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Belsomra®: A Novel Dual Orexin Receptor Antagonist for the Treatment of Insomnia

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

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Objectives

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

1. List medications currently approved for treatment of insomnia.
2. Enumerate the limitations of benzodiazepines and non-benzodiazepines for insomnia treatment.
3. Describe the mechanism of action of suvorexant.
4. List the major adverse effects of suvorexant.
5. Describe the role of the pharmacist in counseling and managing patients on suvorexant therapy.

Abstract

Insomnia is a disease state characterized by a persistent difficulty in falling asleep, and results in enormous health-related and economic costs to both the individual and society. Several medications are currently available for the treatment of insomnia; however, these medications are associated with several limitations including anterograde amnesia, dependence, withdrawal symptoms upon stopping the medication and rebound insomnia. The U.S. Food and Drug Administration recently approved suvorexant (Belsomra®) as a treatment for insomnia. Suvorexant is a first-in-class dual orexin receptor antagonist for the treatment of insomnia. This review will first describe the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria used for diagnosing insomnia and current treatment options for insomnia and then will characterize the role of orexin neurons in the pathophysiology of sleep. Subsequently, pivotal clinical trials that evaluated the safety, efficacy and adverse effects associated with suvorexant will be discussed. Finally, the review will delineate the role of the pharmacist in managing patients on suvorexant. Current available data suggests that suvorexant possesses superior efficacy compared to placebo and a better safety profile compared to alternative insomnia treatments. Further study of suvorexant in larger and diverse populations is necessary to confirm existing findings. In particular, trials with longer durations, direct comparisons with currently available sleep medications and more participants would increase the confidence among prescribers and healthcare providers and promote the use of suvorexant for treatment of insomnia.

Key Terms

Belsomra®; Benzodiazepine; Dual Orexin Receptor Antagonist; DORA, Insomnia, Insomnia Treatment, Orexin, Suvorexant

Introduction

Insomnia refers to a disease state that involves persistent difficulty falling asleep and/or frequent awakenings during sleep. Over 35 percent of the adult population exhibits one or more symptoms associated with insomnia, with 12 percent to 20 percent actually demonstrating a symptom profile sufficient for diagnosis of the disorder.[1] The lack of restful sleep may lead to symptoms such as daytime fatigue, daytime sleepiness, memory or concentration deficits, anxiety, depression, irritability, reduced energy and lack of motivation. Furthermore, insomnia is associated with changes in mood, poor job performance, disturbed personal relationships and difficulty in carrying out daily activities. Ozminkowski and colleagues have estimated that insomnia results in an enormous economic loss to society of approximately $30 billion per year, mostly through reduced productivity and absenteeism.[2] Thus, effective insomnia treatments could not only improve quality of life via symptom relief but also have tremendous economic benefits to society.

Several treatment options are available for the treatment of insomnia; however, adverse effects associated with these treatment options make the management of insomnia challenging. Recently, suvorexant (trade name Belsomra®) was approved by the U.S. Food and Drug Administration (FDA) on Aug. 13, 2014, as a Schedule IV drug for insomnia.[3] Suvorexant is a dual orexin receptor antagonist, and is the first medication in this class, offering a novel mechanism for the treatment of insomnia. This article will discuss the role of orexin neurons in sleep, the mechanism of action of suvorexant, various clinical studies that demonstrate efficacy of suvorexant, and finally the role of the pharmacist in dispensing and managing patients taking suvorexant. Additionally, potential challenges and unanswered questions associated with suvorexant treatment will be discussed.

Insomnia: Diagnosis, Current Treatment Options and Challenges With Current Treatment

Insomnia can be broadly divided into primary and secondary insomnia.[1] The diagnosis of primary insomnia is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a sleep disturbance that affects sleep quantity or quality, causes impairment in activities of daily living, occurs at least three nights per week for at least three months, and is not due to substance use, other medical conditions and other sleep-wake disorders.[4] Additionally, insomnia can be secondary to other medical diseases, may exacerbate other

disease states or can even render insomniacs susceptible to other disease states.[5] The prevalence of insomnia in the population is clustered among patients with one of several risk factors.[1] For example, insomnia is more prevalent in divorced patients than in those who are married or have never been married. Insomnia is also more commonly present in females, African-Americans and in patients with depression. Lower socioeconomic status is also a risk factor for insomnia.

