Dapagliflozin: A Newly Approved SGLT2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus

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Objectives

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

1. Identify the mechanism of action and pharmacological implications of therapy with dapagliflozin.
2. Explain dapagliflozin's place in therapy in the treatment of diabetes.
3. Describe possible advantages of combination therapy with current diabetes medications.
4. Identify the appropriate monitoring requirements for dapagliflozin treatment.
5. Discuss the various side effects associated with dapagliflozin use.

Abstract

Type 2 diabetes mellitus (T2DM) is a chronic disease in which a hyperglycemic state is induced by insulin resistance. While there are numerous treatment options available to manage T2DM, many patients require changes in therapy throughout treatment, as well as multiple medications. The sodium/glucose cotransporter 2 (SGLT2) inhibitors, canagliflozin and dapagliflozin, offer a therapeutic alternative in T2DM management through the utilization of a unique mechanism of action to provide intensified glycemic control. This article will evaluate the safety and efficacy of dapagliflozin in the management of T2DM.

Introduction

The recent introduction of the sodium/glucose cotransporter 2 (SGLT2) inhibitor drug class presents a novel treatment option in the type 2 diabetes mellitus (T2DM) therapeutic arsenal. Janssen Pharmaceuticals, Inc. manufactures the inaugural member of this class, canagliflozin (Invokana®), which gained U.S. Food and Drug Administration (FDA) approval in 2013.[1] The introduction of dapagliflozin (Farxiga®) by Bristol-Myers Squibb, which was granted approval in early 2014, offers a second, "me too," alternative to this novel class.[2] Both canagliflozin and dapagliflozin are oral agents indicated to improve glycemic control in conjunction with dietary and exercise modifications in patients not adequately responding to current therapy.[1,2]

MOA/Pharmacology/Kinetics

Reabsorption of glucose in the kidney is reliant on the mechanism of the SGLT2 protein, a low-affinity, high-capacity 1:1 sodium/glucose transporter.[3] Its characterization as a low-affinity transporter indicates that a molecule of glucose attaches to the protein with less force and at an abbreviated time interval as compared to a high-affinity counterpart, sodium-glucose cotransporter 1 (SGLT1). Nearly the entire portion of the 144 grams of glucose filtered by the glomerulus on a 24 hour basis is reabsorbed in the renal tubules.[4] The SGLT2 is highly expressed in the S1 segment of the proximal convoluted tubule and serves as the primary site for mammalian glucose reabsorption.[3] A second sodium/glucose cotransporter, SGLT1, is present in both the kidney and the intestine. The SGLT1 is characterized as high-affinity and possesses the additional capacity for galactose transport that is absent in SGLT2.[3] The SGLT1 is located in the S3 segment of the proximal tubule to reabsorb any remaining glucose that escaped transport by SGLT2 from the lumen into the bloodstream (Figure 1).

Inability to reach glycemic targets in addition to prevalent side effects of existing therapies has prompted researchers to investigate therapeutic alternatives. Selective inhibition of SGLT2 is a viable alternative in the treatment of T2DM.[3] During hyperglycemia, SGLT2 is upregulated in an attempt to meet the demand of additional glucose reabsorption. Selective inhibition of these transporters in the hyperglycemic state of diabetic patients results in elevated urinary glucose levels and decreased blood glucose levels. Canagliflozin and dapagliflozin are both approved for use as adjuncts to diet and exercise in adult diabetic patients who are not adequately controlled on metformin or a sulfonylurea.[2] Because of the novelty of this drug class and limited clinical experience with its members, trials directly comparing canagliflozin and dapagliflozin therapy have yet to be conducted.

Dapagliflozin reaches maximum plasma concentration within two hours of fasting administration, and the oral bioavailability of a standard 10 mg dose is 78 percent.[2] It can be taken without regard to meals. Dapagliflozin is 91 percent protein bound, and UGT1A1, an enzyme in the glucuronidation pathway, is responsible for the majority of its metabolism to an inactive metabolite, dapagliflozin 3-0-glucuronide. It is primarily eliminated through the kidneys with a mean plasma terminal half-life of 12.9 hours subsequent to a single 10 mg oral dose. In vitro, dapagliflozin did not significantly impact the pharmacokinetics of coadministered drugs, nor did the coadministered drugs significantly impact dapagliflozin. Therefore, no dosing adjustments need to be made during concurrent therapy with other oral medications based on

Figure 1. Diagram of a Kidney Nephron
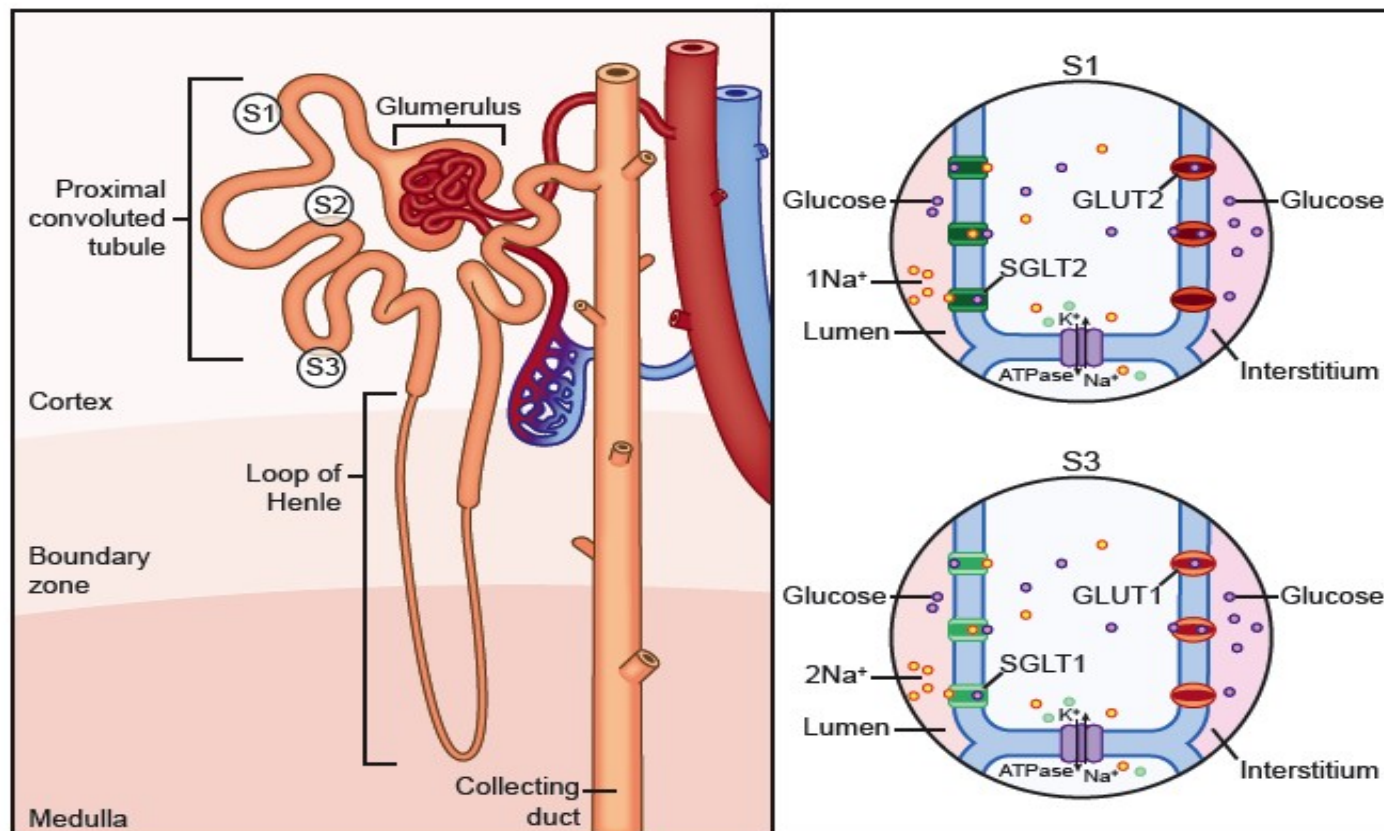
Illustration by Diantha La Vine. MUTAGENETIX (TM), B. Beutler and colleagues, Center for the Genetics of Host Defense, UT Southwestern, Dallas, Texas. Accessed Aug. 12, 2014, at https://mutagenetix.utsouthwestern.edu/phenotypic/phenotypic_rec.cfm?pk=598.

pharmacokinetics. The pharmacokinetic parameters of canagliflozin are similar, with 65 percent oral bioavailability and 99 percent protein binding; primarily to albumin.[1] Canagliflozin undergoes O-glucuronidation as the major metabolic elimination pathway to two inactive metabolites.

Indication/Usage
Type 2 diabetes mellitus is characterized by chronic hyperglycemia resulting from the development of insulin resistance, impaired insulin secretion and increased hepatic glucose production.[5] A strength of the SGLT2 inhibitor class is its ability to work independently of insulin. By removing insulin resistance as a confounding interference in treatment, significant reductions in blood glucose levels can occur regardless of a patient's degree of insulin resistance. Therefore, SGLT2 inhibitors are a viable option for type 2 diabetics with substantial insulin resistance. Dapagliflozin has been studied and approved for use as both monotherapy and combination therapy.[2]

Dosing, Frequency and Side Effects
The recommended starting dose of dapagliflozin is 5 mg once daily, which can be increased to 10 mg once daily if well tolerated and the patient requires intensified glycemic control.[2] It should be taken in the morning without regard to meals. Patients with pre-existing volume abnormalities should be regulated prior to use. Through clinical trial evaluation, da-

pagliflozin therapy has been most directly associated with adverse events including female genital mycotic infections, nasopharyngitis and urinary tract infections.[6] A reduction in body weight was observed when dapaglifozin was used in combination with other DM medications. It is contraindicated in those with known hypersensitivity to dapagliflozin, severe renal impairment, end stage renal disease (ESRD) and patients on dialysis.[2]

UTIs and Genital Infections
According to a retrospective cohort study performed by Iglay and colleagues, patients with T2DM were more likely to have a urinary tract infection (UTI) compared to the general population.[7] Multiple studies evaluating the safety and efficacy of dapagliflozin have also reported a higher incidence of UTIs and genital infections in those patients receiving dapagliflozin than in patients receiving a placebo. A meta-analysis by Johnsson and colleagues pooled twelve randomized placebo-controlled trials of patients receiving dapagliflozin or placebo for either 12 or 24 weeks.[8,9] While various other dosing strengths were utilized in the trials, they only reviewed the incidence of UTIs and genital infections for dapagliflozin 2.5, 5 and 10 mg groups, as these were the doses pursued in further drug development. Within these groups, a slightly higher incidence of UTI occurred in the 5 mg and 10 mg groups compared to the 2.5 mg and placebo groups (2.5 mg—3.6%, p=0.8373; 5 mg—5.7%, p=0.0201; 10 mg—

4.3%, p=0.4823; placebo—3.7%), of which only 5 mg reached statistical significance assuming a traditional p value of 0.05.[8] There was also a statistically significant increased number of genital infections (including vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis and genital fungal infection), vulvovaginal pruritus, genital pruritus and balanitis in all of the dapagliflozin groups in comparison to the placebo groups (5 mg—5.7%, p<0.0001; 10 mg—4.8 percent, p<0.0001; 2.5 mg—4.1 percent, p<0.0001; placebo—2.1%).[9] A higher incidence was also reported in women in comparison to men and in patients with a history of recurrent genital infections. The researchers did not find the rate of genital infections to be directly related to dose, in that they did not increase consistently with each dose increment. Collectively, the genital infections were all classified as mild to moderate, except for one severe case. All were efficiently treated using standard therapy.[8,9]

Special Populations
Pregnancy
Dapagliflozin is a pregnancy category C drug, indicating that animal studies have shown risks to the fetus but sufficient human studies have not been performed. In this case, the development of the kidneys may be compromised during the second and third trimester. The risks to the fetus, as well as the benefit of treatment for the mother, should be evaluated before administration of dapagliflozin in pregnancy.[2]

Renal Impairment
Kasichayanula and colleagues evaluated the effects that renal impairment would have on the glycemic effects of dapagliflozin.[10] Type 2 diabetics with varying levels of renal impairment based on creatinine clearance and supported by iohexol administration were evaluated. Renal function was defined as: no impairment, or normal renal function (CL_{CR} > 80 ml/min), mild impairment (CL_{CR} 51-80 ml/min), moderate impairment (CL_{CR} 30-50 ml/min), and severe impairment (CL_{CR} <30 ml/min). They found that there was no significant difference in urinary glucose levels after administration of dapagliflozin in the non-renal impairment and mild renal impairment groups. Unexpectedly, those in the moderate and severe renal impairment groups had lower urinary glucose levels in comparison to the groups with better renal function, despite increased half-life and drug accumulation. Even though the half-life of dapagliflozin was increased in those with moderate and severe renal impairment, the researchers found this decrease in urinary glucose elimination to be due to the decreased glomerular filtration rate (GFR). Because the GFR was significantly reduced in the moderate and severe impairment patients, there was a decrease in renal fluid movement, therefore less glucose was able to reach the SGLT2 receptors in the proximal tubule of the kidney despite the increased half-life of dapagliflozin. Renal function testing was not, however, available after dapagliflozin administration in this study, therefore it is unclear if some of the impairment was caused by the drug or if it was completely independent of dapagliflozin.

Dapagliflozin should be discontinued in those with a glomerular filtration rate of less than 60 ml/min or those with end-stage kidney disease.[2] Dapagliflozin is not recommended in patients undergoing hemodialysis, as this has not been studied.

Hepatic Impairment
There are currently no recommendations in regard to impaired liver function and dapagliflozin administration because safety has not been evaluated.[2]

Efficacy of Monotherapy
Dapagliflozin is approved for use alone or in conjunction with other T2DM medications in order to appropriately stabilize and lower the patient's risk for hyperglycemia and decrease hemoglobin A1c (HbA_{1c}) levels.[2] Two monotherapy studies to evaluate its efficacy are discussed below.

In a randomized, double-blinded, placebo-controlled phase III trial, Ferrannini and colleagues studied the effects of dapagliflozin in T2DM patients who had poorly controlled hyperglycemia when using diet and exercise as their only intervention.[11] Two weeks before the study began subjects were given a placebo in addition to counseling on proper diet and exercise. Subjects were then divided into placebo and dapagliflozin groups. The dapagliflozin groups were further subdivided into 2.5, 5, or 10 mg groups and morning or evening administration. Results presented below are for the 5 mg and 10 mg daily doses only, as there were no significant changes in the 2.5 mg daily group. After 24 weeks, a statistically significant decrease in HbA_{1c} from baseline (primary end point) was seen in the 5 mg (-0.58%, p=0.0005) and 10 mg (-0.89%, p<0.0001) dapagliflozin groups compared to placebo (-0.23%, assuming a p<0.05, although not explicitly stated). Dapagliflozin also significantly decreased fasting plasma glucose from baseline (secondary end point) in comparison to the placebo group. Utilizing a 95 percent confidence interval, the placebo group's fasting plasma glucose decreased by 4.1mg/dL from baseline (-11.8-3.5), the 5 mg group's decreased by 24.1 mg/dL (-32.5-15.6) from baseline, and the 10 mg group's decreased by 28.8 mg/dL (-36.8-20.9) from baseline. A slight increase in weight loss and decrease in blood pressure was also noted for the dapagliflozin group, although it was not statistically significant. Administration in the morning in comparison to evening yielded similar results. Finally, dapagliflozin monotherapy did not significantly alter electrolyte, serum albumin, serum creatinine or blood urea nitrogen levels.

A second randomized, double-blinded, placebo-controlled, parallel-group, phase III study was conducted by Ji and colleagues in order to evaluate the efficacy of dapagliflozin monotherapy in the Asian population.[12] The selected patients included T2DM patients who were drug naive, using inclusion criteria similar to the study conducted by Ferrannini et al.[11] HbA_{1c} was measured in the placebo, 5 mg and 10 mg groups over a 24-week period. Compared to placebo the dapagliflozin groups had a significant reduction in HbA_{1c} from baseline. The 5 mg dapagliflozin group had a 1.04 percent (p < 0.0001) reduction from baseline, the 10 mg dapagliflozin group had a 1.11 percent (p < 0.0001) reduction from baseline, and the placebo group had a 0.29 percent reduction

Table 1. Summary of Dapagliflozin Clinical Trials

Reference	Treatment groups	Number of subjects*	Decrease in HbA$_{1c}$ from baseline (p value)**	Change in weight from baseline (p value)**
Bailey, et al.	Metformin + placebo	134	0.3%	0.9 kg loss
	Metformin + 2.5 mg Dapagliflozin	135	0.67% (p = 0.0002)	2.2 kg loss (p < 0.0001)
	Metformin + 5 mg Dapagliflozin	133	0.7% (p < 0.0001)	3 kg loss (p < 0.0001)
	Metformin + 10 mg Dapagliflozin	132	0.84% (p < 0.0001)	2.9 kg loss (p < 0.0001)
Strojek, et al.	4 mg glimepiride + placebo	143	0.13%	0.72 kg loss
	4 mg glimepiride + 2.5 mg dapagliflozin	154	0.58% (p < 0.0001)	1.18 kg loss (p = 0.1410)
	4 mg glimepiride + 5 mg dapagliflozin	142	0.63% (p < 0.0001)	1.56 kg loss (p = 0.0091)
	4 mg glimepiride + 10 mg dapagliflozin	150	0.82% (p < 0.0001)	2.26 kg loss (p <0.0001)
Rosenstock, et al. Pioglitazone dose was either 30 or 45 mg daily (24 weeks)	Pioglitazone + placebo	139	0.42%	1.64 kg gain
	Pioglitazone + 5 mg Dapagliflozin	141	0.82% (p = 0.0007)	0.09 kg gain (p < 0.0001)
	Pioglitazone + 10 mg Dapagliflozin	140	0. 97% (p < 0.0001)	0.14 kg loss (p < 0.0001)
Rosenstock, et al. Pioglitazone dose was either 30 or 45 mg daily (48 weeks)	Pioglitazone + placebo	139	0.54%	2.99 kg gain
	Pioglitazone + 5 mg Dapagliflozin	141	0.95%	1.35 kg gain
	Pioglitazone + 10 mg Dapagliflozin	140	1. 21%	0.69 kg gain

*Number of subjects that completed the trials and were included in statistical analyses
** p-values are listed only if reported by the authors

from baseline. In general, monotherapy with dapagliflozin appears to have a statistically significant impact on HbA$_{1c}$.

Coadministration Therapy
Dapagliflozin has also been studied in combination with metformin, glimepiride and pioglitazone. Each of the following studies were randomized, double-blinded, placebo-controlled trials in subjects with inadequately controlled T2DM. The primary outcome was change in HbA$_{1c}$ from baseline after 24 weeks of treatment. In all three studies, the combination therapy resulted in a significant decrease in HbA$_{1c}$ from baseline and favorable effects on patient baseline weight.[6,13,14] A summary of the results is presented in Table 1.

In a study conducted by Bailey and colleagues, all participants remained on their original metformin therapy throughout the trial.[13] The results showed a statistically significant decrease in HbA$_{1c}$ and body weight from baseline at week 24 compared to placebo plus metformin.

The next two studies investigated the combination of dapagliflozin with glimepiride or pioglitazone. Combination with a sulfonylurea (glimepiride) and thiazolidinedione (pioglitazone) were of particular interest because they also reported on the influence of dapagliflozin to combat the weight gain associated with sulfonylureas and thiazolidinediones as well as the edema associated with thiazolidinediones.[6,14]

The efficacy of combination dapagliflozin and sulfonylurea therapy was assessed in a clinical trial conducted by Strojek and colleagues.[6] Regardless of the original sulfonylurea used, all subjects were switched to glimepiride 4 mg/day with an eight-week lead-in period. The results showed a statistically significant decrease in HbA$_{1c}$ and body weight from baseline at week 24 compared to placebo, except for body weight with dapagliflozin 2.5 mg.
Pioglitazone is known to result in weight gain and peripheral edema, while dapagliflozin results in diuresis and is associated with weight loss. Naturally, a combination therapy might then be of considerable benefit. Rosenstock and col-

leagues studied the efficacy and side effect incidence in 420 subjects receiving combination therapy with pioglitazone.[14] During a 10-week dose-optimization period preceding the trial, all participants were put on pioglitazone 30 mg/day and increased to 45 mg/day if tolerated. At the end of the twenty-four week study, patients in the dapagliflozin group had significant mean reductions in HbA$_{1c}$. In the 24 week extension of this trial, those receiving dapagliflozin had additional HbA$_{1c}$ reductions, but no statistical analysis was performed.

Side effects of weight gain and peripheral edema were measured at 24 and 48 weeks.[14] At week 24, the placebo plus pioglitazone group had a 1.64 kg weight gain, while the combination therapy groups had a 0.09 kg gain with 5 mg and a 0.14 kg loss with 10 mg dapagliflozin. Statistical significance was found between the placebo and the dapagliflozin groups at week 24. At week 48, the placebo plus pioglitazone group had a 2.99 kg weight gain, while the combination therapy groups had weight gains of 1.35 kg with 5 mg and 0.69 kg with 10 mg. However, statistical analysis was not performed.[14] The incidence of peripheral edema was evaluated at week 48. Overall, 6.5 percent of those receiving pioglitazone plus placebo experienced peripheral edema, while only 4.3 percent experienced peripheral edema with 5 mg dapagliflozin plus pioglitazone and 2.1 percent experienced it with 10 mg dapagliflozin plus pioglitazone.

Considering the decreased peripheral edema and lessened weight gain observed in the experimental groups, dapagliflozin appears to have attenuated the adverse effects of pioglitazone, although statistical analysis was not performed for the 48-week end points.[14] Therefore, dapagliflozin may be a reasonable option for combination therapy with pioglitazone.

