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FDA Approves New Inhaled Insulin: Afrezza® (Technosphere® Insulin)

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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. Identify the different types of diabetes and each of their pathophysiologies.
2. Name several investigational methods for insulin administration.
3. Describe the pharmacokinetics and pharmacodynamics of Technosphere® insulin.
4. Explain the advantages and disadvantages of inhaled insulin compared to injectable insulin.
5. Evaluate the efficacy and safety of Technosphere® insulin based on data from clinical trials.

Abstract

Diabetes is an endocrine disease caused by deficiency or malfunction of insulin that results in high blood glucose levels and places patients at higher risk for a number of complications. This chronic disease is difficult to manage and affects millions of people in the United States, costing the health care system billions of dollars a year. Of a variety of antidiabetic agents used to control blood glucose, insulin is perhaps the most effective, but until recently it was only available in injectable form. As of June 27, 2014, a new inhaled insulin called Afrezza® (Technosphere® insulin) was approved by the U.S. Food and Drug Administration (FDA) and will soon be coming to market. This rapid-acting insulin is administered through the lungs and offers an alternative to traditional dosage forms. This article further explores some background about Technosphere® insulin, its mechanism of action and literature regarding its efficacy.

Key Terms

Administration, Inhalation; Blood Glucose; Chronic Disease; Diabetes Mellitus; Disease Management; Endocrine System Diseases; Humans; Hyperglycemia; Hypoglycemic Agents; Insulin; Insulin, short-acting; Review Literature

Introduction

According to the 2014 National Diabetes Statistics Report, approximately 29.1 million people (9.3%) in the United States have diabetes.[1] Direct and indirect health care costs related to diabetes are estimated to total about $245 billion a year, placing a large burden on patients and providers alike.

Disease State

Diabetes mellitus (DM) is an endocrine disease that results in high blood glucose levels due to deficiency or malfunction of the hormone, insulin, that is responsible for most of glucose absorption from the blood stream.[1] Patients with diabetes are at higher risk than nondiabetics for a number of other health complications including hypoglycemia or hyperglycemia, hypertension, cardiovascular problems, blindness and kidney disease. Diabetes is usually classified into type I, type II and gestational diabetes (GDM). Type I DM (approximately 5% of diabetes cases) is caused by the body's immune system destroying the insulin-producing beta cells in the pancreas, resulting in an insulin deficiency without cure or prevention. Type I DM usually appears in young adults, although it can happen at any age. Patients diagnosed with type I DM require exogenous insulin to survive. Type II DM (90 to 95% of diabetes cases) starts with insulin resistance in various tissues, placing an increased demand for insulin on the beta cells of the pancreas. The increased stress on these cells eventually reduces their ability to produce enough insulin to meet the demand. Treatment for type II DM depends on the patient's individual combination of insulin resistance and reduced insulin secretion. Gestational diabetes develops during pregnancy when increased blood glucose levels cause the mother to develop intolerance to glucose. During pregnancy, high blood glucose is dangerous for the mother and fetus and requires treatment. Even after birth, both mother and child are at increased risk for type II DM.

Treatment

Type I DM requires insulin therapy to maintain normal blood glucose levels.[1] Type II DM has a wider variety of progressive treatment options including oral agents (such as metformin, glucagon-like peptide-1 agonists and others) and insulin.[2] These agents can be used in conjunction to maintain glycemic control.

Although insulin replacement therapy is acknowledged as the most effective glucose-reducing treatment, its administration by injection is a considerable barrier to many patients.[3] A study performed by Cramer and Pugh estimated that subjects taking insulin used 77 percent of their prescription on average.[4] Although this average indicates an intention to take the insulin as prescribed, there was still an underuse of insulin and this often resulted in poor glycemic control. Peyrot and colleagues suggested that reasons for nonadherence with insulin therapy were often related to discomfort or inconvenience of the injection.[3] Of 502 subjects studied, 23 to 25 percent reported the injections interfered

with various daily activities, 22 percent had to mentally prepare themselves before each injection and 33 percent experienced a level of dread toward taking their insulin injections.[3]

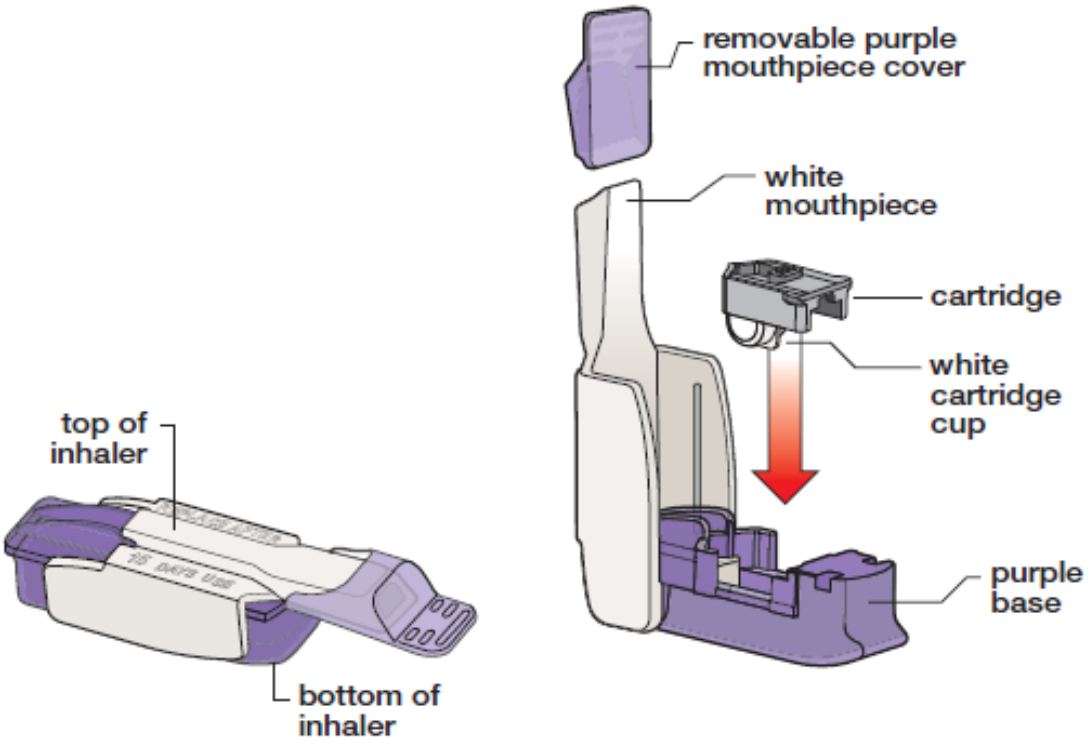
Due to these barriers for insulin administration, the pharmaceutical industry continues to search for alternative insulin delivery methods. Potential alternatives such as oral, nasal or transdermal insulin often have low bioavailability.[5] Exubera® (insulin inhalation), produced by Pfizer, was approved by the FDA on Jan. 27, 2006, and became the first inhaled insulin to make it to market.[6] Insulin inhalation was shown to be as effective as short-acting injectable insulin, although it had to be administered in conjunction with an injectable long-acting basal insulin.[7] Despite its efficacy, Pfizer decided to withdraw insulin inhalation from the market in 2007 due to poor sales and low demand.[8]

Afrezza (Technosphere® insulin, abbreviated TI) is a new inhaled insulin developed by MannKind Corporation and was approved by the FDA for marketing as of June 27, 2014.[9] It is a very rapid-acting insulin dispensed as a powder from a DreamBoat® inhaler (Figure 1). The DreamBoat® inhaler is small, portable and easy to use, giving TI an edge in convenience over previous inhaled insulin. Technosphere® insulin does not replace long-acting basal insulin, but it could potentially reduce the number of injections that a patient has to take. Clinical studies indicate promising efficacy results, but patients and prescribers may hesitate to use TI due to the negative impression left by the withdrawal of Exubera® (insulin inhalation). The purpose of this article is to evaluate the mechanism of action and clinical significance of TI, supported by data from clinical trials, and to educate pharmacists about this new medication.

About Technosphere® Insulin

Technosphere® insulin is an inhaled, prandial, very rapid-acting insulin product.[10,11] The specially-formulated powder is available for absorption via the lung and achieves 37 percent of the bioavailability of subcutaneous insulin administration. The formulation method involves the use of an excipient, fumaryl diketopiperazine (FDKP), which self-assembles via hydrogen bonds in a slightly acidic environment. The hydrogen bonding forms microspheres, which are optimally sized for inhalation deep into the lung. The FDKP microsphere formation can be used to incorporate peptides and proteins (such as insulin) into a solution. The newly formed microspheres containing the drug product are freeze-dried to create the powder used in the inhalers for administration. When a patient inhales this product, the microspheres are introduced into the neutral pH of the lungs allowing for the rapid and extensive absorption of insulin into systemic circulation. Once the insulin is absorbed via the lung mucosa into systemic circulation, the insulin mechanism of action is the same as with subcutaneous and intravenous administration

Figure 1: **DreamBoat® inhaler marketed with Technosphere® insulin.**



Used with permission of Afrezza (insulin human) Inhalation powder [package insert on the Internet].
Danbury (CT): MannKind Corporation; 2014 Jun [cited 2014 Oct 9].
Available from: www.mannkindcorp.com/Collateral/Documents/English-US/Afrezza_PrescribingInformation.pdf.

methods: acting as a hormone that helps the body utilize glucose by pulling glucose from the blood into the cells to use for energy.

As a mealtime insulin, TI reaches peak levels of insulin concentration within 15 minutes of administration, much quicker than current rapid-acting injected insulin products (e.g., aspart, lispro, glulisine insulin reach peak levels between 30 and 90 minutes).[10, 11, 12] This quick time-to-peak also leads to higher maximum concentrations relative to injected insulin. Technosphere® insulin has faster elimination from the body and, coupled with the fast onset of action, this more closely resembles endogenous prandial insulin release than currently available rapid-acting injected insulin.

Studies show that patients with chronic obstructive pulmonary disease (COPD) and those who smoke do not show evidence of decreased efficacy with the use of this product, including mean peak insulin levels, median time to achieve maximum concentrations and mean insulin exposure time from zero to 240 minutes post-dose.[10,11,13]

Adverse effects with TI include hypoglycemia and cough (25% and 19%, respectively).[10,11,14] Other adverse effects discovered were anemia and suspected hypersensitivity. Another concern with inhalation administration is that there can be accumulation or deposition of the excipient FDKP and insulin in the lungs. Evidence shows that both FDKP and insulin concentrations in the lung decline to minimal levels (from 12% to 0.3%) over a 12-hour period after taking a dose.[10,11,15,16]

Comparison

A study by Rave and colleagues, which compared TI versus subcutaneously injected normal human insulin in postprandial coverage, indicated that peak blood glucose levels were significantly lower with the use of TI.[14] Technosphere® insulin also showed improved results with lower postprandial blood glucose (PPG) levels compared to that of regular insulin 30 to 120 minutes following a meal. Several studies show that TI and biaspart insulin (biaspart insulin is a human insulin analogue suspension containing 70% insulin aspart protamine suspension and 30% insulin aspart [rDNA origin]) produced similar decreases of the patient's glycosylated hemoglobin (HbA1c) (at one year, -0.58% and -0.70%, respectively).[10,11] However, TI was shown to impact fasting plasma glucose (FPG) levels more than biaspart insulin (one year average=171 versus 208mg/dL, respectively, p=0.0001).[10,11,17,18]

Patient Counseling/Education Points

One limitation seen in the past with inhaled insulin products (such as Exubera®) was ensuring proper use of the special inhaler, which was produced specifically for inhalation of insulin.[10,11] With the past product, the inhaler was larger and difficult to use. The Exubera® inhaler also had to be cleaned in a specific way and replaced frequently with a new inhaler. Technosphere® insulin utilizes an improved inhaler, which provides for easier use. The package insert for TI provides clear instructions for its use.[9]

Main points for patient counseling include:[9]

- The cartridges must be refrigerated.
- The inhaler and the cartridge must be at room temperature for at least 10 minutes prior to its inhalation and administration.
- When the patient is using the inhaler, it must remain level and upright in the proper orientation; this is because the cartridge is punctured when it is placed into the base of the inhaler, and the powder becomes loose and can spill out if not kept parallel to the ground.
- This inhaler must be thrown away and exchanged for a new one every 15 days.
- Inside the packaging, there are two blister cards in a foil pack.
    - In each blister card, there are five strips, and each strip contains three cartridges.
    - A patient is to rip off one strip at a time when using this product.
    - When a strip is torn from the main blister card, the strip (of three cartridges) must be used within three days; after that it must be thrown away.
- The blue cartridges contain four units of insulin, and the green cartridges contain eight units of insulin.
    - Each dispensed package will only come in one strength (blue [four units] or green [eight units]).

Literature Review

Trial 1

Tack and colleagues performed a double-blind, placebo-controlled, randomized controlled trial as part of phase 2 clinical trials for the approval of TI.[19] The trial was designed to test efficacy and evaluate dose-dependent response of four different doses of TI and compare them to placebo over the course of 11 weeks. The population used included 227 patients with type II DM and poor glycemic control with other medications. In addition to either TI or placebo, all patients were switched from their previous regimens to insulin glargine for basal maintenance dosing. The subjects were then randomized into five groups: TI cartridge doses of 14, 28, 42 or 56 unit equivalents (U*) or placebo. Assuming administration by inhalation provides a bioavailability of 26 percent, the TI doses were assigned equivalents to usual subcutaneous regular human insulin of 3.6, 7.3, 10.9 and 14.6 U*, respectively. Patients to be given the higher doses started an initial dose of 3.6 U* and were titrated up by 3.6 U* per week until the assigned dose was reached. Efficacy endpoints included reduction in HbA1c, area under the glucose curve ($AUC_{glucose}$), and maximum concentration of plasma glucose reached after eating a meal (C_{max}). Each of these measures was compared to baseline and adjusted for baseline differences by comparing to placebo. Specific goals for significant HbA1c reduction were set for each dose prior to the beginning of the trial. To reach desired goal for HbA1c compared to baseline, a change -0.4, -0.5, -0.5 and -0.6 (p-value<0.05) was required for 3.6, 7.3, 10.9 and 14.6 U* doses, respectively. When adjusted relative to placebo, HbA1c reduction should reach -0.4, -0.67, -0.7 and -0.78 (p-value<0.04) for above doses to be statistically significant. Secondary end-

Table 1: Summary of HbA1c Results from data by Tack and colleagues[19]

	3.6 U* TI	7.3 U* TI	10.9 U* TI	14.6 U* TI	Placebo
HbA1c change from baseline	-0.4±1.2	**-0.5±1.2**	**-0.5±0.9**	**-0.6±1.1**	0.2±0.9
p-value	0.05	**0.004**	**0.002**	**0.001**	0.098
HbA1c change from placebo (corrected for baseline and basal insulin)	**-0.4**	**-0.67**	**-0.7**	**-0.78**	---
p-value	**0.04**	**0.001**	**0.001**	**<0.001**	---

points were to test safety by monitoring occurrence of adverse events.

Table 1 outlines HbA1c results related to TI efficacy for the trial, with statistically significant values in **bold**. Based on this data, all doses of TI demonstrated a significant reduction in HbA1c compared to placebo.[19] Other measurements of TI efficacy found statistically significant results when comparing TI to placebo at 10.9 and 14.6 U* doses for $AUC_{glucose}$ and 7.3, 10.9 and 14.6 U* doses for C_{max} measurements. The data shows with sufficient confidence that the reduction in HbA1c is linked to increased dose of TI, and $AUC_{glucose}$ also decreases at higher doses. No statistically significant differences were found between TI and placebo groups regarding adverse reactions, and TI doses were well tolerated.

Tack and colleagues performed a strong clinical study by standardizing titration of TI doses, thoroughly documenting criteria and data, and accounting for baseline differences (although minimal) in their statistical analysis. The necessary sample size (260) to achieve 80 percent power was calculated before the trial was performed, but only 227 patients could be gathered, and only 205 completed the entire trial, so there is a risk of type II error.[19] The authors indicated the forced titration design did not optimize treatment of patients, and the study was of short duration. Additionally, it should be noted that this trial employed the MedTone® inhaler, not the DreamBoat® inhaler that MannKind is now marketing with TI.

Trial 2

Rosenstock and colleagues performed a randomized, multicenter, open-label, parallel-group study, funded by MannKind, assessing the efficacy and safety of prandial TI compared with twice daily biaspart insulin.[20] The efficacy endpoint was a change in HbA1c, and the main safety endpoints were hypoglycemia and cough. There were 677 patients included in the study (462 completed the study and 448 were analyzed in per-protocol population) aged 18 to 80 years with type II DM and HbA1c greater than 7 percent and less than 11 percent. Patients must have been nonsmokers for at least six months before the study, have forced expiratory volume in one second (FEV_1) of 70 percent, have total lung capacity of 80 percent or higher, have a body mass index (BMI) ≤40kg/m^2, and need less than 1.4 IU insulin per kg. Patients excluded from the study were those who had clinically significant diabetes complications, hepatic/renal disease, severe/several allergies, chronic pulmonary disease, present drug or alcohol abuse, major psychiatric disorders, myocardial infarction/stroke in the last three months or unstable diabetes (two or more episodes of severe hypoglycemia or any emergency room visit for diabetes in the last six months). The data was collected over a period of 19 months.

Randomization was completed by an independent system (ClinPhone, East Windsor, NJ, USA) to place the patients into two groups in a 1:1 ratio, where one group would receive prandial TI powder plus bedtime insulin glargine by subcutaneous injection and the other would receive twice daily premixed biaspart insulin by subcutaneous injection.[20] No blinding was used for this study because of the multicontinental study design and the drug administration times.

