys over time. De-

hydration will result in decreased blood flow to the kidneys as well, so it is recommended that patients on NSAIDS drink more fluid to help alleviate the decrease in kidney blood circulation. Besides these effects, it is now accepted that NSAIDS hinder the healing of ligaments, tendons, bone, and cartilage. Thus, the old adage of RICE is coming back as the preferred mode of treatment.

More recent research challenges the viewpoint that NSAIDs are safe for short-term use. The Danish National Patient Registry was used to identify roughly 83,000 patients who were admitted to the hospital with a first myocardial infarction. Forty-two percent were determined to either have died or have recurrent MI related to NSAID use during the 14-week study period.[73] In general the overall increase in risk was seen after only 10 days of use, 7 days was associated with the Cox-2 inhibitors. Naproxen produced the lowest risk of death or recurrent MI, and diclofenac had the highest risk, which was determined to be even greater than that for rofecoxib (Vioxx) which was withdrawn in 2004 because of its cardiac risks.

DRUGS AFFECTING THE CARDIOVASCULAR SYSTEM AND EXERCISE PERFORMANCE

The most commonly used drugs for hypertension include β-blockers, α-blockers, calcium channel blockers, diuretics, and the drugs that interfere with angiotensin II production or binding. While they all have relative effectiveness in reducing blood pressure, they have varying effects on exercise responses and performance depending on the cardiac health of the patient.

Beta-blockers reduce blood pressure by reducing heart rate and contractility both during rest and exercise. Research has shown that the drugs produce a reduction in exercising HR by 20% to 30%, allowing for greater diastolic filling time of the coronary arteries and thus a greater myocardial oxygen supply.[74] Additionally, beta blockers contribute to vasodilation by blocking renin release from the kidney and reducing circulating levels of angiotensin II, with a resultant drop in peripheral vascular resistance. For patients with moderate to severe coronary artery disease (ejection fraction < 40%), the greater supply of oxygen, results in an increased work capacity. Studies suggest that using percent of Heart Rate Reserve (HRR using the Karvonen formula) is useful and appropriate for determining training intensity in patients using beta blockers post MI.[75] If the patient does not have a stress test, then the target heart rate should be 20 beats above resting, which is an acceptable standard practice. [76]

In individuals with hypertension who otherwise demonstrate adequate cardiovascular function, beta blockers reduce exercise capacity.[77] Depending on the study and exercise protocol, reductions in aerobic work is reduced from 4% to 10%, with a greater reduction associated with the nonselective beta blockers (propranolol) compared to selective blockers (metoprolol and atenolol).[78-81] However metoprolol did not reduce or augment cardiac work in the average trained individual with moderate-intensity exercise, but reduced the cardiac work of endurance trained subjects at the same exercise intensity.[82] Cardiac workload was reduced for both groups of individuals at high intensity exercise. A reason for this reduction in exercise capacity may include a decrease in cardiac output. Even though stroke volume is improved with training, it will plateau at 40% of VO_2max thus making heart rate the main variable to increasing cardiac output in these relatively healthy individuals.[83-85] But since beta blockers blunt the heart rate response both with a single bout of exercise as well as with training, cardiac output will not increase to meet the metabolic demands of the exercise.[83] Beta blockers also produce metabolic effects that reduce exercise performance. These metabolic effects include decreasing glycogenolysis and glucagon secretion, as well as inhibiting lipolysis, all of which increases fatigue.[86-88]

Calcium channel blockers also have the potential to decrease exercise capacity in physically active hypertensive individuals without coronary artery disease, depending upon the drug prescribed. Verapamil for example, reduces cardiac contractility and conduction of impulses through the AV node, and hence lowers both resting and maximal exercise heart rate to reduce myocardial oxygen consumption. Improvements in exercise performance are seen in patients with coronary artery disease with this drug but not typically seen in patients with only hypertension. Contractility is depressed limiting volume of blood available to active working muscles.[89] In contrast, the dihydropyridines (nifedipine, amlodipine) act to reduce blood pressure by dilating the peripheral vessels that in turn produces a reflex increase in heart rate and therefore less negative effects on central parameters. This is borne out in studies comparing the two types of calcium channel blockers in hypertensive patients.[90] Both drug categories may affect exercise performance but the dihydropyridines to a lesser extent. Diuretics reduce blood pressure by preventing reabsorption of sodium through the kidney tubules forcing a diuresis.[91] These drugs have been prescribed to patients with hypertension more than any other agent in part due to their low cost and relative effectiveness. However they should not be blindly considered a first choice agent for all patients.

Diuretics can produce dehydration, orthostatic hypotension, and negatively alter electrolyte balance causing hypokalemia. Dehydration alone can be a reason for reduced exercise capacity due to altered thermoregulation affecting heat dissipation, increased cardiovascular strain, reduced skeletal muscle blood flow, altered skeletal muscle metabolism, and increased perception of effort required to complete an exercise.[94-96] Greater than a 2% loss in body mass produces exercise intolerance based on these mechanisms listed.[95] Electrolyte imbalance leads to dysrrhythmias, muscle weakness, and cramping, also affecting performance. There is no doubt that these drugs are useful for individuals as an add-on drug for difficult to control hypertension, but clearly they are not indicated for healthy physically active individuals.

Out of all of the drugs used in the treatment of hypertension, the angiotensin converting enzyme inhibitors (ACE I) have the least effect on exercise performance. These drugs block the production of angiotensin II, a powerful vasoconstrictor, and the leading cause of essential hypertension.[96] The ACE inhibitors plus the related ACE receptor blockers do not adversely affect cardiac function, lipid levels, glucose utilization, or heart rate.[97-99] Athletes and patients alike, report limited side effects with these drugs and no evidence of fatigue that might impair ones motivation to exercise. Additionally there is some indica-

tion that these drugs can actually enhance endurance performance with potential for becoming a doping agent. Studies are ongoing to delineate the mechanism involved in the potentiation of endurance performance; however, at this time these mechanisms are unclear.[100] See Table 4 for cardiac medications and their affects on cardiac variables.

CONCLUSION

In this article we have documented some drug-exercise interactions and also have made some predictions about other interactions. The expected interactions include the need for dosing changes with insulin, reduction in exercise performance with some antihypertensive agents, and increased absorption of drugs delivered via a patch with activity. Less definitive interactions include the effect of NSAIDs and statins on the musculoskeletal system. Additionally we cite the research demonstrating the sometimes unpredictable and variable effects of exercise on drug pharmacokinetics. The take home message is that even though drugs may be prescribed appropriately and have no adverse effects at rest, they may have significant exercise related interactions.

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Table 4. Hemodynamic Changes in Patients with Hypertension in Response to Drug Therapy

Variable	Diuretics	β1 blockers	Dihydropyridines	ACE Inhibitors
RHR	⇔	⇓	⇔/⇑	⇔
MHR	⇑	⇓	⇑	⇑
SBP	⇓	⇓	⇓	⇓
CO	⇓	⇓	⇔/⇓	⇔/⇑
SV	⇓	⇔/⇑	⇔/⇓	⇑
VO_{2max}	⇓	⇓	⇔/⇓	⇔
Fatigue	⇑	⇑	⇔/⇑	⇔

⇑ Increase; ⇓ Decrease; ⇔ No Effect; RHR Resting Heart Rate; MHR Maximum Exercise Heart Rate; SBP Systolic Blood Pressure during Exercise; CO Cardiac Output during Exercise; SV Stroke Volume during Exercise; VO_{2max} Maximum Oxygen Consumption;(102, 103)

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CARDIAC MEDICATIONS: A PRIMER FOR PHYSICAL THERAPISTS

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INTRODUCTION

Geriatric physical therapists are faced with treating patients with many co-morbidities including a wide variety of cardiac conditions. Oftentimes cardiac patients are taking many different medications for their condition(s) which have side effects that may affect their progress in therapy. It is important for therapists to be aware of the medications and side effects of cardiac drugs and how these medications may alter physiological responses to exercise and functional training. The major heart related conditions to be discussed here are hypertension, myocardial infarction, angina, cardiac arrhythmias, and heart failure.

