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FDA Approves New Tuberculosis Drug: Bedaquiline (Sirturo®)

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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. Describe the pathophysiology of tuberculosis.
2. Evaluate the need for new drug therapies in the treatment of multidrug-resistant tuberculosis.
3. Explain the mechanism of action of bedaquiline.
4. List the major side effects of bedaquiline.
5. Discuss how bedaquiline will positively impact current therapy.

Abstract

Tuberculosis (TB), caused by the acid-fast bacilli (AFB) Mycobacterium tuberculosis, is an infectious disease that continues to greatly impact morbidity and mortality worldwide; in 2011 it caused 1.4 million deaths. Some strains of the bacteria have become resistant to current treatment regimens, resulting in multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. The emergence of these resistant strains of bacteria calls for new treatment regimens that can quickly and effectively eradicate the organism. The U.S. Food and Drug Administration (FDA) recently approved Sirturo® (bedaquiline) with the indication of MDR pulmonary TB. Bedaquiline introduces a novel mechanism of action via the inhibition of bacterial adenosine triphosphate (ATP) synthase. In this article we will further explore the background information for TB, current treatment regimens, adverse effects of bedaquiline and studies that explore the place for bedaquiline in the treatment of TB.

Introduction

Tuberculosis, caused by Mycobacterium tuberculosis, remains a prevalent disease globally with approximately one third of the world's population infected.[1] According to the Centers for Disease Control and Prevention (CDC), 10,528 cases of TB were reported in the United States in 2011, which is a 5.8 percent decrease from the number of cases reported in 2010. However, the World Health Organization (WHO) estimates that in 2011 there were 8.7 million new cases and 1.4 million deaths from TB worldwide.[2] Tuberculosis is a major consideration for human immunodeficiency virus (HIV) infected patients, being the leading killer of this population. This shows that while TB is on the decline in the United States, the vast impact on worldwide incidence and mortality remains a concern.

Mycobacterium tuberculosis is transmitted via inhalation of droplets in the air and typically infects the lungs when active.[3] Tuberculosis can be latent or active in an individual. Latent TB occurs when a healthy individual inhales the organism, the lungs allow the organism to enter the body via macrophages and the lymphatic system, but the body does not allow the bacteria to actively grow.[3,4] Patients with latent TB will not feel ill or be contagious; however, a latent infection may become active if an individual's immune system becomes compromised. Active TB presents with symptoms such as severe cough, chest pain, hemoptysis, fatigue and fever. Individuals that are immunocompromised, such as those with HIV infection, are at increased risk of developing the active infection.

A Mantoux tuberculin skin test may identify, but not differentiate, both latent and active TB; a chest x-ray and AFB smear can confirm an active infection.[5,6] Tuberculosis is an AFB, rendering it impossible to identify via gram stain, and requiring identification via special AFB smears.[3] Culturing of a sputum sample must be done to test the specimen for susceptibility to drug regimens.

To avoid producing resistant strains of TB and to ensure complete eradication of the organism, it is recommended to use multiple agents when treating active TB.[6] Despite such precautions, MDR TB and XDR TB continue to present an obstacle in treatment. MDR TB is defined as being resistant to the drugs isoniazid and rifampin; this presents an obstacle to treatment because these are two drugs commonly used to treat TB.[7] Extensively drug-resistant TB is resistant to these two drugs as well as any fluoroquinolone and any of the injectable second-line drugs for TB, such as amikacin or kanamycin. Research and development of new drugs to treat TB are needed for multiple reasons including shortening the duration of treatment regimens and improving treatment of MDR and XDR TB.[6]

Current Treatment

The American Thoracic Society, CDC, and the Infectious Diseases Society of America (IDSA) have partnered to publish treatment guidelines for TB in the United States.[6] For drug susceptible strains of TB, an initial treatment regimen of ethambutol (EMB), isoniazid (INH), rifampin (RIF), and pyrazinamide (PZD) for two months is recommended followed by a maintenance treatment of six to nine months using various combinations of the same drugs. If drug resistant forms of TB develop during treatment, at least two or three new drugs should be added to the regimen in replacement of

Table 1. Options for Initial Phase of Drug Susceptible Tuberculosis.[6]

Drug Combination	*Frequency and Duration*	*Options for Continuation**
INH, RIF, PZA, EMB	7 days/week for 8 weeks *or* 5 days/week for 8 weeks	1,2,3
INH, RIF, PZA, EMB	7 days/week for 2 weeks then twice weekly for 6 weeks *or* 5 days/week for 2 weeks then twice weekly for 6 weeks	2,3
INH, RIF, PZA, EMB	3 times weekly for 8 weeks	4
INH, RIF, EMB	7 days/week for 8 weeks *or* 5 days/week for 8 weeks	5

**Referenced in Table 2*

Table 2. Options for Continuation Phase of Drug Susceptible Tuberculosis.[6]

Option #	*Drug Combination*	*Frequency and Duration*
1	INH/RIF	7 days/week for 18 weeks *or* 5 days/week for 18 weeks
2	INH/RIF	Twice weekly for 18 weeks
3	INH/RPT*	Once weekly for 18 weeks
4	INH/RIF	Three times weekly for 18 weeks
5	INH/RIF	7 days/week for 31 weeks *or* 5 days/week for 31 weeks *or* Twice weekly for 31 weeks

**RPT (rifapentine)*

the agents to which resistance has been acquired. These drugs should be selected based upon susceptibility testing and may include drugs such as streptomycin, amikacin, kanamycin, *p*-aminosalicylic acid, or a fluoroquinolone.

The current treatment regimen, as described above, presents multiple obstacles to optimal treatment of TB.[1] The high pill burden along with the duration of treatment of at least six months leads to patient noncompliance. Direct observation therapy has been implemented to avoid this issue, but is expensive and time-consuming. The current first-line treatment regimen presents many potentially severe side effects, such as hepatotoxicity and permanent visual impairment.[8] Rifampin decreases the concentrations of protease inhibitors, which are a class of drugs used to treat HIV infection; the common presence of HIV and TB as comorbidities presents a treatment dilemma. These are a few of the foremost reasons why new drugs for TB are desperately needed. The potential impact of bedaquiline on TB treatment and these treatment obstacles will be explored throughout the remainder of the article.

Development

Bedaquiline (Sirturo®) was approved on December 28, 2012, by the FDA for MDR pulmonary tuberculosis after going through the FDA's priority review and has received orphan-product designation.[9] Fast tracking this medication has made it available to patients sooner but comes with less substantial data than is usually seen with a newly marketed drug. The accelerated approval of bedaquiline allowed it to be placed on the market with data that show it is reasonably likely to provide clinical benefits to patients. Janssen Therapeutics (the manufacturer of bedaquiline) will continue to conduct studies to confirm the drug's effectiveness and safety.

Mechanism of Action

Bedaquiline is of the diarylquinoline class of drugs and has been seen to act through inhibition of bacterial ATP synthase by inhibiting the c subunit of the enzyme.[10] Bedaquiline contains two chiral centers giving the molecule several possible stereoisomers, of which the (R,S) configuration has been seen to be the most active against TB. This stereoselectivity is indicative of specific binding to a target protein. Through gel electrophoresis of two eluted proteins from an affinity column, the ATP subunits were identified as the target. Further testing with a BIAcore carboxymethyl-Sepharose chip identified ATP synthase subunit c as the primary target for bedaquiline. Current treatments target cell wall synthesis, ribonucleic acid (RNA) transcription, and pH levels of the environment (isoniazid and ethambutol, rifampin, and pyrazinamide respectively). The novel method of targeting ATP synthase with bedaquiline allows for use against resistant TB

and latent TB by depleting the bacterium's energy supplies. An extensive target study by Haagsma et al. has confirmed the action of bedaquiline takes place at the c subunit of ATP synthase, specifically at the interface between subunits a and c to block conformational changes in ATP synthase. The study also shows that bedaquiline does not compete with protons for a common binding site and, thus, is not affected by proton motor force like such drugs as sodium azide and other ATP synthase inhibitors which increases the efficacy of bedaquiline. Bedaquiline, however, is dependent upon electrostatic attractive forces that bind subunit c.[11] It was seen that as sodium chloride concentrations increased in the body, bedaquiline binding affinity decreased. It is also noteworthy to include that bedaquiline's activity is not affected significantly by pH changes in the range from 5.25 to 7.5. This is advantageous due to the acidic environment of the lung where latent TB can often be found but is extremely difficult to treat.

Unique Features

Bedaquiline has shown to be a viable drug for targeting latent mycobacteria. Its novel mechanism of action provides another option for treatment in MDR TB, which by definition is resistant to the more familiar mechanisms of action.[12] Researchers found that dormant mycobacteria have active and functional ATP synthase. Depleting ATP in the dormant bacteria by bedaquiline mediated inhibition of ATP synthase leads to bactericidal activity. Researchers also found that bedaquiline was slightly more effective in dormant bacilli compared to replicating bacilli, while the present first and second-line TB antibiotics exhibited strong bactericidal activity on replicating mycobacteria but not on the dormant bacilli. This unique feature of bedaquiline could reduce the time needed to treat infection when used in combination with current first and second-line therapies. Bedaquiline was seen to be effective at a dose of 400 mg at days 4 through 7 in an early bactericidal activity study by Rustomjee.[13] This study suggests that bedaquiline could be used as a sterilizing agent in current TB regimens because of the drug's ability to deplete mycobacterium energy stores.

Adverse Effects

When used in the appropriate situation, bedaquiline offers health care providers and patients with another weapon against MDR TB; however, it is important to note that use of bedaquiline has been associated with serious adverse events that warrant attention and monitoring. The FDA has placed two black box warnings on bedaquiline. The first warns that patients may experience QT prolongation. The concern with QT prolongation is the increased risk of the development of arrhythmias, especially torsade de pointes.[14] Torsade de pointes is a ventricular arrhythmia that is life threatening and has specifically been linked to QT prolongation.[15] Other risk factors that increase the risk of adverse outcomes from QT prolongation include uncompensated heart failure, low serum electrolyte levels and hypothyroidism. Because of bedaquiline's possible effect on QT prolongation, it is recommended that an electrocardiogram be recorded at the beginning of therapy and at weeks 2, 12, and 24.[14] If an arrhythmia develops, therapy should be discontinued. Additionally, baseline liver enzymes and serum electrolyte levels should be recorded in case there is a need for compensation during therapy. The second FDA black box warning alerts health care providers that in trials bedaquiline was associated with a higher risk of death compared to placebo.[14] In one of the clinical trials that led to bedaquiline's approval, the number of deaths in the treatment group was statistically significantly higher than the placebo group; however, all of the placebo deaths and roughly half of the bedaquiline deaths "seemed to be related to tuberculosis."[16] The black box warning instructs health care providers to only use bedaquiline "if no other effective treatment regimen is available."[14] This black box warning truly demonstrates why bedaquiline is reserved for those patients who have no other options. The early approval of a drug with such a warning demonstrates the urgent need for effective treatment of MDR TB. Janssen will be distributing educational material with the medication to ensure the drug is used appropriately.[16]

The most common patient-reported side effects are nausea, painful or stiff joints, headache, chest pain and hemoptysis.[14] These adverse events fall within the mild to moderate range, and only nausea has been reported statistically as significantly higher than placebo.[17] As a major substrate for CYP3A4, bedaquiline should be administered with caution with drugs that induce or inhibit CYP3A4. Bedaquiline should also not be administered with alcohol, ivabradine, mifepristone, St John's Wort or tocilizumab.[14] Also, it is important that health care providers monitor patients' liver function. If aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations last for longer than two weeks, it is advised that therapy should be stopped. Through animal studies, bedaquiline has been rated at pregnancy risk factor B.

Literature Review

The diarylquinoline TMC207 for multidrug-resistant tuberculosis.[22,23]

As part of the phase 2 trials for bedaquiline, Diacon et al. performed a double-blind, randomized placebo-controlled study in South Africa. Eligible study participants had confirmed MDR TB and received either placebo (24 patients) or bedaquiline 400 mg (23 patients) once daily for weeks 1 and 2, followed by 200 mg three times a week for weeks 3 through 8 along with a preferred background regimen of kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or terizidone (modifications could be made following susceptibility testing or adverse events). After the eight weeks of study medication, participants continued the background medication regimen only and were followed for a total of two years. Administration of each dose of study medication was supervised to ensure compliance. The authors reported results after eight weeks and also at two years. Outcomes were measured via sputum samples cultured in a liquid broth medium (MGIT system) before treatment initiation and weekly thereafter during study medication administration. Quantitative serial sputum colony counting was also performed. Blood samples were monitored for plasma levels of bedaquiline.

In the literature published at eight weeks, the authors con-

Table 3. Common Adverse Effects of Conventional TB Therapy Compared To Bedaquiline.[9,18-21]

	Ethambutol	Isoniazid	Rifampin	Pyrazinamide	Bedaquiline
Cardiovascular	Myocarditis	Hypertension, tachycardia	Edema, flushing	**X**	Chest pain, **Black box warning for QT prolongation**
CNS	Confusion, hallucinations, headache	Depression, fatigue, fever, headache	Ataxia, headache	Fatigue	Headache
Endocrine	Acute gout	Gynecomastia, hyperglycemia, metabolic acidosis	Adrenal insufficiency	Gout (rare)	**X**
Gastrointestinal	Anorexia, nausea/ vomiting	Anorexia, nausea/vomiting	GI upset	Anorexia, nausea/ vomiting	Anorexia, nausea/vomiting
Hematological	Anemia, leukopenia, thrombocytopenia	Agranulocytosis, anemia	Agranulocytosis anemia, leukopenia, thrombocytopenia	Thrombocytopenia (rare)	**X**
Hepatic	Elevated liver enzymes and toxicity	**Black box warning for hepatitis**	Increase liver enzymes (rare hepatitis)	Dose related hepatotoxicity (rare) Fever	Increase liver enzymes
Neuromuscular	Peripheral neuropathy	Dose related peripheral neuropathy	General numbness	Myalgia	Arthralgia
Ocular	Impairment of color vision (inflammation of optic nerve)	Blurred vision	**X**	**X**	**X**
Renal	Nephritis	**X**	Elevations in BUN and uric acid leading to potential renal failure	**X**	**X**
Respiratory	Pneumonitis	**X**	**X**	**X**	Hemoptysis
Miscellaneous	**X**	Lupus-like syndrome	**X**	**X**	**X**

cluded that taking bedaquiline resulted in crucial time-dependent bactericidal activity. The bedaquiline group had quicker conversions to a negative sputum culture (hazard ratio 11.8, 95 percent confidence interval: 2.3 to 61.3). In the eight weeks, 48 percent of the treatment group converted to a negative culture, while 9 percent of the treatment group did. Log_{10} colony forming units (CFU) declined more rapidly in the treatment group. At eight weeks, and also at two years, nausea was the only side effect that appeared significantly more in the treatment group than the placebo group. In the two year follow-up article, the authors noted that 50 percent culture conversion for the treatment group occurred at 78 days, while this occurred at 129 days in the placebo group; this again demonstrates the advantageous time-dependent activity of bedaquiline. After two years, it was also seen that more patients receiving placebo (4/18) than treatment (0/16) that were initially susceptible to ofloxacin developed resistance to it; suggesting bedaquiline lowers the risk of acquiring additional drug resistance throughout therapy.

This study shows that bedaquiline may be an important drug for reducing time for treating MDR TB and may potentially

decrease the incidence of newly formed resistance during treatment. Although the study was well designed, the small sample size (47 patients) is a limitation to the external validity of the study. Due to this, larger trials investigating more safety aspects of the drug are needed to determine the future place for this new drug in the TB guidelines.

14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomized trial.[24]

Diacon et al. performed a phase 2A, partially double-blinded, randomized trial to assess early bactericidal activity (EBA), safety, tolerability, and pharmacokinetics of various combinations of various TB drugs (Table 4). This study was designed recognizing the need for shorter and better tolerated regimens needed to treat TB worldwide.

Patients were from two outpatient clinics in South Africa and included if they were otherwise relatively healthy and had confirmed fully drug susceptible TB. Bedaquiline and PA-824, a nitroimidazo-oxazine in the pipeline, were the new agents included in the study and were chosen based upon their synergism with pyrazinamide in murine experiments. Rifafour e-275 was used as the control in the study, representing current standard treatment. Rifafour e-275 contains isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg, and ethambutol 275 mg; patients received two (30-37 kg), three (38-54 kg), or four (55-70 kg) a day based on body weight. Experimental group dosing is described in Table 4. Fifteen patients were included in each study group and 10 patients were included in the control group.

The primary outcome of the study was the 14 day early bactericidal activity (EBA) of each combination based upon the daily fall in CFU per mL of sputum measured via $\log_{10}$ CFU; sputum sample were collected daily overnight. Safety monitoring included daily vital signs and physical examination as well as 12-lead electrocardiogram (ECG) on days 1, 3, 8, and 14. After the two weeks, patients were referred to local TB clinics for a standard course of therapy and returned for study follow-up visits at 14, 28, and 90 days after study completion. The study was not powered to compare differences between treatment groups and the control.

The results showed that the mean 14 day EBA of PA-824, moxifloxacin, and pyrazinamide was 0.233 [SD 0.128], which was higher than any other group. The other groups were bedaquiline at 0.061 [0.069]; bedaquiline and pyrazinamide at 0.131 [0.102]; bedaquiline and PA-824 at 0.114 [0.050]; PA-824 and pyrazinamide at 0.154 [0.040], and rifafour e-275 at 0.140 [0.094].