There are a wide range of treatment options available for insomnia patients. The two primary treatment strategy groups are cognitive-behavioral therapy (CBT) and pharmacological therapy. These treatment options are often used effectively in combination. Cognitive-behavioral therapy most commonly includes behavioral adjustments, such as having patients maintain a sleep diary, changing specific habits associated with pre-sleep behavior, and other priority changes for the patient.[1] Currently, most commonly used medications for insomnia target the inhibitory neurotransmitter gamma aminobutyric acid (GABA). Broadly, pharmacological agents acting on the GABA receptors can be divided into benzodiazepines (BZD) such as flurazepam, triazolam, estazolam, and lorazepam, and non-benzodiazepines (non-BZD) such as zolpidem, eszopiclone, zaleplon, and zopiclone. In addition to GABA, histamine neurotransmission has been an important target for insomnia medications. Tricyclic antidepressants such as trazodone, doxepin and pivagabine, which have significant antihistaminic properties, and antihistamines such as diphenhydramine are sometimes used in the treatment of insomnia due to their sedative effects. Finally, a third group of drugs that are useful in insomnia treatment are anticonvulsants which can act by enhancing GABA neurotransmission or depressing neuronal activity in general.[6]

Benzodiazepines and non-BZDs are the most common drug classes used as a product of their efficacy, however, they still present many challenges in clinical use. In terms of efficacy, both BZD and non-BZD drugs have been shown to significantly improve acute insomnia as measured by subjective total sleep time (sTST) (total length of time asleep, as measured by the patient) and time to sleep onset (sTSO) (total length of time from lying in bed to sleep initiation, as measured by the patient).[6] Additionally, the adverse event profiles of BZD and non-BZD drugs are similar, with symptoms such as headache, fatigue and dizziness. BZDs are also associated with a number of serious adverse effects such as anxiety, anterograde amnesia, poor balance associated with an increase in falls and morning somnolence.[1] Patients taking BZDs for insomnia also have reported abnormal sleep behaviors, such as sleep-related walking, eating, driving and sexual activity. Additionally, BZDs and non-BZDs are susceptible to abuse and dependency as they can produce either withdrawal symptoms after use or rebound insomnia upon treatment discontinuation, thus limiting their use for chronic insomnia. Currently, only eszopiclone (non-BZD) has been approved for chronic use in insomnia patients.[6] Therefore, these concerns with adverse effects, abuse and dependency fostered a desire to develop a novel insomnia treatment that would offer patients a superior treatment option.

Suvorexant: A Novel Medication for Treatment of Insomnia Targeting Orexin Transmission

Suvorexant (Belsomra®) is a dual orexin receptor antagonist marketed by Merck Sharp & Dohme Corp.[7,8] The action of suvorexant is achieved through interaction with a collection of neurons known as the orexin system, which coordinates the body's transition from a sleep-state to an alert-state.[9] There are approximately 100,000 orexinergic neurons spread across the brain, but these neurons are located principally in the lateral hypothalamus and lower brainstem nuclei.[10] The role of orexin in the sleep-wake cycle was elucidated by studying narcolepsy patients. Narcolepsy is a state characterized by excessive daytime sleepiness and intermittent uncontrollable episodes of daytime sleepiness. Narcolepsy patients were found to lack orexigenic neurons or have low levels of orexin, a neuropeptide.[11] This discovery eventually led to the conclusion that the death of these neurons or absence of these neuropeptides is a leading cause in the narcolepsy-cataplexy disease state. Consistent with these findings, the knockout of orexin genes in animals resulted in the development of narcolepsy in animals. The effects of orexin released by orexigenic neurons is mediated by two receptors: orexin R1 (OX_1R) and R2 (OX_2R). Both orexin receptors are G-protein-coupled receptors. Animal studies support the important role of OX_2R over OX_1R in the regulation of the sleep-wake cycle.[12] Binding of orexin to orexin receptors activates the brain's "wake-promoting system."[12] Suvorexant reversibly inhibits both orexin receptors and, thus, promotes sleep by preventing activation of the wake-promoting system.

Clinical Studies Demonstrating Efficacy of Suvorexant

Several clinical studies have evaluated the efficacy and adverse effect profile of suvorexant. A summary of the trials discussed in this article can be found in Table 1.

