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Pharmacists' Role in Preconception Care

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

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Objectives

After completion of this program, the reader should be able to:

1. Explain the need for preconception care for women of childbearing age, regardless of pregnancy intentions, and the importance to public health.
2. Discuss roles for pharmacists in preconception care.
3. Describe the 14 evidence-based interventions recognized by the Centers for Disease Control and Prevention, and be able to identify how these interventions can be incorporated in practice.
4. Evaluate a woman's need for preconception care in the context of comorbid disease states, lifestyle and behavioral factors.

Abstract

Within the current health care system, preconception care is often a misunderstood topic and, in many cases, a missed opportunity to improve women's health and decrease adverse pregnancy outcomes. It is important that preconception care is delivered to all women of childbearing age, regardless of pregnancy intentions, as the interventions associated with preconception care can help improve a woman's health overall. In 2006, the Centers for Disease Control and Prevention (CDC) released four goals, 10 recommendations, and 14 evidence-based interventions regarding preconception care. Pharmacists can have a significant role in ensuring preconception care for all women through the application of the 14 evidence-based interventions which can be viewed in terms of three broad categories: direct provision of care, education and referrals. Diabetes management, hepatitis B and rubella vaccination administration, and oral anticoagulant, antiepileptic, and isotretinoin drug therapy modifications are interventions that can be applied by pharmacists through direct provision of care. Pharmacists can also educate women on folic acid supplementation, obesity control, alcohol intake and smoking cessation. Referrals are recommended for human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and sexually transmitted infection (STI) screening and for the management of maternal phenylketonuria and hypothyroidism. The pharmacist's role in preconception care also expands beyond the 14 evidence-based interventions, as pharmacists can play an important role in helping women and men develop reproductive life plans. Providing preconception care to all women of childbearing age represents an opportunity to encourage healthy behaviors and lifestyle changes that could improve population-based outcomes, while preparing individual patients for a potential pregnancy.

Key Terms

Health Behavior; Life Style; Obesity; Preconception Care; Pregnancy; Reproductive Life Plan; Vaccination; Women's Health

Case Scenario: KR is a 33 year old female with type 2 diabetes (BMI=31). She currently smokes one pack of cigarettes per day and reports moderate alcohol use. She has not received any vaccines or immunizations since starting college at age 18. She has been using combined oral contraceptives for the past 10 years but states that she would like to become pregnant within the next few years. What recommendations for preconception care would be appropriate for KR?

Introduction

In the United States, approximately half of pregnancies are unintended.[1] Unintended pregnancies include pregnancies that are unwanted and those that are mistimed. With unintended pregnancies occurring in a high percentage of patients, prenatal care often occurs too late to address the risks and modifiable behaviors associated with preventable birth defects and poor pregnancy outcomes. Organogenesis and embryogenesis have already begun by the time many women learn that they are pregnant, with the fetus being the most vulnerable during the first four to 10 weeks of pregnancy.[2,3] This means that the potential consequences of behaviors deemed risky for pregnancies, such as smoking tobacco, consuming alcohol and consuming inadequate folic acid intake, may have already impacted the development of the fetus before a woman recognizes her pregnancy and can change her habits. In the United States in 2010, the infant mortality rate was 6.15 deaths per 1,000 live births.[4] Although the infant mortality rate is impacted by various causes, the rates of infant and birth defects can be reduced through the provision of preconception care to all women of childbearing age.[3]

What is Preconception Care?

Preconception care provides health care professionals with an opportunity to address a public health issue that is too often missed. Preconception care consists of a set of interventions meant to minimize behavioral, social and health-related risks to a woman's overall health and to improve outcomes for potential pregnancies.[1] Reduction of modifiable risks and proper management of those risks that

cannot be changed, such as chronic disease states, is how optimal preconception health can be achieved in women of childbearing age with the help of health care professionals. In the United States, approximately 25 percent of women of childbearing age report smoking before pregnancy recognition, 24 percent admit to binge drinking and 25 percent were overweight before learning they were pregnant.[1] So, it is clear that many women are engaging in modifiable behaviors that are known risks to pregnancy. Even if healthier habits were adopted upon pregnancy recognition, the interventions may be too late as the fetus has already been in its most vulnerable state while pregnancy was still unrecognized; therefore, risk reduction must occur prior to conception.

Providing preconception care encourages women to create healthy lifestyles that they can maintain throughout their life, regardless of whether or not they ever have a child. In February 2013, the Centers for Disease Control and Prevention (CDC) launched the Show Your Love campaign to help educate women about preconception care and to improve the health of women and infants.[5] Recognizing that women have differing reproductive life goals, marketing materials were created to target two groups of women: those who plan to have a child and those who do not. For women planning a pregnancy, the campaign states, "Show your love. Your baby will thank you for it;" while the materials targeting women who do not want to become pregnant read, "Show your love. Your body will thank you for it." The CDC's Show Your Love campaign emphasizes that preconception care can improve the health of all women, not just those currently planning a pregnancy. Unfortunately, many women of childbearing age, as well as some health care professionals, lack full understanding of the goals and application of preconception care.[6] The Show Your Love campaign materials, available from the CDC's website, can be used to help demonstrate to patients the importance of preconception care.

Before the specific goals and application of preconception care can be discussed, the distinction must be made between preconception care and prenatal or perinatal care, which is provided throughout pregnancy.[7] Though perinatal and preconception care refer to differing stages of a woman's reproductive life cycle, many of the recommended interventions overlap. Interconception care, or care delivered in between pregnancies, is also considered a part of preconception care. Many incorrectly believe that preconception care is meant to be given immediately preceding pregnancy and that it only needs to target couples who are currently trying to have a child.[6] It is true that preconception care is important for those trying to become pregnant in the near future, but it is also applicable to all women and men of childbearing potential, regardless of pregnancy intention. In fact, in a study of women who were seeking pregnancy, receipt of preconception care was positively associated with beneficial lifestyle changes of cessation of drinking alcohol and improvement in the use of daily multivitamins in the month before conception.[8]

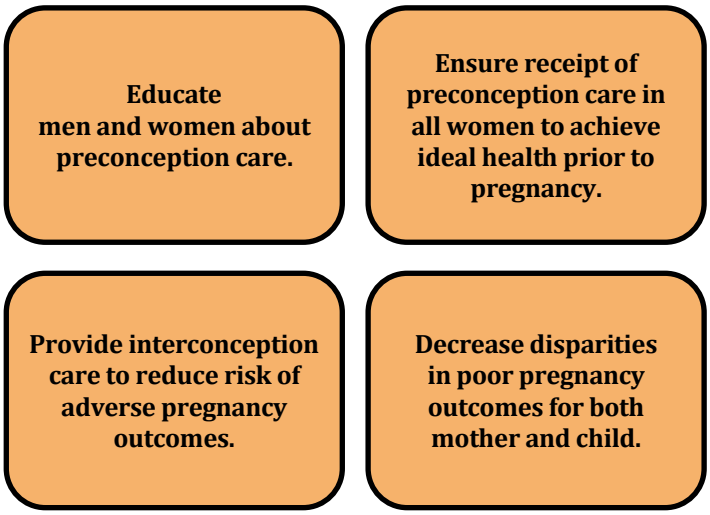
It cannot be overlooked that preconception care has also been associated with improvements in behaviors that can benefit a woman's overall health even if she is not currently planning a pregnancy.[8] Therefore, preconception care should be given to women, and their partners if possible, regardless of pregnancy intentions. Appropriate contraceptive methods are considered part of preconception care for a woman who does not intend to become pregnant. Statistics have shown that 53 percent of women who had an unintended pregnancy were not using contraceptive methods at the time of conception, highlighting another area of preconception care that needs improvement.[1] Counseling patients who do not intend to become pregnant in regard to their contraceptive options and helping patients to develop reproductive life plans are two ways health care professionals can help reduce unintended pregnancies.[9] Reproductive life plans encourage women and men to consider their overall life goals, including education and career plans, and then consider how having children would potentially fit into those goals. The pharmacist can encourage patients to consider how many children they would like to have and what types of family planning methods they intend to use. Tools for working with patients to develop reproductive life plans are available online through the CDC.[9] Providing appropriate preconception care to women, regardless of the pregnancy intentions identified in their reproductive life plans, allows for optimization of a woman's physical, social and emotional well-being and also promotes a healthy pregnancy and child, should she become pregnant in the future. In order to achieve the goal of offering preconception care to all women, this type of care must be fully recognized by health care providers and be integrated into the current health care system.[10]

A Public Health Priority

Healthy People 2020 consists of objectives set by the U.S. Department of Health and Human Services that are used to guide health promotion and disease prevention.[11] These science-based goals are developed every 10 years to increase awareness of specific health concerns affecting the nation and to promote an improvement in quality of life for all people. Healthy People 2020 not only addresses health disparities and current health concerns, but also outlines measurable, objective goals that allow the improvements in public health to be monitored. The goals are presented in such a way that they can be applied at the community, state and national levels to improve overall health care and address needs through evidence-based interventions. Healthy People focuses on targeting diseases with preventable causes and unhealthy behaviors that can be modified. Preconception care has a preventive care focus in regard to improving both maternal and infant health. Healthy People 2020 addresses several preconception care goals such as increasing the proportion of women of reproductive potential who take adequate folic acid, receive preconception care and adopt preconception health behaviors, use contraception to plan pregnancy, maintain a healthy weight before pregnancy and do not smoke before becoming pregnant.[12]

Also recognizing preconception care as a public health priority, the CDC published the Preconception Health and Health Care Initiative in 2006.[11] This plan was guided by four broad goals (Figure 1), 10 recommendations for integrating pre-

Figure 1. CDC: Four Goals of Preconception Care.[11]



conception care into health care (Figure 2) and 14 evidence-based interventions (Figure 3). The goals and recommendations have been added for completeness, but this article will expand on the evidence-based interventions and the pharmacists' role. The objective of the CDC's action plan was to enhance the knowledge of both women and their partners about preconception care. The 14 interventions can be split into four main categories: physical assessment, screenings, vaccinations and counseling for healthier behaviors.[13] Although additional interventions may be proposed for preconception care, the remainder of this article focuses on those evidence-based interventions identified by the CDC and how they can be incorporated into pharmacy practice through direct provision of care, education and referrals.[14]

Fourteen Proven Interventions

The Select Panel on Preconception Care, a CDC-chosen group of specialists in relevant areas of health care including obstetrics and gynecology, public health and family practice, defines preconception care as "a set of interventions that aim to identify and modify biomedical, behavioral and social risks to a woman's health or pregnancy outcomes through prevention and management."[1] The CDC's Preconception Health and Health Care Initiative illustrates how health care providers can proactively play a role in preconception care and thereby reduce adverse birth outcomes such as preterm and low birth weight deliveries, infant deaths, birth defects, maternal pregnancy complications and unintended pregnancies.[15] Although the national recommendations and proven interventions have been in circulation since 2006, they have yet to be fully incorporated into routine clinical practice by health care professionals.[16] Pharmacists have an opportunity to improve pregnancy outcomes by actively becoming involved in the proven interventions and educating the public and other health care providers about the importance of implementing the recommendations into everyday clinical practice. Pharmacists can become involved in three main ways: direct provision of care, education and referrals.

Direct Provision of Care

Vaccinations

Pharmacists can have direct involvement with proven interventions by administering services such as vaccinations to women of reproductive age per state law. Women at risk for hepatitis B virus (HBV) should be vaccinated to eliminate the potential risk of liver failure, carcinoma, cirrhosis and death that can be associated with HBV.[1,15] Women who test seronegative for rubella should receive the rubella vaccine to protect the fetus against congenital rubella syndrome birth defects. The majority of women born in the United States likely have been vaccinated as a child with the measles, mumps and rubella (MMR) vaccine, but a prepregnancy blood test should be done to confirm immunity to the disease.[17] If an MMR vaccine is needed, the woman should avoid becoming pregnant for at least four weeks after receiving the vaccine, as live vaccinations are contraindicated in pregnancy. There may be other vaccinations recommended during pregnancy; for example, Tdap administration conferring immunity to tetanus, diphtheria and pertussis is recommended during each pregnancy between weeks 27 and 36 of the gestational period.

Diabetes Management

Women with diabetes prior to conception have a threefold increased risk for birth defects compared to women without diabetes.[1] Potential negative pregnancy outcomes in infants born to mothers with poorly controlled diabetes include abnormal development of the heart, brain, or spinal cord, large birth weight (greater than 9 pounds) and low blood sugar after birth. Preterm delivery, miscarriage and stillbirth have also been associated with uncontrolled diabetes.[18] The mother is also at risk for high blood pressure, proteinuria and delivery by cesarean section to avoid potential injury associated with vaginal birth of a large child. These risks are significantly reduced by proper management of glucose levels and correct use of diabetic medications. It is recommended that in the months before conception women should strive to maintain a consistent blood glucose with HbA1C levels of approximately 6 percent, using treatments that would be safe in pregnancy.[19] Women should be counseled to regularly monitor blood glucose levels and consider improvements in exercise and diet in the months prior to conception to aid in lowering A1C levels, further improving overall diabetes control. Women should also be counseled on folic acid intake (see following).

Category X Medications

Preconception care, especially from a pharmacist's perspective, must include a focus on Category X medications, or those medications with proven teratogenic effects. Teratogenic anticoagulants such as warfarin should be avoided or, if possible, changed to a nonteratogenic alternative such as low molecular weight heparin in women of childbearing age, keeping in mind the risk/benefit ratio for patients with certain conditions like mechanical heart valves.[20] Similarly, if possible, antiepileptic drugs should have normal dosages decreased to the lowest effective dose prior to conception.[1] Prescribers should be especially cautious when considering valproic acid as an antiseizure agent as it is the most teratogenic medication of its class. Women utilizing antiepileptic medications should be counseled about folic acid (see following).

Figure 2. CDC: 10 Recommendations to Improve Preconception Care.[11]

Patient Responsibility	• Advise both men and women to make a reproductive life plan.
Public Awareness	• Use a variety of methods to reach patients of all ages, cultures, etc. in order to increase awareness for preconception care and its importance.
Primary Care Visits	• Include risk assessment and educational counseling as part of preventive care to improve pregnancy outcomes.
Interventions for Risks	• Provide follow-up for recommended interventions with a focus on those considered high priority.
Interconception Care	• Focus on care in between pregnancies for those women who had poor pregnancy outcomes in a prior pregnancy.
Prepregnancy Counseling	• Offer prepregnancy health care visits for those who are trying to have a child.
Health Insurance Coverage	• Improve access to health care for lower income women by increasing both private and public health insurance coverage.
Public Health Programs	• Incorporate aspects of preconception care into existing public health programs in local communities.
Research	• Encourage the use of and continue to advance evidence-based interventions in preconception care.
Monitoring Improvements	• Utilize public health surveillance and other data systems to monitor the impact of preconception care.

Figure 3. CDC: 14 Evidence-Based Interventions in Preconception Care.[11]

Direct Provision of Care	Education	Referrals
• Hepatitis B Vaccination • Rubella Vaccination • Diabetes Management • Oral Anticoagulant Therapy Management • Antiepileptic Therapy Management • Isotretinoin Use Management	• Folic Acid Supplementation • Obesity Control • Alcohol Use • Smoking Cessation	• HIV/AIDS Screening & Treatment • STI Screening & Treatment • Maternal PKU Management • Hypothyroidism Management

Additionally, any women receiving a Category X medication should be counseled on consistent and correct use of contraceptives. Other teratogenic agents not specifically addressed in the CDC's 14 interventions, but that are important for the pharmacist to recognize, include ACE inhibitors, angiotensin II blockers and HMG-COA reductase inhibitors (statins).[19]

In addition, women of childbearing age must take extra precautions to avoid conception while using isotretinoin for acne treatment and enroll in the iPLEDGE program before the medication can be prescribed or dispensed.[21] Isotretinoin can result in serious birth defects and miscarriages if conception occurs during use or up to one month after discontinuation of the drug. The iPLEDGE program requires patients to use two forms of contraception simultaneously for one month prior, during and one month after isotretinoin use. Two negative pregnancy tests must be obtained before initial therapy can begin, and a negative test must be obtained each month thereafter during therapy before receiving each prescription. The pharmacist must also verify that the patient has met the required criteria before dispensing the prescription each month.