HYPERTENSION

Hypertension (HTN) is also known as high blood pressure. It is a chronic cardiac condition in which the systemic arterial blood pressure is elevated. The two classifications are primary (essential) and secondary hypertension. The majority of people affected have primary hypertension with no known cause that tends to develop gradually over years. Approximately 5% to 10% have secondary hypertension resulting from other diseases such as kidney, diabetes, and other arterial conditions. Uncontrolled hypertension can increase the risk for myocardial infarction, stroke, aneurysm, kidney failure, and heart failure. Even mild to moderate hypertension can cause decreased life expectancy.[1] When the arteries are narrowed, the pressure in the arteries for the blood to flow increases resulting in high blood pressure.

Most people with high blood pressure have no signs or symptoms even when the blood pressure has become dangerously high. However, some symptoms may include a dull headache, nose bleeds or dizziness. Risk factors include: obesity, family history, lack of exercise, use of tobacco, too much sodium, lack of potassium, excessive alcohol, stress, and chronic conditions such as diabetes, kidney disease, and high cholesterol. Lifestyle changes can help to lower or control high blood pressure. These include eating a healthy diet low in salt, managing stress, exercising, maintaining a healthy weight, limiting alcohol, and avoiding the use of tobacco.[2,3]

Medications

In many cases medications are needed to treat hypertension. Medications to treat high blood pressure include diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, and renin inhibitors and vasodilators.

Diuretics or "water pills" work with the kidneys to eliminate excessive body fluid by increasing the amount of sodium in the urine and reducing the amount of fluid in the bloodstream, thus decreasing the pressure on the arterial walls and reducing blood pressure. Combining diuretics with other high blood pressure medications can be more effective, and will allow for smaller doses of each, reducing side effects and cost. There are 3 types of diuretics available: thiazide, loop, and potassium-sparing. Each works on a different part of the kidney, with different uses and side effects. Thiazide diuretics are usually the first choice in treating high blood pressure because of their effectiveness. If thiazide diuretics are not sufficient in lowering blood pressure, then other types of diuretics and medications will be used. Examples of thiazide diuretics include chlorothiazide and metolazone (Zaroxolyn). Examples of loop diuretics include furosemide (Lasix), torsemide (Demadex), and bumetanide (Bumex). Examples of potassium-sparing diuretics include spironolactone (Aldactone) and amiloride. Side effects of diuretics include: increased urination, dizziness, muscle cramps, increased blood sugar, low blood sodium (hyponatremia), excessive blood potassium levels (hyperkalemia, which may occur with potassium–sparing diuretics), and low blood levels of potassium (hypokalemia is more likely with thiazide diuretics).

Alpha blockers, also called alpha-adrenergic antagonists, work by blocking the effects of the hormone norepinephrine, resulting in relaxation of the blood vessels, which reduces blood pressure. There are long-acting alpha blockers, which take longer to start working but have longer lasting effect (such as doxazosin and tamsulosin), and short-acting alpha blockers (such as prazosin), which work quickly, but whose effect lasts only a few hours and may require multiple dosing. Side effects of alpha blockers include nausea, weight gain, and a pounding heartbeat. Caution must be used when first taking alpha blockers, because patients may experience extremely low blood pressure and dizziness, especially with positional changes, such as sitting to standing.

Beta blockers, also known as beta-adrenergic blocking agents, work by blocking the effects of the hormone epinephrine, also known as adrenaline. The heart will beat more slowly and with less force, resulting in lower blood pressure. Because beta-blockers blunt heart rate response to activity, it is important to use other measures to monitor patients for activity tolerance. One measure that has become the current gold standard for monitoring response to exercise in these patients is the Borg rate of perceived exertion (RPE) scale. It is also important to carefully monitor blood sugar levels of diabetic patients taking beta blockers, because the drugs prevent the rapid heartbeat that is usually a warning sign of low blood sugar. Examples of beta blockers include atenolol (Tenormin), metoprolol, and propranolol (Inderal LA). Other common side effects include fatigue, diz-

ziness, diarrhea, and constipation.

Angiotensin-converting enzyme inhibitors help to relax blood vessels by preventing the production of angiotensin II, a hormone that constricts blood vessels and raises blood pressure. Examples include enalapril (Vasotec), lisinopril (Prinivil, Zestril), quinapril (Accupril), and ramipril (Altace). Side effects may include: dry cough, increased blood-potassium level (hyperkalemia), and dizziness. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, can decrease the effectiveness of ACE inhibitors.

Angiotensin II receptor blockers block the action of angiotensin II, allowing blood vessels to relax and dilate, thus reducing blood pressure. Examples of angiotensin II receptor blockers include: irbesartan (Avapro), losartan (Cozaar), olmesartan (Benicar), and valsartan (Diovan). Side effects may include: dizziness, lightheadedness, back and leg pain. However, most people taking ARBs do not experience side effects.

Calcium channel blockers, or calcium antagonists, prevent calcium from entering cells of the heart and blood vessel walls, resulting in dilating of blood vessels and reducing blood pressure. Examples include amlodipine (Norvasc), diltiazem (Cardizem LA, Tiazac), and nifedipine (Procardia, Procardia XL, Adalat CC). Side effects may include: dizziness, drowsiness, swelling in legs and feet, and rapid heartbeat (tachycardia). Due to the swelling caused by these drugs and their decreased effectiveness compared to other drugs prescribed for HTN, calcium channel blockers are not usually the first choice of prescription and may be prescribed when other medications are not sufficient in controlling blood pressure. Patients taking calcium channel blockers should avoid grapefruit and grapefruit juice, which decrease the body's ability to metabolize the drug.

The last two categories of medications used to control HTN are renin inhibitors and vasodilators. Renin inhibitors slow down the production of rennin, an enzyme produced by the kidneys that starts a chain of chemical steps that results in elevated blood pressure. An example of a renin inhibitor is aliskiren (Tekturna). Vasodilators act directly on arterial and venous smooth muscle to cause dilation, allowing blood to flow more freely and reducing blood pressure. Examples include Hydralazine and Minoxidil.[2,3]

MYOCARDIAL INFARCTION

Myocardial infarction, commonly referred to as a heart attack, occurs when a blood clot blocks the flow of blood through the coronary arteries. Coronary artery disease (CAD) is the major underlying cause of a myocardial infarction. Coronary artery disease results when cholesterol builds up in the arteries, resulting in plaque or atherosclerosis. During a heart attack, a plaque may rupture, resulting in a clot that blocks the flow of blood to the heart. The resulting ischemia (restriction in blood supply) and oxygen shortage, if left untreated for a sufficient period of time, can cause damage or death (infarction) of heart muscle tissue (myocardium).

There are many signs and symptoms of a heart attack, although some people may experience none at all. The onset of symptoms is gradual and usually occurs over several minutes. However, the more symptoms a person is having, the more likely it is that the person is having a heart attack. Common symptoms include: pain and pressure in the center of the chest; upper abdominal pain; increasing episodes of chest pain; prolonged sense of doom; shortness of breath; nausea and vomiting; diaphoresis; unexplained fatigue; and pain radiating into the shoulder, arm, back, or jaw. Risk factors include age (men over age 45 and women over age 55), use of tobacco, diabetes, high blood pressure, obesity, stress, lack of exercise, high level of triglycerides, and family history. A healthy diet, exercise, and managing stress can help recovery from a heart attack and can also decrease the effects of risk factors that lead to heart attacks.[4,5]

Medications

Myocardial infarction is a medical emergency and requires immediate treatment, which includes aspirin (to reduce clotting of the blood), oxygen, and nitroglycerin (for chest pain). Thrombolytics help to dissolve the blood clot. The sooner a person having a heart attack is given these drugs, the greater the chance of survival, and less damage is likely to occur to the heart.