A 90 percent power was provided for the sample size of 677 patients for the comparison of HbA1c.[20] The study used analysis of covariance (ANCOVA) to analyze the change in HbA1c, FPG, PPG, weight and pulmonary function tests from baseline after 52 weeks. The study utilized a paired t-test for within-treatment comparisons, odds ratio for at least one hypoglycemic event, Poisson regression model for rates of hypoglycemic events, ANCOVA for between-treatment differences and logistic regression analysis to show the treatment difference in responder rates. A short form-36 quality of life (SF-36 QoL) and insulin treatment questionnaires were also used to assess progress.

Data gathered from the trial with upper 95 percent confidence intervals (CI) less than 0.4 showed TI and insulin

glargine was noninferior to biaspart insulin in HbA1c mean changes from baseline.[20] Mean FPG for TI plus insulin glargine versus biaspart insulin at 52 weeks was 7.8mmol/L (2.0mmol/L change from baseline; SD 0.3, 95% CI -2.5 to -1.5) and 8.7mmol/L (1.0mmol/L change from baseline; SD 0.2, 95% CI -1.5 to -0.5), respectively. The between-group difference was -1.0mmol/L (SD 0.3, 95% CI -1.6 to -0.3, p=0.0029). Postprandial blood glucose AUC for zero to 360 minutes was similar between both treatment groups: 59.8mmol/h per L for TI and insulin glargine and 56.7mmol/hr per L for biaspart insulin. However, the mean one hour PPG levels were lower with TI and insulin glargine versus biaspart insulin (9.5mmol/L; SD 0.3 and 11.6mmol/L; SD 3.9, p=0.0001). After two hours, glucose excursions were higher with TI and insulin glargine versus biaspart insulin, and glucose levels remained below baseline with biaspart insulin after 200 minutes. Adverse events occurred in 272 patients (84%) on TI and insulin glargine and in 296 patients (89%) on biaspart insulin. Hypoglycemia was the most common adverse event occurring in 99 patients (31%) on TI and insulin glargine and 163 patients (49%) on biaspart insulin. Cough was reported frequently with 103 patients (32%) on TI and insulin glargine and 14 patients (4%) on biaspart insulin. Most of the coughs from patients on TI and insulin glargine occurred within 10 minutes of inhalation. There were no significant differences between the two groups with pulmonary function.

Rosenstock and colleagues conclude that TI plus insulin glargine is an effective alternative to conventional subcutaneous insulin therapy in patients with type II DM, and it may result in less weight gain and hypoglycemia.[20]

Trial 3

Raskin and colleagues performed a prospective, randomized, open-label study to determine the pulmonary safety of TI versus usual diabetes medications in patients with DM.[21] The patients had either type I DM or type II DM and were stratified by DM type prior to randomization into prandial insulin TI (n=743) or usual antidiabetic (n=824) treatment groups. The definition of "usual care" was determined by doctor discretion and could include any range of oral antidiabetic medications with or without insulin, and patients in the TI group also remained on other diabetes medications as needed. The study also included a control group of 145 patients who did not have DM and were not receiving treatment in order to assess standard lung function. The primary objective of the study was to evaluate change in pulmonary function of each treatment group and determine if TI pulmonary safety was noninferior to usual care. To accomplish this, Raskin and colleagues measured lung function by the primary endpoint, FEV_1, and secondary endpoints forced vital capacity (FVC), total lung capacity (TLC) and lung diffusion capacity for carbon monoxide (DL_{CO}) for each patient at zero, three, six, 12, 18 and 24 months. Any adverse reactions were also assessed. Baseline demographics and pulmonary function were determined to be similar between treatment groups of DM patients.

Calculations for statistical analysis were based on the null hypothesis that difference in FEV_1 change was not less than 0.050 L/year ± 0.100 L in TI groups compared to usual care groups.[21] To achieve 80 percent power and alpha of 0.05, it was calculated a sample size of 50 patients for each treatment arm would be necessary. The number of patients enrolled well exceeded these requirements, so type II error in statistical analysis is unlikely. Of 2,053 patients originally enrolled in the study, 763 dropped out (mainly due to withdrawal of consent, not as a result of any major side effects), leaving 1,699 patients who were included in the analysis.

Pulmonary function declined marginally in all groups compared to baseline, and overall pulmonary safety of TI was determined to be noninferior to usual care over the course of two years.[21] The primary endpoint met the noninferiority goal with a mean change (TI minus usual care) over two years in FEV_1=0.037 L (95% CI 0.014 to 0.060). Secondary endpoint mean differences were FVC=0.034 L (95% CI 0.008 to 0.06), TLC=0.005 L (95% CI −0.042 to 0.031), and DL_{CO}=0.269mL/min/mm Hg (95% CI −0.037 to 0.574). There was a greater initial decline (zero to three months) in lung function in the TI group compared to the usual care group, but when compared with data from three to 24 months, there was no statistically significant difference between the groups. Generally TI was well tolerated with no safety concerns. The most common treatment-related adverse effect in both groups was hypoglycemia. The second most common adverse effect, a mild, nonproductive cough that occurred within 10 minutes of inhalation, was more common in the TI group, but it did not affect overall lung function. It was reported by patients within the first month of therapy and declined over time. No lung malignancy was reported in either group. Raskin and colleagues concluded that any differences in the change in lung function between the TI and usual care groups was observed early and did not progress over two years, so this is unlikely to have clinical significance. Overall, the study was sufficient to indicate that TI does not pose any serious pulmonary safety concerns when used as intended.

Conclusion

Technosphere® insulin has great potential to meet the need for medication that can imitate the fast-acting effects of endogenous insulin. Trials have proven it to be safe and efficacious as a rapid-acting insulin. The DreamBoat® inhaler is small, portable and easy to use. Although effective as a rapid-acting insulin, it is important to remember that TI therapy still requires administration of either injectable long-acting insulin or other antidiabetic therapy to maintain basal insulin levels, and therefore it may not completely eliminate the use of needles from a patient's therapy. The true benefit of TI remains to be seen. Largely its success will depend upon patient preference and whether or not the advantages it offers can overcome the negative impression left by previous inhaled insulin.

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Assessment Questions

1. For what kinds of complications are DM patients at higher risk than patients without DM?
    A. Cardiovascular problems
    B. Blindness
    C. Kidney disease
    D. All of the above

2. What is the cause of type 1 DM?
    A. Insulin resistance
    B. The immune system destroys the beta cells in the pancreas
    C. Increased blood glucose levels during pregnancy
    D. Obesity

3. According to the study done by Cramer and Pugh, patients used what percent of their insulin prescriptions?
    A. 50 percent
    B. 67 percent
    C. 77 percent
    D. 80 percent

4. Which of the following were mentioned in this article as alternative methods of insulin administration under investigation?
    A. Oral
    B. Nasal
    C. Transdermal
    D. All of the above

5. What was the generic name of the inhaled insulin made by Pfizer?
    A. Insulin inhalation
    B. Technosphere® insulin
    C. Exubera®
    D. Afrezza®

6. Which of the following accurately describes the pharmacokinetics of Technosphere® insulin?
    A. Achieves 37 percent bioavailability
    B. Reaches peak insulin levels in 15 minutes
    C. Lower postprandial blood glucose (PPG) levels compared to subcutaneously injected insulin 30 to 120 minutes following a meal
    D. Two of the above
    E. All of the above

7. Which of the following accurately describes the pharmacodynamics of Technosphere® insulin?
    A. The neutral pH of the lungs slows absorption
    B. Absorbed through the lung tissue into systemic circulation
    C. Smoking decreases its absorption
    D. Two of the above
    E. All of the above

8. True or False: Technosphere® insulin's mechanism of action is identical to prandial subcutaneously injected insulin.
    A. True
    B. False

9. All of the following are advantages of inhaled insulin when compared to injectable insulin EXCEPT which one?
    A. Lower peak blood glucose
    B. Lower PPG levels 30 to 120 minutes following a meal
    C. Lower $AUC_{glucose}$
    D. Lower FPG levels

10. How does the efficacy of Technosphere® insulin compare to biaspart insulin?
    A. Significantly better efficacy
    B. Noninferior efficacy
    C. Poor efficacy
    D. Not enough information

11. What is the most common adverse reaction regarding Technosphere® insulin?
    A. Mild, nonproductive cough within 10 minutes of inhalation
    B. Decreased lung function
    C. Lung cancer
    D. None of the above

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Program Title: **FDA Approves New Inhaled Insulin: Afrezza® (Technosphere® Insulin)**
UAN: 0048-0000-14-216-H01-P CEUs: 0.1 for pharmacists only

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Program Content:	**Strongly Disagree**				**Strongly Agree**
The program objectives were clear.	**1**	**2**	**3**	**4**	**5**
The program met the stated goals and objectives:					
Identify the different types of diabetes and each of their pathophysiologies.	**1**	**2**	**3**	**4**	**5**
Name several investigational methods for insulin administration.	**1**	**2**	**3**	**4**	**5**
Describe the pharmacokinetics and pharmacodynamics of Technosphere® insulin.	**1**	**2**	**3**	**4**	**5**
Explain the advantages and disadvantages of inhaled insulin compared to injectable insulin.	**1**	**2**	**3**	**4**	**5**
Evaluate the efficacy and safety of Technosphere® insulin based on data from clinical trials.					
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 E**	**10. A B C D**
2. A B C D	**5. A B C D**	**8. A B**	**11. A B C D**
3. A B C D	**6. A B C D E**	**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 12/18/2017.

Marijuana and Its Cardiovascular Implications

Albert Bui, fifth-year pharmacy student from Los Angeles, Calif.; Daniel Powell, fourth-year pharmacy student from Pittsburgh, Pa.; Victoria Cho, fourth-year pharmacy student from Olmsted Falls, Ohio; Kelsey Lindsley, fifth-year pharmacy student from Port Clinton, Ohio; Lindsey Peters, PharmD, visiting 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): 0048-0000-14-215-H04-P

Objectives

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

1. Know the prevalence of recreational and medicinal marijuana use.
2. Identify characteristics that align with the potential for marijuana abuse.
3. Understand the pharmacological effects of marijuana on the heart.
4. Recognize the risks and damages to the cardiovascular system from marijuana use.
5. Summarize the pharmacist's role in counseling over marijuana use.

Abstract

As marijuana becomes legalized for medical use, it is important for prescribers and pharmacists to be knowledgeable about the important aspects of marijuana such as mechanism of action, indications and abuse potential. Although marijuana's medicinal benefits are frequently reported, the risks, namely cardiovascular risks, associated with its utilization are often overlooked. Use of marijuana has been reported to increase the risk of myocardial infarction, tachycardia and hypotension, among others. Health care providers must determine if marijuana's benefits outweigh such risks when marijuana therapy is an option. It is also important for pharmacists to understand how to successfully counsel patients using medical marijuana so that the patient has an effective course of therapy.

Key Terms

Cannabinoids; Cannabis; Cardiovascular Diseases; Food and Drug Administration (U.S.); Humans; Hypotension; Medical Marijuana; Myocardial Infarction; Pharmacists; Review Literature; Risk; Risk Factors; Tachycardia

Introduction

The utilization of medicinal marijuana has been commonplace since the earliest of civilizations. Most of marijuana's positive medicinal qualities are noted because of this long period of use. However, due to the criminalization of marijuana, the determination of marijuana's negative qualities has lagged behind. Because of marijuana's resurgence and shifting public opinion, identifying possible negative effects is an important consideration when discussing marijuana as a treatment option.

Medicinal marijuana dates back centuries to the year 2737 B.C.E. when it was first recorded by the Chinese Emperor, Shen Neng, that Cannabis tea was effective for use in the treatment of gout, malaria, beriberi, rheumatism and poor memory.[1] Centuries later, the founder of surgery, Hua T'o, used a Cannabis tincture as an anesthetic in patients.

In more recent times, the Ohio State Medical Society recognized the potential uses of medicinal Cannabis in 1860 C.E., noting that it was especially useful in treating pain, inflammation and cough.[1] Even the 1868 edition of the United States Dispensatory listed Cannabis tinctures for indications such as decreased appetite, decreased sexual interest, mental illnesses, gout, cholera, hydrophobia and insomnia. Cannabis containing products were popular enough that the Squibb Company released a morphine and Cannabis product named "Chlorodyne." Eli Lilly and Parke-Davis also manufactured Cannabis containing products to be used as antispasmodics, sedatives and analgesics. At the conclusion of the Mexican-American War, Mexican migrants introduced recreational use of marijuana to the United States. However, instead of promoting marijuana usage, the Great Depression created many irrational xenophobic sentiments causing a fear of the "Marijuana Menace."[2] The decreased popularity of marijuana allowed the Marijuana Tax Act of 1937 to be passed, which put a burdensome tax on marijuana sales and significantly reduced production of Cannabis containing compounds. Eventually in the 1950s, the Boggs Act and Narcotic Control Act made marijuana possession and distribution a federal offense.[1] Despite marijuana's criminalization, it remains an extremely popular recreational drug as well as medicinal agent.

Throughout the last five decades, researchers have been investigating what gives marijuana its medicinal and hallucinogenic properties. In 1967, Mechoulam and Gaoni successfully identified and synthesized the main psychoactive ingredient in marijuana, (−)-trans-Δ9-tetrahydrocannabinol (THC).[3] It was not until 1990 that Matsuda et al. were able to identify and genetically sequence the endogenous cannabinoid receptors. They found that these receptors, which comprise the endocannabinoid system, are highly concentrated in the brain. They are known as CB_1 receptors. Soon thereafter, a second type of cannabinoid receptor was discovered in the periphery and the immune system and was named the CB_2 receptor. Since that time, medications that utilize the endo-

cannabinoid system have been an area of great interest. There are currently two U.S. Food and Drug Administration (FDA) approved medications that partially agonize the endocannabinoid system: dronabinol (synthetic THC) and nabilone (synthetic cannabinoid).[4] These are used in patients experiencing nausea, vomiting and loss of appetite.

Indications

Marijuana is currently prescribed for pain secondary to cancer, neuralgia, headaches and glaucoma.[5] It is also used to reduce muscle spasms in patients suffering from multiple sclerosis. Cancer and human immunodeficiency virus patients often use marijuana therapy to suppress nausea and induce an appetite, which decreases weight loss. Additionally, marijuana has been found to alleviate irritable bowel symptoms associated with Crohn's disease. Finally, marijuana can be used to reduce seizures in epileptic patients.

Epidemiology

There are approximately 200 million marijuana users in the world. This is approximately 4 percent of the worldwide adult population.[6,7] The highest percentage of marijuana users are located in Australia followed by North America.[7] Approximately 40 percent of the North American population that uses marijuana for a lifetime are 12 years and older while 60 percent were nonusers or occasional users. As of November 2014, Oregon and the District of Columbia were the most recent areas to legalize recreational marijuana. However, there are still legalization issues surrounding the District of Columbia due to it being a district and not a state. Recreational marijuana is now legalized in a total of four states: Alaska, Colorado, Washington and Oregon.[6,8] In comparison, medicinal marijuana use is legal in 23 states, making medicinal marijuana use more prevalent than some people realize.[9]

There are more males who use medicinal marijuana than females; more than 75 percent are males while the remaining 25 percent are females, as indicated by Figure 1.[10] The average age of males who use medicinal marijuana is 31 years while average age of females who use medical marijuana is 36 years. When the medicinal marijuana users were divided based on race, the highest percentage of users were Caucasian followed by African American, Hispanic, Asian and other. Almost 69 percent of the medicinal marijuana users were Caucasian, which is shown in Figure 2. Although the prevalence of Asian and Hispanic users is lower than Caucasian, younger users were more likely to be Asian or Hispanic. When evaluating education levels, nearly half of the users had a high school diploma. In descending order following the high school degree, medicinal marijuana users were those who had a bachelor's degree, did not complete high school, had an associate's degree, had a master's degree, and had a doctorate, which is indicated by Figure 3. In summary, the average medicinal marijuana user could be a Caucasian male who has finished high school.

Figure 1. Prevalence of medicinal marijuana users based on sex.[10]

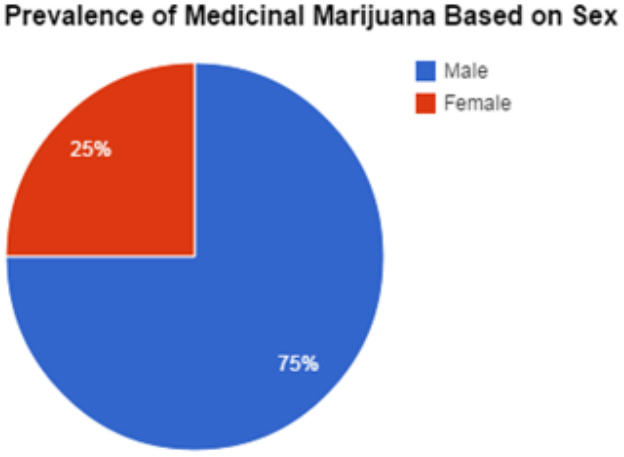


Figure 2. Prevalence of medicinal marijuana users based on race.[10]

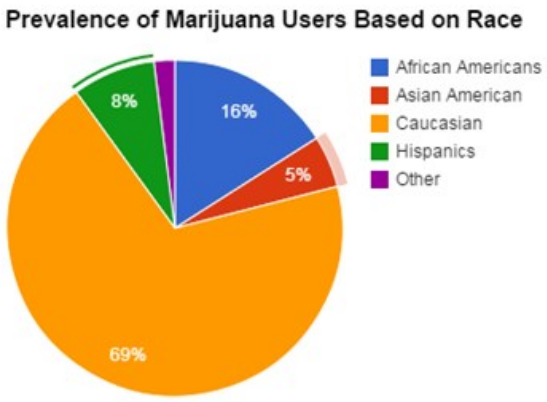
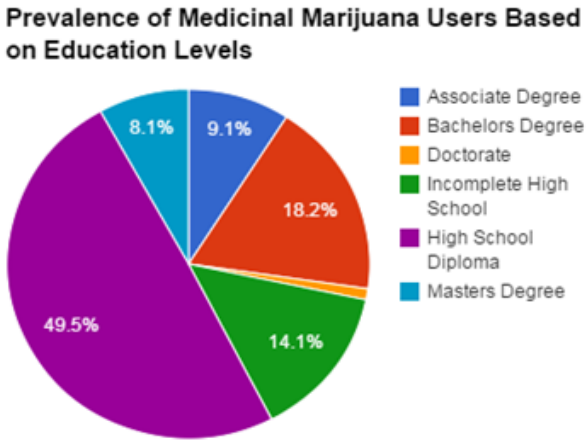


Figure 3. Prevalence of medicinal marijuana users based on education level.[10]



Potential Abuse

Of the 200 million marijuana users, approximately one in 10 users will become dependent on Cannabis.[7] Just like narcotics and other drugs, the risk of becoming dependent on Cannabis increases when it is used more frequently. Fifty percent of daily users of marijuana will become dependent users. Some of the potential causes of marijuana use disorder

include genetics, environmental influences and use of other drugs.[7,11] Studies have suggested there are three genes possibly associated with Cannabis use disorder, which are C17orf58, BPTF and PPM1D.[12] As for environmental influences, disruptive homes and users who had first-degree relatives that are abusers are 5.8 times more likely to abuse as well.[13] Over the years, Cannabis has become easier to obtain, which has increased the chance of users abusing marijuana.[14] There are over 13 million people who depend on Cannabis.[15] Cannabis dependence is more likely to occur in younger people such as adolescents.[7] The most common profile of someone who abuses marijuana is a male between the ages of 20 and 24 years who lives in a high income region.