Education

Folic Acid Supplementation

Folic acid is a B vitamin that the body uses to create healthy new cells.[22] Daily use of folic acid has been proven to reduce the incidence of neural tube defects in unborn children by two-thirds compared to mothers with folic acid deficiency.[1] For most women, the CDC recommends a daily dose of 400 mcg starting at least one month before conception and continuing throughout pregnancy.[22] However, women with certain characteristics should be recommended higher doses: women with diabetes are usually recommended to take 4 to 5 mg/day; women using antiepileptic drugs, usually 4 mg/day; or women having experienced a previous neural tube defect-affected pregnancy, usually 4 mg/day.[33] Many multivitamins contain 400 mcg of folic acid, but folic acid supplements are also available. As it is difficult to obtain a minimum of 400 mcg of folic acid through diet alone, all women of childbearing potential should be encouraged to use a vitamin or supplement daily.

Obesity Management

Obesity is defined as having a body mass index (BMI) of greater than or equal to 30.[24] Obesity increases the risk of the mother developing complications such as gestational diabetes, hypertension, infection, thrombosis, obstructive sleep apnea, overdue pregnancy, labor problems, cesarean section and pregnancy loss. Maternal obesity is also associated with fetal effects, including above average birth weight, heart abnormalities, neural tube defects and the development of heart disease and/or diabetes in adulthood.[24] Proper education and encouragement of obese women to begin eating a healthier diet and participating in a regular exercise routine can help them to reach a healthy weight before pregnancy. Scheduling a preconception appointment with their health care provider is also recommended to prevent adverse obesity-related outcomes for both the mother and the fetus.

Elimination of Alcohol Use

Alcohol is not considered safe to consume at any stage of pregnancy. Women who are pregnant or may become pregnant should avoid alcoholic beverages in order to prevent damage to the fetus.[1] Alcohol in the mother's blood is transferred to the child through the umbilical cord during pregnancy and can result in miscarriage, stillbirth and a variety of disabilities known as fetal alcohol spectrum disorders (FASD).[25] Fetal alcohol spectrum disorders may include facial abnormalities, below average height, low body weight, learning disabilities, vision or hearing problems and issues with the heart, kidneys and bones. It is imperative that women of childbearing age are educated on the adverse outcomes of alcohol use during pregnancy as many women will not recognize their pregnancy until after the first four to six weeks of gestation.

Smoking Cessation

Smoking negatively impacts a woman's ability to become pregnant as well as the health of the unborn child.[26] Smoking may lead to miscarriage, preterm birth, low birth weight, cleft lip or cleft palate and sudden infant death syndrome (SIDS).[15,26] Tobacco use can also cause the placenta to prematurely separate from the womb, causing unexpected bleeding. The most effective method of preventing such adverse events is to encourage smokers to participate in smoking cessation programs prior to conception and continue to avoid the use of tobacco products throughout the duration of pregnancy.

Referrals

HIV/AIDS Screening and Treatment

Human immunodeficiency virus status must be determined for best preconception care. Perinatal transmission, or transmission of HIV from mother to child during pregnancy, delivery or through breastfeeding, is the most common route of HIV infection among HIV positive children.[27] All pregnant women should be screened as early as possible during each pregnancy for HIV infection. Early detection of HIV allows for timely development of antiretroviral regimens that can potentially prevent the virus from being transferred from mother to child.[1] Properly taking antiretroviral medications early in pregnancy can reduce the risk of transmitting the virus from mother to child to less than 1 percent.[27]

STI Screening

Sexually transmitted infections (STIs) during pregnancy have been associated with physical and developmental deformities as well as fetal death.[15] Sexually transmitted infections screening prior to pregnancy can help to identify and eradicate infections, such as gonorrhea and chlamydia, that often lead to ectopic pregnancy, infertility and chronic pelvic pain in the mother and possible blindness and mental retardation in newborns. The risk of contracting an STI prior to conception can be reduced by consistently using barrier methods and/or being in a long-term mutually monogamous relationship. If a woman fails to consistently follow preventive measures and becomes pregnant, the CDC recommends testing for the following STIs during every pregnant woman's first prenatal visit: chlamydia, gonorrhea (if at risk), syphilis,

HIV, hepatitis B.[28] Most STIs can be safely and effectively treated during pregnancy through the use of antibiotics.

Maternal PKU

A woman with phenylketonuria (PKU) who is considering pregnancy should make an appointment with her health care provider and return to a low phenylalanine diet if not currently following recommended dietary restrictions.[29] Any degree of PKU poses risks to the fetus, but the condition can be effectively managed through adherence to a strict diet with limited intake of phenylalanine by avoiding foods high in protein.[1,30] Appropriate treatment of maternal PKU prior to conception and during pregnancy has been shown to reduce the risk of PKU-related intellectual disabilities and cardiac defects in the fetus.[30]

Thyroid Medication Adjustment

The doses of levothyroxine needed for treatment of hypothyroidism increase during early pregnancy and must be adjusted to ensure proper neurologic development of the fetus.[1] Any woman considering pregnancy should regularly have her thyroid stimulating hormone (TSH) levels checked by a health care provider to ensure that she is being optimally treated prior to becoming pregnant.[31] After becoming pregnant, levothyroxine doses often need to be increased by 25 to 50 percent; therefore, patients must be forewarned that frequent monitoring is important. Although not specifically addressed in the CDC's interventions, hyperthyroidism must also be appropriately managed prior to and during pregnancy.

Preconception Care Recommendations for Men

Although preconception care is primarily targeted toward women of childbearing age, there are preconception recommendations that can improve men's health. Providing preconception care to men benefits pregnancy outcomes as damaged DNA in sperm can lead to birth defects.[32] Damaged DNA can be due to negative health behaviors such as smoking, alcohol use, anabolic steroid use, poor diets and excessive caffeine intake, all of which are modifiable factors. Encouraging men, in addition to women, to improve their health behaviors further reduces pregnancy outcome risks. Men receiving this care can also improve women's health through proper screening and treatment of sexually transmitted infections. In addition, both male and female partners making changes to adopt healthier behaviors together provides support and encouragement which helps to improve adherence to the changes.

In addition to alcohol and tobacco use, other exposures that should be addressed as a part of preconception care for men include recreational drug use, anabolic steroid use, workplace exposures and hobbies that expose a man to heavy metals or organic solvents such as repairing or painting cars, refinishing furniture or cleaning guns.[32] A thorough family health history should also be taken as a part of preconception care and with the creation of a reproductive life plan. It is recommended to take the history for three generations as some genetic diseases skip generations. Along with family history, information should also be gathered regarding a man's medications and disease states as some medications or conditions can contribute to low fertility. Additionally, some medications are known risks to a fetus even when used in men.[21] For example, due to the high risk of birth defects associated with isotretinoin use, males must also be enrolled in the iPLEDGE program and meet with their prescriber monthly before a pharmacist can dispense the medication.

Another topic to address with men is the importance of a well-balanced diet.[32] This not only improves overall health and weight management, but certain antioxidants, like folate and zinc, help counteract the damaging effects of reactive oxygen species to sperm DNA. For a man with poor weight management, this can also be an opportunity to encourage healthier behaviors. Keeping a healthy weight is important for male fertility and can also be a way to support a woman's health improvement efforts. It is important for men to be included in preconception care because this motivates their involvement in family planning. Couples should be encouraged to develop reproductive life plans together, and recommendations regarding preconception care can then be tailored to fit their specific goals.[9]

Pharmacists' Role in Preconception Care

Although all women of reproductive age would benefit from receiving preconception care, in a recent survey only 18.4 percent of women with a live birth reported receiving preconception care counseling, whereas 88.2 percent had postpartum check-ups.[1] There is an opportunity for pharmacists to work with other health care professionals to close this gap in care and increase general knowledge of preconception care. Ideal preconception care includes screenings, risk evaluation and general education regarding modifiable risk factors as well as interventions when needed.[7] Many of these components can be easily provided by pharmacists.

One of the barriers to implementing these recommendations into primary care is the lack of knowledge among health care professionals about the evidence associated with the proven interventions.[15] Other barriers include lack of time in a standard appointment for counseling and lack of reimbursement by insurance companies.[15] Poor public knowledge on the importance and availability of preconception care and, consequently, patients being unwilling to spend more time to receive this care are also barriers.[6] Patients need health care professionals to help make them aware of the resources that are available to them.[15] Pharmacists have an opportunity to become patient advocates in the field of preconception care and promote health care for women of reproductive age. Simple things that pharmacists can begin doing in every setting is asking women of reproductive age if they intend to become pregnant within the year and educating women about certain health conditions and medications that can adversely affect pregnancy. Even if women do not intend to become pregnant in the near future, preconception care interventions are still applicable to these patients in improving their overall health. Educating women about these topics not only promotes the well-being of the mother and child throughout pregnancy but also encourages women to have planned pregnancies that are discussed with health care professionals and proactively achieve a healthy lifestyle before

conception. This education also improves a woman's overall health, even if she does not ever become pregnant. As pointed out by the CDC's Show Your Love campaign, informing the general public of the benefits and accessibility of preconception care will allow women to make informed decisions regarding their own health and the health of their future child should they become pregnant.[5]

Pharmacists can have a significant role in incorporating preconception care into health care. With an easily accessible position in the community as well as health system settings, pharmacists have the potential to provide preconception care to patients who have a high burden of modifiable risk factors. Additionally, pharmacists interact with patients outside of physician visits and are able to help with monitoring and management of disease states. With access to medication records, pharmacists can identify patients with teratogenic medications, identify disease states based on medications and potentially review vaccination records. As the drug experts, pharmacists can appropriately counsel a woman who is on a medication that may be high risk should she become pregnant.[3] In one study, 50 percent of women had at least one medication that they took regularly in early pregnancy, so this type of counseling is an important part of preconception care.[1, 3] Pharmacists are also the health care professionals with an opportunity to counsel women on over-the-counter medications and vitamins to improve general health as well as prepare for pregnancy, such as promoting folic acid use or selecting an appropriate prenatal vitamin. Tobacco cessation products and appropriate contraceptive methods are other counseling points that pharmacists are in prime position to address.[3]

Delivery of preconception care could be achieved as a part of medication therapy management (MTM).[33] Medication therapy management is a type of care that is delivered by pharmacists that aims to optimize and monitor patients' drug therapies and to encourage patients to take an active role in their health in order to achieve better outcomes. There are several core elements to the MTM model, including the comprehensive medication review (CMR) and targeted medication review (TMR); both of which could be used as opportunities to deliver preconception care. A CMR allows the pharmacist and patient to fully discuss all their medications and disease states. This would be an ideal time to deliver preconception care to women of childbearing age and address any conditions a patient may have and how it impacts her health. A TMR could be used in identifying teratogenic medications that a woman may be taking, deciding whether an alternative medication is appropriate, as well as identifying medications that may not necessarily be teratogenic but still require strict monitoring in women who desire to become pregnant. A TMR may also be a useful way to recommend folic acid products or vaccines. In general, a lack of reimbursement has been identified as a barrier to delivering preconception care; however, some third-party payers, such as some state-managed Medicaid programs, will reimburse pharmacists for delivering MTM services.

Another opportunity for pharmacists to deliver preconception care is through counseling on management of chronic disease states.[3] Counseling, whether it is through MTM or not, can have a significant impact on women's management of chronic conditions that impact their preconception health. In one study, less than one-third of women with a chronic disease state fully understood how their condition would impact a future pregnancy, and only 15 percent of women of childbearing age who were taking category C, D or X prescriptions were aware of the associated risks.[34] Women's knowledge of these disease states and medications can be greatly increased through counseling by pharmacists. One example of a chronic condition in which a woman would benefit from preconception counseling is hypertension, another health concern not specifically addressed in the CDC's 14 interventions. Approximately 5 percent of pregnant women have hypertension before pregnancy or 20 weeks before gestation.[3] Hypertension is known to increase the risk of delivery via caesarean section, development of gestational diabetes, preeclampsia, preterm delivery and delivery of an infant that is small for gestational age.[1, 3] This is an important area for preconception care counseling because hypertension and gestational hypertension account for one in 50 stillbirths as well as one in every three cases of severe maternal morbidity.[35] However, because hypertension does have modifiable risk factors, such as consuming less sodium and increasing exercise, this chronic disease state, in addition to all those previously mentioned, would benefit from preconception care counseling.

Recommendations for case scenario using the evidence-based interventions:

Diabetes Management: KR should be counseled on management strategies for her type 2 diabetes. It should be emphasized how important it is to carefully keep track of her blood glucose levels. KR should be counseled that if she decides she wants to become pregnant, an A1C goal of less than 6.3 percent is recommended, and less than 6 percent in the second and third trimesters of pregnancy.[19] When ready to conceive, a comprehensive medication review should be performed to reduce the risk of fetal exposure to a teratogenic medication; until that point, KR should be counseled on consistent and correct use of contraceptives.

Weight Management: An overarching goal of reducing her BMI to the "normal" range (18.5 to 24.9) should be initiated by setting small, achievable goals such as losing 1 to 2 pounds per week. Recommend KR eat a balanced diet and adopt an exercise plan.

Alcohol Use and Smoking Cessation: KR should also be encouraged to eliminate alcohol use and begin a smoking cessation program. A pharmacist could help KR in this process by helping her select an appropriate smoking cessation product, encouraging change and following up with KR about her progress.

Vaccinations: KR should be updated on her vaccines, such as rubella and hepatitis B.

Folic Acid: A pharmacist should also recommend that KR begin taking a folic acid supplement. As she has diabetes, her recommended daily dose should be 4 to 5 mg/day.[23]

Screenings: Screening for STIs and HIV/AIDS should also be encouraged and treatment initiated as needed.

Conclusion

Regardless of a woman's intention to become pregnant, providing preconception care to all women of childbearing age is an often-missed opportunity to encourage healthy behaviors and lifestyle changes that can improve population-based outcomes while preparing individual patients for a potential pregnancy. Although the benefits of this type of care are widely recognized and proven, it has yet to be effectively integrated into the current health care system. Pharmacists can use their role in the health care team to incorporate preconception care into practice, both in the community and hospital settings. Using the 14 evidence-based interventions outlined by the CDC, pharmacists, in collaboration with other health care providers, can ensure this care becomes routine for women of childbearing age through direct provision of care, patient education and referrals.

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Assessment Questions

1. Approximately, what percentage of pregnancies in the United States are classified as unintended?
    A. One-quarter
    B. One-third
    C. One-half
    D. Three-fourths

2. A 24 YOF comes into your pharmacy and mentions that she and her husband are trying to become pregnant. She would like to know if any vaccinations are recommended for her to receive prior to conception. Based on the CDC's 14 evidence-based interventions, which statement would be correct to tell your patient?
    A. All patients should receive the hepatitis B vaccination, regardless of risk factors.
    B. Women who are seronegative to rubella should consider MMR vaccination prior to conception to avoid congenital rubella syndrome.
    C. The Tdap vaccination must be given prior to conception because it is contraindicated during pregnancy.
    D. After receiving the vaccination for rubella, the patient should try to become pregnant as soon as possible.

3. Ideally, preconception care should be administered to _____.
    A. women with the intent to become pregnant.
    B. women of childbearing age who are not trying to conceive.
    C. men.
    D. All the above.

4. According to the American Diabetes Association, what is the A1C goal for a woman with type 2 diabetes who is planning to become pregnant in the near future?
    A. <6.0%
    B. <6.3%
    C. <6.5%
    D. <7.0%

5. Which of the following are risks associated with maternal obesity during pregnancy?
    A. Neural tube defects
    B. Pregnancy loss
    C. Cesarean section
    D. All the above

6. Teratogenic medications must be properly managed and/or discontinued prior to pregnancy. Which of the following medications is not specifically mentioned in the CDC's 14 evidence-based interventions but is still important for pharmacists to recognize as a concern for women of childbearing age?
    A. Lisinopril
    B. Warfarin
    C. Valproic Acid
    D. Isotrentinoin

7. Why are pharmacists in an ideal position to provide preconception care?
    A. Pharmacists are accessible to patients in the community.
    B. Pharmacists are able to review medication records to identify high risk drugs and disease states.
    C. Pharmacists lack the appropriate amount of time to provide interventions.
    D. A & B

8. All of the following statements are true, except:
    A. Interconception care is considered part of preconception care.
    B. Preconception care also includes contraceptive methods for women not planning a pregnancy.
    C. Interventions made in the first trimester of pregnancy can be classified as preconception care.
    D. The recommendations made in preconception care and perinatal care are often very similar.

9. Which of the following are positive lifestyle modifications that are considered part of preconception care and can benefit women, regardless of pregnancy intentions?
    A. Reduction in alcohol intake
    B. Smoking cessation
    C. Maintenance of normal BMI
    D. All of the above

10. If not properly treated, infections like gonorrhea and chlamydia are associated with risks for _____.
    A. ectopic pregnancy.
    B. pelvic pain.
    C. infertility.
    D. All the above.

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Program Title: **Pharmacists' Role in Preconception Care**
UAN: 0048-0000-15-005-H04-P CEUs: 0.1 for pharmacists only

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid email address.