After a person has suffered from a myocardial infarction they are typically placed on long-term medications to prevent secondary cardiovascular events. These medications include antiplatelet drugs such as aspirin and clopidogrel (Plavix), which help to decrease rupture of plaque; beta blockers (such as metoprolol and atenolol), which work to reduce the strain on the heart by lowering the blood pressure; and ACE inhibitors (such as ramipril and lisinopril), which work to prevent heart failure and lower blood pressure. Lipid lowering statins are another choice of medication. Statins, such as lovastin, simvastin, and pravastatin, have been shown to stabilize plague and lower blood cholesterol.

ANGINA

Angina (angina pectoris) is pressure or pain in the chest. It is often the first outward sign of heart disease. Angina occurs when the coronary arteries are not delivering a sufficient amount of oxygen-rich blood to the heart. Angina is a sign that there is narrowing in one or more coronary arteries.

There are two types of angina, stable and unstable. Stable angina occurs from an increase in physical exertion, such as climbing stairs or running across a street, that results in an increased demand for oxygen-rich blood to the heart. Unstable angina is more serious and occurs with less physical exertion or even at rest. Unstable angina that occurs at rest is the most serious, and is usually caused by a blood clot that can result in a heart attack. Immediate medical attention is required if angina increases in frequency, occurs at rest and with exertion, or increases in duration and severity. This includes calling 911, chewing 2 tablets of aspirin, and/or taking fast-acting nitrates.[6]

Medications

Preventative treatment for angina includes taking aspirin, maintaining blood pressure of 140/90 or lower, and keeping total cholesterol lower than 200mg/dl. LDL ("bad") cholesterol should be kept below 130 mg/dL, and HDL (good) cholesterol should be above 40 mg/dL for men and 50 mg/dL for women. Triglycerides should be below 150 mg/dL. Prevention also includes a healthy diet, exercise, and weight control. Medication to treat and prevent angina includes fast-acting nitrates in sublingual or spray form to widen blood vessels and stop angina when it occurs. Long-acting nitrates

are available as capsules, skin patches, and topical ointments, and defend against angina by releasing nitroglycerin slowly into the bloodstream.[6]

CARDIAC ARRHYTHMIAS

Cardiac arrhythmia is an abnormal heart rate or heart rhythm. The heart can beat too fast (tachycardia), too slow (bradycardia), or irregularly. The 3 categories of arrhythmias are supraventricular arrhythmia (which includes atrial fibrillation, atrial tachycardia, and atrial flutter), ventricular arrhythmia (which includes ventricular tachycardia, ventricular fibrillation), and bradyarrhythmia (which includes SA node, AV node, or HIS-Purkinje system). Atrial fibrillation, or a-fib, is the most common cardiac arrhythmia in the United States. In fact, according to the American Heart Association, approximately two million Americans suffer from a-fib. The condition occurs when multiple circuits of disorganized electrical activity in the two upper chambers of the heart (the atria) take over the organized electrical activity normally generated by the heart's sinus node. This produces a fibrillating, or quivering, of the atria, as opposed to a regular heartbeat. The electrical impulses are so fast that the atria cannot contract and squeeze blood into the ventricle. "Although A-fib isn't directly life threatening, it's often debilitating, because it produces a fast, irregular pulse that can cause fatigue and contribute to additional heart problems over time, such as congestive heart failure. Other symptoms include palpitations, chest discomfort, shortness of breath, and dizziness.[7-10]

Medications

There are several different types of medications used to treat cardiac arrhythmias depending on the type of arrhythmia and presence of co-morbidities such as heart, liver, or kidney disease. The main categories include beta blockers, calcium channel blockers, and antiarrhythmic drugs. Beta blockers, such as metoprolol (Toprol), and Lopressor, are commonly used to slow the heart rate by blocking the effects of adrenaline on the heart. Calcium channel blockers are used to disrupt the flow of calcium through the heart and blood vessels and slow the heart rate. They include verapamil (Calan) and diltiazem (Cardizem). Antiarrhythmic drugs restore the heart to normal rhythm, maintain normal rhythm, and help prevent blood clots. Different antiarrhythmic drugs are available, such as flecainide, propafenone, sotalol, and amiodarone. Each of these drugs has different side effects. A common side effect to all antiarrhythmic drugs is pro-arrhythmia, ie, the occurrence of dangerous arrhythmias, which is why these medications should only be prescribed by a specialist. Patients taking these drugs should have an electrocardiogram done every 6 months to check for any evidence of medication toxicity. Anticoagulant or antiplatelet therapy medications, such as warfarin (Coumadin) or aspirin, reduce the risk of blood clots and stroke, but they do not eliminate the risk. Regular blood tests are required when taking Coumadin to evaluate the effectiveness of the drug.[7-10]

HEART FAILURE

Heart failure represents the final common pathway of many risk factors and cardiovascular disease. Many of these diseases can be prevented by implementation of aggressive lifestyle changes and pharmacological interventions.[11] Heart failure has been categorized by different classification systems. The New York Heart Association (NYHA) system is a functional classification that "represents a subjective assessment by a health care provider" that can change frequently over short periods of time. Treatments based on the NYHA system did not differ significantly across the classifications. The American College of Cardiology/American Heart Association (ACC/AHA) staging system was developed to link unique treatments to each stage of the illness. The ACC/AHA staging system provides a more objective way to identify patients during the course of their disease progression. It differs from the NYHA system in that once a patient is moved up a stage (eg, from stage B to stage C), they cannot move back to the previous stage. Expectations for the disease course are either to stay at the diagnosed stage or to worsen over time, progressing to the next stage.

Appropriate medical interventions for patients with heart failure or at risk for heart failure depend on the stage the patient is in. Using the staging system, phy-

Table 1. Medication Classes Used to Treat Heart Failure

Medication Class	Action of Medication
Angiotensin-converting enzyme inhibitors (ACE inhibitors). Called the "prils." Enalapril, lisinopril, captopril	ACE inhibitors are a type of vasodilator, a drug that widens blood vessels to lower blood pressure, improve blood flow and decrease the workload on the heart.
Angiotensin II Receptor Blocker (ARB's) Losartin, valsartin.	ARB's work similarly to ACE inhibitors and have many of the same benefits as ACE inhibitors. They may be an alternative for people who can't tolerate ACE inhibitors.
Digoxin Lanoxin, digitalis	This drug increases the strength of heart muscle contractions. It also tends to slow the heartbeat. Digoxin reduces heart failure symptoms and improves your ability to live with the condition.
Beta-Blockers. Called the "ol"s Carvedilol, metoprolol, bisoprolol	This class of drugs slows your heart rate and reduces blood pressure. These medicines also reduce the risk of some abnormal heart rhythms.
Diuretics Commonly prescribed are furosemide (lasix) and bumetanide (Bumex)	Often called water pills, diuretics make you urinate more frequently and keep fluid from collecting in your body. Diuretics also remove potassium and magnesium, so, supplements of these minerals may be necessary and monitoring levels of potassium and magnesium in your blood through regular blood tests is often performed.
Aldosterone antagonists. Spironolactone (aldactone), epleronone (inspra)	They are primarily potassium-sparing diuretics, but they have additional properties that help the heart work better, may reverse scarring of the heart and may help people with severe heart failure live longer.

sicians have a consistent framework from which they can decide how to provide the best care to their patients. Some of the medications to be discussed here have been discussed earlier in this article related to specific cardiac conditions. In this section, the medications will be discussed in the context of prevention and management of heart failure.

According to the Mayo Clinic, there are 6 classes of medications most commonly used in the prevention and treatment of heart failure: ACE inhibitors, ARBS, digoxin (inotropes & pressors), beta blockers, diuretics, and aldosterone antagonists.[12] See Table 1.