The authors conclude that bedaquiline/PA-824 and PA-824/pyrazinamide/moxifloxacin showed activity comparable with that of current standard treatment and thus may be studied further as building blocks of future front line regimens. There is currently a trial sponsored by the Global Alliance for TB Drug Development exploring the combination of bedaquiline, PA-824, clofazimine, and pyrazinamide for EBA activity.[24]

Safety, tolerability, and pharmacokinetic interactions of the antituberculosis agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS clinical trials group study A5267.[25]

In April 2012, Dooley et al. published a study in the Journal of Acquired Immune Deficiency Syndrome that examined the pharmacokinetic related interaction of bedaquiline therapy alone, as well as in conjunction with the HIV medication efavirenz. The rationale behind this study was that roughly 15 percent of patients infected with TB also suffer from HIV. This study is important because it also investigates the pharmacokinetic properties of bedaquiline monotherapy.

Conducted in the United States, this phase 1 trial consisted of healthy individuals 18 to 65 years in age. Notable exclusion criteria included positive HIV antibody test, elevated hepatic enzymes, below average hemoglobin, white cell count, or platelets, irregular ECG, estimated creatinine clearance below 50 mL/min, or any indication of possible TB infection. Additionally, "women of reproductive potential" and current users of a prescription drug known to inhibit CYP3A were excluded. To begin the study, participants were given a single 400 mg dose of bedaquiline. Plasma levels of bedaquiline and

Table 4. Treatment Group Regimen Description.[24]

Treatment Group	Bedaquiline Day 1- 700 mg Day 2- 500 mg 400 mg daily thereafter	Pyrazinamide Placebo Daily	PA-824 200 mg daily	Pyrazinamide 25 mg/kg daily	Moxifloxacin 400 mg daily	Rifafour e-275
1	X	X				
2	X		X			
3	X			X		
4			X	X		
5			X	X	X	
Control						X

one of its metabolites (M2) were measured 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, 168, 216, 264, and 336 hours after the dose. This was designated period 1. Over the next 14 days, participants received 600 mg of efavirenz nightly. On day 28 of the trial (day 14 of efavirenz therapy) the participant's efavirenz plasma levels were drawn 1, 2, 3, 4, 8, 12, and 24 hours postdose. The following day, 400 mg of bedaquiline was again administered to participants in addition to the continuation of 600 mg efavirenz nightly. Plasma bedaquiline/M2 levels were collected per the same schedule as period 1.

At the end of the study the researchers compared the area under the curve (AUC), maximum concentration (C_{max}), time to maximum concentration (T_{max}), and half-life ($t_{½}$) of bedaquiline and M2 as a monotherapy and compared these values to the ones taken when efavirenz was administered concomitantly. Of statistical relevance, efavirenz was found to decrease the AUC of bedaquiline by about 20 percent. It is important to note though, that the participants' bedaquiline levels were still therapeutic. Additionally, it increased the C_{max} of M2; however, the AUC of M2 was unchanged. This correlates to an increased clearance of M2 in the presence of efavirenz. While this study addressed a key consideration in the treatment of MDR TB, it is only a beginning. Dooley et al. achieved a power above 80 percent. While this is commendable, they still only used a small sample size of healthy volunteers. A much larger study needs to be conducted that targets a population similar to the patients for whom bedaquiline is intended .[25]

Conclusion

Worldwide, tuberculosis is the second highest cause of death from an infectious disease.[17] Of those patients who are currently infected with tuberculosis, 35.3 percent of the newly diagnosed patients have a MDR strain, while 76.5 percent of previously treated patients have a MDR strain. These statistics alone demonstrate the importance of bedaquiline and other new TB drugs. While bedaquiline is currently only approved for MDR TB, some early studies show potential for this drug to be included in the early phase of future treatment regimens to reduce the total time of treatment; this in turn would have a positive impact on patient compliance. Also, it appears as if bedaquiline could be important in the treatment of patients with both TB and HIV; this is shown by the small impact of efavirenz on bedaquiline levels as noted above in the literature review. Though there are serious adverse events associated with bedaquiline therapy, health care professionals must weigh these risks against the fact that there are not many options for patients with MDR TB. When used appropriately, bedaquiline can offer some help to patients suffering from this tenacious disease.

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Assessment Questions

1. Tuberculosis (TB) is an important consideration for patients with _____ since it is the leading cause of mortality in this population.
   A. Diabetes mellitus
   B. HIV
   C. Hypertension
   D. Sleep apnea

2. TB most commonly infects which part of the body?
   A. Heart
   B. Liver
   C. Skin and soft tissue
   D. Lungs

3. Multidrug-resistant (MDR) TB is defined as:
   A. TB that no longer responds to any medications
   B. TB that is resistant to a fluoroquinolone
   C. TB that is resistant to isoniazid and rifampin
   D. TB that responds well to first-line treatment options

4. Which of the following is NOT a reason for using multiple medications in a regimen for treating active TB?
   A. To avoid resistance development
   B. To ensure complete eradication of the organism
   C. To attack the organism with multiple mechanisms of action
   D. To make sure the dose of one particular medication is not too high for tolerance of side effects

5. Which of the following is a potential benefit of including bedaquiline in an MDR TB regimen?
   A. Reducing total time of treatment
   B. Allowing a single medication to be used for the treatment of active TB
   C. Availability in a wide variety of dosage forms
   D. None of the above are benefits of bedaquiline treatment

6. What is the primary target for bedaquiline?
   A. Cell wall synthesis
   B. ATP synthase
   C. RNA transcription
   D. pH levels

7. Bedaquiline is affected by which of the following?
   A. Electrostatic attractive forces
   B. Proton motor force
   C. pH from 5.25 – 7.5
   D. All the above

8. Bedaquiline has shown to be a viable drug for targeting latent mycobacteria.
   A. True
   B. False

9. Bedaquiline contains a black box warning for which side effect?
   A. Hepatotoxicity
   B. Gastrointestinal bleeding
   C. QT prolongation
   D. None of the above

10. Prior to bedaquiline therapy, which patient-specific baseline levels should be measured?
    A. Liver enzymes
    B. ECG
    C. Serum electrolytes
    D. All of the above

To receive continuing education credit for this program, you must answer the above questions and fill out the evaluation form. Please visit www.onu.edu/pharmacy to enter the required information. Please allow two to three weeks for electronic distribution of your continuing education certificate, which will be sent to your valid email address in PDF format.

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Office of Continuing Education at the Raabe College of Pharmacy
Ohio Northern University
525 South Main Street
Ada, Ohio 45810

Ohio Northern University Continuing Education Registration & Evaluation Form
Raabe College of Pharmacy Continuing Education Evaluation Form

Program Title: **FDA Approves New Tuberculosis Drug: Bedaquiline (Sirturo®)**
UAN: 0048-0000-13-176-H01-P CEUs: 0.1

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.

Name:			
Address:			
City:	**State:**	**Zip:**	
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:					
Describe the pathophysiology of tuberculosis.	**1**	**2**	**3**	**4**	**5**
Evaluate the need for new drug therapies in the treatment of multidrug-resistant tuberculosis.	**1**	**2**	**3**	**4**	**5**
Explain the mechanism of action of bedaquiline.	**1**	**2**	**3**	**4**	**5**
List the major side effects of bedaquiline.	**1**	**2**	**3**	**4**	**5**
Discuss how bedaquiline will positively impact current therapy.	**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:

_____

_____

_____

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**

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).

Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is eligible for credit until 05/16/16.

Makena®: A Drug for Reducing the Risk of Preterm Labor

Amanda Lovell, fifth-year pharmacy student from Lexington, Ky.; Kasie Bellmann, fourth-year pharmacy student from Kalida, Ohio; Kelsey Fink, fourth-year pharmacy student from Hudson, Ohio; Jessica Beck, fifth-year pharmacy student from Gibsonburg, Ohio; Michelle Musser, PharmD, assistant professor of pharmacy practice

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): 0048-0000-13-177-H01-P

Objectives

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

1. Recognize for which patients Makena® is indicated.
2. List risk factors for preterm labor and potential consequences for premature infants.
3. State the side effects associated with Makena®.
4. Explain the potential role of the pharmacist in dispensing Makena®.

Abstract

Makena®, hydroxyprogesterone caproate, is an intramuscular injection that is U.S. Food and Drug Administration (FDA) approved to reduce the risk of preterm delivery before 37 weeks of pregnancy in pregnant women with a history of spontaneous preterm birth, who are not currently carrying multiple children. One in nine babies born in the United States each year is born prematurely, or before 37 weeks gestation, and mothers who have previously delivered a premature baby are 2.5 times more likely to deliver another baby prematurely. Makena® is administered by a health care professional as a single intramuscular injection to the hip and has a strict window for safe administration. Hydroxyprogesterone caproate has been available as a compounded product for years since the removal of Delalutin® from the market in 2000. The price of Makena® has been a controversial subject since its introduction into the market due to the increase in cost as compared to the compounded injections that have been available in the past.

Introduction

A synthetic progestin, 17-alpha-hydroxyprogesterone caproate, (17-OHPC, Makena®) is an intramuscular injection that was approved by the FDA on Feb. 4, 2011, to reduce the risk of preterm delivery before 37 weeks of pregnancy in pregnant women with a history of at least one spontaneous preterm birth, who are not currently carrying multiple children.[1] Makena® was accepted under accelerated approval regulations that allow drugs to be approved based on a surrogate endpoint. For Makena®, this endpoint was the reduction of risk of delivery before 37 weeks of pregnancy. The approval committee determined that the reduced risk of delivery before 37 weeks gestation observed with Makena® treatment was reasonably likely to predict a clinical benefit to mothers at risk for preterm delivery.[1]

Preterm Labor

One in nine babies born in the United States each year is born prematurely, or before 37 weeks gestation.[2] Mothers who have previously delivered a premature baby are 2.5 times more likely to deliver another baby prematurely, compared to mothers who have delivered full term.[3] Prevalence of premature births is greater in women who are African American, less than 17 years old but older than 35 years old, and those women with low income.[2]

There are many risk factors for preterm labor, ranging from the physical anatomy of the uterus and cervix to certain lifestyle factors and disease states.[2] Women who have previously had a preterm labor, women who are pregnant within six months of a previous pregnancy, women who are pregnant with more than one baby, women who underwent *in vitro* fertilization, and women who have certain uterus and/or cervical abnormalities are all at an increased risk of preterm labor. Lifestyle factors such as smoking, alcohol and drug use, standing for long periods of time, long working hours, and exposure to chemicals and pollutants can increase the risk of premature delivery. Additionally, stress, injuries/accidents, violence/abuse and lack of social support can lead to a greater risk. Certain disease states can also put a woman at higher risk for preterm labor including diabetes, high blood pressure or preeclampsia, obesity or underweight and infections (sexually transmitted infections, urinary infections, vaginal infections, placental infections). Birth defects present in the unborn baby can also put the mother at increased risk for premature delivery.

Premature infants may experience several complications involving multiple organs and organ systems.[4] Occurrence of complications often depends on how early the infant is born. The respiratory system matures by week 36, but this can often vary depending on the infant's individual development. Infants born before 36 weeks gestation are at an increased risk of having immature lungs, which can lead to a variety of consequences. One potential risk is the development of respiratory distress syndrome (RDS), where the infant's immature lungs do not produce enough surfactant, which normally prevents the lungs from collapsing. Transient tachypnea can also occur, causing the infant to have shallow and rapid breathing. In addition to tachypnea, infants may also experience apnea, or the absence of breathing, and bradycardia, or a slowed heart rate. Infection and pneumonia are also a risk due to a reduced ability to fight infections as well as possible immature lungs.

Other consequences of prematurity include jaundice, or yellowing of the skin due to the buildup of bilirubin in the blood, and anemia due to abnormally low levels of red blood cells.[4] Due to their small size and low body fat, premature infants may also be unable to maintain their own body temperature. The heart can be affected by a condition known as patent ductus arteriosus (PDA) in which a specialized blood vessel in the fetal heart, the ductus arteriosus, does not close. Patent ductus arteriosus can lead to respiratory problems and may ultimately cause heart failure if left untreated. The infant's gastrointestinal system is also at risk for complications. Infants born early may not have a fully developed gastrointestinal tract, which can lead to the inability of the infant to absorb nutrients properly and effectively. Parts of the gastrointestinal tract may also receive inadequate blood flow, which can lead to bowel wall infection and cause a serious and potentially life threatening condition known as necrotizing enterocolitis. If born before 34 weeks of gestation, the newborn may experience additional complications such as intraventricular hemorrhage (IVH) and retinopathy of prematurity (ROP). Intraventricular hemorrhage is a condition that leads to bleeding in the brain due to immature blood vessels that are unable to handle the strain of labor and birth, which can lead to mental retardation, learning disabilities and cerebral palsy. Retinopathy of prematurity can potentially cause blindness in the newborn.[2,4]

Management of Preterm Labor

Women experiencing premature labor are often put on bed rest to decrease physical activity and are advised to increase fluid intake. Doctors may also tell women to refrain from the use of tampons and douches and to avoid having sex. If the cervix starts to open too early, a procedure known as a cerclage is performed. During a cerclage, a stitch is put in the cervix and left in place until the mother is 37 weeks pregnant.[2]

Pharmacologic treatment of preterm labor often involves the use of progesterone and tocolytics.[5] Tocolytics include drugs such as magnesium sulfate, indomethacin, nifedipine and terbutaline, and may also be used to slow contractions during preterm labor. Health care providers may give tocolytics after 17 to 20 weeks gestation and prior to 34 weeks gestation. The specific medication used as well as duration of therapy depend on time in pregnancy, the status of the fetus and the overall risk of actual preterm labor. Tocolytics can delay labor for approximately 48 hours, but for some women labor may be delayed several days.

Progesterone is used, either as a vaginal gel or as an injection, to relax the uterus and prevent contractions.[6] Progesterone injections may be used weekly starting at 16 weeks, while the gel can be started around 20 weeks and is applied daily. The gel or injection may be used until 37 weeks gestation. To qualify for the use of the injections, a woman must be pregnant with only one baby or have previously experienced preterm labor with a single baby.

Makena®

Makena® is a synthetic progestin that has effects similar to progesterone. Progesterone is needed for implantation of a fertilized egg into the uterus and is also responsible for maintaining pregnancy. The mechanism in which progesterone accomplishes this is unknown, but is hypothesized to help relax the muscles of the uterus and reduce the rate of cervical shortening.[7,8] The synthetic progestin appears to have differing effects on the muscles of the uterus and has either produced no change or increase in uterine contraction.[9] A review by O'Brien[9] analyzed several studies primarily to determine the safety of progesterone and 17-OHPC. The author makes a distinction that natural progesterone is handled differently in the body from the synthetic and, therefore, may have different safety profiles. The author also reviews differences in the efficacy and safety when comparing women with singleton pregnancies to those with multiple pregnancies. The studies have shown that in patients with multiple fetuses, 17-OHPC can reverse the intended agonism on the progesterone receptor and create an antagonistic effect. Progesterone receptor antagonism is based on the patient's genotype and the number of fetuses per pregnancy. It may also lead to a miscarriage or impaired fetal growth in some populations. Studies have shown that the progesterone receptor gene is located on chromosome 11q. Polymorphisms in this gene may result in adverse events in pregnancy such as preterm labor. Manuck et al.[10] examined the progesterone receptor polymorphisms in women with previous spontaneous preterm births and the clinical response to 17-OHPC. This was an exploratory study conducted as a secondary review of patients from a previous study [11] so the results must be considered with caution. The authors noted several polymorphisms associated with a greater risk of spontaneous preterm births, as well as differences in response to 17-OHPC depending on genotype.[10] Therefore, based on the patient's progesterone receptor, treatment with 17-OHPC may trigger preterm labor; however, at this time genetic testing is not required or suggested prior to starting Makena® therapy.

The approval of Makena® did not mark the first instance of FDA approval of hydroxyprogesterone caproate. In 1956, Delalutin® was approved by the FDA for indications that included the threat of miscarriage.[1,12] This was prior to the FDA Drug Amendment Act of 1962 which required that efficacy be shown in a controlled clinical trial for market approval. In 2000, the FDA removed Delalutin® from the market at the request of the manufacturer (who was no longer producing the drug); this withdrawal was unrelated to safety.[1,12] A compounded form of injectable hydroxyprogesterone caproate has been used off-label for many years. The approval of Makena® was made on a single controlled clinical trial with the expectation that the manufacturer would provide additional data. The study conducted was a multicenter, randomized, double-blind clinical trial that enrolled 463 women who were pregnant with a single fetus and had a history of preterm birth. In the placebo control group of the study, 55 percent of patients delivered before week 37 as compared to 37 percent delivered before week 37 in the group treated with 17-OHPC.[1,11] There was also a significant decrease in preterm deliveries at weeks 35 and 32 as compared to the placebo group, although this was not as strong statistically. The authors calculated the number-needed-to-

treat (NNT) to prevent one preterm delivery before 37 weeks in patients with similar risk to those in this study was between five and six (95 percent confidence interval, 3.6 to 11.1).[11] In order to prevent one preterm delivery before 32 weeks, the NNT was calculated to be 12 (95 percent confidence interval, 6.3 to 74.6). Given that the greatest risk to the neonate is when delivery is prior to 32 weeks, the use of 37 weeks as the surrogate endpoint may not be as telling.[12] The authors did review outcomes in the infants and found in patients who received 17-OHPC versus placebo a significant decrease: in infants weighing less than 2500 gm at birth; in rates of necrotizing enterocolitis; in IVH of any grade; and need for supplemental oxygen.[11] There was a decrease (nonsignificant) in: infants weighing less than 1500 gm at birth; neonatal death; transient tachypnea; respiratory distress syndrome; bronchopulmonary dysplasia; ventilator support; patent ductus arteriosus; and retinopathy. Of concern was a nonsignificant increase in fetal death in the 17-OHPC treated group. Further trials are needed to evaluate this and more long term effects on the children born to mothers treated with 17-OHPC.