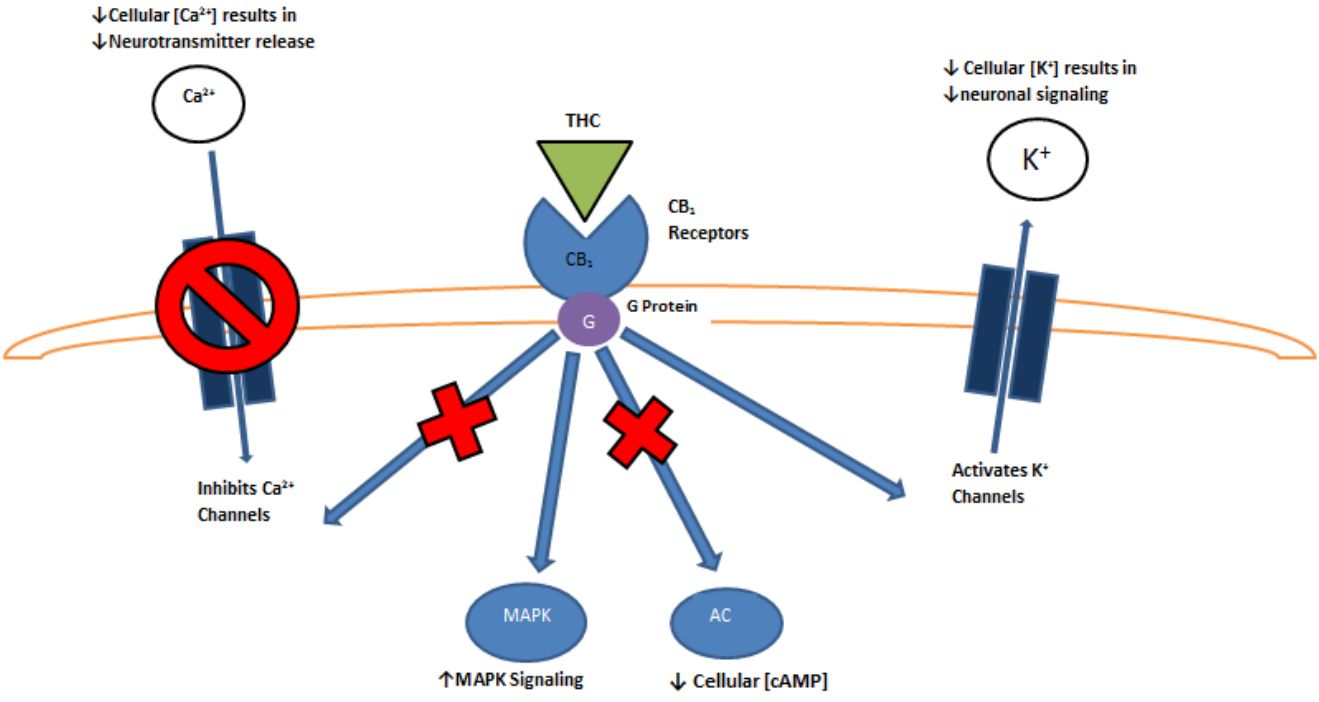
Pharmacology

Marijuana's active chemical, THC, binds to CB_1 receptors, which are G protein coupled.[16] These receptors are located on the neuronal surface, acting as a partial agonist of the endocannabinoid system. This activates a G_i protein causing the α-subunit to dissociate from the βγ-subunit, which will inhibit the activation of adenylate cyclase (AC) while activating the mitogen activated protein kinase (MAP). Inhibiting AC decreases the levels of intracellular cyclic adenosine monophosphate (cAMP). With decreased levels of cAMP, cAMP-dependent protein kinase A (PKA) will not be activated. Furthermore, without active PKA, outward rectifying potassium channels are not as highly phosphorylated, allowing potassium to exit the cell, leading to decreased neuronal signaling. Mitogen activated protein kinase, however, leads to cellular growth. N-type and P/Q-type calcium channels are also inhibited. This reduces the intracellular calcium concentration, resulting in a decreased release of neurotransmitters such as glutamate, gamma aminobutyric acid (GABA), norepinephrine, dopamine, serotonin and acetylcholine.[16,17] This process is illustrated in Figure 4.

Systemically, acute administration of THC causes sinus tachycardia by sympathetic stimulation, leading to increased sinus node automaticity.[18] Sympathetic stimulation causes the release of acetylcholine, which activates nicotinic receptors in the post ganglionic neurons. This stimulates the release of norepinephrine, which binds to β-1 receptors of the heart resulting in positive chronotropic and inotropic cardiac effects. Increased cardiac output occurs secondary to the increased heart rate and peripheral vasodilation from sympathetic activation. This increases sympathetic tone and decreases parasympathetic tone. The increased heart rate causes a shortened pre-ejection period while prolonging left ventricular ejection time with no difference in afterload, suggesting cardiologic improvement. However, there are parameters negatively affected by marijuana usage. Supine tachycardia and increased blood pressure are noted, with hypotension occurring in the upright position.[19]

When marijuana is smoked, the bioavailability of THC is between 2 and 56 percent, reaching peak plasma concentrations nine minutes after the first inhalation.[20] Psychoactive effects begin almost instantly and reach their peak two to three hours later. Effects can last between four and 12 hours depending on the dose and user.[21] Marijuana is rapidly absorbed through the lungs and is distributed to highly perfused tissues such as the lung, heart, brain and liver. This is due to THC's highly lipophilic properties. Tissue concentrations reach their peak four to five days after use and have an elimination half-life of seven days.[22] The THC is metabolized mainly through the cytochrome P450 (CYP450) system of the

Figure 4. Summary of THC's effects.[16,17]



liver, with metabolites detectable as early as 13 minutes after the initial inhalation of marijuana.[20] After five days, 80 to 90 percent of THC is excreted either in the feces (65%) or in the urine (20%). The THC urine concentration detection window varies by frequency of utilization. A first time marijuana user can test negatively for THC a few hours after smoking, but a chronic user can test positively for THC up to 67 days from the time of marijuana use.

Risks/Damages to the Cardiovascular System

Although medicinal marijuana is beneficial to some, there are many negative consequences related to medicinal marijuana use. There are known cardiovascular issues related to the use of marijuana. For instance, users are 4.8 times more likely to experience a myocardial infarction within one hour of using marijuana.[6] Those who do experience a myocardial infarction while using marijuana have a higher mortality rate compared to a person who does not use marijuana. In general, patients who use marijuana more than once per week are at a 4.3 times higher risk for mortality. Marijuana use also increases the risk of ischemic stroke. Due to decreased oxygen delivery from smoking, users have a higher oxygen demand. Patients who do use marijuana recreationally or medicinally should be aware of an increased risk for cardiovascular events. There is a lot of interest in determining how this cardiovascular damage occurs.

Due to the ethical and moral issues concerning marijuana, there are a limited number of controlled studies that definitively explain a correlation between independent variables (marijuana use versus mortality/cardiovascular stress). The majority of the cases discussed are individual events that have been reported throughout the United States. Although statistical significance of a cause-and-effect relationship cannot be achieved without comparison to other subjects, these cases give insight to what patient outcomes can occur.

The majority of patients studied after marijuana use either had healthy coronary arteries or minimal coronary irregularities. A reported case of a 34-year-old man showed a right bundle-branch-type ventricular tachycardia precipitated by slow coronary blood flow.[23] Upon admission to the emergency department (ED), the patient presented with palpitations, shortness of breath (SOB), chest pain and near syncope from working in his garden. He also claimed a three month history of occasional "heart fluttering" with dizziness. The patient admitted to tobacco use (<½ pack a day) and marijuana use (twice daily). Coronary angiogram indicated healthy vessels with no stenosis; however, coronary blood flow was markedly reduced (flow grade of 1 to 2) according to the thrombolysis in myocardial infarction (TIMI) classification. Coronary blood flow was relatively antegrade beyond an occlusion with some filling of the distal coronary bed. Coronary flow was normalized after administration of verapamil and cessation of marijuana. Ventricular tachycardia was no longer inducible in the electrophysiology laboratory. This case suggests that marijuana could precipitate some abnormalities in coronary microcirculation that could potentially lead to ventricular tachycardia.

Myocardial infarctions (MI), specifically ST-elevated myocardial infarctions (STEMI), have also been reported after the use of marijuana. A 37-year-old obese man presented to the ED with chest pain and increased perspiration immediately after marijuana use.[24] The patient denied any family history of coronary disease and diabetes. The patient also denied SOB, syncope, dizziness and palpitations. The patient used Viagra 100mg approximately 36 hours before the onset of pain. The patient's hypertension was controlled with Norvasc 5mg daily. The patient presented with an unremarkable blood pressure (BP) and heart rate. Electrocardiogram (EKG) results showed a STEMI as evidenced by an elevated ST segment and increased creatinine kinase-MB fraction and troponin levels. After percutaneous intervention, the patient was discharged home with a normal ejection fraction per echocardiogram. In this study, marijuana effects to the heart were amplified due to Viagra's CYP3A4 inhibition. Without CYP3A4 metabolism of marijuana, the active chemical led to coronary vasospasms regardless of previously healthy coronaries.

To assess the long-term mortality associated with marijuana use, a multicenter inception cohort study was conducted.[25,26] The study was titled "The Determinants of MI Onset." Three thousand eight hundred eighty-eight patients were evaluated from 1989 to 1996 and followed up for mortality via the National Death Index. After such time, 519 patients died, including 22 of 109 reporting marijuana use before their MI. No statistical significance was established for the association between marijuana use and mortality. However, reported users of marijuana had a mortality rate 29 percent higher (95% confidence interval (CI) 0.81-2.05, P=0.28) than nonusers. Also, the rate of MI is 4.8 times greater in the hour after marijuana use compared with other times (95% CI 2.4-9.5). Thus, smoking marijuana is possibly a trigger of acute MI.

Atrial fibrillation (AF) has been recorded in a systematic review of six patients.[27] All patients, age 24.5 ± 7.8 years, experienced AF shortly after marijuana use. In three of the patients, sinus rhythm was recovered via pharmacological therapy. One patient experienced palpitations identified as sinus tachycardia. Two of the patients had loss of consciousness (one of them fell) as marijuana suppresses the central nervous system (CNS) and induces postural hypotension. Only one had hypertension as a comorbidity. All patients had favorable outcomes as AF subsided with marijuana cessation.

So far, there have been no reported cases of short-term or long-term use of Cannabis causing congestive heart failure (CHF).

In these studies discussed, comorbidities (e.g., hypertension) and lifestyle habits (e.g., tobacco use/alcohol consumption) were confounding factors that could have contributed to the aforementioned cardiovascular events. Because these factors' impact on cardiovascular function was not taken into account, it seems that marijuana cannot be the sole contributor. Further controlled trials need to be conducted to clarify marijuana's effect on the heart.

Currently, there are two FDA approved agents on the market that contain THC. Dronabinol (Marinol®) is primarily used to treat chemotherapy-associated nausea and acquired immune deficiency syndrome (AIDS)-related anorexia. Tachycardia, heart palpitations and facial flushing have been reported in 1 percent or more of these patients taking dronabinol in placebo-controlled trials.[28] Nabilone (Cesamet®) contains a synthetic cannabinoid similar to THC and is used for the same purpose. Tachycardia and orthostatic hypotension have been reported in these patients (<1% and 8%, respectively).

Pharmacist's Role

As health care providers, pharmacists can play a key role in counseling and advising patients who are using marijuana. First and foremost, pharmacists must comply with all local, state and federal laws regarding the use of medical marijuana while adhering to the stricter laws. Marijuana remains a schedule 1 substance in all states and infractions of the law can result in strong disciplinary measures from the state licensing board.[29] Some states are suggesting that pharmacies dispense marijuana. If that is the case, all relevant procedures and protocols should be followed in terms of dispensing and identifying possible diversion.[30] Pharmacists should work closely with primary care physicians to ensure marijuana is the most appropriate and effective therapy available and to ensure drug-drug and drug-disease interactions are screened.[29] Drugs that have interactions with THC include barbiturates, sedatives, benzodiazepines, theophylline, disulfiram, fluoxetine and warfarin. Conditions that can be exacerbated with THC include chronic obstructive pulmonary disorder (COPD), hepatitis C, heart disease, stroke or hypertension. If there is a potential interaction or a safer alternative therapy available, pharmacists should use their professional judgment.[31] In terms of counseling, the benefits and risks should be voiced to the patient including potential side effects. After a comprehensive social and medical history is obtained, pharmacists should look for signs of dependence or addiction such as insomnia, increased appetite, sweats, chills and possible hallucinations. Pharmacists should also be able to explain the biological fundamentals of addiction: decreased levels of dopamine in the limbic system translates to decreased feelings of reward. This should include strategies to correct medical withdrawals and helping to prevent relapse.[29] Patients on medical marijuana treatment should be advised to strictly adhere to the therapeutic regimen. Overuse could lead to dependence, withdrawal and, eventually, addiction. If addiction occurs, patients should seek medical attention to initiate marijuana cessation and possible counseling or psychotherapy. There are many local and national addiction lifelines and websites available for patients such as www.lifelineintervention.com. Patients can also call 1-844-238-3665 for help with addiction.

Pharmacists should be able to retrieve and evaluate drug literature and clinical trials to answer completely and accurately any questions that patients may have.[29] Patients that use medical marijuana should be closely supervised during the course of therapy to ensure that compliance is maintained. However, marijuana is still illegal in most states, and pharmacists should not advise patients on how to obtain marijuana. Lastly, pharmacists on Pharmacy and Therapeutics (P&T) committees are key players in the proper dispensing of marijuana. Dispensing entities may rely on these committees for guidance on the proper regulations and dispensing of THC products.

Conclusion

In conclusion, Cannabis has been used medicinally since 2737 B.C.E. The use of marijuana has increased and will continue to increase as its medicinal use becomes legalized in more states. Pharmacists should be aware of Cannabis dependence, which can be caused by various genetic and environmental factors. Pharmacologically, marijuana mediates its effects through CB_1 receptors in the heart and induces the aforementioned cardiac events. There are not enough studies to conclude that cardiac issues are caused by marijuana. However, there is some indication that marijuana can produce detrimental cardiovascular outcomes such as myocardial infarction and atrial fibrillation. Pharmacists can directly impact the lives of those who use marijuana by explaining how it affects the human body, discussing possible adverse reactions and educating on the potential for abuse.

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Assessment Questions

1. The main psychoactive ingredient in marijuana is:
   A. (−)-trans-Δ9-tetrahydrocannabinol
   B. Anandamide
   C. Nabilone
   D. Cannabidiol

2. Medical marijuana use is indicated for:
   A. Pain
   B. Crohn's disease
   C. Epilepsy
   D. All of the above

3. True or False: THC is excreted through the feces only.
   A. True
   B. False

4. What is the most likely profile of a medicinal marijuana user?
   A. Caucasian female with a high school degree
   B. Hispanic male with master's degree
   C. Caucasian male with a high school degree
   D. Asian male with a bachelor's degree

5. True or False: Recreational marijuana is legal in 23 states.
   A. True
   B. False

6. What is the cause of marijuana use disorder?
   A. Genetics
   B. Use of other drugs
   C. Disruptive homes
   D. All of the above

7. True or False: There is sufficient clinical data to definitively show a correlation between marijuana and cardiovascular disease
   A. True
   B. False

8. Marijuana has NOT been shown to precipitate which of the following cardiovascular events?
   A. Reduced coronary flow
   B. Atrial fibrillation
   C. Congestive heart failure
   D. Myocardial infarction

9. Viagra is an ___of the ___ enzyme which can ___ the levels of marijuana.
   A. inducer, CYP3A4, increase
   B. inhibitor, CYP2C19, decrease
   C. inducer, CYP2C19, increase
   D. inhibitor, CYP3A4, increase

10. True or False: Comorbidities (e.g., diabetes, hypertension) are NOT contributing factors to cardiovascular events
    A. True
    B. False

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Program Title: **Marijuana and Its Cardiovascular Implications**
UAN: 0048-0000-14-215-H04-P CEUs: 0.1 for pharmacists only

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Program Content:	**Strongly Disagree**				**Strongly Agree**
The program objectives were clear.	**1**	**2**	**3**	**4**	**5**
The program met the stated goals and objectives:					
Know the prevalence of recreational and medicinal marijuana use.	**1**	**2**	**3**	**4**	**5**
Identify characteristics that align with the potential for marijuana abuse.	**1**	**2**	**3**	**4**	**5**
Understand the pharmacological effects of marijuana on the heart.	**1**	**2**	**3**	**4**	**5**
Recognize the risks and damages to the cardiovascular system from marijuana use.	**1**	**2**	**3**	**4**	**5**
Summarize the pharmacist's role in counseling over marijuana use.	**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
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8. A B C D
9. A B C D
10. A B

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Cannabinoids for the Treatment of Chronic Headaches

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Abstract
Species of the Cannabis plant genus were among the earliest medicinal plants cultivated by man, with historical accounts of their medicinal uses dating back before the Common Era. Despite its current legal status, Cannabis has garnered nationwide attention as a therapeutic agent for various disease states, including chronic headaches, due to its medical indications as an antispastic, analgesic, antiemetic, neuroprotective and anti-inflammatory agent. Since headaches have a high prevalence in the American population and greatly impair simple daily aspects of living, chronic headaches have become a particular point of interest in regard to the therapeutic potential of Cannabis. Clinical trials and case reports have shown that Cannabis administration for headaches has greatly improved the quality of life and decreased the use of adjuvant medications for some patients. Studies are limited and conflicting, mostly due to the legal issues associated with Cannabis. Pharmacists play a major role in managing patients who are treating their chronic headaches and need to be able to educate patients about Cannabis. Patients may consider trying to treat their headaches with Cannabis even though it has legal restrictions regarding its use and is not U.S. Food and Drug Administration (FDA) approved. Pharmacists should understand federal and state restrictions, drug interactions, potential health risks, psychoactive effects and types of delivery systems for Cannabis use.