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Phone:	**Email:**		
Pharmacy License #:	**State:**	**ONU Alumni?**	**Y N**

Program Content:	**Strongly Disagree**				**Strongly Agree**
The program objectives were clear.	**1**	**2**	**3**	**4**	**5**
The program met the stated goals and objectives:					
Explain the need for preconception care for women of childbearing age, regardless of pregnancy intentions, and the importance to public health.	**1**	**2**	**3**	**4**	**5**
Discuss roles for pharmacists in preconception care.	**1**	**2**	**3**	**4**	**5**
Describe the 14 evidence-based interventions recognized by the Centers for Disease Control and Prevention, and be able to identify how these interventions can be incorporated in practice.	**1**	**2**	**3**	**4**	**5**
Evaluate a woman's need for preconception care in the context of comorbid disease states, lifestyle and behavioral factors.					
The program met your educational needs.	**1**	**2**	**3**	**4**	**5**
Content of the program was interesting.	**1**	**2**	**3**	**4**	**5**
Material presented was relevant to my practice.	**1**	**2**	**3**	**4**	**5**

Comments/Suggestions for future programs:

_____

_____

_____

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C D	**4. A B C D**	**7. A B C D**	**10. A B C D**
2. A B C D	**5. A B C D**	**8. A B C D**	
3. A B C D	**6. A B C D**	**9. A B C D**	

Any questions/comments regarding this continuing education program can be directed to Lauren Hamman, Advanced Administrative Assistant for the Office of Continuing Education (email: l-hamman@onu.edu, phone 419-772-2280).

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Potential Use of Dopamine and Dopamine Agonists as Angiogenesis Inhibitors in the Treatment of Cancer

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-15-208-H01-P

Objectives

After completion of this program, the reader should be able to:

1. Explain the processes of angiogenesis and tumorigenesis and the role of each in cancer metastasis.
2. Describe the actions of dopamine on tumorigenesis and its relationship with vascular endothelial growth factor.
3. Discuss the methodology and results of the initial trials suggesting the use of dopamine and dopamine agonists in cancer treatment.
4. Evaluate the potential use of dopamine for cancer treatment in regard to side effect profiles and cost of therapy in comparison to current angiogenesis inhibitors.

Abstract

In recent years, there have been numerous developments in monoclonal antibodies used as anticancer drugs with a focus on reducing the ability of cancers to metastasize and produce new vasculature. These agents are called angiogenesis inhibitors and although these agents have been proven effective in treating certain types of cancers, production and administration of monoclonal antibodies comes at a steep cost with a severe side effect profile. Under normal physiologic conditions, angiogenesis is an important mechanism to create new blood vessels from preexisting vessels, usually occurring in adults. Tumor cells can hijack the angiogenesis pathway to produce new distant tumors sites, which may lead to poor prognosis. In an ongoing effort to discover alternative therapeutic options for cancer treatment, researchers have discovered that dopamine (DA) is able to inhibit angiogenesis through a mechanism involving vascular endothelial growth factor (VEGF) and the D_2 receptors. When the D_2 receptor is activated, this causes the VEGF receptor 2 (VEGFR2) to undergo endocytosis thereby preventing VEGF binding and stopping the creation of new vessels. Endocrine and gastrointestinal cancers have a high expression of D_2 and VEGF receptors and therefore are potential targets of therapy. Although DA may provide better tolerability and cost benefits, future studies in humans must be conducted to clearly determine its safety and efficacy as a treatment for cancer.

Key Terms

Angiogenesis Inhibitors; Antineoplastic Agents; Dopamine; Endothelial Growth Factor A; Gastrointestinal; Neoplasms; Pathologic Neovascularization; Vascular Endothelial Growth Factor A

Introduction

Angiogenesis is a natural process used by our bodies to produce new vasculature to increase blood flow to certain areas which have need of additional oxygenation.[1] When cancers proliferate, an increased demand for energy emerges. Cancers utilize the process of angiogenesis to increase blood flow to the area to allow for continued growth of a tumor in a process known as tumorigenesis. Inhibiting this action is one strategy of therapy used today to prevent further growth of the cancer. Due to high costs of traditional angiogenic inhibitor therapy for cancer, other options are a welcome sight. One option currently being studied is dopamine.

Angiogenesis and Tumorigenesis

Angiogenesis occurs in a four-step process: cellular injury, migration, proliferation and survival. The first step can be induced by a number of stimuli, including hypoxia.[1] A hypoxic environment can be caused by lack of perfusion to a local area, leading to a decrease in available oxygen and nutrients, which in turn stimulates Hypoxia-Inducible Factor 1 (HIF-1), a heterodimer consisting of an alpha and beta subunit. Hypoxia-Inducible Factor 1 is stabilized by the hypoxic environment and binds to gene sequences that allow for the upregulation of glucose transporters, erythropoietin and vascular endothelial growth factor (VEGF). Hypoxia-Inducible Factor 1 also induces upregulation of the VEGF receptor (VEGFR), namely VEGFR2, which is involved in the process of angiogenesis. The VEGF/VEGFR complex is an important activator of endothelial cell function by a number of signal transduction pathways, allowing for an increase in proliferation, permeability, migration and survival.

The VEGF/VEGFR complex also regulates the release of matrix metalloproteinases (MMPs), which degrade the basement membrane of the endothelial cells, enabling cellular migration toward chemicals secreted from the hypoxic areas through the process known as chemotaxis.[2] A key agent in angiogenic chemotaxis is VEGF. Cells are able to move by using membrane projections consisting of actin-sensing chemoattractants (filopodia) and the formation of a leading edge of the cell by cytoplasmic actin (lamellipodia). Finally, through a complex mechanism, endothelial cells arrive at the hypoxic site and form a tubule stabilized by pericytes from surrounding vasculature and differentiated mural cells[1].

In tumorigenesis, the initial neoplastic lesion can only grow between 2 to 3 mm^3 because of the lack of vascularity and the diffusion barrier of oxygen.[1] To overcome this limitation, the tumor must find a way to obtain access to vasculature in order to continue its proliferation. The tumor is able to grow through activation of the "angiogenic switch," occurring when the inhibitory factors are outnumbered by the positive factors, leading to development of new vascularization. The p53 tumor suppressor gene normally works to inhibit excessive angiogenesis by blocking the expression of the necessary growth factors, including VEGF; however, p53 is mutated and inactivated in almost 50 percent of cancer, rendering this inhibitory pathway futile. Additionally, because the environment of tumors is likely hypoxic, there is often an overexpression of HIF-1 stimulating the release of VEGF-A, an isoform of VEGF, and leading to the angiogenic sequences described above. Because of the hyperexpression of VEGF-A, Bcl-2 is also overexpressed in cancers and inhibits apoptosis by maintaining mitochondrial membrane integrity by overwhelming the effects of Bax, which normally induces apoptosis.[3] Additionally, survivin, usually a negligible protein in healthy individuals, is overexpressed due to elevated VEGF-A levels in cancers.[1] Survivin is thought to inhibit caspase activity, an apoptosis inducing protease, adding a second mechanism for endothelial cell survival and tumorigenesis.

Introduction to Dopamine

Dopamine, also known as 3-hydroxytyramine, is a monoamine metabolic product of the amino acid tyrosine.[4] It is stored in vesicles located in the presynaptic terminals of neurons after being taken in from the cytosol through the vesicular monoamine transporter 2 (VMAT2).[5] Dopamine is released into the synaptic cleft and exerts its actions by binding to postsynaptic G-protein coupled receptors (GPCR) of two different classes, which are differentiated based on their biochemical effects and gene sequencing.[6] It should also be mentioned that DA has different affinities (nanomolar to micromolar) for each receptor subtype which in turn has implications on receptor subtype sensitivity to DA agonists and antagonists.[4] Remaining DA in the synapse can undergo reuptake via the dopamine active transporter (DAT) back into the presynaptic neuron or undergo enzymatic degradation by either monoamine oxidase (MAO) or catechol-o-methyltransferase (COMT).

The D_1 receptor class consists of the postsynaptic D_1 and D_5 receptors and activates the $G\alpha_{s/olf}$ protein family to increase adenylate cyclase activation to produce cAMP. In contrast, the D_2 receptor class includes the D_2, D_3 and D_4 receptors, with D_2 and D_3 located both presynaptically and postsynaptically.[5] These are coupled to the $G\alpha_{i/o}$ protein family that inhibit adenylate cyclase to decrease cAMP.[4] By altering the levels of cAMP, the activity of various downstream signaling molecules are regulated.[6] Additionally, there are routes of dopamine receptor signaling that are independent of cAMP. In fact, many intracellular signaling pathways can be mediated through various enzymes, such as ERK, Epac 1 and GRK 2.

In terms of expression, DA receptors are found both in the central nervous system (CNS) and peripheral areas of the body.[5] Within the brain, dopaminergic neurons project to four major DA pathways associated with learning, cognition and motor function. In peripheral areas, the different subtypes are found on vascular smooth muscle, on various renal and mesenteric arteries and in the endocrine system.[7] Many actions may result from DA binding, such as diuresis and natriuresis in the kidneys and regulation of norepinephrine release. Dopamine receptors may play a role in the immune system with nervous and renal inflammation and autoimmune reactions. Lastly, another important result of receptor activation is the downstream effect of altering glutamate signaling.

Currently, DA and other agents that work by agonizing or antagonizing its receptors are used to treat a variety of conditions, especially within the CNS. Dopamine precursors and agonists are indicated in Parkinson's disease (PD) therapy while DA antagonists are used as atypical antipsychotics for schizophrenia.[4] Other uses include the treatment of endocrine disorders, hypertensive crisis and as prokinetic agents.

Additionally, DA is utilized for its effect on alpha-receptors and beta-receptors in the cardiovascular system for vasodilation and its inotropic effect on the heart.[8] This counteracts its ability to induce NE release in the periphery for vasoconstriction. It is indicated for hypotension with bradycardia and may be used in combination with other agents to treat post-resuscitation shock. At higher doses, DA will cause systemic and splanchnic constriction of the arteries. It may therefore be used to increase renal blood flow for acute oliguric renal failure and low cardiac output in critically ill patients.[9] However, it has not been supported in trials for renal insufficiency prevention or to decrease mortality or morbidity.[10]

More recently, the potential anticancer effect of DA has been discovered and its role in treatment is being researched.[6] Therefore, with the various existing therapeutic indications for DA, it is widely available and determining its anticancer effects may be useful in terms of costs, therapy management and side effects.

Dopamine and VEGF

While already acknowledged as an important neurotransmitter in the CNS, it has been suggested that DA, acting through the D_2 receptor, can inhibit tumor growth by a number of different pathways. One mechanism shows that DA increased association between the D_2 receptor and Sarcoma Homology Phosphatase-2 (SHP-2) at the surface of the cell.[11] The association stimulates the phosphorylation of SHP-2, inhibiting activation of the VEGFR-2. Another theory suggests that DA stimulation of the D_2 receptor actually causes the endocytosis of the VEGFR-2, which prevents VEGF from binding and causing its associated effects.[12] This demonstrates an association between the nervous system and angiogenesis that was previously unknown. This allows for D_2 receptor agonists that are already in existence to be used in other clinical settings.

Evidence for the Use of Dopamine

The connection between DA and VEGF to the associated effects on angiogenesis and tumorigenesis has prompted

researchers to consider DA as a potential agent to target these mechanisms which cancer cells use to thrive. It has been found that DA selectively inhibits the actions of VEGF by acting on the D_2 receptor and/or causing endocytosis of VEGFR-2. However, since this is a selective inhibition, other modulators of angiogenesis are still promoting angiogenesis, and the process is not completely inhibited.[12,13] This selective inhibition means there is room to study DA and D_2 agonists (since they both activate the DA receptors and have the similar effects) to see if its use can be successful in the treatment of cancers.

Both an animal study utilizing rats and a small human study were conducted to compare the outcome of treating ovarian hyperstimulation syndrome (OHSS) when using cabergoline, a long-acting D_2 receptor agonist. Ovarian hyperstimulation syndrome is caused when there is ovarian hypersecretion of VEGF which activates VEGFR-2.[14] The results of the study showed a decrease in the incidence of OHSS in rats treated with cabergoline (100 µg/kg/day) and, with the limited side effects seen in the rodent trial, the researchers decided to do a small trial on humans as well. For humans, cabergoline treatment was given only to individuals who were oocyte donors at high risk for developing the syndrome. The human test subjects were being treated with prophylactic doses of 5 to 10 µg/kg/day of cabergoline. Results on humans showed a 65 percent occurrence of OHSS in the control group compared with 25 percent in the treatment group. Since OHSS is dependent upon high concentrations of VEGF, these results show that activating the D_2 receptor may possibly have beneficial effects to decrease the rate of angiogenesis and tumorigenesis in humans suffering from cancer. However, the specifics about how the researchers performed this study, the sample size and other parameters were not available at the time of publication.

Another animal study showed that rats with a hyperactive dopaminergic system had decreased tumor angiogenesis.[15] The researchers bred rats to have hyperactive dopaminergic systems, a requirement for the study, and then implanted rat adenocarcinoma cells into the rats in order to observe the tumor growth. It was discovered that rats with hyperactive dopaminergic systems had about 35 percent smaller tumors compared to the placebo rats. Fewer lung metastases were observed in the experimental group (hyperactive dopaminergic system rats) compared to the control group (nonhyperactive dopaminergic system rats) macroscopically after all test rats had died. On the 24th day after implanting the cancerous cells into the rats with either hyperactive or nonhyperactive dopaminergic systems, all rats with nonhyperactive dopaminergic systems had died and none of the rats with hyperactive dopaminergic systems had died. Most importantly, it was found that rats with hyperactive dopaminergic systems had decreased tumor angiogenesis by determining hemoglobin content in tumors from both groups of rats. Hemoglobin content in tumors were significantly lower in rats with hyperactive dopaminergic systems compared to those with nonhyperactive dopaminergic systems (hyperactive: 40.6±7.6 mg/dL; nonhyperactive: 76.9±13 mg/dL, $P<0.05$). The lower hemoglobin content in the tumor corresponded to decreased tumor growth. No medication was used in this study. The data gathered was based upon the premise that rats with hyperactive dopaminergic systems would have increased levels of DA in their system, allowing for the effects of naturally produced DA to show its action. This further suggests that DA has a mechanism by which angiogenesis is inhibited.

A study was conducted on gastric cancerous tissue in rats and mice.[16] Gastric cancer is known to require increased angiogenesis activity to survive and the possibility of using doses of DA to inhibit the growth of this cancerous tissue was being examined. In the study, some rats and mice were pretreated with domeperidone, a D_2 receptor antagonist, to confirm that the actions of DA were through the D_2 receptor. The researchers found that when rats or mice were pretreated with domeperidone followed by treatment with DA, there was no effect, confirming that the D_2 receptor is responsible for the effects shown in the study. The results showed that even low doses of DA (50 mg/kg/day or about 5 percent of the median lethal dose in rodents) would inhibit the growth of the cancer tumor substantially (tumor size: 311.5 ± 11.9mm^3 in placebo group, 106.0 ± 7.4 mm^3 in treatment group, $P<0.05$). What is even more interesting is that in all of the samples of tissue examined, the concentrations of endogenous DA were very low, almost negligible, and the concentrations of VEGF were increased. Cancers deplete the stores of DA in the tissue, allowing for the growth of the cancer with increased expression of VEGF. This explains why even low doses of DA would inhibit the growth of the cancer; the DA administered to the site would be able to act on every receptor available since all or most of the endogenous DA was gone. The DA would be able to endocytose many of the VEGFR-2 and thereby decrease the angiogenic properties of the gastric cancer.

Since human cancers utilize this same mechanism of angiogenesis to provide their sustenance, animal studies can provide a good basis for comparison. Human studies will need to be conducted to confirm that this effect can be mirrored in the human physiology and allow for this to be a treatment option for those with cancers and tumors sensitive to DA therapy, such as endocrine tumors.[17,18] Human studies will need to be used to determine the dose of DA that may be administered in treating cancers, as this is not known at this time.