Using the best-available evidence, the ACC/AHA task force has released practice guidelines to provide physicians with a guide for treating heart failure (HF), which is a multifaceted clinical condition. The guidelines use the ACC/AHA staging system to organize the prevention and treatment protocols.[13] There are 4 stages: A, B, C, and D. Stages A and B represent people that are at risk for heart failure, whereas stages C and D represent people with heart failure.

In stage A are people who are at a high risk for HF but who are without structural heart disease or symptoms of HF. Stage A treatment goals include treating hypertension, treating lipid disorders, encouraging smoking cessation, encouraging regular exercise, discouraging alcohol intake, and controlling metabolic syndrome. Metabolic syndrome is also called syndrome X and includes any 3 of the following: abdominal adiposity, hyper-triglyceridemia, low high-density lipoprotein, hypertension, and fasting hyperglycemia. The most commonly prescribed medication classes include ACE inhibitors or ARBs to treat hypertension and cholesterol lowering medications.

Angiotensin-converting enzyme inhibitors (vasodilators) work for people at risk for heart failure by widening the arteries to lower blood pressure, improve blood flow, and reduce the work load on the heart (reduce after load). Angiotensin II receptor blockers work similarly to ACE inhibitors, but are not as effective as ACE inhibitors at reducing blood pressure and lowering after load. Angiotensin II receptor blockers may be taken with ACE inhibitors or alone, and are used for people who do not tolerate ACE inhibitors. One adverse effect often experienced by patients on an ACE inhibitor is a dry, non-productive cough. Other medications that are often prescribed with ACE inhibitors for patients with HF include smoking cessation medications, medications to control diabetes mellitus, and drugs to assist with smoking cessation.

For people in stage B, by definition, there is structural heart damage, but no signs or symptoms of heart failure. Therapy goals for stage B include all those for stage A, however; additional medications may be prescribed for the structural heart damage. One such medication class is the beta blockers. For persons with a myocardial infarction (MI), beta blockers have been shown to have cardio-protective effects for the myocardium. For this reason, beta-blockers are recommended for all patients with recent or remote history of MI, regardless of ejection fraction or presence of heart failure. Beta-blockers are also indicated for all patients without history of MI who have reduced left ventricular ejection fraction (LVEF) with no HF symptoms.

Stage C patients have known structural heart disease, shortness of breath, fatigue, and reduced exercise tolerance. Stage D patients have marked symptoms at rest, despite maximal medical therapy (e.g. recurrent hospitalizations). Patients in stage C have the same treatment goals as those of stage A and B. In addition, diuretics and salt restrictions are indicated for those with current or prior symptoms of HF and reduced LVEF with evidence of fluid retention. It is in stage C that patients may have acute exacerbations of congestion and fluid overload, requiring increasing diuretic or multiple diuretic medications. Digitalis may be beneficial, in patients with current or prior symptoms of HF and reduced LVEF, to decrease hospitalization for HF. Digitalis works to increase contractility. Drugs known to "adversely affect patients with current or prior symptoms of HF should be avoided or withdrawn whenever possible (eg, nonsteroidal anti-inflammatory drugs, most anti-arrhythmic drugs, and most calcium channel blocking drugs)."[13, 14]

The treatment goals for stage D include the goals of stages A, B and C, as well as end of life care/hospice. Patients in stage D have poor activity tolerance and shortness of breath and fatigue at rest and/or with minimal activity. Medication treatment follows the same as stages A, B, and C, with the addition of experimental medications if accepted into clinical studies.

CONCLUSION

As the physical therapy profession continues its push towards autonomous practice, direct access, and providing best practice using evidenced-based principles, the need to understand medication classes, side effects, and impact on physical performance ability is paramount. With CMS moving towards a pay for performance model of reimbursement, the best possible outcomes will be a requirement. But, more important than reimbursement or any professional issue, it is the focus on the safety, best care, and best practice for our geriatric patients that is paramount. Understanding the use of medications to treat the various cardiac conditions described above is truly required to provide the best care possible.

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PHARMACOLOGY AND PHYSICAL THERAPY INTERVENTION FOR PAIN MANAGEMENT

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PAIN AND THE OLDER ADULT

Designing effective physical therapy interventions for older adults often involves the consideration of management of pain. Approximately 50% of community-dwelling older adults have pain, and approximately 85% of nursing home residents experience pain. More than 80% of older adults have chronic medical conditions that are typically associated with pain, such as osteoarthritis and peripheral vascular disease. Older adults often have multiple medical conditions, both chronic and/or acute, and may suffer from multiple types and sources of pain. This has major implications for older adults' health, functioning, and quality of life. If unrelieved, pain is associated with the following: depression, sleep disturbances, withdrawal, decreased socialization, functional loss, increased dependency, exacerbation of cognitive impairment, cardiovascular compromise, and increased health care utilization and costs.

To begin a discussion about physical therapy intervention and pain management, we must review some definitions:

1. *Pain* is defined as "an unpleasant sensory and emotional experience"[1] "whatever the experiencing person says it is, existing whenever he says it does."[2] These definitions highlight the multidimensional and highly subjective nature of pain. Pain is usually characterized according to the duration of pain (eg, acute versus persistent) and the cause of pain (eg, nociceptive versus neuropathic) that have implications for pain management strategies.
2. *Acute pain* defines pain that results from injury, surgery, or tissue damage. It is usually associated with autonomic activity, such as tachycardia and diaphoresis. Acute pain is usually time-limited and subsides with healing.
3. *Persistent pain* defines pain that *persists* for a prolonged period (usually more than 3 to 6 months).[1] Persistent pain may or may not be associated with a diagnosable disease process and autonomic activity can be present.
4. *Nociceptive pain* refers to pain caused by stimulation of specific peripheral or visceral pain receptors. This type of pain results from disease processes (eg, osteoarthritis), soft-tissue injuries (eg, falls), and medical treatment (eg, surgery, venipuncture, and other procedures). It is usually localized and responsive to treatment.
5. *Neuropathic pain* refers to pain caused by damage to the peripheral or central nervous system. It manifests itself as burning and diffuse pain. It is more responsive to anticonvulsant medications and less responsive to analgesics. This type of pain is associated with diabetic neuropathies, post-herpetic and trigeminal neuralgias, stroke, and chemotherapy treatment for cancer.
6. *Central Pain Syndrome* is when the brain detects indistinct or confusing pain signals and recruits additional brain matter to sort out the situation. This recruitment (called the NMDA system) becomes so powerful that it can kill brain cells. To avoid cell death, a separate inhibitory system (called the GABA system) begins to shut down blood flow to various brain parts. This conflict between the two systems is central pain syndrome (CPS), in which the pain doesn't make sense, but it exists. The various components of CPS are: muscle pain, dysesthesia, hyperpathia, allodynia, shooting pain, circulatory pain that mimics circulatory insufficiency, and peristaltic pain in the visceral organs. These people are sensitive to bright lights, loud noises, medications, temperature, may have hypersensitivity to touch, and mechanical pressure.[3,4]

PHARMALOGICAL MANAGEMENT OF PAIN

Pharmacologic management is the most common treatment for pain control in older adults. There are a variety of pharmacologic agents to treat pain in the elderly, and no two patients will respond in the same way. It is important to understand specific properties of drugs that are prescribed and common age-related changes that can influence how drugs are metabolized and absorbed. Starting with a low dose and titrating upward until pain relief is achieved must be balanced with the development of intolerable side effects or toxic serum levels. Using the least invasive route of administration and reassessing the effect of the drug are important components of effective analgesic management.