Key Terms
Analgesics; Antiemetics; Cannabinoids; Cannabis; Food and Drug Administration (U.S.); Headache; Headache Disorders; Humans; Marijuana Smoking; Pharmacists; Plants, Medicinal; Quality of Life; Review Literature

Introduction and Background

Species of the Cannabis plant genus (e.g., *Cannabis* sativa, *Cannabis* indica) were among the earliest medicinal plants cultivated by humans, with historical accounts of their medicinal and entheogenic uses dating back before the Common Era, primarily in Ancient India and other Asiatic regions.[1] In 1860, the Ohio State Medical Society organized the first conference examining the clinical benefits of Cannabis (also known as marijuana), and by 1870 the United States Pharmacopoeia recognized Cannabis Americana in a separate monograph as a legitimate medical compound with analgesic, sedative and hypnotic potential. Despite revision of the Cannabis monograph in 1880, the United States Pharmacopoeia removed Cannabis, USP in 1941, largely due to various legal restrictions on its agricultural production. Although efforts to elucidate the pharmacologic action and further therapeutic potential of Cannabis were published in the 1950s and 1960s, Cannabis was eventually classified as a schedule I substance under the Controlled Substances Act of 1970, claiming Cannabis as a drug with no accepted medical use and a high potential for abuse.

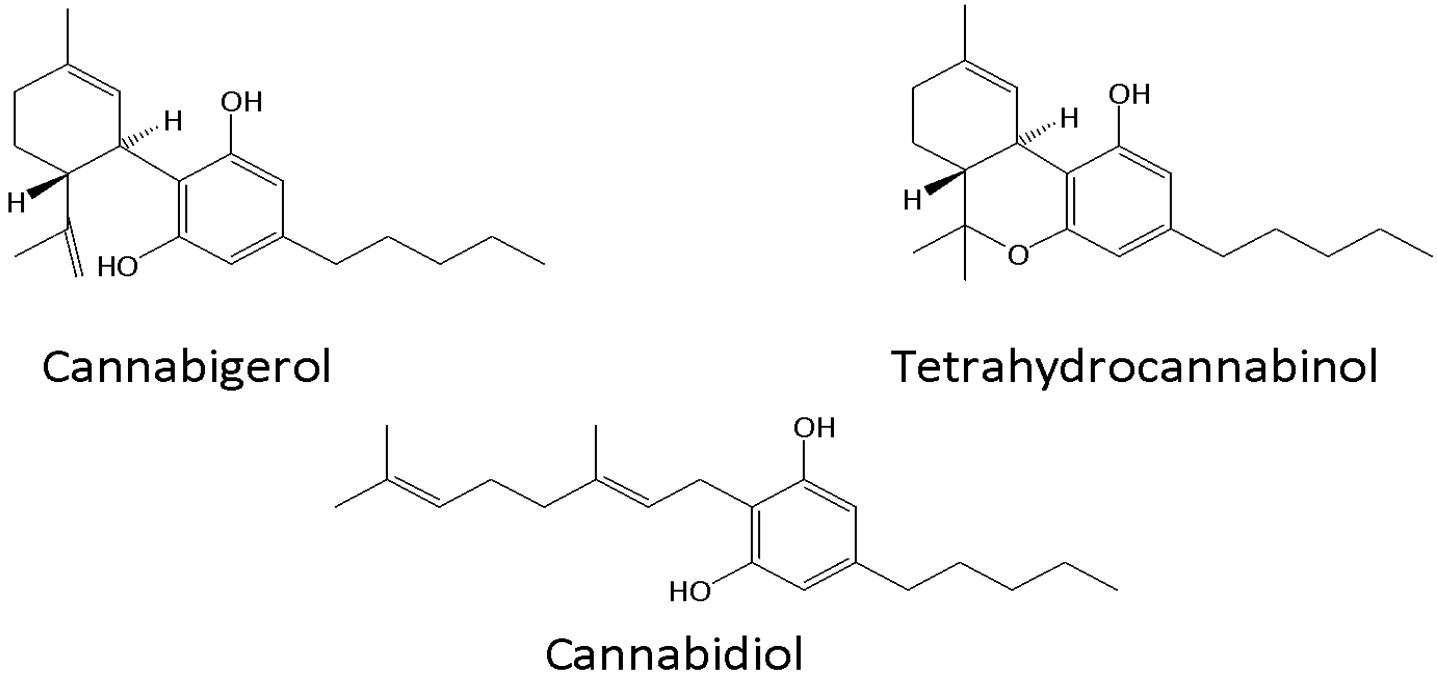
Despite its current legal status, Cannabis has garnered nationwide attention as a potential therapeutic agent. Due to its medical properties as an antispastic, analgesic, antiemetic, neuroprotective and anti-inflammatory agent, it has demonstrated positive effects toward the therapy of various disease states such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), various forms of cancer, multiple sclerosis (MS), chronic neuropathic pain, Parkinson's disease, Tourette's syndrome and certain psychiatric diseases.[2] Currently 20 states and the District of Columbia have enacted laws that allow medical Cannabis use with the recommendation of a physician.[3] Among the various disease states that Cannabis may treat, chronic headaches—headaches lasting more than 15 days a month for three months or longer—have become a particular point of interest with respect to Cannabis therapy.[4] This is primarily due to the high prevalence of chronic headaches in the American population and impairment of simple aspects of daily physical, social and occupational living. In the 21st century, efforts to examine the therapeutic potential of Cannabis in chronic headaches have largely focused on cannabinoids, the pharmacological compounds unique to both the Cannabis genus and endogenous compounds in animal species.

Pharmacology and Medicinal Chemistry of Cannabinoids

The term cannabinoid describes the group of terpenophenolic compounds present both in Cannabis and in the nervous and immune systems of a variety of animal species.[5,6] Cannabinoids are further classified as (a) phytocannabinoids, those which occur uniquely in the Cannabis plant; (b) endocannabinoids, those which are endogenously produced in animal species; and (c) synthetic cannabinoids, those which are chemically synthesized typically in a laboratory setting for the purpose of additional pharmacological studies or eventual marketing as a pharmaceutical preparation. At least 66 cannabinoids have been identified and isolated from the Cannabis plant, most of which differ in cyclization patterns from the terpenophenolic precursor molecule cannabigerol (Figure 1).

Efforts to examine the pharmacologic activity and therapeutic potential of cannabinoids, though limited due to federal legal restrictions, have largely focused on phytocannabinoids, particularly Δ^9-tetrahydrocannabinol (THC) and (-)-cannabidiol (CBD) (Figure 1).[7] Along with other cannabinoids, THC and CBD exert their pharmacologic effects on the endogenous cannabinoid system, or endocannabinoid system, located in human neural tissue and immune cells. The receptors comprising the endocannabinoid system include the cannabinoid receptor type 1 (CB_1 receptor) and the

Figure 1. Cannabigerol, Tetrahydrocannabinol, Cannabidiol.



cannabinoid receptor type 2 (CB_2 receptor). Specifically, CB_1 receptors are densely located in neuron terminals of the basal ganglia, cerebellum, hippocampus, neocortex, hypothalamus and limbic cortex, whereas CB_2 receptors are located chiefly in immune cells. The extensive distribution of CB_1 receptors in the central nervous system renders the CB_1 receptor an attractive target for potential treatment of the neurological symptoms associated with chronic headaches.

Chronic headaches consist of a variety of disorders including cluster headaches, hemicranias continua, idiopathic intracranial hypotension, migraines, tension type headaches and a mixture of various types; however, the exact mechanism of action of chronic headaches is not completely known, and the onset of a chronic headache event may be completely unpredictable by the patient.[8] In the United States, 70 to 80 percent of patients admitted to specialized headache clinics are diagnosed with chronic headaches and report a diminished quality of life due to impaired physical, social and occupational function. Furthermore, over half of chronic headache patients report sleep disturbances, depression and anxiety, which may worsen their symptoms.[4] Research suggests that the physical and neurological symptoms associated with chronic headaches may stem from the inflammation of cranial nerves and blood vessels, changes in cranial blood vessel sizes, cranial muscle tension and irregular changes in the release of neurotransmitters (e.g., serotonin, norepinephrine, dopamine) that regulate pain pathways.[9]

The principal psychoactive component in Cannabis, THC, has demonstrated therapeutic potential to treat and manage mild to moderate pain associated with chronic headaches, primarily due to its action as a partial agonist of the CB_1 receptor.[6,7] According to several small pharmacologic studies, the analgesic effects of THC may stem from its neuroprotective potential. Specifically, THC has demonstrated an ability to modulate rostral ventromedial medulla (RVM) activity, disrupt descending pain pathways and inhibit synthesis of prostaglandin, an endogenous regulator of inflammation associated with chronic headaches.[7] In neural tissue, the action of THC on CB_1 receptors reduces the contractile output and neurotransmitter release in smooth muscle, ultimately producing characteristic analgesic effects.[6] In contrast to the established therapeutic indications of THC, the pharmacologic activity of CBD, a nonpsychotropic component of Cannabis, is not well understood, and there are conflicting views regarding the mechanism of CBD in the endocannabinoid system.[7] Though CBD has no direct affinity for either the CB_1 or CB_2 receptors, several studies have indicated that it may serve as an allosteric antagonist on either cannabinoid receptor, therein reducing the psychoactive effects of THC on CB_1 and CB_2 receptors.[5] By reducing the affinity of THC for CB_1 and CB_2 receptors, CBD may modulate the analgesic effects of THC in neural and immune tissue. Although one of the primary medical delivery systems of phytocannabinoids in humans is by smoking herbs of the Cannabis flower, THC and CBD can also be administered by noncombustive vaporization of Cannabis herbs and oral ingestion of edible products containing Cannabis-infused oils.[7] Upon smoking, THC has an estimated bioavailability of 10 to 25 percent, a distribution phase half-life of 0.5 hours and a terminal phase half-life of 30 hours, primarily due to its extensive lipophilicity. On the other hand, CBD has a similar lipophilic profile but a shorter terminal phase half-life of nine hours. Following pulmonary administration, whether by combustive smoking or vaporization, the analgesic effects useful to providing relief associated with chronic headaches may occur as quickly as 30 seconds to three minutes and typically last for two to three hours.[5]

Current pharmacologic medications indicated for the treatment of chronic headaches include those that mimic serotonin effects (e.g., triptans and dihydroergotamine-45), modulate serotonin levels (e.g., selective serotonin reuptake inhibitors (SSRIs)), reduce inflammation (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids), stabilize blood vessels (e.g., calcium channel blockers and beta blockers) and decrease muscle tension (e.g., muscle relaxants).[9] Despite the historical success of these medications as a maintenance therapy in relieving symptoms associated with chronic headaches, these drugs fail to provide the immediate relief that fits the almost instantaneous and unprecedented onset of a chronic headache event. For example, some drugs, such as beta blockers and SSRIs, may take four to six weeks for any prolonged effect to occur, and other analgesic drugs, such as NSAIDs and corticosteroids, may induce rebound headache events. Furthermore, as single active pharmaceutical compounds, these drugs typically only target one of the many neuropathic features associated with chronic headaches, limiting the possibility of a collective therapeutic approach to all symptoms. Cannabinoids, which provide a relatively fast onset of action, extensive half-life and pharmacologic potential to act on numerous signaling pathways by way of CB_1 receptors, serve as an attractive therapeutic option in treating chronic headaches.

Human Clinical Trials

Clinical data on Cannabis use among chronic headache patients is limited due to the fact that marijuana is classified as a schedule I substance in the United States.[10] Therefore, its use is strictly regulated and still illegal in many states; although some states have legalized the use of medicinal marijuana, it is still illegal on a national level. Another limiting factor is that the exact pathophysiology of headaches is not completely known, and it is likely that multiple different mechanisms can produce headaches. Despite marijuana's illegal status, some patients use it for relief of headache, which is made easier by the increasing number of states that are legalizing medical marijuana. There are no blinded studies on headache subjects from which true efficacy can be assessed. However, many observational case studies and case reports have demonstrated resolution of headache symptoms with administration of Cannabis or dronabinol, the pharmaceutical formulation of THC.

In 2012, Pini et al. published a randomized, double-blind, active-controlled, crossover study regarding medication overuse headache (MOH) in which they evaluated the efficacy and safety of nabilone (a synthetic THC analogue) in reducing pain and frequency of headache.[11] Medication overuse headache is a chronic headache lasting more than 15 days per month that develops from primary headaches (migraine, tension-type headaches) as a result of overuse of a pharmaceutical agent. The authors also evaluated quality of life and analgesic intake in patients with MOH. Thirty MOH patients were enrolled in a study at the University of Modena's Interdepartmental Centre for Research on Headache and Drug Abuse (Italy), which compared safety and efficacy between oral nabilone 0.5mg/day and oral ibuprofen 400mg/day. Patients were given eight weeks of nabilone followed by eight weeks of ibuprofen, or vice versa, with a one week washout period between regimens. At the end of the study, both treatments demonstrated improvements from baseline, but nabilone showed greater efficacy in reducing pain intensity, daily analgesic intake, and medication dependence. Adverse events due to nabilone were uncommon and mild, and included dizziness, decreased appetite, vomiting, nausea, epigastric discomfort and dry mouth. Overall this study demonstrated the potential benefit of nabilone in relieving headache, decreasing analgesic consumption and improving the quality of life while being relatively well tolerated. Due to the small sample size of this study, larger clinical trials are needed to determine the clinical relevance of these findings.

A case cohort report by Leroux et al. about the frequency of Cannabis use in cluster headache patients reported the effects Cannabis had on the headache attacks.[12] From July to October 2009, 139 patients with cluster headaches answered questionnaires in two French headache centers regarding Cannabis use and its effects on cluster headaches. It was reported that 27 patients (19.4%) had tried Cannabis to treat cluster headache attacks, of which 25.9 percent reported some efficacy, 22.3 percent negative (worsening) effects and 51.8 percent variable or uncertain effects. The authors concluded that Cannabis use is relatively frequent in patients with cluster headaches, but it has limited efficacy in treating attacks due to the variable effects observed by patients. Multiple factors may have affected the data collected in the study, such as the variations in amount of Cannabis inhaled and possible differences in the cannabinoids produced in the marijuana plants obtained by patients. Furthermore, the study had a small sample size of 27 patients who had tried Cannabis to treat their headaches, questioning if the power of the study was sufficient to make adequate conclusions. Additionally, collecting information by patient survey introduces many uncontrollable variables, and data that could affect marijuana efficacy was not collected (patient current medications, diet, exercise, genetics, etc.). The authors concluded that a recommendation for use of Cannabis to treat cluster headaches is not justified unless further controlled trials using synthetic cannabinoids demonstrate more convincing evidence for efficacy. This study, although very limited, shows that some patients are using marijuana to self-treat their cluster headaches and that it is beneficial for some patients.

An observational case study by Robbins et al. involved a 19-year-old male patient reporting to the Montefiore Headache Center (New York City) for management of his cluster headaches.[13] When untreated, the patient's headache attacks occurred for about four hours every other day for a two week period followed by a headache-free period of four to six weeks. Prophylactic medications (verapamil, lithium, sodium valproate, melatonin, topiramate, nifedipine, indomethacin, zonisamide, venlafaxine, ergotamine tartrate and clonazepam) were administered with either minimal success or intolerable adverse effects. Treatment for the patient's headaches with sumatriptan tablets, zolmitriptan nasal spray, ergotamine/caffeine, oxycodone, aspirin/butalbital/caffeine, acetamino-

phen/dichlorphenazone/isometheptene and indomethacin were all ineffective as well. However, the patient stated that administration of marijuana by inhalation at the onset of the headache consistently led to complete relief within five minutes. Due to the lack of response to multiple other medications, the patient was given dronabinol 5mg as a replacement for marijuana for acute treatment of the headaches. Dronabinol was found to consistently and dramatically relieve the patient's cluster headaches within five to 15 minutes of administration. The authors noted that the relief from headaches was probably not due to a placebo effect due to the large number of agents used that failed to prevent or treat the patient's headaches. However, other patients suffering from cluster headaches have reported that marijuana use can trigger cluster headaches or worsen a current headache. This case study shows that marijuana may have chemical components that could be effective in the treatment of headaches, especially those refractive to other medications, but it must be used with caution because it has also been shown to trigger headache attacks in some patients.