A study was conducted to evaluate the prevalence of the D_2 receptors and VEGF in various pituitary adenomas.[19] Knowing this information would be beneficial in the plan to treat patients with certain kinds of cancers, as it could tailor the therapy to target a specific receptor if it is known to have increased expression in that cancer. The study examined 197 tissue samples from patients with various types of pituitary adenomas. A streptavidin-peroxidase method was used for staining the samples of cancerous tissue obtained from the patients. These stains were then scored on a 0 to 7 scale which accounted for the strength of the stain (0 to 3, where 0 is negative, 1 is weak, 2 is medium, 3 is a strong stain) and the extent of the stain (0 to 4, where a percentage of the staining area compared to the whole carcinoma sample was

evaluated; 0 (0 percent), 1 (1 to 25 percent), 2 (26 to 50 percent), 3 (51 to 75 percent), 4 (76 to 100 percent)). Any score above 3 was considered a high expression stain. Results showed that 64.9 percent of the pituitary adenomas had a high expression of D_2 receptors and 58.9 percent had a high expression of VEGF. From this data, it can be inferred that over half of pituitary adenomas could potentially benefit from DA therapy to decrease the cost of treatment and help reduce tumor size, since these tumors would be more sensitive to treatment with DA due to high D_2 receptor expression.

Side Effects

Side effects associated with the costly VEGF inhibitors can include bleeding, clots that can lead to a stroke or heart attack, high blood pressure, proteinuria and gastrointestinal disturbances. Rarer side effects can include GI perforation, fistulas of the bile duct and even certain cancers. Birth defects have been seen in animal models, but have yet to be seen in humans. Generally, VEGF inhibitors carry a larger, more severe side effect profile that occurs more often than with an agent like dopamine.[20] Furthermore, because both dopamine and VEGF inhibitors work via similar mechanisms, treatment will require concurrent therapies with chemotherapeutic agents, like 5-Fluorouracil.[21] The use of VEGF inhibitors could be problematic in patients suffering from cardiovascular conditions in addition to cancer, whereas DA or D_2 agonists could be a safer option in patients with or at risk for cardiovascular complications.

While DA agonists may be considered as an anticancer treatment, the severity of side effects must be postulated from their current indications in other therapies. Dopamine agonists have been observed to cause peripheral edema, orthostatic hypotension, hallucinations, sudden-onset of sleeping ("sleep attacks") and impulse control disorders (ICDs).[22] Characteristics of ICDs include hypersexuality and compulsive eating, gambling and buying. This particular adverse effect has been found in 17 percent of PD patients taking DA agonists and may eventually have other negative consequences relating to finance, behavior and social relationships. Addressing these effects includes either discontinuing or tapering DA therapy. Strategies for tapering may include substituting other medications such as L-dopa; however, this may worsen the disease being treated. Furthermore, tapering may be ineffective in some patients and can result in dose-dependent dopamine agonist withdrawal syndrome (DAWS). Dopamine agonist withdrawal syndrome has been characterized by both psychological and physical symptoms including anxiety, panic attacks, depression, agitation, fatigue, flushing, nausea and vomiting. These symptoms are similar to withdrawal from other psychostimulants. Additionally, there is currently no treatment for the syndrome and the only way to alleviate DAWS is by restarting or increasing the DA agonist therapy. Therefore, to prevent DAWS, prevention strategies must be in place before beginning therapy. It is recommended to remain cautious with patients with a high risk of ICD because this side effect is highly associated with DAWS. Additionally, patients should avoid using high doses of DA agonists for long periods of time as this is a risk factor for ICD. Therefore, patients must provide informed consent and become educated on the potential consequence of DAWS. They also should be screened for ICD risk during therapy and report any ICD and DAWS symptoms right away.

An animal model examining endometrial angiogenesis used DA agonist cabergoline and observed reduced neoangiogenesis.[23] It was noted that DA safety considerations needed to be studied in the future since DA therapy may interfere with pregnancy. Researchers noted that lower doses of 0.05 mg/kg cabergoline were as effective as higher doses of 0.1 mg/kg, implying that using the lowest effective dose may help lower the incidence of side effects if used in humans. Although dosing has not yet been established for DA in anticancer treatments in humans, this may be a dosing consideration in terms of maximizing efficacy while minimizing side effects.

Even with the concern for DAWS, DA agonists have already been used for a length of time, making their side effects well known and manageable, and can be generally considered safe.[24] However, addressing side effects by tapering therapy may not be practical in cancer treatment. Therefore, the risk of DA side effects must be sufficiently studied when DA is used at anticancer doses in humans.

Cost Implications

One of the major barriers of utilizing newer anticancer treatments, especially monoclonal antibodies, is the price associated with them. For example, one study looked into the cost of three angiogenesis inhibitors: the VEGF inhibitor bevacizumab (Avastin) and two protein kinase inhibitors, sunitinib (Sutent) and sorafenib (Nexavar). It found that the per-patient per-month cost associated with these three medications was: $5,639 for sunitinib, $5,214 for sorafenib and $13,664 for bevacizumab.[25] These prices do not include the costs of additional procedures and/or the treatments related to the adverse events. However, for a vial of 400mg/5mL DA the hospital cost is around 50 cents per vial, which is 10,000 times less expensive than the angiogenesis inhibitors.[26] For the D_2 agonist cabergoline, the daily cost is between $10 and $15, so the cost per month would be roughly $300 to $450.[27] With the significant cost differences between DA and VEGF inhibitors, this provides an added benefit to its potential anticancer effects.

Conclusion

From the limited number of animal studies currently published, it seems that treatment with DA and D_2 agonists potentially has a great benefit in patients with cancers known to have high expression of D_2 receptors, such as endocrine tumors and gastrointestinal tumors. While large human studies have yet to be performed, there is strong evidence from the animal studies and the small human study that DA and D_2 agonists decrease the effects of the VEGFR-2 and inhibit angiogenesis and tumorigenesis. Applying this to cancer treatment regimens could lead to decreased costs for health care systems and reduced adverse events, as DA and D_2 agonists are less expensive and potentially safer options compared to the conventional angiogenesis inhibiting regimens. Since the first priority of health care is the safety and well-being of the

patient, despite the initial promise of using DA and D_2 agonists for cancer treatment, it cannot be fully recommended until additional research is completed. Future trials with humans must be conducted to determine the full spectrum of safety, dosing and efficacy of utilizing DA as a potential new anticancer treatment.

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Assessment Questions

1. Referring to OHSS, which of the following doses were used in humans who were oocyte donors at high risk for developing the syndrome?
    A. 100 µg/kg/day
    B. 150 µg/kg/day
    C. Prophylactic doses of 5-10 µg/kg/day
    D. Prophylactic doses of 50-100 µg/kg/day

2. Rats with hyperactive dopaminergic systems had tumors which were what percent smaller in size compared to the nonhyperactive dopaminergic system rats?
    A. 12%
    B. 30%
    C. 56%
    D. 35%

3. Which two types of cancer have shown to have a high expression of D_2 receptor density?
    A. Lung and Prostate
    B. Endocrine and Gastrointestinal
    C. Breast and Testicular
    D. Pancreatic and Gastrointestinal

4. Angiogenesis involves which of the following steps:
    A. Migration
    B. Proliferation
    C. Cellular injury
    D. Survival
    E. All of the Above

5. The overexpression of which growth factor is primarily behind angiogenesis?
    A. Growth Differentiation Factor 9
    B. Vascular Endothelial Growth Factor
    C. Transforming Growth Factor Alpha
    D. Migration Stimulating Factor

6. VEGF inhibitors carry no cardiovascular side effects.
    A. True
    B. False

7. The mechanisms in which dopamine inhibits VEGF receptors include:
    A. SHP-2
    B. Receptor Endocytosis
    C. A and B
    D. None of the above

8. Which of the following drugs may be used to block the D_2 receptor?
    A. Dopamine
    B. Cabergoline
    C. Domeperidone
    D. All of the above

9. The treatment for DAWS includes:
    A. Antidopamine therapies
    B. Risperidone
    C. Apomorphine
    D. Currently no treatment is available

10. Dopamine's effects are mostly observed in:
    A. The central nervous system
    B. The cardiovascular system
    C. The pancreas
    D. Both A and B

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Program Content:	**Strongly Disagree**				**Strongly Agree**
The program objectives were clear.	**1**	**2**	**3**	**4**	**5**
The program met the stated goals and objectives:					
Explain the processes of angiogenesis and tumorigenesis and the role of each in cancer metastasis.	**1**	**2**	**3**	**4**	**5**
Describe the actions of dopamine on tumorigenesis and its relationship with vascular endothelial growth factor.	**1**	**2**	**3**	**4**	**5**
Discuss the methodology and results of the initial trials suggesting the use of dopamine and dopamine agonists in cancer treatment.	**1**	**2**	**3**	**4**	**5**
Evaluate the potential use of dopamine for cancer treatment in regard to side effect profiles and cost of therapy in comparison to current angiogenesis inhibitors.	**1**	**2**	**3**	**4**	**5**
The program met your educational needs.	**1**	**2**	**3**	**4**	**5**
Content of the program was interesting.	**1**	**2**	**3**	**4**	**5**
Material presented was relevant to my practice.	**1**	**2**	**3**	**4**	**5**

Comments/Suggestions for future programs:

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Thank you!
Answers to Assessment Questions—Please Circle Your Answer

1. A B C D	**4. A B C D E**	**7. A B C D**
2. A B C D	**5. A B C D**	**8. A B C D**
3. A B C D	**6. A B**	**9. A B C D**

10. A B C D

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The Role of a Home Health Care Pharmacist—Medication Management for Patients with Feeding Tubes

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Abstract
Home health care is a method of medical care that patients receive inside their home under the supervision of a collaborative team of physicians, nurses, pharmacists and sometimes other health care professionals. Home health provides patients with the same standard of care that they would be receiving in a nursing home or hospital. However, the treatment and continued monitoring at home reduces health care costs and makes the patient feel more comfortable. Pharmacists analyze, resolve and prevent medication-related problems in home health care in order to minimize hospitalizations and improve patient quality of life. Pharmacist involvement with other health care professionals in the patient transition of care can help maximize the quality of patient care. To become a home health care pharmacist, neither a residency nor certification is required. Home health pharmacists perform medication reconciliation, comprehensive medication reviews, monitor intravenous drug therapy and enteral therapy, identify high-risk medications and adverse drug reactions, prevent polypharmacy and improve patient adherence. Patients that must be fed through enteral nutrition tubes in the home health care setting have a set of special concerns that the home health care team must address. Pharmacists' extensive knowledge of medication necessitates their involvement on the home health care team.

Key Terms
Enteral Nutrition; Home Health Care; Patient Care Team; Pharmacist; Health Care Costs

Role of the Home Health Care Pharmacist

Patients receiving home health care frequently rely on their personal financial assets, such as their ability to afford medications and personal health aid, as well as their level of health literacy to manage their medications and health.[1] This unstructured environment may lead to undesirable medication problems which may interfere with the goals of therapy. One of home health care's biggest roles is to prevent the use of unnecessary and duplicate medications or the omission of proper drugs.[2] In addition, patients may be using inappropriate doses and possibly experiencing drug-drug interactions. Each of these issues provides an opportunity for the home health care pharmacist to assist in patient care. Currently, neither a residency nor certification is required for this specialty.[3] In the home health care environment pharmacists perform medication reconciliation to identify and prevent complications. These complications could be due to drug-drug interactions or unnecessary medications which can be identified by comparing a patient's medical records to hospital admissions, transitions of care and discharge orders.[4]

Typically, a home health pharmacist may visit or interact with at least five patients each day for about 30 to 60 minutes.[2] The patient-pharmacist meeting may be conducted in several ways including telephone interviews, home health visits, chart reviews or a combination of each. Prior to the appointment, the home health pharmacist examines the patient's information and performs a comprehensive medication review to include all prescriptions, over-the-counter medications and any dietary or herbal supplements. During the appointment, the pharmacist and patient discuss the appropriate indications for current medications as well as the safety and efficacy of these medications. The pharmacist also assesses the patient's adherence and compliance to the suggested therapeutic plan. The pharmacist is required to properly document all of the current medications, health conditions and medication-related problems discussed with patients during these meetings. The patient-pharmacist meeting provides a great opportunity for pharmacists to be personally involved with their patients and allows them to detect any issues earlier and more readily.

According to an abstract from a study done by Lipton et al., out of 236 ambulatory care patients that were 65 years of age and above, 88 percent presented with at least one clinically significant medication problem.[5] This is an opportunity for pharmacists to encourage and aid other health care workers in employing evidence-based prescribing for all patients, with special consideration for those at home.[6] As a result, the number of medication problems can decline to hopefully decrease overall patient mortality and medical costs. Additionally, pharmacists can aid in the adjustment of medication regimens and treatment to patient's learning ability, which is especially important for those receiving health care at home. This involves assessing a patient's reading level, ability to comply with medication regimens and understanding of medication administration and safety, all of which can be done by a home health care pharmacist.

Home Health Pharmacist Assistance in Transitions of Care

According to Hester et al., almost two-thirds of medication errors happen during transitions of care into the home health setting, and approximately one in five older patients are readmitted within one month after hospital discharge due to a preventable medication error.[4] Common medication classes that cause these readmissions include anti-infective, cardiovascular, central nervous system, endocrine and hematologic medications, with the most problematic medications being oral antiplatelets, oral hypoglycemics, insulin and warfarin. Starting in 2012, these preventable hospital readmissions are being monitored by the Centers for Medicare and

Medicaid Services (CMS), which monetarily penalizes hospitals for high readmission rates.

One way to improve the transition of care is for pharmacists to continually perform medication reconciliations, during which they analyze the patient's medications to avoid drug interactions, duplicative therapies or indication errors.[4] Improving the communication between home health, community and hospital-based pharmacists can also help clarify questions and identify medication discrepancies. Additionally, pharmacists in all settings can aid in the transition of care by keeping an open line of communication with the physicians and nurses that are treating the patient.

Enteral Nutrition

Enteral nutrition (EN) is utilized to improve quality of life through the prevention and treatment of malnutrition and improve growth in children, while also aiding in the treatment of chronic gastrointestinal disease states such as Crohn's disease.[7] Several chronic disease states such as dementia, cystic fibrosis, peritoneal dialysis, oro-pharyngeal and esophageal malignancy and amyotrophic lateral sclerosis (ALS) can also benefit from home-health monitoring. Diseases such as Crohn's disease, pancreatitis and ulcerative colitis may require patients to be put on feeding tubes for nutritional support.[7,8] Feeding tubes assist patients by retaining hydration (decreasing the possibility of aspiration or choking), managing weight as well as preserving energy.[8] For patients with a functioning gastrointestinal (GI) tract, EN is preferred over total parenteral nutrition (TPN). In contrast to TPN which is administered intravenously, EN utilizes a feeding tube directly placed in the GI tract. As a result, the overall risk of infection is decreased, providing better patient outcomes.

Enteral nutrition involves the administration of a formulated liquid, also known as medical food, to help the distinct dietary needs for a patient's particular disease state or condition.[9] These formulations contain fats, carbohydrates, vitamins, proteins and minerals to exceed 1,350 kilocalories a day. Enteral nutrition should be considered when nutrition and hydration are insufficient, dysphagia and aspiration occur frequently or weakness and weight loss lead to decreased energy.[8] Contraindications to EN use include active coagulopathies, thrombocytopenia, sepsis, peritonitis, ascites, anorexia and pyloric obstruction.[7] Part of the pharmacist's role in patients with feeding tubes is to ensure that the patient's daily nutritional needs are met and successfully coincide with their medication needs without interactions.[10]

Although EN provides great benefits for patients, some may fear having a surgical procedure to implant the tube or the possibility of infection or pain at the insertion site.[8] Before a patient is placed on EN, a health care professional must ensure that the patient and their caregivers are capable of implementing this therapy.[11] Ongoing medical supervision is necessary for those receiving EN products in order to avoid complications. This supervision includes the assessment of patient motivation, financial status, educational ability, nutritional and medical benefit, physical limitations and capacity to adhere to safety standards. This is an area in which home health pharmacists are needed to maintain an open flow of communication between health care members, as well as to properly educate patients on EN administration, how to administer medications while utilizing a feeding tube and common complications that may arise with both EN feedings and medication administration through the tubes.

Enteral Feeding Tube Selection and Administration

There are many important considerations when a patient is enterally fed. The type of feeding tube to be used is determined by the patient's disease state and the severity of their condition as well as the length of time that they will need to receive tube feeding.[12] Nasoenteric tubes are most often used for short-term (one to three weeks) nutritional support due to their low cost and easy insertion through the nose directly into the GI tract. These include nasogastric (NG) and nasoduodenal (ND) as well as nasojejunal (NJ) tubes. Orogastric (OG) tubes are also used for short-term feeding and are inserted through the mouth into the stomach. Orogastric tubes are used for short-term feeding when the tube cannot properly be placed nasally due to injury, deviated septum or sinusitis. For long-term (four to six weeks or more) tube feeding, the tubes are surgically placed directly from the outside of the body into the stomach or intestine, bypassing the upper part of the GI tract. The most commonly used tube is the percutaneous endoscopic gastrostomy (PEG)-tube because of its relatively easy method of placement.