Makena® is administered by a health care professional as a single intramuscular injection to the hip.[3] Women may receive 250 mg of Makena® via intramuscular injection once weekly starting between 16 weeks and zero days, and 20 weeks and six days of gestation. The weekly doses of Makena® continue until week 37 of gestation or delivery of the baby.

The most common side effects of Makena® are pain, pruritis, and/or swelling at the injection site, as well as some gastrointestinal upset such as nausea and diarrhea.[13] Some women may experience urticaria, or hives, in the area of injection. A more serious side effect that is often a risk when taking hormone replacement therapy is a thromboembolic disorder. This can become a life threatening event and the patient should receive medical attention if a thromboembolic disorder develops.[4] Women should not use Makena® if they have a history of thromboembolic events, have hormone sensitive cancer, unusual vaginal bleeding, active liver disease or uncontrolled hypertension.[13] Makena® is not shown at this time to have negative impacts on the infants later in life. Further safety studies are continuing to detect these potential outcomes. Hydroxyprogesterone caproate is a CYP3A substrate and a strong CYP2A6 inhibitor. Drug interactions can be expected with other drugs that affect these enzyme systems.[14]

Controversy has surrounded this drug and its manufacturer, KV Pharmaceuticals, since its approval. The compounded form of hydroxyprogesterone caproate was available for around $15 per injection. When Makena® came on the market, the cost was $1,500 per injection.[15] When the FDA made its original approval as an orphan drug, KV Pharmaceuticals was allowed exclusive rights to the product for seven years. The FDA, however, decided not to enforce the exclusivity of KV pharmaceuticals and allowed pharmacists to continue to compound hydroxyprogesterone caproate at a lower price. This led to a large drop in stock of Makena® and eventually KV pharmaceuticals decreased the cost of the drug to $690 per injection.[16] Even with this reduction in price, the cost of use of Makena® may still exceed the savings in overall health care costs due to less preterm births. Based on a conservative NNT of 14, 139,000 at-risk women would need to be treated to prevent 10,000 premature births.[17] The total direct and indirect medical costs for 10,000 premature births is estimated at $519 million. Even at the new, reduced price of $690 per injection of Makena®, the cost of treatment of 139,000 women with Makena® for 20 weeks would exceed $1.9 billion. In comparison, the cost of the compounded form of 17-OHPC to treat 139,000 women would be approximately $41,700,000—considerably less than the medical costs associated with 10,000 premature births.

To help assist patients with the costs of Makena®, KV pharmaceuticals developed a patient assistance program. The financial aid is based on the patient's insurance status, as well as their household income. This financial assistance may make Makena® an option for those who need it but cannot afford it.[18] Table 1 displays the financial assistance available based on a family's income and insurance for Makena®.

Conclusion

Makena®, though not the first drug of its kind, has been FDA approved for the treatment of preterm labor in patients at risk. This medication has gained recent media attention due to the FDA decision to not enforce the exclusivity of KV Pharmaceutical to market the drug, which has significantly increased patient awareness of this drug and its benefits in preventing preterm delivery. As pharmacists, it is important to understand how Makena® works and which patients qualify for administration in order to refer patients to their gynecologist for further treatment. Though this product is very expensive, pharmacists are available to give information about the compounded hydroxyprogesterone caproate injection that may be available in their area, as well as information on financial assistance for Makena®. The accessibility of pharmacists within the community allows for an increased availability to patients and physicians with questions about preterm labor and the benefits that treatment options, such as Makena®, may provide.

Table 1. Assistance Provided by the Patient Assistance Program for Makena®.[18]

Coverage	Income Level	Copay/Financial Assistance*
Uninsured	Up to $60,000	Receive Makena® at no cost
Uninsured	Above $60,000	Receive Makena® at cost equivalent to what insured patients pay out-of-pocket under the Makena® copay assistance program
Insured	Up to $120,000 *(represents 85 percent of household incomes based on 2009 census data)*	Copay of $0-$20 per injection for Makena®
Insured	Above $120,000 *(represents 15 percent of household incomes based on 2009 census data)*	Copay of $40-$80 per injection for Makena®

** This encompasses 85% of U.S. household incomes. Source: 2009 U.S. Census Data.*
**Gross annual household income and insurance coverage are factors that determine the level of copay or financial assistance for which a patient is eligible. There are additional eligibility requirements (i.e. have a Makena® prescription, etc.) and these can be discussed on patient-by-patient basis with a representative from the Makena® Care Connection, a program designed to help ensure access to Makena®. http://www.kvph.com/Makena/cost-of-bringing-makena-to-market.aspx; reprinted with permission: Medical Information, Ther Rx, division of KV Pharmaceuticals. Accessed May 23, 2013.*

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Assessment Questions

1. Makena® is indicated for:
   A. Women with no prior history of preterm birth
   B. Women carrying multiple children
   C. Women with a singleton pregnancy
   D. Women that are greater than 37 weeks gestation

2. Makena® is a(n):
   A. Self-administered intramuscular injection
   B. Tablet
   C. Intravenous drip
   D. Intramuscular injection administered by a health care professional

3. Hydroxyprogesterone caproate was previously FDA approved under the name:
   A. Delalutin®
   B. Endometrin®
   C. Mirena®
   D. Prometrium®

4. Women who have previously delivered a premature baby are how many more times likely to deliver prematurely again?
   A. 5
   B. 3.5
   C. 2.5
   D. 3

5. Other treatment options for premature labor include:
   A. Tocolytics
   B. Progesterone
   C. Cerclage
   D. A and B
   E. All of the above

6. All of the following increase incidence of premature birth EXCEPT:
   A. Asian descent
   B. Age <17 and >35
   C. Low income
   D. In vitro fertilization

7. Potential risks for the premature baby include:
   A. Respiratory distress syndrome
   B. Jaundice
   C. Intraventricular hemorrhage
   D. All of the above are potential risks of premature delivery

8. Some common side effects a patient receiving Makena® may experience include all of the following EXCEPT:
   A. Pain and swelling at the injection site
   B. Hives in the area of the injection
   C. Headache
   D. Nausea and vomiting

9. Which serious side effect is life-threatening in which the patient should seek medical attention immediately?
   A. Respiratory distress syndrome
   B. Seizures
   C. Depression
   D. Thromboembolic disorder

10. What is/are the best way(s) a pharmacists can assist a patient that may be a candidate for Makena®:
   A. Explaining the benefits Makena® can have on a preterm pregnancy
   B. Provide information about financial assistance to help pay for Makena®
   C. Understand which patients qualify for Makena® and refer the patient to her gynecologist
   D. All of the above are ways a pharmacists can assist a patient

To receive continuing education credit for this program, you must answer the above questions and fill out the evaluation form. Please visit www.onu.edu/pharmacy to enter the required information. Please allow two to three weeks for electronic distribution of your continuing education certificate, which will be sent to your valid email address in PDF format.

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Office of Continuing Education at the Raabe College of Pharmacy
Ohio Northern University
525 South Main Street
Ada, Ohio 45810

Ohio Northern University Continuing Education Registration & Evaluation Form
Raabe College of Pharmacy Continuing Education Evaluation Form

Program Title: **Makena®: A Drug for Reducing the Risk of Preterm Labor**
UAN: 0048-0000-13-177-H01-P CEUs: 0.1

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Name:				
Address:				
City:	**State:**	**Zip:**		
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:					
Recognize for which patients Makena® is indicated.	**1**	**2**	**3**	**4**	**5**
List risk factors for preterm labor and potential consequences for premature infants.	**1**	**2**	**3**	**4**	**5**
State the side effects associated with Makena®.	**1**	**2**	**3**	**4**	**5**
Explain the potential role of the pharmacist in dispensing Makena®.	**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**	**7. A B C D**
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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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Antidepressant Therapy: A Review of Current Treatment Options and A Glance at the Future

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Abstract
Depression and anxiety disorders are two of the most common mental illnesses experienced by people within the United States, affecting 6.7 percent of the adult population per year. This article will focus on one specific type of depression, major depressive disorder (MDD), characterized by two or more weeks of depressed mood and/or decreased interest in normally enjoyed activities. Depression complicates treatment of other disease state(s), making successful treatment of depression essential in the management of a patient's overall health. This review will evaluate the pathophysiology, antidepressant treatment, and new approaches to treatment, specifically vortioxetine, for MDD.

Introduction
Depression and anxiety disorders are two of the most common mental illnesses experienced by people within the United States, affecting 6.7 percent of the adult population per year.[1] Although there are several classifications of depression, this article will focus on major depressive disorder (MDD). Our objective is to review the pathophysiology, treatment and new approaches to treatment of MDD for pharmacists and clinicians.

The major symptoms of MDD, as defined by the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM IV) guidelines, include two or more weeks of depressed mood and/or anhedonia, which is a decreased interest in activities that one normally enjoys. Other symptoms include mental slowing, poor concentration, insomnia or hypersomnia, significant weight loss or gain, altered eating patterns, altered levels of activity, feelings of guilt and worthlessness, decreased energy and libido and suicidal ideation.[2] Depression may occur independently, but frequently follows chronic disease states such as diabetes, hypertension, and chronic obstructive pulmonary disease, as well as following a life-changing diagnosis such as cancer or multiple sclerosis. Depression complicates treatment of other disease state(s), making successful treatment of depression essential in the management of a patient's overall health. Antidepressants play a key role in the treatment of this disorder.

Pathophysiology of Depression
In order to understand the mechanism of antidepressants, it is necessary to review the complex pathophysiology of depression. Neurotransmitters are the chemicals that the brain uses to communicate and control various aspects of central nervous system (CNS) function. The neurotransmitters most implicated in depression are monoamines, specifically serotonin, norepinephrine, and dopamine.

Serotonin (5-HT) is one of the major neurotransmitters implicated in depression while also functioning to regulate sleep, appetite, mood and emotional processing.[3] Decreased levels of serotonin transmission have been observed in patients with depression and linked to an increased risk of suicide. Low levels of norepinephrine (NE) can also cause symptoms of depression. Norepinephrine is involved in sensory processing, mood, and anxiety, as well as sympathetic autonomic functions such as increasing blood pressure and heart rate. Finally, low levels of dopamine (DA) are implicated in depression as well. Dopamine is involved in mood, reward, motivation and concentration. Deficiencies in these neurotransmitters often coincide with one another, making it ideal to use a medication with multiple mechanisms of action.

Although the actual cause of the neurotransmitter deficiencies remains unknown, bolstering their levels has been clinically shown to improve the symptoms of depression. Unfortunately there is a delay in therapeutic onset, leading researchers to explore the adaptive changes induced by antidepressants. It has been found that chronic exposure to antidepressants leads to a change in the sensitivity of the neurotransmitter receptor. Therefore, the homeostatic balance of neurotransmitter systems is thought to be more important than the increase and decrease of independent neurotransmitters. Effective antidepressant agents aim to restore efficient regulation to the multiple neurotransmitter systems.[4]

Monoamine Oxidase Inhibitors
The first antidepressants utilized for MDD were the monoamine oxidase inhibitors (MAOIs). Since their debut in therapy, MAOIs have been indicated for patients with atypical depression, and for those patients who are unresponsive to other antidepressant therapy.[5] Some of the most common MAOIs indicated for depression include isocarboxazid, phenelzine, and high dose selegiline. These drugs act by inhibiting the monoamine oxidase enzyme responsible for the breakdown of monoamine neurotransmitters.

There are two types of MAO enzymes (A and B), both of which are non-selectively inhibited by MAOIs. Blockage of this enzymatic process results in a decrease in the metabolic decomposition of neurotransmitters, allowing for an increase in monoamine concentrations in the brain.[5] MAOI-B selective inhibitors have also been used as monotherapy for symptomatic treatment of Parkinson's disease.[6]

Monoamine oxidase inhibitors have proven to be fairly well-tolerated in most patients and convenient due to their once to twice daily administration without dose titration.[6] In addi-

tion, the drugs irreversibly bind the MAO enzyme, causing a lag time between discontinuation of the drug and return of normal MAO activity, prolonging therapeutic effects.[5] Conversely this lag time could be seen as a disadvantage. It prevents initiation of any additional therapy with another serotonin modulating agent for at least two weeks due to a risk of serotonin syndrome, a term used to describe a constellation of adverse effects such as increased agitation/ anxiety, muscle rigidity, fever, hypertensive crisis, convulsions and even death. There are several other drawbacks to MAOIs in the treatment of MDD. In general, they are contraindicated with other MAOIs or any drugs with similar activity because of the risk of serotonin syndrome.[6] Additional concerns have led to a black box warning for MAOIs regarding "Suicidality and Antidepressant Drugs" indicating an increased risk of suicidal thinking and behavior in children, adolescents, and young adults who take these drugs.[5] Lastly, patients taking MAOIs must be aware of certain food restrictions while on these medications. Monoamine oxidase inhibitors have a specific interaction with foods containing high amounts of tyramine which can lead to hypertensive crisis. These include high-protein foods that have been exposed to any "aging, fermentation, pickling, smoking, etc." such as cheese, meats, fish, dairy, beer, and wine—all of which may be difficult to avoid for some patients.[5] Overall, while MAOIs were the first drug class marketed for antidepressant therapy, newer drug classes have replaced them due to these side effects and restrictions.

Tricyclic Antidepressants

One of the first alternative drug classes to avoid the challenges presented by MAOIs is tricyclic antidepressants (TCAs). This class of antidepressants is named from the three-ringed structure of its drug molecules.[7] Tricyclic antidepressants were considered first-line therapy for depression until the late 1980s, when selective serotonin reuptake inhibitors (SSRIs) were approved.[8] Today, TCAs are still used for depression as well as for the treatment of panic disorder, attention deficit hyperactivity disorder (ADHD), migraines, eating disorders, smoking cessation, neuropathic pain and anxiety. According to the World Federation Societies of Biological Psychiatry treatment guidelines, TCAs are generally considered to be second-line therapy for depression although they may be considered first-line in some instances, such as in hospitalized patients with severe depression.[9] Frequently prescribed TCAs include amitriptyline, nortriptyline, desipramine and imipramine.[7,10]

The mechanism of TCAs is not completely understood, but it is thought they increase serotonin and norepinephrine levels by blocking their reuptake. TCAs are non-selective and also bind to histamine, cholinergic and alpha 1-adrenergic receptors. Their mechanism is different from that of selective serotonin or serotonin/norepinephrine reuptake inhibitors, which primarily inhibit the reuptake of serotonin.[7,10] There are two structural types of TCAs; secondary and tertiary amines. The secondary amines, like nortriptyline and desipramine, may play a larger role in blocking the reuptake of norepinephrine. Tertiary amines such as amitriptyline and imipramine may be more selective for blocking the reuptake of serotonin. Even though their structures vary, both secondary and tertiary amines effectively treat depression.[10]

Tricyclic antidepressants have certain advantages over other classes of antidepressants. Firstly, they do not interact with tyramine containing compounds and therefore do not cause the hypertensive crises for which the MAOIs are known.[8] Secondly, TCAs have several indications and may be beneficial for patients who suffer from other conditions that TCAs treat, such as neuropathic pain, as well as depression.[7]

Although TCAs may be beneficial for patients who do not respond to other antidepressants, there are disadvantages in choosing an antidepressant from this class. Many patients have difficulty tolerating TCAs due to their many adverse effects. Tricyclic antidepressants have an increased risk of overdose and are not as selective as the SSRIs. This risk of overdose is due to cardiac disturbances, which can result from patients consuming alcohol or taking other medications, such as central nervous system (CNS) depressants and thyroid agents, with their TCA. Children have an increased risk of acute overdoses that result in fatality.[7,10,12] The many adverse effects of TCAs result from the class' lack of selectivity. Since TCAs bind non-selectively to a variety of receptors, they may cause weight gain, dry mouth, constipation, and drowsiness.[7,13] The weight gain and anticholinergic effects of secondary amines are less severe than that caused by tertiary amines.[11] Additionally, TCAs may cause orthostatic hypotension. The alpha-1 receptor blocking activity of TCAs is responsible for the postural drop in blood pressure.[12,14] Stimulation of norepinephrine receptors make desipramine and nortriptyline safer options for patients who are at risk for orthostatic hypotension.[11] Patients who experience orthostatic hypotension have an increased risk of falling and fainting, especially those in the elderly population who may already be on antihypertensive medications. Therefore, secondary amines may be preferential in the elderly population.[12,14]

In addition to their anticholinergic and antihistamine effects, both classes of TCAs lower the threshold for and may cause seizures. Patients with seizure disorders who also take a TCA must be monitored closely.[12] Tricyclic antidepressants should not be taken with the other antidepressants and should be used with caution in patients who are at an increased risk for suicide.[7] The lack of selectivity of the TCAs led to the development of the SSRIs.

Selective Serotonin Reuptake Inhibitors/ Serotonin-Norepinephrine Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are the current first-line therapy for the treatment of major depressive disorder.[15] They are also prescribed and used as anxiolytics with demonstrated efficacy in the treatment of generalized anxiety, panic, and obsessive compulsive disorder (OCD).[16] Some examples of SSRIs include fluoxetine, paroxetine, sertraline, citalopram, escitalopram and fluvoxamine.