Role of the Pharmacist

Due to the prevalence of chronic headaches in the United States and the growing interest in Cannabis as a viable medicinal agent, patients suffering from chronic headaches may be interested in cannabinoids as agents for improving their headaches. Important features of cannabinoids include the ability of phytocannabinoids to be administered through rapidly-acting delivery systems, such as inhalation, and to provide a steady, collective relief from many of the neuropathic features of chronic headaches. These benefits may lead patients to consider the use of cannabinoids as a replacement to their current pharmacologic therapies. However, due to the controversial legality of Cannabis, as well as its concerning psychoactive effects, many patients may consult health care providers such as pharmacists for guidance. Pharmacists should have a good understanding of the potential benefits of cannabinoid treatment for chronic headaches as demonstrated through clinical studies and case reports, and they should also be mindful of federal and state restrictions on Cannabis use. As Cannabis remains a schedule I substance in the United States and has no federally-recognized accepted medical uses, it is important that the pharmacist not actually recommend use of Cannabis, but rather explain that several studies have demonstrated potential therapeutic benefits associated with the treatment of chronic headaches for some patients. Not recommending these agents avoids any legal consequences, but more importantly educates the public that compounds in Cannabis may be beneficial to treating treatment-resistant headaches and can greatly impact the quality of life of some patients. Some cannabinoids may also be useful for treating chemotherapy-related nausea and vomiting that has not been alleviated by conventional treatments.

Additional counseling points about cannabinoids should include cautioning patients about the possible health risks. These include lung or respiratory infections, chronic cough, heart attack, psychosis and depression relating to certain delivery systems for administering Cannabis (e.g., smoking); potentially unwanted psychoactive effects that may lead to cognitive impairment in daily social and occupational functioning, including hallucinations, paranoia, anhedonia, dizziness, driving impairment, decreased appetite, vomiting, nausea and asthenia; and legal and occupational consequences associated with drug use in the workplace.[14] Pharmacists should also be aware of drug interactions of Cannabis or its components in case patients admit that they are using Cannabis or are prescribed a cannabinoid. Major drug interactions include propoxyphene, buprenorphine, levomethadyl acetate, sodium oxybate, alcohol and drugs causing central nervous system depression.[15]

Conclusion

Many patients in the United States who suffer from chronic headaches seek treatment because of the debilitating effects of headaches in physical, social and occupational functioning. Headache relief has been documented with administration of Cannabis or its extracted ingredients in several case studies and case reports; therefore Cannabis and its respective cannabinoids are worth studying despite strict and conflicting legal restrictions in the United States. One major problem with Cannabis use in the treatment of headaches is that although activation of cannabinoid receptors may induce pharmacologic effects that provide headache relief in some patients, it may not provide relief in all patients, since the mechanisms of chronic headaches are highly complex and different among individual cases. Despite these challenges, cannabinoids may still provide a more desired immediate relief and an ability to treat multiple symptoms at once beyond the scope of conventional pharmaceutical treatments that may only exhibit a limited number of pharmacologic effects. Pharmacists play an important role in educating patients regarding the potential efficacy and safety of Cannabis use in treating chronic headaches; however, additional studies are required to establish long-term safety and efficacy.

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Outbreak of Ebola Virus Disease

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Abstract
Ebola virus disease (EVD) has existed as a major health concern with devastating and, many times, fatal symptoms. The recent outbreaks of EVD in West Africa and the Democratic Republic of the Congo (DRC) have incited international concern. In this article, the implications of EVD will be discussed including the etiology, transmission, signs and symptoms, diagnosis and treatment of the disease. In addition to this discussion, the manner in which major health care organizations, including the World Health Organization (WHO), are dealing with treating infected patients and containing spread of the disease will be covered.

Key Terms
Africa, West; Congo; Disease Outbreaks; Hemorrhagic Fever, Ebola; Humans; Review Literature; World Health Organization

Introduction

International attention has recently focused on the fatalities caused by the Ebola virus disease (EVD). Previously known as Ebola hemorrhagic fever when first discovered in 1976, EVD has become an epidemic. Two cases occurred simultaneously in Sudan and DRC. The current outbreak has spread outside of Africa and 13,675 laboratory-confirmed cases were reported to WHO and the Centers for Disease Control and Prevention (CDC) between December 2013 and January 2015.[1-6] On Oct. 4, 2014, a case of Ebola virus disease was confirmed in the United States by the CDC and there have, in total, been four cases of EVD treated in the United States to date.[2] With the recent outbreak, fear and questions surrounding EVD have risen; health care professionals have a duty to respond to patient concerns about EVD. This article will discuss the etiology, transmission, symptoms and treatment of EVD.

Disease Etiology

Ebola virus disease is native to regions of Africa. Its natural reservoir is unknown but is believed to be fruit bats.[3,4] There are five species of viruses of the ebolavirus genus, four of which are known to cause disease in humans. Each is named for the geographical location from which it originated. Ebola virus, or Zaire ebolavirus, first identified in DRC, is the species associated with the highest mortality rate, and the species of the current 2014 outbreak.[3,5]

The current outbreak has spread over West Africa in the countries of Guinea, Liberia and Sierra Leone with a total of 22,057 cases reported, and 13,675 of those cases being laboratory confirmed Ebola virus.[6] Because this outbreak has affected areas of large population, the increased rate of transmission makes this the largest outbreak to date. There are four reported cases confirmed in the United States (two travel-associated and two locally acquired) and one travel-associated case in Spain. There were also 66 documented cases of Ebola virus in DRC, but they are not associated with the current outbreak in West Africa. However, with the outbreak in DRC having no new cases since November, the outbreak was declared over on Nov. 21, 2014.[7] Patient zero of the West Africa outbreak was a pregnant woman from Ikanamongo Village who handled bush meat and became ill with symptoms consistent with Ebola virus. She died on Aug. 11, 2014, and several health care workers were exposed to the virus. No one associated with this outbreak reported traveling to the areas of West Africa where the largest outbreak originated.[7] Those who have come in contact with wildlife infected with Ebola virus are at high risk for infection, as the virus can be transmitted through improperly cooked meat or contact with the animal's bodily fluid. Health care workers taking care of infected individuals and people who have had close contact with the patients' bodily fluids are at greatest risk for contracting the infection.

The ebolaviruses are negative-sense ribonucleic acid (RNA) viruses.[5] The exact mechanism for how the virus damages host cells and causes infection has not been clearly studied due to limited research resources in the areas of Africa where the virus is found. However, certain evidence has suggested that the specific glycoproteins on the viral surface envelope attribute to certain progressive properties of the disease. One glycoprotein (GP) contributes to the hemorrhagic symptoms by allowing the virus to insert its contents into monocytes and endothelial cells, causing a release of cytokines leading to inflammation and damage to host blood vessels, respectively. Another GP, sGP, binds to and inhibits neutrophils. This suppression of the host's immune response allows the virus to infect the host unopposed. Furthermore, infected neutrophils transport the virus to the lymph nodes, liver and spleen, which increases the perpetuation of the infection.

Transmission

With limited treatment options for EVD, it is important to reduce the spread and transmission of the virus among hosts because the virus is thought to originate in fruit bats. Individuals are not only warned to avoid contact with these animals, but also other wildlife including monkeys, chimpanzees, gorillas, forest antelope and porcupines.[1] In addition to avoiding the blood, organs, secretions or other fluids from these animals, individuals should refrain from consuming raw meat from any potentially infected species.[8] Live-animal market places are often the culprit of animal to human transmission for a multitude of diseases due to the vast exposure and the mixing of different species. This, combined with poor hand hygiene, results in a greater risk of transmission

of Ebola from animals to humans.[9] It is important to practice meticulous hand hygiene to not only prevent the transmission of the virus from wildlife but also from other humans.[8]

Ebola virus is spread from human to human by direct contact. Individuals may acquire the virus by directly touching any body fluids including blood, semen, feces, saliva, urine and vomit of an infected individual, which then enters through broken skin or a mucous membrane. The virus can also be spread indirectly across surfaces or materials that are contaminated with any such infected body fluids.[1] Perhaps the best way to prevent the transmission from person to person is to avoid any and all blood or body fluids as well as careful hand washing with soap and water or an alcohol-based cleanser.[8] Wearing gloves while handling animals or contaminated individuals is also recommended. Communities in affected areas are advised to avoid funeral or burial rituals that include direct contact of those who have died of Ebola.[1,8] As long as the blood and body fluids of the deceased contain the virus, the individual is considered infectious; thus, facilitating a role in the transmission of the virus.[1] In those areas of outbreak, the WHO suggests quarantining the sick individuals from the healthy individuals and closely monitoring one's health for 21 days if possible exposure has occurred. This 21-day quarantine coincides with the incubation period, or the period of time from infection of the virus until symptoms appear. If no symptoms of Ebola occur within the 21 days, the individual may return to a normal lifestyle.

Health care workers are at significant risk for contracting Ebola virus. Their close contact and direct care with patients infected with the virus increases the potential for transmission of the disease. Due to the nonspecific signs and symptoms of the virus in the beginning stages, the importance of using personal protective equipment in all patient cases regardless of diagnosis is stressed to all health care personnel.[10] Protective devices such as two pairs of gloves, a gown, nonpermeable shoes and a face mask should be put on before entering patient areas and worn during direct care to prevent transmission of the virus Health care facilities are encouraged to place an infected patient in isolation and limit access to those directly caring for that patient. Supplies such as medications, syringes, stethoscopes, thermometers and other frequently used equipment should be kept directly in the room to avoid spreading the virus from one area to another. Visitors should be limited or prohibited during the time of treatment for the infected individual and health care workers should keep a distance of at least one meter from the patient if not providing direct care. The disposal and containment of any needles, linens or wastes should be handled separately from other medical discarded products, and containers should be clearly labeled and disinfected before leaving the isolation area. The WHO stresses the importance of engagement and awareness of the transmission of Ebola for not only health care workers but also for the community as a whole.[1] Case management and containment, as well as thorough adherence to personal protection, may help limit the transmission of Ebola virus for all individuals. Risk reduction should be a central focus regarding the transmission of this disease.

Signs and Symptoms

The incubation period for the virus is extended and varied. The time from infection to symptom presentation is two to 21 days, the average being eight to 10 days.[4,9,11] Once onset of symptoms has occurred, the virus is contagious and can be spread to other people in close contact with the patient.[4]

- Early symptoms after the incubation period can include:[4,9,11,12]
  - sudden onset of fever at least 101°F (38.3°C)
  - malaise
  - headache
  - sore throat
  - muscle pain/weakness
  - lower back pain
  - nausea/vomiting/diarrhea
- Late symptoms are far more severe and fatal including:
  - unexplained hemorrhaging from eyes, ears, nose, mouth or rectum
  - impaired kidney and liver function
  - eye swelling
  - genital swelling
  - extensive blood-containing body rash

Diagnosis

Ebola virus disease is diagnosed using a variety of tests, as early symptomatology, alone, does not distinguish it apart from other diseases such as influenza, typhoid fever, meningitis and malaria. For these reasons, early diagnosis can be difficult; if a person is experiencing early symptoms and has been exposed to the fluids of a person or animal infected with Ebola, or has recently traveled to areas that are experiencing an outbreak, that person should seek medical care immediately. Isolation is imperative and samples from the patient should be tested for confirmation of infection.[11] The tests include:[4,9,11]

- Nonspecific:
  - Complete blood count
  - Liver function tests
  - Coagulation studies
- Specific:
  - Antigen-capture enzyme-linked immunosorbent assay (ELISA)
  - Antibody-capture ELISA
  - Reverse transcriptase polymerase chain reaction (RT-PCR) assay
  - Virus isolation by cell culture
  - Serum neutralization test
  - Electron microscopy

Treatment

There are currently no approved treatments or vaccines for EVD in humans.[13] Isolation of EVD-infected individuals is perhaps the most important component of current therapy. With no approved treatments and high death rates of those infected, prevention of the spread of the virus is key. Current therapy consists only of supportive care.[8] The rapid spread of EVD in the body along with its ability to interfere with blood clotting and electrolyte balance commonly leads to dehydration in infected individuals. Utilization of oral or intravenous electrolyte-containing fluids for rehydration is

important in maintaining appropriate intravascular volume and blood pressure. Electrolyte levels, blood pressure, organ function and patient comfort must be monitored closely. Changes in fluid administration should be made accordingly in order to avoid further complications such as multi-organ failure, shock and death. If multi-organ failure occurs, organ transplant will provide the most successful survival rates. Organ support through dialysis and maintaining adequate blood flow is crucial to keep EVD-infected patients alive and strong enough to fight infection. In cases of disseminated intravascular coagulation, heparin and clotting factors should be given if needed for excess clotting or mass bleeding, respectively. Maintaining oxygen status through ventilation as well as preventing further infection through proper isolation and aseptic technique are critical components in the treatment of EVD-infected patients. The specific supportive care varies from patient to patient based on their presenting symptoms and individualized needs. The key is ensuring the patient is comfortable while restoring optimal organ function to adequately prevent mortality.

While there are no treatments or vaccines currently available for clinical use, there are several under investigation. Compassionate use of these investigational options is controversial because the safety and efficacy has not been adequately studied.[14] However, the WHO states that in certain circumstances of the current outbreak and with specified conditions met, it is ethical to use unproven treatment and/or vaccines in order to provide optimal patient care. These specified conditions include patient groups that will likely have greater benefit than risk while using the agents and those who are "most likely to generate scientific insights that will inform its evidence-based use in the next epidemic."[14] In these cases, investigational options are being used under emergency use protocol. It is important that clinicians know there is a moral obligation to collect and share all data associated with these potential treatments.[15] Recently, the need for urgent development of both preventative and post-exposure treatment has risen. There are several mechanistic treatment options being studied to prevent the spread of EVD, further outbreaks and acts of bioterrorism.[13,16] Potential options include recombinant anti-Ebola monoclonal antibody-based therapy, RNA interference therapy, preventative adenovirus-based vaccines and, most recently, an antiviral oral nucleotide.[8,13]

Mapp Biopharmaceutical has developed ZMapp, a combination of three anti-Ebola monoclonal antibodies produced from Nicotinina plants.[14] The antibodies bind to the proteins of Ebola virus and prevent it from spreading in those already infected. The product first came onto the investigational therapy map in January 2014 and quantity is currently very limited due to minimal manufacturing. ZMapp has not been tested for safety or effectiveness in humans and no randomized controlled trials have been conducted at this point. However, it has been tested in animals and used compassionately in the treatment of EVD-infected American health care workers who returned to the United States from West Africa after the recent outbreak. While some individuals given ZMapp have recovered from the virus, it is unclear whether or not ZMapp played a significant role. Because it has not yet been studied for safety in humans, the risks and side effect profile are unknown. A movement for accelerated studying of ZMapp has been put in place by the company and the U.S. government with hopes of approval for humans by 2015.[8,13] The minimal availability of the product may lengthen the time to approval as it may take months to produce sufficient quantity to be used in research.[14]

A small RNA-interfering molecule developed by Tekmira Pharmaceuticals, TKM-Ebola, is being studied as another potential treatment option for those exposed to Ebola virus.[17] TKM-Ebola is formulated as a stable nucleic acid-lipid particle and works as an inhibitor of an enzyme that catalyzes the viral RNA replication of Ebola. It binds specifically to L polymerase, VP24, and VP35 regions within the RNA sequence. The molecule has performed well in animal studies, but has not yet been approved for safety or efficacy in humans. The U.S. Food and Drug Administration (FDA) recently eased safety restrictions and lifted a hold on the experimental molecule giving it opportunity for advancement in its path to approval.[18] However, human studies have raised safety concerns with the incidence of chills, low blood pressure, nausea and shortness of breath in healthy humans taking TKM-Ebola. This could slow the speed of approval of the drug, but studies are ongoing as Tekmira Pharmaceuticals works to resolve these issues. Animal studies have shown that it takes multiple doses of TKM-Ebola to reach efficacy, which is another concern and potential limitation in its use as EVD therapy.

An emergency investigational new drug application (EIND) by Chimerix, Inc. for brincidofovir has recently been authorized by the FDA.[19] Brincidofovir is an oral nucleotide analog lipid-conjugate. Clinical trials of brincidofovir have progressed to phase III for the use in cytomegalovirus and adenovirus over the past several years. These trials provide data on the safety and dosing of brincidofovir that can be translated to a potential use in EVD. To date, no evidence of kidney or bone marrow toxicity has been found in patients treated with this agent. This lack of toxicity has stimulated further studies of brincidofovir as a promising treatment option. Chimerix is working closely with the FDA to progress in the clinical trials of this agent, as no clinical data has been established yet.

Many mechanisms and molecules have been tested for vaccination purposes. Use of a recombinant vesicular stomatitis virus (VSV) in which the VSV glycoprotein is replaced with a glycoprotein of Ebola virus has shown protection in studies of administration in animals.[16] It is known as rVSV-EBOV. Enzyme-linked immunosorbent assays (ELISA) following administration of rVSV-EBOV have displayed IgG and IgM antibodies against Ebola virus.[17] The adenovirus-based vaccine has shown favorable effects when administered in the live-attenuated form, but shows no protection when administered as an inactivated molecule. This suggests the potency of the vaccine is largely based on the replication of the virus.