Although dapagliflozin combination therapy was associated with better HbA$_{1c}$ outcomes than metformin, glimepiride and pioglitazone monotherapies, adverse events may limit its use. As would be expected with increases in urine glucose levels, genital infections were higher in dapagliflozin groups than in the placebo groups.[6,13,14] On the other hand, UTIs were observed with similar prevalence across all groups in the combination therapy trials. Hypoglycemia was also monitored closely. The Bailey et al. and Rosenstock et al. trials reported similar proportions of hypoglycemia between the placebo and the dapagliflozin groups.[13,14] However, in the Strojek et al. trial, the dapagliflozin groups had more frequent hypoglycemia (6.9-7.9%) than the placebo (4.8%).[6]

Comparison of Dapagliflozin and Canagliflozin
A meta-analysis of randomized, double-blinded, controlled trials was conducted by Berhan and Barker in 2013, to evaluate the safety and efficacy of a number of studied SGLT2 inhibitors accounting for variations in the dosing regimen as monotherapy and combination therapy.[15] This meta-analysis included 17 total studies of dapagliflozin, canagliflozin, ipragliflozin and empagliflozin conducted in human patients. Reductions from baseline in HbA$_{1c}$ (-0.78%, 95% CI, -0.87 to -0.69), fasting plasma glucose (-0.70%, 95% CI, -0.79 to -0.61) and body weight (-0.59%, 95% CI, -0.65 to -0.52) were

statistically significant for all observed doses, both as monotherapy or in combination with other agents. No significant impact on therapeutic efficacy was observed upon variation of dosing or duration, and improvements in overall glycemic control remained consistent across agents. Dapagliflozin and canagliflozin therapies demonstrated a statistically significant occurrence of genital tract infections, and a higher prevalence of UTIs was noted with dapagliflozin therapy in comparison with canagliflozin. Additionally, one study established an increased risk of vulvovaginal candidiasis in canagliflozin patients, which did not seem to impact those taking dapagliflozin to the same degree. Mycotic infections were generally more prevalent in patients with a previous history. Regardless of doses and frequency of therapy used (canagliflozin: 50 mg QD – 300 mg BID, dapagliflozin: 1 mg QD -50 mg QD, empagliflozin: 5 mg QD – 25 mg QD, ipragliflozin: 12.5 mg QD – 300 mg QD), there were no significant differences in dropout rates between treatment and placebo groups.[15]

Pharmacist Information and Counseling Points
Cost
Although specific pricing information has not yet been released by AstraZeneca and Bristol-Myers Squibb, patients meeting certain age and insurance criteria are eligible to participate in the Farxiga SavingsRx program to alleviate the potential financial burdens of dapagliflozin therapy.[16]

Monitoring
The traditional monitoring of T2DM also applies to dapagliflozin including regular HbA$_{1c}$ and renal function tests. Additionally, annual check-ups to monitor for diabetic complications should be performed by specialists such as a cardiologists, podiatrists and ophthalmologists. As with other anti-diabetic medications, hypoglycemia is a possibility and should be monitored. Patients specifically taking SGLT2 inhibitors are also at risk for hypovolemia due to increased blood glucose leading to increased urine excretion. Other complications of hypovolemia include orthostatic hypotension or hypotension, so the importance of staying adequately hydrated while taking dapagliflozin should be stressed. For geriatric patients, dosage adjustments do not need to be made unless that patient has moderate to severe impaired renal function (CrCl ≤ 60 ml/min) or end-stage kidney disease.[2] A phase 1 clinical trial is currently recruiting patients age 10 to 17 years, diagnosed with T2DM, to evaluate the pharmacokinetics and pharmacodynamics of dapagliflozin in that specific patient population.[17]

Conclusion
Dapagliflozin (Farxiga®), an oral "me too" alternative to canagliflozin, is a recently approved SGLT2 inhibitor for the treatment of T2DM. Due to the insulin independent nature of the mechanism, both dapagliflozin and canagliflozin have the potential to be a therapeutic niche for patients with a high degree of insulin resistance. As a relatively new class of diabetic medications, there remains a lack of head-to-head comparison data in regard to significant discrepancies in clinical efficacy. Adequate hydration and frequent monitoring of fluid status and renal function are important considerations

in all patients. Although no hepatic or renal dosing adjustments are recommended, dapagliflozin should be discontinued in end stage renal disease or if GFR falls below 60 ml/min. Contraindications to therapy include known hypersensitivity, severe renal impairment and hemodialysis. The most common adverse events include genital mycotic infections and UTIs, with the highest incidence in women and those with a history of prior genital infections. Clinical trials indicate statistically significant reductions in fasting plasma glucose and HbA$_{1c}$ compared to placebo when dapagliflozin is used as monotherapy. Studies also have shown a significantly greater reduction in HbA$_{1c}$ in combination therapy containing dapagliflozin as compared to monotherapy with an alternative antidiabetic agent. Although the high incidence of adverse events and cost may ultimately limit its clinical utility, this novel therapy presents a potential therapeutic consideration for patients requiring greater glycemic control.

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Assessment Questions

1. In which of the following patient populations is dapagliflozin most appropriately indicated?
   A. T1DM patients
   B. T2DM patients requiring intensified glycemic control
   C. Patients with significant insulin resistance
   D. Both B and C

2. Which of the following is the mechanism of action associated with dapagliflozin therapy?
   A. Agonist at SGLT1 in the proximal convoluted tubule
   B. Agonist of intestinal SGLT2
   C. Inhibitor of SGLT2 in the proximal convoluted tubule
   D. Inhibitor of intestinal SGLT1

3. What is the recommended starting dose when initiating dapagliflozin?
   A. 10 mg once daily
   B. 100 mg twice weekly
   C. 5 mg once daily
   D. 5 mg BID

4. Which dapagliflozin combination therapy resulted in attenuated weight GAIN?
   A. Dapagliflozin + metformin
   B. Dapagliflozin + glimepiride
   C. Dapagliflozin + pioglitazone

5. Which dapagliflozin combination therapy resulted in statistically significant differences from baseline HbA_{1c} compared to oral diabetic medication monotherapy plus placebo?
   A. Dapagliflozin + metformin
   B. Dapagliflozin + glimepiride
   C. Dapagliflozin + pioglitazone
   D. All of the above

6. What side effect was noted with highest prevalence in ALL the dapagliflozin combination therapies in the studies mentioned?
   A. UTIs
   B. Genital infections
   C. Hypoglycemia
   D. All of the above

7. Due to its mechanism of action, which of the following should be stressed to the patient before taking dapagliflozin?
   A. Increased foot care/monitoring
   B. Increased HbA_{1c} testing frequency
   C. Adequate hydration
   D. None of the above

8. At what level of renal impairment should dapagliflozin therapy be stopped?
   A. Moderate to severe renal impairment
   B. Moderate renal impairment only
   C. Severe renal impairment only
   D. Dapagliflozin should not be given with any renal impairment

9. Dapagliflozin therapy in pregnant females is…
   A. Contraindicated
   B. Not sufficiently studied, so risks should be evaluated prior to treatment
   C. Indicated
   D. Safe and effective

10. How did the incidence of UTIs compare between dapagliflozin and placebo treatments?
    A. There was a higher incidence in all dapagliflozin groups
    B. There was a higher incidence in the 5 and 10 mg dapagliflozin groups
    C. There was a lower incidence in dapagliflozin groups
    D. There was a lower incidence in the 5 and 10 mg dapagliflozin groups

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

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Program Title: **Dapagliflozin: A Newly Approved SGLT2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus**
UAN: 0048-0000-14-174-H01-P   CEUs: .075 for pharmacists only

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

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

Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals and objectives:					
Identify the mechanism of action and pharmacological implications of therapy with dapagliflozin.	1	2	3	4	5
Explain dapagliflozin's place in therapy in the treatment of diabetes.	1	2	3	4	5
Describe possible advantages of combination therapy with current diabetes medications.	1	2	3	4	5
Identify the appropriate monitoring requirements for dapagliflozin treatment.	1	2	3	4	5
Discuss the various side effects associated with dapagliflozin use.					
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

_____

_____

_____

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

1. A B C D   4. A B C   7. A B C D   10. A B C D

2. A B C D   5. A B C D   8. A B C D

3. A B C D   6. A B C D   9. A B C D

Ibrutinib (Imbruvica™) for Treatment of Mantle Cell Lymphoma

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Objectives

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

1. Identify current first-line treatments for mantle cell lymphoma (MCL) when considering functional status of the patient and stage of the cancer.
2. Explain the importance of MCL cell migration, as seen in ex vivo study of ibrutinib.
3. Describe the pharmacology of ibrutinib.
4. Discuss the benefits of ibrutinib treatment in relapsed/refractory MCL observed in phase II development.
5. State key patient counseling points, including side effects and dosing of ibrutinib for MCL.

Abstract

Mantle cell lymphoma (MCL) is a rare and moderately aggressive form of non-Hodgkin's lymphoma (NHL) that predominantly presents at an advanced stage in older males. Patients often present with multiple involvement in the lymph nodes, blood, spleen, bone marrow and gastrointestinal tract (GIT). Some patients may be asymptomatic in early stages or present with an incurable, indolent (slow progressing) form, while other patients display rapid growth of more aggressive lymphomas. Overall survival for patients diagnosed with MCL is four to five years and treatment should be initiated in those who are symptomatic. Mantle cell lymphoma responds well to first-line treatment, but recurrent relapses are common, and no regimen has been proven superior for relapsed or refractory MCL. The U.S. Food and Drug Administration (FDA) has recently approved ibrutinib (Imbruvica™) as breakthrough MCL therapy. Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor that interferes with malignant B-cell proliferation and survival. In a recent clinical study, ibrutinib proved to be a highly active monotherapy with a favorable toxicity profile in 111 patients with relapsed or refractory MCL. As an oral chemotherapy drug, ibrutinib has the potential to improve patient compliance. Additionally, specialty pharmacies dispensing ibrutinib will be able to play an important role in patient counseling and monitoring.

Introduction to Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a rare form of NHL with about 4,000 new cases each year in the United States.[1,2] Most patients with MCL present at the advanced stages, stage III and IV, with lymphadenopathy that is generalized and not bulky.[1] The lymphoma will likely affect multiple tissues and organs including lymph nodes, blood, spleen, and bone marrow, and lymphomatoid polyposis, which are lymphoid polyps in the gastrointestinal tract (GIT), may be present.[3] Clinically, a patient with MCL may present with enlarged lymph nodes, swollen abdomen, chest pain or pressure, or satiety after a small amount of food due to enlarged tonsils, liver or spleen. Presentation may also include dyspnea, fever, unexplained weight loss, nausea and vomiting, fatigue due to anemia or drenching night sweats.[2,4] MCL presents most commonly at a moderately aggressive stage in men in their fifth and sixth decades of life.[1]

If a patient presents with suspected MCL, a tumor biopsy is performed to confirm diagnosis.[1] An MCL biopsy lacks blastic cell involvement, but otherwise resembles other lymphomas. Cyclin D1 overexpression, elevated lactate dehydrogenase, and beta-2 microglobulin may assist in diagnosis of MCL.[5] Overexpression of cyclin D1, a promoter of cell cycle progression, is present in up to 90 percent of MCL cases, due to a (11;14) chromosomal translocation involving IgH and cyclin D1 loci.[3] Elevated levels of lactate dehydrogenase and beta-2 microglobulin are present in 25 to 50 percent of patients with MCL.[5,6] About 20 percent of MCL patients will progress to an incurable, indolent lymphoma, accompanied by the rapid growth of aggressive lymphomas.[1] This unique presentation of MCL contributes to a general life expectancy of four to five years past the diagnosis. Patients in this stage will often present similarly to chronic lymphocytic leukemia (CLL), having a lymphadenopathy that is slow to progress and a low tumor count.[7] If asymptomatic, the patient should be observed; however, in symptomatic patients who present with bulky lymphadenopathy or splenomegaly, constitutional symptoms, or present with cytopenia requiring transfusion, treatment is required.

Current Treatments

First-line treatments for MCL vary according to the physical status of the patient. Stem cell transplants are the first-line treatment for patients who are younger than 65 years and have good performance status, as they are more likely to tolerate this intensive treatment.[7] These patients receive high-dose chemotherapy (HDT), including Ara-C and rituximab, followed by an autologous stem cell transplantation (ASCT).[1] In eligible patients, this treatment is recommended once, and provides a longer time to treatment failure (TTF) and im-

proved overall survival (OS) as compared to protocols that do not utilize rituximab.

Many patients, however, present at late stages of MCL and/or may not be eligible for a transplant.[1] Radiation therapy is usually ineffective at late stages and, therefore, chemotherapy is the mainstay of treatment.[7] Generally, patients receive the R-CHOP regimen, which consists of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.[1] This therapy increases overall response rate (ORR), the percentage of patients whose cancer responds favorably to the treatment, and complete response (CR) in which all signs of cancer are eliminated due to treatment, but there is no improvement in OS.[1,8] While other treatment regimens are available, R-CHOP therapy has the best evidence.[1]

First-line treatments for MCL are often successful, but nearly all patients will relapse within two years.[1] The high relapse rate has directed research to identify novel therapies. While no regimen has yet been shown superior, many agents are currently undergoing clinical trials. Bortezomib is a proteosome inhibitor with an ORR of 33 percent.[21,7] Temsirolimus and other mammalian target of rapamycin (mTOR) inhibitors are also being studied and have an ORR of 22 percent. Lenalidomide is an immunomodulator with an ORR of 53 percent. Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor with an ORR of 68 percent, CR of 22 percent, and partial response (PR), a decrease in tumor size or cancer extent due to treatment, of 46 percent. Ibrutinib was recently FDA approved for the treatment of relapsed MCL and is the focus of this article.[9]

Ibrutinib Pharmacology and Pharmacokinetics

Ibrutinib was approved in November 2013, for treatment of MCL in patients who have been treated at least once previously.[9] Ibrutinib was also approved in February 2014, for chronic lymphocytic leukemia in patients who have received one prior therapy.[10] This paper will focus on the indication for MCL, which was approved via the accelerated approval program, as ibrutinib received breakthrough therapy designation.[9,11] Ibrutinib inhibits BTK, a terminal non-receptor tyrosine kinase, which promotes downstream activity of growth factors, B-cell antigens, chemokines and innate immune receptors.[12] Normally, BTK signaling promotes development, differentiation, and functioning of B-cells. By inhibiting BTK, ibrutinib inhibits proliferation of the lymphoma in MCL.

Ibrutinib inhibits kinase activity of BTK through covalent binding to the non-catalytic cys-481 residue of BTK, which is present in only 10 other kinases at this exact position.[13] Therefore, ibrutinib is a fairly selective inhibitor of BTK, being 1,000 times more selective for BTK of B-cells than CD69 of T-cells. Ibrutinib irreversibly inhibits BTK-driven gene expression. When compared with a known reversible inhibitor of BTK, ibrutinib inhibited gene up-regulation following a washout period while the reversible inhibitor did not. In vitro, one-hour exposure compared to continuous exposure to ibrutinib has the same inhibitory activity, demonstrating that one-time exposure is sufficient to inhibit BTK. Ibrutinib is relatively potent with an IC_{50} of 0.5 nM.

In vitro, ibrutinib appears to induce apoptosis of B-cells by two main mechanisms: inhibiting anti-apoptotic mechanisms and stimulating pro-apoptotic mechanisms. First, ibrutinib blocks anti-apoptotic pathways by decreasing ERK phosphorylation, decreasing NF-kB signaling, and decreasing expression of Akt, a serine threonine kinase that promotes cell cycle progression.[14-18] Secondly, ibrutinib stimulates pro-apoptotic mechanisms in B-cells by activating caspases.[14]

Additionally, ibrutinib decreases anti-IgM-induced signaling that stimulates B-cells by decreasing adhesion to VCAM, an adhesion molecule, and fibronectin, a glycoprotein involved in adhesion and migration.[17,19,20] Ibrutinib also decreases signaling induced by chemokines such as CXCL-12 and CXCL-13, that are secreted by stromal cells, and decreases production of cytokines such as interleukin-10.[15,17,21] By interfering with this signaling, ibrutinib inhibits the migration, adhesion, and proliferation of malignant B-cells.

The cellular mechanisms of ibrutinib that were delineated in vitro were substantiated in a study published by Chang and colleagues.[22] This study provided ex vivo insight to the mechanism of action of the anti-tumor effect of ibrutinib by examining the migration of MCL cells from the tumor into the peripheral blood and the characteristics of these malignant cells once in the periphery. Phenotyping, adhesion molecule assessments and migration assays were performed on blood samples collected from 22 patients participating in ibrutinib clinical trials. Following ibrutinib treatment, there was a statistically significant increase in the absolute lymphocyte count (ALC) in the peripheral blood, demonstrating the migration of malignant cells to the periphery, which contributes to the death of these cells. The lymphocytes tested, CD19 and CD5, had a decreased expression of CXCR4, CD38, and Ki57, all of which are surface molecules necessary for successful cell cycle progression. Ibrutinib suppressed the B-cell receptor (BCR)-stimulated cytokine and chemokine production from MCL cells and inhibited BCR-stimulated adhesion of MCL cells.

By inhibiting adhesion molecule expression, chemokine production and the downstream signaling of BTK, ibrutinib therapy forces malignant cells to migrate from their host tissue and enter the peripheral blood.[22] These micro events were further documented at the macro level as the lymph tissue mass clinically decreased. Ibrutinib decreased expression of CXCR4, a protein necessary for chemotaxis of malignant cells back to preferred tissues. The entrance and maintenance of malignant cells in the periphery is important because the MCL cells meet their demise in the peripheral blood. In the periphery, these cells do not have soluble factor exposure and other necessary components for proliferation and survival, and consequently, the malignant cells die and are cleared from the body. This study is important as it shows the mechanisms of anti-tumor action of ibrutinib and provides micro level insight of the positive macro level clinical results.

Pharmacokinetic studies on ibrutinib have also been conducted. Without food, the T_{max} of ibrutinib is approximately one to two hours, with an area under the curve (AUC) of 953 ng*h/mL at steady state.[23] In the body, the drug is highly protein bound, evidenced by a volume of distribution of 10,000 L at steady state. Ibrutinib is primarily metabolized by CYP3A4, with some metabolism via CYP2D6. The half-life of ibrutinib is four to six hours, and the majority of metabolites are excreted in feces.

Clinical Study

A phase II open-label, non-randomized, multicenter, monotherapy study by Wang and colleagues investigated the use of oral ibrutinib in 111 patients with relapsed or refractory MCL.[24] Other clinical trials are currently in progress, but the accelerated approval of ibrutinib was based on this trial.[9,25] The study enrolled subjects into two cohort groups based on their treatment history.[24] The first group included subjects who had previously received at least two, but not more than five, cycles of bortezomib therapy, while the second group included those who had received less than two complete cycles or no prior bortezomib therapy. Eligible patients were required to have a confirmed diagnosis of MCL. Diagnosis was based on either cyclin D1 overexpression or chromosomal translocation break points and an increase in lymph node diameter as a measure of staging the disease.

The primary end point was ORR, defined as the proportion of study subjects who achieved either complete or partial remission as their best overall response as defined by the modified Revised Response Criteria for Malignant Lymphoma.[24,26] According to the Response Criteria, complete remission was the disappearance of all evidence of disease, and partial remission was regression of measurable disease with no new sites.[27] Efficacy, safety, pharmacokinetics, and patient-reported outcomes regarding quality of life were all considered as secondary end points.[26] Subjects received 560 mg of oral ibrutinib daily in 28-day cycles until progression of the disease or an unacceptable level of adverse events was observed.[24] The timing of patient visits and assessments were based on the treatment cycles.[26]

The response rate for all patients was 68 percent, which included a partial response in 47 percent of subjects and a complete response in 21 percent.[24] The response rate did not vary with baseline characteristics or risk factors among the 111 subjects. Based on near equivalence of response between the two cohorts, the ORRs were reported together as a single percentage. The median time to a response was 1.9 months, the estimated median response duration was 17.5 months, and the estimated median progression-free survival was 13.9 months among all treated. The National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 were used to evaluate adverse events.[26] The criteria include a scale of grades corresponding with the severity of adverse events: grade 1 (mild), grade 2 (moderate), grade 3 (severe or medically significant but not immediately life threatening), grade 4 (life threatening), and grade 5 (death related to adverse events).[28] The majority of the adverse events observed with ibrutinib treatment were classi-

fied as grade 1 or grade 2, while grades 3, 4 and 5 were uncommon.[24] Over 20 percent of patients experienced mild side effects such as diarrhea, fatigue, nausea, peripheral edema, dyspnea, constipation, upper respiratory tract infection, vomiting and decreased appetite.

Peripheral blood lymphocytes were characterized post-ibrutinib treatment, and it was found that 34 percent of subjects had an increase in ALC that decreased and then tapered off by cycle 4 or cycle 5.[24] The increase included mostly CD19+CD5+CD3- lymphocytes with a pattern of light chain restriction that is consistent with MCL cells in peripheral blood. Investigators also found that ibrutinib caused a decrease in the secretion of macrophage inflammatory proteins 1-alpha (CCL3) and 1-beta (CCL4), macrophage-derived chemokine (CCL22) and TNF-alpha in most patients.

In a separate study, Chang and colleagues effectively demonstrated the ability of ibrutinib to inhibit the adhesion of MCL cells ex vivo, resulting in their mobilization to the peripheral blood.[22] Similar inhibitory effects were observed with in vitro ibrutinib treatment for CLL.[29] Wang and colleagues cited these findings as part of their reasoning for investigating the presence of MCL cells in the peripheral blood of study subjects. The ex vivo analysis, conducted by investigators within the in vivo study, also indicated that ibrutinib caused a transient increase in blood lymphocytes as well as a decrease in the secretion of certain inflammatory molecules.[24] Therefore, the phase II trial by Wang and colleagues demonstrates the benefit of ibrutinib treatment on a micro level in study subjects who also exhibited favorable macro level effects such as high response rate accompanied with a favorable level of toxicity. These effects indicate that ibrutinib has the potential to be a less intensive but more effective regimen than other treatments available for relapsed and refractory MCL.

Investigators in this phase II trial concluded that ibrutinib is a highly active, single agent with considerable duration of activity in relapsed and refractory MCL along with a favorable toxicity profile.[24] A major strength in the study design was the combination of two cohorts that allowed representation of a broad population of subjects with relapsed or refractory MCL within a moderately small sample size. Patients receiving ibrutinib demonstrated statistically and clinically significant data indicating the potential for ibrutinib as a new treatment for relapsed and refractory MCL.

Pharmacist Focus

Dosing for ibrutinib is 560 mg daily, which equates to four 140 mg capsules once daily. Dosing is based on evidence from the previously discussed clinical trial.[24] Ibrutinib may cause fetal harm in pregnant women and secretion into breast milk is unknown, as therapy should be carefully considered in the affected population.[23] Concurrent CYP3A inducers should be avoided, as they can decrease the plasma concentration of ibrutinib. Concurrent CYP3A4 inhibitors increase the risk of toxicity by increasing the AUC and C_{max} of ibrutinib, and ibrutinib should be discontinued if short-term therapy with a CYP3A4 inhibitor is utilized.

An advantage of ibrutinib is a more favorable adverse effect profile for certain patient populations in comparison to other agents for relapsed MCL including bortezomib, temsirolimus and lenalidomide. The more severe adverse effects of these drugs include profound myelosuppression, anemia, cardiac effects, metabolic acidosis and hepatotoxicity.[30-32] Serious adverse effects of ibrutinib include hemorrhage, infections, myelosuppression, renal toxicity and risk of secondary primary malignancies.[23] While ibrutinib still exhibits serious adverse effects, it is a preferred choice for patients who have cardiac or hepatic complications.

Being an oral chemotherapy agent, ibrutinib has many benefits acknowledged by health care providers. These benefits include patient convenience and comfort, more favorable risk-benefit profiles and the availability of specialty pharmacies to help with reimbursement challenges and financial assistance and are among the top reasons oncologists would be more likely to prescribe an oral chemotherapy agent over an intravenous (IV) agent.[33,34]

Another benefit of oral ibrutinib is the ability of patients to utilize outpatient services to obtain the medication. In regard to outpatient pharmacy services, specialty pharmacies, as previously mentioned, are expected to be often utilized. While their place in care is evolving, specialty pharmacies are essentially "niche" pharmacies.[35] As defined by Scott Kober, "[Specialty pharmacy] serve[s] a limited number of patients with a small number of high-cost, low-volume and high-maintenance conditions…."[35] These pharmacies offer special services such as high-quality counseling and assistance in navigating payment options for treatment.[34,36] As an oral chemotherapy agent, ibrutinib will likely be frequently dispensed at specialty pharmacies.

Conclusion

There is a need for effective chemotherapy agents that can be used to treat relapsed or refractory cases of MCL. Molecularly targeted drugs such as bortezomib, temsirolimus and lenalidomide have shown anti-lymphoma activity useful in treating difficult cases of MCL.[6] As a BTK inhibitor, ibrutinib also works on a molecular level to interfere in the malignant B-cell signaling cascade.[6,22] Clinical trials have shown impressive response rates for this newly introduced therapy.[24] Treatment with ibrutinib offers advantages including oral route of administration and a favorable toxicity profile compared to other more intensive treatments. Furthermore, some oncologists have indicated that they prefer oral chemotherapies over IV regimens, with one reason being the role that specialty pharmacies may then take in optimizing patient care through counseling and monitoring.[7,33,34] Although MCL is a moderately aggressive form of NHL, high response rates with ibrutinib therapy offers patients a chance for progression-free survival when first-line therapies have failed.