Michelson and colleagues assessed the safety and efficacy of suvorexant over a one year period, followed by a two month discontinuation phase.[13] They reported that suvorexant significantly improved sTST, sTSO and other common measures of sleep quality as compared to placebo over the course of therapy ($P<0.0001$). Specifically, a 9.5 minute average reduction in sTSO and a 22.7 minute average increase in sTST relative to placebo were demonstrated with suvorexant treatment. Importantly, no effect on mood was demonstrated, and the most common adverse effects were somnolence (13.2%), fatigue (6.5%), dry mouth (5.0%), dyspepsia (1.9%) and peripheral edema (1.7%). Abrupt discontinuation of suvorexant was well-tolerated, with rebound insomnia more predominant in those who were switched from suvorexant to placebo during the two-month discontinuation study. Additionally, no significant difference was observed between the suvorexant-suvorexant or suvorexant-placebo group in patients with withdrawal symptoms. Overall, the trial illustrated that suvorexant was effective in treating insomnia over the long-term with minimal adverse effects.

Two other phase III, randomized, double-blinded clinical trials, conducted by Herring and colleagues, investigated the efficacy and safety of suvorexant versus placebo in over

Table 1. Summary of Major Trials.* [10, 13-15]

	Michelson D, et al.[13]	Herring WJ, et al.[14]	Sun H, et al.[10]	Bettica P, et al.[15]
Study Design	Phase III, randomized, double-blinded, placebo-controlled	Two Phase III, randomized, double-blinded, placebo-controlled, parallel-group trials	Randomized, double-blinded, placebo-controlled, 2-period cross-over study	Randomized, double-blinded, placebo-controlled, 4-period cross-over study
Number of Patients	781 (522 suvorexant, 259 placebo)	Trial 1: 1021 total (254 suvorexant 20/15 mg; 383 suvorexant 40/30 mg; 384 placebo) Trial 2: 1009 total (239 suvorexant 20/15 mg; 387 suvorexant 40/30 mg; 383 placebo)	25 total	51 total
Study Duration	1 year, followed by 2-month discontinuation phase (primary endpoint: relapse prevention)	3 month trials, each with 1 week run-out period (discontinuation phase) to assess withdrawal and rebound insomnia	4 days per period with 7 day washout period. 2 periods total	2 nights per treatment session with 7 day washout period. 4 periods total
Inclusion Criteria	Patients aged 18 years and older who met primary insomnia criteria in DSM-IV	Patients aged 18 years and older who met primary insomnia criteria in DSM-IV	Patients aged 18-85 years with diagnosis of Chronic Obstructive Pulmonary Disease (COPD)	Male patients aged 18-55 years, body weight >50kg, body mass index within 18.5-29.9kg/m^2, average bedtime 10pm-12am 5-7 days per week, average sleep duration of 6.5-8.5 hours over previous 3 months
Exclusion Criteria	Those who had confounding neurological disorders, unstable medical disorders, substance abuse, major affective or psychotic illness	Those who had other sleep disorders, confounding neurologic disorders, unstable medical disorders, substance abuse, major affective or psychotic psychiatric illness	Those who used continuous oxygen therapy, had other respiratory disorders, or had sleep disorders other than insomnia	Those who consumed medications or beverages that could interfere with study treatments, those with sleep apnea or other sleep disorders, those not prepared to meet study protocol requirements
Dose(s) Used	40 mg: patients aged 18-64.9 years 30 mg: patients aged 65 years and above	Both trials assessed: 20 mg, 40 mg: patients aged 18-64 years 15 mg, 30 mg: patients aged 65 years and above	40 mg: patients aged 18-64.9 years 30 mg: patients aged 65 years and above	Suvorexant 10 mg or 30 mg Zolpidem 10 mg
Primary Endpoint(s)	Assess tolerability and safety of suvorexant	Change from baseline in sTST and sTSO at months 1 and 3	Mean oxygen saturation (spO_2) for total sleep time (TST) on day 4	Change from baseline in sTST, wake after sleep onset and latency to persistent sleep
Secondary Endpoint(s)	Changes in sTST and sTSO	Changes from baseline in sTST and sTSO at week 1	Mean spO_2 on day 1 and in each sleep stage	Effect on REM and non-REM sleep

*Studies listed here utilized the 4th edition of the Diagnostic and Statistical Manual. There is minimal change in definition of primary insomnia between the 4th and 5th editions (the 5th edition is currently in use).