SSRI treatment causes stimulation of receptors on cell bodies in the raphe nucleus and on the serotonergic terminals. With repeated treatments of SSRIs, there is a gradual down-

regulation and desensitization of the receptor mechanisms causing an inhibition of the reuptake of serotonin at the presynaptic neuronal membrane. Additionally, repeated treatments decrease the expression of serotonin transporters (SERT) in the nerve terminal, resulting in reduced clearance of serotonin from the synapse. This enhances and prolongs the serotonergic neurotransmission due to inability of serotonin to be removed and terminated from the cleft.[16]

There are several advantages of choosing an SSRI over other antidepressant medications. SSRIs, in contrast to TCAs, are well-tolerated and have a more benign cardiovascular profile, making them preferred as initial agents for treatment of depression in individuals with cardiovascular disease. The recent American Heart Association science advisory suggests sertraline and citalopram as first-line drugs for patients with both depression and coronary heart disease.[17] SSRIs also have few anticholinergic and adrenolytic effects. Sedation is minimal or nonexistent, but some patients tend to be fatigued during the first few weeks of therapy. Drug interactions are relatively uncommon, except with drugs that also affect serotonergic neurotransmission, including monoamine oxidase inhibitors and antipsychotic agents.[15] More recently citalopram has been reported to have a dose-related effect on QT interval prolongation and possible development of torsades de pointe. The manufacturer does not recommend use of citalopram with other drugs known to prolong the QT interval.[10]

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are similar to SSRIs, but have dual serotonin and norepinephrine action. Inhibition of both SERT and norepinephrine transporters (NET), causes enhanced serotonergic and/or noradrenergic neurotransmission. Like SSRIs, the initial inhibition of SERT and NET induces activation of autoreceptors, but decreases serotonergic neurotransmission presynaptically via a negative feedback mechanism until the receptors are desensitized. Thus, the serotonin concentration can still interact with the postsynaptic serotonin receptors. Drugs in this category include venlafaxine, desvenlafaxine and duloxetine.[16]

There are several disadvantages that patients should be aware of due to similar toxicities between SSRIs and SNRIs. These classes are associated with an increased bleeding risk, especially in the elderly or in those taking other drugs with the potential of damaging the gastrointestinal mucosa or interfering with clotting.[18] Some patients, especially young adults and children, can show signs of worsening depression or become increasingly suicidal during the first few months of taking SSRIs/SNRIs. They may also cause weight issues like weight gain or anorexia. Sexual dysfunction, including decreased libido and erectile dysfunction, occurred in some patients. Discontinuation symptoms may arise if a drug in this class is stopped abruptly, so tapering off is beneficial. Symptoms of withdrawal include nausea, chills, muscle aches, insomnia, fatigue and anxiety.[15]

Bupropion

Mechanistically unrelated to the previously mentioned antidepressants is the drug bupropion (Wellbutrin®). While the mechanism of action is not completely understood, the drug is known to be an aminoketone, and has proven to selectively inhibit the neuronal reuptake of dopamine, but not serotonin. It also lacks any actions on MAO and it is thought to achieve its therapeutic effects mainly by dopaminergic and/or noradrenergic actions.[19, 20] In terms of its indications, the brand Wellbutrin® and the associated generic products include labels for depression and seasonal affective disorder (SAD).[19, 21] The brand Zyban® has been specifically approved for smoking cessation.[21]

Due to its unique mechanism, bupropion could be advantageous for patients who seek a different type of treatment method than the other existing drug classes. Specifically, bupropion is well-tolerated in patients who experience orthostatic hypotension while using TCAs.[19] Another side effect of the drug that could be advantageous is weight loss, with the caveat of a black box warning for use in anorexic patients.[20] In addition to this, the CNS-stimulating effects of bupropion are dose-related, which can be helpful for general drug administration (i.e. predictable outcomes and adjustments). The drug's few disadvantages are very serious and should still be considered. These severe side effects are summed up by a black box warning on bupropion for suicide ideation and increased risk for seizures. Caution is advised when using bupropion with other drugs known to increase the risk of seizures and is contraindicated in patients with a history of seizures. As with other antidepressants, bupropion is not FDA approved in children due to risk of suicidal thoughts.[19,21]

Mirtazapine

Another antidepressant with a novel mechanism of action is mirtazapine. It was developed as an alternative therapy for patients who could not tolerate TCAs or SSRIs.[22] Mirtazapine is structurally different than all other antidepressants on the market. It has a tetracyclic structure and is part of the piperazinoazepine class.[23, 24] Mirtazapine is an alpha-2 antagonist; blocking alpha-2 receptors on presynaptic neurons. This blockade causes an increase in norepinephrine release, which is normally deterred by negative feedback from alpha-2 agonists. The alpha-2 receptors on serotonergic neurons are called heteroreceptors. When these receptors are blocked, there is an increase in serotonin release. Elevated levels of serotonin and norepinephrine are associated with antidepressant and anxiolytic activity.[23-25] Mirtazapine also blocks 5-HT2 and 5-HT3 receptors.[23, 24] Due to its activity on alpha-2 and certain serotonin receptors, mirtazapine is used for the treatment of depression.[22-26] Mirtazapine may be used in combination or augmented with other medications when patients need additional antidepressant therapy.[9]

In addition to its antidepressant activity, mirtazapine also has anxiolytic effects; therefore, it may be beneficial in patients who suffer from both anxiety and depression. Mirtazapine is known to improve the sleeping patterns of depressed patients. It is better tolerated and has a faster onset of action than the other antidepressants.[23, 26] Its quick onset of action may be due to its dual mechanism of action.[24] Since mirtazapine has significantly increased activity at central alpha-2 receptors, it has few peripheral side effects. It does

not act on dopaminergic or muscarinic receptors, which may also explain its decreased number of side effects.[23] Mirtazapine does not have the sexual side effects caused by SSRIs and has decreased seizure and overdose risks when compared to TCAs.[22, 24] The incidence of erectile dysfunction and decreased libido are higher in SSRIs, since increased levels of extracellular serotonin decrease norepinephrine levels. Norepinephrine is necessary for normal sexual function.[27]

Certain patients tolerate mirtazapine better than others. Mirtazapine can cause dry mouth, sedation, increased appetite and weight gain. The weight gain associated with mirtazapine is less pronounced than that caused by TCAs.[23-25] In clinical trials, small numbers of patients experienced hypotension due to mirtazapine's alpha blocking activity, but this side effect is less common than in patients taking TCAs.[23] Like the other antidepressants, mirtazapine has a black box warning for an increased risk of suicidal thoughts. It should not be taken with MAOIs or SSRIs, due to the risk of drug-drug interactions.[8, 25] Patients should not abruptly stop mirtazapine, since there is a risk for withdrawal.[25]

Vortioxetine

All of the drug classes mentioned thus far are used currently in antidepressant therapy today, albeit some more than others based on the advantages and disadvantages of each class. However, the need for more efficacious therapies with fewer side effects continues to fuel further drug development**.** A new drug that has currently entered the process of FDA approval is LU AA2104, known as vortioxetine. Vortioxetine works by a novel, multifaceted mechanism of action. In studies, it has demonstrated action as a 5-HT1d, 5-HT3 and 5-HT7-receptor antagonist, 5-HT1a-receptor agonist, 5-HT1b -receptor partial agonist, and inhibits the 5-HT reuptake transporter. All of these effects would increase the antidepressant action of serotonin, and the drug may also increase levels of norepinephrine, dopamine, acetylcholine and histamine. It is believed that all of these mechanisms are involved in the clinical effects of the medication.[28]

Current studies have released tentative results about vortioxetine. They have consistently shown safety, mild adverse events and tolerability of the drug. Several project a benefit from baseline compared to placebo, and comparable efficacy to drugs that were used as active references in the study. One such study was a double-blind, placebo-controlled study of vortioxetine in patients with MDD.[29] Patients were assigned to one of four treatment arms: 5 mg vortioxetine, 10 mg vortioxetine, venlafaxine titrated up to 225 mg/day, or placebo. The patients participated in a six week experimental period, followed by a two week taper. Both venlafaxine and vortioxetine showed statistically significant superiority (p-value <0.0001) to placebo when mean change from baseline in the Montgomery–Asberg Depression Rating Scale (MADRS) total score was measured at week 6. Side effects in this study were generally mild across all treatment groups. Out of the 426 patients, a total of 30 patients dropped out of the study due to adverse effects. Of the 30 patients who dropped out, 16 were in the venlafaxine group, accounting for 14 percent of that treatment arm. Of the placebo group, four patients (4 percent of placebo arm) dropped out. In the vortioxetine groups, patient dropout was three (3 percent of treatment arm) and seven (7 percent of treatment arm) for the 5 mg and 10 mg doses, respectively. Over half of the patients who dropped out were in the venlafaxine group, with vortioxetine showing low levels of dropouts at each dose. However, by looking at both doses of vortioxetine as a whole, the dropout rate was not statistically different.

In analysis of the primary endpoint of this study, both treatments were superior to placebo, with reducing depression and anxiety at a significantly higher level than placebo. The authors concluded that vortioxetine displayed efficacy, and suggested further trials be conducted. Several studies have found similar results, indicating that vortioxetine is effective in treating MDD. However, one study that compared vortioxetine to placebo did not show a significant change in baseline for either treatment arm. The authors postulated that the restrictive nature of their assessment tool, as well as their more limited population pool, may have contributed to the lack of benefit seen in this trial compared to the trials demonstrating efficacy.[30] Upon reanalyzing their data using another method, they found a significant improvement from baseline with vortioxetine. These results are questionable, given that the study was not designed to use the method that researchers used to reanalyze the data.

In short, vortioxetine appears to be safe and tolerable, with nausea as the most common adverse effect. It has also shown efficacy in several trials, warranting further investigation. It is based on the combined data from these studies that the FDA has decided to accept the submission of the new drug application for vortioxetine in the treatment of MDD.[28] Takeda Global Research and Development Center, Inc and H. Lundbeck A/S have announced that, should the FDA approve vortioxetine, it will be marketed under the trade name Brintellix ®.

Prior to vortioxetine, the development of novel mechanisms to treat depression had stagnated. Vortioxetine would introduce a meaningful contribution to the field, and the current results indicate that it may be useful in preventing relapse in patients with MDD. Results also show that it may have a milder adverse effect profile than the other antidepressant treatments.

Major depressive disorder is a highly prevalent disease state in the United States. Pharmacological interventions focus on the principle of normalizing key neurotransmitters, such as serotonin, norepinephrine and dopamine. Progress has been made in the formulation of antidepressants over the last several decades with a goal of maximizing clinical effect while minimizing adverse effects. Despite these advancements, limitations to the use of each antidepressant class merit investigation of additional clinical options. This research appeared to have stagnated until the introduction of vortioxetine and its novel mechanism of action (MOA). Should this agent gain FDA approval, it would represent an important developmental step in the continuing efforts to treat and alleviate depression.

Drug Class	Examples of Drugs in Each Class	MOA	Place in Therapy	Advantages	Disadvantages
MAOI	isocarboxazid phenelezine selegiline	Inhibit the metabolism of monoamines via Monoamine Oxidase	Atypical depression Patients resistant to other therapies	Daily and twice daily dosing No titrations Well-tolerated	Dietary restrictions of tyramine containing foods Risk of hypertensive crisis Many drug interactions
TCA	**Secondary Amines:** desipramine nortriptyline **Tertiary Amines:** amitriptyline imipramine	Block reuptake of NE and 5-HT	Depression Panic Disorder ADHD Migraines Eating disorders Smoking cessation Neuropathic pain Anxiety	No dietary restrictions Multiple indications	Increased risk of acute overdose Nonselective Anticholinergic effects Antihistamine effects Orthostatic hypotension Increased seizure risk
SSRI	fluoxetine paroxetine sertraline citalopram escitalopram fluvoxamine	Desensitize receptors Blocks SERT expression	First-line treatment for depression Anxiety Panic Disorder OCD	Selective Limited CV effects Few anticholinergic and adrenolytic effects	Sleepiness Weight gain Bleeding Risk Inhibit CYP450s Worsening of symptoms in the first few months of therapy Withdrawal symptoms if stopped abruptly Sexual dysfunction
SNRI	venlafaxine duloxetine desvenlafaxine	Inhibit both SERT and NET Desensitize receptors	Depression Anxiety Panic disorder OCD	Dual MOA	Weight gain Bleeding Risk Worsening of symptoms in the first few months of therapy Withdrawal symptoms if stopped abruptly
	bupropion	Selectively inhibits the reuptake of DA	For patients who experience orthostatic hypotension on TCAs Depression Nicotine withdrawal Social anxiety disorder	Does not cause orthostatic hypotension	Lowers seizure threshold
	mirtazapine	Alpha-2 antagonist Blocks 5-HT2 and 5-HT3 receptors	Depression in patients who cannot tolerate TCAs or SSRIs Patients who suffer anxiety and depression	Improves sleeping patterns Faster onset of action than other antidepressants Few peripheral adverse effects Lacks sexual side effects of SSRIs	Withdrawal risk Can cause blood pressure to drop Weight gain and seizures (less than TCAs)

Abbreviations: MAOI-monoamine oxidase inhibitors, TCA-tricyclic antidepressants, SSRI-selective serotonin reuptake inhibitor, SNRI-serotonin-norepinephrine reuptake inhibitor, OCD-obsessive compulsive disorder, ADHD-attention-deficit and hyperactivity disorder, CV-cardiovascular, SERT-serotonin transporter, NET-norepinephrine transporter. Note: All have an increased risk of causing suicidal thoughts.

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Understanding the Pharmacokinetic Interaction Between Alcohol and Long-Acting Opioids

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Abstract

In response to the fatal interaction of alcohol with extended-release hydromorphone, the U.S. Food and Drug Administration (FDA) approved a class-wide Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER) and long-acting (LA) opioid analgesics in July 2012. Due to the rising concern of dose-dumping effects, it is important for pharmacists to understand the pharmacokinetic interaction between two of the most commonly prescribed LA opioids (oxycodone and morphine) and alcohol. Clinical trials have looked at the pharmacokinetic profile of these long-acting formulations in conjunction with alcohol, and the results have varied depending on the formulation. For this reason, it is important to know which LA opioids have a serious interaction with alcohol so as to better serve the patient.

Introduction

Pharmacists, in evaluating a patient's response to drug therapy, recognize drug interactions as a cause of toxicity or inefficacy. As most drug interactions are based on pharmacokinetics (PK) or pharmacodynamics (PD), it is important to understand and apply these relationships to daily practice. One such drug relationship exists between alcohol and opioids. Though there have been many studies showing the pharacodynamic relationship between alcohol and opioids, few have examined the pharmacokinetic interactions.[1] With the approval of the REMS for ER and LA opioids, now is a critical time for pharmacists to understand the pharmacokinetics of alcohol and opioids and the harm associated with their concomitant use.[2] These interactions stem from the overlap in metabolism of alcohol and opioids and the altered pharmacokinetics, as is seen in patients with cirrhosis. With an understanding of the pharmacokinetics of individual substances, the interaction can further be examined. Studies of the pharmacokinetics of ER and LA morphine and oxycodone, two of the most commonly used opioids, have been performed.[1,3,4] These studies identified the importance of examining the pharmacokinetics of the drug and determining the influence of various formulations on concentration-time relationships, all in the context of a patient's response to a given dosage form. Once all of these factors have been examined, pharmacists will have the information necessary to educate and monitor their patients.

The Alarm and the FDA Response

According to the 2007 National Survey on Drug Use and Health, one-half of Americans 12 years of age and older report alcohol use.[1] Opioids are also widely used by Americans. While only constituting 4.6 percent of the world's population, Americans consume nearly 80 percent of the world's opioid supply.[5] When each of these substances are used responsibly and correctly, there are few concerns regarding drug interactions and patient safety. The true concern surfaces when these substances are used concomitantly—whether intentionally or not. After a study performed on ER hydromorphone (Palladone®) showed a potentially fatal interaction with alcohol, the FDA requested its removal from the market in 2005.[3,6] While actions, such as black box warnings (BBW) seen in Table 1, have been provided to inform health care providers of the potential toxicity due to the pharmacokinetic interaction between alcohol and opioids, the FDA has only recently approved a more active approach to the issue.[1,2] In July of 2012, the FDA approved its first class-wide REMS for ER and LA opioid analgesics. Introduced in March of 2013, the current REMS features pharmacists as one of the key contributors who will work with both prescribers and patients to ensure correct use of these ER and LA opioids.[2] The platform of patient education regarding the effects of these ER and LA opioids with concomitant use of alcohol is an important one for pharmacists and should not be overlooked. As the number of different ER and LA formulations of opioid analgesics increases, and as altered liver function is recognized in relation to drug metabolism, keeping current with pharmacokinetic research for this issue is imperative for patient care. With a proper understanding of how alcohol affects the pharmacokinetics of a patient's ER or LA opioid analgesic, the pharmacist may better help patients avoid dangerous adverse events and achieve the desired therapeutic outcome.