Nutrition support via enteral feeding can be provided in different ways depending on the type of tube and patient's condition. Feedings can be continuous, cyclic, bolus or intermittent.[12] Continuous feeding over a 24-hour period is the preferred method for the initiation of EN therapy in critically ill patients due to the constant administration of nutrients. However, continuous feedings are commonly interrupted when patients need to take their medications. Cyclic feedings are a continuous supply of nutrients over an eight to 20 hour period and typically take place throughout the night when the patient is sleeping. Bolus feedings occur four to six times per day to allow the nutrients to infuse over a short time period at specified intervals. This method is convenient for health care professionals to administer medications between nutrient feedings. In this circumstance, EN should be stopped 30 minutes before giving the medications to allow gastric emptying. Then, EN may be started 30 minutes after the medication is given which allows time for absorption. Intermittent feeding is similar to bolus feeding but used over a longer duration. Continuous and cyclic feedings are preferred when feeding into the stomach or small intestine, whereas bolus and intermittent feedings are generally used only in the stomach and not in the small intestine. Feeding tubes sizes are typically small-bore (5 to 12 French units) or large-bore (14 or more French units) where 1 French unit is equivalent to 0.33 mm. Both small and large bore tubes are used for percutaneous routes into the stomach and small intestine. In contrast smaller bore tubes are more commonly used for nasal routes and larger tubes for oral routes. Smaller tubes are generally more comfortable than larger tubes. However, they become clogged more easily by thick nutrition formulations or medications administered through the tube.

It is very important to avoid tube occlusions, or blockages, because they prevent the patient from receiving their proper nutrients and medications. Regardless of the dosage form used, the tube needs to be flushed with about 30 mL of sterile water before and after medication administration to help prevent occlusions.[13] In addition to flushing and irrigation, patients may be given a prophylactic dose of alkalinized enzyme solution with a pH of 7.9 to prevent occlusion.[12] This solution typically consists of one crushed pancrelipase tablet (lipase 8,000 units, amylase 30,000 units, protease 30,000 units) mixed with one crushed sodium bicarbonate tablet (324 mg) which is then dissolved in 5 mL of warm water. The administration of alkalinized enzyme solution may also be used to try to unclog an occluded tube.

Medication Considerations for Patients on Feeding Tubes

Patients receiving feeding tube nutrition require special considerations for the administration of medications due to the underlying disease state inhibiting the patients' ability to take drugs orally.[12,13] Drug absorption for patients on EN is affected by the dosage form of the medication as well as the placement of the feeding tube.[12] For instance, some oral medications can be crushed and given through feeding tubes, conveniently depositing the medication directly into the patient's GI tract. However, some oral medications may not be crushed for administration due to their coatings because the medication will not have extended release properties and, therefore, it will not absorb correctly (i.e., acetaminophen, ferrous sulfate, omeprazole).[13] Nonetheless, liquid formulations of some of these medications are available, solving this issue. Possible interactions may also exist between the drug and the compounds in the nutrition regimen (i.e., phenytoin, carbamazepine, warfarin).[12,13] Delayed and extended release tablet coatings may not be crushed due to their release characteristics; if the coating is broken, the drug will not be administered the way in which it was intended. Instead, all of the drug would be released/absorbed at once rather than delayed or extended over time. In addition to the properties of the drug itself, it is also important to make sure that the drug formulation is able to physically pass through the tube and into the GI tract without causing an occlusion or damaging the tube. If any of these interactions or occlusions occur, the patient will not receive the proper dose of the drug.

In addition to solid dosage forms, several other oral dosage forms may be administered through the EN tube.[12] Liquid preparations are preferred because they are readily absorbed, do not have to be crushed, and are less likely to cause tube occlusions. Suspensions and elixirs are preferred over syrups because of their decreased viscosity. The tonicity, osmolality and sorbitol content of liquid preparations should be closely monitored to prevent adverse events such as diarrhea, bloating, nausea or cramping. Solutions may be diluted with sterile water if necessary. Liquid-filled capsules are also able to be administered enterally, and in most cases the capsule may be dissolved and all contents can be put through the tube. Capsules that contain beads or powders may be broken so that only the beads or powders may pass through the EN tube.

When considering drug absorption issues due to the placement of the feeding tube, the pharmacist has to examine the pharmacokinetics of the particular medication.[12-14] Most medications are typically absorbed in the small intestine, but some drugs such as antacids, sucralfate and bismuth have actions in the stomach.[12,13] If a patient has a feeding tube placed in the small intestine but needs a drug that acts in the stomach, the administration of the drug through their intestinal feeding tube will have minimal effects. Another example of this involves ketoconazole and itraconazole. In order for these medications to be properly absorbed, they must interact with the acidic gastric environment. However, if the feeding tube is in the small intestine, these drugs will have decreased bioavailability due to the absence of interaction with the stomach environment. Another consideration should be taken into account for drugs such as opioids, tricyclic antidepressants, beta-blockers and nitrates that undergo extensive first-pass hepatic metabolism. If these drugs are administered through a feeding tube that deposits into the jejunum, their absorption will increase leading to greater systemic effects. It is extremely important for pharmacists to check drug compatibility with the placement of the tube for home health patients to avoid changes in drug absorption/bioavailability.

Medications generally should not be coadministered with the nutrition formulation, with the exception of any necessary electrolyte supplements.[12] Combining the medication with the nutrition formulation will increase the probability for a drug-nutrient interaction, alteration of the bioavailability of the medication, occurrence of tube occlusions and potential microbial contamination. Pharmacists should be knowledgeable of possible drug-nutrient interactions causing reduced medication bioavailability.[10] For example, the effectiveness of antimicrobials such as levofloxacin, ciprofloxacin and moxifloxacin can be decreased by calcium, magnesium and iron during tube feeding.[12] Also, enteral feeding should be held one to two hours before and after the administration of either phenytoin or warfarin to avoid decreased bioavailability of these medications caused by binding to the protein component of the medical food. Although medical food formulations are compatible with some medications, it is necessary to check package inserts or drug information sources to ensure the safety of concurrent administration of a medication with EN.

Patients with enteral feeding needs that are on medications present a very important area of concern for the home health pharmacist—the drug expert of the home health team. Each medication the patient is taking should be evaluated by the pharmacist to determine how it needs to be administered, if there are any absorption issues due to the EN and if there are any possible interactions between the medications and nutrition regimen.[12,13] A comprehensive list of medications that cannot be crushed is available from the Institute for the Safe Use of Medications at www.ismp.org/tools/donotcrush.pdf. Additionally, pharmacists can refer to the package insert of specific medications using drug information sources such as Clinical Pharmacology, Lexicomp®, Micromedex® or Facts & Comparisons®. Alternative routes of administration, such as

intravenous infusions and intramuscular injections as well as transdermal patches and sprays, must be considered for medications that cannot be given through the tube.[12] In these instances, pharmacists may also consider finding a different, therapeutically equivalent medication that can be administered through an enteral tube.

Conclusion

The growing use of EN in home health requires home health pharmacists to become more involved in patient care. On the home health care team, physicians are responsible for prescribing medications, while nurses are responsible for administering them to the patients. Pharmacists, as drug experts, are able to maximize medication therapies for EN patients through ensuring that medications are administered in the proper dosage form, and that there is little to no risk of drug interactions. In order to have the best outcomes for home health EN patients, pharmacists must work with other health care providers to decrease medication-related errors, reduce feeding tube complications and provide a better quality of life for each patient.

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Special Considerations in Pediatric Burn Patients Regarding Drug Dosage and Administration

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Abstract
Pediatric burn patients are a high-risk patient population to treat. These patients have altered physiologic function as a result of the burn injury, in addition to their smaller size and developing bodies. This creates unique challenges during treatment. Accommodations for these patients are made through unique drug dosages and routes of administration. When treating pediatric burn patients, properly assessing and treating pain promptly and effectively is of utmost importance. Nurses who utilize accurate and appropriate pain assessment scales will provide the best treatment of pain. Proper assessment allows the patient to receive the correct analgesic regime, ensuring a faster and more comfortable recovery process.

Key Terms
Analgesics; Antibiotics; Burns; Child; Pain; Pediatrics

Introduction

In burn patients, many physiologic functions are altered which require unique dosing, routes of administration and intensive care regarding treatment. Due to the significant amount of skin loss, patients are at an increased risk of infection and should be treated with preventive antibiotics.[1] Upon admission into the hospital, burn wounds will be cleansed and dead tissue will be surgically removed before antibiotics are started. If the burn covers a large area, skin grafting may be necessary to help cover the wound and protect it from infection.[2] Stress hormones are also released as a part of the inflammatory response, which induces a hypermetabolic state. This leads to an increased need for nutritional therapy, typically given through the parenteral route. Respiratory airways may be obstructed due to chemical irritants released from fire accidents and thermal injury from the inhalation of hot vapor or liquids. One of the most significant effects related to burn patients is edema, which may affect localized tissues, the pulmonary airway, brain or liver. Edema leads to decreased cardiac output, initially, as stroke volume decreases. This leads to a decrease in the glomerular filtration rate; renal drug clearance is impaired and dosing needs to be adjusted accordingly. In addition to hepatic edema, albumin and other hepatic protein production is decreased, so hepatic dosing adjustments need to be made. The body readjusts to maintain homeostasis and increase cardiac output, leading to reperfusion.[1]

Most medications are modified for the pediatric population due to their smaller body mass and developing physiology. In pediatric burn patients, additional variables need to be taken into account to select the best treatment. Pediatric patients have about three times the body surface area (BSA) of adults, and more of their weight is water based.[3] Therefore, it is crucial to accurately calculate BSA as a percentage of body burned to correctly dose medications and fluids. In a study conducted in 71 pediatric burn patients, 79 percent of BSAs were overestimated or underestimated, highlighting the prevalence of faulty initial assessment.[4] Substantial capillary damage is also sustained, leading to increased fluid losses and tissue perfusion that needs intense fluid and electrolyte resuscitation. Children are also more susceptible to hypothermia because of their larger BSA to water ratio. For those under the age of two, skin is thinner, attenuating the risk of hyperthermia and increasing metabolic needs because of excessive shivering in an attempt to return to thermal homeostasis.[3,5]

Using Antibiotics to Prevent Infection in Pediatric Burn Patients

In first degree burn patients, topical antibiotics are not typically used because the burn resides in the epidermal level. These treatments are reserved for second and third degree burns when infection risk is high. Topical antibiotics should be used instead of intravenous forms for preventive use and in early admittance to the hospital when the bacterial organism has not yet been identified. In second degree burns, ointments are preferred because they are occlusive and better tolerated by pediatric patients. For third degree burns, creams should be used for their ability to penetrate to deeper layers of skin, spread over a large surface area, ease of application and soothing effect. Patients with third degree burns may undergo skin grafting, in which case liquid forms of topical antibiotics should be used. Ointment and cream forms will impede skin graft healing, while liquids can be used to irrigate and hydrate the burned area.[2]

Nursing Roles in Assessing and Controlling Pain

According to Williams, pain that children experience related to burn injuries can be extremely severe.[8] Furthermore, Vincent and Denyes explain that severe pain that goes untreated can lead to slower recoveries and delayed wound healing in children.[9] As a result, it is extremely important to accurately assess and control pediatric patients' pain when they are suffering and recovering from burn injuries. Nurses are at the forefront of patient pain assessment, therefore utilizing appropriate assessment tools specifically for a pediatric patient allows for effective pain management throughout treatment. Pain in pediatric burn patients needs to be assessed accurately in order to treat the patient correctly, so these assessment tools are of utmost importance to the nurse, as well as to the prescriber and pharmacist. According to Wong and Baker, quantitatively assessing pain in children is the only way to determine how to appropriately treat and man-

Table 1. Common Topical Antibiotics Used to Treat Pediatric Burn Patients.[2,6,7]

Antibiotic	Degree of Burn Treated	Pathogen Targeted	Adverse Effects	Important to Note
Bacitracin	Second	Gram positive	Anaphylaxis (rare)	---------
Neomycin	Second	Gram positive & negative	Cutaneous Hypersensitivity, Ototoxicity, Nephrotoxicity	Can be used with bacitracin to minimize adverse effects
Silver Sulfadiazine	Second & Third	Gram positive & negative, Yeast	Pain, Burning, Pruritis, Anemia	Contraindicated in patients with sulfur allergies, increases wound healing time, leaves white residue on skin
Mafenide acetate	Third & Post-Skin Graft	Gram positive & negative	Cutaneous Rash, Metabolic Acidosis	Can be used with nystatin to decrease fungal infection, increases wound healing time, decreases inflammatory response
Silver nitrate	Post-Skin Graft	Staph, pseudomonas, yeasts	Burning, Irritation	Can be used in patients with sulfur allergies, monitor electrolytes, stains black
Neomycin & Polymixin B	Post-Skin Graft	Gram positive & negative, Exception for pseudomonas	Dermatitis, Ototoxicity, Nephrotoxicity	Not for large areas

age their pain. Wong and Baker researched and compared the effectiveness and preference of six different pain assessment scales to be utilized by nurses for children aged 3 to 18 years.[10]

The pain assessment tools that Wong and Baker studied included the simple descriptive scale, numeric scale, faces scale, glasses scale, chips scale and color scale.[10] Comparing each of these pain assessment scales, the authors determined that the faces scale, which uses facial expressions coordinated with numerical values to reflect severity of a patient's pain, was the preferred method for children to report their pain to nurses. Wong and Baker also found that the reliability and validity did not differ significantly from scale to scale. Therefore, all pain assessment methods are equally effective in monitoring children's pain. In addition, the researchers concluded that the older the children, the more reliable and valid the pain assessment scales became. The only significantly different portion of data in the study was the children's preference of the pain assessment scale, which illustrates that different assessment scales work better for different children.[10] As a result, when caring for pediatric patients, nurses need to try different pain assessment scales and determine which one works best for each child. This will help nurses and other health care professionals to decide what the most appropriate intervention is for pain management.

Administering Pain Medication

Not only is the nurse's assessment of pain an important part of the treatment of pediatric burn patients, but the nurse's administration of appropriate analgesic medications is also crucial to effective pain management. Administering analgesic medications in pediatric burn patients can treat the pain caused from the initial burn injury or treat pain prophylactically during a wound dressing change. In a study conducted by Vincent and Denyes, nurses' administration of pain medication was compared to the pain rating that children verbalized to the nurse.[9] The authors found that nurses were more likely to administer analgesic medications in children reporting both experiencing pain and showing physical signs of pain, such as increased heart rate or painful facial expressions. If pediatric patients reported pain without any physical signs of pain, the nurses were less likely to administer analgesics. This becomes an issue because the experience of pain is very individualized and subjective. A child may be experiencing pain without physically appearing to be in pain, so accurately assessing and treating this pain is imperative. Vincent and Denyes further explain that 26 percent of children who reported pain received no analgesia, and only 51 percent of children who reported a moderate or high level of pain received analgesic medication. The authors emphasize that one of the significant contributing factors to undertreated pain in children is the inaccurate assessment of pain by nurses.[9] Determining the appropriate pain assessment scale for each child will help nurses to precisely identify pain as well as manage pain in the correct administration of analgesics.

There are many different routes by which analgesic medications can be administered. Some of the common routes used in the pediatric population comprise oral (including nasogastric tubing), intravenous and transcutaneous administrations. According to Dyer et al., oral medication administration in pediatrics is the most common route and usually takes the form of tablet or suspension.[11] When giving a medication through a nasogastric (NG) tube, typically the oral tablet is crushed and/or dissolved into solution for

administration. Oral medications (tablet or gelatin capsule) that are designed to be fast-acting and absorbed quickly can be crushed and dissolved in solution. Sustained action or any dosage form that is designed to extend the drug delivery period cannot be crushed or dissolved because it risks toxicity or gastrointestinal upset. Thick liquids can be diluted to make them easier and safer to administer. Buccal and sublingual drugs are ineffective if crushed or dissolved and can still be given by the typical route if there is no oral mucosa damage. To ease administration, liquids are the dosage form of choice when NG tube administration is necessary. Typically NG tubes are also the means of administration for nutritional feedings, so it must be verified that medication administration will not interact with feeding and vice versa. For drugs that require an empty stomach, the feed should be stopped for at least 30 minutes before and after drug administration.[12] Patients who are in pain related to burns, especially young children, may find it easier to swallow an analgesic suspension. The authors emphasize that when nurses administer oral suspensions, it is important to mix the solution well and accurately measure the prescribed amount of medication so that the child's pain can be managed as well as possible.[11]

Dyer et al. also discuss the intravenous route of medication administration which is used in more critical situations, including pediatric patients who experience significant burn injuries.[11] Intravenous medication administration is beneficial in the treatment of pain because the analgesics take effect rapidly and maintain therapeutic levels in the body more easily. Large bore intravenous (IV) catheters should be used for burn patients so that rapid fluid resuscitation and analgesic infusion can occur. Oftentimes, the antecubital area is used to initiate IV therapy in burn patients. It is important for nurses to dilute the medication if indicated, flush the IV line to determine line patency, and to identify the compatibility of IV injections and infusions if analgesics are being administered along with replacement fluids, as is often seen with burn patients.[1] This route of medication administration is extremely effective in pediatric patients who suffer from a high level of pain due to significant burn injuries.