Older persons are more susceptible to adverse drug reactions for several reasons: Physiologic changes resulting from aging vary among elders. Body fat composition (muscle-to-fat ratio) changes as people age and impacts protein binding, which in turn impacts drug effectiveness. Decreased protein stores due to poor nutrition, for example, will affect the protein-binding capacity of certain medications. Similarly, given that many older adults are on multiple medications, the drugs may compete for protein-binding sites, rendering one or more medications ineffective. Functions that affect the absorption, metabolism, and clearance of drugs, include slowed gastrointestinal motility as well as decreased cardiac output and glomerular filtration rate. These changes in function may cause side effects, such as sedation or confusion, for some patients using both opioid and nonopioid medications, including antidepressants and anticonvulsants.

Acetaminophen is generally considered the first line of treatment for elders with mild-to-moderate pain, especially of musculoskeletal origin. It must be used with caution in patients with liver disease, end-stage renal disease, or history of alcohol abuse. In patients with renal or liver

disease, a reduction of the maximum daily dose of 4 g of acetaminophen by 50% to 75% has been recommended.[1] If this is ineffective, progression to nonsteroidal anti-inflammatory agents is suggested. These types of agents are helpful only for short-term therapy. Gastrointestinal toxicity, platelet dysfunction, renal dysfunction, and sodium retention, limit their usefulness in some patients. *"Conservative calculations estimate that approximately 107,000 patients are hospitalized annually for nonsteroidal anti-inflammatory drug (NSAID)-related gastrointestinal (GI) complications, and at least 16,500 NSAID-related deaths occur each year among arthritis patients alone."*[5] In a recent article, the conclusions stated that even short term treatment with NSAIDs is not recommended because of increased of death and recurrent MI in patients with prior MI.[6] These cautions make it more appealing to use NSAID iontophoresis and/or transdermal NSAID creams such as Voltarin Gel or Flector patches which have minimal GI and MI complications.[7]

Opioid analgesic drugs may help relieve moderate-to-severe pain. Although previously shown to be effective in treating patients with cancer pain, they are emerging as acceptable to use in patients with noncancer pain as well. One of the benefits of these medications is that they have no ceiling effect. In other words, escalating doses will not cause organ damage. They are limited, however, by side effects, such as: nausea, dependency, vomiting, itching, sedation, respiratory depression, and constipation. Usually, the patient will become tolerant to most of these side effects. If not, it is sometimes helpful to switch to another opioid medication or add an antiemetic. It is important to monitor older people for safety due to dizziness or potential for dehydration due to nausea and vomiting. All individuals on opioids should have a bowel regimen initiated to maintain regularity.

Adjuvant medications are those medications not formally classified as analgesics, but have pain-relieving properties. They have been shown to be most helpful for treating neuropathic pain. Topical agents, such as lidocaine 5% patch (*Lidoderm*) and capsaicin, have been helpful in relieving pain associated with postherpetic neuralgia and diabetic neuropathy. Specific antidepressants and anticonvulsants have been helpful in treating various nerve-related pains as well. Adverse reactions such as dizziness, fatigue, seizures, and dry mouth should be monitored.

PHYSICAL THERAPY MANAGEMENT OF PAIN

Physical therapy is the mainstay of pain management, because the treatment techniques help reduce pain without medication's adverse events. They also enable people to decrease their medication intake, improve function, and learn self pain management skills. In a study of 80 people who had OA of the knee, the group who received 4 weeks of physical therapy had 5% of patients go on to receive a total joint replacement 52 weeks postintervention, the placebo group had 20% receive a TKR.[8] The treatment group received manual therapy of the lumbar spine, hip, and ankle as needed, a standard strengthening program of the knee muscles, and a home exercise program. The control group was treated with subtherapeutic 10% duty cycle pulsed ultrasound to the knee at 0.1 W/cm^2. Some of the active treatments in this study are illustrated in the following case study.

CASE STUDY

The patient was a 68-year-old female, referred to physical therapy after developing severe low back pain during a hospitalization for the surgical treatment of a brain aneurysm 6 months prior. While hospitalized, she underwent a series of 3 epidural injections with corticosteroids and Marcaine, with minimal pain reduction. She had a past medical history of L4-5, and L5-S1 spinal fusion done 5 years previously. Her medications included: Crestor, Amlodipine Besylate (Norvasc), Lyrica, Bystolic, Lisinopril, Ultram, metamucil, multiple vitamins, calcium with vitamin D, and fish oil. She had allergies to Zoloft, Morphine, and Vicoden. She was not able to take NSAIDs or acetaminophen due to persistent kidney failure. Ultram was to be used with caution due to kidney failure. Her complaint was of constant right-sided low back pain, rated as 6/10 on the Visual Analog Scale (VAS), which radiated a burning sensation down the right leg to the lateral aspect of the right foot, with a Back Index of 43% disability. Her major difficulties were sleeping at night, standing 10 minutes, and lifting a bag of groceries, all of which she could do 6 months ago.

Evaluation

Her LE and LS ROM were near normal, considering she had a 2-level spinal fusion. Neurological tests of sensation, DTR, and dural glides, as well as lower extremity pulses, were normal. She only had strength deficits of the abdominals and bilateral hip flexors of 3+/5. The anterior SI stress test was positive with point tenderness, allodynia, and inspissation over the right SI joint. There was a 5° F increase of skin temperature over the right SI, as compared to the left. She reported sensitivity to bright lights and loud noises. Blood pressure was 154/88, pulse was 64 BPM. There were soft bilateral diastolic murmurs in the carotid arteries, and O_2 saturation was 98%.

Discussion and Treatment

This lady had persistent right SI rotation with concurrent CPS (indicated by light and sound sensitivity), and a neuropathic pain component. Her treatment plan consisted of the following local modalities: Dexamethasone iontophoresis to the right SI, because of the constant pain and increased skin temperature; manual therapy to mobilize the SI, performed with medium frequency electrical stimulation to improve her SI mechanics; and pulsed ultrasound for the mechanical effects, such as cavitation and acoustic microstreaming, which are more important in the treatment of soft tissue lesions than are the thermal effects. Cavitation occurs when gas filled bubbles expand and compress because of the ultrasonically induced pressure changes in tissue fluids, with a resulting increased flow in the surrounding fluid. Regular or stable cavitation is considered to be beneficial to tissue.[9,10] Transcranial microcurrent electrical stimulation was used to decrease the CPS.[11,12] She was instructed in self mobilization and core strengthening techniques to prevent reoccurrences.

After the first week of treatment her ion was changed from Dexamethasone to Salicylate for the NSAID/decongestive effects, as her pain was intermittent. Her anterior SI mobilization was continued with the medium frequency and tran-

scranial electrical stimulation, as was the pulsed ultrasound. She was instructed on stabilization exercises of abdominal sets, planks, and ball planks. Evidence-based literature reviews indicate that the multimodality approach is more effective than any single modality, or the combination of mobilization and exercise, in the patient who has long standing pain.

She was treated 3 times a week for 4 weeks and had a complete resolution of pain (0/10 VAS) and no functional deficits. She reported that she was not bothered by lights or sounds as much, and she felt the best that she had in years. She was able to stop the Lyrica (used for her neuropathic pain component) and Ultram.

This case demonstrates how a complete multi-modality physical therapy program is used to treat the geriatric patient to enable them to decrease their medication intake and reduce the risk of long term medication induced health deficits.

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PHARMACOTHERAPY AND WOUND HEALING IN THE ELDERLY ADULT

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INTRODUCTION TO WOUND HEALING PROBLEMS IN THE ELDERLY ADULT

Populations around the world are aging and the issue of chronic wound problems in the elderly adult is presenting major problems for health care providers, patients, and payers everywhere. Leg ulcers (neuropathic, arterial, and venous) and pressure ulcers and poor surgical wound healing contribute to high degrees of mortality and morbidity and impaired quality of life. Leg ulcers are often the precipitating event leading to lower extremity amputation. Diabetes is increasing, and the lifetime risk of foot ulceration for diabetics is 15% to 25%, with 7% to 20% of these ulcers leading to amputation.[1]

The health management of elderly adults often includes polypharmacy. In this article we consider how pharmacotherapy for wounds and other comorbidities may contribute to wound healing success or failure. Knowledge of effects and side effects of medications directly affects physical therapists' ability to design and prescribe effective wound management strategy. For instance, when using physical therapy interventions like electrical stimulation (ES), it may be best to schedule the treatment session a certain period of time after administration of medications such as systemic antibiotics. There is evidence that combining ES with antibiotics has the potential for killing biofilms.[2] Biofilms are colonies of bacteria that produce cytotoxins detrimental to the wound and are difficult to kill with either antibiotics or antiseptics.