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Assessment Questions

1. KL is a 68 year old male with poor functional status who has recently been diagnosed with late stage MCL. He is about to start his first treatment. Which of the following is the most appropriate treatment regimen for him?
   A. External beam radiation therapy
   B. Ibrutinib x 28 day trial
   C. Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP)
   D. Stem cell transplantation
   E. More than one of the above

2. Which of the following CORRECTLY describes the importance of MCL cell migration?
   A. By inhibiting adhesion molecule expression, MCL cells are forced to enter peripheral blood.
   B. Ibrutinib decreases expression of CXCR4, which prevents malignant cells' return to their tissues.
   C. Once in the periphery, MCL cells do not have the necessary components for survival and die.
   D. Two of the above
   E. Three of the above

3. TR is a 57 year old female coming to your specialty pharmacy. She has arrived to pick up her new prescription for ibrutinib to treat her relapsed MCL. While excited that there are no needles involved with this drug, she is nervous about starting the new treatment and any adverse effects it might bring. What counseling points about the adverse effects do you offer her?
   A. "You may bleed more easily. Take care to avoid injury."
   B. "If you feel very tired or weak, have an upset stomach, have a fast heartbeat or are breathing fast, call your doctor. These may be signs of too much acid in your blood."
   C. "This drug makes you more likely to catch illnesses, such as the flu or a cold. Stay away from people who are sick."
   D. Two of the above
   E. Three of the above

4. Ibrutinib works by inhibiting which protein?
   A. Proteasome
   B. CD20
   C. Bruton's tyrosine kinase
   D. Epidermal growth factor receptor
   E. Cyclin D1

5. What is the dosing of ibrutinib for MCL?
   A. 560 mg daily
   B. 140 mg TID
   C. 560 mg BID
   D. 280 mg daily
   E. 280 mg BID

6. Which enzyme is primarily responsible for ibrutinib's metabolism?
   A. CYP2C19
   B. VKOR
   C. CYP2A9
   D. CYP3A4
   E. Ibrutinib is excreted unchanged in urine

7. Which of the following statements accurately describes the toxicity profile associated with ibrutinib:
   A. Ibrutinib is not associated with a high occurrence of severe side effects such as grade 4 hemorrhagic events.
   B. Patients taking ibrutinib most commonly experience grade 1 or 2 adverse events.
   C. Possible side effects of ibrutinib include diarrhea, fatigue, dyspnea, and decrease in appetite.
   D. Two of the above
   E. Three of the above

8. What were the major advantages associated with ibrutinib treatment in the main phase II clinical trial utilized for accelerated FDA approval?
   A. All participants achieved a complete response.
   B. Ibrutinib was found to be a highly active, single agent.
   C. Ibrutinib therapy had a considerable duration of action.
   D. Two of the above
   E. Three of the above

9. During clinical development, both ex vivo and in vivo research indicated that ibrutinib had the potential to be a less intensive but more effective regimen than other treatments currently available.
   A. True
   B. False

10. The protein target of ibrutinib normally has what function in a healthy body?
    A. Induces apoptosis of B-cells
    B. Stimulates chemokine release
    C. Promotes B-cell development
    D. Two of the above
    E. Three of the above

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Program Title: **Ibrutinib (Imbruvica™) for Treatment of Mantle Cell Lymphoma**
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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 current first-line treatments for mantle cell lymphoma (MCL) when considering functional status of the patient and stage of the cancer.	1	2	3	4	5
Explain the importance of MCL cell migration, as seen in ex vivo study of ibrutinib.	1	2	3	4	5
Describe the pharmacology of ibrutinib.	1	2	3	4	5
Discuss the benefits of ibrutinib treatment in relapsed/refractory MCL observed in phase II development.	1	2	3	4	5
State key patient counseling points, including side effects and dosing of ibrutinib for MCL.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

_____

_____

_____

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

1. A B C D E   4. A B C D E   7. A B C D E   10. A B C D E

2. A B C D E   5. A B C D E   8. A B C D E

3. A B C D E   6. A B C D E   9. A B

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

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Advances in Treatment of
Chronic Hepatitis C Virus (HCV) Infection

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Abstract
Hepatitis C virus (HCV) infection is a prominent cause of chronic liver disease and may lead to serious complications such as liver failure and need for a transplant. The virus is transmitted via exposure to blood and is classified into various genotypes based on genetic mutations in the virus. Current treatment options for HCV infection are not effective in all patients, and there are limited options for patients infected with a genotype other than genotype 1. Two new medications have been approved recently for treatment of HCV infection. Simeprevir (Olysio®) gained U.S. Food and Drug Administration (FDA) approval in November 2013, and sofosbuvir (Sovaldi®) was approved in December 2013. Information from clinical trials with each of the medications supports their safety and efficacy in appropriate patient populations. The adverse effects are generally tolerable; however, for some patients, the adverse effects, drug interactions and cost can be limiting factors.

Introduction

Hepatitis C virus is a blood-borne pathogen leading to long-term hepatic complications if not properly treated.[1] Current therapy for HCV includes ribavirin (RBV), peg-interferon alfa (PegIFN) and two options for protease inhibitors (boceprevir and telaprevir), which can only be used in one genotype of HCV infection.[2-4] Two new medications were recently approved for treatment of chronic HCV infection: simeprevir (Olysio®) in November 2013 and sofosbuvir (Sovaldi®) in December 2013.[5,6] These new medications can provide more treatment options to patients with different genotypes or for whom prior treatment with RBV and PegIFN was unsuccessful.[7,8] Safety and efficacy have been demonstrated in several clinical trials.[9-12] The adverse reactions and cost of these medications are important factors to consider when determining treatment for HCV infection in a patient.

Disease State Overview

Hepatitis C infects approximately 170 million individuals worldwide, which has become both a public health and an economic issue.[13] Being the most common blood-borne pathogen, the HCV is one of the leading causes of chronic liver disease and the third leading cause of death in patients with end stage renal disease.[1,2] All individuals who are infected with HCV are at a greater risk for developing long-term complications such as cirrhosis, liver failure and hepatocellular carcinoma.[14]

Hepatitis C virus is a single-stranded, positive RNA virus, which has a high rate of mutation, leading to therapy resistance and immune system evasion.[15] Presentation varies from patient to patient in that some patients may present with mild hepatitis or inflammation of the liver, while others experience scarring or even liver cancer.[16] The first phase begins with HCV exposure which results in high viral titers being expressed in the blood. In this early stage, which typically lasts six to eight weeks, a T-cell mediated immune response is apparent in the absence of liver damage. The second phase of HCV infection begins with the generation of HCV specific antibodies and T-cells. This phase is also characterized by an increase in liver enzyme levels, which is evidence of hepatocyte destruction. Phase three, which takes place 12 to 24 weeks after infection, shows variations in HCV viremia as well as decreasing capabilities of functional T-cells. Phase four, or 24 weeks post-infection, marks the end of the acute phase of the HCV infection as cellular immunity continues to evolve.

The virus itself does not cause damage to the liver, but rather the response it elicits from the immune system causes healthy liver tissue to be replaced with scar tissue.[18] Typically, the preferred treatment for HCV is PegIFN along with RBV, a nucleoside analogue, to which approximately 55 percent of patients respond. For those patients who are non-responders, few treatment options exist, which has led to further research and development of HCV medications.

Treatment for HCV has evolved over the past years owing to advances in research and drug therapy.[2] Treatment in the mid-1990s consisted of interferon monotherapy, which was injected three times a week for a total duration of six to 12 months. In the late 1990s, RBV was added to interferon, which dramatically increased a patient's sustained virologic response (SVR). A sustained virologic response is defined as a lack of HCV in the blood after 24 weeks of treatment and remains the best indication of how successful therapy is in a patient.[18] Therapy evolved once more to the current regimen of PegIFN in addition to RBV.[2] The ultimate goal of treatment in patients with HCV is to reach an SVR, as defined above. Currently, there is no vaccine to prevent HCV.[19]

Genotyping plays an important role in determining treatment for HCV.[20] Currently, there are six clinically significant genotypes (1-6) identified for HCV, of which some are found to be more prevalent in different parts of the world. For example, genotypes 1 through 3 are more common in the United States and Europe, genotype 4 is found most often in Egypt, and genotype 6 is more common in South Asia. Based on what genotype a person has, treatment and also response to treatment will differ. HCV genotyping is done to provide

the most effective therapy and to get the maximum response out of the medication prescribed.

Overview of New Medications

Two new medications have recently been approved for the treatment of chronic HCV infection.[6] The first is simeprevir (Olysio®), approved Nov. 22, 2013.[5] The second is sofosbuvir (Sovaldi®), approved Dec. 6, 2013.

Simeprevir is a HCV NS3/4A protease inhibitor to be used in combination with PegIFN and RBV to treat chronic HCV infection in patients with genotype 1 HCV infection.[7] The HCV NS3/4A protein is a serine protease that is essential in cleaving the single HCV polyprotein precursor into the 10 individual proteins needed for HCV maturation and replication.[21,22] Inhibition of NS3/4A prevents the viral replication of HCV.[21] Simeprevir is the third HCV NS3/4A protease inhibitor to receive approval, with the previous two being boceprevir (Victrelis®) and telaprevir (Incivek®), each approved in 2011.[5] Simeprevir differs from the other two protease inhibitors in that it is administered only once daily; however, all three protease inhibitors are only effective in genotype 1 HCV infection and must be used with both PegIFN and RBV.[3,4,7] Simeprevir is a 150 mg capsule taken once daily with food.[7] The treatment schedule is 12 weeks of simeprevir with PegIFN and RBV for 24 or 48 weeks, depending on prior treatment status.

Sofosbuvir is a NS5B polymerase inhibitor.[8] The HCV protein NS5B is an RNA polymerase that transcribes viral RNA in order to produce HCV proteins.[8,23] Sofosbuvir is a nucleotide prodrug that is converted in the liver to a uridine analog, which then inhibits the work of NS5B by incorporating into HCV RNA and acting as a chain terminator, thereby preventing the completion of viral replication. Sofosbuvir has shown efficacy in treating genotypes 1, 2, 3 and 4 HCV infection.[8] Sofosbuvir is a 400 mg tablet taken once daily without regard to food. Genotype of HCV infection determines treatment duration and PegIFN requirement. Genotype 1 is treated with sofosbuvir plus PegIFN and RBV for 12 weeks, or if ineligible for PegIFN, sofosbuvir plus RBV for 24 weeks. Genotype 2 is treated with sofosbuvir plus RBV for 12 weeks, and genotype 3 has the same treatment extended to 24 weeks. Genotype 4 is treated with sofosbuvir plus PegIFN and RBV for 12 weeks. Sofosbuvir is the first drug in its class and the first drug that does not necessarily require concomitant use of PegIFN for the treatment of chronic HCV infection.[6]

Review of Clinical Trials

Several clinical trials have evaluated the safety and efficacy of these two new medications. One of the clinical trials evaluated by the FDA in considering the approval of simeprevir was the ASPIRE trial.[10] ASPIRE was a phase IIb, randomized, double-blind trial. This trial evaluated the safety and efficacy of simeprevir plus PegIFN/RBV in comparison to PegIFN/RBV alone in patients with HCV genotype 1 who have previously failed to respond to treatment with PegIFN/RBV. Four hundred sixty-two patients began the trial and were divided into seven groups. All groups received PegIFN/RBV for 48 weeks. Each group also received either 100 mg or 150 mg

simeprevir once daily for 12, 24 or 48 weeks, or no simeprevir, designated as the control group. The primary end point of the study was the proportion of patients maintaining SVR at 24 weeks after end of treatment (SVR24). In the simeprevir groups, 60.6 to 80.0 percent of patients achieved SVR24 compared to 22.7 percent of the control group, demonstrating efficacy of the addition of simeprevir over PegIFN/RBV alone. In the 150 mg simeprevir groups, 72.9 percent of patients achieved SVR24 compared to 65.6 percent of patients in 100 mg simeprevir groups, supporting the choice of 150 mg capsules. Duration of treatment with simeprevir showed no improvement in SVR24 rate beyond 12 weeks (68.2% in 12-week groups, 69.2% in 24-week groups and 70.2% in 48-week groups) supporting the use of simeprevir for only 12 weeks.

The ASPIRE trial further looked at the efficacy of simeprevir versus the control group in patients with prior null response, prior partial response and relapse to previous treatment with PegIFN/RBV.[10] In prior null response patients (patients that did not achieve SVR in previous treatment with PegIFN/RBV), SVR24 rates were 37.5 to 58.8 percent in simeprevir groups versus 18.8 percent in control group. In prior partial response patients (patients that had reduced HCV RNA in previous treatment with PegIFN/RBV but did not achieve SVR), SVR24 rates were 47.8 to 86.4 percent in simeprevir groups versus 8.7 percent in control group. In prior relapse patients (patients that achieved SVR at end of treatment (EOT) with PegIFN/RBV but had detectable HCV RNA 24 weeks later), SVR24 rates were 76.9 to 88.9 percent in simeprevir groups versus 37 percent in control group. This indicates potential efficacy in patients with prior treatment failure. The safety profile in simeprevir groups was similar to that of the control group (PegIFN/RBV alone). All groups had similar total incidence of adverse events (AEs) and severe AEs, with fatigue, headache, pruritus, influenza-like illness and neutropenia most frequently reported. Groups treated with simeprevir had higher frequency of rash (26.5% versus 18.2%) and pruritus (34.1% versus 16.7%) than PegIFN/RBV groups, although severity of these AEs was similar.

Another clinical trial evaluating simeprevir was the PILLAR trial.[11] PILLAR was a phase IIb, randomized, double-blind trial that assessed the safety and efficacy of simeprevir plus PegIFN/RBV in comparison to PegIFN/RBV alone in treatment-naïve patients with HCV genotype 1. The trial began with 386 patients divided into five groups. All groups received PegIFN/RBV for 48 weeks unless the patient was eligible to end all treatment at 24 weeks. Each group also received either 75 mg or 150 mg simeprevir once daily for 12 or 24 weeks, or no simeprevir, designated as the control group. If a simeprevir-treated patient achieved rapid virologic response (RVR; defined by HCV RNA undetectable at week 4) and had undetectable HCV RNA at weeks 12, 16 and 20, PegIFN/RBV could be stopped at week 24 rather than finishing the full 48 weeks. The primary end point was the proportion of patients maintaining SVR at week 72 of the trial (SVR72), with treatment ending at week 48 or earlier. There was a statistically significant difference in SVR72 between the 150 mg, 12-week simeprevir group versus control

group (77.9% versus 64.9%, P<0.05) and between the 150 mg, 24-week simeprevir group versus control group (84.8% versus 64.9%, p<0.05), indicating that the addition of 150 mg daily simeprevir leads to greater success in therapy than PegIFN/RBV alone. No differences in SVR rates were noted between different durations of simeprevir treatment. RVR was achieved by 68.0 to 75.6 percent of simeprevir patients versus 5.2 percent of patients in the control group. Of simeprevir-treated patients, 79.2 to 86.1 percent were eligible to complete all treatment at week 24. This is significant because it allowed these patients to cut treatment duration in half, saving money, time and inconvenience. Adverse events and serious AEs were similar across all groups. The most frequently reported AEs were fatigue, influenza-like illness, pruritus, headache and nausea, typically associated with PegIFN/RBV therapy. This trial did not show higher frequency of rash and pruritus in simeprevir groups compared to PegIFN/RBV alone.

The FDA approval of the other new HCV treatment medication, sofosbuvir, was dependent on the FISSION trial and the POSITRON trial, among others.[9,12] The FISSION trial was a phase III, randomized, open-label trial.[12] This study evaluated the safety and efficacy of sofosbuvir plus RBV in comparison to PegIFN/RBV alone in treatment-naïve patients with HCV genotype 2 or 3. At the beginning of the trial, 499 patients were randomized to receive either 400 mg sofosbuvir once daily plus RBV for 12 weeks or to receive PegIFN/RBV for 24 weeks. The primary end point was defined as the proportion of patients maintaining SVR at 12 weeks after EOT (SVR12). The primary end point was achieved in 67 percent of patients in the sofosbuvir/RBV group versus 67 percent in the PegIFN/RBV group, indicating that sofosbuvir/RBV therapy is not inferior in efficacy to PegIFN/RBV therapy. This is significant in that it allows patients the option to receive treatment with only oral medications. Patients with genotype 2 achieved SVR12 in 97 percent of sofosbuvir/RBV group versus 78 percent of PegIFN/RBV group, supporting the efficacy of sofosbuvir/RBV therapy in genotype 2 HCV. Patients with genotype 3 HCV achieved SVR12 in 56 percent of sofosbuvir/RBV group versus 63 percent of PegIFN/RBV group, indicating sofosbuvir/RBV for 12 weeks is not as effective as PegIFN/RBV for 24 weeks in these patients. The FDA recommends using sofosbuvir/RBV for 24 weeks (not 12 weeks) in patients with genotype 3.[8] Adverse events in this trial occurred more frequently in PegIFN/RBV group than the sofosbuvir/RBV group, and serious AEs were low among all groups. The most common AEs in all groups were fatigue, headache, nausea and insomnia.[12]

Another clinical trial used by the FDA in consideration of sofosbuvir was the POSITRON trial.[9] POSITRON was a phase III, randomized, double-blinded trial. This trial evaluated the safety and efficacy of sofosbuvir/RBV compared to RBV alone in patients with HCV genotype 2 or 3 unable to take PegIFN. The trial began with 278 patients randomized to receive RBV and sofosbuvir 400 mg once daily for 12 weeks or to receive RBV and placebo for 12 weeks. The primary end point was SVR12. The primary end point was achieved in 78 percent of sofosbuvir/RBV group versus 0 percent of RBV

group. At EOT (12 weeks prior to this measurement), 100 percent of sofosbuvir/RBV group versus 0 percent of RBV group had achieved SVR. This difference in SVR in the sofosbuvir/RBV group was due to viral relapse after EOT. All cases of relapse that were reported occurred within 12 weeks after EOT, with no new cases of relapse reported between 12 to 24 weeks after EOT. Treatment with sofosbuvir/RBV led to SVR12 in 93 percent of patients with HCV genotype 2 versus 61 percent of patients with HCV genotype 3. Adverse events occurred more frequently in the sofosbuvir/RBV group than the RBV group, particularly fatigue, insomnia and anemia. The rate of AEs was overall low in both groups. The rate of serious AEs was similar between the two groups. Although the use of RBV alone is not a valid treatment option for the treatment of chronic HCV, giving the impression that this study is invalid, treatment with RBV alone may be the only option for patients who cannot tolerate PegIFN, especially in patients with non-genotype 1 HCV infection. This study supports the idea that treatment with sofosbuvir/RBV has better efficacy for patients with genotype 2 and 3 than RBV alone.[9]

Pharmacists' Impact
A look at the new medications' AEs and drug interactions can help a health care provider decide if these new medications would be right for his or her patient. Pharmacists can help counsel on the new drugs' adverse reactions, helping to ensure a safe introduction of these new medications.

There are two major AEs with simeprevir: teratogenicity and sun sensitivity. Male and female patients taking simeprevir with RBV must use two forms of birth control while on the therapy and for six months after discontinuation.[24] Female patients must be monitored monthly via pregnancy tests. Severe rashes may develop with simeprevir. These rashes occur with sun exposure and usually develop within the first four weeks of treatment. Patients should be encouraged to contact a health care provider if any sort of redness, rash or conjunctivitis occurs. Severe cases may require hospitalization, so patients should be urged to wear sunscreen and protective clothing (such as hats) if they are going to be outside for long periods of time. As it contains a sulfonamide moiety, simeprevir should be used with caution in those patients with sulfa allergies. Simeprevir is contraindicated with various medications ranging from over-the-counter supplements such as St. John's Wort to prescription hypertension medications. Patients should provide health care providers with a complete drug list, and pharmacists should monitor use of these contraindicated medications in patients taking simeprevir.

Similar to simeprevir, sofosbuvir requires two forms of birth control and pregnancy monitoring due to use with RBV, along with two negative pregnancy tests prior to beginning therapy.[7] Other sofosbuvir side effects include central nervous system effects such as depression, insomnia and nausea with headache and fatigue being the most common. Abnormalities in lab values including bilirubin, creatinine kinase, and lipases were also seen in patients taking sofosbuvir. The main drug interaction involved in sofosbuvir use is seen in potent intestinal P-glycoprotein inducers such as St. John's

Wort or rifampicin. These medications can alter the concentrations of sofosbuvir; therefore, their concurrent use is discouraged.

Neither of the medications has recommended renal or hepatic dosing adjustments at this time, due to insufficient evidence in these patient populations.[7,8] Each therapy is to be given over 12 weeks (with the exception of sofosbuvir in genotype 3), while monitoring different levels for dosing adjustments. Hemoglobin levels should be monitored with use of sofosbuvir due to ribavirin co-administration.[8] In patients with no history of cardiac disease, it is recommended that ribavirin be reduced to 600 mg/day with hemoglobin levels less than 10 g/dL and discontinued with levels less than 8.5 g/dL. In patients with a history of stable cardiac disease, ribavirin levels should be reduced with any drop in hemoglobin levels of over 2 g/dL over a four-week period or discontinued if hemoglobin levels drop below 12 g/dL. Hepatitis C virus RNA levels are monitored with use of simeprevir.[25] It is recommended to discontinue simeprevir, as well as PegIFN and RBV, if HCV RNA levels reach 25 IU/mL or greater at any point during the therapy duration.

Cost should be considered when weighing risks versus benefits of these therapies. Both therapies have gained media attention for their cost, many noting that these medications should be saved for those with severe cases of hepatitis C.[26] Simeprevir's 12 week therapy runs at $66,360, while sofosbuvir is priced at $84,000.[27,28]

Place in Therapy

The American Association for the Study of Liver Diseases (AASLD) provides working guidelines for the treatment of HCV infection that expound upon the place in therapy for these two new medications.[29] Because these medications were approved relatively recently, the AASLD has created web-based 2014 guidelines that are continuously being modified as new data become available. In general, the AASLD 2014 guidelines recommend the use of sofosbuvir with RBV as first-line treatment in nearly all patients (treatment-naïve and treatment-experienced patients with genotype 1 through 6), also including PegIFN when appropriate. The guidelines find sofosbuvir with RBV to have the best balance of high efficacy and AEs. Simeprevir with RBV/PegIFN is listed by the AASLD as an alternative regimen for treating genotype 1 and 4 (despite lack of FDA approval for use in genotype 4). The AASLD guidelines no longer recommend the use RBV/PegIFN alone for nearly all patients, claiming that therapy with RBV/PegIFN alone is inferior to the addition of sofosbuvir or simeprevir, due to lower efficacy, higher rate of serious AEs, and longer treatment duration when RBV/PegIFN is used alone. The guidelines prefer simeprevir over telaprevir and boceprevir, claiming comparatively lower efficacy, lower tolerability, and higher pill burden for telaprevir and boceprevir. Sofosbuvir and simeprevir may be used more prominently for the treatment of HCV infection as these guidelines are finalized.

Conclusion

Hepatitis C virus is one of the most common blood-borne pathogens and can lead to serious long-term complications.[1] Simeprevir and sofosbuvir have been shown to be effective and safe in multiple studies for the treatment of chronic HCV infection in both treatment-naïve and treatment-experienced patients.[7,8] Simeprevir is approved for the treatment of genotype 1 HCV and requires concurrent RBV and PegIFN.[7] Sofosbuvir can treat genotype 1 through 4 HCV with concurrent RBV and sometimes PegIFN.[8] The side effect profile, drug interactions and cost of each of these new medications must be weighed against the potential benefit to the patient in treating chronic HCV infection.

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Gastroenterology

Crohn's Disease: Management, Emerging Therapies and the Role of the Pharmacist

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Abstract

Crohn's disease is a relapsing-remitting disorder of the gastrointestinal tract caused by a mixture of genetic and environmental factors. Pharmacologic treatment of Crohn's disease is patient-specific, and regimens vary widely between individuals. Drug regimens are typically based on 5-aminosalicylate therapy and may include a combination of steroids, histamine 2 receptor antagonists, proton pump inhibitors, immunomodulators, antibiotics, biologic agents and other medications aimed at symptom relief. A new medication, vedolizumab, is currently in phase III clinical trials awaiting U.S. Food and Drug Administration (FDA) approval for use in Crohn's disease. Vedolizumab is an alpha-integrin inhibitor, which is anticipated to have a better safety profile than Tysabri® (natalizumab), an alpha-integrin inhibitor already approved for treatment of Crohn's disease. Pharmacists have an opportunity to educate Crohn's disease patients about nonpharmacologic management including counseling on diet, exercise, stress-relief therapy and use of multivitamins as well as the importance of regular colonoscopies and visits to a primary care practitioner. Pharmacists can also educate patients and practitioners about alternative therapies including probiotics, fecal microbiota transplantation and fish oils which may help manage the disease.