Finally, another common route of analgesic administration in children is the transcutaneous route, which is often delivered through a dermal patch. Dyer et al. explain that the rate of transcutaneous absorption is significantly faster in children compared to that of adults.[11] The researchers point out that nurses need to wear gloves when administering this form of medication so that the analgesic does not get absorbed by their own skin. Furthermore, it is important for nurses to rotate skin sites on the patient when using topical medications to prevent irritation and to remove old patches when placing new patches on the skin to prevent analgesic overdose. The severity of the injury, as well as the child's pain rating, often determines the route of analgesic administration in pediatric burn patients. Nurses are responsible for accurately assessing pain and correctly administering analgesic medications. Accuracy will help decrease pediatric patients' pain and, in turn, will promote a more rapid recovery and healing process. The table below highlights common analgesics utilized.

Study Evaluation

After a patient has been acutely treated for a burn injury, the painful healing process begins. A burn patient experiences two types of pain: background and procedure associated pain. The injured tissue inflammation and healing processes

Table 2. Common Analgesics Used in Pediatric Burn Patients.[13-19]

Analgesic	Degree of Burn Treated	Adverse Effects	Important to Note
Acetaminophen	First	Nausea, Vomiting, Constipation, Pruritis, Atelectasis	Can be used with opioids
NSAIDs	First & Second	Nausea, Vomiting, Pruritis, Urinary Retention	Can be used with opioids
Morphine	Second & Third	Nausea, Vomiting, Pruritis, Urinary Retention, Sedation	Common Patient Controlled Analgesia use ≥ 5 years of age
Hydromorphone	Second & Third	Nausea, Vomiting, Pruritis, Urinary Retention, Hypertension	Equivalent to morphine
Fentanyl	Second & Third	Nausea, Vomiting, Pruritis, Urinary Retention, Hypotension, Bradycardia	Equivalent to morphine but with faster onset time; Can be used in renal impairment
Pethidine	Second & Third	Nausea, Vomiting, Pruritis, Urinary Retention, Anxiety, Seizures	Contraindicated in renal impairment
Methadone	Second & Third	Nausea, Vomiting, Pruritis, Dizziness, Arrhythmias, Seizures	For chronic pain management
Ketamine	Second & Third	Nausea, Vomiting, Pruritis, Arrhythmias, Respiratory Depression	Can be used with opioids

cause background pain, while procedural pain is an increase in discomfort experienced by the patient when undergoing necessary therapy associated with burn treatment. Typically more analgesia is required due to increased pain experienced by the patient as a result of procedural pain.[13] Each type of pain needs to be evaluated and appropriately treated for pain management. This course can provoke anxiety and is especially difficult in children who do not understand that painful adjunct procedures, such as dressing or tube changes, will reduce infection risk, limit scarring and decrease the healing time.[13,20] During this distressing time, a child can develop insomnia, depression, anxiety, academic problems, longer healing times and an overall decrease in quality of life. To limit these side effects, it is imperative for the patient's pain to be properly treated.[21,22] The analgesia regime is individualized for each patient and is chosen at the discretion of the medical team. The decision is made from multiple factors regarding the pain symptoms such as severity, length, type, ease of transition between intravenous and by mouth administration and patient specific factors including discharge versus inpatient care, daily activities, history of adverse reaction and patient goals in pain management.[23]

From Table 2, it is easy to conclude that there are many medication options available for the treatment of pain in pediatric burn patients, and there is not a consensus about which agent is superior. "For the pediatric population the optimal analgesic is one that is easy to administer, well-tolerated, [with a] rapid-onset of analgesia effects, limited sedation and short duration of action."[13] Two options that can be used are fentanyl and morphine. A study conducted by Rhonda et al. was designed to assess the analgesic effectiveness between oral transmucosal fentanyl citrate and oral morphine in pediatric burn patients when dressings or tubing were changed.[24] Patients assessed in the study were above 10 kg, were able to describe their pain using the Face Pain Rating Scale and had a wound that required a 30 minute or longer tubing procedure. Those under 3 years of age, over 18 years of age and with any previous diagnosis of physical or mental illness were excluded from the study. Those with a past adverse reaction with either of the two agents or that had taken a monoamine oxidase inhibitor containing agent in the last 14 days were also excluded.[24] The study was double-blinded, reverse crossover, time randomized and placebo-controlled. The study participants were randomly split into two treatments groups and they only differed in the sequence in which they received the medications. The dosing sequence between the two groups was as follows: The medications for each group were given 30 to 40 minutes prior to the tubing procedure. Both a self and nurse assessment of the patient's pain level, associated anxiety, cooperation and sedation were assessed before, during and after the procedure.[24] The anxiety and cooperation ratings were included because secondary outcomes of proper pain management are a decrease in patient anxiety level and increased cooperation in painful procedures. Pain assessment was completed using the Face Pain Rating Scale with a 0 to 5 rating scale. Anxiety was measured by the Fear Thermometer on a scale from 0 to 4. Patient pain and anxiety were recorded at medication administration, every 15 minutes until the procedure concluded and three and a half hours after the procedure.[24] If a patient complained of pain with a Face Pain Rating of greater than 4, they were given a rescue dose of 0.4 mg/kg of morphine for increased analgesia. Side effects and level of sedation were also documented.[24] The study concluded that fentanyl was superior to morphine in managing the pain and anxiety associated with procedures of pediatric burn patients. The fentanyl treatment was also found to decrease anxiety levels in those patients suffering from comorbid anxiety. Neither medication had any significant side effects reported, and sedation levels between the two medications were roughly equivalent. A limitation of this study was the small sample size, with a total of just eight patients participating. More research in pediatric burn pain management is needed to make better clinical decisions.[24]

Implications in Pharmacy and Nursing Practice

Pain management in pediatric burn patients is an imperative process. If addressed properly, the patient will recover more quickly and experience less pain anxiety during recovery. Assessing a patient's pain is complicated because every person feels pain differently, and patients are often unable to adequately explain the type and severity of pain that they are experiencing. This is especially true in the pediatric patient population where nonverbal cues are a key component in communication. Using pain scales that include a nonverbal factor helps the medical team better assess the patient's pain status. This leads to proper medication selection without overtreating or undertreating a patient's pain symptoms. Overtreatment of pain medications can cause serious side effects such as increased sedation or respiratory depression. Pediatric patients are more susceptible to this side effect.

Table 3. Dosing Strategy Between Patient Groups.[24]

Dosing Strategy		
	Patient Group 1	**Patient Group 2**
Day 1	Fentanyl and placebo morphine	Morphine and placebo fentanyl
Day 2	Morphine and placebo fentanyl	Fentanyl and placebo morphine
Dosing Levels (Therapeutic Equivalent)	Fentanyl citrate dose: 10 μg/kg	Morphine: 0.6 mg/kg

Undertreatment may cause increased anxiety leading to problems such as insomnia, academic issues and a longer healing time. The key to pain management is proper assessment. If the patient is properly assessed, they are more likely to receive the correct medication for their pain and will have a greater chance of achieving positive outcomes than those that do not have their pain properly managed.

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Combined Neprilysin and Angiotensin Inhibitor for the Treatment of Heart Failure

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Abstract

Heart failure (HF) is a highly prevalent disease state worldwide that can progress into a disabling condition. It is pertinent to have a treatment regimen that is effective in lowering the number of HF exacerbations and, therefore, hospital readmission rates. A novel medication currently in clinical trials, LCZ696, blocks both neprilysin and angiotensin type I receptors. The overall effects are an inhibition of the breakdown of natriuretic peptides which leads to a decrease in renin and aldosterone release. This, combined with the antagonization of angiotensin type I receptors, leads to a decrease in blood pressure, blood volume and systemic vascular resistance. The PARAMOUNT trial compared the therapeutic effectiveness of LCZ696 to valsartan monotherapy. This study demonstrated that patients taking LCZ696 had better improvements in symptoms and biomarkers. The PARADIGM-HF trial compared LCZ696 to enalapril. LCZ696 showed significant reductions in cardiac death, hospitalizations and HF symptoms over enalapril. Although this new medication looks promising as a future treatment option for HF patients, additional studies should be completed to look at the long-term patient outcomes associated with LCZ696.

Key Terms

Cardiac Output; Heart Failure; Natriuretic Peptides; Neprilysin; Renin-angiotensin System; Enalapril; Omapatrilat; Valsartan

Introduction

Cardiovascular disease has been the number one cause of death in the United States almost every year since 1935.[1] Heart failure (HF), characterized by a lack of blood perfusion due to decreased cardiac output, is a debilitating condition worldwide. Fortunately, through extensive drug development, scientists and clinicians have been able to slow the decline of cardiac function. Currently, angiotensin-converting-enzyme inhibitors (ACE-I) are the first line therapy options for HF patients based on recommendations from the 2013 American College of Cardiology Foundation/ American Heart Association guidelines.[2] They are effective in preserving Left Ventricular Ejection Fraction (LVEF) and decreasing hypertension symptoms associated with HF. However, recent research points to a novel approach in better managing HF. In clinical trials, LCZ696, a dual neprilysin and angiotensin blocker, has consistently demonstrated clinical effectiveness in many cardiac parameters. Future studies need to be conducted before LCZ696 is introduced into the market and incorporated into the guidelines as an alternative option to ACE-I, the current mainstay treatment for HF.

Epidemiology

With a prevalence of more than 5.8 million people in the United States and 23 million people worldwide, HF is a serious public health concern.[3] Each year, there are more than 550,000 new cases diagnosed in the United States alone. Heart failure prevalence is highest among black and Hispanic populations.[2] Male and female populations have a similar incidence and prevalence of HF. However, women more commonly develop HF later in life and tend to survive longer with the disease than men. Even though HF can occur at any age, the prevalence is only about 1 to 2 percent in populations younger than 55 years of age and increases to approximately 10 percent in populations over 75 years of age. Heart failure is a complicated clinical syndrome that is the consequence of a structural or functional cardiac disorder. It results in an impaired ability of the heart to pump blood sufficiently enough to meet the requirement of metabolizing tissues.[2,3] There are different types of HF which may result in various outcomes. Left-sided HF can cause fluid backup in the lungs resulting in shortness of breath, while right-sided HF can cause fluid backup into the abdomen and lower extremities causing edema.[4] Heart failure can also be classified as systolic or diastolic. Systolic HF, also known as HF with reduced ejection fraction, occurs when the left ventricle cannot contract with enough force to pump out adequate amounts of blood. Diastolic HF, also known as HF with preserved ejection fraction, occurs when the left ventricle does not fill completely. Many conditions can damage the heart resulting in HF including coronary artery disease, myocardial infarction, hypertension, obesity, arrhythmias and other chronic diseases such as diabetes and dyslipidemia. Following are tables of both the ACCF/AHA Stages of HF and the New York Heart Association (NYHA) Functional Classification from the ACCF/AHA Practice Guidelines.[2]

Table 1. ACCF/AHA Stages of HF.[2]

ACCF/AHA Stages of HF	
A	At high risk for HF with no structural heart disease or symptoms of HF
B	Structural heart disease without symptoms of HF
C	Structural heart disease with prior or current symptoms of HF
D	Refractory HF requiring specialized interventions

Table 2. NYHA Functional Classicfication.[2]

NYHA Functional Classification	
I	No limitation of physical activity. Ordinary physical activity does not cause HF symptoms
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in HF symptoms.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes HF symptoms.
IV	Unable to carry on any physical activity without symptoms of HF, or experience HF symptoms at rest.

Adapted from Table 4 in the 2013 ACCF/AHA Guideline for the Management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task force on practice guidelines. *Circ.* 2013; 128: e248.

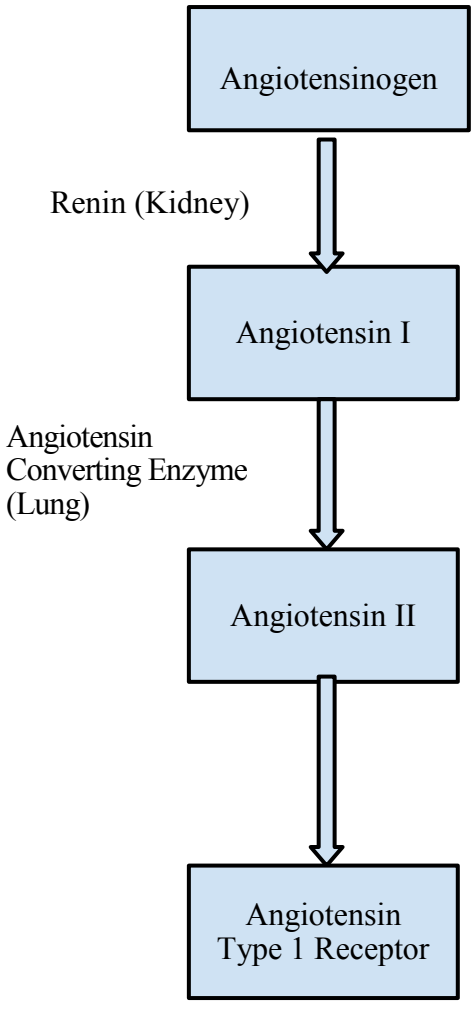
With numerous possible causes of HF, it can be difficult to diagnose. A compilation of data from a patient's medical history, physical examination and chest radiograph along with the presence of indicating symptoms and elevated filling pressures are used when diagnosing HF.[3] Symptoms a patient with HF may experience include dyspnea at rest or during exertion, fatigue or weakness, edema in the lower extremities, tachycardia, chest pain or palpitations.[2,4] When a patient presents with these symptoms, a family history as well as serial assessments of weight, jugular venous pressure and vital signs should be obtained.[2] Risk factors are also taken into consideration and include conditions that can damage the heart muscle. These risk factors include sleep apnea, viral infections, obesity, alcohol or tobacco use and use of the diabetes medications rosiglitazone and pioglitazone, which can increase edema and worsen HF.[4] Many diagnostic tests are used to identify the causative conditions or risk factors of HF. One test used to distinguish between systolic and diastolic HF is an echocardiogram, which measures the ejection fraction and produces a video image of the heart to show how well it is pumping blood.

Hospitalization for treatment intensification is usually required for periodic exacerbations of HF.[3] Almost 1 million hospitalizations for HF occur each year and it is the most frequent cause for hospitalization of patients over 65 years of age. Readmission rates of HF patients are 25 percent within 30 days of initial hospitalization and can reach up to 50 percent within six months.[2,3] Both initial hospitalization and readmission rates for HF patients continue to rise.[3] It is difficult to establish a robust risk model for readmission because there are many factors to consider that vary from patient to patient.[5] There are, however, some clinical predictors for readmission. If levels of cardiac biomarkers (such as natriuretic peptides and cardiac troponins) remain high at discharge, readmission is likely.[2,5] Worsening renal function during the course of hospitalization for HF is a strong predictor of readmission.[5] Having lower hospital readmission rates would improve the patient's quality of life and also benefit the hospital financially. New treatment options to help reduce hospital readmission rates are needed. One new option is LCZ696, which targets the renin-angiotensin-aldosterone system.

Pharmacology

In the renin-angiotensin-aldosterone system (also known as RAAS), renin from the kidney is responsible for the rate limiting step, which is the conversion of angiotensinogen to angiotensin I (ANG I).[6] From this point, ANG I is converted to angiotensin II (ANG II) via the angiotensin converting enzyme (ACE), which is produced in the lung. Eventually, ANG II binds to the angiotensin type 1 receptor (AT1) as seen in Figure 1A.