Another example is the impact of anticoagulant or antiplatelet drugs on the selection of wound debridement methods. Because sharp debridement may cause excessive bleeding in patients on anticoagulants, debridement with enzymes may be the best choice. Collaboration with the physician, pharmacist, and nurse will ensure understanding about the coordination and interaction of medications, including topical agents and nutraceuticals, with the physical therapy prescription.

REVIEWING THE PATIENT MEDICAL AND PHARMACEUTICAL HISTORY

The *Guide to Physical Therapist Practice* specifies guidelines for management of the integumentary system.[3] The guide lists a series of steps for patient management. The first step is to determine the reason for referral to the physical therapist. Is it to heal the ulcer, to prepare the wound bed for healing, to salvage the limb, or for pain relief? After this is established, the next steps are to review the medical history and to do a systems review to determine the patient's health status, eg, presence of comorbidities (COPD), healed conditions (osteomyelitis), or conditions in remission (rheumatoid arthritis or cancer). Each medical condition and the pharmacological agents used for treatment should be listed in the patient medical record, except perhaps some over-the-counter remedies and neutroceuticals. It is important for the PT to recognize the category of drugs and evaluate it for potentially positive or negative effects on healing. For example, patients with a condition like polymyalgia rheumatica or chronic obstructive pulmonary disease (COPD) use steroids, patients with diabetes take insulin, and many patients take anticoagulants and other cardiovascular medications, all of which can affect wound healing. The wound may be treated topically with antibiotics, antifungal or anesthetic medications, or a combination of agents like silver or Cadexamer iodine imbedded in wound dressings. The patient may be immune compromised due to co-morbidities and taking antiretroviral drugs. Patients who are currently or have taken antineoplastic (cancer) drugs, which are neurotoxic and damage nerve cells and nerve conduction, may have medication induced peripheral neuropathy that can lead to foot ulcers.[4]

Anticoagulant and antiplatelet medications are used to thin the blood; however, they increase the risk of subcutaneous bleeding. Even mild trauma can cause hemorrhaging into the tissues. Since the clotting factors of the blood are inhibited, hemostasis, or clot formation, does not occur or occurs minimally, leaving unclotted blood in the subcutaneous tissues, and decreased oxygen and nutrient supply to anatomic structures like muscles. Tissue then becomes hypoxic, anoxic, and finally necrotic. This process creates a high risk for developing an open ulcer. Many deep tissue pressure ulcers and venous ulcers have this pathogenesis. Extra care must be used in bed and wheelchair positioning, and in the application of dressings and wraps for patients in this group to avoid bleeds.

Pain is one of the cardinal signs of inflammation, and pain history should be part of patient history. Excessive pain, including pain in areas away from the site of the wound, inhibits healing,[5] reduces patient acceptance of treatment, and adversely affects quality of life. Anxiety is often associated with wound care pain, and short or intermediate acting benzodiazepines such as lorazepam may be the best choice to ameliorate this in older adults.[6] Later in this article, principles and steps to using analgesic therapy are presented.

Clinical Implications: Two specific instances when pain needs to be addressed by the PT before treatment are prior to wound debridement and at wound dressing changes.[7,8] Premedication with a lidocaine soak (15-20 minutes before the procedure) or oral anti-anxiety medication (45-60 minutes prior) are recommended.[8]

When taking the medical history and checking the medication list of patients, physical therapists need to discover the factors that will impact healing. In the following section of this article, the pharmacist half of this collaboration discusses effects of drugs on wound healing for the elderly adult population.

MEDICATION EFFECTS ON WOUND HEALING OUTCOMES

Medication use in older patients for the management of chronic diseases plays an important role in either the stimulation or retardation of wound healing. All medications exert both positive and negative effects on the systems of the body. Pharmaceuticals are used both directly and indirectly in wound management practice. Drugs are applied topically and used systemically in many wound patients. Medication is used regularly for infection, pain management, immunosuppression, and supplementation.

The effects of systemic medications on the healing wound vary greatly. We commonly see medications prescribed for a condition unrelated to the wound, but which may have side effects that inhibit or stimulate healing. Medications interfere with specific phases of wound healing and will affect cells, pathways, growth factors, cytokines and other important components of the wound healing cascade. In addition, some drugs will, as a side effect, reduce blood flow, blood cells, and organ functions critical to wound healing.[10,11] Table 1 shows drugs with negative and positive effects on wound healing. In the following sections each group of drugs will be discussed. Some information presented in this section was previously published in the journal, *Pharmacist,* but has been updated as needed for this application and used with the journal's permission.[12]

DRUGS WITH NEGATIVE IMPACTS

In this section you will learn about drugs with negative impacts on healing including: Corticosteroids, antineoplastic drugs, nicotine, carbon monoxide, hydrogen cyanide, nonsteroidal anti-inflammatory drugs (NSAIDS), anti-platelet drugs, anti-coagulants, vasoconstricting drugs, anti rheumatoid arthritis (RA) drugs, antibiotics, colchicine, nitric oxide, growth factors, and anesthetics.

Corticosteroids

Steroids are a group of widely used drugs for a number of indications, and they have systemic effects. Such drugs include the various forms of cortisone, such as prednisolone and prednisone. Low doses may interfere with wound healing by causing mild anorexia and undernutrition. High doses of steroids have a major effect on wound healing, because their anti-inflammatory action interferes during the inflammatory phase of healing. They also reduce immunocompetent lymphocytes, decrease antibody production, and diminish antigen processing, resulting in failure of leucocyte migration (such as polymorphs and macrophages) into the wound, which in turn diminishes fibroplasia and neovascularization during the proliferative phase.[13] Finally, there will be the delayed epithelialization and wound contraction, and increased susceptibility to infection.[10,14-16]

Topically applied steroids, used to treat eczema or other dermatologic conditions will cause vasoconstriction at the wound edge, and inhibit fibroblast proliferation and collagen synthesis if inadvertently applied too close to the edge of a wound. Therefore, you should leave about a 2 cm gap between the topical steroid used to treat the skin rash and the wound edge.

Antineoplastic drugs (Anti-cancer drugs)

Antineoplastic drugs (anti-cancer drugs) are cytotoxic but not cancer cell-specific. They act on rapidly replicating cancer cells and are designed to interrupt cell reproduction, which can negate growth of new cells by damaging cell DNA or preventing DNA repair. Effect on healing is more likely to occur during active therapy and immediately after.[13] However, neurotoxic effects may be manifest during or post therapy as peripheral neuropathy, which is a potential pathogenesis for ulceration. During therapy, there is the risk of an extravasation injury from leakage of the drug into the soft tissue, and due to the hematological changes that may affect healing by reducing most red and white blood cells. These drugs can cause myelosuppression, and be neurotoxic (cis-platinum, Vinblastine, Vincristine, Carboplatin, Vindesine and Hexamethylamine). Hydroxyurea (Hydrea®) is also known to be responsible for ulcers with long term or high doses, due to damage of basal keratinocytes, which leads to dermal atrophy and causes platelet mediated inflammatory response, eventually causing micro-thrombi formation and diabetic peripheral neuropathy.[16,17]