Introduction

Crohn's disease is an inflammatory bowel disease (IBD), which can negatively affect the lives of many patients. While there are both pharmacologic and nonpharmacologic steps all patients can take to suppress the disease and its complications, treatment is highly individualized. Many patients will often not respond to initial therapy or may lose responsiveness over time. The need for new medications to combat Crohn's disease is highly recognized. Vedolizumab has completed phase III clinical trials and is awaiting FDA approval. Its safety and efficacy in these trials are encouraging for potential use in Crohn's disease patients. Pharmacists can play a large role in the management of these patients, as they will be instrumental in monitoring complex drug therapies, ensuring appropriate laboratory testing, and educating patients on diet, other nonpharmacologic treatments, and new investigational therapies. Pharmacists have the opportunity to make a difference in improving the quality of life of Crohn's disease patients in multiple settings, which include community, institutional, specialty pharmacy and primary care practice.

Background of Disease and Traditional Therapy

Crohn's disease is an increasingly prevalent idiopathic form of IBD. Since it affects all ages and ethnicities, as well as both men and women, Crohn's disease plays a significant role in the lives of approximately 6 million Americans.[1] The chronic, relapsing autoimmune inflammatory nature of this disease typically presents as a discontinuation of the mucosa of the gastrointestinal tract (GIT) and may result in complications such as strictures, fistulas, lesions, obstructions or abscesses. Lesions of the intestine are oftentimes irreversible. While the mucosa of the entire GIT from the mouth to the anus can be affected, the majority of cases are located in the terminal ileum and colon. Clinical implications include diarrhea or constipation, fever, abdominal pain, passage of mucus and blood in the stool, signs of bowel obstruction, mouth sores and clubbing of the fingernails.[2,3] Diarrhea, as demonstrated by an increase in frequency and decrease in consistency of stool, is the most common clinical implication. Abdominal pain, another common symptom, is typically seen in the right lower quadrant and is exacerbated by eating.[3] As a result of this exacerbation with food, weight loss is a frequent occurrence in Crohn's disease.[4]

Crohn's disease is not a reportable condition in the United States, which limits the ability to determine which populations are at highest risk. Data is also skewed by the difficulty in differentiating Crohn's disease from a similar form of IBD known as ulcerative colitis. Researchers have conducted multiple studies to determine the populations that have the highest incidence of Crohn's disease. Crohn's disease may occur at any age, but most cases are diagnosed in early adulthood with a large peak in adults 20 to 30 years old. A second peak of incidence occurs in adults 50 to 60 years old.[1,5] About 25 percent of IBD diagnoses occur during childhood and, unfortunately, pediatric patients generally present with a more severe form.[5] Pediatric cases of Crohn's disease occur more often in boys than girls, but in adults more cases occur in women than men. Data indicate more cases of Crohn's disease in the Northeast and Midwest regions of the United States when compared to the Southern and Western regions.[1] Historically, Crohn's disease is most common in Caucasians, with a genetic-based increase in prevalence among individuals of Eastern European (Ashkenazi) Jewish descent.[6] However, recent studies have shown an increase in the rate of African-Americans presenting with Crohn's disease, and the rate of Crohn's-induced hospitalizations of African-Americans is now similar to Caucasians. Incidence in Asian-Americans and Hispanic-Americans is significantly lower compared to Caucasians and African-Americans.[7]

The exact cause of Crohn's disease is unknown, but the disease seems to be influenced by both genetics and environmental factors. Genome-wide association studies have shown genetic variance to be the major contributor to about 23 percent of cases. These genetic variants have been shown to alter the regulation and efficiency of key molecular pathways

in the body such as microbial defense, innate immune responses, autophagy, reactive oxygen species generation, and lymphocyte differentiation.[8] Due to altered regulation, the GIT is more prone to chronic injury and infection. Although microorganisms such as Escherichia coli, Salmonella spp. and Campylobacter spp. have been hypothesized to trigger the onset of Crohn's disease, researchers have not been able to pinpoint one specific microorganism as the causative agent.[9] These harmful microorganisms can adhere to epithelial cells of the intestine, replicate and stimulate an immune response, which induces epithelial cell injury, causing inflammation and discontinuation of the intestinal mucosa. Crohn's disease patients are also commonly postulated to have a "leaky gut" in which intestinal permeability is increased, resulting in intestinal substances leaking out into the bloodstream. Moreover, most Crohn's disease patients have altered bowel flora, which leaves the GIT unable to defend against the activity of harmful microorganisms.[3,8]

Many factors contribute to an increase in harmful microorganisms in the intestinal mucosa. For example, the consumption of refined sugars and preservatives present in many foods in the United States and other industrialized areas favor growth of detrimental bacteria in the intestine. As a result, diet can be a key component in the management of Crohn's disease. Children growing up in areas with poor sanitation are exposed to an increased repertoire of pathogens and infections, and thus, develop a more robust immune system. Therefore, these children may be protected against agents which may induce Crohn's disease, resulting in lower prevalence in children in areas of poor hygiene compared to children who grow up with increased sanitation and less pathogen exposure in industrialized areas. This idea is known as the hygiene hypothesis and is theorized as a contributor to the development of IBD.[10] Drug-induced Crohn's disease is also possible. Chronic use of antibiotics can kill protective bacteria in the intestine leaving the epithelial cells more prone to injury by harmful microorganisms. Other risk factors for developing Crohn's disease include cigarette smoking and use of oral contraceptives.[7]

Currently, no definitive diagnostic test exists for Crohn's disease. Analysis of symptoms and clinical laboratory values as well as endoscopic, histologic, and radiologic examination criteria lead to confirmation of the disease.[2,4] There is no gold standard when it comes to treating Crohn's disease. There are several different treatment guidelines available, including those from the American Academy of Family Physicians (AAFP), the American College of Gastroenterology (ACG), and the American Gastroenterological Association (AGA). However, the guidelines do not agree on a strong first-line recommendation. Therefore, optimal first-line therapy is patient-specific and dependent on the location, severity and any complications of the disease that are present. The two primary goals of therapy are to treat acute flare-ups of symptoms and maintain remission. Other goals of therapy are limiting exposure to corticosteroids, minimizing adverse effects of therapy, decreasing hospitalizations and improving patients' quality of life.

Five classes of drugs affecting the small and large intestine are typically utilized for Crohn's disease: 5-aminosalicylates, immunomodulators, antibiotics, corticosteroids and biologics. For mild to moderate disease, 5-aminosalicylates such as mesalamine, sulfasalazine, olsalazine and balsalazide are most commonly used as first-line therapy to achieve remission. Topical mesalamine in the form of suppositories or enemas can be effective in treating distal Crohn's disease and maintaining remission in mild to moderate patients. Immunomodulators such as azathioprine, mercaptopurine (6-MP), and methotrexate (MTX) are useful in maintaining remission when 5-aminosalicylates fail, in steroid-dependent disease and in fistulizing disease. The use of the immunomodulator cyclosporine is limited to cases of severe disease in which other treatments have failed, due to its risk of serious side effects. It is typically administered intravenously as a last ditch effort to a hospitalized patient in an effort to prevent or delay surgery. Antibiotics, including ciprofloxacin and metronidazole, can be used to treat fistulizing disease and flare-ups, while also playing a role in achieving remission in mild to moderate disease when 5-aminosalicylates are not sufficient. Corticosteroids such as prednisone can be used to treat acute flares and to induce remission in moderate to severe disease, but should never be used long-term to maintain remission since it has a high incidence of serious side effects including infection, osteoporosis, adrenal insufficiency, glaucoma, muscle wasting, fat redistribution and hypertension. Corticosteroids should be tapered down slowly and as early as possible in order to avoid these serious complications. Biologics are typically reserved for fistulizing disease or severe disease refractory to other medication classes. Biologics are commonly used as an alternative to immunomodulators or occasionally in combination with immunomodulators, although combination of these two classes is highly debated.[11] Biologics include tumor necrosis factor alpha (TNF-α) inhibitors adalimumab, infliximab, and certolizumab pegol, as well as the alpha-4 integrin inhibitor, natalizumab.

New Drug Therapy: Vedolizumab
Patients with moderate to severe Crohn's disease have often tried and failed many medications including TNF-α inhibitors such as adalimumab, infliximab and certolizumab pegol. There is an unmet need for new therapies to treat patients with severe disease. A new class of medications, known as alpha-4 integrin inhibitors, has been developed for this purpose. This class includes the medication natalizumab (Tysabri®), which is FDA approved for Crohn's disease. Integrin inhibitors act to prevent leukocyte extravasation (crossing the endothelium of blood vessels) into the mucosa of the GIT, which decreases the inflammatory response in patients who have an upregulated, dysfunctional immune system.[12] Extravasation of leukocytes involves the coordinated efforts of leukocytes and vascular endothelial cells. Integrins on the surfaces of leukocytes bind to receptors on endothelial cells and activate intracellular signaling. The extravasation process involves multiple steps including tethering, rolling, activation, adhesion, extravasation and migration as the leukocytes enter the GIT.[12,13] In Crohn's disease, it is the T-cells expressing α4β7 integrin, which exclusively bind to endothelium in the GIT and lymphoid tissue.[12] The α4β7

integrin binds to mucosal addressin-cell adhesion molecule-1 (MAdCAM-1), which is a receptor only expressed on the vasculature of the GIT.[12,14] MAdCAM-1 increases T-cell deposition in the GIT and is a major contributor to inflammation in this region. Natalizumab was developed as a monoclonal antibody, which binds to the α4 integrin monomer, resulting in binding both α4 integrin heterodimers on T cells, α4β7 and α4β1, to block their respective attachments to the vascular cell adhesion molecule-1 (VCAM-1) and MAdCAM-1. Binding to α4β7 and α4β1 prevents integrin association with the endothelial receptors and reduces extravasation of inflammatory cells. Natalizumab has been used successfully for treatment in Crohn's disease, ulcerative colitis and multiple sclerosis.[12] While it has displayed efficacy in multiple diseases, natalizumab has a major drawback of causing a serious and often fatal disease known as progressive multifocal leukoencephalopathy (PML) caused by the John Cunningham (JC) virus.[12] Natalizumab was withdrawn from the market by the FDA and reintroduced in 2006 with a specialized Risk Evaluation and Mitigation Strategy (REMS) safety prescribing program.[12] The reason for this effect with natalizumab is prevention of α4β1 integrin from binding to VCAM-1, which is thought to negatively affect immunity in the central nervous system and increase the risk for development of PML.

Vedolizumab, a humanized version of a mouse antibody, selectively binds the α4β7 integrin.[12,13] Vedolizumab is a smaller molecule than natalizumab allowing it to selectively target GIT integrins. Also, vedolizumab does not affect binding to VCAM-1 and has not yet been associated with development of PML.[12,14] Like natalizumab, vedolizumab is administered intravenously. Vedolizumab has completed phase III clinical trials and is awaiting FDA approval to be brought to market.[12]

A phase III randomized, parallel-group, placebo-controlled, double-blinded study conducted from December 2008 to May 2012 evaluated the safety and efficacy of vedolizumab as induction and maintenance therapy for Crohn's disease. Inclusion criteria included patients 18 to 80 years old with at least a three month history of Crohn's disease with a Crohn's Disease Activity Index (CDAI) of 220 to 450 (CDAI scores range from 0 to 600 with higher scores pointing to greater disease activity). Patients also had to have other gastrointestinal markers of certain severity including: C-reactive protein, colonoscopy findings or fecal calprotectin. Patients had to be unresponsive or previously display unacceptable side effects with glucocorticoid therapy, immunosuppressive agents, or TNF-α inhibitors. Exclusion criteria encompass patients with severe disease complications such as stoma, extensive small-bowel or colon resections, strictures, abdominal abscesses, cancer and tuberculosis. Patients were screened using physical exams, neurologic exams and questionnaires, including one to classify symptoms of PML as well as the Inflammatory Bowel Disease Questionnaire.[15]

The trial investigated both induction and maintenance treatment using vedolizumab. For the induction component, patients were randomized to receive placebo or vedolizumab 300 mg at weeks 0 and 2 and were assessed for disease status through week 6. A second open-label cohort received the same regimen of vedolizumab as the previously mentioned group receiving induction therapy. This group of patients was included in the study to meet sample size requirements for the maintenance phase of the trial. Patients eligible for the maintenance phase of the study were patients from both cohorts who displayed a clinical response to vedolizumab at week 6. Participants were randomized in a 1:1:1 fashion to vedolizumab dosed every four weeks, every eight weeks or placebo (frequency not specified) for 52 weeks. Patients who did not achieve a clinical response to vedolizumab by week 6 of induction therapy continued to receive vedolizumab 300 mg every four weeks for 52 weeks. Patients in the placebo group during the induction phase remained in the placebo group for the maintenance phase.[15]

Primary end points for the induction trial were clinical remission defined by a CDAI less than or equal to 150 and a CDAI-100 response, defined as a 100 point CDAI score reduction. The secondary end point was the change in C-reactive protein from baseline to 6 weeks. Statistical significance for the entire trial was set at 5 percent (alpha=0.05). Results showed 14.5 percent of patients receiving vedolizumab and 6.8 percent of patients receiving placebo reached clinical remission by week 6 (p=0.02). Of those receiving vedolizumab and placebo, 31.4 percent and 25.7 percent, respectively, had a CDAI-100 response (p=0.23). Changes in C-reactive protein were similar across both groups.[15]

The primary end point for the maintenance trial was clinical remission at week 52 and the secondary end points were CDAI-100 response at week 52, remission at week 52 without the use of glucocorticoids, and clinical remission at greater than or equal to 80 percent of all study visits including the final visit at week 52. Results showed 36.4 percent of patients receiving vedolizumab every four weeks and 39 percent of patients receiving vedolizumab every eight weeks were in clinical remission at week 52. Only 21.6 percent of patients in the placebo group reached clinical remission, producing comparison p-values of p=0.004 and p<0.001 for the four-week and eight-week vedolizumab groups compared to placebo, respectively. Vedolizumab groups also showed a trend towards greater proportions of patients with a CDAI-100 response and glucocorticoid-free remission than with placebo; however, the differences in clinical remission were not significant.[15]

This trial displayed moderate effects on induction and maintenance of clinical remission in patients with moderate to severe Crohn's disease who received vedolizumab therapy. Patients enrolled in the study had refractory disease and approximately 50 percent of patients had prior treatment failure to other medications, including TNF-α inhibitors. Further trials are necessary to determine which patients may benefit most from vedolizumab therapy. Once it comes to market, vedolizumab will likely be a safer choice than natalizumab for Crohn's disease due to a lower incidence of PML.[15]

On Dec. 9, 2013, a joint meeting of the FDA's Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk

Management Advisory Committee recommended vedolizumab for use in Crohn's disease as well as ulcerative colitis. Specific recommendations for vedolizumab therapy in Crohn's disease included use in patients who failed TNF-α inhibitors or conventional therapy to reduce signs and symptoms, to achieve clinical remission or glucocorticoid-free remission and to stimulate mucosal healing in moderate to severe Crohn's disease. The committee reached unanimous agreement that Takeda Pharmaceuticals appropriately characterized the low risk of PML with vedolizumab therapy to support approval.[16] Although the committee has shown support, vedolizumab still needs FDA approval. The FDA has set a Prescription Drug User Fee Act (PDUFA) Priority Review action date for the indication of vedolizumab in ulcerative colitis as May 20, 2014. This date is a target for the FDA to make a final decision on approval. A PDUFA standard review action date for indication in Crohn's disease has been made for June 18, 2014.[17] If approved, vedolizumab will enter the market under the brand name Entyvio®.

Nonpharmacologic Treatment

Along with standard pharmacologic treatments, nonpharmacologic treatments have proven beneficial for Crohn's disease patients. Lifestyle modifications such as dietary changes and symptomatic or supportive treatment are important. Maintaining a well-balanced diet promotes healing and relieves symptoms in many patients suffering from Crohn's disease. Good nutrition helps compensate for nutritional losses due to Crohn's disease. Dietary suggestions are different depending on whether the patient is in a period of active or inactive disease. When the disease state is inactive, patients should stay hydrated and consume low fiber carbohydrates like legumes, oat bran, and barley, proteins such as lean meats and eggs, healthy fats like olive oil, fruits, and vegetables. When a patient's disease is active, health care professionals can recommend applesauce, bananas, bland foods, soft foods, plain cereals, proteins as accepted, and small, frequent meals.[18] Patients with active disease should also be educated to avoid high fiber foods, high fat foods, nuts, seeds, popcorn, gluten, caffeine, alcohol, raw fruits, raw vegetables, dairy, spicy foods, and larger portions. However, all dietary recommendations remain patient specific. Each patient may also possess his or her own specific trigger food, which should be avoided, because it may cause flares of symptoms and decreased quality of life. Patients should be advised to keep a food diary, which should include all foods eaten each day as well as Crohn's disease symptoms such as abdominal pain, a description of bowel habits and overall well-being. This process helps identify triggers, encourages patients to eat well-balanced foods and allows positive dietary habits to be observed. Overall, Crohn's disease manifests differently between individuals; therefore, it is best to individualize each patient's diet to alleviate symptoms.

Maintaining a healthy diet is important, but there are other nonpharmacologic therapies that may help reduce flare-ups and prevent symptoms. First, those suffering with Crohn's disease should stop smoking as this worsens symptoms and can decrease responsiveness to certain treatments.[19] Also, stress relief and general health maintenance are beneficial in providing symptomatic relief and preventing exacerbations. Options for stress relief include relaxation, breathing exercises, meditation, acupuncture, reading books and other relaxing activities.[20] Implementing low-intensity exercise for 30 minutes three times per week aids in diminishing depression, which often accompanies Crohn's disease.[21]

Numerous other complementary alternative medicines are available. These are believed to be safe, but may require additional studies to elucidate efficacy in the treatment of Crohn's disease. These options include probiotics, fecal microbiota transplantation and fish oils. Probiotics are living microbial food ingredients, which beneficially alter the intestinal flora in an unknown mechanism. Although studies regarding probiotics in Crohn's disease have resulted in mixed conclusions on efficacy, the use of VSL#3 specifically may help patients achieve remission. VSL#3 is a mixture of eight different strands of bacteria, which influence the immune response by several mechanisms.[23] Fecal microbiota transplantation represents an alternative therapy to use when standard treatments have failed. This process involves transferring a safe, donated stool into the patient via an enema or nasogastric tube in order to replenish and balance bacteria in the colon.[24] Fish oils and omega-3 fatty acids may have positive anti-inflammatory effects in the intestines.[22] Even though all of these options are still under investigation, they may be good options for the treatment of Crohn's disease.

After medications and nonpharmacologic treatments fail as treatment for Crohn's disease, surgery is the final option. According to the National Cooperative Crohn's Disease Study, the probability of requiring surgery is 78 percent after 20 years of Crohn's disease symptoms, and the probability jumps to 90 percent after 30 years of symptoms.[25] Possible procedures include strictureplasty, resection, colectomy, removal of abscesses (pus-filled sacs) and correction of abnormal tracts or fistulas.[26] However, surgery is not curative and is a last-ditch effort for treating Crohn's disease.

The Pharmacist's Role

As health care providers, pharmacists must be educated in Crohn's disease pharmacologic and nonpharmacologic treatments as well as appropriate patient counseling and recommendation points. Pharmacists should highlight the importance of avoiding non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen due to bleeding risk. Within one week of therapy with NSAIDs, approximately 25 percent of patients have flares.[19] Many Crohn's disease patients experience deficiencies in folate and vitamin B12. Vitamin B12 deficiency is especially prevalent when the ileum is affected since this is the primary site of absorption of vitamin B12. Therefore, pharmacists should recommend frequent screenings and supplementation. Since sulfasalazine and methotrexate impair folate metabolism, patients taking these medications require more folic acid than patients not on these therapies.[27] Vitamin D and calcium may also be depleted in Crohn's disease patients due to impaired absorption putting patients at increased risk for osteoporosis.[28] Vitamins and supplements should be taken during both the active and inactive phases of the disease to

replenish deficiencies.[22] Another counseling point to emphasize is the necessity for periodic colonoscopies in which the frequency is determined by disease severity, duration and personal or family history of colorectal cancer. The risk of acquiring colorectal cancer significantly increases eight to 10 years after development of Crohn's disease, and at that point, patients may require regular colonoscopies every one to two years.[29] It is important to ensure that patients keep a list of any supplements, over-the-counter or prescription medications they take in order to keep their doctors, pharmacists and other health care professionals informed. Pharmacists should also counsel patients on nonpharmacologic treatments, including foods and drinks to avoid and those that may be better options. As the most accessible health care provider, it is important for pharmacists to remain knowledgeable and up-to-date on new treatments, recommendations and counseling points to benefit patients suffering from Crohn's disease.

Conclusion

Crohn's disease patients may feel overwhelmed or burdened by their disease state and the complexity of their medication regimens. When experiencing a disease flare, the quality of life of a Crohn's disease patient is negatively affected. Pharmacists play a large role in helping these patients to better manage their medications and can provide great insight into the various pharmacologic and nonpharmacologic therapies available for treatment of Crohn's disease.

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New Cholesterol Guidelines: An Update for Pharmacists

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Abstract

The American College of Cardiology and American Heart Association published new blood cholesterol guidelines in November 2013. The new guidelines place an emphasis on evidence-based treatment of dyslipidemias and primarily use randomized controlled trials to create recommendations for health care providers. Major changes from the previous guidelines include eliminating low-density lipoprotein goals, the classification of statins by lipid-lowering potential and the creation of four major statin benefit groups. The new guidelines also establish the role of non-statins in dyslipidemias and use the Pooled Cohort Risk Assessment Equations to calculate patients' risk for cardiovascular events and the need for cholesterol-lowering medications. Pharmacists play a vital role on the health care team and should be aware of the changes in the cholesterol guidelines in order to improve patient care.

Introduction

According to the Centers for Disease Control and Prevention (CDC), 33.5 percent of American adults have elevated levels of low-density lipoprotein cholesterol (LDL-C), causing hyperlipidemia.[1] This is problematic because high LDL-C levels are linked with an increased incidence of coronary heart disease (CHD), heart attack and stroke.[2] Cardiac death remains the number one cause of mortality in the United States.[3] Many factors influence cholesterol levels, including diet, weight, physical activity, gender, heredity variables and age.[4] Because so many variables exist, treating hyperlipidemia can be a complex process. Treatment complexity creates a need for guidelines to help health care professionals manage their patients' hyperlipidemia. The purpose of the following review is to inform pharmacists about the major changes between the Adult Treatment Panel (ATP) III hyperlipidemia guidelines and the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines that were published in 2013.