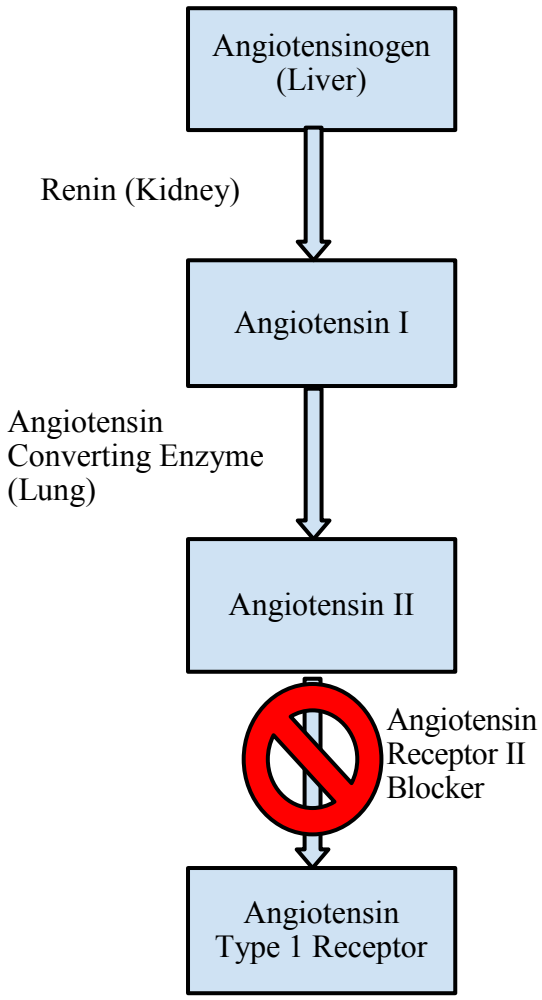
Figure 1A. Renin-Angiotensin-Aldosterone System.[6]



Once ANG II binds to its receptor, different areas of the body are affected, including the cardiovascular system, sympathetic nervous system and pituitary gland.[6] In general, ANG II promotes cell growth and proliferation, inflammatory response and oxidative stress. In the cardiovascular system, ANG II causes vasoconstriction, which leads to an increase in blood pressure and cardiac contractility. This can lead to vascular and cardiac hypertrophy. As ANG II travels to the adrenal cortex, it facilitates aldosterone secretion which helps regulate sodium and potassium balance. These two electrolytes ultimately influence the extracellular volume. With aldosterone release, more sodium and water is reabsorbed in the distal convoluted tubule and collecting duct. This process promotes the excretion of potassium. ANG II also activates the sympathetic nervous system, which promotes vasoconstriction and increases blood pressure. Furthermore, ANG II increases vasopressin, also known as antidiuretic hormone (ADH), which is released from the pituitary gland and increases water reabsorption. Lastly, while ANG II is activating different systems, it also inhibits the atrial natriuretic peptide (ANP) and nitric oxide. When ANP and nitric oxide are inhibited, the body's natural way of decreasing renin and promoting vasodilation is prevented.

Since ANG II affects many locations in the body (especially the heart), angiotensin II receptor blockers (ARB) are important in patients with HF.[7] As seen in Figure 1B, the mechanism of action is selective inhibition of ANG II by competitive antagonism of the ANG II receptors, more specifically the AT1 receptor. When ANG II is blocked from attaching to the receptor, the actions mediated by AT1 receptors are inhibited.[6] This leads to a reduction in blood pressure by decreasing the systemic vascular resistance. The sympathetic nervous system activity is reduced as well. There is an inhibition of aldosterone release from the adrenal gland and, therefore, less sodium is reabsorbed when ANG II cannot bind to the AT1 receptor. While the RAAS is working, the natriuretic peptides system maintains cardiovascular homeostasis such as the vascular tone, cardiovascular remodeling and fluid regulation.[8] The natriuretic peptides system is the body's natural defense to overactive RAAS or sympathetic nervous system. This system consists of three peptides: ANP, B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). Atrial natriuretic peptide is made in the atria and responds to atrial distention while BNP is produced in the ventricular myocytes and responds to volume overload. C-type natriuretic peptide is secreted from the vascular endothelium and responds to cytokines. Overall, the natriuretic peptides system decreases the release of renin and aldosterone, which leads to the suppression of RAAS. Due to the suppression of RAAS, the blood pressure and blood volume are decreased. While the sympathetic nervous system activity is inhibited, the parasympathetic nerve activity increases. When natriuretic peptides are released, the opposite effects of sympathetic nervous system and RAAS occurs such as vasodilation and decrease in renin secretion (see Figure 2A).

Figure 1B. Site of Action for Angiotensin II Receptor Blockers.[6]



Neprilysin (NEP) is an enzyme that degrades the natriuretic peptides specifically ANP and CNP.[8] In addition, NEP degrades ANG II, bradykinin and substance P. Bradykinin and substance P are vasoactive peptides and are responsible for vasodilation. One of the treatments for HF is NEP inhibitors, as shown in Figure 2B, which increase natriuretic peptides and allow more vasodilation to occur. Since ANG II degradation is also inhibited, there can be an increase in vasoconstriction. Therefore, NEP inhibitors depend on the balance between the vasoconstrictor and vasodilator effects.

The angiotensin receptor neprilysin inhibitor (ARNI) may serve as a novel treatment option for HF management and is currently in clinical trials.[9] This drug is currently called LCZ696 and must be taken orally in order to become activated. As seen in Figure 3, once LCZ696 is in the body, it dissociates into valsartan and Sacubitril (AHU377), which is an ARB and a prodrug, respectively. Sacubitril (AHU377) is enzymatically cleaved into LBQ657, which is the active form of the neprilysin inhibitor. While LBQ657 is inhibiting neprilysin, the valsartan blocks the angiotensin type 1 receptor. Since NEP inhibitors are dependent on the balance between the vasoconstrictor and vasodilator effects, the valsartan blocks any of the vasoconstrictor effects while the vasodilator effects are activated.

Figure 2A. Role of Natriuretic Peptide Hormones.[8]

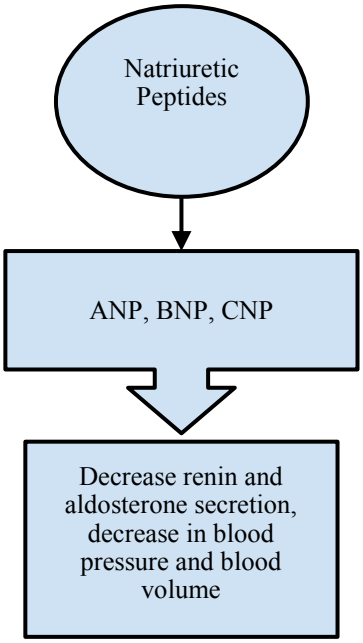
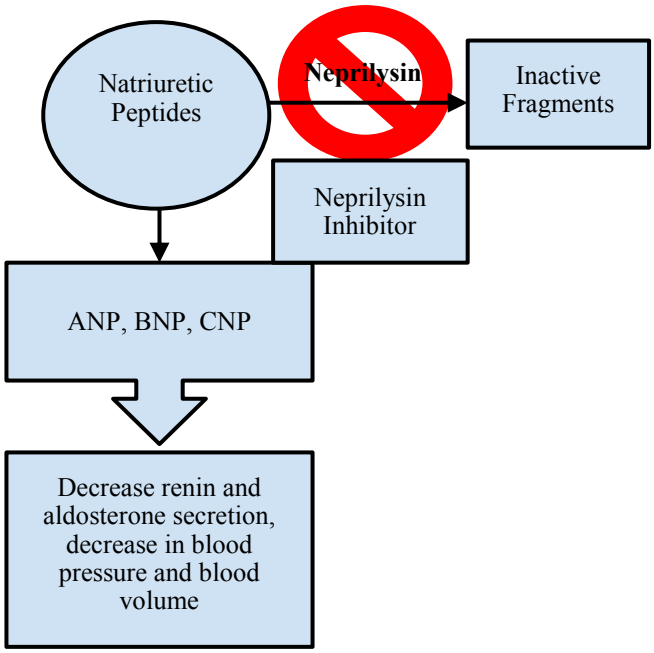


Figure 2B. Site of Action of Neprilysin Inhibitors.[8]



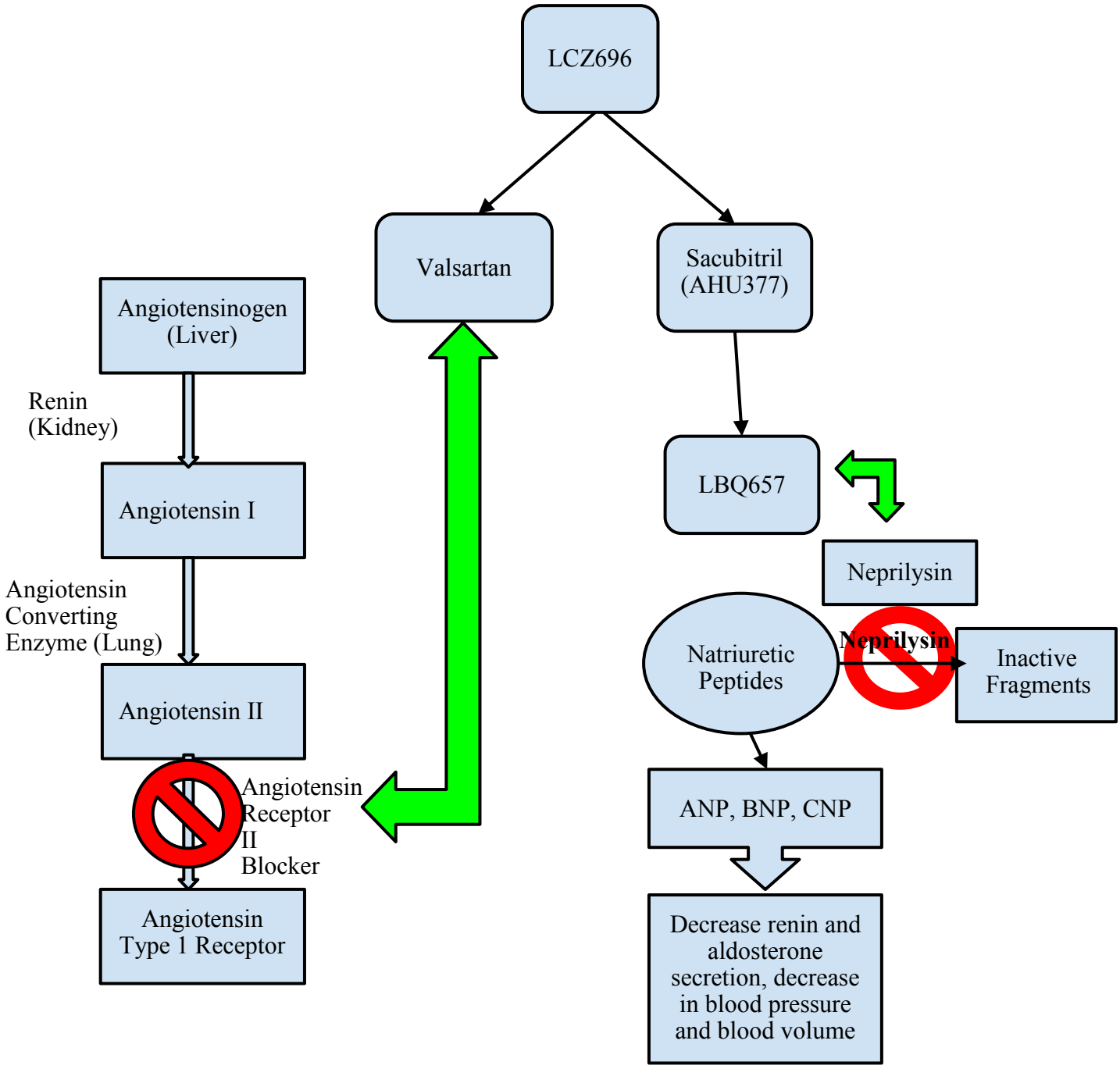
ANP=atrial natriuretic peptide; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide

Treating HF solely through the means of increasing NEP appears to be therapeutically insufficient. The ASCEND (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated HF) trial assessed nesiritide's role in the prevention of rehospitalizations and improvements of dyspnea symptoms in HF patients.[10] As a double-blind, placebo-controlled trial, 7,141 patients who were hospitalized with acute HF were randomly assigned to either nesiritide (recombinant natriuretic peptide) or placebo for 24 to 168 hours. Nesiritide slightly improved symptomatic dyspnea at six hours (P=0.03) and 24 hours (P=0.007) compared to placebo. However, there was no significant difference in 30-day mortality rate (3.6 percent with nesiritide versus 4.0 percent with placebo; absolute difference of -0.4 percentage points; 95 percent confidence interval, -1.3 to 0.5) or rates of worsening renal function, as defined by greater than 25 percent decrease in estimated glomerular filtration rate (GFR). Additionally, nesiritide was associated with increased rates of hypotension. Thus, the use of nesiritide should not be the standard treatment for HF patients. Similarly, ecadotril, a NEP inhibitor, showed little to no improvements in HF symptoms and quality of life in a placebo-controlled trial including 279 patients.[11] Patients on ecadotril showed no difference in the six minute walk test (6MWT) compared to placebo patients. The 6MWT is an outcome measure typically utilized in clinical trials to assess the efficacy of HF treatments. Lastly, ecadotril is not frequently used in practice due to its serious side effect profile (aplastic anemia at higher doses). Candoxatril, another NEP inhibitor, was tested in 11 healthy men and did not demonstrate a promising therapeutic option.[12] Although central venous pressure was reduced, systolic pressure was increased, most likely due to increased levels of epinephrine and endothelin.

Omapatrilat was the first combination drug manufactured to target both neprilysin and ACE. The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial compared its efficacy to an ACE-inhibitor (enalapril) in a randomized, double-blind trial of 5,770 patients.[13] The omapatrilat group demonstrated a 9 percent lower risk of cardiovascular death or hospitalization (P=0 .024) and a 6 percent lower risk of mortality. (P=0.339). Although showing much promise, omapatrilat does not demonstrate a definite clinical superiority over enalapril in reducing a primary clinical event (death and rehospitalization). Omapatrilat was shown to have a higher occurrence of angioedema which led to its withdrawal from the market. Angioedema most likely resulted due to increased plasma concentrations of bradykinin. Bradykinin induces vasodilation and vascular permeability. As a result, angiotensin receptor blockers (ARBs) were further studied as a combination product due to a decreased risk of angioedema.

LCZ696 is the first combined drug to incorporate inhibition of neprilysin and angiotensin receptor blockade. It was extensively studied in HF with HFpEF and HF with HFrEF patients.[14,15] The PARAMOUNT (Prospective Comparison of ARNI with ARB on Management of HF with Preserved Ejection Fraction) trial was a randomized, parallel group, double-blind study which compared LCZ696's therapeutic effectiveness to valsartan monotherapy.[15] Patients included in this study were required to be classified as a NYHA class II to III (see Table 1 and Table 2), have a left ventricular ejection fraction greater than 45 percent and have an N-terminal B-type natriuretic peptide (NT-proBNP; marker of ventricular wall stress) greater than 400 pg/ml. Change in serum NT-proBNP concentrations 12 weeks from baseline

Figure 3. Comparisons to other HF medications on the Market: Clinical Trial demonstration.[9]



ANP=atrial natriuretic peptide; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide

was the primary endpoint in this study. Patients were then followed through 36 weeks for additional endpoints. At the start of the trial, 308 patients were randomized to LCZ696 200 mg twice daily or valsartan 160 mg twice daily (both doses were bioequivalent). After 12 weeks, NT-proBNP levels were significantly reduced in the LCZ696 group compared to valsartan group (p=0.005). At 36 weeks, LCZ696 patients had better improvements in left atrial size, greater improvements in NYHA class, and greater reductions in blood pressure. Additionally, GFR was higher in patients receiving LCZ696 compared to patients receiving valsartan. Further prospective studies need to be conducted in order to assess whether these observed effects would translate to improved patient outcomes. Future experiments should increase the duration of follow-up in order see the long-term clinical benefits of LCZ696.

In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in HF) trial, 8,442 patients were randomly assigned to receive either LCZ696 (200 mg twice daily) or enalapril (10 mg twice daily).[15] Patients were required to be classified as a NYHA class II to III, have a left ventricular ejection fraction of less than 40 percent and have a NT-proBNP level of greater

than 600 pg/ml. Other inclusion criteria were GFR greater than 30 ml/min/1.73 m^2, systolic blood pressure greater than 95 mmHg and potassium less than 5.4 mmol/l. The primary endpoint was the composite of death from cardiovascular causes or hospitalizations from HF. There were 558 deaths from cardiovascular causes in the LCZ696 patients and 693 deaths in the enalapril patients. LCZ696 was found to reduce hospitalizations by 21 percent and decrease symptoms and physical limitations of HF (P= 0.001). This study ended early due to the clear and "overwhelming benefits" of LCZ696 over enalapril.

From these clinical trials, LCZ696 has consistently demonstrated its clinical efficacy via improvements in many cardiac parameters. Dual inhibition of neprilysin and the renin-angiotensin-aldosterone system provides a new method to effectively and safely treat HF patients.