Table 1. Negative and Positive Effects of Drugs on Wound Healing

Drugs with Negative Effects on Wound Healing	Drugs with Positive Effects on Wound Healing
Corticosteroids	Hemorheologics
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	Pentoxifylline (Trental®) and Other Methyl Xanthines
Cytotoxic	Estrogen
Vasoconstricting	Retinoids
Nicotine, Carbon Monoxide and Hydrogen Cyanide	Vitamins A
Anti-leprotic	Vitamin C
Anti-coagulant/Antiplatelet	Zinc
Antibiotics	Topical Antibiotics
Immuno-suppressives	Anesthetics
Colchicine	

Nicotine, carbon monoxide and hydrogen cyanide

Smoking adversely effects wound healing via nicotine, carbon monoxide, and hydrogen cyanide. Nicotine diminishes red blood cells, fibroblasts and macrophages, and increases platelet adhesiveness, which produces cutaneous vasoconstriction. Carbon monoxide affects the transport of oxygen via hemoglobin; and hydrogen cyanide inhibits enzyme systems necessary for oxygen transport at the cellular level, as well as oxidative metabolism. One cigarette reduces the peripheral blood flow by 50% for one hour and reduces oxygen tension for two hours. Smoking can therefore be a major cause of the non-healing wound. In addition, patients who smoke are 76% more likely to develop a pressure ulcer than nonsmokers.[18] The use of smoking cessation products may have a negative effect on healing, however if these drugs are successful in stopping smoking, they are acceptable.

Anti-platelet drugs

Antiplatelet drugs like clopidogrel (Plavix®), aspirin, and NSAIDs inhibit prostacyclin synthesis, a potent vasodilator, which inhibits platelet activation and has anti-inflammatory properties.[16] Antiplatelet drug effects are dose dependant. Since inflammation is the initiating phase of wound healing, absence or blunted inflammation by antiplatelet drugs can have negative effects on progress towards the proliferative phase, and inhibit angiogenesis from occurring. Even a baby aspirin can cause maximum inhibition of platelet function and primary hemostasis responsible for initiating the healing cascade. However, when these drugs are halted, platelet function returns to normal within 12 hours of administration.[19] Thus communication with physician and pharmacist during the inflammatory phase is indicated if these drug therapies are noted. Alternative treatment may be designed.

Anti-coagulants

Anticoagulant drugs include Warfarin and Heparin. They inhibit coagulation and can adversely affect wounds by increasing the risk of hematomas and seroma formation. They can cause tissue necrosis "purple toe syndrome." There is some evidence of risk in terms of wound healing. Tissue necrosis can also be caused by drugs (eg, cytotoxics or sclerosant) leaking from veins into the tissue around the veins.[16]

Vasoconstricting drugs

Adrenaline, nicotine, and cocaine can cause tissue hypoxia, affecting the microcirculation and tissue formation. Some local anaesthetics have vasoconstricting properties, and care must be taken if used as a pain reliever (eg, Lidocaine).[11,16]

Antibiotics

Antibiotics are overused in treatment of acute and chronic wounds. Antibiotics by their nature kill bacteria but do not improve wound healing. They are important in the treatment of wound infection; however they play no role in non-infected wounds, and may cause increased antibiotic resistance. Penicillins may interfere with the tensile strength of wounds by affecting the crosslinking of collagen. Tetracyclines/erythromycin demonstrate anti-inflammatory properties through the inhibition of leukocyte chemotaxis, which will delay healing. Topical antibiotics like neomycin are potent sensitizers of the skin, result in adverse cutaneous reactions, and should be avoided in chronic wound patients, although some may be useful, as described later.

Clinical Implications

Oral and IV antibiotics taken by elderly adults cause side effects including gastrointestinal symptoms like nausea, vomiting, and diarrhea, as well as other systemic reactions, so should be used judiciously.[6]

Colchicine

Colchicine is used in the treatment of gout and severe vasculitis and has a number of negative effects on wounds. It reduces granulocyte migration and cytokine release, is vasoconstrictive, reduces fibroblast synthesis, interrupts extracellular transport of procollagen and collagenase synthesis, and increases collagenlysis and inhibits wound contraction.[16]

Anti-rheumatoid arthritis drugs

Anti-rheumatoid arthritis drugs, like D-Penicillamine, inhibit the metallo-enzyme lysyl oxadase, causing decreased cross-linking of collagen, increased collagen degradation, and decreased breaking strength. Methotrexate partially blocks DNA & RNA synthesis. It is 100-1000x more cytotoxic to macrophages and T cells than epithelial cells. It inhibits Interleukin-1 (IL-1) and decreases synthesis of Interleukin-6 (IL-6). The full impact of this drug is not yet clear, but the physical therapist needs to be aware of this potential wound healing complication.[16]

Medications with a Positive Effect on Wound Healing

There are some medications which may have a positive impact on wound healing. Examples include: hemorheologics , pentoxifylline (Trental®), other methylxanthines, estrogen, phenytoin, retinoids, vitamins, and topical antibiotics.

Pentoxifylline/oxpentifylline (Trental®)

Pentoxifylline/oxpentifylline (Trental®) is used to improve healing, by changing the flow characteristics of blood, reducing platelet aggregation and leukocyte adhesion, and increasing red blood cell membrane flexibility. It is used to treat PVD and intermittent claudication. It increases blood flow to ischemic tissue, inhibits TNF alpha, and has vasodilator effects.[11,16,20-22.]

A Cochrane review indicates that Pentoxifylline appears to be an effective adjunct to compression bandaging for treating venous ulcers.[23] Pentoxifylline, in the absence of compression, may be effective for treating venous ulcers, although the evidence should be treated cautiously. The majority of adverse effects are likely to be tolerated by patients with gastrointestinal disturbances, the most frequent adverse effect.

Estrogen

Estrogen plays a role in wound healing, particularly in postmenopausal women who are known to have reduced dermal collagen and dermal thickness. Changes occur in the levels of transforming growth factor beta (TGF beta 1), as compared to levels of younger women, suggesting that the hormone aids in the modulation of TGF beta 1 levels. TGF beta is involved in many cellular processes including cell growth, cell differentiation, apoptosis, and cellular homeostasis. In some studies, the application of topical estrogen to non-healing leg ulcers in

postmenopausal women has improved wound healing.[24]

Phenytoin

Phenytoin is a drug used in the treatment of seizures. When given orally, it is known to cause gingival hyperplasia. Some studies have been published on the topical application resulting in a decrease in inflammatory response, an increase in collagen synthesis, and an increase in new blood vessel formation.[11,15,21,25] The efficacy of topical Phenytoin in the treatment of diabetic foot ulcers was evaluated in a controlled inpatient study, which found that the mean healing time with Phenytoin was significantly shorter than for the control group.[10]

Vitamin A

Vitamin A, a fat soluble antioxidant enzyme catalyst, stimulates both humeral and cell mediated immune mechanisms, and some studies show that it can reverse the delayed wound healing effect of oral corticosteroids. It reverses the stabilizing effect of lysosomal membranes, restimulates fibroplasia, and has a significant effect on epithelialization. Vitamin A analogues have been used for a number of years in dermatology. Isotretinoin (Roaccutane®), approved for cystic acne, is associated with reversal of steroid induced inhibition of healing, with positive effects on wound contraction, and improvement in epithelialization of wounds. Use caution with use of this drug to avoid hypervitaminosis A.[11,16]

Vitamin C

Vitamin C is an essential antioxidant and as such, one of the most important agents in wound healing. It is involved in all phases of wound healing, including: the inflammatory phase, when it is essential for both neutrophil and fibroblast function; the proliferative phase, where it stimulates fibroplasia and strengthens and promotes neoangiogenesis (new blood vessel formation); and the remodeling phase, when it is required for the hydroxylation of lycine and proline during the synthesis of collagen, and is critically important for the tensile strength of a wound. In addition, vitamin C influences resistance to infection.