Background—Development of New Cholesterol Guidelines

Before the new guidelines were established, the ATP III guidelines released in 2001, and subsequently revised in 2004, were utilized by many health care professionals. These guidelines had nine steps and set LDL-C goals, which were the primary targets of therapy. They also suggested target levels of total cholesterol and high-density lipoprotein (HDL-C). Through the nine-step process, the evaluation of a patient was completed and therapy was determined; treatment options included HMG-CoA reductase inhibitors, bile acid sequestrants, nicotinic acid and fibric acids. Additional risk (via predisposed factors and a calculated Framingham Score) could be calculated, and specific treatment guidelines were outlined if the patient was presenting with metabolic syn-

drome or excessively high levels of triglycerides (TGs). Overall, these previous guidelines were widely accepted by the health care community.[5]

The new guidelines were written by the ACC and the AHA to achieve the goals of decreasing the incidence of cardiovascular diseases and the management of existing disease states through education, research, guidelines and standard practice. Four guidelines were created for: cardiovascular risk, lifestyle modifications, management of blood cholesterol, and management of obese and overweight adults. The ACC and AHA collaborated with the National Heart, Lung and Blood Institute (NHLBI) to develop these guidelines in the hopes that they would improve upon the previous ATP III guidelines. The process for writing the new guidelines began in 2008 where the NHLBI wished to develop critical questions (CQs) that would define the new guidelines through systematic evidence reviews. In 2011, the decision was made to select only the highest quality evidence to review, in response to the Institute of Medicine's report of trustworthy clinical guidelines. In June 2013, NHLBI began work with the ACC and AHA to complete the four guidelines mentioned above, making them pertinent to the widest population possible for review. Expert panels did not evaluate evidence beyond 2011 (unless specified) and these guidelines are to be updated in 2014.[6]

Rigorous evidence review was performed in the creation of these new guidelines. The ACC/AHA recruited unspecified expert reviewers to examine the content of each document to be used for the new guidelines and to certify that each one had been peer reviewed by NHLBI Advisory Council representatives, key federal agencies and scientific experts; there were no substantive changes made in content used as most was undisputed. Evidence found through these randomized controlled trials (RCTs), meta-analyses and observational studies provided the ACC/AHA with information to classify recommendations of treatment and procedures through the grading of the strength of those recommendations with grades A through E and grade N, which they established themselves. Grade A indicates a strong recommendation, meaning there is a high certainty that the net benefit is substantial with respect to evidence found. Grade D indicates a recommendation against treatment due to evidence of risk or harm to the patient. Grades B and C fall between these two. Grade E shows that evidence is insufficient but a recommendation was still made, and grade N shows that evidence suggests no recommendation for or against. If evidence was ambiguous or minimal, recommendations were not made using those sources. These grades are used to notify the primary care physicians or other medical professionals of the best course of action to take based on evidence.[6]

Three CQs embodied the guidelines: 1) What is the evidence for LDL-C and non-HDL-C goals for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD)? 2) What is the evidence for LDL-C and non HDL-C goals for the primary prevention of ASCVD? and 3) For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?

Key Differences

No LDL Treatment Goals

The ATP III guidelines recommended LDL-C treatment goals for patients depending on their risk of coronary heart disease. Those with CHD, a CHD risk equivalent (carotid artery disease, peripheral artery disease, abdominal aortic aneurysm or diabetes), or a 10-year Framingham risk over 20 percent had an LDL-C goal of less than 100 mg/dL. Patients with moderate risk of cardiovascular events had an LDL-C goal of less than 130 mg/dL, and those with a lower risk had an LDL-C goal of less than 160 mg/dL. Risk factors included age (men 45 years or older and women 55 years or older), family history of premature CHD, cigarette smoking, low HDL-C (less than 40 mg/dL) and hypertension (above 140/90 mmHg or on medications for blood pressure).[5] The 2004 update to ATP III added an optional LDL-C goal of less than 70 mg/dL in high-risk patients; this included patients who have CHD with diabetes, metabolic syndrome, acute coronary syndrome or severe uncontrolled risk factors.[7] Therapeutic lifestyle changes as well as cholesterol-lowering medications could be used to reach an LDL-C goal.[5]

The Expert Panel that established the new ACC/AHA guidelines eliminated LDL-C and non-HDL treatment goals for patients. Instead, the panel created four major statin benefit groups with a specific statin intensity level that provides optimal treatment of patients within each group. Treatment goals were not included because the Panel did not find evidence in RCTs to support utilizing specific LDL-C and non-HDL goals. All RCTs reviewed by the Panel compared statins to a placebo or compared lower dose statins to higher dose statins; no RCTs that involved titrating statin doses to reach specific LDL-C or non-HDL goals were found, and there was thus no evidence to recommend specific treatment goals for patients like those included in ATP III. The RCT evidence instead showed that it is necessary to use the appropriate statin intensity in the major statin benefit groups in order to reduce the risk of ASCVD.[6]

Additionally, the Expert Panel found that treating LDL-C to a certain goal allowed undertreatment or overtreatment of many patients at risk for ASCVD. For instance, a patient who has not reached the LDL-C goal assigned by his doctor may have been prescribed a non-statin to help further lower cholesterol; this new medication puts the patient at risk for more side effects and drug interactions. This would now be considered overtreatment if the patient is already taking the recommended intensity of statin for his ASCVD risk factors; non-statins will be discussed later in this article, but overall the new guidelines do not support the use of non-statins in cholesterol-lowering alone or in combination with statins.

Undertreatment can occur when a patient reaches their LDL-C goal while taking a suboptimal statin dose for his risk of ASCVD, and therefore his or her dose is never increased to an appropriate level as defined by the new guidelines.[6]

To monitor a patient's adherence to statin therapy, a baseline lipid panel should be taken as well as a second lipid panel four to 12 weeks after statin therapy is started; after this initial assessment, lipid panels should be completed every three to 12 months as necessary. Baseline liver function tests should be obtained, but it is not necessary to continue measuring liver function unless the patient has symptoms of hepatotoxicity. In patients with an increased risk of muscle pain (such as those with a personal or family history of muscle pain, statin intolerance or the presence of a concomitant medication that increases the risk of myopathy), it is reasonable to get a baseline creatine kinase and then remeasure creatine kinase if muscle symptoms develop.[6]

Statin Classification Groups

The Panel defines the intensity of statin therapy based on the expected percent LDL–C response to a certain statin and its dose. The definitions "high-intensity," "moderate-intensity" and "low-intensity" statin therapy were developed from the Panel's systematic reviews of RCTs and meta-analyses. High-intensity statin therapy lowers LDL–C by ≥50 percent, moderate-intensity statin therapy lowers LDL–C by 30 percent to <50 percent, and low-intensity statin therapy lowers LDL–C by <30 percent. Evidence showed the relative decrease in ASCVD risk from statin medications is related to the degree by which LDL–C is lowered, rather than having a specific treatment goal.[6] See Table 1 for a summary of lipid lowering potential of the various statins.

Four Major Statin Benefit Groups

Whereas ATP III classified patients into risk groups in order to develop LDL-C treatment goals, the new guidelines created four major statin benefit groups in which the benefits of reducing the risk of ASCVD outweigh potential adverse effects of statins. These groups were established from RCT data that showed primary and secondary prevention of ASCVD with moderate-intensity and high-intensity statins; evidence of ASCVD outcomes was used to determine "who should get which therapy at what intensity."[6]

The first benefit group consists of individuals with clinical ASCVD, which is defined as a history of myocardial infarction, acute coronary syndromes, coronary or arterial revascularization, stable or unstable angina, peripheral arterial disease of an atherosclerotic origin, or stroke or transient ischemic attack. Because these patients have a high risk of ASCVD events and subsequent death, high-intensity statins are recommended if they are 75 years old or younger. Moderate-intensity statins should be used in patients over 75 years of age because there is no data to show additional ASCVD risk reduction with high-intensity statins in this population, but there is an increased risk of adverse events.[6]

Patients with an LDL-C of 190 mg/dL or higher constitute the second major statin benefit group. Elevations of LDL-C of

Table 1. High-Intensity, Moderate-Intensity and Low-Intensity Statin Therapy[6]

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%
Atorvastatin 40†–80 mg **Rosuvastatin 20 (*40*) mg**	**Atorvastatin 10 (*20*) mg** **Rosuvastatin (*5*) 10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40 (*80*)** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40mg bid** *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Specific statins and doses in bold were evaluated in RCTs or meta-analysis and demonstrated a reduction in major cardiovascular events. Statins and doses that are italicized are approved by the FDA but were not tested in the RCTs.
*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice.
 There may be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg
 is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

190 mg/dL or higher lead to a higher lifetime risk of ASCVD and are often associated with a genetic predisposition for hypercholesterolemia. High-intensity statins are recommended for these patients to reduce ASCVD risk; non-statins can also be used in these patients to further lower LDL-C if it has not reached the expected level of lowering or the level is still undesirable for the patient's risk of ASCVD.[6]

Individuals with diabetes between the ages of 40 and 75 years make up the third statin benefit group. Diabetes causes an increased lifetime ASCVD risk and leads to greater morbidity and mortality once ASCVD develops. Diabetics with an estimated 10-year ASCVD risk calculated with the Pooled Cohort Risk Assessment Equations (which will be described later in this article) of 7.5 percent or greater should receive high-intensity statin therapy; moderate-intensity statins are recommended for diabetics with a lower estimated 10-year ASCVD risk. Clinical judgment should be exercised when evaluating diabetics who are less than 40 years old or over 75 years old.[6]

Finally, the last major statin benefit group is comprised of patients between 40 and 75 years old with an LDL-C between 70 and 189 mg/dL who do not have clinical ASCVD or diabetes. The risk of ASCVD in these patients who have a 7.5 percent or higher estimated 10-year ASCVD risk is reduced with either moderate-intensity or high-intensity statin therapy. Clinical judgment and patient preference should be included in the decision as to what intensity is appropriate for the patient and for patients with a lower estimated 10-year ASCVD risk.[6]

For all benefit groups, patients who cannot tolerate the recommended statin intensity should be prescribed the highest intensity statin that they are able to tolerate.[6]

Role of Non-Statins
Another significant change related to cholesterol therapy recommendations involves non-statin medications; however, first-line recommendations are similar to previous guidelines. Like the ATP III guidelines, the new guidelines recommend statins as the drugs of first choice for treating hyperlipidemia.[6] Research has consistently shown that statins are the most effective drugs for lowering LDL-C. Additionally, statins are generally safe and well-tolerated medications.[5,6] The Panel concluded that statin therapy is far superior to any other medication on the market. The clinical trials reviewed on non-statin medications lacked clinical efficacy or were unreliable. With numerous trials supporting statin use and limited evidence favoring non-statin medications, the Panel restricts its recommendations on non-statin medications to a few circumstances.[6]

Non-statin therapies discussed in the old guidelines included bile acid sequestrants, nicotinic acid, fibric acid derivatives (fibrates), hormone replacement therapy (HRT) and selective estrogen receptor modulators (SERMs). Though statins were still recommended as first-line treatment, these non-statin therapies were recommended liberally. For instance, bile acid sequestrants could be used in patients with moderate elevations in LDL-C, in younger patients with high LDL-C levels, in women with high LDL-C considering pregnancy, in patients only needing modest decreases in LDL-C and for

combination therapy in patients with highly elevated LDL-C.[5] Under the new guidelines, non-statin therapy is only recommended if the following criteria are met: the patient has a high ASCVD risk and is currently on the maximum tolerated intensity of statin therapy and continues to have a response less than expected and if the ASCVD risk-reduction benefits outweigh the potential for adverse effects **or** if a patient is a candidate for statin treatment but is completely statin intolerant. Statin intolerant patients are those who experience serious side effects such as myalgia, rhabdomyolysis and elevated hepatic aminotransferases during statin use. High-risk individuals include those with clinical ASCVD <75 years of age, individuals with baseline LDL ≥190 mg/dL, and individuals 40 to 75 years of age with diabetes.[6] See Figure 1 for a summary of the recommendations.

The Panel suggests that health care providers review patients' adherence to both lifestyle changes and medications and rule out secondary causes of hyperlipidemia before considering non-statins. Research showed non-statins do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects. In the few studies on non-statin medications that have been conducted, non-statins did not show significant additional ASCVD event reductions as compared to statins.[6,8]

As an example, in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) trial, researchers looked at whether or not increasing HDL-C with extended-release niacin along with decreasing LDL-C with simvastatin would decrease the number of cardiovascular disease events. All patients were given 40 mg of simvastatin and then randomized to receive either niacin or placebo. Patients taking simvastatin with niacin saw increased reductions in LDL-C and TGs with increases in HDL-C. However, there was no difference in the number of CVD events as compared to placebo. The trial was discontinued early due to a lack in incremental benefit in CVD events and an unexplained increase in ischemic stroke in the niacin treatment group.[6,9,10]

Similarly, in the Action to Control Cardiovascular risks in Diabetes (ACCORD) trial, researchers sought to determine whether or not fenofibrate treatment reduces the risk of CVD events. Patients were randomized into two groups: simvastatin with fenofibrate or simvastatin plus placebo. Again, the addition of a non-statin did not significantly reduce the risk of CVD events. Unlike niacin combination therapy, fenofibrate combination therapy did not additionally lower LDL-C levels and only had a minimal to moderate impact on HDL-C and TGs respectively. In a small patient group on fenofibrate and simvastatin, patients might have had a decrease in CVD events. Participants affected included those with TGs ≥204 mg/dL and HDL–C ≤40 mg/dL. Side effects in both treatment groups were similar except in regard to increased creatinine levels and elevated alanine aminotransferase levels. Patients on fenofibrate and simvastatin had an increased incidence of an alanine aminotransferase (ALT) greater than five times the upper limit of normal. The number of CVD events in women with controlled diabetes was higher in the fenofibrate and simvastatin group as compared to placebo. The lack of a significant decrease in CVD events and the seemingly increased risk of certain adverse events with fenofibrate use with simvastatin led the Panel to forgo recommending fenofibrate as first-line therapy for hyperlipidemia.[6,11]

The Panel also questioned the validity and generalizability of the other non-statin studies reviewed.[8] These new non-statin recommendations may decrease the sales of non-statins and simplify patients' treatment regimens, since they highly encourage physicians to prescribe statins.

Pooled Cohort Risk Assessment Equations
The Pooled Cohort Risk Assessment Equations were developed by the Risk Assessment Work Group in order to estimate the 10-year ASCVD risk, which is utilized to identify individuals who are candidates for statin therapy. These equations can be used to predict stroke in patients and to also predict CVD related events in patients who are non-Hispanic Caucasians and African-Americans. Patients who can be evaluated with these equations may be between ages 40 and 79, may be with or without diabetes, and have LDL-C levels of 70 to 189 mg/dL. The risk assessment does not require the counting of risk factors for determining statin therapy initiation. Rather, it focuses on evidence from a global ASCVD risk assessment. This assessment is derived from trials in which statin effectiveness in various patient subgroups was determined (where statins reduce ASCVD events despite existing risk factors). Statin efficacy for improvement of ASCVD events versus statin adverse effects was used for identifying groups of patients who could benefit from the use of statins. Currently, there is an underestimation of high-risk patients who would benefit from statin therapy given the evidence found through reviewing RCT data, but the new guidelines also overestimate the portion of the population who are considered low-risk patients who may benefit from statin therapy. These 10-year ASCVD risk assessments create a large gray area in the medical field in regard to where the use of statins may now be warranted, because some patients who would not have qualified to receive a statin according to the previous ATP III guidelines, would now qualify based on the new guidelines.[6,12]

Limitations to the New Guidelines
There are several limitations to these new cholesterol guidelines. First, the guidelines focus on patient populations that are represented well in RCTs; there are some patients with a high risk of ASCVD who were not represented well in RCTs and were thus excluded from the guidelines. Clinical judgment is important in patient care, particularly where RCT data is lacking as well as in patient populations excluded from the guidelines; the guidelines should not replace clinical judgment, but should be used to inform health care providers. Another limitation is that an independent contractor graded the quality of the evidence used to develop the guidelines. The Expert Panel only considered RCTs, systematic reviews, and meta-analyses graded as fair to good quality by the independent contractor and therefore could have missed

Figure 1. Statin Therapy Monitoring Therapeutic Response and Adherence.
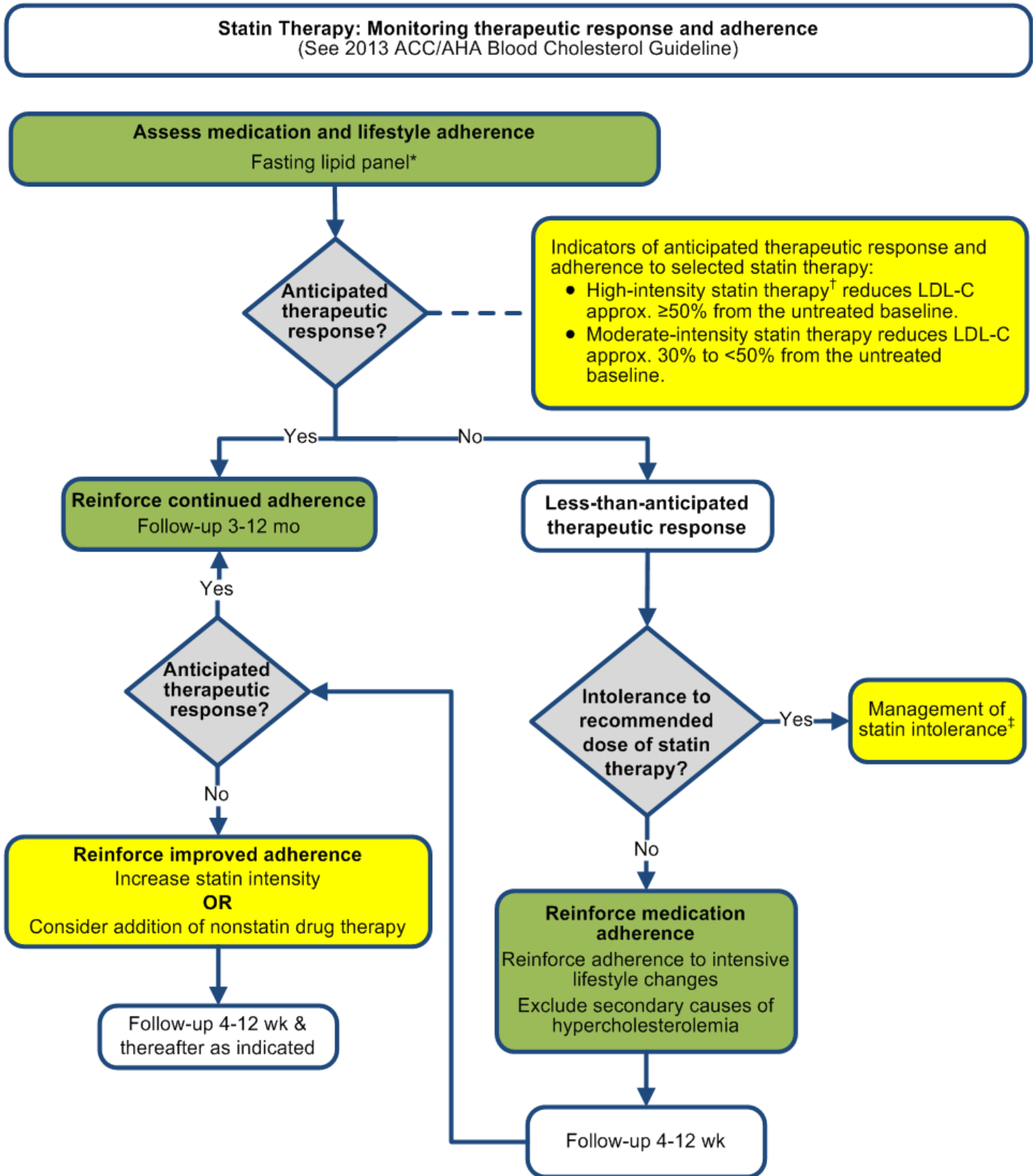
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potentially relevant data in observational studies not included in the analysis.[6]

Further research is necessary in order to update the guidelines in the future, particularly in areas where evidence is currently lacking. The RCTs in the future could study the effects of titrating a statin dose to achieve a specific LDL-C goal compared to a single fixed dose. Other subgroups that could benefit from statin therapy may also be found through RCTs and observational studies as well as additional information on the current benefit groups. Studies can also be conducted to learn more about adding non-statin therapies to achieve cholesterol-lowering and potential LDL-C treatment goals.[6,13]

These new ACC/AHA cholesterol guidelines have been very controversial among health care professionals. First, many providers disagree with the lack of LDL-C or other treatment goals for patients; the lack of goals makes long-term follow-up and monitoring seem unnecessary if there is no way to monitor the patient's progress. Additionally, patient's LDL-C values helped to monitor the residual risk of ASCVD events while on statin therapy, and the new guidelines do not account for the pathophysiology of cardiovascular disease. Next, the new guidelines state that non-statins do not add to cholesterol lowering and reduction of ASCVD risk when combined with statins. This may deter pharmaceutical companies from pursuing the production of non-statin medications and prevent new cholesterol-lowering medications from being developed. Because multidrug therapy is frowned upon in these guidelines, patients who could benefit from multiple cholesterol-lowering medications can be prevented from receiving this treatment; this includes patients with cardiovascular disease who are on the maximum dose of a high-intensity statin and still have high cholesterol.[13-15]

The new guidelines only cover patients who are between the ages of 40 and 75, which leaves providers with no guidance for patients who are younger or older than this; by the time a patient without ASCVD who has an LDL-C of 180 mg/dL and other risk factors for ASCVD is 40 years old, it is often too late for effective prevention of ASCVD itself, but statins must be used to reduce the risk of recurrent ASCVD events. Finally, the guidelines did not include LDL-C treatment goals because the Expert Panel believed that treatment goals lead to undertreatment or overtreatment of many patients in order to reach the LDL-C goal. However, the new guidelines can still lead to undertreatment and overtreatment. In the example above, the patient with ASCVD risk factors is not receiving statin therapy to prevent the development ASCVD because the risk calculator is not designed to be used until age 40, and even then the patient might not have a 7.5 percent or higher estimated 10-year ASCVD risk; this would be considered undertreatment since he or she is not receiving appropriate care to prevent ASCVD.[13-15]

Role of Pharmacists

Pharmacists play an important role in cholesterol management and need to be aware of the changes made with the ACC/AHA guidelines. Pharmacists are able to educate patients on the proper use and adverse effects of the medications they are prescribed; in addition, they can answer questions that patients have about their cholesterol and the new guidelines. As the drug experts on the health care team, pharmacists can inform other providers on appropriate statins to use in specific patient populations and about non-statin options in patients who need additional cholesterol lowering or cannot tolerate statins as well as ensure that statins are a necessary and safe addition to a patient's therapy.[16,17]

Conclusion

The new ACC/AHA cholesterol guidelines are a major shift in the treatment approach to dyslipidemias. Statins are considered the mainstay of cholesterol-lowering therapy and should be the drug of choice in any patient requiring treatment for dyslipidemia or to prevent ASCVD. Non-statins play a minor role in lipid-lowering therapy and are therefore not recommended by the guidelines unless a patient is statin intolerant. The guidelines created four major statin benefit groups, and each group has a statin intensity appropriate to treat patients falling within that category. Pharmacists are well positioned to apply the new guidelines in cholesterol management as well as educate patients about the new guidelines and the role of statins in lowering cholesterol.

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Pharmacists' Role in Emergency Preparedness and Response

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Abstract
Over the past decade, an increased recognition of the need for budgeting and planning in case of terrorist attacks, use of infectious agents as weapons or major weather disasters has brought emergency preparedness to the forefront within health care systems and federal organizations. Pharmacists have taken active roles in activities related to emergency preparedness and response. New training initiatives and a comprehensive understanding of the overall needs in emergency situations enables pharmacists to utilize their drug knowledge and accessibility to the public to provide vital medical care in stressful situations.

Background
Pharmacists are taking a more active role and becoming involved in numerous areas of health care and public health.[1] As one of the most accessible and trusted health care professionals, pharmacists have responsibilities that extend beyond the more "traditional" realms of community or hospital-based pharmacy practices. One of these responsibilities includes taking action in disasters and public health emergencies. During a public health emergency, a pharmacist can take on a variety of roles, including clinical and specialized response tasks.

Types of Public Health Emergencies
The Centers for Disease Control and Prevention (CDC) recognizes six specific public health emergencies: natural disasters, bioterrorism, chemical emergencies, disease outbreaks, radiation emergencies and mass casualties.[2] Health care professionals, including pharmacists, can play a critical role in preparing for and responding to these emergencies.

Natural Disasters and Severe Weather
Natural disasters and severe weather cover a large variety of emergency scenarios.[3] Hurricanes, tsunamis and tornadoes can easily be identified as natural disasters, but events such as thunderstorms, floods and extreme temperatures can also result in emergency situations. After a natural disaster strikes, general public safety concerns include illness and injury, as well as decreased access to resources due to power outages and destruction.[4] Populations may become displaced to a new geographical area, lack adequate food and water, and suffer from both physical and mental health effects. Although the consequences of a natural disaster can impact all populations, those with the most need for health care services are generally children, the elderly and the poor. Because of the increased demand for medical services accompanying a natural disaster, health care professionals, such as pharmacists, must be prepared to respond efficiently to changes in patient volume and health care needs.