The U.S. government has planned "fast-track development" for approval of three additional adenovirus vaccine candidates by the National Institutes of Health (NIH) and Thomas

Jefferson University, Crucell and Profectus Biosciences.[13] GlaxoSmithKline has collaborated with the National Institute of Allergy and Infectious Diseases (NIAID) to derive a replication-defective chimpanzee adenovirus type 3-vectored ebolavirus vaccine (cAd2-ZEBOV) that has rapidly advanced into clinical phase I evaluation, known as the VRC 207 study.[20] The adenovirus serves to carry genetic material derived from the Zaire Ebola species and the Sudan Ebola species. The vaccine delivers one part of the Ebola genetic material to human cells, but rather than replicating it allows the cells receiving the vaccine to express a single Ebola protein, which prompts an immune response. In the VRC 207 study, a monovalent vaccine containing genetic material derived from only the Zaire Ebola species, as well as a divalent vaccine containing genetic material derived from both the Zaire Ebola species and the Sudan Ebola species, began to be tested. The study includes 10 healthy adults receiving the monovalent vaccine and 10 healthy adults receiving the divalent vaccine. Preliminary safety and efficacy data will provide information on the potential benefits and use of this vaccination.

Response from World Health Organization

The passing of Thomas Duncan, the first patient to be treated for Ebola in the United States after having been exposed to the general population, has prompted major discussion on how the United States might deal with containing the disease. Popular media extensively covered this particular case, raising public concern for the possibility for an outbreak in America. As of Aug. 28, 2014, the WHO published its three-point plan with the goal of containing and eliminating Ebola within the next six to nine months, beginning with the countries that are most severely affected.[21] First, the WHO plans to fully respond to all areas where "widespread and intense transmission" are present. The second point is the development and application of full response for those countries that may have Ebola exposure via localized transmission. Finally, the WHO hopes to prepare all countries, especially those that border lands with the highest rates of transmission and those that are major travel hubs, to self-sufficiently deal with the possibility of exposure.

The CDC has recently released a number of online resources consistent with the WHO protocols on disease prevention and readiness, including preparedness checklists to ensure that the United States is ready for a potential outbreak.[22] There are checklists created for emergency medical providers, health care facilities, hospitals, health care coalitions and for the general public. A typical checklist is charged with three primary categories, which are “Prepare to Detect,” “Prepare to Protect,” and “Prepare to Respond.” Within these three primary aims are specific metrics to ensure readiness for the disease. Following the checklist are quick resources for the personnel who would likely be reading the particular checklist. In conjunction with these primary readiness materials, the CDC website also currently contains a regularly updated newsfeed of WHO news and information.

Conclusion

The current outbreak of Ebola is a serious, growing epidemic accompanied with a great amount of worldwide fear. It is important for health care professionals to stay informed and updated as the disease and resulting panic spread. Their potential close contact with infected patients further adds to the need to be ready to respond in accordance with WHO protocol. Early symptoms of the virus can be difficult to differentiate from other common diseases, so it is crucial that anyone who has come in contact with an infected individual seeks medical help as soon as possible if experiencing such symptoms.[11] There are currently no approved treatments or vaccines for EVD in humans, but there are prospects currently in drug development trials that may show promise in treating and preventing EVD.[13] Supportive care for those infected is extremely important as it greatly decreases mortality.[8] The WHO currently has a plan in place to contain the current outbreak.[21] Both the WHO and CDC have step-by-step protocols available on their websites with the intention of helping health care facilities prepare and be able to respond in the event an infected individual needs to be treated at their hospital.[21,22]

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Memantine: Can it be Used to Treat Children with Autism Spectrum Disorder?

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairment in social, behavior and communicative skills. The current therapy for ASD only targets the associated symptoms such as aggression, self-harming acts or temper tantrums but not the core symptoms of social dysfunction. The pathology of ASD is not fully understood. Interestingly, imaging studies in ASD patients have reported abnormal high levels of glutamate in certain brain regions that play an important role in social interaction and communication. Thus, it has been hypothesized that medications attenuating glutamate transmission may be used as treatment for some of the core symptoms of ASD. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been approved for the treatment of Alzheimer's disease, and has shown promise in alleviating some of the symptoms of ASD in children. In this review, we will discuss the pathology of ASD, findings from studies that evaluated memantine in ASD patients, the adverse effects of memantine and the potential use of memantine in the treatment of ASD. Finally, we will discuss the role of the pharmacist in managing patients with ASD.

Key Terms

Aggression; Alzheimer Disease; Brain; Child; Child Development Disorders, Pervasive; Glutamic Acid; Humans; Interpersonal Relations; Memantine; N-Methylaspartate; Pharmacists; Review Literature; Social Behavior

Introduction

Autism spectrum disorder is a heterogeneous neurodevelopmental disorder[1] characterized by core features including developmental delays in communication and social interaction and repetitive behaviors and/or restricted interests.[2] Deficits in communication and social interaction manifest as shortfalls in "social-emotional reciprocity," nonverbal communication and difficulty with relationships. In addition, patients with ASD show repetitive behaviors, interests, movements or atypical interests in sensory aspects of their environment. The full clinical diagnosis of ASD is defined by the diagnostic statistical manual–V (DSM-V).

According to the Centers for Disease Control and Prevention (CDC), in 2012, about one in 68 children were identified with ASD.[3] Interestingly, boys are about five times more likely to be diagnosed with ASD than girls. Screening for ASD is usually done at well-child doctor visits.[4] If the physician/pedia-trician notices any abnormalities, such as the ones described above, a comprehensive diagnostic evaluation is performed, which includes a detailed evaluation of the child's behavior and development and an interview with the parents. Diagnoses made by age 2 or older are considered very dependable[5], but ASD could possibly be identified before 18 months of age.[4]

Currently, antipsychotic medications risperidone and aripiprazole are approved by the U.S. Food and Drug Administration (FDA) for the treatment of associated symptoms of ASD including aggression, self-harming acts and temper tantrums commonly seen in autistic patients between 5 and 16 years of age.[6,7] There are currently no FDA approved medications that directly target the pathological mechanisms underlying autism or treat the core symptoms of ASD described above.

Recent studies, however, suggest abnormalities in glutamate transmission in autism that could possibly be a target for treatment. Glutamate is the primary fast-acting excitatory neurotransmitter within the central nervous system (CNS).[8] The actions of glutamate in the CNS are mediated by ionotropic receptors such as the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate and N-methyl-D-aspartate (NMDA) receptors.[9] A few clinical studies have evaluated the effects of memantine, an antagonist of the NMDA glutamate receptor,[9] in patients diagnosed with ASD. In this review, we will first discuss glutamate abnormalities in specific brain regions that have been reported in ASD patients. In addition, we will discuss findings from studies that evaluated memantine in ASD patients, the adverse effects of memantine and the potential adverse effects of memantine in the treatment of ASD. Finally, the role of the pharmacist in managing ASD patients will be reviewed.

Pathology in Autism Spectrum Disorder

The etiology of ASD is not known, although research has shown that there is a strong hereditary influence accompanied by genetic mutations.[1] More than 20 different mutations have been identified. Also implicated are further epigenetic changes, which include modifications in gene expression that do not change the deoxyribonucleic acid (DNA) sequence. Overall, the genetic mutations and epigenetic changes affect proteins that are responsible for neuronal function, cell metabolism, protein synthesis and gene expression.

Irregularities in glutamate concentrations within the brain have been reported in ASD patients. Concentrations of glutamate in the brain can be measured using proton magnetic resonance spectroscopy (^{1}H MRS). In a study that utilized ^{1}H MRS, Brown et al. reported elevations in glutamate + glutamine signal (Glx) in certain brain regions of ASD patients.[10] For example, the Glx in the auditory cortex was found to be significantly elevated in the ASD patients when compared to the control groups. It should be noted that the ASD patients (n=13) were ages 25 to 48 years, and they were compared with healthy adults (n=15) and parents of ASD children not included in the study (n=15). In addition, Page and colleagues found that adults with ASD (n=20) had a significant increase in Glx in the amygdala-hippocampal complex

(P<0.05) compared to healthy patients (n=13).[11] Using ^{1}H MRSI (proton magnetic resonance spectroscopic imaging), Bejjani et al. showed that children with ASD (n=26) had increased Glx in the right pregenual anterior cingulate cortex (P<0.05) compared to typically developing children (n=16).[12]

In contrast to the above described studies, some studies report a decrease in Glx signal. For instance, Bernardi et al. found that the right anterior cingulate cortex had a decreased Glx signal in ASD adults (n=14, P<0.006) than in healthy controls (n=14).[13] One possible reason for the contrasting findings with respect to anterior cingulate cortex Glx signal and glutamate levels between the studies of Bernardi et al. and Bejjani et al. could be due to differences in age of subjects evaluated in the two studies. For example, subjects included in the study of Bernardi et al. were adults (age range 21 to 50 years), while the subjects studied in Bejjani et al. were children (age range 6.1 to 17.5 years). In addition, Horder et al. found that ASD patients had decreased Glx in the basal ganglia (P<0.0001).[14] Overall, the imaging studies suggest that the direction of alteration in glutamate levels in ASD patients may be dependent on the age group of patients and the particular brain region studied.

In addition to irregularities in glutamate levels described above, alterations in glutamate receptor mRNA expression or density have been reported in ASD patients. A postmortem study conducted by Purcell et al. examined brain samples from the cerebellar cortex of autistic patients (n=10) and control patients (n=23), which were matched based upon age and gender.[15] They reported a significant increase (P<0.05) in levels of AMPA 1, 2, 3 mRNA in the cerebellar samples of autistic subjects (n=10) compared to control subjects (n=10). Furthermore, increased levels of AMPA 1 (P<0.001) and NMDA receptor 1 (P<0.05) subunit proteins were reported in brain samples of autistic subjects (n=9) compared to controls (n=11). However, despite elevations in the mRNA and protein levels of specific AMPA and NMDA receptor subunits, Purcell et al. reported decreased density of AMPA receptors in the granule (P<0.05) and molecular cell layer (P<0.01) of the cerebellum in samples of autistic subjects compared to control subjects using autoradiography. Interestingly, there was no difference in density of the NMDA receptors in the different layers of the cerebellum. In summary, the above evidence from molecular studies suggests elevation of glutamate receptor expression (mRNA and protein) in specific brain regions in ASD patients.

Binding of glutamate to the NMDA receptor allows the entry of calcium and sodium ions into the neuron.[8] This entry of calcium and sodium ions via opening of the NMDA receptors results in depolarization and activation of the neurons. However, excessive release of glutamate and activation of the NMDA receptors can result in excitotoxicity and loss of neurons. Hence, it is hypothesized that attenuating glutamate transmission will have a neuroprotective effect and prevent loss of existing neurons. Consequently, memantine, a non-competitive NMDA receptor antagonist,[9] may provide the desired neuroprotective effects and promotion of neurogenesis. Currently, memantine is approved by the FDA for moderate to severe dementia caused by Alzheimer's disease. Several studies have evaluated memantine in children with ASD. Because the DSM-V criteria for ASD were released only recently (May 2013), most of the studies described in this article have used the DSM-IV-TR criteria, which was the standard criteria at the time the studies were conducted.

Clinical evaluation of Memantine in ASD

In a retrospective observational study, Erickson et al. evaluated the effects of memantine on symptoms associated with autism, such as social withdrawal, communication impairment, irritability and inattention/hyperactivity.[16] The study included 18 patients (mean age of 11.4 years) who had more than one symptom and were treated at an outpatient treatment center for autism. All patients were evaluated by psychiatrists and met the DSM-IV-TR criteria for autism. Patients began with either 2.5mg or 5mg memantine daily depending on their weight, which was titrated up by either 2.5mg or 5mg every two weeks to a maximum of 20mg daily or until a response or side effects were observed. Thirteen patients were taking concurrent medications, mainly anticonvulsants, antidepressants or second-generation antipsychotics, which were maintained during the trial. Of those taking second-generation antipsychotics, three patients were either on risperidone or aripiprazole, which are FDA approved medications for autism patients. A clinical global impressions-severity subscale (CGI-S) and CGI-Improvement subscale (CGI -I) was completed at baseline and during clinic visits to document changes in symptoms. The CGI-S was rated from 1 to 7 (1-normal, 7-extremely ill) while the CGI-I was also rated from 1 to 7 (1-very much improved, 7–very much worse). Patients with a CGI-I rating of 1 or 2 after the trial were considered treatment responders. Only six patients had completed scores at baseline and post-trial conducted on the aberrant behavior checklist-community (ABC-C) irritability subscale, a 58-item subscale used to assess disruptive behavior and developmental disabilities. The range of the study period was 1.5 to 56 weeks (mean of 19.3 weeks) with a mean dose of 10.1mg/day. The CGI-S scores showed a significant decrease from baseline (p<0.01) although the CGI-I improvement was not substantial. Patients with CGI-I ratings of much improved (n=6) or very much improved (n=5) were considered as treatment responders. For patients who did have ABC data, the only significant improvement was the hyperactivity subscale (p<0.05). Adverse effects occurred in seven of the patients and included irritability (n=4), rash (n=1), emesis (n=1), increased seizure frequency (n=1) and excessive sedation (n=1). Two patients stopped treatment due to unresponsiveness, while four stopped treatment because of adverse effects. Overall, the results reflected the beneficial use of memantine, especially in improving social interaction and attention. There were, however, several limitations to this study. The sample size of the study was small, thus making it difficult to form true associations within this observational study. The length of the treatment for each patient was not addressed by the authors, which varied and may not have allowed enough time to determine the efficacy and side effects of memantine. Importantly, only five patients were on monotherapy with memantine during the study, indicating that the other 13 patients were taking other concurrent medications, which could

have influenced the data with their varying therapies. Lastly, ratings on the CGI scales were not made by the same physician for each patient, indicating that scores may have been affected by the subjective impressions of the different physicians.

An open-label study by Chez et al. evaluated the efficacy of memantine in the treatment of language and social behavioral symptoms in patients diagnosed with autism.[17] The study included 151 patients who were found eligible through clinical observation and the DSM-IV criteria for autism (n=105) and pervasive developmental disorder not otherwise specified (PDD-NOS; n=46). Pervasive developmental disorder is characterized by severe impairment in developing reciprocal social interaction due to impaired communication skills or behavior.[18] Patients were predominantly male (mean age of 9.31 years). Those taking concurrent medications, which were primarily selective serotonin reuptake inhibitors, atypical antipsychotics, stimulants, alpha-adrenergic antagonists and cholinesterase inhibitors, were required to take them consistently for at least eight weeks before treatment and during the study. Of these patients, 31 were taking risperidone, while five were taking aripiprazole. Patients with Fragile X or Rett syndrome genetic disorders, metabolic disorders or brain malformations were excluded from the study. The starting dose of memantine was 5mg/day, which was titrated up or down every four to six weeks in 2.5 or 5mg increments up to 30mg/day. Patient follow-up was carried out via phone calls or email every four weeks and clinical assessments were conducted every eight to 12 weeks. The duration of the study had a range of one to 20 months (mean=9.27 months). Assessments of the treatment were conducted by a primary clinician and caretaker through interviews, diaries, clinical examinations and observations. These were translated onto the CGI-I seven-point scale for language by examining receptive skills and utterances, behavior through cognitive improvement in social interactions and self-stimulatory activity by observing the amount and type of patient activity. The CGI-I for behavior was observed through social interaction, ability to cooperate at home and school and attentiveness to others. A score of either 1 or 2 was considered to be significant improvement in all three categories. The CGI-I for language and behavior had a significant improvement in about 70 percent of both autism and PDD-NOS patients together, with changes occurring in the first two to four weeks. Improvement was also found to increase as length of therapy increased. When excluding the PDD-NOS patients, however, language improvement in autism alone was not found to be significant. More specifically, 65/105 and 67/105 autism patients were found to have ratings of significant improvement in language and behavior respectively. When excluding those who stopped treatment, language improvement was still significant for both the autistic and PDD-NOS patient groups, while behavioral improvement was not. Lastly, for the CGI-I for self-stimulatory stereotypic behaviors, only those observed with these behaviors at baseline were included (n=116). Only nine of the patients with autism were found to have significant improvement and there was found to be no progress in self-stimulatory behavior and duration of treatment overall for both autism and PDD-NOS patients. From the sample, 22 patients experienced worsening of symptoms and dropped out, while five patients stopped therapy because of a lack of response. Although abnormal electroencephalography findings were observed in patients, these changes were concluded to be normal for this patient population. For patients with concurrent therapy, hematological, serum chemistry and hepatic profiles were examined and found to have no changes. The results of the study seem to suggest that memantine is a safe adjunct therapy for patients with autism for improvement of language and behavioral symptoms. Importantly the study showed that memantine resulted in improvement of language and behavioral symptoms in a majority of patients, although improvements were not statistically significant when patients who withdrew from the study were excluded from the analysis. A major limitation of the study was that the researchers relied on CGI-I subscale scores, which were not scored by the same clinician or caretakers, indicating possible subjectivity in ratings, which may have affected the results. Furthermore, concurrent medications being taken by the patients were not the same for all the patients and may have influenced the results.