Zinc

Zinc is very important to wound healing because of its part in the structural integrity of protein. It is essential for the functioning of at least 200 enzymes in the body and plays a vital role in vitamin A metabolism. It is involved in the cross-bonding of collagen and promotes re-epithelialization. Zinc has been applied topically as a paste bandage for many years in the management of venous leg ulcers.[11,20]

Topical antibiotics

In general, topical antibiotics are not recommended, because they may cause antibiotic resistance, making the systemic form of the agent ineffective, as well as causing skin sensitization. An exception is topical doxycycline, a member of the tetracycline family of antibiotics, which inhibits metalloproteinases (MMPs). Metalloproteinases are involved in chronic inflammation and slowed wound healing. Studies demonstrate that doxycycline effectively inhibits TACE (tumor necrosis factor alpha converting enzyme) and MMPs, and suggest that topical 1% doxycycline treatment improves healing of chronic diabetic foot ulcers.[16,26-28]

Immune suppressants

These drugs play an important role in the treatment of inflammatory diseases (eg vasculitis). Vasculitis is a cutaneous condition that reveals itself as nodular erythema, punched-out ulcers, or digital gangrene due to muscular-vessel vasculitis. In general, systemic symptoms accompany all cutaneous vasculitic syndromes, and these symptoms include fever, malaise, weight loss, arthritis, and/or arthralgia. In the majority of patients, vasculitic lesions will affect the lower extremities, mostly at dependent sites or underlying tight fitting clothes, and may be mistaken for venous ulcers. Steroids are often used to treat this condition, and sometime colchicine is prescribed. With the exception of steroids, there is no strong evidence of significant inhibition of healing exerted by immune suppressant drugs. There is some evidence that they may have positive effects on healing.[16]

Nitric oxide and L-arginine

Nitric oxide (NO) is a key modulator of cell responses, both vascular and inflammatory, to various stimuli such as infections, allergens, and wounds. Production of NO is highly regulated by tissue/cell type-specific isoenzymes, allowing for increased control relative to regional tissue demands, and it participates in the orchestration of wound healing . Nitric oxide is formed from the amino acid L-arginine and stimulates the nitric oxide pathway, resulting in increased vasodilation, immunity, angiogenesis, and insulin secretion. It appears that oral L-arginine supplementation restores diabetic NO levels toward normal values, and can partially reverse the impaired healing of diabetes and, in parallel, restore wound NO levels toward more normal values significantly enhancing wound breaking strength.[28-31]

Growth factors

There is considerable research in the area of growth factors (cytokines). We are beginning to understand the importance that these cytokines have in wound healing, although their precise role is not yet clear.

Tissue generated growth factors include platelet derived growth factor, macrophage growth factor, fibroblast growth factor, transforming growth factor alpha and beta, and epidermal growth factor just to mention a few. They are produced by various systems within the wound itself and play an important role in all phases of healing, including the stimulation of enzymes to remove necrotic tissue from a wound, the deposition of new granulation tissue, and the break down of collagen strands to enable cross-linking and, ultimately, turn off the enzymes to end this process. There have been a number of studies, described below, in which applying growth factors directly to wounds has had mixed results. Two kinds of growth factors are described.

Platelet derived growth factor

Therapeutic growth factors used for wound healing include platelet-derived growth factor (PDGF), a topical gel containing 0.01% recombinant human platelet-derived growth factor (rhPDGF), FDA approved and marketed for treatment of diabetic ulcers. A prospective, multicenter, double-blind, placebo-controlled, parallel group, randomized study was conducted to evaluate the safety and efficacy of a topical gel containing 0.01% rhPDGF for healing of chronic

lower-extremity diabetic ulcers. Results of the study showed that rhPDGF-based gel healed a greater percentage of patients, and also healed patients faster and caused a greater reduction in the ulcer size than placebo.[32-33]

Hematopoietic growth factors

Hematopoietic growth factors include granulocyte colony stimulating factor, granulocyte macrophage stimulating colony factor, and erythropoietin. Their function is to increase the blood cell population, and they have been used particularly in the management of anemia associated with renal failure, for patients undergoing hemodialysis, and as a rescue for patients receiving chemotherapy. There are some studies where hematopoietic growth factors placed on a wound caused some improvement in wound healing.[34-35]

Analgesics

Pain plays an important role in the healing of both acute and chronic wounds. Most analgesics do not have negative effects on wound healing, with the exception of NSAIDs, both Cox-1 and Cox-2. In this section we consider the following 3 things:

1. Analgesic recommendations, applying the World Health Organization (WHO) pain ladder.
2. Clinical applications of analgesics.
3. Treatment principles for proper use of analgesics.

World Health Organization pain ladder

Adapted from the WHO pain ladder, there are 3 recommended steps to pain management appropriate for use in elderly adults[35]:

Step1, Mild pain (VAS scale 1-3): Treat with non-opioid analgesics, such as acetaminophen, at moderate doses to prevent pain rather than to treat pain once it has occurred. Maximum safe dosage for adults is 1000 mg, taken 4 times daily, for short term use. However half that dose is recommended as the maximum amount for the elderly adult.[6]

Step 2, Mild to moderate pain (VAS4-6): Consider use of acetaminophen as adjuvant therapy with opioids, and avoid NSAIDS.[6] When used together, these medications produce an additive effect, while minimizing the dose of opioids required, thus minimizing undesirable side effects. The opioid sparing strategy is the backbone of the WHO "analgesic ladder." Tramadol, an atypical opioid, can be used with acetaminophen and is better tolerated than opioids. It is not considered a controlled substance, is not habit forming, and is better tolerated by older adults than opioids.[6] Another adjuvant treatment is the lidocaine patch, 5%, that has efficacy controlling neuropathic pain and postherpetic neuralgia. It is also reported to be used effectively for treatment of nociceptive pain.[9,36]

Step 3, Moderate to severe pain (VAS 7-10): Use opioid analgesics. Codeine, hydromorphone, and morphine all affect the central nervous system to alter the perception of pain, and because of this mode of action have adverse effects of sedation, confusion, constipation, falls, and respiratory depression. They are administered either orally or intravenously. Dosages are usually titrated to reach optimal pain management.

Clinical Implication

- Assume all wounds are painful and may become more painful over time (hyperalgesia).
- Know that pain inhibits wound healing and may be a sign of infection.
- Accept that the skin surrounding the wound can become sensitive and painful (central sensitization).
- Accept that for some patients the lightest touch can be intensively painful (allodynia). Refer for specialist assessment if pain increases or there are signs of malodor or purulent wound drainage.

Treatment principles for proper use of analgesics:

1. Analgesic medications are used to provide symptomatic pain relief. They do not modify the underlying cause of pain.
2. Combining pharmacological and nonpharmacological approaches may allow lower drug doses to be employed.
3. Selection of medication should be based on the highest likelihood of gaining pain relief, with the lowest likelihood of side effects.
4. The goal of analgesic therapy needs to be established. Is the aim to eradicate pain or to reduce it to tolerable levels? Complete pain relief is rarely achievable when dealing with pain of neuropathic origin.
5. Pain management requires a balance between pain relief and the maintenance of function.
6. The timing of analgesic medications is often as important as the medication selected. A short-acting analgesic should be used for infrequent or incident pain. Sustained-release analgesics are best given regularly, for persistent or frequently recurring pain.
7. Remember, there is no such thing as PRN (as needed) if pain is an issue. Regular medication is essential to ensure drugs in the system are maintained at therapeutic levels.
8. Medications should, generally, be commenced at a low dose, monitored, and increased slowly as required. If pain becomes more severe, more frequent monitoring and higher doses should be implemented.
9. Adverse effects other than pain, such as constipation, insomnia, and depression, may significantly impact an individual. Treatment of these adverse effects is an important part of pain management strategy.

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For age is opportunity, no less than youth itself, though in another dress,

and as the evening twilight fades away, the sky is filled with stars, invisible by day.

- Henry Wadsworth Longfellow

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