Reports from Hurricane Katrina, a devastating storm which hit the Gulf Coast of the United States in 2005, can provide valuable insight into the roles of pharmacists during public health emergencies and how pharmacists can be better prepared for similar emergencies in the future.[5,6] The two main issues facing pharmacists after this disaster were setting up a functional pharmacy to support a makeshift hospital and a significantly increased workload in community pharmacies in unaffected areas nearby. In general, pharmacists who volunteer to work in a makeshift hospital must be prepared to take on additional responsibilities besides medication dispensing.[5] Pharmacists can act as the first-line health care professional to assess the needs of evacuees, determine the urgency of care and provide therapy recommendations. The role of medication dispensing in this setting cannot be overlooked, as the pharmacy must be built from scratch. Refrigerators, shelving, medical references, counting trays, labels and prescription vials are just a few of the basic items that must be brought in to facilitate the dispensing process. The initial supply of medications may be provided by the Strategic National Stockpile, a CDC-run program equipped to supplement medical facilities during a public health emergency when approved by federal and local authorities, and additional samples may be provided by pharmaceutical manufacturers.[5,6] As pharmacies within the community may feel the pressure of an increased prescription volume, pharmacists must be knowledgeable about their state's emergency refill laws.[6] These laws outline which classes of medications can be dispensed without a refill prescription and the number of days for which an emergency supply can be dispensed. New temporary refill protocols may be put into place expanding day-supply limits and requiring referrals to physicians for some requests. No matter the practice setting after a natural disaster, a pharmacist must have a plan in place to triage evacuees, be prepared for a strain on resources, consider how to provide care when medical records are unavailable and stay up-to-date on changes in dispensing and prescribing laws.[5,6]

Bioterrorism/Chemical Emergencies
Although the majority of people rarely consider themselves at risk of a bioterrorism attack, the threat is more real and more complex than many would like to think. In the event that a biological agent—specifically, a bacterial agent, virus or an agent derived from a living organism such as botulinum toxin or ricin—is intentionally released, pharmacists will bear a large responsibility in treating, educating and counseling those affected.[7,8] It is not unlikely that an attack may go unnoticed for days or weeks until the symptoms of those affected are attributed to a biological agent, by which time the infection may have spread far beyond the initial site of release. Bioterrorism agents are classified into one of three

categories, depending upon the ease of spread and the severity of infection. Table 1 provides examples of biological organisms that represent each category as well as clinical presentation.

Table 1. Biological Organisms

Category[8]	Biological Agent[8]	Clinical Presentation[7, 12, 14-16]
A— pose the highest risk for morbidity, have the highest rates of mortality, and spread easily throughout the population	*Bacillus anthracis* (Anthrax)	Inhalational: fever, malaise, fatigue, chest pain, cough, respiratory distress, septicemia, shock, meningitis Cutaneous: vesicles that become black scabs (eschar), may progress to systemic disease similar to inhalational anthrax
	Yersinia pestis (Plague)	Fever, chills, weakness, swelling of affected lymph nodes (eventually become necrotic); secondary sepsis Pneumonic plague: fever, cough, dyspnea, GI symptoms; profound respiratory insult may cause death within 2-4 days
	Variola major (Smallpox)	Early (incubation period, approximately 12 days): malaise, fever, vomiting, headache Late: maculopapular rash that spreads, becomes vesicular, then pustular; scabbing after 1 week
	Clostridium botulinum toxin (Botulism)	Bilateral descending muscle paralysis, starting with eyes (visual disturbances), face, respiratory failure, etc.
	Francisella tularensis (Tularemia)	Abrupt onset of fever, headache, chills, weakness, weight loss, and upper respiratory symptoms (including cough) that progress to pneumonia
	Viral Hemorrhagic Fever (Ebola, Marburg virus, etc.)	Myalgias, fever, prostration, conjunctival injection, mild hypotension, flushing, petechial hemorrhaging that can progress to shock
B— cause moderate incidences of illness and fewer deaths but do not spread as easily as Category A agents	*Ricinus communis* toxin (Ricin)	Derived from castor beans Fever, weakness and cough followed by hypotension and cardiovascular collapse
	Coxiella burnetii (Q-Fever)	Fever, chills, headache, fatigue, diaphoresis (excessive sweating), malaise, anorexia, myalgias; cough with chest pain in some cases; complications include hepatomegaly, splenomegaly, jaundice
C— may pose a risk in the future due to availability, ease of production and spread of infection, as well as potentially high rates of death and infection	Nipah virus	Early: fever, headache, drowsiness, disorientation and mental confusion (encephalitis), respiratory symptoms Late: coma
	Hantavirus	Early: fatigue, fever, myalgias, headache, dizziness, chills, nausea/vomiting/diarrhea Late: cough, shortness of breath, tightness in chest, fluid-filled lungs

Chemical emergencies are similar to bioterrorism but have a few distinct differences. Due to the number of chemical agents used in the United States every day, from pesticides and household cleaners to pharmaceuticals and food preservatives, there are infinite opportunities that a chemical emergency, whether isolated or widespread, may occur and have significant impact on the exposed individuals.[9] In the case of a chemical emergency, fewer people are typically affected than in a bioterrorism attack because chemical agents tend to act more quickly than biological agents, usually within minutes to hours. Because this will often put first responders such as police and paramedics at a higher risk of injury, pharmacists can be involved in the direct care and triage of first responders and can provide care to patients who may not be able to get to a hospital or emergency care facility.[11] Like infectious agents that may become bioterrorist weapons, the different types of chemicals that can precipitate emergency situations are extremely varied. Table 2 lists the different types of chemical agents that may be responsible for an emergency, provides examples of some of the different agents in each class and details the chemicals' general effects.

Pharmacists are often the most accessible health care professionals and, during a bioterrorism attack or a chemical emergency, they can fill several major roles both as medical specialists and as professionals.[8] Personal preparedness is a

Table 2. Chemical Agents[3,6]

Type of Chemical Agent	Examples	Clinical Effects
Nerve Agents (cholinomimetics)	Organophosphate fertilizers, sarin, tabun, soman	Nicotinic: tachycardia, muscle paralysis Muscarinic: diarrhea, urination, miosis, bradycardia, bronchoconstriction and increased bronchial secretions, lacrimation, sweating
Blistering Agents	Nitrogen and sulfur mustard, lewisite, phosgene oxime	React with skin, eyes, and airways, causing erythema, burns and blisters, damage to eyes, vomiting, and bone marrow suppression
Pulmonary (Choking) Agents	Chlorine gas, phosgene	Pulmonary edema, coughing, wheezing, irritation of eyes and mucous membranes, headache, possible respiratory distress, tachycardia, and cyanosis
Blood Agents	Cyanide, arsine, stibine	Cyanide: bradycardia, hypotension, metabolic acidosis, seizures Arsine: weakness, fatigue, headache, muscle cramps, dark or red urine, renal failure, jaundice, convulsions, respiratory failure, paralysis
Incapacitating Agents	Anticholinergics, fentanyl derivatives, lysergic acid diethylamide, benzodiazepines, α_2-agonists	Delirium, mydriasis, tachycardia, flushing, urinary retention, hallucinations, impaired memory, respiratory distress
Riot Control Agents	Chloracetophenome, chloro-benzylidene maloritrile	Lacrimation, burning of mucous membranes, blurred vision, rash, drooling, nausea, vomiting
Toxic Industrial Chemicals	Fluorine, ammonia, formaldehyde, sulfuric acid	Cardiac arrhythmias

vital first step. All pharmacists should be up-to-date with immunizations, CPR certification and be first-aid trained and certified. It is also important to be prepared with appropriate attire and the proper protective equipment (gloves, mask, gown, etc.) to safely allow direct contact with patients.[11] In keeping with their regular duties, pharmacists are also responsible for ensuring that affected patients receive the most appropriate drug therapy, taking into account the susceptibility of the biological agent and choosing the safest drug that is likely to be effective in each patient.[7] Dispensing emergency prescriptions may also be an important duty for a pharmacist during an emergency (in these cases, pharmacists must be aware of emergency dispensing laws and protocols).[8] Pharmacists' extensive training in managing chronic drug therapy also makes them good candidates for managing treatment in patients with chronic conditions like hypertension, heart failure, and diabetes, and in those with acute conditions that may impact tolerance and appropriateness of therapy.[11] In the event of a biologic or chemical emergency where certain drugs are scarce or unavailable, a pharmacist may help to choose safe and effective alternatives in patients with chronic diseases.[8] Pharmacists can also help with mass administration of prophylactic agents and immunizations, as well as identification of patients who are the best candidates for prophylactic treatment (for example, those who are immune-compromised or HIV-positive) and screening patients for possible contraindications that may prohibit administration of certain vaccines or medications.

Community pharmacists, with their increased accessibility to the public, should assume the responsibilities of providing education on the appropriate ways to self-treat symptoms using over-the-counter agents or supportive therapy and keeping patients calm and informed about the situation and the treatments used.[10,11] It is also important for pharmacists to discourage patients from attempting to stockpile medications and treat themselves without the assistance of a health care professional, which can result in adverse drug reactions, interactions, and other negative outcomes.

The effects of a bioterrorism attack or a chemical emergency can be greatly minimized with awareness of global events and of potentially harmful agents and an understanding of the best method of treatment for each agent.[10] All pharmacists should make an effort to prepare for emergencies by establishing emergency protocols and staying informed about national, state and regional guidelines for responding. Before emergencies arise, pharmacists may be recruited to help select which drugs to keep on hand in the event of a bioterrorism attack or a chemical emergency. A pharmacist's role does not always come to an end with the resolution of a biological attack or a chemical emergency. Community and health-system pharmacists must work with physicians and other health care providers to improve the transition of care from the emergency room or hospital and properly follow up with the affected patients to ensure that their recovery continues.

Large-Scale Outbreaks
Outbreaks of diseases and infections can be classified as a

public health emergency, especially when they have the potential to reach epidemic or pandemic proportions. Concerns for outbreaks and epidemics often vary by country. According to the World Health Organization's (WHO) Department of Pandemic and Epidemic Diseases, top-priority diseases include, but are not limited to avian influenza, severe acute respiratory syndrome, cholera, yellow fever and viral hepatitis.[17] Worldwide, the influenza virus is one of the most recognized threats to cause a pandemic due to its route of transmission through respiratory droplets and its ability to quickly mutate.[18-20] Non-human influenza viruses, such as the avian flu strains H5N1 and H7N9, are particularly dangerous, as humans have little natural immunity against infection from these strains.[18] Because pandemics are not confined to a local area, health resources, including vaccines and antiviral medications, can be in short supply.[20,21] Public health officials may be forced to make decisions regarding which groups within a population are defined as high-risk and should receive first access to care. Patients will likely have uncertainties when they hear of a influenza pandemic, and some may become panicked. They will heavily rely on health care professionals, such as pharmacists, for medical advice and treatment.

In 2009, the WHO confirmed a pandemic involving the H1N1 swine influenza virus.[18,21] The public health response was well-documented, and this real-world example can be used to explain the role of a pharmacist in influenza pandemics. Pharmacists can be classified as first responders due to their accessibility to and direct interaction with patients. Because of this, they can have a profound impact on the course of the pandemic by helping to efficiently immunize the population.[20,21] The laws regarding influenza vaccines given by pharmacists may vary by state, so pharmacists should stay educated on the laws of the specific area. Particularly affected are pharmacists in a community setting, who will need to respond to a sharp rise in demand for services while dealing with inadequate staff and possible medication shortages.[19-21] To combat these issues, prior to the influenza season, all health care employees should be immunized and contingency plans with manufacturers and wholesalers should be reviewed.[19] Pharmacists must maintain sufficient stock of commonly used medications and supplies such as gloves, masks, disinfectants and antibacterial soaps.[18,19] Within the pharmacy, symptomatic patients may be required to wear masks or be placed in a separate waiting area to prevent the spread of the influenza virus.[19] Because the course of a pandemic can be unpredictable, lack of supplies and manpower may force pharmacies to consolidate to a few critical sites to more effectively serve the patient population.

Radiation Emergencies
A radiation emergency involves the release of radioactive materials into the environment, which can result from an accident, a natural event or an act of terrorism.[22] The CDC classifies radiation emergencies into two main categories: exposure and contamination. Exposure is described as energy in the form of radiation penetrating the body, such as x-rays. Contamination involves radioactive material being in or on a person and is often more severe than exposure. Re-

gardless of the classification, health care professionals are key players in response to radiation emergencies.

A 2013 CDC summary report states that the United States has been working since the Japan nuclear accident in 2011 to find the most efficient process to respond to a radiation emergency.[22] The report included the data from a panel with frequently asked questions and discussion topics regarding the incident in Japan from the American Association of Poison Control Centers (AAPCC) and from poison center (PC) toxicologists. Based on the data collected from the two above sources and from previous CDC reports, PCs are the primary resources for communication and response to radiation emergencies. However, PCs have limited experience in reacting to such emergencies, and only a few centers have specific protocols for radiation emergencies. In these centers, the roles of a pharmacist include serving as a source of communication and information as well as responding to emergencies as needed.

In the 2013 CDC summary report, the panel defined two main goals of a PC during a radiation emergency: 1) triage information (i.e. phone calls, communication with state public health departments and radiation control programs) and 2) find and utilize current guidelines and recommendations and act accordingly.[23] Currently, PC members have limited knowledge and experience in responding to radiation emergencies. The 2013 CDC article emphasizes the urgency for PC personnel to complete specialized response training and for PCs to improve collaboration with local, state and federal agencies. Table 3 below lists various sources for information on radiation emergency response.

Mass Casualty Event

The CDC classifies a mass casualty as an event that causes injury, such as bleeding wounds, shrapnel embedded in the body or burns to a large group of people after an intentional or unintentional explosion.[24] Usually, if a weapon is used, it is a bomb or some other type of explosive. As medical professionals in a mass casualty emergency, health care providers must be prepared for a second attack where more injury can occur.[25] In many cases, injuries are non-life threatening. Many people are in shock after the explosion, leading to communication difficulties as victims may be temporarily deaf or have ringing in their ears. If major injury does occur, the most imperative injury to treat is a punctured lung because patients must be stabilized quickly in order to restore adequate breathing. It is vital to stay updated with the situation from emergency officials, and this can be done through the CDC's Health Alert Network.[26] This network was established to communicate information about an emergency from the federal, state and local levels to the general public. It is important to stay informed in order to know if the explosion released a biological or radiological agent, and if any changes in medical treatment are warranted.[25] To preserve resources at the site of attack, only triage the critically injured first and instruct the less severely injured patients to go to a nearby medical facility for treatment. If necessary, health care professionals working at hospitals experiencing excessive patient volume due to the event can send less severely injured patients to hospitals farther away in order to help as many critically injured people as possible. For patients with wounds that broke the skin, Hepatitis B and tetanus vaccinations should be administered if the patient is not up-to-date. Although the roles of a pharmacist in this type of emergency

Table 3. Radiation Response Information Sources

Resource	Information	Website
Centers for Disease Control (CDC)	Emergency preparedness and response information	http://www.bt.cdc.gov/radiation
Conference of Radiation Control Program Directors (CRCPD)	Professional agency for radiation prevention	http://www.crcpd.org/
National Poison Data System (NPDS) – American Association of Poison Control Centers (AAPCC)	Comprehensive poison exposure surveillance database	http://www.aapcc.org/data-system/
Oak Ridge Institute for Science and Education (ORISE)	Resource for emergency medical consultation	http://orise.orau.gov/reacts/default.aspx
Radiation Emergency Medical Management (REMM)	Diagnosis and treatment information	http://www.remm.nlm.gov/

Table 4. Emergency Preparedness Training Opportunities for Health care Professionals (non-exhaustive list) [27]

Agency	Information	Overview
Centers for Disease Control and Prevention: emergency preparedness and response	www.bt.cdc.gov/training	Emergency specific training opportunities
Emergency Management Institute, Department of Homeland Security	www.training.fema.gov	Portal for multiple government groups that offer emergency preparedness training
Center for Public Health Preparedness, School of Public Health, University at Albany	www.ualbanycphp.org	Training opportunities focused on public health and community response
Northwest Center for Public Health Practice, University of Washington	http://www.nwcphp.org/training/opportunities	Access to online and on-site training for emergency response

event can vary, they can help to ensure that all victims of the event receive proper psychological treatment even if there was no physical injury. Unaddressed stress after a traumatic event can lead to major psychological issues in the future if left untreated.

Final Considerations
Pharmacists are one of the most accessible health care professionals in a community and they have the opportunity to use their skills to better serve patients in emergency preparedness and response.[27] As the drug experts among health care professionals, pharmacists should play an integral part in creating public health guidelines. Pharmacists can especially influence protocol regarding drug supply and distribution during an emergency situation.[28] These guidelines should encompass both the national and local level responses and how to prepare a stockpile of medications and other supplies in coordination with the local plan. (Individual pharmacists or specific pharmacies should not create their own stockpile).[28] The formulated guidelines must be shared with other health care professionals along with information about specific disaster response systems for their area and ways to access answers for any questions that they might have regarding the drug recommendation and usage. Pharmacists can take charge in the education of other health care professionals and advise them on how to use stockpiled medications properly in case of an emergency. Pharmacists

can also become involved in organizations such as the National Pharmacy Response Team or the Medical Reserve Corps.

In order to be adequately prepared, pharmacists should be well aware of the surroundings in which they live and know if the area is prone to natural disasters or severe weather.[28,30] It is also important to be generally prepared for emergencies that can happen anywhere, such as mass casualty or bioterrorism. Table 4 is a non-exhaustive list of the training opportunities that pharmacists and other medical care professionals can attend to become proficient in using their skills in an emergency situation.

Finally, pharmacists should be aware of state and local laws and regulations, which may authorize a change in scope of practice during an emergency. Through preparation and training, pharmacists can be equipped to improve and protect public health in the case of an emergency.

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Pharmacogenetics: CYPs, NAT2 and 5-HTT Related to Antidepressants

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Abstract
Pharmacogenetics (PGt), the study of a gene's influence on patient response to a drug, shows strong potential for explaining issues with efficacy related to antidepressant medications. Each year, antidepressants are one of the most commonly prescribed medications due to the millions of Americans affected by depression. Importantly, it is recognized that there is wide interpatient variability in drug response to antidepressants caused by genetic mutations, which can alter the pharmacodynamic (PD) and pharmacokinetic (PK) properties of various drugs used to treat depression. Proteins that are mainly involved in how patients respond to medications include receptors, drug-targeted proteins, drug transport proteins and drug-metabolizing enzymes. Specifically in depression, variations in the serotonin reuptake transporter (SERT-1 or 5-HTT), N-acetyltransferase (NAT2), cytochrome P450 (CYP) 2C19, 2D6, and 1A2 can affect the outcomes of patients receiving certain antidepressant medications. Utilizing PGt can help prevent the trial and error in prescribing antidepressants and lead to better patient outcomes in the treatment of depression. Pharmacists can utilize genetic information to help primary care physicians choose drug regimens that are more likely to benefit their patients. Although advances are being made in this subject matter, some major efforts of future research will evaluate the efficacy of drug regimens and the dosing of drugs based on patient genetics.

Glossary:[1]
Allele—Alternate sequences or versions of the same gene inherited from each parent.

Extensive Metabolizers/Normal Metabolizer (EM/NM)—An individual with two "normal-function" alleles relative to a drug-metabolizing enzyme.

Genotype—The specific set of alleles inherited at a locus on a given gene.

Haplotype—A series of polymorphisms that are inherited together.

Indel—Insertion or deletion of deoxyribonucleic acid (DNA) either as single nucleotides or spanning regions of DNA involving many nucleotides.

Intermediate Metabolizers (IM)—In general, an individual with one "loss-of-function" allele and one "normal-functional" allele relative to a drug-metabolizing enzyme.

Personalized medicine—The use of patient-specific information and biomarkers to make more informed choices regarding the optimal therapeutic treatment regimen for a given patient.

Pharmacodynamics (PD)—The relationship between drug exposure and pharmacologic response.

Pharmacogenetics (PGt)—The study of a gene involved in response to a drug.

Pharmacogenomics (PGx)—Studying and understanding the genes, in some cases the entire genome, involved in response to a drug.

Pharmacokinetics (PK)—The relationship of time and drug absorption, distribution, metabolism and excretion.

Phenotype- An individual's expression of a physical trait or physiologic function due to genetic makeup and environmental and other factors.

Polymorphisms—A mutation in DNA in a given population that may be observed at greater than 1 percent frequency.

Poor Metabolizer (PM)—In general, an individual with two "reduced-function" or "loss of function" alleles relative to a drug-metabolizing enzyme.

Reference Sequence Number (rs)—A unique and consistent identifier of a given single nucleotide polymorphism (SNP).

Single Nucleotide Polymorphism (SNP)—A variant DNA sequence in which a single nucleotide has been replaced by another base.

Ultra Metabolizers (UM)—An individual with a "gain-of-function" allele (e.g., overexpression of a metabolic enzyme).

Wild-Type Gene—The typical or normally occurring genotype of an organism.

Introduction/Background
According to statistics, one of every 10 adults in America have reported symptoms of depression, and specifically, major depressive disorder (MDD) is one of the most commonly diagnosed disorders in the United States.[2,3] These current numbers aside, it is also estimated that at least 10 percent of Americans will experience MDD at some point in their lives.[4] This trend in disorders is reflected in drug use as well. According to the U.S. Centers for Disease Control and Prevention, in 2010, prescribers wrote nearly 122 million prescriptions for antidepressant drugs—the third highest of any other type of medication prescribed out of the total 3.2 billion prescriptions written in both hospitals and doctors' offices.[5] Altogether, the number of depressed patients plus the antidepressant medications they are prescribed each year makes it obvious that this type of mental disorder utilizes a significant portion of our health care system resources.

In terms of current treatment guidelines for depression, health care professionals are first advised to manage patients with sleep hygiene and low-intensity psychosocial interventions such as cognitive behavioral therapy.[6] After employing this nonpharmacologic therapy, the first-line drugs of choice for depression are antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs).[6,7] Depression is a disor-

der of the brain involving neurotransmitters. The SSRIs, and other antidepressants, successfully target specific neurotransmitters, including serotonin, norepinephrine and sometimes dopamine.[8]

As mentioned previously, SSRIs are the first-line pharmacologic choice for treatment of depression. In comparison to other antidepressant drugs, in general SSRIs are safer and have fewer intolerable side effects.[9] Some of the most commonly prescribed SSRIs are fluoxetine (Prozac®), sertraline (Zoloft®), escitalopram (Lexapro®), Paroxetine (Paxil®), and citalopram (Celexa®).[8] Another factor to consider regarding the popularity of antidepressant drug use is the high frequency of a comorbid anxiety disorder. Almost 50 percent of patients diagnosed with depression are diagnosed with an anxiety disorder as well.[10] Some of the most common types of mental disorders diagnosable by Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) criteria are depressive disorders, anxiety disorders, trauma- or stressor-related disorders, and obsessive-compulsive and related disorders.[11] More specific examples include generalized anxiety disorder (GAD), panic disorder (PD), post-traumatic stress disorder (PTSD), seasonal affective disorder (SAD) and obsessive compulsive disorder (OCD), all of which have a first-line treatment that includes SSRIs per the American Psychological Association guidelines for treatment.[12-14]

Overall, considering the popularity in use of antidepressant drugs, based on the number of prescriptions written per year, it would seem that antidepressants must be a successful treatment strategy regarding depression and anxiety disorders. However, there is a downside to this type of treatment that cannot be ignored. Despite the medication successfully treating patients for their mental disorders, the actual response to these drugs is very slow and delayed. It can take four to six weeks before patients will see the full effect of antidepressants.[8] According to current treatment guidelines it is recommended that individuals undergo an initial therapeutic trial of four to eight weeks to determine their response to the medication.[7] Not only does it require this period of waiting to see the full therapeutic effects of the drug, but this also includes a delay in time before patients may exhibit adverse side effects from drug use as their body adjusts to the medication.[7,9]

The requirement of patience when using antidepressants can be a difficult feat to achieve when treating individuals with mental disorders. These patients are already experiencing symptoms that are negatively impacting their lives and are requiring treatment. Adding on the stress of "waiting" to see if the drug will work can prove to be a definite challenge for many individuals who seek an immediate "fix." Also, unfortunately, there is the chance that the drug will not even reach therapeutic effects in the patient regardless of how long he or she waits (i.e., treatment-resistant depression). Another problem is that physicians use trial and error prescribing as the primary method of prescribing antidepressants. Trial and error prescribing is a method by which the physician "blindly" chooses a medication that tends to work, in hope that a response will be seen. This is very inefficient because it

can take months before discovering an efficacious therapeutic regimen for patients. The National Institute of Mental Health has published research that shows that patients who do not find success from their first medication usually find resolution with their second treatment on a different type of medication.[8] However, this fact can make it even more difficult for patients to accept when asked to "wait" for their therapy to reach full effect. "It has been estimated that about 20 to 30 percent of patients with major depression fail to respond to treatment with a single antidepressant drug given in adequate dosage for an appropriate period."[15] This is a problem to be addressed, and the answer may be a consequence of pharmacogenetics (PGt).