Pharmacist Role

Although LCZ696 has been well-tolerated by patients overall, it is still imperative that pharmacists counsel patients on the potential side effects and the importance of adherence to their medication regimen. A potential adverse reaction is hypotension, so patients should be consulted about the symptoms of low blood pressure including dizziness; syncope; blurred vision; nausea; cold, clammy, pale skin and rapid, shallow breathing.[9] Angioedema rarely occurred in trials, but patients should be educated on signs and symptoms so they may seek care early to avoid airway compromise. Medication noncompliance is a risk factor for hospital admission. Counseling on the importance of HF medication adherence helps the patients to understand why they are taking the medication because they may not always physically feel an impact.[2]

It is important that pharmacists educate their patients not only about the medications they are taking but also about their disease states and how lifestyle modifications can impact them. Stressing the benefits of weekly physical activity, dietary sodium and fluid restriction and staying within a healthy weight to patients can help reduce the incidence of HF exacerbations.[2] Encouraging patients to find a support system has been shown to reduce hospitalizations and mortality because patients are more likely to adhere to their treatment regimen and live a healthier lifestyle. Being the most accessible health care providers to some patients, pharmacists should follow-up with recently discharged HF patients for education to prevent readmission and lower HF exacerbations.[5]

Conclusion/Outlook for the Future

Each year there are many new cases of HF, a disease responsible for increased hospital readmission rates. Currently, ACE-I are used to control HF, which is insufficient alone. A novel drug, LCZ696, may be an alternative to the current first line therapies of ACE-I and ARB for HF, specifically HFrEF. LCZ696 is an angiotensin receptor neprilysin inhibitor, which inhibits neprilysin through LBQ657 and blocks the AT1 receptor through valsartan.[9] Overall, LCZ696 had less cardiovascular mortality and HF hospitalizations compared to other monotherapies. In addition, patients tolerated this drug better than omapatrilat, which had higher incidence of angioedema.[13] In comparison to enalapril, LCZ696 had less hospitalizations and less physical limitations in patients.[15] Currently, LCZ696 has been studied in patients with HFpEF; however, longer follow-up is needed in order to determine long-term effects of LCZ696.[14] Pharmacists should be anticipating the use of this novel drug and educate patients on ways to improve their quality of life through medications and lifestyle modifications. Overall, pharmacists can help reduce hospital readmission and HF exacerbations through improved patient education.[5]

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Testosterone Replacement Therapy in Aging Males

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Abstract
The U.S. Food and Drug Administration (FDA) cautions health care providers and patients regarding the use of testosterone replacement therapy products for the aging process, including a decrease in muscle strength, muscle mass, and lack of energy or sexual desire, due to an increased risk of heart attacks and strokes. Testosterone replacement therapy products are indicated for genetic defects, chemotherapy damage, or damage to the hypothalamus or pituitary gland, where testosterone is produced. A patient and his team of health care professionals must seriously consider the risks and benefits when using these products for other indications. Use of testosterone replacement therapy products for low testosterone due to natural aging has been on the rise due to disease state awareness, pharmaceutical marketing and media attention. Pharmacists can make a difference in patients' lives by conducting patient education and counseling for these products.

Key Terms
Hormone; Hormone Replacement Therapy; Aging; Testosterone; Androgen

Introduction

Testosterone replacement therapy (TRT) has received recent attention in the scientific community as the U.S. Food and Drug Administration (FDA) has communicated that caution should be advised when using testosterone products for the aging process, including for symptoms such as declining muscle mass, muscle strength and libido. In September 2014, the FDA used input from an advisory committee of experts to conclude that there may be an increased cardiovascular risk with testosterone use.[1] With a March 2015 update, the FDA states that testosterone products are now required to include labels indicating increased risk of heart attacks and strokes. Health care providers are encouraged to inform their patients of these risks.[1]

Testosterone replacement therapy products are indicated in male patients who have genetic defects causing lack of testosterone production by the testes, damage from chemotherapy to the testes or damage to the hypothalamus or pituitary gland. However, many males who receive testosterone products have been diagnosed with idiopathic hypogonadism, which is a low level of testosterone due to no other determined reason except for aging. Within the past six years, there has been a significant increase in the use of TRT products; 1.3 million patients received TRT prescriptions in 2009 compared to 2.3 million in 2013, with 70 percent of those patients between the ages of 40 and 64 years.[2] The increase in use of TRT may be due to confounding factors including the rise in the baby boomer generation, pharmaceutical marketing or media attention for low testosterone. Moreover, with the use of TRT nearly doubling in recent years, ongoing investigational research studying the potentially harmful, long-term effects of TRT is invaluable. Patients obtain medical advice from numerous outlets, many of them unreliable. Thus, it is important that health care professionals are aware of current research to provide appropriate and trustworthy clinical advice and counseling to all patients.

Hypogonadism and Testosterone Replacement Therapy Recommendations

Hypogonadism is the manifestation of testosterone deficiency or infertility in males, the symptoms of which vary depending on age. Symptoms in males before puberty include small testes, phallus and prostate, decreased growth of pubic hair, delayed epiphyseal closure resulting in disproportionately long limbs, gynecomastia, high-pitched voice and loss of testicular function. Older patients with lower levels of testosterone may experience fatigue, decreased libido, impotence, decreased sperm production, loss of lean muscle mass, hot flashes and osteoporosis.[3]

Testosterone replacement therapy may be prescribed to patients with low testosterone levels to reduce the severity of these symptoms and improve the patient's overall quality of life. Short-term studies have shown an increase in lean body mass and production of blood cells and a decrease in low-density lipoprotein (LDL) levels in patients using hormone replacement. Libido has also been shown to improve in older men.[3]

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology protocol for standardized production of clinical guidelines recommend the use of testosterone replacement for the following indications:

- Management of congenital or acquired primary hypogonadism resulting from orchiectomy (surgical removal of one or both testes) or testicular failure.
- Management of congenital or acquired primary hypogonadism resulting from idiopathic gonadotropin/gonadotropin-releasing hormone deficiency or from pituitary-hypothalamic injury caused by tumors, trauma or radiation.
- Androgen deficiency and acquired immune deficiency syndrome (AIDS) wasting in human immunodeficiency virus (HIV)-infected men.
- Low serum testosterone concentrations (less than 300 ng/dL) in patients receiving long-term corticosteroid therapy.
- Improvement of body composition, strength, bone density, frailty, cognitive function, mood, sexual function, quality of life and to induce secondary sex

characteristics in men with symptomatic androgen deficiency when the benefits outweigh potential risks.[4,5]

The Endocrine Society has recommended that a patient be diagnosed with androgen deficiency only when displaying consistent symptoms of low serum testosterone levels diagnosed by measuring morning total testosterone levels by a reliable assay. Measurement of total testosterone levels should be repeated for confirmation. The panel of experts disagreed on the exact level of serum testosterone. Some panelists saw the benefits of treating patients with serum testosterone levels of 280 to 300 ng/dL, which is the lower limit of normal for a healthy adult male. Clinical trial data indicates a level of 200 ng/dL or less would be appropriate for diagnosis and initiation of replacement therapy. Goal testosterone levels, once replacement therapy has been initiated, should be mid-normal levels (normal range 300 to 1,050 ng/dL) and consistently monitored.[6,7]

The Endocrine Society has recommended against the use of TRT in patients with breast or prostate cancer or a palpable prostate nodule. It is also not recommended to use TRT in patients with levels of prostate-specific antigen (PSA), a glycoprotein enzyme that can serve as a biomarker for prostate disorders, above 4 ng/dL or in men at high risk for prostate cancer.[6] It is the general consensus of both the FDA and Endocrine Society that TRT should not be generally offered to all older male patients with low testosterone levels.[1,6] Before testosterone therapy is recommended, physicians should discuss the potential risks and benefits with their patients.[6] Use of TRT for erectile dysfunction is currently not an FDA labeled use in men with normal serum testosterone levels, although it has been prescribed for this indication.[1,6] Because men presenting with hypogonadism tend to have increased likelihood of mood disturbances including depression, low self-esteem and learning problems, it is recommended that TRT be combined with psychiatric counseling for the most beneficial results.[3]

Testosterone replacement therapy seems to have a positive effect on patients' symptoms and quality of life in short-term follow-up. However, research evaluating the long-term effects of TRT is scarce. Studies assessing the potential cardiovascular complications and cancerous associations with TRT have shown conflicting results. Ongoing long-term research and increased awareness of the potential risks will only help improve patient care.[3]

Increased use of TRT in Men and Performance Enhancement

Idiopathic hypogonadism associated with aging has been shown to affect between 5 percent and 40 percent of males between the ages of 40 and 79 years. Lower testosterone levels manifest in ways that can deeply affect a patient's quality of life, but may not warrant immediate action from a physician. However, in recent years, there has been increased awareness of this disorder which has resulted in increased prescribing for testosterone replacement. Largely due to media attention and pharmaceutical marketing, patients have begun to seek treatment for hypogonadism. This can be evidenced by the 500 percent increase in prescriptions since 1993.[7] Most likely stemming from a desire to retain the level of wellness and physical activity one had at a younger age, consumer spending on testosterone therapies has exponentially increased. In 2011, $1.6 billion was spent on TRT prescriptions, almost tripling what was spent in 2006.[8]

Also contributing to the surge of TRT prescriptions is use of testosterone for enhancement of physique and increased muscle mass used most significantly by athletes and bodybuilders. According to the New England Journal of Medicine, androgen therapy for the purpose of performance enhancement began in the1940s and has since skyrocketed. Doses of TRT for performance enhancement are 100 times larger than those used for appropriate indications and require significant periods of time off therapy in order to allow the body to recover from adverse reactions caused by such large doses.[9]

As the baby boomer generation ages and direct-to-consumer advertising becomes more popular, TRT prescriptions are projected to increase. Without readily available research of long-term TRT or the proper awareness of potential complications of TRT, concern for patient safety should be of the utmost importance.[10]

Risks Associated with Testosterone Replacement Therapy

It is currently agreed upon that there may be some long-term risks involving TRT. The AACE published a comprehensive report on treating men with hypogonadism, reporting on TRT as a treatment option and the identification of potential side effects that might accompany treatment.[3] One potential adverse event is cardiovascular morbidity. However, a consensus has not been reached as to how TRT and testosterone levels in the aging male body affect cardiovascular health. There is a large body of literature suggesting that testosterone therapy may increase the risk of certain adverse cardiovascular events, including nonfatal myocardial infarction and stroke in older men (due to testosterone's tendency to increase platelet aggregation), and in young men with preexisting heart conditions.[3,10,11]

In 2010, Malkin and colleagues published a paper suggesting that low serum testosterone (i.e., endogenous) levels correlate with increased mortality in men with coronary heart disease.[12] Other work by Malkin and his colleagues has demonstrated that testosterone therapy improves functional capacity and reduces symptom severity in men with moderate severity heart failure.[13] The important distinction to make between the conflicting evidence is that low *endogenous* testosterone levels were related to adverse cardiovascular effects, whereas TRT, by definition, introduces *exogenous* testosterone to the endocrine system. This does, however, raise questions as to whether it is worth the risk to utilize TRT as a treatment for hypogonadism in male patients with preexisting cardiovascular risks.

In addition to the adverse effects that TRT may have on cardiovascular health, the AACE report also emphasizes the need to evaluate elevated risks of prostate cancer that may or may not be associated with TRT.[3] It has already been es-

tablished that patients with prostate cancer are not recommended to receive TRT.[3,4] However, it is less clear as to whether there is a direct relationship between TRT and increased risk of prostate cancer in cancer-free patients at baseline. A 2005 paper from the Brady Urological Institute at Johns Hopkins Hospital showed a correlation between high levels of free serum testosterone with higher incidences of prostate cancer, leading the authors to directly call into question the safety of TRT as it relates to elevated risk of prostate cancer.[14] Information regarding adverse effects and formulation-specific adverse effects of TRT are presented below in Table 1 and Table 2.

In the opposing camp, Rhoden and Morgentaler (2003) concluded that TRT is not an ill-advised treatment option in hypogonadic patients, even in those who have prostatic intraepithelial neoplasia (PIN), a precancerous prostatic lesion that often leads to the development of prostate cancer.[15] In a later 2010 study, Morgentaler and colleagues further concluded that testosterone therapy in men with untreated prostate cancer was not associated with progression of the disease in the first three to 12 months. They recommended that the discouraged use of testosterone therapy in men with less severe prostate cancer or treated prostate cancer should be reconsidered.[14] Recently, TRT is being consid-

Potential Adverse Side Effects and Various Types of Testosterone Replacement Therapy.[5]

Table 1. General Testosterone Administration Adverse Effects.

Adverse events for which there is evidence of association with testosterone administration	Erythrocytosis Acne and oily skin Detection of subclinical prostate cancer Growth of metastatic prostate cancer Reduced sperm production and fertility
Uncommon adverse events for which there is weak evidence of association with testosterone administration	Gynecomastia Male pattern balding (familial) Growth of breast cancer Induction or worsening of obstructive sleep apnea

Table 2. Formulations and Formulation Specific Adverse Effects.

Formulation	Specific Adverse Effects
Intramuscular injections of testosterone ethanate, cypionate or undecanoate	Fluctuation in mood or libido Pain at injection site Excessive erythrocytosis (especially in older patients) Coughing episodes immediately after the intramuscular injection*
Transdermal patches	Frequent skin reactions at application site
Transdermal gel	Potential risk for testosterone transfer to partner or another person who is in close contact (need to remind patient to cover application sites with clothing and to wash skin and hands with soap before having skin-to-skin contact with another person) Skin irritation
Buccal testosterone tablets	Alterations in taste Irritation of gums
Pellet Implants	Infection, expulsion of pellet
Oral tablets	Effects on liver and cholesterol (methyltestosterone)†

*The mechanism of cough, which has been reported rarely after intramuscular injections of testosterone undecanoate and even more rarely after testosterone enanthate and cypionate, is unknown, but it has been attributed to oil embolization.
†Liver toxicity has been reported mostly with oral 17-alpha alkylated androgens. The frequency of skin reactions is higher with the testosterone patch than with the transdermal gels.

ered in patients with hypogonadism associated with prostate cancer comorbidities in some cases, although consistent monitoring is strictly encouraged.[15]

Monitoring Parameters

Treatment monitoring is important to ensure the patient safety remains at the center of all individualized therapy regimens. Testosterone and its byproducts stimulate the growth of the prostate gland and seminal vesicles. While current research has failed to definitively prove a direct correlation between TRT and increased PSA levels or abnormal prostate growth, monitoring of these parameters is still essential. Follow-up appointments every three to four months is crucial for all patients receiving TRT during the first year of therapy.[13] Patients receiving injected testosterone should have their serum testosterone measured at the midpoint between injections; the level should be within a mid-normal range.[3]

Digital rectal exams (DRE) are recommended every six to 12 months and PSA levels should be measured annually in older males. If PSA levels are determined to be abnormally high (greater than 4 ng/dL), TRT should be discontinued and the patient may need to be referred for urologic consult. In patients concurrently receiving finasteride, further evaluation may be warranted if PSA levels show a significant increase.[3]

Because testosterone increases production of blood cells by the bone marrow, hematocrit should also be routinely monitored every six to 12 months so that coagulation does not result. TRT should be discontinued if hematocrit rises above 50 percent. Other side effects reported with testosterone therapy include gynecomastia resulting from the chemical change testosterone undergoes in the body to produce estrogen and an increased risk of alopecia. This should be considered when assessing the risk versus benefit analysis for each patient.[14]

How Can Pharmacists Help?

As with any prescription, counseling from a pharmacist is highly recommended. Considering the added risks of hormone therapy, patient education of TRT is a necessity. Testosterone therapy is available in a wide range of formulations including injection, transdermal patches and topical gels, each with their own set of precautions and specific directions for application. Successful and safe utilization of therapy for each patient requires thorough comprehension of their TRT prescriptions.

It is also important that a patient be equipped with all the relevant information regarding the risks of initiating TRT at the point of prescribing. Physicians should attempt to present accurate information to each patient, especially in a society where faulty information is only a click away, and help the patients make the best possible decision in accordance with their own individual health and wellness.

Conclusion

Testosterone therapies are a rapidly-growing option for aging men that will continue to expand with the aging of the baby boomer generation, due to a higher incidence of hypogonadism in the aging population. Increased use of TRT coupled with its high potential for abuse make counseling and education an essential step for pharmacists at the time of dispensing. The growing demand for testosterone replacement in conjunction with the FDA requirement to label the increased risk of heart attacks and strokes on testosterone products necessitates that health care providers utilize caution when prescribing these therapies and share their awareness of the potential risks and benefits associated with using these products with patients.[1]

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