Ghaleiha et al. examined the effects of memantine as an adjunct therapy with risperidone.[19, 20] Forty children between the ages of 4 and 12 years (mean age of 7.42 years), who met the diagnostic DSM IV-TR criteria for autism confirmed by a child psychologist, were included in the 10-week double-blind randomized placebo-controlled trial. Inclusion criteria also comprised a screening and baseline ABC-C irritability subscale score of ≥ 12. Children who had concomitant schizophrenia, psychotic disorders, a history of drug or alcohol abuse, tardive dyskinesia, active clinical seizures, significant medical problems, had taken memantine previously or had taken an antipsychotic drug treatment six months before enrollment began were excluded from the study. Patients were randomized into two equal parallel groups, and an equal number of girls and boys were included in each group. One group received memantine and risperidone, while the other group received a placebo and risperidone. The starting dose of risperidone was 0.5mg tablet/day, which was gradually titrated up 0.5mg weekly to a maximum of 2mg/day for children weighing 10 to 40kg, and a maximum of 3mg/day for children weighing >40kg. Memantine doses started at 5mg caplet/day and were titrated up or down in 5mg increments each week to a maximum of 15mg/day for children weighing 10 to 40kg and 20mg/day for children weighing >40kg. All drugs, including placebo, began at the same time and any psychosocial intervention therapy was stopped. The primary outcome was the irritability subscale measured by the ABC-C. This was used to evaluate five types of behavioral abnormalities, where three were core deficits (lethargy/social withdrawal, stereotypic behavior, inappropriate speech) and two were associated disturbances (irritability, hyperactivity/noncompliance). Ratings on the ABC-C scale followed standardized instructions by a trained resident of psychiatry and the children's parents every two weeks. Scores at baseline were compared to scores during treatment weeks 2, 4, 6, 8, and 10 (end point). The extrapyramidal symptoms rating scale was also used to measure extrapyramidal symptoms, such as tardive dyskinesia, akinesia, akathisia and parkinsonism.[21] Independent raters and a medical

student documented side effects every two weeks. All patients were able to complete the trial and none were lost to follow-up. The memantine treatment group showed a significant difference in ratings when compared to the placebo in the ABC-C irritability, stereotypic behavior and hyperactivity/noncompliance subscales. No significant difference was observed in the lethargy/social withdrawal or inappropriate speech subscales. In addition, there were no significant differences found between groups in extrapyramidal symptoms or the frequency of side effects, which included abdominal pain, changes in appetite, dizziness, insomnia, nausea, sedation and rash. There were several limitations of the study. Primarily, the short trial duration of 10 weeks did not allow for an extended length of time to observe side effects, and/or efficacy of memantine in causing symptomatic improvement. Furthermore, different scorers for the different subscales could have led to subjective variability in ratings, which could have influenced the data. Overall, the results of the trial indicated a positive effect of memantine on one core and two associated symptoms of autism.

More recently, five clinical trials of memantine use in pediatric patients with ASD were completed and Forest Pharmaceuticals submitted the results for review by the FDA in June 2014.[22] The complete trial details of these studies were unavailable at the time of writing this article. However, the FDA clinical review is available on its website and has provided some insight into the trials. Two of the five studies were reviewed for the efficacy of memantine in pediatric (ages 6 to 12 years) ASD patients. Both studies were 12-week double-blind placebo controlled trials with 114 patients in MD-57A and 471 patients in MD-68. The MD-57A trial was a two-part trial. The first part of the trial was excluded from the clinical review because it was open-labeled. The second part of the trial consisted of patients who met DSM-IV specifications for autism according to the autism diagnostic observation schedule (ADOS) and the autism diagnostic interview-revised (ADI-R). These patients were then placed on two weeks of single-blind placebo. By the end of the two weeks, if the patients still met the inclusion criteria, they were randomized to either placebo or weight-based flexible-fixed memantine doses (3 to 15mg) in a 1:1 ratio. The primary efficacy endpoint of the 12-week trial was the mean change from baseline of the SRS (social responsiveness scale) scores at the end of the trial. According to the FDA clinical review, memantine did not show superiority to placebo treatment. The common adverse events observed in this trial were agitation, ear infection, affective disorder, allergic rhinitis, influenza, laceration, enuresis and frequent bowel movements.

The MD-68 trial was a parallel group, multicenter, double-blind, randomized, withdrawal study with 471 ASD patients between the ages of 6 and 12 years. In addition, these patients had already completed 12 weeks of open-label memantine administration and had at least a 10 point decrease in the SRS total raw score in the MD-91 trial. Patients were then randomized in a 1:1:1 ratio with full dose memantine, 50 percent memantine dose or placebo. According to the FDA clinical review, memantine did not demonstrate superiority to placebo. Also, the adverse events observed in the trial were of little clinical significance in the opinion of the clinical reviewer. Dose related adverse events were not observed, but the lead-in study may have affected these results. Based on these more recent studies, the FDA clinical review recommended approval of the memantine indication for adolescents/children with autism despite lack of efficacy to treat the core symptoms of autism. Further scrutiny of the data and the FDA clinical review will only be possible when the complete studies are available for review to the larger clinical community.

In summary, studies published to date in the literature assessing memantine either as an adjunct therapy or monotherapy for the core symptoms of ASD had limitations either due to small sample size or study design. Therefore, these trials have limited external validity. Although all of these published studies suggested positive benefit using memantine, further double-blind studies with robust sample sizes and study design will be required to determine the role of memantine in the treatment of ASD patients. Based on more recent studies, the data of which is available only to the FDA currently, the FDA clinical review has recommended approval of memantine for treatment of ASD in adolescents/children despite lack of clinical efficacy.[22] However, Forest Pharmaceuticals, memantine's manufacturer, does not plan to seek a pediatric indication of memantine at this time.

Pharmacist Role and Counseling Points

Memantine is approved by the FDA to treat moderate-to-severe Alzheimer's disease. Memantine is prescribed off-label for treatment of ASD as described above, and the pharmacist has a significant role in educating parents and patients about the therapeutic efficacy and adverse effects of memantine for this patient population.[23]

Memantine is available in several dosage forms including tablets, capsules in extended release forms and a solution. The cost varies depending on the dosage forms and strengths (See Table 1). Namenda® titration packs are blister packages containing 49 tablets of 28 x 5mg and 21 x 10mg. Namenda®

Table 1. Memantine's dosage forms and prices.*[25]

Namenda : Tablets, oral	5mg (60), 10mg (60)	$374.99
Namenda Titration Pak: Tablets, oral	5mg (28), 10mg (21)	$306.18
Namenda XR : Capsules, extended release, oral	7mg (30) 14mg (90) 21mg (30) 28mg (90)	$356.26 $1068.74 $356.26 $1068.74
Namenda XR Titration Pack Oral : Capsules, extended release, oral	7mg (7), 14mg (7), 21mg (7), 28mg (7)	$332.51
Namenda : Solution, oral	2mg/mL (360mL)	$725.32

* Costs without insurance coverage

extended release titration packs are blister packages containing 28 capsules of 7 x 7mg, 7 x 14mg, 7 x 21mg and 7 x 28mg. The solution form may contain sorbitol, and capsules may contain sugar.[24] Oral pediatric dosing adjustment is not yet established, but the clinical studies involving adolescents start with a low dose of 2.5mg daily or 5mg daily, and titrate up to maximum of 15mg, 20mg or 30mg daily depending on the weight of the patient.[16,17,19]

Memantine is well tolerated with low adverse events when it is used to treat dementia. In addition, no significant side effects were observed when the medication was given to adolescents for autism. Adverse reactions are similar to immediate and extended release formulations. If the patient has hypersensitivity to memantine or any component of the formulation, the drug should not be used. Bupropion, carbonic anhydrase inhibitors, sodium bicarbonate and trimethoprim are known to interact with memantine. Memantine is a substrate of organic cation transporter (OCT 2), and bupropion may increase the serum concentration of OCT 2 substrates. Carbonic anhydrase inhibitors and sodium bicarbonate may decrease the excretion of memantine with the exception of brinzolamide and dorzolamide. Trimethoprim may enhance the adverse and toxic effects, especially the risk of myoclonus and/or delirium. Therefore, these four drugs should be monitored when memantine is given to patients.[25]

The CDC has analyzed several alternative treatment options including behavior and communication approaches, dietary approaches and complementary and alternative medicine (CAM). One behavior and communication approach, known as applied behavior analysis (ABA), is a widely accepted treatment option to help children with ASD. The objective of ABA treatment is to encourage positive behaviors and discourage negative behaviors so that patients can progress toward positive activities. Applied behavior analysis includes different types of treatment, and other therapies can be a part of a program (See Table 2). Dietary approaches are not recommended because treatments are based on the unproven idea that some food or lack of vitamins and minerals may cause symptoms of autism. Removing certain types of foods may be harmful to a child, so refer to the physician if this treatment option is being considered. In addition, CAM is not recommended. Complementary and alternative medicine includes special diets, chelation (a treatment to remove heavy metals such as lead from the body) and body-based systems such as deep pressure. The efficacy of these treatments are very controversial and may even cause dangerous consequences to a child's health. Therefore, patients should consult with their physician prior to implementing treatment.[26]

Conclusion

Currently, there are no medications to treat the core symptoms of autism such as communication and social deficits. The FDA approved medications for autism, namely risperidone and aripiprazole, treat related symptoms of aggression, self-harming acts or temper tantrums in children between

Table 2. Description of Applied Behavior Analysis (ABA) and Other Therapies.[26]

ABA	Discrete Trial Training (DTT)	Broken down into smaller steps. Rewards for positive behaviors and incorrect answers are ignored.
	Early Intensive Behavior Intervention (EIBI)	ABA for younger children of usually younger than 5 or often younger than 3.
	Pivotal Response Training (PRT)	Focus on communication and social skills.
	Verbal Behavior Intervention (VBI)	Focus on verbal skills.
Developmental, Individual Differences, Relationship-Based Approach (DIR; "Floor time")		Focus on emotional and relational development. Focus on how the child reacts to sights, sounds and smells.
Treatment and Education of Autistic and related Communication-handicapped Children (TEACCH)		Use visual aids such as picture cards.
Occupational Therapy		Focus on the child's daily activities such as dressing, eating, bathing, and relating to people. Reinforce independence.
Sensory Integration Therapy		Focus on sensory information to help a child who is disturbed by sounds or touch.
Speech Therapy		Focus on communication skills.
The Picture Exchange Communication System (PECS)		Use picture symbols to improve communication skills.

the ages of 5 and 16 years. An FDA approved drug for treating Alzheimer's disease, memantine, has been suggested as a possible treatment option to treat the core symptoms of ASD. Imaging studies report increased glutamate levels in certain brain regions in ASD patients. Similarly, postmortem studies suggest increased mRNA levels of NMDA receptors in certain brain regions of ASD patients. Consistent with these findings, several published clinical studies reviewed here demonstrate possible benefits of using memantine, an NMDA antagonist. However, the studies published thus far are not very robust due to their small sample sizes and weak study designs. Based on studies still not available to the larger scientific community, the FDA clinical review has recently recommended approval of memantine for use in ASD patients despite lack of efficacy. Pharmacists must undertake a significant role in understanding memantine's use in ASD patients in light of unreliable efficacy, as well as in understanding other therapies widely utilized for ASD management.

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Ramucirumab: A New Agent for Advanced or Metastatic Gastric Junction Adenocarcinoma

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Abstract
Ramucirumab (Cyramza®), approved April 21, 2014, is a vascular endothelial growth factor receptor 2 (VEGFR2) antagonist with a U.S. Food and Drug Administration (FDA) indication for the treatment of advanced or metastatic gastric/gastroesophageal junction adenocarcinoma. Gastric cancer is a prevalent cancer in the United States with a poor prognosis. The phase 3 trial, REGARD, shows that ramucirumab, when used within four months after the last dose of first-line chemotherapy or six months after the last dose of adjuvant chemotherapy, increases overall survival. Also, ramucirumab has been included in combination therapy, such as in the RAINBOW trial, which demonstrated its effectiveness in combination with paclitaxel as a second-line treatment option. Notable adverse reactions to ramucirumab are severe hypertension and injection site reactions. Because it is a newer anticancer agent, ramucirumab's full potential may not yet be recognized. Possible future uses of ramucirumab may include the treatment of other forms of cancer or utilization as a first-line agent.

Key Terms
Adenocarcinoma; Antibodies, Monoclonal; Antineoplastic Agents; Chemotherapy, Adjuvant; Combined Modality Therapy; Food and Drug Administration (U.S.); Hypertension; Paclitaxel; Prognosis; Review Literature; Stomach Neoplasms; Vascular Endothelial Growth Factor A; Vascular Endothelial Growth Factor Receptor-2

Introduction/Epidemiology

Gastric cancer is one of the most prevalent cancers worldwide, and is currently the 14th most common form of cancer in the United States.[1,2] Adenocarcinoma-type gastric cancers account for 90 to 95 percent of all gastric malignancies. While gastric cancer is most commonly diagnosed in elderly patients, excluding those cancers affecting the gastric cardia, recent decades have revealed a nearly doubled incidence in gastric cancer among U.S. patients between the ages of 25 and 36 years (0.27 up to 0.45 per 100,000 between 1977-1981 to 2002-2006, respectively). Recent incidence rates for gastric adenocarcinomas involving the gastric cardia and/or gastroesophageal junction are around two and 1.94 per 100,000, respectively.[2] The American Cancer Society projects that in the United States there will be 22,220 new cases and 10,990 deaths due to gastric cancers for the year 2014.[3]

Gastric cancer is often difficult to detect until later stages of development, and only 10 to 20 percent of cases are diagnosed in an early stage. Therefore, most patients do not present until the cancer has already metastasized.[2,4] At best, five-year survival is typically around 50 percent for cases localized in distal regions of the stomach. Five-year survival drops to almost 0 percent for nonlocalized distal cases and is 10 to 15 percent for cases involving proximal regions of the stomach. Thus, it is recommended that high risk individuals undergo routine screening to monitor for development of gastric cancer.[4]

Known risk factors that contribute to the development of gastric cancer include: age (most common between 60 and 80 years), male gender and a family history of gastric cancer.[1,2] Lifestyle factors contributing to gastric cancer include a diet low in fruits and vegetables and/or high in salted and preserved foods, smoking and certain industrial occupations.[1,4] Gastric cancers also tend to be more prevalent among individuals of African, Asian and Native American descent.

Current treatments of gastric cancer include surgery, radiotherapy, chemotherapy and, most recently, targeted therapy.[1,4] With utilization of first-line agents including fluoropyrimidine, platinum and surgery, there will still be over 10,000 deaths in the United States in 2014 directly caused by gastric cancer. Consequently, new treatment options with improved efficacy toward gastric cancer are needed. Trials of drugs such as bevacizumab (a monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A) to inhibit angiogenesis) have been conducted to evaluate alternative mechanisms to successfully treat gastric cancer and thus reduce mortality. Ramucirumab, a monoclonal antibody targeting the vascular endothelial growth factor receptor (VEGFR), is the latest angiogenesis inhibitor that helps to increase the survival rate of gastric cancer patients. This novel mechanism categorizes ramucirumab as targeted therapy, which provides a new and unique treatment option for gastric cancer to prolong survival.

Pathophysiology

There is a well-documented correlation between Helicobacter pylori (H. pylori) infections and development of gastric cancer.[1,2] These gram-negative bacteria are associated with cases of severe and chronic gastritis as they secrete a number of substances such as proteases, phospholipases, ammonia, acetaldehyde and reactive oxygen species that are capable of inducing histological and genetic changes. These alterations lead to malignant cell growth in infected areas of the stomach. This can initiate a cascade of histopathological changes in gastric mucosa leading to the development of a gastric malignancy, particularly in patients with genetic susceptibility and poor diet.

Gastric adenocarcinoma presents in two histologically distinct forms: intestinal and diffuse.[1] Intestinal gastric adenocarcinomas form differentiated clusters of cohesive neoplastic cells that easily ulcerate. This type tends to have a better prognosis and is more common in the elderly, males and African Americans. It is also heavily influenced by environmental factors, including diet, H. pylori infections and obesity. Diffuse gastric adenocarcinomas are not as differentiated and, instead, manifest as a generalized thickening of the stomach wall. Diffuse-type is more common in females, younger patients and may have a genetic predisposing factor linked with type A blood. Advanced or invasive gastric adenocarcinomas develop along a cascade of histological changes.[5] Initially, atrophy of the stomach lining leads to changes in the parietal cells, which is followed by intestinal metaplasia where the normal gastric cells begin to display an intestinal cell phenotype. Lastly, neoplastic intestinal dysplasia develops and may lead to carcinoma in the affected area. This cascade is more relevant to intestinal-type carcinomas versus diffuse-type.

The link to family history and the actions of H. pylori indicate that a number of inherited and pathologically induced genetic changes can lead to the onset of gastric adenocarcinoma.[1] Investigators have determined that, on average, 4.18 gene changes are needed. Mutations in p27, p53, the K-ras oncogene and various cell signaling pathways are commonly seen. More aggressive gastric adenocarcinomas also develop the ability to express VEGF leading to an increased incidence of metastasis.

Clinical Presentation

As previously mentioned, gastric adenocarcinomas are often difficult to detect in early stages as patients are often asymptomatic.[4] In approximately 50 percent of cases, patients present with minor symptoms, such as dyspepsia, which are associated with a wide variety of gastrointestinal ailments. Due to the lack of symptom manifestation, 80 percent to 90 percent of patients present with locally advanced or metastatic tumors and complain of anorexia and weight loss as well as abdominal pain. Nausea and vomiting can occur with obstructive tumors while ulcerated tumors may cause bleeding that leads to hematemesis, melena and gastrointestinal hemorrhaging. Palpable masses, cachexia, bowel obstruction, ascites, hepatomegaly and lower extremity edema can also indicate advanced gastric adenocarcinoma. In these instances, the tumor has often already metastasized to neighboring structures and/or lymph nodes.

Treatment

Surgical intervention is the primary means of treating gastric adenocarcinomas.[2] Given the high incidence of presentation in advanced stages of the disease, surgery is often complemented with adjuvant radio- and/or chemotherapy. Surgery can be performed for cases with a localized tumor in the stomach and for cases limited to local node involvement. Cases with distal node involvement or metastasis to other structures outside the stomach often necessitate adjuvant or neoadjuvant chemotherapy. Stage III patients require radical surgery followed by chemoradiation therapy, while patients presenting at stage IV typically receive intensive palliative chemotherapy and radiotherapy.