Like all other drugs, antidepressants possess pharmacodynamic (PD) and pharmacokinetic (PK) properties. The PD characteristics relate to the therapeutic effects antidepressants have on neurotransmitters in the brain, while the PK properties can result in increased drug exposure leading to adverse effects, or decrease exposure leading to treatment failure. Pharmacogenomics (PGx), looking across a larger number of genes relative to drug response, takes both PD and PK into account. Therefore, it can be assumed that PGx could be used to "screen and predict whether patients will respond to antidepressants and be able to tolerate the medications."[7]

Depression and antidepressants actually serve as a perfect platform for PGx research since genetics play a large role in both the disease and drug therapy. First, most antidepressant drugs are metabolized via CYP450 enzymes, and it has already been proven through many studies that the CYP450 enzymes have numerous variations and mutations based on different genes and alleles that exist within the human population.[7,15] Therefore, if professionals can identify specific polymorphisms in patients they can predict their inherent metabolic capacity to metabolize antidepressant drugs before ever beginning treatment. Second, depression itself has shown to be 40 to 50 percent due to "heritability." This means that nearly 50 percent of all cases of depression are actually related to genetics.[4] That being said, if a family member has previously responded well to a certain antidepressant, this could be a positive indication that the same drug will also work for a relative with a similar genetic profile. Ultimately, health care professionals can use genetics first to designate a patient's predisposition for depression, and then add the use of PGx to determine their metabolic capacity to process antidepressant drugs. As a result, health care providers can have some expectation of treatment effects before beginning therapy and, thus, they can better predict drug responses to antidepressant medications and minimize the burdensome requirement to "wait."[7]

In an attempt to transform subjective data into objective data, four distinct phenotypic categories have been created for placement of individuals based on their CYP450 genotype "star nomenclature." These include: poor metabolizer (PM), intermediate metabolizer (IM), extensive (normal) metabolizer (EM;NM), and ultrarapid metabolizer (UM).[1] For example, PMs cannot metabolize the drug as efficiently as needed

which may result in increased side effects or even toxicity as the drug accumulates. If the medication is a prodrug, metabolism by a CYP enzyme is required for activation, and in this case would be compromised leading to decreased efficacy. Conversely, a UM would metabolize an active drug very efficiently, resulting in a decrease in efficacy and a greater dose would be required to achieve therapeutic levels.

Due to the variance in patient outcomes and the need to know a patient's genetic composition for predicting the effectiveness of an antidepressant, genetic testing of the genes that code for enzymes that metabolize antidepressant medications would help optimize therapy. Various companies exist that can perform this type of genetic testing for patients. One such company is Genelex Corporation. This company provides a software product called YouScript® which is a tool that can help pharmacists and other health care providers in the interpretation of genetic information. YouScript® includes a three-step process for patients interested in having individual SNPs identified that are relevant to their disease state. First, the patient would need to talk with his or her physician to have a prescription form completed for the testing. Depending on what genes are being tested and a patient's insurance, the testing may be covered. Next, the prescriber would follow the kit instructions and send in a cheek swab sample from the patient. After about five to seven days, the results of the genetic testing would be returned, which could be used by a physician to assess the likelihood of how effective a medication would be. Although there is some lag time to get the results of a genetic test, this is still less than the typical time to analyze the efficacy of an antidepressant through standard practice as described earlier. For a patient starting a new antidepressant therapy, he or she will not need their entire genome sequenced. Genetic variance needs to be identified for genes that are relevant to the antidepressant medications a patient will be taking. As it relates to antidepressants, the genetic information for the genes that code for the enzymes NAT2, CYP2D6, CYP2C19, and CYP1A2, and the reuptake transporter 5-HTT may be needed depending on the medications being prescribed.[16] Although these four enzymes and transporter are involved, the majority of antidepressants are metabolized in the liver by either CYP2D6 and/or CYP2C19.[17] By knowing and understanding a patient's genetic profile, physicians and pharmacists will be better able to serve a patient and individualize his or her therapeutic regime.

Cytochrome P450 2D6 (CYP2D6)
Cytochrome P450 2D6 (CYP2D6) is an enzyme coded by CYP2D6 gene which is found on chromosome 22 and is expressed in many tissues, particularly the liver.[17] This enzyme (CYP2D6) biotransforms approximately 25 percent of known drugs that are metabolized by the CYP family and is one of the most important enzymes for metabolism of antidepressants.[17] The CYP2D6 gene has more than 100 different variations, some of which are shown in Table 1.[16,18,19] Depending on the SNPs, the enzyme could have active, inactive or partially active function. Additionally, CYP2D6 is not considered an inducible enzyme (via drug interactions) and varied responses of the action of this enzyme among patients is due to their inherited genetics.[20] Because there are so many different alleles of CYP2D6, it can be a challenging gene in terms of determining if a medication will likely be effective.[20] For antidepressants, CYP2D6 is important for the metabolism of SSRIs and tricyclic antidepressants (TCA).[16] Tricyclic antidepressants are hydroxylated by CYP2D6 to less active forms. The polymorphisms that a patient has will influence his or her likelihood to experience a therapeutic response or adverse events. For example, a patient that is a poor metabolizer because of inactive or partially active forms of the enzyme is at increased risk of experiencing adverse events because of elevated TCA plasma levels. In these individuals, alternative medications may be needed.[18] In addition, medications can be metabolized by other enzymes, which may also be controlled by genes with many variants.

Cytochrome P450 2C19 (CYP2C19)
In addition to the CYP2D6 enzyme, cytochrome P450 2C19 (CYP2C19) is also an important enzyme for the metabolism and activation of antidepressants. CYP2C19 is the gene coding for this enzyme which is found on chromosome 10 and also has a wide range of variation with as many as 34 polymorphisms identified.[19,21] Some antidepressant medications such as amitriptyline, clomipramine, doxepin, imipramine and trimipramine are in a less active form and have to be demethylated to active metabolites by CYP2C19 in order to induce their therapeutic effect.[18] In a patient that has a genotype for partially active or inactive CYP2C19 enzyme (Table 2), this individual may not achieve the desired response because not enough of the compound is in the active form. By knowing the PGt of an individual prior to antidepressant medication prescribing, a health care professional could recognize that the patient would likely not respond to

Table 1. Polymorphisms for CYP2D6 [16]

	CYP2D6 Polymorphisms
Active	*1, *2, *35
Inactive	*3, *4, *5, *6, *7, *8, *11, *12, *14, *15, *19, *20
Partially Active	*9, *10, *17, *29, *41

Table 2. Polymorphisms for CYP2C19 [16]

	CYP2C19 Polymorphism
Active	*1
Inactive/ Loss-of-Function	*2, *3, *4, *5, *6, *7, *8, *12
Partially Active	*9, *10
Gain-of-function	*17

amitriptyline if he or she has a certain polymorphism of the CYP2C19 enzyme. This would help eliminate the guessing game of prescribing antidepressant medications. The variations of the enzymes that are genetically determined yet again demonstrate the need for genetic testing for people being prescribed a new antidepressant therapy.

Cytochrome P450 1A2 (CYP1A2)
Cytochrome P450 1A2 (CYP1A2) is another important cytochrome P450 metabolic enzyme (comprising of 13 percent of all CYP proteins) that is coded by the CYP1A2 gene located at chromosome 15 with other CYP1 genes (CYP1A1 and CYP1B1).[22,23] Over 100 substrates for CYP1A2 have been reported including drugs such as caffeine (major substrate), procarcinogens and endogenous substrates.[22] Some important inducers of CYP1A2 include cigarette smoking, proton pump inhibitors (esomeprazole and omeprazole), cruciferous vegetables (cauliflower, cabbage, broccoli and similar green leafy vegetables), whereas some important inhibitors include ciprofloxacin (Cipro®) and other fluoroquinolones, fluvoxamine (Luvox®) (SSRI), oral contraceptives, verapamil (Calan®) and grapefruit juice; a more complete list can be found at http://youscript.com/uploads/P450chart.pdf.[16] Also, similar to other main drug-metabolizing CYPs, a number of allelic variants have been identified that clearly explain the phenotypic variability in CYP1A2 gene expression or inducibility.[24]

Over 40 haplotype variants have been discovered in CYP1A2 and only 12 of these variants have been clearly associated with one of four phenotypes including normal enzymatic activity, inducer of enzymatic activity, decreased or abolished expressivity, or decreased enzymatic activity (inhibitor) with most being classified as inhibitors.[19,25] The allele accounting for normal enzymatic activity is CYP1A2*1A. One important allelic variation in CYP1A2 is a SNP at nucleotide position 163 where adenosine (A) replaces cytosine (C) which is designated by 163C>A. This SNP has been reported to result in increased (induced) enzymatic activity and is noted by the reference sequence number (rs #, refSNP, rs) rs762551.[25,26] Three other allelic variations that decrease or abolish expression of CYP1A2 include *3, *4, and *6. The remaining seven allelic variations are clearly associated with phenotypes linked to decreased enzymatic function include *1C, *1K, *7, *8, *11, *15, *16.[19,25] Relatively little

is known about other CYP1A2 polymorphisms (SNPs) in terms of their functional consequences possibly due to lack of research because CYP1A2 is not as prevalent as other CYP enzymes and is not a major metabolizing enzyme of most drugs.[26]

Within the classes of antidepressant drugs, fluvoxamine (Luvox®) is the only SSRI in which CYP1A2 plays a minimal role (5-10%) in metabolism.[22] The metabolic pathway for fluvoxamine through CYP1A2 is methyl-ether demethylation, which is when a methyl ether is replaced with a hydroxyl group that causes the drug to be inactivated.[22] Since CYP1A2 plays a very minimal role in fluvoxamine metabolism, it is highly unlikely that the dosage will need to be adjusted in these patients. Coincidentally, a study done by Christensen et al. found that fluvoxamine is a strong inhibitor of CYP1A2 and CYP2C19 due to results showing significant (40-50%) inhibitory effect on both enzymes even at low doses.[27] Patients taking fluvoxamine need their medication profiles reviewed to identify medications that utilize CYP1A2 or CYP2C19 as a major metabolic pathway, due to the inhibitory effect of fluvoxamine. Primary care physicians will need to make dose adjustments for some medications or switch patients to a different drug regimen to avoid drug toxicity from occurring. Furthermore, patients may need therapy adjustments if they choose certain diets or lifestyles (e.g., smoking) that induce or inhibit enzymatic activity of CYP1A2. There are a few other antidepressants that are major substrates for CYP1A2 including amitryptyline (Elavil®), chlorpromazine (Thorazine®), duloxetine (Cymbalta®), imipramine (Tofranil®), olanzapine (Zyprexa®); a more complete list including antidepressants that are metabolized by CYP1A2 and additionally CYP2D6, CYP2C19, and other enzymes can be found at http://www.plasmaspiegel.at/TDM_consensus_document_2011.pdf.[28] Undoubtedly, there is still an unmet need for research in determining variant allele associations with phenotype groups for CYP1A2. The hope is that future studies will be able to adequately guide recommendations for treatment adjustments for patient phenotypes that either affect metabolic efficiency or expressivity of CYP1A2.[25]

Table 3. Polymorphisms for CYP1A2 [19,25]

Phenotype	CYP1A2 Allele
Wild-Type	*1A
Abolished / Decreased Expression	*3, *4, *6
Enzyme Inducer	*1F
Decrease Enzyme Activity (Inhibitor)	*1C, *1K, *7, *8, *11, *15, *16

Not all factors of drug response rely on hepatic metabolism. In the case of antidepressants, as well as many anticancer agents and other drugs, drug response is also determined by mutations in the expression of transporters and other cell proteins.[16] In other words, a patient's CYP genotype is not the sole factor in determining their response to antidepressant therapy. Currently, the U.S. Food and Drug Administration (FDA) recognizes 155 clinically significant biomarkers directly affecting patients' response and tolerance to medications.[29] In a study by Lee and associates, a mutation in the gene coding for an intracellular signaling protein was associated with a significantly better response to SSRI therapy.[30] Dysfunctions in a protein controlling the activation of brain-derived neurotrophic factor (BDNF) as well as the enzyme catechol O-methyltransferase (COMT) gene have also been established in predicting antidepressant response outcomes.[31,32] These newly identified biomarkers affecting drug metabolism and response serve as future drug targets for better patient-specific therapy.

N-acetyltransferase 2 (NAT2)
N-acetyltransferase 2 (NAT2) is an enzyme coded by the gene NAT2 which is found at chromosome 8 (specific location: p21.3-p23.1). This enzyme is responsible for acetylation of the nitrogen atom in many drugs, including antidepressants.[33] N-acetyltransferase 2 acts on 1 percent of drugs in current clinical use and is thought to contribute to the breakdown of different classes of drugs including antidepressants. The proportion of slow, intermediate, and rapid metabolizers (acetylators) is known to differ between different ethnic populations.[16] The only specific inhibitor for NAT2 is acetaminophen which weakly inhibited the enzyme by 30.9 percent in rapid acetylators and 19.3 percent in slow acetylators (no data for intermediate acetylators given).[34] There are currently over 87 variants that have been identified in NAT2 with the wild-type identified as NAT2*4.[25] Allelic variations are associated to low enzymatic activity (*5, *6, *7, *14, *17, *22), rapid (normal) enzymatic activity (*11, *12, *13, *18, *20, *21, *23, *24, *25, *27), and no enzymatic activity (*15, *19A, *19B).[25] Three phenotypes are identified between varying alleles in these categories that can be classified as rapid (normal) acetylators (two rapid activity alleles), intermediate acetylators (one low activity one rapid activity allele), or slow acetylators (two low activity alleles).[35] Assigning acetylator phenotype according to alleles is very challenging due to the fact that six different SNPs influence the phenotype presentation in which patients can have any

different number of them. In order to determine if patients are rapid, slow, or intermediate acetylators, a free online program called the NAT2 website predictor (NAT2PRED), http://nat2pred.rit.albany.edu, implements a pattern recognition according to the combination of SNPs found in NAT2 at positions 282, 341, 481, 590, 803 and 857.[35] Patient SNPs in NAT2 can be identified by genetic testing, and the website allows selection between the different SNPs the patient may contain. Once submitted, the predictor assigns one of the three NAT2 phenotypes based on the combination of SNPs inputted whereby health care providers can make adjustments to dosing of medications.[35] Clinicians should also be aware that NAT2 activity is also dependent upon hepatic and renal function status and age.[16] Some dosing recommendations (for drugs impacted by NAT2) provided by youscript.com include starting at the lowest dose possible of a drug in which efficacy can be seen and employing therapeutic drug monitoring in intermediate acetylators and slow acetylators.[16] Further studies are required to determine whether genotyping of NAT2 is clinically useful for determining a patient's dosage for efficacy of treatment and to avoid drug toxicity, especially in antidepressants.[25]

Serotonin Reuptake Transporter (SERT-1 or 5-HTT)
The serotonin reuptake transporter 1 (SERT-1 or 5-HTT) is coded by the gene, SLC6A4, and is a protein mainly found on serotonergic presynaptic neurons in the brain, playing a primary role in the termination of the synaptic effects of serotonin (5-hydroxytryptamine or 5-HT) following its presynaptic release.[37-39] The role of the transporter is to carry extracellular 5-HT across the cell membrane into the neuron, via a conformational change, which allows the cell to either recycle intracellular 5-HT into storage vesicles or metabolize unpackaged intracellular 5-HT with enzymes.[37-39] The promoter activity of SLC6A4 is located at chromosome 17 (specific location: q11.1-q12) and may contain an indel (insertion or deletion of DNA) polymorphism in a region known as the 5-HTT gene-linked polymorphic region (5-HTTLPR). A polymorphism in this region can alter transcriptional efficiency (production) of the transporter protein itself causing problems with the regulation of serotonin.[38,39]

About 40 percent of the North American population, especially in populations of European ancestry, have a genetic variation in 5-HTTLPR which is associated with reduced efficacy of SSRIs, a slower overall onset of treatment, and often times an indication for a change in therapy.[16] The short (S)

Table 4. Polymorphisms for NAT2 [25,35]

Phenotype	NAT2 Allele
Wild-Type (Rapid Enzymatic Activity)	*4
Slow Enzymatic Activity	*5, *6, *7, *14, *17, *22
Rapid Enzymatic Activity	*11, *12, *13, *18, *20, *21, *23, *24, *25, *27
No Enzymatic Activity	*15, *19A, *19B

allele is associated with lower transcriptional efficiency of 5-HTT (due to a deletion with an overall length of 44 base pairs), whereas the long (L) allele maintains normal transcriptional efficiency of 5-HTT.[38-40] Patients will contain one of three possible allele pairs (genotypes) including homozygous L/L, heterozygous S/L and homozygous S/S.[1] Depressed patients containing the L/L or L/S variant genotypes have demonstrated a better response to SSRIs than those patients with the S/S (short) variant.[1] Although the L allele is significantly associated with better treatment outcomes with SSRI therapy, it is unclear exactly why the L allele would confer a favorable outcome. One proposed mechanism surmises that the L allele makes the HTTLPR region better able to regulate the transporter's response to dynamic changes in extracellular concentrations of 5-HT; such as those affected by environmental changes and/or administration of SSRIs (mainly due to the activation of a stronger feedback mechanism).[41] Some more recent studies now suggest that the presence of promoter binding elements may increase with antidepressant treatment due to evidence from a differential effect (the effect of applying one treatment instead of the other) with the promoter region insertion.[41] Other studies have proposed possible mechanisms explaining the association between the L allele and better treatment outcomes, however, future research should evaluate these mechanisms to define a more distinct answer. Furthermore, studies have not researched the possible genotype effect on a dose response curve which would indicate whether dosing could optimize antidepressant treatment based on the patient's genotype.[41] Clinically, there are no clear recommendations for dosing medications based on individual genotypes, however, educating patients about their individual genotypes can be beneficial in optimizing treatment. Patients carrying a genotype that is associated with a less beneficial treatment outcome compared to others should be made aware of possible alternative approaches if SSRI treatment fails. In addition, patients could also be encouraged to try alternative therapies due to the different mechanisms that other treatments target.

Clinical Relevance

In addition to genetic differences related to PK, drug-drug interactions also have their place regarding antidepressant dosing and medication choice. Citalopram primarily undergoes its metabolism by the enzymes CYP3A4 and CYP2C19 while sertraline is subject to CYP2D6 metabolism.[42,43] These SSRIs, both of which are in the top 20 most prescribed drugs of 2012, demonstrate a high potential for interaction with medications sharing the same enzyme.[44] The easy-to-acquire, over-the-counter proton pump inhibitors, omeprazole and lansoprazole, also require metabolism by CYP2C19 and can decrease the metabolism of other 2C19-dependent medications.[43] These enzymes are also known metabolizers of many of the top 100 prescribed drugs, and substrates of these enzymes may compete for the enzyme's activity, resulting in a drug-drug-gene interaction known as a phenotype conversion or phenoconversion. These interactions can either be synergistic or antagonistic and can enhance or decrease a drug's effect, respectively, possibly rendering a previous EM to a UM or PM.

With knowledge of patients' genotypes, both pharmacists and prescribers are able to personalize therapy and provide the optimal drug and/or dose for better patient outcomes. Depression and mental disorders can now be managed accurately and aggressively, and traditional guess-and-check methods will no longer need to be employed for starting antidepressant treatment. In a recent study by Ferreri and associates, community pharmacists performed PGt testing for the CYP2C19 genotype in patients currently taking clopidogrel.[45] The CYP2C19 enzyme is responsible for converting the prodrug, clopidogrel, to its active metabolite, and its gene is found to have at least one loss-of-function allele in 30 percent of the population.[46,47] It was found that half of the patients in the study had at least one variant allele (*2 or *17). Recommendations of therapy were made by the pharmacist based on the genotype outcome, and were approved by the prescriber 89 percent of the time.[45] The remaining 11 percent consisted of therapy changes, including the prescriber knowing the patient's intolerability (via prior experience) to the suggested treatment, and a discontinuation of clopidogrel for a patient not supposed to be receiving it. The knowledge of a patient's genotype allowed the pharmacists to make recommendations to change therapy and perhaps improve outcomes in 50 percent of those who participated.

This study demonstrates the potential for pharmacists' genetic testing in a community setting and direct involvement with improving patients' health and well-being. Initiation of a collaborative agreement between providers (prescriber and pharmacist) will help to streamline therapy regimens and decrease any risk of drug-drug or drug-gene interactions. A comprehensive medication review will most likely become required with PGx testing as to eliminate any potential for adverse events. The possibility to improve outcomes exists prior to initiating treatment by ordering testing upon diagnosis, whether by a primary care physician, specialist or a clinical pharmacist. For antidepressants, preemptive genetic testing before prescribing can provide the greatest immediate benefit by determining an effective medication with which to begin treatment.

Significant barriers exist for implementing PGx testing, especially in a community pharmacy setting. The average time spent by a pharmacist from initially performing the testing and communicating with prescribers to counseling the patient totals over one hour, with lab results averaging over five days, and almost two weeks to receive approval from the prescriber.[45] At first glance, this laborious process can be seen as a suboptimal business model in the world of fast paced retail chains, but as health care information technology catches up with this blueprint of highly integrated transition of care, we can expect this timeline to dramatically decrease. Billing and reimbursement also remain a factor as all claims sent to medical insurance companies, including Medicare Part D plans, were initially rejected for having the pharmacist listed as the provider, and not the prescriber. Also related to cost are the implications of PGx testing and its overall cost/benefit profile for antidepressant drugs. Additional research is necessary to provide solid evidence dis-

playing increased patient remission rates for depression directly related to genetic testing.

Fortunately, all of these barriers can be overcome with correct implementation of health care information technology and laws. As more and more clinically relevant outcomes are proven relating an individual's genotype to his or her drug response, we can expect to see a paradigm shift in the prescribing and treatment regimen for antidepressant medications as well as other CYP dependent medications. Over 130 FDA-approved drugs currently include PGx information in the package labeling, with 30 of them being classified for psychiatry and/or neurology.[29] The increase in evidence will help validate the need for genetic testing and, combined with the decreasing cost of DNA sequencing, will accelerate the acceptance of reimbursement by insurance companies.

Conclusion

Pharmacists maintain a major role in applying and utilizing personalized medicine and are beginning to base many clinical decisions on PGt in both the community and health-systems setting. Personalized medicine is reaching antidepressant therapy due to the increased research in PGt and the reduction of cost in genetic testing.[17] Pharmacists can utilize genetic information to help primary care physicians choose drug regimens that are more likely to be beneficial to their patients. Pharmacists can also make recommendations to patients' diet and lifestyle choices (e.g., smoking) that might cause an increase or decrease in drug efficacy. It is also important for pharmacists to be aware of medications that may induce or inhibit the normal enzymatic activity and to understand what enzymes are major metabolic pathways of each drug which ultimately affects what treatment regimens are chosen.