Alcohol and the Liver

In order to appreciate the interaction between alcohol and LA and ER opioids, the hepatic metabolism of alcohol must be considered. Alcohol's metabolism involves many steps and multiple enzymes. In the main pathway, alcohol is oxidized by alcohol dehydrogenase (ADH) to acetaldehyde, and then further oxidized to acetate by aldehyde dehydrogenase (ALDH) (Figure 1).[7,8] Acetaldehyde can bind to proteins and form adducts. These adducts can impair protein secretion and cause hepatomegaly.[9] The major metabolic point where alcohol and opioids interact is through cytochrome P-450 (CYP) enzymes. In the liver, CYP2E1, 1A2, and 3A4 all contribute to alcohol oxidation.[9] CYP2E1 metabolism in the brain also oxidizes alcohol. The excess oxidation by CYP enzymes in the liver increases the oxygen consumption in the liver. This can cause some areas of the liver to become hypoxic. The metabolism also causes the formation of reactive oxygen species (ROS) in the liver. This oxidative stress along with the hypoxia can cause acute liver damage and hepatitis or cirrhosis with chronic use of alcohol.[9,10]

Table 1. Long-acting Opioid Products and black box warning (BBW) for Alcohol.[14-26]

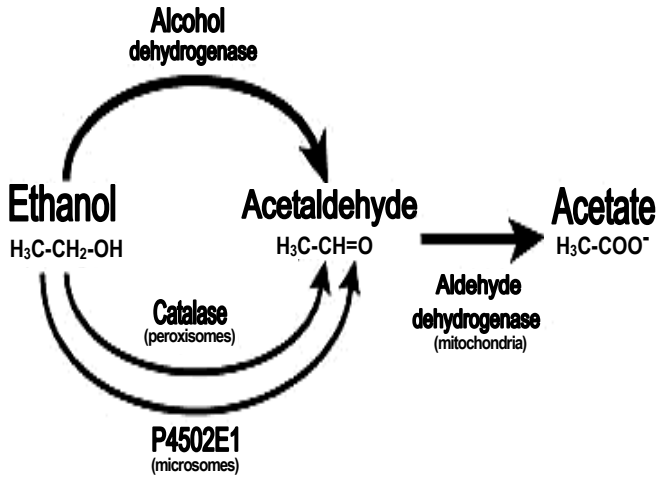
Trade Name	Generic Name	Sponsor	BBW for Alcohol: Yes/No
Avinza	Morphine sulfate extended-release capsules	Pfizer	Yes
Butrans	Buprenorphine transdermal system	Purdue Pharma	No
Dolophine	Methadone hydrochloride tablets	Roxane	No
Duragesic	Fentanyl transdermal system	Janssen Pharmaceuticals	No
**Embeda	Morphine sulfate and naltrexone extended-release capsules	Pfizer	Yes
Exalgo	Hydromorphone hydrochloride extended-release tablets	Mallinckrodt	No
Kadian	Morphine sulfate extended-release capsules	Actavis	No
MS Contin	Morphine sulfate controlled-release tablets	Purdue Pharma	No
Nucynta ER	Tapentadol extended-release oral tablets	Janssen Pharmaceuticals	Yes
Opana ER	Oxymorphone hydrochloride extended-release tablets	Endo Pharmaceuticals	Yes
OxyContin	Oxycodone hydrochloride controlled-release tablets	Purdue Pharma	No
*Palladone	Hydromorphone hydrochloride extended-release capsules	Purdue Pharma	Yes

**No longer being marketed, but is still approved.*
***Not currently available due to a voluntary recall, but is still approved.*

With progression of liver disease, the composition of the body changes, thereby changing the volume of distribution (Vd). Liver disease can also cause metabolic changes. Liver failure with cirrhosis also alters the metabolic enzymes of the liver. More significantly, liver disease affects phase I enzymes, involved in oxidation-reduction reactions, more than phase II enzymes which are involved in conjugation reactions.[10] The phase I enzymes, including CYP enzymes, are more sensitive to hypoxia, which is prevalent in liver disease.

Hepatic metabolism is the primary elimination route for lipophilic drugs. Hepatic clearance is dependent upon hepatic blood flow, plasma protein binding, and intrinsic clearance. The hepatic extraction ratio (Eh) of the drug determines which factors influence clearance most significantly. Clearance of high extraction drugs with an Eh>0.7 are mainly dependent upon liver blood flow whereas low extraction compounds with Eh<0.3 are mainly dependent upon plasma protein binding and intrinsic metabolic clearance.[10] In healthy patients, and in those with mild cirrhosis, morphine is a high extraction compound with an Eh of approximately 0.7, meaning hepatic blood flow will be the main contributor to morphine's clearance. Therefore, when considering patients with chronic liver disease, morphine clearance is not significantly altered until severe cirrhosis has developed.[11] In addition to altering hepatic blood flow, liver disease with cirrhosis also impairs production of plasma proteins albumin and a-acid glycoprotein. As a drug "becomes" a low extraction compound, its clearance switches from being dependent on hepatic blood flow to being dependent on intrinsic clearance and fraction of unbound drug. With clearance decreased and volume of distribution increased, the half-life gets longer.

Figure 1. The Main Oxidative Metabolic Pathway of Alcohol.[7]



Alcohol and CR Oxycodone

To further understand the interaction between opioids and alcohol, it is necessary to understand the kinetics of individual opioids. Each drug in the opioid class has its own set of pharmacokinetic parameter values. Two opioids, oxycodone and morphine, have pharmacokinetics profiles that have been examined extensively.

Controlled-release (CR) oxycodone has become one of the most commonly used CR opioids in the United States, making it crucial to understand its kinetic interaction with alcohol.[12] CR oxycodone is absorbed in a bi-exponential fashion. The initial rapid phase has an absorption half-life of 37 minutes. During this time, 38 percent of the drug is absorbed. The rapid phase is then followed by a slow phase with an absorption half-life of 6.2 hours and duration of action of 12 hours.[12,13] CR oxycodone bioavailability is 60 to 87 percent, and it undergoes first-pass metabolism. Ten percent is metabolized through O-demethylation by CYP2D6 to the minor metabolite, oxymorphone, which is 14 times as potent as oxycodone. Then, N-demethylation produces noroxycodone, a weak analgesic that is the major metabolite of CR oxycodone.[12] Because protein binding is relatively low, hepatic cirrhosis and decreased plasma protein production will not greatly affect Vd.

Recognizing the metabolism of both alcohol and CR oxycodone, one would conclude the interaction could be predicted. Results of recent clinical trials, however, have proven otherwise. For example, Friedmann et al.[4] looked at the new REMOXY (oxycodone) capsule. REMOXY is formulated to have an increased viscosity to prevent crushing and decrease "dose-dumping." As the capsule cannot be crushed, it cannot be dissolved in alcohol to induce a euphoric high from quick dissolution. The study found that there were no significant changes in the pharmacokinetics of the formulation when taken with 4 percent, 20 percent, or 40 percent alcohol acutely. The researchers concluded that, while still not recommended, concomitant use of alcohol and this new controlled-release formulation is safer compared to current formulations of CR oxycodone. This study exemplifies the need to consider a medication's formulation when examining clinically important pharmacokinetics parameters.

Alcohol and ER morphine

In addition to CR oxycodone, ER morphine has been undergoing pharmacokinetic testing to examine its effects when used with alcohol. Similar to CR oxycodone, ER morphine is formulated to have an immediate release component upon contact with GI fluids, followed by a sustained-release component that generally lasts 12 to 24 hours.[3] The bioavailability of oral morphine can increase from 40 percent to 100 percent in patients with severe cirrhosis.[10,11] Furthermore, while CR oxycodone is metabolized by CYP450 enzymes, ER morphine is glucuronidated in the liver to two metabolites, morphine-3-glucuronide (M3G) and to a lesser extent, morphine-6-glucuronide (M6G)

Studies have been performed to evaluate the effects of alcohol combined with ER morphine and its pharmacokinetic profile. When alcohol is used acutely and in reasonable amounts with ER morphine, there is minor concern of increased opioid exposure. One product (Embeda) is a morphine sulfate ER capsule, which possesses a polymer around the beads in the capsule to achieve extended release characteristics. When ingesting 240 mL of 20 percent alcohol (similar to approximately 12 ounces of wine, a pint of beer, or 2.5 glasses of a mixed drink) the rate of absorption and the extent of exposure for morphine did not increase in patients. A change in pharmacokinetics was seen, however, upon concomitant use of morphine extended-release and 240 mL of 40 percent alcohol. This amount of alcohol is equivalent to five 1.5-ounce shots of hard liquor. Although there was no change in bioavailability for morphine, the average maximum concentration (C_{max}) was doubled and the median time to maximum concentration (T_{max}) was decreased from nine hours to four hours. Although this kinetic profile may seem alarming, cumulative morphine exposure while taking Embeda is not similar to that of an immediate-release morphine solution combined with alcohol. This suggests that "dose dumping" is not particularly of concern when mixing Embeda and acute alcohol use.[1] However Embeda still has a BBW for alcohol use. Clinically, all interactions must be taken into account, including pharmacokinetics and pharmacodynamics.

The effect of alcohol on the pharmacokinetics of another ER morphine product, Kadian, has also been studied. Subjects in the experimental groups were either given 100 mg ER morphine with 240 mL of 40 percent alcohol under fasting conditions or ingestion of a high-fat meal. The control received 100 mg of ER-morphine and 240 mL of water under fasting conditions. All three groups had a T_{max} of eight hours, and the area under the curve (AUC) was similar between them as well. Because the mean AUC and C_{max} for each regimen were within 80 percent to 125 percent, no drug interaction was declared. Therefore, no BBW for Kadian and concomitant alcohol consumption currently exists.[3]

The pharmacokinetic interaction of alcohol and opioids is definitely intricate and multifactorial. Influenced by the separate pharmacokinetics of alcohol and opioids, cirrhosis and its effect on hepatic metabolism, and the development of new formulations, the subject can be difficult to understand. Thus it is critical for pharmacists to be aware of these relationships and monitor patients appropriately. Newer CR products like Embeda and Kadian are reducing the risks associated with this pharmacokinetic interaction. The REMS for ER and LA opioids is leading the way by educating pharmacists and physicians of proper prescribing practices. To further advance pharmacist knowledge, continuing education should be offered to pharmacists. With proper prescribing and monitoring, LA and CR opioids can be used effectively in all patients, regardless of their alcohol consumption.

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Novel Oral Anticoagulants: A Comparative Study of the Clinical Potential for Dabigatran, Rivaroxaban, and Apixaban versus Warfarin

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Abstract

Although Coumadin® (warfarin) has been the standard outpatient anticoagulant for long-term prevention of thrombosis for many decades, it presents with significant challenges for both patients and health care providers in optimizing standards of care including dietary and drug restrictions, regular monitoring of the patient's International Normalized Ratio (INR), and difficulty maintaining therapeutic levels. Despite its unmistakable effectiveness, there has been an interest from the medical community in developing potential alternative drug therapies. As a result, within the past three years the U.S. Food and Drug Administration (FDA) has approved the use of three new oral anticoagulant drugs (dabigatran, rivaroxaban, and apixaban) specifically targeting thrombin or factor Xa that have overcome many of the barriers seen in warfarin therapy. The use of these new oral anticoagulants is of particular interest in patients who have failed warfarin therapy or for whom warfarin therapy is contraindicated, in situations when monitoring is not feasible or interactions are problematic, or if patient INR control is poor. All of these novel agents are currently approved for prevention of thrombosis in patients with nonvalvular atrial fibrillation, and with ongoing clinical research these agents may present health care providers with additional therapeutic options in a greater variety of disease states. For the comparative purposes of this article, we have combined all of the recent clinical evidence and major landmark trials for each of these new agents as well as benefits and drawbacks of therapy in specific patient populations when compared to warfarin.

Introduction

Warfarin, a vitamin K reductase antagonist (VKA), has been the standard outpatient anticoagulation medication for decades. Indications for use include: prophylaxis and treatment of embolism development, prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement, and reduction in thromboembolic events such as stroke or systemic embolization after a myocardial infarction (MI). While numerous injectable forms have entered the market over the years, only recently have new oral agents become available.[1] Warfarin has several drawbacks that establish a need for these new anticoagulants. Due to warfarin's mechanism of action interfering with bio-synthesis of vitamin K dependent clotting factors, it takes several days to reach effective levels of anticoagulation. For this same reason, the effects of warfarin take days to wear off. Warfarin therapy also requires constant monitoring of INR to be sure the patient has the correct level of anticoagulation. Vitamin K is the antidote to warfarin's action and is present in many beverages and food products, creating many potentially significant dietary interactions. Drug-drug interactions are very common with warfarin therapy as well.

In certain patient populations there is an obvious need for these new anticoagulants and the goal of this article is to bring forth information from current research to see where these new medications will fall into place in regard to anticoagulation therapy. Along with the American Heart Association (AHA)/American Stroke Association (ASA) recommendations made for a new approach to anticoagulation therapy, there is a greater emphasis on the pharmacist's role in drug recommendation to maximize the benefits of patient care while simultaneously minimizing the potential for adverse events. Therefore, continuing education, especially concerning updates to current guidelines with regard to the most recent additions for stroke prevention, is essential in order for pharmacists to make decisions based not only on effective treatment strategies, but also on cost analysis and individual patient variations. In this article, three of the new oral anticoagulation medications will be compared to warfarin in regard to efficacy, safety, cost and monitoring.

Dabigatran (Pradaxa®)

Dabigatran (Pradaxa®) is a direct thrombin inhibitor with an FDA-approved indication for the reduction in risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The clinical effects of dabigatran can be seen within a few hours, whereas warfarin takes up to two to three days to reach full effect. Atrial fibrillation is an increasingly common arrhythmia with an incidence of greater than 2.3 million people in the United States and greater than 4.5 million people in Western Europe. It is a sign of underlying heart disease and poses a significant threat, primarily in the form of stroke. Stroke associated with atrial fibrillation is generally ischemic due to clot embolization originating in the left atria and is 4.5 times more likely in this patient population.[2] In the RE-LY trial, over 18,000 patients with atrial fibrillation from 967 centers and 44 countries were randomized to warfarin, dabigatran 150 mg twice daily, or dabigatran 110 mg twice daily.[2] The primary endpoint of the study was reduction in stroke or systemic embolism, and patients were treated for an average of two years. Patients included in the study experienced atrial fibrillation and were at risk for cardiovascular or thromboembolic events. The average age of the study population was 72, mean CHADs score of 2.1, history of myocardial infarction (17 percent), heart failure (32 percent) and

stroke (20 percent); half of the patients had no previous exposure to warfarin treatment. Regarding the primary endpoint, 198 patients in the warfarin group had a stroke or systemic embolism. The 150 mg dabigatran group had 133 patients experience a stroke or systemic embolism. The 110 mg dabigatran group had 182 patients experience stroke or systemic embolism. These results were analyzed and the conclusions were made that dabigatran 110 mg twice daily is noninferior to warfarin therapy (P<0.001), and that dabigatran 150 mg twice daily is noninferior to warfarin therapy (P<0.001). Compared with warfarin, major bleeds were less for dabigatran 110 mg twice daily (2.74, P=0.002), but similar for 150 mg twice daily (3.22, P=0.32). A potential limitation to the study was that patients and investigators were not blinded to which medication was being given. They were, however, blind to the dose of dabigatran given. In a sub-group analysis of the RE-LY study, dabigatran was compared to warfarin in patients with atrial fibrillation who had previously experienced a transient ischemic attack (TIA) or stroke.[3] A total of 3,623 patients from the original RE-LY study had previously had a TIA or stroke and were included in the analysis. The breakdown by group was: 1,195 patients from the 110 mg dabigatran twice daily group, 1,233 from the dabigatran 150 mg twice daily group, and 1,195 from the warfarin group. In these sub-groups, stroke or systemic embolism occurred in 65 of the warfarin patients, 55 of the dabigatran 110 mg patients, and 51 of the dabigatran 150 mg patients. The results from this sub-group analysis were consistent with the original RE-LY study in that 110 mg dabigatran twice daily was noninferior to warfarin therapy and that 150 mg dabigatran twice daily was also superior to warfarin therapy in preventing stroke and systemic embolism. The rates of major bleeds were also consistent with the original RE-LY study. One other study showing the same results was conducted using the RE-LY study's original data to compare two subpopulations: patients who were naïve to warfarin or other vitamin K reductase antagonists (VKA) and patients who were VKA-experienced.[4] The VKA naïve group represented 50.4 percent of the patients in the original warfarin group. Stroke and systemic embolism rates were similar in the dabigatran 110 mg and both VKA-naïve and VKA-experienced cohorts (P=0.65; P for interaction=0.72). The dabigatran 150 mg group had significantly lower risk of stroke and embolism in both the VKA-naïve and the VKA-experienced group (P=0.005, P=0.007, respectively; P for interaction=0.84). The authors of the study concluded both doses of dabigatran produced beneficial effects regardless of previous VKA exposure. Based on clinical trials, the standard 150 mg twice daily dose is superior to warfarin therapy in attempt to prevent stroke and embolism in patients with atrial fibrillation. Also, the standard dose, 150 mg twice daily, of dabigatran carries a very similar risk for causing a bleed when compared to warfarin treatment. Only the 150 mg strength received FDA approval for use.

Cost is also a major aspect of comparing medications used to treat the same disease state. A decision-analysis model was developed to compare multiple anticoagulation therapies. This cost-effective study utilized data from multiple trials, including the RE-LY trial, and analyzed cost and quality-adjusted survival.[5] Results were broken up into high, medium, and low risk for atrial fibrillation patients to develop a stroke or embolism. Dabigatran 150 mg twice daily was the most cost-effective in individuals that were at high risk of hemorrhage or stroke unless the INR was well-controlled on warfarin. Warfarin was cost-effective in moderate risk patients unless INR control was poor. Aspirin monotherapy was cost-effective for low risk patients.