Chemotherapeutic agents commonly used in the treatment and palliation of gastric cancers include 5-fluorouracil (5-FU), methotrexate, docetaxel and cisplatin.[2] Methotrexate and 5-FU are antimetabolites that disrupt normal deoxyribonucleic acid (DNA) synthesis while cisplatin is a platinum-containing alkylating agent that acts to directly damage DNA. Docetaxel is a taxane compound that interferes with mitosis.[6] There are multiple standard combination protocols as well as numerous clinical trials underway evaluating new combination protocols.[2, 7] Recent progress in the development of targeted therapies has led to an increase in studies for potential future treatments of a wide variety of cancers including gastric. Several drugs showing significant promise in the treatment of advanced gastric cancer include the monoclonal antibodies trastuzumab (for HER-2 positive cancers) and ramucirumab (anti-VEGFR2).[8, 9]

Indications and Mechanism of Action

Ramucirumab is approved for the treatment of advanced or metastatic gastric or gastroesophageal junction adenocarcinoma as a single agent.[10] This treatment regimen should be used if disease progression occurs with or after fluoropyrimidine- or platinum-containing chemotherapy.[11] Ramucirumab is an antineoplastic agent and a recombinant monoclonal antibody in the IgG1 class.[10,11] The drug binds to the vascular endothelial growth factor receptor 2 (VEGFR2) with a high affinity.[11] By binding to the VEGFR2 receptor, ramucirumab blocks the binding of VEGFR ligands, including VEGF-A, VEGF-C, and VEGF-D, which inhibits the activation of the receptor. Ligand-induced proliferation and migration of endothelial cells are inhibited. Therefore, tumor vascularity and growth are reduced. Ramucirumab does not affect initial levels of VEGF ligands, unlike bevacizumab, another VEGF inhibitor (which binds to the ligand VEGF itself).[12] By antagonizing the receptor rather than binding the ligand, ramucirumab may have less resistance.

Pharmacokinetics

Ramucirumab is given intravenously (IV) at a dose of 8mg/kg every two weeks.[12] The half-life of ramucirumab at steady-state is 200 to 300 hours and accumulates with increasing doses.[12, 13] A phase 1 clinical trial conducted by Spratlin and colleagues studied the pharmacokinetics and pharmacodynamics of ramucirumab.[13] Patients with advanced solid malignancies received escalating doses of ramucirumab as a one hour intravenous infusion. The clearance rate of ramucirumab decreased disproportionately as the dose was increased. This nonlinear effect suggests that the drug is eliminated by saturable receptor-mediated clearance.[12, 13] There have not yet been studies evaluating the effects of hepatic or renal impairment on the pharmacokinetics of ramucirumab.[12] The trial by Spratlin and colleagues also showed that circulating VEGF-A concentrations increased almost immediately after treatment to 1.5- to 3.5-fold higher than pretreatment concentrations and remained elevated until the next treatment.[13] As long as ramucirumab was present, VEGF-A levels remained elevated. The soluble vascular

endothelial growth factor receptors one and two (sVEGFR-1 and sVEGFR-2) concentrations tended to decrease immediately after ramucirumab was administered, but they recovered to near-pretreatment levels. Neither the VEGF-A, sVEGFR-1 or sVEGFR-2 levels were related to the dose of ramucirumab. The pharmacokinetic profile of ramucirumab suggests that weekly dose administrations of the drug are biologically relevant. The minimum target trough level was selected to be greater than or equal to 20 μg/mL based on the pharmacodynamic and efficacy data gathered from human tumor xenografts implanted in mice. This trough level was achieved in all the treated patients from this trial.

Adverse Events/Toxicity

The most prevalent adverse events observed in patients were hypertension, diarrhea, anemia and infusion-related reactions.[11] Hypertension occurred in 16 percent of patients with 8 percent of patients experiencing grade 3 or 4, which is classified as severe with a blood pressure reading of greater than or equal to 180/110mm Hg (versus a grade 1 or 2, which is considered mild to moderate with a blood pressure reading of 140 to 179/90 to 109mm Hg).[11, 14] The current recommendation is to temporarily stop the infusion until the hypertension is controlled with antihypertensive medication or to permanently discontinue ramucirumab infusion if the hypertension is severe and uncontrolled.[11] The infusion reactions associated with ramucirumab, which usually occur with the first or second infusion, include chills, flushing, hypotension, bronchospasm, dyspnea, hypoxia, wheezing, chest pain or tightness, supraventricular tachycardia, back pain or spasms, rigors or tremors, and paresthesia. Patients should be continuously monitored for infusion reaction symptoms and the treatment should be immediately and permanently discontinued for grade 3 or 4 reactions. Ramucirumab was shown to increase the risk of hemorrhage, including cases of severe and fatal bleeding. Consequently, in the United States, a black box warning for ramucirumab exists, which states that it should be permanently discontinued in patients who experience serious hemorrhagic events. Other serious adverse events that have occurred in patients receiving ramucirumab include arterial thrombotic events, gastrointestinal perforation, and reversible posterior leukoencephalopathy syndrome, which causes lesions in the parieto-occipital regions of the cerebral hemispheres and is characterized by altered mental status, headache, seizure and visual disturbances.[11,15] If any of these events occur, it is recommended to discontinue treatment.[11] Wound healing impairment is commonly seen in patients who are receiving antiangiogenic therapy; however, ramucirumab has not yet been studied in patients with serious or nonhealing wounds. It is recommended to stop treatment prior to, during and after treatment of such wounds and to continue ramucirumab infusions only when the wound is fully healed.

Drug interaction studies have not yet been conducted with ramucirumab. However, based on its therapeutic category, there are several drugs that should be avoided while on ramucirumab.[12] Monoclonal antibodies have been shown to enhance adverse and toxic effects of belimumab, an IgG1-lambda monoclonal antibody that blocks binding of soluble human B lymphocyte stimulator protein to receptors on B lymphocytes (and therefore preventing the survival of B lymphocytes), so it has a risk factor of X (avoid combination with ramucirumab).[11,16] The adverse and toxic effects of bisphosphonate derivatives such as alendronate and ibandronate may be enhanced by systemic angiogenesis inhibitors, which gives them a risk factor of C (monitor therapy when used with ramucirumab).

REGARD Trial: Patient survival rate

Ramucirumab monotherapy for previously treated advanced gastric or gastroesophageal junction adenocarcinoma was evaluated in an international randomized, multicenter, placebo-controlled, phase 3 trial.[17] Also known as REGARD, this is the trial that led to the FDA approval of ramucirumab. The purpose of the trial was to quantify the advantage in survival rate in patients who received ramucirumab versus those who did not. With a sample size of 355 patients and a 2:1 ratio of those who received ramucirumab versus placebo, there was an increased median overall survival rate in those receiving ramucirumab of 5.2 months versus 3.8 months for the placebo group. The study was conducted as a double-blind, randomized placebo-controlled trial in 29 countries all across the world. Inclusion criteria for the study gathered patients ages 24 to 87 with gastric adenocarcinoma, disease progression within the past four months of prior treatment, and an eastern cooperative oncology group (ECOG; see Table 1) performance score of 0 or 1.[17, 18] Exclusion criteria included grade 3 or higher gastrointestinal (GI) bleeding within three months of randomization, arterial thromboembolic events within six months of randomization and uncontrolled hypertension.[17] All parties involved were masked except for in emergencies only. Every patient received recommended supportive care, excluding any additional investigational drugs, and received ramucirumab or placebo until confirmed disease progression, intolerable toxicity or death. The primary measure within the study was overall survival rate. Secondary measures included rates of adverse effects and progression-free intervals. Tumor and quality of life assessments were also obtained. Results of the study concluded that ramucirumab therapy was superior to placebo therapy. Not only did the study conclude that the drug increased the overall survival rate, but also that the risk of death and disease progression were reduced between the two groups. These results, along with ramucirumab's unique mechanism of action compared to other drugs used to treat gastric cancer, prompted the indication for second-line treatment of gastric or gastroesophageal adenocarcinoma. When overall survival rates with ramucirumab therapy were compared to those of bevacizumab (a monoclonal antibody targeting VEFG-A), bevacizumab had slightly better rates, which was deemed to be statistically insignificant.

RAINBOW Trial: Combination Therapy

A double-blind, randomized phase 3 trial, ramucirumab plus placlitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastroesophageal junction adenocarcinoma, was conducted by Wilke and colleagues.[19] Also known as the RAINBOW trial, this study evaluated the effects of ramucirumab in combination with

Table 1. Eastern Cooperative Oncology Group (ECOG) Performance Scale.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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The ECOG Performance Status is in the public domain and therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

paclitaxel in patients with previously treated advanced gastric cancer. The objective of the study was to determine if overall survival rate increased in patients treated with ramucirumab plus paclitaxel versus placebo plus paclitaxel. In this placebo-controlled, multicentered phase 3 trial, patients who had disease progression within four months after platinum plus fluoropyrimidine with or without an anthracycline as a first-line chemotherapy treatment were eligible for the trial. Patients were randomized to receive either 8mg/kg of ramucirumab or a placebo intravenously on days 1 and 15, and both groups received paclitaxel 80mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle. The primary endpoint was overall survival of the patients. The overall survival rate among the patients in the ramucirumab plus paclitaxel group was significantly higher than in the control group, with median survival periods of 9.6 and 7.4 months, respectively. Further, the 12-month overall survival rate was 40 percent in the ramucirumab group and 30 percent in the control group. Taken together, the findings suggest that this combination therapy could become a new standard second-line treatment for patients with advanced gastric cancer. In addition, although this particular study is complete, 13 patients in the ramucirumab plus paclitaxel group and seven in the control group are continuing to receive their respective treatments in order to evaluate an extension phase of the study to determine the long-term results of the treatments.

Handling of Ramucirumab

Vials of ramucirumab are supplied in a concentration of 10mg/ml, and the calculated dose should be diluted with normal saline.[20] Ramucirumab is not stable in solutions containing dextrose. The mixture should be inverted to ensure even displacement in a final volume of 250mL. Ramucirumab should be stored under refrigeration at a temperature between 2 degrees and 8 degrees Celsius (36 degrees to 46 degrees Fahrenheit). The diluted mixture should be stored no longer than 24 hours. When preparing ramucirumab, it is important to ensure quality by inspecting vials for any discoloration or loose particles.[21] If present, discard the vial immediately. Any unused ramucirumab, as well as supplies used for preparation and administration, and any patient or equipment waste, should be discarded in indicated yellow chemotherapy bins for incineration or according to company policy.

Standard dosing of ramucirumab is 8mg/kg every two weeks.[20] This should continue unless the disease progresses or there is evidence of unacceptable toxicity. Before administering ramucirumab, pre-medicate the patient with an H1 antagonist such as diphenhydramine. If the patient has experienced a grade 1 or 2 reaction previously, also medicate with dexamethasone and acetaminophen before ramucirumab is initiated. The patient should be pre-medicated at an appropriate interval prior to administering ramucirumab in order to ensure optimal patient comfort and tolerance level. Diphenhydramine may only take five minutes to take effect if given IV, but up to two hours if taken orally. Similarly, dexamethasone should be administered anywhere from 15 to 30 minutes before treatment initiation, and acetaminophen can be administered five to 10 minutes before.[11]

The infusion itself takes place over 60 minutes through a single infusion line. Ramucirumab should not be infused in the same IV line as electrolytes or other medications, and should not be given as an IV push.[20] During administration, it is important to monitor for any infusion reactions: signs of tremors, back pain, chest pain and tightness, chills, flushing, dyspnea, hypoxia and paresthesia. More serious cases of in-

fusion reactions include bronchospasms, hypotension and supraventricular tachycardia. Close monitoring is required at every administration of ramucirumab as the incidence of infusion-related reactions is slightly more prevalent in the first or second administration but presents a risk throughout treatment. If a grade 1 or 2 infusion reaction occurs, reduce the infusion rate by 50 percent and continue treatment. If a grade 3 or 4 reaction presents itself, permanently discontinue ramucirumab.[11]

Safety for Health Care Professionals

While the effects of ramucirumab on patients are documented, the effects on those who prepare, administer and dispose of the drug are not. Occupational exposure to hazardous drugs, namely chemotherapy, are highest in pharmacists during its preparation and nurses during its administration.[21] Lack of chemotherapy precautions at any stage of drug handling can result in hair loss, contact dermatitis and skin injury in the short term, as well as a higher rate of genotoxicity, cancer, fetal loss and infertility in the long term. Appropriate precautions include the use of specific safety cabinets for preparation and appropriate personal protective equipment (PPE). For preparation, this includes a ventilated cabinet that takes both employee safety and product sterility into account, which includes proper disposal of vapors and air circulation. Further precautions include wearing two pairs of chemotherapy-tested gloves to safeguard the preparer against any potential contact with the drug or waste contents, a chemotherapy-tested gown and a face shield or respirator if there is any risk of inhalation or splattering of chemotherapy agents. These same necessities carry to the bedside when nurses administer antineoplastic agents including further precautions such as using needleless systems and ensuring that IV tubing is primed with normal saline or a nonhazardous drug by a pharmacist prior to patient administration. Identical precautions are needed in order to dispose of bodily fluids from a patient receiving chemotherapy, in addition to placing an absorbent pad over the toilet when flushing in order to prevent splashing and contact.[22] Disposal of any equipment used in the administration of ramucirumab or care of a patient receiving treatment should be placed in a biohazard bag and be placed in a yellow chemotherapy bin for incineration. This includes absorbent pads, IV tubing and any PPE. Any sharps or needles used in administration or maintenance of ramucirumab should be placed in a specified chemotherapy sharps container for proper disposal and incineration.[21] These precautions should persist after the initial treatment, as chemotherapy and other hazardous drugs remain in the patient's body for up to 48 hours and are subsequently excreted through waste such as urine, stool and emesis. Education on similar precautions, as well as disposal methods, should be provided to the family and caregivers of those on chemotherapy in order to prevent any accidental exposure.[22]

Management of Adverse Effects

As stated earlier, hypertension is one of the most clinically significant adverse effects of ramucirumab.[11] Any existing hypertension should be well-controlled before treatment is initiated, and blood pressure should be monitored starting two weeks prior to infusion initiation and continued every two weeks throughout the course of therapy. More frequent monitoring may be indicated if the patient has a history of hypertension or if the patient develops hypertension over the course of ramucirumab administration.[20] If a hypertensive crisis occurs, immediate medical intervention, such as nitroprusside administration, may be indicated, although side effects must also be monitored.[23] Educating patients on measuring their blood pressure at home may help prevent a hypertensive crisis from occurring. It is also important to ensure that patients are aware of side effects, such as flushing, headaches and heart palpitations, which may indicate a hypertensive crisis. This knowledge, as well as health care provider contact information, may help patients avoid a crisis and follow a medication regimen that effectively controls their blood pressure. Education on medication compliance, as well as lifestyle modifications, may provide additional benefit over the course of treatment.

The incidence of bleeding and hemorrhage risk in those taking ramucirumab is slightly increased over those who received a placebo.[20] A proactive approach to this adverse effect is prevention and, consequently, the use of bleeding precaution procedures should be followed in both the health care setting and as the patient is discharged. This involves avoiding unnecessary invasive procedures, such as rectal temperatures. In addition, the use of small gauge needles and direct pressure on bleeding sites for up to five minutes may help with clotting.[23] Monitoring blood counts for abnormal values in platelets or prothrombin time, as well as hemoglobin and hematocrit values that may indicate an internal bleed, is crucial. Observing trends in vital signs while the patient is in the hospital to monitor for signs of tachycardia and hypotension may alert health care providers to any potential hypovolemia indicating the presence of an internal bleed. Related to personal hygiene, soft toothbrushes and safety razors should be used. Any sharp corners that may cause bleeding should be covered in padding. Patients should receive education on providing these safety measures at home, as well as observing for abnormal bruising or feelings of dizziness and heart palpitations. Patients should be instructed to immediately report to their health care provider if they notice any of these symptoms.

Cancer-related fatigue (CRF), while comparable among the treatment modalities, still affects 36 percent of patients on ramucirumab.[23] Cancer-related fatigue is defined by Horneber et al. as "the syndrome of fatigue and exhaustion in cancer patients."[24] This syndrome affects all aspects of health and manifests itself not only by a lack of energy, but also by a loss of drive and social withdrawal in addition to impaired concentration and memory loss. Many of these symptoms are subjective and can be identified by thorough communication between the patient and the health care provider. Symptoms may not be directly observed due to a focus on the treatment modality of the cancer itself, or they may not be reported if the patient withholds information due to fear of judgment or delay in treatment. A degree of patient trust, as well as constant follow-up, may help providers to diagnose CRF more readily and, consequently, facilitate initiation of appropriate

treatment. Of all the side effects that accompany cancer patients undergoing treatment, CRF is considered the worst due to its severe debilitation on the patient's quality of life. It can occur at any stage of the disease process including after admission. Proper education on CRF as a condition is imperative for treatment as patients who recognize the symptoms are more open to treatment options.

While pharmacological components such as hematopoietic growth factors and corticosteroids may improve CRF, they are only effective for a minority of patients and are often a short-term solution with added risks. However, nonpharmacologic activities such as physical exercise may provide the same benefits without as many of the risks. In a meta-analysis completed by McMillan and Newhouse, it was shown that all modes of physical activity, especially aerobic exercise, and to a lesser degree resistance exercise, may help not only decrease the manifestations of CRF, but also the symptom clusters that accompany it such as depression and anxiety.[25] Improvement in cardiac reserve, lung ventilation and perfusion may explain such changes, especially since such characteristics are diminished in cancer patients both during and after treatment.

Conclusion

Gastric cancer is a prevalent disease that has a very low survival rate once it becomes advanced or metastatic. Once disease progression has led to metastasis, survival rates significantly drop despite the utilization of first-line therapies. Ramucirumab is a monoclonal antibody that targets VEGF receptors and is used for the treatment of advanced or metastatic gastric or gastroesophageal junction adenocarcinoma as a single agent. Through studies such as REGARD and RAINBOW, ramucirumab has been shown to be an effective second-line therapy as monotherapy or combination therapy with paclitaxel in prolonging survival over placebo. Ramucirumab is a novel anticancer agent, as treatment with this agent is categorized as "targeted therapy." However, its application in other types of cancer should also be considered. Because of the efficacy demonstrated by ramucirumab, it is crucial for health care professionals to properly manage adverse effects, such as hypertension and hemorrhage, to allow continuation and success of ramucirumab therapy in the treatment of gastric or gastroesophageal junction adenocarcinoma.

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