The future of personalized medicine, including PGt testing related to PK and PD, could ultimately lead to better clinical outcomes. Studies show that patients utilizing individualized therapy based on genotypes have better outcomes and achieve efficacious therapeutic regimens quicker. Although most antidepressant treatment does not have distinct pharmacotherapy guidelines based on polymorphisms, the expectation is that more extensive research will result in the development of guidelines for dosing and drug selection based on patient genotypes. Nevertheless, pharmacotherapy adjustment guidelines are currently seen for drugs in diseases that present less complex heritability models such as warfarin and clopidogrel.[39] Recently, many discoveries have been made toward the pathophysiology of mood disorders and their treatment mechanisms, however a major target for research should be to evaluate the efficacy of therapies and dosing based on patient genotypes. Another major target for future research is the development of genotyping kits at lower costs in order to individualize patient treatments more effectively.[39] Genotyping, especially for patients on antidepressants, will prevent the primary care physician from having to use trial and error prescribing to find an effective drug and dose for their patients. Furthermore, screening a patient's genotype eliminates therapeutic options that would have been deemed effective in most other patients.

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Treatment of Attention-Deficit Hyperactivity Disorder in Children and Adolescents: Benefits and Challenges

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Abstract
Attention-deficit hyperactivity disorder (ADHD) is a neuro-behavioral disorder affecting approximately 11 percent of the country's children and adolescents, between the ages four to seventeen years. Stimulant medications such as methylphenidate and amphetamines are the first-line of treatment for ADHD. The increasing use of these stimulant medications has resulted in increased media attention and raised questions about their efficacy and safety. This review focuses on the history of stimulant use in ADHD, the disease's pathophysiology, the long-term benefits of pharmacotherapy, and the possible subsequent adverse effects associated with prolonged stimulant use in children and adolescents suffering from ADHD. Furthermore, we will highlight the important role of the pharmacist in both the long-term management of ADHD patients and in preventing the misuse/abuse of prescription stimulant medications. In addition, we briefly discuss the role of non-stimulants in the treatment of ADHD. Overall, a detailed review of the available literature suggests that there is an urgent need to conduct well-designed, long-term studies to more clearly understand the benefits and adverse effects associated with stimulant and non-stimulant use in the treatment of ADHD in children and adolescents.

Background of ADHD
Attention-deficit hyperactivity disorder (ADHD) is a neuro-behavioral disorder characterized by developmentally inappropriate levels of hyperactivity, impulsivity and lack of focus and attention to the task on hand. As of 2011, approximately 6.4 million children and adolescents between the ages 4 to 17 years have been diagnosed with ADHD in the United States.[1] The prevalence of ADHD in children has steadily increased and varied by state ranging from 5.6 percent to 18.7 percent in 2011. Importantly, it has been found that children with ADHD, if left untreated, have poor academic performance, low self-esteem, frustration and problems with social relationships.[2] Further, it has been observed that untreated children are at increased risk of developing several types of psychiatric disorders in adulthood such as conduct disorder, mood disorder, substance use disorder and anxiety disorder.[1] Thus, it is extremely important to both diagnose and treat children and adolescents with ADHD.

The most common treatment option for ADHD is stimulants, such as amphetamines and methylphenidate.[2] In many children, stimulants reduce hyperactivity and impulsivity to improve their ability to focus and learn. Additionally, long-term treatment with stimulants has shown to improve academic performance and reduce the incidence of psychiatric disorders in adulthood. Despite these beneficial effects of stimulants, there is some concern regarding potential side effects associated with chronic, long-term use. Non-stimulants are viable second-line agents for treatment of ADHD, which can be used to avoid the side effects of stimulants. The major focus of this review is on the benefits and challenges associated with use of stimulants in treatment of ADHD in children and adolescents. The use of non-stimulants in ADHD treatment is also briefly discussed.

History of Stimulants
Amphetamine was synthesized in the laboratory by G.A. Alles in 1927. Alles reported for the first time that amphetamines could produce insomnia or arousal.[3] Subsequently, it was also shown that administration of amphetamines led to improved performance on intelligence tests, stress relief, concentration enhancement and better intellectual performance. In addition, amphetamine was investigated as a medication for asthma in the 1920s and was used in the United States in the early 1930s for congestion and respiratory disorders.[4] During World War II, amphetamines were used as 'energy pills' for allied forces.[3] Amphetamines could be obtained with or without a prescription in the '50s and '60s to treat obesity, depression, narcolepsy and encephalitic Parkinsonism treatment. The widespread use of amphetamines resulted in significant abuse of the medication for recreational purposes resulting in development of amphetamine dependence in otherwise healthy individuals. In order to stem the misuse/abuse of amphetamines, the government made amphetamine a schedule II drug in 1972, which limited its sale only to individuals for treatment of their medical condition and required patients to obtain a prescription in order to possess amphetamines. The classification of amphetamine as a schedule II drug ultimately resulted in a decline in amphetamine use for medical conditions, although its abuse for recreational purposes continued.[5]

Currently, amphetamines are medications of choice for the treatment of ADHD.[3,4] The first amphetamine on the market was Benzedrine®, a racemic α-methylphenethylamine, registered by the pharmaceutical company Smith, Kline, and French.[3] Later, the same company synthesized both the dextro- (d-) and levo- (l-) isomers and began to market d-amphetamine as Dexedrine® in 1937, as the more potent isomer. Clinical trials in the 1970s showed that both the l-isomer (Cydril®) and the d-isomer were clinically effective in the treatment of ADHD. The use of α-methylphenethylamine began to decrease dramatically after a report by Gross in 1976 showed that the racemate was less effective than d-amphetamine.[6] Currently, l-amphetamine is only used in mixed salt ADHD medications which are a three to one enantiomeric mixture of d-amphetamine and l-amphetamine respectively.[3] This mixture is available as immediate and extended-release Adderall®. Administering an extended-release stimulant allows for the patient to take the medication under parental supervision in the morning and reduces the han-

dling of children and adolescents. The extended-release formulation has also shown to decrease abuse potential by introducing tamper evident tactics to the medications. Recently, the prodrug lisdexamfetamine dimesylate (Vyvanse®) has been used in ADHD management in children (age 6-12 years), adolescents (age 13-17 years) and adults. Lisdexamfetamine dimesylate contains the naturally occurring L-lysine bound covalently to d-amphetamine through an amide-linking group. It is metabolized in the bloodstream by red blood cells to yield the stimulant d-amphetamine and the natural amino acid L-lysine in a rate-limited enzymatic hydrolysis. As a prodrug, lisdexamfetamine diverts abuse by creating a slower release of d-amphetamine, thus decreasing the pleasurable effects associated with the abuse of the drug. Overall, the availability of amphetamine in different formulations such as a prodrug and as an extended-release formulation has helped in the treatment of ADHD by improving adherence and limiting its abuse.

Pathophysiology
Attention-deficit hyperactivity disorder is caused by deficient maturation in the cortical and subcortical structures of the brain.[7] This disease state specifically affects the prefrontal cortex (PFC), the part of the brain that is responsible for regulating attention, behavior and emotions. The PFC is also interconnected with other critical structures, such as the basal ganglia. The basal ganglia consists of subcortical nuclei that are mainly responsible for suppressing excessive voluntary motor function through its communication with the PFC. Neuro-imaging studies conducted in children diagnosed with ADHD have reported a decrease in gray matter volume of the globus pallidus, a major component of the basal ganglia.[7-9] It is hypothesized that the decreased functioning of the basal ganglia is responsible for the hyperactivity symptoms, such as tremors and jerking, commonly observed in ADHD patients. Overall, lesions or malformations in the PFC can dramatically decrease attention span and attenuate concentration while heightening voluntary motor function.

Pprefrontal cortex function is mediated by microcircuits of glutamatergic pyramidal cells interacting with gamma-aminobutyric acid (GABA)ergic inhibitory interneurons. The pyramidal cells are activated by N-methyl-D-aspartate (NMDA) synapses on dendritic spines and help maintain the necessary neurotransmission for working memory or inhibiting inappropriate motor behaviors. Intensity of the NMDA-mediated signaling is modulated/fine-tuned by endogenous neurotransmitters, such as norepinephrine (NE) and dopamine (DA). Increased stimulation of NE and DA receptors (i.e., α2 and D1, respectively) facilitates improved connectivity between different brain regions involved in attention and learning. Norepinephrine binds to α2A adrenergic receptors and thereby increases attention toward stimuli of interest (signal).[10] At the same time, dopamine binds to D1 dopaminergic receptors and helps suppress activation of PFC circuits due to competing or distracting stimuli (noise).[10,11] These neurotransmitters thus amplify signal: noise ratio and help in improving focus and attention toward stimuli of interest. In ADHD patients, synaptic levels of NE and DA in the PFC are decreased. These deficits can be corrected by admin-istering stimulant and non-stimulant medications, which help in either increasing NE/DA concentration and/or increasing respective receptor stimulation.

Pharmacology
Norepinephrine and DA are cleared from the neuronal synapses via uptake transporters located on presynaptic nerve terminals; therefore, the most efficient way to increase synaptic DA/NE levels is to block their uptake via these transporters.[12] Central nervous system (CNS) stimulants, like methylphenidate and amphetamine, dramatically increase the amount of extracellular NE and DA available in the PFC via blockade and/or reversal of the norepinephrine uptake transporter (NET) and dopamine uptake transporter (DAT).[12] In addition, amphetamines also disrupt vesicular storage of these neurotransmitters in the presynaptic terminal, allowing them to accumulate in the cytoplasm. Furthermore, amphetamine inhibits the degradative enzymes monoamine oxidase A and B (MAO-A, MAO-B), which allows cytosolic accumulation and promotes release in the synapse.[12] In addition, the U.S. Food and Drug Administration (FDA) has approved non-stimulants for the treatment of ADHD such as atomoxetine, clonidine and guanfacine. Atomoxetine selectively inhibits the presynaptic reuptake of NE in the PFC, thus increasing synaptic NE levels. In contrast, guanfacine and clonidine are α2 adrenergic receptors agonists and thus help in increasing activity of α2 adrenergic receptors. Non-stimulant medications are considered second-line treatments and are reserved for patients who are unresponsive to stimulants or in whom stimulants cannot be used, for example patients with cardiovascular abnormalities or patients predisposed to addiction/substance abuse. Overall, this stimulant/non-stimulant-induced increase in DA/NE receptor activity improves neuronal communication by amplifying the signal to noise ratio; and thus, ultimately results in improved attention and working memory. However, increasing concentrations of DA/NE is beneficial up to a certain point. Excessive increase in DA/NE levels results in suppression of neuronal firing in the PFC networks and can ultimately lead to worsening of ADHD symptoms.[8] Thus, there is an "inverted U"-shaped dose dependent relationship between PFC function and DA/NE levels.

Beneficial Effects of Chronic Stimulant Use
Long-term use of stimulants in children and adolescents diagnosed with ADHD does have significant beneficial effects. These effects are apparent in children/adolescents who are between 6 and 18 years old taking methylphenidate and those who are older than 3 years old taking amphetamine.[13,14] Studies have shown that there is a positive correlation between ADHD medications and academic performance in elementary school. Children, ages 9.11±1.22 years, who were treated with stimulants for at least one year outperformed their control counterparts in all tests measuring academic achievement.[15] Additionally, longitudinal case-control prospective studies of ADHD patients (males and females aged 6-18 years) were conducted to assess the psychiatric consequences of long-term stimulant use. Results suggest that lifetime stimulant treatment may prevent psychiatric outcomes such as antisocial, addictive, mood and anxiety

disorders.[16,17] Addiction and subsequent substance use disorder (SUD) is precipitated by untreated ADHD. For example, in a longitudinal study of boys (aged 6 to 17 years) with ADHD, incidences of SUD was compared in young adults without ADHD (Group 1), young adults with untreated ADHD (Group 2), and young adults with ADHD treated with stimulants (Group 3). Baseline SUD was initially recorded and remeasured after 4 years. In this study, SUD consisted of alcohol, marijuana, hallucinogen, stimulant and cocaine abuse. Rates of SUD were as follows: Group 1 (75%), Group 2 (25%) and Group 3 (~18%). Medicated children with ADHD were almost 85 percent less likely to develop a SUD. These data suggest that untreated ADHD patients could have an increased substance abuse potential and that pharmacotherapy may protect children from this risk.[18,19] Therefore, it is important to treat ADHD to minimize this increase in substance abuse potential. Non-stimulants, commonly prescribed to adults and children with ADHD, have not been extensively studied in clinical trials to assess their long term efficacy.[20] Overall, studies suggest that pharmacological treatment of ADHD in general can lead to improved quality of life.

Acute and Long-Term Side Effects
Central nervous system stimulants are considered first-line therapy as they have been shown to be more effective than non-stimulants in managing ADHD.[21] The use of stimulants for treating ADHD has increased dramatically from decade to decade. One study has reported an increase in stimulant use for treatment of ADHD from 0.9 to 3.4 per 100 children between 1987 to 1997.[22] However, like all other medications, stimulants are associated with acute and long-term side effects. Acute side effects of stimulants include nervousness, insomnia, decreased appetite, headache, stomachache, nausea and dizziness one hour after oral administration. These symptoms are possibly due to an increase in sympathetic activity resulting from increased NE levels.[20]

In addition, long-term administration of stimulant medications is associated with possible negative mental and physical consequences. Addiction is one of the most common chronic side effects of stimulant use. Methylphenidate and amphetamine increase concentrations of NE and DA in the brain, which results in a sense of alertness, increased energy and euphoria. Abuse of stimulant medications by taking them more frequently, or in doses higher than prescribed, can result in stimulant dependence in ADHD patients. Certain genetic polymorphisms may also increase predisposition to stimulant abuse.[23] These genetic quirks alter the function of certain proteins involved in the reward pathways - networks in the brain responsible for motivation and incentive drive. Specifically, ghrelin is a peptide responsible for activating appetite. Polymorphisms in the pre-proghrelin and GHS-R1A (GHSR) gene equate to weight gain and increased alcohol/smoking use in humans. A case control analysis showed that individuals with a single nucleotide polymorphism to the GHSR gene had a higher Addiction Severity Interview composite score of drug use.[23] Genetic alteration in ghrelin is currently not a diagnostic indication for amphetamine dependence; however, the role it has on addiction should not be ignored. This observation allows for possible drug development for the treatment of such addictive behaviors. Because of the high incidence of abuse, stimulant medications come with black box warnings which remind patients of the risk of dependence and that illicit use of stimulants is strictly prohibited.[24,25] Non-stimulants, although not medications of choice for treatment of ADHD, are safer alternatives to stimulants because they do not present the same risk for abuse and addiction.[26]

Adverse cardiovascular events are widely associated with the chronic use of stimulants.[27] Methylphenidate and amphetamine are sympathomimetics, analogs that stimulate the sympathetic nervous system, which if abused can lead to hypertension, tachycardia, vasoconstriction, arrhythmias, coronary artery disease, myocardial ischemia and cardiomyopathy. Therefore, adolescents with underlying cardiac abnormalities or with a family history of unexplained syncope, angina and other cardiac issues should take extreme caution with using CNS stimulants. Long-term studies exploring the relationship between methylphenidate/amphetamine use and cardiovascular events indicate that there were small but significant increases in blood pressure and heart rate without significant changes in the electrocardiograms after a six-month to one-year treatment.[20] However, these studies conclude that these cardiac changes are predictable and quite benign. Ways to minimize cardiovascular events include avoiding stimulant abuse and only titrating the dose as needed for effective therapy. Patients should also avoid use of any other NE/DA reuptake inhibitors or MAO inhibitors as they can enhance the hypertensive effects of stimulants. Atomoxetine may also increase blood pressure with short and long-term treatment. Although, long-term use of extended release guanfacine leading to cardiovascular events is uncommon, it still remains contraindicated in children with clinically significant cardiovascular history.

Effects of stimulants on growth are a major issue of debate in the treatment of ADHD children. Stimulants have been observed to decrease growth rate in newly medicated patients. Some formulations, such as the transdermal and osmotic controlled release oral delivery system methylphenidate, have been proven to affect rate of weight gain and linear growth.[20] These data, however, need to be confirmed by further studies. Atomoxetine has also showed minimal effect on height.[20] An increase in tics/Tourette's syndrome is sometimes observed in children with ADHD who are being treated with stimulants. However, there is no current data that support the exacerbation of tics/Tourette's syndrome is due to use of stimulant medications. One possible reason for the above observation could be that half of the children with chronic tics/Tourette's syndrome potentially qualify as an ADHD patient as well.[20] Nevertheless, developing children and those with comorbid conditions such as Tourette's must be closely monitored during the course of stimulant treatment. Interestingly, a meta-analysis of nine studies demonstrated that tics and symptoms of Tourette's symptoms are effectively attenuated upon administration of non-stimulant medications such as α2 agonists and atomoxetine in children with comorbid ADHD.[28] Regardless, stimulants such as methylphenidate appear to provide the best alleviation of ADHD symptoms.

A study has reported dopaminergic and serotonergic toxicity in primates after six weeks of treatment with amphetamine at doses used to treat ADHD patients.[29] This study prompts a concern that chronic therapeutic doses of amphetamines can lead to similar toxicity in ADHD patients. Koeller et al. suggests that these neurotoxicities may not be observable in ADHD patients due to the fact that diseases such as Parkinson's disease require 80 to 90 percent depletion in dopaminergic neurons before signs and symptoms appear. Despite these alarming reported amphetamine-induced toxicities in primates, it is possible that such toxicities may not appear in ADHD patients due to a few key reasons. Unlike primates, humans are able to prevent the neurotoxic accumulation of amphetamines through their extensive metabolism. Also, human and nonhuman subjects such as primates may differ in their sensitivity to amphetamine-induced toxicity. Finally, it is possible that amphetamine-induced toxicity may be observed only in healthy human subjects who abuse amphetamine for recreational purposes and do not actually suffer from ADHD.[29] Patients suffering from ADHD have a deficiency of dopamine and norepinephrine and therefore may be less vulnerable to amphetamine-induced toxicity compared to healthy subjects. In summary, further studies are required to fully understand the implications of chronic stimulant exposure in ADHD patients.

The Role of the Pharmacist in Management of ADHD and Abuse

With pharmacists being the most accessible health care professionals, it is crucial for pharmacists to know both diagnostic and treatment guidelines. Guidelines for diagnosis have been established by the American Association's Diagnostic and Statistical Manual, also known as DSM-5. In regard to treatment, the National Collaborating Center for Mental Health recommends that initial treatment begins with stimulants, and more specifically methylphenidate.[30] When a patient initiates this therapy, it is important as pharmacists to ensure the patient is starting with a low dose with the potential to titrate up as needed. Supplemental treatment such as behavioral therapy should also be initiated. In regard to these guidelines, it is crucial for pharmacists to understand that there is no specific treatment algorithm for the treatment of ADHD. Stimulants are considered first-line whereas non-stimulants can be used as second-line therapy. Regardless of which treatment option is initiated, the therapy should start with low doses with the intent to titrate up as needed and always be supplemented with nonpharmacologic management such as behavioral therapy and parent training.

Considering that ADHD is a chronic disease that is diagnosed in childhood and continues well into adulthood, there is a need to carefully monitor and manage the therapy in these patients to maximize the beneficial effects and minimize the adverse effects. The pharmacist can play a pivotal role in the long-term management of these patients. The first goal of therapy should be to manage the patient's symptoms such as hyperactivity, inability to concentrate and lack of attention. As described above, stimulant medications compared to non-stimulant medications are more effective in managing ADHD patients. Also, another important goal of the pharmacist

should be to minimize acute and long-term side effects resulting from medications prescribed for ADHD. This can be achieved through appropriate patient education and counseling. Patients must be made aware of the potential side effects such as tachycardia, palpitations, mood changes, agitation, insomnia and headaches.[13] Furthermore, pharmacists need to stress to patients the importance of medication adherence. Medications must be taken as they are prescribed. Patients must also be made aware that taking the medication more frequently or in larger amounts can result in adverse long-term consequences such as development of drug dependence and/or neurotoxicity. Finally, it is important for the pharmacist to consistently monitor and record changes in weight, height and psychological status of these ADHD patients. The ultimate goal of ADHD treatment should be to improve the quality of life of the patient.

As health care professionals, it is imperative to monitor patients for important parameters such as weight, growth, psychological status, efficacy of medication, compliance and adverse events such as cardiovascular issues and mental status alterations. To avoid these side effects and ensure quality of life for ADHD patients, it is crucial that pharmacists educate parents and other family members, as well as have them inform their teachers at school. This education will help with patient adherence as well as increase monitoring for adverse effects.

Another important role of the pharmacist in the management of ADHD patients is in preventing drug interactions. As a pharmacist, it is vital to review medication lists to ensure the patient is not at high risk for an adverse event. For example, a patient who is taking anti-arrhythmic medication may be at a greater risk for a cardiovascular event due to stimulant therapy for ADHD. It is important that pharmacists know and understand alternative pharmacologic and nonpharmacologic approaches for treatment of ADHD. In addition to nonstimulant medications, there are also many nonpharmacologic therapies, such as cognitive behavioral therapy, family therapy, parent training and social skills that can be useful in these situations. These can be aided by services offered through schools as well as follow-up visits with the prescriber.[31] In summary, as health care professionals, it is imperative to assess the efficacy of medication and compliance, and to prevent adverse effects including potential drug interactions.

Due to the benefits of stimulants such as alertness and focus, there is a larger abuse potential in those with or without a prescription. Abuse of stimulant medications can lead to development of drug dependence in ADHD patients.[32] This dependence can then lead to psychosocial alterations in patients who have already been diagnosed with another psychiatric disorder. This helps explain why ADHD medications have a black box warning and require strict monitoring. Pharmacists are the final line of defense against abuse and overuse of these medications and can monitor the exposures each month. Pharmacists can utilize tools such as Ohio Automated Rx Reporting System (OARRS) to track what controlled prescriptions a patient has, the quantity filled and

how often they have filled a specific medication. Thus, this system may help control abuse by allowing pharmacists to identify abnormal filling tendencies of these medications and contact the prescribing doctor to ensure the integrity of the prescription. In addition to monitoring data that suggests abuse, it is important that the pharmacist look out for psychosocial behavioral changes and/or withdrawal symptoms.

Due to the pharmacological effects of stimulants such as increased alertness, increased energy and euphoria, there is a large potential for abuse of prescription stimulants by individuals without a prescription. In fact, abuse of stimulant medications is on the rise among college students for it is believed to improve performance on examinations. There are reports of prescription medications being sold to classmates because of their desired effects. Furthermore, there are reports that students are falsely reporting signs and symptoms of ADHD to their health care providers in order to obtain prescription stimulants.[32] Despite regulations to monitor to whom these prescriptions are dispensed, it is much harder to regulate what patients do with their prescriptions. As described above, stimulant-induced neurotoxicities are more likely to occur in healthy subjects compared to patients with ADHD. Importantly, individuals abusing ADHD medications not prescribed to them will not be monitored and are therefore more vulnerable, compared to ADHD patients, to adverse consequences of these stimulant medications. In the future, all of the challenges associated with prescription stimulants such as abuse, misuse and malingering will need to be collectively addressed by pharmacists and other health care providers.[29]

Conclusion

There are warranted and appropriate uses of stimulants such as amphetamines and methylphenidate; however, these should be used with extreme caution. These stimulants have shown the ability to improve the patient's quality of life when therapy parallels the strict guidelines such as those set by DSM. Appropriate therapy helps eliminate unnecessary exposure to adverse effects as well as misdiagnoses. Further, the role of non-stimulant medications needs to be further investigated to provide safe alternatives to ADHD therapy for those who have pre-existing conditions or sensitivities toward stimulants that disqualify them from stimulant therapies. Finally, it is imperative that the long-term effects, both beneficial and adverse, of stimulants and non-stimulants be evaluated in prospective cohort studies in order for prescribers and pharmacists to be aware that the added benefits of therapy outweigh the potential short-term and long-term risks.

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