Finally, there are notable advantages and disadvantages of dabigatran treatment compared to warfarin. Advantages include a wider therapeutic window, fewer food and drug interactions than warfarin and frequent monitoring is not necessary for dabigatran use.[6] Possible disadvantages include the lack of an antidote for dabigatran, compliance issues due to twice daily dosing, more strict storage requirements, and dabigatran dose may need to be lowered or discontinued due to low renal function. Proper storage of dabigatran requires the patient leave the capsules in the original bottle, immediately close the bottle after a capsule was taken out, and to discard any capsules that have not been taken in four months. Hemodialysis is a possible option for the reversal of dabigatran effects but has only shown to remove up to 60 percent of the drug from the blood stream in two to three hours. Overall, dabigatran is just as effective as warfarin and has shown to have less severe adverse effects. It can be considered first-line anticoagulation therapy in atrial fibrillation patients that have adequate compliance and proper renal function.[7]

Rivaroxaban (Xarelto®)

Rivaroxaban (Xarelto®) is an orally active, direct competitive inhibitor of Factor Xa in the coagulation cascade. The major role of active Factor X is the generation of thrombin via proteolysis of prothrombin precursors, thereby providing the final common link of the intrinsic and extrinsic clotting pathways. Factor Xa can additionally amplify the production of thrombin molecules through its role in the prothrombinase complex that consists of Factor Xa, Factor V, free calcium (Ca^{2+}), and various phospholipids. Factor Xa inhibitors can more efficiently prevent clots than directly inactivating free thrombin molecules because it is calculated that one molecule of Factor Xa is capable of generating approximately 138 molecules of thrombin.[8]

Available in three different strengths: 10 mg, 15 mg and 20 mg tablets, rivaroxaban is renally and hepatically cleared with high oral bioavailability. This novel anticoagulant has numerous benefits over traditional therapies like warfarin, such as lack of routine monitoring, less food and drug interactions and more predictable pharmacokinetics. Since rivaroxaban allows for fixed doses, it has the potential to increase patient adherence due to simpler medication regimens. Rivaroxaban has a quick onset of action with its full anticoagulant effects occurring two to four hours after administration versus warfarin's two to three days. As a result, rivaroxaban does not require bridging therapy pre and post-surgery and should be discontinued at least 24 hours before a procedure.

Rivaroxaban also has a shorter terminal half-life of five to nine hours compared to warfarin's terminal half-life of approximately 40 hours.[9, 10] Thus, warfarin's anticoagulant effects can last much longer, and overdose can lead to prolonged bleeding events such as intracranial or gastrointestinal hemorrhaging. Unlike warfarin, there is currently no antidote available for rivaroxaban. Consequently, in emergency cases of severe bleeding or required surgery, there is no way to immediately reverse its effects. Since rivaroxaban is a relatively new drug, there is little data and limited studies available on counteracting its effects. One such study done in 2011 suggested the use of prothrombin complex concentrate (PCC) to overcome the anticoagulation effects of rivaroxaban. PCC contains high amounts of blood coagulation factors II, VII, IX, and X and promotes the generation of thrombin used in clot formation. The randomized, double-blinded, placebo-controlled crossover study performed in 12 healthy volunteers compared rivaroxaban 20 mg twice daily and dabigatran 150 mg twice daily. Rivaroxaban significantly prolonged prothrombin time (PT) (15.81.3 versus 12.30.7 seconds at baseline; P<0.001), which was rapidly reversed by the infusion of 50 units/kg of PCC on day 3 (PT=12.81.0; P<0.001) versus an equal volume of saline placebo, which had no effect on the prolonged PT. For dabigatran there was no significant difference between placebo and PCC administration in neutralizing a prolonged thrombin time (TT).[11]

As an alternative to warfarin, rivaroxaban was FDA approved in 2011 for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[9] The ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) was a randomized, double-blinded, multinational trial that compared fixed-dose rivaroxaban to dose-adjusted warfarin in prevention of stroke or systemic embolism. The study randomized 14,264 patients to receive 15 or 20 mg rivaroxaban daily with a meal or warfarin (titrated to INR 2.0-3.0). Inclusion criteria included moderate-to-high-risk of stroke (mean $CHADS_2$ risk score=3.3) and nonvalvular atrial fibrillation. The primary endpoint was time to first stroke or embolism, which occurred in 188 patients in the rivaroxaban group (1.7 percent) and 241 in the warfarin group (2.2 percent). Hazard ratio was 0.79 for the rivaroxaban group, 95 percent confidence interval (CI) 0.66-0.96, and p<0.001 for noninferiority. The study also concluded that there was no significant difference between the rivaroxaban and warfarin groups for risk of major or minor bleeding events; however, the rivaroxaban group had lower rates of intracranial hemorrhage (0.5 percent versus 0.7 percent). ROCKET-AF proved that rivaroxaban was safe, efficacious, and noninferior to warfarin for stroke and embolism prevention.[12] A limitation of ROCKET AF was that patients on warfarin were in the therapeutic INR range only 55 percent of the time. One study done by Melamed et al. defined poor anticoagulation control as time in therapeutic range (TTR)<60 percent, good control between 60 percent and 70 percent, and excellent anticoagulation control>75 percent.[14] Another study done by Morgan et al. found that when warfarin TTR>70 percent there were the greatest benefits in stroke prevention.[15] Therefore, poor anticoagulation control with warfarin may not be a good comparator for all clinical situations. This inadequate warfarin control may not be necessarily due to poor study design, but instead due to complications of managing warfarin itself, such as diet influences and drug interactions. Even within the guidelines of a well-designed study, INR ratios still fall outside of the therapeutic range one-third of the time.[16] Warfarin has been proven successful as an anticoagulant, however poor quality of anticoagulation control in clinical practice may limit its effectiveness.[17]

Since there have been limited studies comparing anticoagulation control of rivaroxaban versus dose-adjusted warfarin, it is difficult to say which offers more efficacious anticoagulation effects. Rivaroxaban is not considered first-line therapy for stroke prevention in atrial fibrillation patients and should only be taken into consideration as an alternative treatment choice for those patients contraindicated for or not well-controlled on warfarin. Currently, the guidelines on stroke prevention from the American Heart Association, American College of Cardiology Foundation, and Heart Rhythm Society recommend dabigatran as a second-line alternative to warfarin for patients with moderate-to-high risk of stroke. Therefore, rivaroxaban would be likely considered a third-line or fourth-line choice for anticoagulation and stroke prevention.[13]

Rivaroxaban is also indicated for treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE). The EINSTEIN-DVT trial was a randomized, open-label, noninferiority study examining the safety and efficacy of rivaroxaban compared to traditional therapy for treatment of DVT. The study included 3,449 patients with acute DVT and without PE who were randomized to receive either rivaroxaban 15 mg twice daily for three weeks, followed by 20 mg once daily versus subcutaneous injections of enoxaparin followed by warfarin or acenocoumarol, another VKA, for up to 12 months. The primary outcome was recurrent venous thromboembolism (PE and/or DVT). The primary safety outcome was major or clinically relevant minor bleeding. The primary outcome occurred in 2.1 percent of the rivaroxaban group and 3.0 percent of the standard-therapy group (hazard ratio=0.68; 95 percent CI 0.44-1.04; p<0.001). The EINSTEIN -DVT trial demonstrated that rivaroxaban alone was as safe and effective as standard therapy for treatment of acute, symptomatic DVT. Based on these results, rivaroxaban is indicated for outpatient treatment of DVT compared to standard heparin and VKA therapy.[18]

The EINSTEIN-PE trial was a randomized, open-label, noninferiority trial with 4,832 patients randomized to rivaroxaban or enoxaparin followed by a VKA. This study was similar to the EINSTEIN-DVT trial except inclusion criteria were patients with PE with or without DVT. Primary outcomes and safety were the same. In the rivaroxaban group, the primary outcome of recurrent venous thromboembolism (VTE) was 50 and 44 in the standard-therapy group (2.1 percent versus 1.8 percent). Frequency of minor bleeding events in the rivaroxaban group was observed in 10.1 percent versus 11.4 percent of the patients for the standard therapy group and 1.1 percent to 2.2 percent for major bleeding. This study

demonstrated noninferiority of rivaroxaban for acute and long-term treatment of PE with a better side effect profile.[19]

Rivaroxaban is approved for DVT prophylaxis, which may lead to PE in patients who have undergone knee or hip surgery replacement. The RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) clinical trial program included three studies, RECORD 1-3, for patients undergoing orthopedic surgery. The RECORD trials were randomized, double-blinded studies looking at the safety and efficacy of rivaroxaban compared to enoxaparin for prevention of DVT and accompanying PE in patients who have had hip or knee replacement surgery. Depending on the assigned treatment group, patients were also given placebo injections or placebo tablets. Rivaroxaban was given at least six to eight hours after wound closure and enoxaparin was started 12 hours preoperatively and restarted six to eight hours after wound closure.

RECORD 1 (hip)

- Patients randomized to receive:
  - rivaroxaban 10 mg by mouth once daily for 31 to 39 days or
  - enoxaparin 40 mg subcutaneously once daily for 31 to 39 days
- **Primary endpoint:** any combination of DVT, nonfatal PE, and all-cause mortality 30 to 42 days after surgery
- Primary outcomes occurred in 1.1 percent of patients on rivaroxaban versus 3.7 percent of those on enoxaparin (absolute risk reduction 2.6 percent; 95 percent CI 1.5-3.7; p<0.001). Major venous thromboembolism occurred in 0.2 percent of the rivaroxaban group versus 2.0 percent of patients in the enoxaparin group.
- **Conclusion:** Rivaroxaban was proven to be significantly more effective than enoxaparin for thromboprophylaxis in patients undergoing hip surgery.[20]

RECORD 2 (hip)

- Patients randomized to receive:
  - rivaroxaban 10 mg by mouth once daily for 31 to 39 days (long term) or
  - enoxaparin 40 mg subcutaneously once daily for 10 to 14 days (short term)
- **Primary endpoint:** any combination of DVT, nonfatal PE, and all-cause mortality 30 to 42 days after surgery
- Analyses done in the modified intention-to-treat population: 864 patients randomized to the rivaroxaban group and 869 to the enoxaparin group.
  - Primary outcome of total VTE (proximal and/or distal VTE, nonfatal PE, and death from any cause) was 2.0 percent for rivaroxaban and 9.3 percent for enoxaparin (absolute risk reduction 7.3 percent, 95 percent CI 5.2–9.4; p<0.0001). Bleeding events were similar for both groups (6.6 percent for rivaroxaban versus 5.5 percent for enoxaparin; p=0.25).
  - **Conclusion:** Extended anticoagulation (31 to 39 days) with rivaroxaban was significantly more successful than short term (10 to 14 days) enoxaparin for prevention of venous thromboembolism in patients undergoing hip surgery.[21]

RECORD 3 (knee)

- Patients randomized to receive:
  - rivaroxaban 10 mg by mouth once daily for 10 to 14 days or
  - enoxaparin 40 mg subcutaneously once daily for 10 to 14 days
- **Primary endpoint:** DVT, nonfatal PE, and or death from any cause 13 to 17 days after surgery
- Primary outcomes observed in 79 of 824 (9.6 percent) patients on rivaroxaban and 166 of 878 (18.9 percent) patients on enoxaparin (absolute risk reduction 9.2 percent; 95 percent CI 5.9-12.4; p<0.001).
- **Conclusion:** Patients undergoing knee arthroplasty showed 10 mg rivaroxaban was superior to 40 mg enoxaparin subcutaneously once daily for thromboprophylaxis.[22]

Currently, rivaroxaban is not recommended as a first-line agent for any health condition and is contraindicated in patients with poor renal function (CrCl<15 mL/min for atrial fibrillation and CrCl<30 mL/min for all other indications) or moderate to severe hepatic impairment (Child-Pugh class B or C).[9] However, among the new novel anticoagulants, such as dabigatran and apixaban, rivaroxaban is the only medication FDA approved for prevention of VTE in post-orthopedic surgery patients. Compared to warfarin, rivaroxaban offers many benefits, such as lack of monitoring due to low patient intervariability, less food and drug interactions, and lower risk of intracranial hemorrhage. Rivaroxaban shows promise as a new anticoagulant; however, further studies and use in clinical practice is needed to fully understand its place among older and more traditional anticoagulation therapies.

Apixaban (Eliquis®)

Apixaban (Eliquis®), another direct Factor Xa inhibitor, provides an attractive alternative therapy for patients at high risk of developing clots compared to warfarin in addition to those who are unable or otherwise unwilling to undergo treatment with a VKA.[23] Although only recently approved for use in the United States by the FDA in December of 2012, apixaban has shown great promise in several large, clinical studies that demonstrate its effectiveness as well as safety compared to more traditional anticoagulant therapies such as warfarin and aspirin.

Apixaban is an orally active compound that is available in 2.5 mg and 5 mg tablets with dosing up to 5 mg twice daily. Metabolism of apixaban is primarily achieved through CytochromeP450 3A4 (CYP3A4) activity along with minor contributions from pathways utilizing CYP1A2, CYP2C8, CYP2C9, and CYP2C19 in addition to being a substrate for

P-glycoprotein (PGP). The dose of apixaban should be reduced to 2.5 mg twice daily when concomitantly administered with drugs that are strong inhibitors of CYP3A4 and PGP such as ketoconazole, clarithromycin, ritonavir or strong inducers such as carbamazepine, rifampin, or phenytoin due to increased risk of bleeding or stroke, respectively.[24, 25] Administration of these drugs should be avoided if the patient is already receiving the reduced dose of apixaban.

Clinical studies have shown that in patients with mild to moderate hepatic impairment there is no noticeable change in anti-Factor Xa activity. While there have been no studies to date detailing the effects of apixaban in patients with severe hepatic impairment, there is no data providing an understanding of how this level of damage alters its anticoagulant activity. Therefore, since biotransformation that renders apixaban inactive occurs in the liver, this drug is contraindicated in patients that have severe hepatic impairment. Unaltered apixaban is the major component of drug concentrations found in the plasma and there are no active metabolites. Apixaban exhibits both renal and fecal elimination with 27 percent of the drug clearance achieved through urine and 50 percent by gastrointestinal or biliary excretion. No dosing adjustments are necessary for geriatric patients or those with any level of renal impairment.

At therapeutic doses, apixaban displays linear pharmacokinetics with a dose-dependent relationship. The oral bioavailability in doses of up to 10 mg is approximately 50 percent with maximum concentrations being achieved within three to four hours. Direct intravenous administrations of apixaban display a half-life of five hours. When taken orally, apixaban has prolonged absorption throughout the gastrointestinal tract, especially within the distal portions of the small intestines and ascending colon, which contributes to an approximate half-life of twelve hours.[24, 25] This characteristic allows for twice daily dosing in order to achieve optimal anticoagulant effects in most patients.

Currently, apixaban is only approved for reducing the risk of strokes or systolic emboli in patients with nonvalvular atrial fibrillation. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial that was conducted from 2006 to 2010 assessed the stroke risk of apixaban compared to warfarin in patients diagnosed with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. As a double-blind, double-dummy, randomized trial enrolling 18,201 patients with atrial fibrillation from 39 countries, ARISTOTLE randomly assigned patients to receive either apixaban 5 mg twice daily or warfarin with a targeted INR value of 2.5 (goal range of 2.0 to 3.0 with 62 percent of time spent in therapeutic range) while comparing the primary outcome of stroke and systolic embolism versus the primary safety outcome of major bleeding.[26] Event rates for primary outcomes were defined as the number of patients who experienced the event divided by the sum of days to the first event across all patients. Safety and efficacy of the experimental group was evaluated through $CHADS_2$ (1, 2, ≥ 3), CHA_2DS_2VASc (1, 2, ≥ 3), and HAS-BLED scores (0-1, 2, ≥ 3), which are typically employed to determine a patient's risk score and assess the likelihood they will experience a major bleeding event.[27] At the point of randomization, patients within each treatment group were equally stratified across all risk levels.

Results of this trial displayed overall noninferiority and superiority of apixaban compared to warfarin in regards to both prevention of primary outcomes (1.27 percent versus 1.6 percent, CI: 0.66-0.95, p= 0.0114) as well as the primary safety outcome of major bleeding (2.13 percent versus 3.09 percent, CI: 0.6-0.8, p <0.0001).[26] Additionally, fewer patients receiving apixaban discontinued treatment compared to those receiving warfarin across all $CHADS_2$ scores, especially in patients with a reported $CHADS_2$ score of three or higher who are considered high risk patients (p for interaction= 0.02), although this was not the case with CHA_2DS_2VASc and HAS-BLED scores.

Although the ARISTOTLE trial was very well-crafted, there was some discrimination in the ability of the $CHADS_2$ score to accurately predict stroke risk, especially in lower risk patients, even though it is the most commonly used method for assessing a patient's risk level. High $CHADS_2$ scores are directly correlated to high HAS-BLED scores and patients were more likely to experience major bleeding events while on oral anticoagulants. It is hypothesized that this association between bleeding risk and high scores may explain the warfarin treatment paradox (i.e. patients at high risk of stroke are less likely to receive anticoagulation therapy due to a higher risk of bleeding). Since the results of apixaban were generally more beneficial than those seen with warfarin across all patient risk groups, the scores could possibly be less effective for tailoring individual patient treatment for those receiving apixaban. Overall, the authors postulate that additional studies are necessary to determine the optimal method of assessing bleeding risk for atrial fibrillation patients who are receiving anticoagulation therapy.[26]

A previously published trial, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES), determined the efficacy of apixaban versus aspirin with or without clopidogrel, which are the two most effective treatment options for atrial fibrillation patients incapable of receiving warfarin therapy. This randomized, double-blind, double-dummy trial recruited 5,600 patients stratified equally to receive either apixaban 5 mg twice daily or aspirin 81 to 324 mg daily in a 1:1 ratio in order to achieve 90 percent power. The trial's primary outcomes and primary safety outcomes are identical to those of the ARISTOTLE trial and were conducted to finish once 226 patients experienced a stroke or systemic emboli.[28] Primary outcomes were monitored using a modified Haybittle-Peto boundary to four standard deviations (SD) once the relative risk (RR) crosses the critical value the first time and three SDs for the second time. If the RR crosses the critical value three times, the safety board may recommend discontinuing the study due to the obvious superiority of apixaban over aspirin.

Table 1. Summary table for comparison of major pharmacology points for dabigatran, rivaroxaban, & apixaban.

Drug	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)
Mechanism of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Prodrug	Yes	No	No
FDA approved dose(s)	150 mg BID	10 mg QD 15 mg BID 20 mg QD	5 mg BID
FDA approved indication(s)	Nonvalvular atrial fibrillation	Nonvalvular A-fib DVT prophylaxis after hip/ knee replacement Treatment of DVT Treatment of PE	Nonvalvular atrial fibrillation
Possible reversal agents	Hemodialysis*	Prothrombin concentrate complex (PCC)*	Prothrombin concentrate complex (PCC)*
Dose adjustments	CrCl 15-30 mL/min-75 mg BID Contraindicated when CrCl<15 mL/min	CrCl 15-50 mL/min-15 mg QD (atrial fibrillation) Contraindicated when CrCl <15 mL/min (atrial fibrillation) Contraindicated when CrCl < 30 mL/min (all indications except A-fib)	2.5 mg BID with 2 or more of the following: age > 80 years, weight <60 kg, sCr > 1.5 mg/dL
Drug interactions	PGP inhibitors or inducers, PPIs	CYP3A4 substrates, PGP inhibitors or inducers	CYP3A4 substrates, PGP inhibitors or inducers
2012 AHA Guideline recommendations [32] Note: Warfarin is Class IA.	Class IB	Class IIa B	N/A

**Not a true reversal agent*

The AVERROES trial was concluded before the projected 226 incidences of strokes/systemic emboli due to achievement of the above-mentioned requirements for superiority of apixaban over aspirin in prevention of primary outcomes (1.6 percent versus 3.7 percent, CI 0.32-0.62, relative risk reduction (RRR)= 57 percent). However, similar incidence of major bleeding was experienced between both treatment groups (1.4 percent versus 1.2 percent, CI 0.74-1.75). [28]

Apixaban is not considered first-line treatment for stroke prevention, but rather as a potential alternative to traditional VKA therapy once more clinical evidence for its use becomes available. Currently, the AHA and the ASA make no recommendations toward apixaban's use over warfarin.

Conclusion

As of 2012, both the AHA and the ASA have updated guidelines to include dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) in treatment algorithms for primary and secondary prevention of stroke with specific agent selection based on level of evidence, risk factors, costs, drug interaction potential, clinical characteristics (e.g. INR) and personal preference.[30, 31] Recommendations for apixaban (Eliquis®) are included below, although they have not been formally endorsed by the AHA/ASA guidelines.

With the conclusion of a considerable number of landmark trials detailing the numerous benefits as well as drawbacks of three recent additions to the previously singular list of oral anticoagulants available on the market, health care providers have begun to see potential alternatives in therapeutic management for nonvalvular atrial fibrillation patients requiring long-term stroke prevention. As more evidence becomes available, these drugs may receive additional therapeutic indications, thereby broadening their use in contemporary medicine.

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Ado-trastuzumab emtansine for HER2 Positive Breast Cancer

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Introduction to Breast Cancer

Breast cancer is the leading cause of cancer related death in women between the ages of 20 and 59 in the United States.[1] In women of all ages, breast cancer is the most frequently diagnosed cancer and second only to lung cancer with regard to cancer related deaths.[2] Women have a 12.3 percent lifetime risk of being diagnosed with breast cancer,[3] and in 2012, there were 232,340 new cases and 39,620 deaths due to breast cancer.[2] The five year survival rate for localized breast cancer is 98 percent; however, as nearby lymph nodes and distant lymph nodes with organs become involved, the survival rate drops to 84 percent and 24 percent respectively.[2] The incidence of breast cancer varies across racial groups with Caucasians having the highest incidence. This is thought to be due to lifestyle, reproductive factors and increased access to screening.[1] Despite this fact, African Americans have the highest rate of mortality, which could be attributed to more advanced stages at diagnosis and possibly more aggressive biologic features.[1] Breast cancer is staged based on three factors: the size of the primary tumor, presence/extent of lymph node involvement, and presence/extent of metastases. The larger the tumor, the more lymph node involvement and a greater extent of metastases all lead to a more advanced stage of cancer.[1] However, there are several other factors affecting the final prognosis.

Poor prognostic factors include the patient being less than 35 years old at the time of diagnosis (because there is an increased likelihood of the breast cancer being more aggressive) and alcohol use, especially in patients who are postmenopausal or obese. Factors which may lead to a better prognosis include the patient following a low fat diet, exercising at least moderately on a regular basis, and maintaining a healthy weight. Every woman diagnosed with breast cancer is tested to see if she has hormone (estrogen and progestin) receptor positive cancer. While this is not a strong prognostic factor, it does predict response to hormone therapy.[1] Likewise, it is important to test for human epidermal growth factor receptor 2 (HER2) gene status; this gene encodes a transmembrane tyrosine growth factor receptor, and is expressed at low levels in the epithelial cells of normal breast tissue. The HER2 receptor is expressed on the cell surface and when activated signals the cell to grow and divide more rapidly. In 20 to 30 percent of breast cancers, this gene is overexpressed and is generally associated with a poorer prognosis. Presence of the HER2 gene indicates the cancer has the potential to respond to trastuzumab therapy.[1] Since HER2 is a poor prognostic factor for a cancer with the potential to be highly fatal if not identified early, it is important to find an effective treatment. While trastuzumab, a recombinant humanized monoclonal antibody that binds to HER2 and inhibits signaling, may improve outcomes in these patients, there are still many patients who fail this therapy. Historically there have been no consistently effective regimens for these patients who have failed trastuzumab therapy.

Traditional Treatments

Though not consistently effective, traditional regimens for HER2 positive breast cancer that does not respond to trastuzumab include combination lapatinib and capecitabine, combination trastuzumab and capecitabine, and combination trastuzumab and lapatinib.[4] Bartsch et al. performed a study regarding combination trastuzumab and capecitabine in patients who had already been treated with several chemotherapy regimens and had failed.[5] This study found the median time to progression was eight months and the median overall survival was 24 months. Overall, the combination was well-tolerated with the most common toxicities being diarrhea and hand-foot syndrome, with seven out of 40 patients in the study requiring a dose reduction of 25 percent. A study conducted by Geyer et al. utilizing lapatinib and capecitabine in combination found the median time to progression was 8.4 months and overall response rate was 22 percent. The most common adverse effects were diarrhea, hand-foot syndrome, nausea, vomiting, fatigue and rash. However, 22 of the women were forced to drop out because they developed intolerable side effects.[6] The combination of lapatinib and trastuzumab showed a median progression free survival of 12 weeks with a median overall survival of 51.6 weeks. Similarly to the other combinations, the most common adverse effects with this combination were diarrhea, rash, nausea, fatigue, vomiting and dyspnea. In addition, one patient died of cardiac failure that was attributed to the treatment, while all other deaths were considered to be independent of treatment.[7] While these therapies are beneficial in many patients, there are still many patients for whom the treatments have failed. The limitations of these regimens, such as combination therapy and the side effects associated with each agent, create a need for a better treatment option, preferably monotherapy. According to the National Comprehensive Cancer Network (NCCN) breast cancer guidelines, ado-trastuzumab emtansine (T-DM1 or Kadcyla®) has become first-line treatment for HER2 positive breast cancer that does not adequately respond to trastuzumab treatment.[4]

Mechanism of Action and Resistance for Trastuzumab and Lapatinib

Trastuzumab is a monoclonal antibody that binds to the extracellular domain of the HER2, potentially causing internalization and receptor down-regulation.[8,9] The antibody is able to decrease the phosphatidylinositol 3-kinase-phosphatase and tensin homolog (PI3K-PTEN) signaling pathway, thus inhibiting AKT (protein kinase B, PKB) activation and therefore cell proliferation.[10,11] Immune mechanisms induced include antibody-dependent cellular cytotoxicity (ADCC) and HER2 major histocompatability complex class I (MHCI) pres-

entation to cytotoxic T cells. Additionally, the cell cycle is stopped in the G_1 phase by trastuzumab, the first gap of interphase marked by cell growth and protein synthesis in preparation for deoxyribonucleic acid (DNA) synthesis.[12,13] Overall, this results in reduced proliferation and death of HER2 positive tumor cells. Unfortunately, the body has been able to create multiple mechanisms of resistance to render HER2 positive cancer unresponsive to trastuzumab. Some methods of resistance include reduced ADCC, concealment of the trastuzumab epitope on the receptor, expression of a constitutively active, smaller version of the receptor, p95HER2, and most notably, changes in the PI3K-PTEN-AKT pathway.[11,14,15,16]

Lapatinib is another therapy used for treatment of HER2 positive cancer that, although it has a different mechanism of action from trastuzumab, it is affected through the same resistance mechanisms. This suggests patients refractory to trastuzumab likely also become refractory to lapatinib.[17,18] As a tyrosine kinase inhibitor, lapatinib is able to inhibit both epidermal growth factor receptor (EGFR) and HER2 by binding to the kinase and preventing it from phosphorylating second messengers, such as AKT, that are responsible for cellular proliferation.[19]

Resistance to capecitabine currently does not seem to be a problem; however, since it is used in combination with either of the above two medications, resistance to these decreases the efficacy of therapy with capecitabine.[20] Resistance to these therapies, in addition to burden of combination therapy, side effect profiles, and tolerability issues prompted the development of T-DM1.

Novel Mechanism of Action of Ado-trastuzumab emtansine

T-DM1 is an antibody-drug conjugate (ADC) that has been developed as an alternative to traditional HER2 therapies in an attempt to lessen systemic chemotherapy toxicities by transporting cytotoxic molecules specifically into tumor cells.[21] This specific ADC is a human epidermal growth factor receptor inhibitor, trastuzumab, linked to DM1 (derivative of maytansine 1 or N-methyl-N-[3-mercapto-1- oxopropyl]-L-alanine ester of maytanisol), which inhibits microtubule polymerization and induces depolymerization by binding tubulin, the building blocks of microtubules.[21,22] Microtubules play a vital role in cellular structural support and mitosis, where they form the apparatus responsible for alignment and separation of the chromosomes. By inhibiting not only the production, but also inducing the disassembly of microtubules, the integrity of the cell is compromised and it cannot divide, eventually leading to apoptosis. Maytansine is a highly potent plant-derived antibiotic that displays antimitotic activity, but produces systemic toxicities too great to be given as traditional chemotherapy.[23] The ability to use ADCs prompted development of maytansine derivatives, such as DM1, to be delivered directly into cancer cells.[24] While previous attempts at maytansine conjugates were linked using disulfide bonds that were not readily cleaved by intracellular lysosomes and endosomes, trastuzumab is connected to DM1 by a thioester linkage that has incorporated a cyclohexane carboxylate spacer.[21] Following HER2 receptor binding to the antibody trastuzumab and internalization into the cell, proteolytic degradation separates T-DM1 at the thioester linkage. Upon cleavage of the thioester, a zwitterionic active metabolite, lysine-Nε-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (MCC)-DM1 is released.[21,25] The charged nature of this molecule greatly reduces its ability to cross cell membranes, therefore keeping it in the HER2 positive cells, and reducing systemic toxicities.

T-DM1 activity has been tested in tissues that overexpress HER2 and are refractory to other targeted HER2 therapies such as trastuzumab and lapatinib, where it has been shown to have direct cytotoxicity.[21] The ability of T-DM1 to precipitate ADCC and mediate immune response, as well as binding affinity to the HER2 receptor, is similar to trastuzumab.[26] Additionally, the ADC works by other mechanisms differentiating T-DM1 from the unconjugated trastuzumab.[27] DM1 is able to be delivered by trastuzumab into cells with HER2 overexpression, thereby inhibiting microtubule polymerization that would eventually lead to apoptosis.[21] Because T-DM1 is able to directly target specific tumor cells, it is able to be much more potent than other chemotherapies, concurrently minimizing systemic cell death.[21,22,26] Another feature of the ADC is increased clearance by a number of mechanisms, including deconjugation, proteolytic degradation, and CYP450 metabolism causing its half-life to be considerably shorter than unconjugated trastuzumab (~four days versus three to four weeks).[27,28] Lastly, the DM1 portion of the ADC is active, even in cells with constitutively active PI3K signaling, which is believed to be a cause of trastuzumab resistance.[26]

Indications

According to the NCCN guidelines, first-line therapy for metastatic or recurrent breast cancer that is HER2 positive includes pertuzumab and trastuzumab plus either docetaxel or paclitaxel.[4] This therapy fails for some patients, and a change in therapy is required. T-DM1 is indicated for patients with metastatic breast cancer that is HER2 positive and has been exposed to trastuzumab and a taxane. If the patient has recurrent breast cancer within six months of completing chemotherapy, T-DM1 as monotherapy is the preferred regimen. Although T-DM1 has no contraindications at this time, it should not be used in pregnant females.[28] Additionally, nursing mothers should discontinue either T-DM1 or nursing based on importance of treatment for the mother.

Efficacy

Krop et al. performed a study of T-DM1 as monotherapy in a phase I, dose escalation trial where patients received 0.3 mg/kg initially and were titrated up to 4.8 mg/kg.[29] The results showed patients had a maximum tolerable dose of 3.6 mg/kg every three weeks based on the side effect of transient, grade 4 thrombocytopenia (platelet count <25,000 /μL) associated with doses of 4.8 mg/kg. Patients who were treated with the maximum dose had a 73 percent chance of having a significant benefit, objective partial tumor response plus stable disease at six months, compared to those patients who received doses of 2.4 mg/kg or less of T-DM1.[29] Barginear et al.

performed an analysis of several studies comparing T-DM1 to lapatinib/capecitabine combination and concluded that T-DM1 prolongs progression free survival.[30] Patients treated with T-DM1 had 9.6 months of progression free survival compared to 6.4 months in patients that were treated with a combination of lapatinib and capecitabine for a p value of <0.0001. Likewise, the authors concluded the median time to symptom progression was longer with T-DM1 (7.4 months) compared to lapatinib/capecitabine (4.6 months).[30] Verma et al. studied 991 patients with HER2 positive and locally advanced or metastatic breast cancer who were randomly assigned to either T-DM1 or lapatinib plus capecitabine. Similar to the previous studies, the investigators also demonstrated that T-DM1 improved progression free survival and median overall survival compared to lapatinib and capecitabine.[12] The one year survival rate in patients treated with T-DM1 was 85.4 percent compared to 78.4 percent for the lapatinib/capecitabine group.[31] More patients in the lapatinib/capecitabine group required a dose reduction due to intolerable side effects. T-DM1 has statistically been shown to be more efficacious than lapatinib and capecitabine in combination in patients previously exposed to trastuzumab.

Safety and Quality of Life

The most common side effects associated with T-DM1 are consistent with many chemotherapy regimens, which include fatigue (37 to 65 percent), anemia (25 to 50 percent), and hypokalemia (2 to 24 percent).[27] While T-DM1 may cause serious adverse effects (such as thrombocytopenia and elevated serum concentrations of aspartate and alanine aminotransferase), the rate at which these occur is lower in T-DM1 compared to lapatinib treatment.[31] Elevation of aspartate aminotransferase was reported in 4.3 percent of patients and alanine aminotransferase was elevated in only 2.9 percent of patients. Thrombocytopenia was more common but still only occurred in 12.9 percent of the 495 patients assigned to T-DM1. The most common time for thrombocytopenia to occur was within the first two cycles of T-DM1, and with therapy modification, most were able to continue the therapy with only 10 patients dropping out .[31] In a study by Hurvitz et al., thrombocytopenia of any grade occurred in most patients on a dose above 1.2 mg/kg; however, this was most often transient. The highest incidence of grade 3 (platelet count 25,000 to 50,000 /μL) or higher thrombocytopenia happened in 11.9 percent of patients who were being treated with T-DM1 and pertuzumab.[24]

Additionally, Hurvitz et al. assessed the quality of life of patients treated with T-DM1 using the Functional Assessment of Cancer Therapy-Breast (FACT-B) trial outcome index, which assesses physical, functional, emotional, and social/family well-being, in addition to breast cancer symptoms. The authors determined that those patients treated with T-DM1 had an improved quality of life across all aspects of the index compared with those treated with trastuzumab and docetaxel.[24]

Pharmacist Role

Pharmacists have an important role in advising physicians on when to use T-DM1 over alternative therapies. The main advantage of T-DM1 over traditional treatments for HER2 positive breast cancer is the increased time to progression and increased overall survival compared to the three alternatives for breast cancer that has already been exposed to anti-HER2 treatment. The use of additional anti-HER2 therapies after T-DM1 showed no benefit over only using T-DM1 in patients previously exposed to trastuzumab therapy. Therefore, decisions for further anti-HER2 treatment after T-DM1 should be based on patient and physician preference.[32] The maximum tolerated dose of T-DM1 was determined to be 3.6 mg/kg every three weeks, which is the current NCCN breast cancer guidelines recommendation.[4,30]

Although T-DM1 is an intravenous therapy and would be administered in an inpatient setting, pharmacists can play a key role in educating both physicians and patients about the common adverse effects and special considerations. Important counseling points would be common adverse effects of T-DM1, most notably nausea, fatigue, musculoskeletal pain, thrombocytopenia and headache. Physicians should be advised that certain adverse effects, such as thrombocytopenia, hepatotoxicity and left ventricular cardiac dysfunction may require a dose reduction, longer duration between doses, or discontinuation of therapy depending on severity and patient tolerability. T-DM1 is pregnancy category D and, if T-DM1 is indicated, use should be delayed until after the child is born. It is important to educate patients on risks to the fetus and the importance of utilizing proper birth control during treatment with T-DM1 and for six months following termination of T-DM1.[28]

The FDA recently issued a safety warning to all health care professionals that the generic name for Kadcyla™ (ado-trastuzumab emtansine) was incorrectly entered in some medication electronic systems and may be confused with the generic for Herceptin™ (trastuzumab). This is a potential risk in any system that uses generic names. It is critical that the pharmacist clarify orders for these products to prevent risk to patients, since the dosing and schedules for these two medicines are different.[33]

Conclusion

Breast cancer is the second leading cause of cancer related deaths in women; therefore, it is important to find adequate treatment that is tolerated by patients.[2] T-DM1 has been shown to be effective in increasing time to progression in patients that have developed targeted HER2 treatment resistance.[27] In addition, T-DM1 has a decreased risk of adverse effects compared to other agents utilized in the same line of therapy, as well as having the benefit of being monotherapy.[24,27,31] T-DM1 should be considered in eligible patients due to the increased overall survival and the decreased rate of adverse effects such as thrombocytopenia.[28] However, cardiotoxicity and hepatotoxicity are possible and may require dosage adjustments or discontinuation based on severity, as well as monitoring of left ventricular ejection fraction and liver function tests (LFTs). T-DM1 has no contraindications but is not recommended during pregnancy or in nursing mothers. After FDA approval of T-DM1 on Feb. 22, 2013, the NCCN included it in the guidelines as preferred treatment for HER2 positive cancer that had been exposed to trastuzumab previously and should be utilized in therapy.[4, 34]

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Signifor® Receives FDA Approval for the Management of Cushing's Disease

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Abstract
Cushing's disease is a disorder characterized by supraphysiologic levels of circulating cortisol due to excessive adrenocorticotropic hormone (ACTH) secretion. Most often hypersecretion of ACTH is due to a pituitary adenoma, where surgical resection of the tumor is considered first-line treatment for the disease. Alternatively, the FDA has recently approved the somatostatin analogue, Signifor® (pasireotide), for the management of Cushing's disease in patients for whom surgery is not an option. In clinical trials, pasireotide has shown a statistically significant reduction in urinary free cortisol levels, as well as significant improvements in quality of life. Based on current data, pasireotide appears to offer a new potential treatment option for patients who are poor candidates for surgery.

Disease State Overview
Cushing's disease, also known as pituitary ACTH dependent Cushing's syndrome, is a rare adrenal disorder characterized by excess glucocorticoid release. While Cushing's syndrome broadly encompasses a number of pathophysiologic causes, the term Cushing's disease is specifically reserved for hypercortisolism resulting from excess ACTH.[1] Most commonly oversecretion of ACTH is due to a pituitary adenoma, causing hypersecretion of cortisol from the adrenal glands. Excessive levels of cortisol can result in weight gain, muscle wasting, hypertension, hirsutism, and a number of other related symptoms.[2]

Each year hypercortisolism is diagnosed in approximately forty out of every million patients. Hypercortisolism generally affects females more than males, and it is most commonly observed in adults during their twenties and thirties while children are nearly unaffected.[1] Cushing's disease often results in chronic hypertension, diabetes, hyperlipidemia, and increased hypercoagulability and is possibly fatal if untreated.[1,2]

The most common symptom noted in Cushing's patients is obesity marked by abnormal fat distribution. Fat is typically deposited centrally, especially in the face and neck (resulting in a characteristic "buffalo-hump"), while the muscles of the arms and legs atrophy. Protein wasting can result in thin skin, stretch marks, slow healing, and osteoporosis. Excess androgen production can cause acne, hirsutism, and menstrual irregularities. [1]

In terms of treatment options, surgery to remove ACTH secreting pituitary tumors should be considered first-line. If the tumor is inaccessible for surgery, clinicians may resort to radiation therapy or adrenal resection in an attempt to suppress cortisol production. Alternatively, mifepristone (Korlym®), indicated in the management of Cushing's-related hyperglycemia due to its ability to antagonize glucocorticoid receptors, may be considered. Non-FDA approved, second-line medications may also be utilized, including ketoconazole, mitotane, or metyrapone, which interfere in adrenal steroid synthesis. However, none of these medications are desirable because they do not address the underlying cause of the disease nor correct the abnormal functioning of the hypothalamic-pituitary axis.[2] Fortunately, pasireotide may offer a new treatment option in patients for whom pituitary surgery is not an option.

Literature Evaluation
Overall, relatively little data has been published regarding the safety and efficacy of pasireotide in humans. This is likely due to a multitude of factors including, but not limited to, the low prevalence of its intended indication—Cushing's disease. In this literature evaluation three key trials regarding pasireotide will be reviewed. The first, and main trial supporting the utilization of pasireotide for Cushing's disease, is a phase three clinical trial concluding that utilizing pasireotide led to a significant reduction in cortisol levels.[3] The next trial reviewed is a phase two clinical trial with a limited number of subjects that witnessed a controllable adverse event profile for pasireotide and concluded that the agent produced a decrease in cortisol levels.[4] The final study reviewed is a very small trial designed to assess the utility of pasireotide when used alone versus in combination with other agents for the treatment of Cushing's disease.[5] As a result of these studies, the conclusion was that pasireotide may play a beneficial role in medication-based therapy for individuals with Cushing's disease. Each of these trials will be analyzed in-depth including study results, strengths, and weaknesses.

The main efficacy trial supporting the use of pasireotide for Cushing's disease is a year-long phase three study conducted by Colao et al.[3] Eligible patients for this trial included adults (>18 years of age) with confirmed persistent or recurrent Cushing's disease (or a new diagnosis if they were not candidates for surgery). Cushing's disease was defined as having a urinary free cortisol level of at least 1.5 times the upper limit of the normal range. The primary endpoint for the study was a normalized urinary free cortisol level without any dose adjustments. Secondary endpoints included normalized urinary free cortisol levels regardless of dose adjustments, changes in clinical signs and symptoms, quality of life and safety.[3]

In the study conducted by Colao et al., 162 patients were randomly assigned to one of two pasireotide dosing groups: 600

μg twice daily or 900 μg twice daily. Power calculations had concluded that 146 enrolled patients would provide 87 percent power given a null hypothesis that less than 15 percent of patients would meet the primary endpoint. Any patient at month 3 who had a urinary free cortisol level less than two times the upper limit of the normal range was maintained on (and kept blinded to) their assigned dose through month 6. All other patients were un-blinded to their treatment group and titrated up to a more efficacious dose at a rate of 300 μg twice daily per change. At month 6, all patients entered an open-label phase lasting through month 12. During this phase, dose increases (up to a maximum dose of 1200 μg twice daily) were provided as necessary to any patient whose urinary free cortisol levels remained above the upper normal limit.[3]

In terms of urinary free cortisol levels, a statistically significant reduction was seen at month 6 in the group that solely received 900 μg twice daily. When patients who had received elevated doses starting at month 3 were included, there was a significant reduction in urinary free cortisol levels for both treatment groups at month 6. It was noticed that patients with lower baseline urinary free cortisol levels responded better to pasireotide. Additionally, the reduction in urinary free cortisol levels typically occurred in the first two months of treatment, which were sustained throughout the remainder of the 12-month trial period. In addition to urinary free cortisol levels, other signs and symptoms were also reduced at month twelve. Systolic blood pressure (p=0.03), diastolic blood pressure (p=0.03), LDL cholesterol (95 percent confidence interval (CI) -23 to -8 mg/dL), weight (p<0.001), and quality of life scores (95 percent CI 6.8 to 15.5) were all significantly improved.[3]

Overall, the most common adverse events (observed in >25 percent of all patients) seen in the study conducted by Colao et al. were diarrhea, nausea, hyperglycemia, cholelithiasis and headache. Most of these issues were relatively minor in severity; however, hyperglycemia (actual values were undefined by the authors) was considered a severe issue in 13 percent of all patients. This finding warrants consistent and steadfast monitoring of blood glucose levels in patients on pasireotide for Cushing's disease.[3]

A precursor to the phase three trial described above was a phase two open-label proof-of-concept trial designed by Boscaro et al. to assess the safety and efficacy of pasireotide in Cushing's disease. The inclusion and exclusion criteria are nearly identical to those described above, and the dosage used in the study was 600 μg twice daily. As is typical with phase two clinical trials, there were very few patients involved (n=39) and no power calculations were conducted. The study showed that the average urinary free cortisol level of the patients decreased from baseline by over 40 percent (p=0.021) and that 76 percent of all enrolled patients witnessed a decrease in urinary free cortisol levels.[4]

In addition, there was a small trial (n=17) conducted by Feelders et al. looking to establish potential synergistic effects of utilizing pasireotide in combination with the dopamine-receptor subtype 2 agonist cabergoline and the steroid enzyme inhibitor ketoconazole.[5] The study dosed pasireotide 100 μg three times daily for 15 days with a primary outcome of normalized urinary free cortisol levels. If levels had not normalized by day 15, the pasireotide dose was increased to 250 μg three times daily. If the levels still had not normalized by day 28, cabergoline was added at a dose of 0.5 mg every other day. If urinary free cortisol levels remained elevated, the add-on cabergoline dose was increased to 1.0 mg every other day at day 33 and 1.5 mg every other day at day 38. Ketoconazole was added at a dose of 200 mg three times daily on day 60 if the urinary free cortisol levels still remained elevated. Pasireotide monotherapy normalized the urinary free cortisol levels of five patients (29 percent), pasireotide-cabergoline combination therapy normalized an additional four patients (24 percent), and pasireotide-cabergoline-ketoconazole combination therapy induced biological remission in a total of 15 of 17 enrolled patients (88 percent) by the 80-day trial endpoint. No safety data was assessed in this trial. These data, while lacking power and repetition, suggest that utilizing pasireotide in combination with other clinically available medications may be a worthwhile therapeutic endeavor in the treatment of Cushing's disease.[5]

These trials showcase the best data available regarding this medication; however, they all possess key limitations that jeopardize the clinical validity of the conclusions. The two main clinical trials by Colao et al. and Boscaro et al. with regard to pasireotide in Cushing's disease were both funded and designed by the manufacturer, Novartis. This fact may introduce bias and should be considered when analyzing the data; however, it may be unavoidable due to the orphan nature of the medication.[3,4] The low prevalence of Cushing's disease also contributed to the low sample size in each of these trials and the ultimate limitations associated with a small sample.

The inclusion criteria for the trials by Colao et al. and Boscaro et al. required cortisol levels to be significantly elevated (at least 1.5 times the upper limit of normal). This restrictive inclusion criteria allows for the potential over-exaggeration of the effects of pasireotide on cortisol levels. Therefore, the clinical significance of the medication may have been overstated due to the study design. Similarly, the primary endpoints in all of these studies was change in urinary free cortisol (UFC) levels. While it is true that UFC levels are indicative of adverse events concerning Cushing's disease, the primary concern in this disease state is the development of the pituitary tumor. Only the phase three trial addressed the effects of pasireotide on tumor size, and it was merely mentioned. Additionally, no formal statistics were done on the data and no conclusions were drawn on the effects of pasireotide on tumor size. This lack of proven efficacy against the primary cause of Cushing's disease may limit the clinical use of the medication.[3,4]

It is critical to state the limitations of the final study by Feelders et al. regarding pasireotide alone versus combination therapy. The study was made up of only 17 patients, making it a little more expansive than a case series. The trial was

entirely open-label, thus allowing for the likely result of confirmation bias. Additionally, few safety data or mechanisms for data collection were presented. Overall, it is quite unclear how the data was attained, and given the open-label nature of the study, this makes the conclusions of the study worthy of skepticism. Even given the drawbacks of this study, the decision to include it in the discussion was due to the fact that it provides some context for how pasireotide might actually be utilized in clinical practice for the treatment of Cushing's. This is viewed as critical information for pharmacists to possess as pasireotide makes its way to the market and into clinical practice.[5]

Pharmacologic Management of Cushing's disease

Secondary to the presence of a corticotropin-secreting pituitary adenoma, the chronic hypercortisolism of Cushing's disease has been treated primarily through transsphenoidal surgery.[6] This procedure involves the removal of pituitary tumors with a microscope or endoscope through the sphenoid sinus. Inconsistent remission rates and lack of clinical efficacy in second-line drug therapies have driven the need for alternative medication therapy options.[6] Pasireotide (Signifor®) is indicated to reduce urinary free cortisol levels in adult patients with Cushing's disease who do not qualify for or have not benefitted from pituitary surgery.[7]

The initial dose recommendation for pasireotide is a 0.6 mg or 0.9 mg subcutaneous injection twice daily, which should be titrated based on patient outcomes within the recommended range of 0.3 to 0.9 mg twice per day. Optimal treatment response is measured through 24 hour urinary free cortisol levels. Patients demonstrating symptomatic improvements should continue therapy as long as it remains beneficial for their disease state. If a dose reduction is indicated due to patient intolerance or adverse reactions, it is recommended to adjust in 0.3 mg intervals.[7] In patients with moderate hepatic impairment (Child Pugh B), the maximum dosage recommendation is 0.6 mg twice per day. Prescriptions for pasireotide require the completion of an enrollment form, and it is available exclusively through a specialty pharmacy.[8] Cost information is not yet available.[7]

Overall, the pasireotide studies conducted to date indicate the following adverse events occur in greater than 20 percent of patients: headache, hyperglycemia and related symptoms, diarrhea, nausea, cholelithiasis and abdominal pain.[9] The elevated frequency of gastrointestinal (GI) symptoms and cholelithiasis in the phase three clinical trial was noted to be comparable to existing somatostatin analog side effects.[6] Therapy modification should be considered for patients prescribed pasireotide concomitantly with cyclosporine or moderate risk QT-prolonging agents. Concomitant therapy should be avoided with high risk QT-prolonging agents, mifepristone, and ivabradine due to the risk of enhancing QT prolongation effects.[9] These and other special considerations which require monitoring through the duration of therapy are further explained below.

Clinical trials have elucidated a number of special considerations that must be taken for every patient receiving pasireotide therapy. Due to the mechanism of ACTH suppression, patients may experience weakness, fatigue, nausea, and other symptoms characteristic of hypocortisolism. Options for treating hypocortisolism include temporarily reducing the dose or discontinuing pasireotide and initiating glucocorticoid replacement therapy.[7] Studies conducted in healthy adult patients have also indicated that hyperglycemia may occur as a result of pasireotide treatment. The drug-induced decrease in insulin and insulin secretion is responsible for this adverse event, as opposed to alterations in insulin sensitivity that may result from the original disease state.[6] Seventy-three percent of phase three study participants experienced adverse events due to hyperglycemia, which in many cases led to the development of pre-diabetes and diabetes.[6] Patients with uncontrolled diabetes mellitus should be stabilized with an anti-diabetic agent prior to initiating pasireotide therapy, and the development of hyperglycemia should also be treated with an anti-diabetic agent.[7] Self-monitoring of blood glucose is imperative during the first few months to both optimize treatment and stabilize blood glucose levels. Additionally, bradycardia and prolongation of the QT interval are further clinical findings. Two percent of patients in the phase three trial experienced a QT prolongation which did not require intervention.[6] Special caution must be taken in patients with existing cardiac disease, hypokalemia, hypomagnesemia, congenital QT prolongation and therapy with other substances that prolong the QT interval. In addition, electrolyte imbalances must be corrected prior to initiation of therapy.[7] Liver enzymes may be elevated during the course of therapy, as evidenced by aspartate aminotransferase (AST) and alanine aminotransferase (ALT) measurements three times greater than the upper limit of normal and elevated bilirubin levels during phase three testing. It is appropriate to monitor enzyme levels after one to two weeks of treatment, monthly for three months, and then every six months. If levels are normal initially and rise to be three to five times greater than the upper limit of normal, values need to be confirmed through repeated laboratory testing. Consistently elevated liver enzymes necessitate the discontinuation of pasireotide therapy until levels are resolved and causes are determined. Due to the number of considerations that need to be taken with regard to pasireotide, it is important for patients to have a baseline fasting glucose level, hemoglobin A1C test, liver tests and an electrocardiogram (ECG) in order to respond appropriately to concerns and optimize therapy.[7]

Pharmacists should educate patients on proper administration. Pasireotide, a clear and colorless solution, is manufactured and distributed by Novartis as 0.3 mg/mL, 0.6 mg/mL, and 0.9 mg/mL single dose ampules. It is administered as a 45˚ angle subcutaneous injection into a fatty area of healthy skin in the upper thigh or abdomen. Rotation of injection sites is an important counseling point to prevent the buildup of scar tissue and ensure proper drug absorption. Patients should be provided a sterile syringe, a long sterile needle (if instructed by physician to draw up medication from the ampule), and a short sterile needle for self-administration. Ampules should be stored at room temperature, protected from light, and discarded if discoloration or particulate mat-

ter is present.[8] If wheezing, chest tightness or other symptoms of a serious allergic reaction occur, patients should contact their doctor.[9] To assist with compliance, an FDA approved medication guide must accompany pasireotide upon dispensing.[8]

Conclusion

Cushing's disease represents a state of excess cortisol secretion, and is commonly manifested by central obesity, protein wasting and hypertension. While pituitary resection is considered the treatment of choice, lack of efficacy among second-line pharmacologic treatments has prompted a need for alternative medications. Fortunately, twice daily pasireotide appears to offer hope for patients who are not candidates for surgery or for those who have previously failed surgical treatment. In clinical trials use of pasireotide resulted in significant reductions in urinary free cortisol levels, as well as improvements in quality of life and secondary symptoms.[3] In terms of side effects, pharmacists should inform their patients that pasireotide may cause headache, hyperglycemia, nausea, diarrhea and may increase the risk of developing gallstones.[9] Overall, however, pasireotide is generally well-tolerated and appears to offer a new, innovative approach toward managing Cushing's disease.

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