2,000 patients.[14] The researchers reported improvement in sTSO, sTST and other sleep measurement endpoints over the duration of suvorexant treatment, with less than 5 percent of patients discontinuing use of the drug due to adverse events. The trial also included a one week, randomized, double-blinded run-out period to assess withdrawal and rebound potential of suvorexant. No marked withdrawal or rebound symptoms were observed in patients after abrupt suvorexant discontinuation.

Bettica and colleagues compared the efficacy of suvorexant and zolpidem (a non-BZD) in a randomized, double-blinded, placebo-controlled trial in adult male volunteers in a simulated noisy environment.[15] Suvorexant 10 mg and 30 mg were both shown to increase sTST by 17 and 31 minutes respectively as compared to 11 minutes by zolpidem. Additionally, rapid eye movement (REM) sleep was increased with suvorexant treatment and decreased with zolpidem. However, the trial did demonstrate more frequent side effects after suvorexant than after zolpidem due to differences in their pharmacological activity. More studies are needed to compare the efficacy of suvorexant to existing pharmacologic insomnia treatments.

Although suvorexant has demonstrated efficacy in promoting sleep maintenance in both healthy subjects and insomnia patients, its effects are more clear in the latter.[10] A 2013 trial assessed the effects of suvorexant in healthy individuals without sleep problems. This study reported no electroencephalogram (EEG) improvements consistent with increases in deep sleep in these individuals, but the study did report improvements in other sleep measures including "latency to persistent sleep" (time before overnight sleep was sustained) and "wake after sleep onset" incidents. In both of these measures, suvorexant improved sleep quality in patients without sleep disorders.

In summary, clinical data available to date suggests that suvorexant is an effective sleep-promoting medication with an adverse effect profile better than currently available medications. Importantly, suvorexant has been shown to produce minimal withdrawal effects upon terminating use. Based on these data it is expected that suvorexant will have minimal to no abuse/dependence potential. However, future clinical studies directly comparing suvorexant to other currently used sleep medications and assessing the long-term effects/abuse potential of suvorexant are required.

Pharmacist's Role in Managing Patients on Suvorexant

Pharmacists have an important role in educating patients on suvorexant use, side effects and cautions. Suvorexant is a white powder that is insoluble in water.[7] Available in 5, 10, 15 and 20 mg strengths, the tablets should be stored at room temperature and protected from moisture and light.[8] The onset of action of suvorexant is approximately 30 minutes, and reaches a maximal plasma concentration (T_{max}) in approximately two hours. Therefore, pharmacists should counsel patients to take suvorexant no more than 30 minutes before bed. Consumption of a high-fat meal delays the time taken to reach maximum levels (T_{max}) by about 1.5 hours. However, this does not otherwise affect the overall maximum concentration reached. Therefore, for rapid onset of action, patients may be advised to avoid taking suvorexant with or directly after a meal.

The adverse effect profile for suvorexant is fairly limited as the drug is generally very well-tolerated.[13] Unsurprisingly, trials have documented somnolence and daytime sleepiness/fatigue.[14] Incidence of dry mouth was increased in suvorexant treatment groups relative to placebo as well. Across the board, adverse effects occurred in a dose-dependent distribution. Furthermore, the long-term effects of suvorexant are not well understood, as most existing trials have had short durations.[16] Central nervous system (CNS) adverse effects occur at very low frequencies and can include headache, abnormal dreams, sleep paralysis, mood changes, confusion, memory loss, hallucinations, somnambulism and suicidal ideation.[17] Pharmacists should inform the patient to contact their doctor or pharmacist if any of these symptoms occur.

Suvorexant does not require laboratory monitoring, however, prescribers and pharmacists alike should monitor patients for signs of CNS depressant effects that could potentially harm the patient (e.g., operating a motor vehicle while experiencing daytime somnolence).[16] Pharmacists should also consult the prescriber if the patient is currently taking any other CNS depressants. Due to their potential for additive effects, doses of CNS depressants and/or suvorexant should be adjusted.

Pharmacists will want to inform patients that a scheduled dose should not be taken if alcohol has been consumed that evening. Additionally, suvorexant should only be taken when the patient expects to receive at least seven hours of sleep. Suvorexant is contraindicated in patients with narcolepsy as suvorexant will exacerbate this condition.[7] Lastly, patients taking high doses of suvorexant (20 mg a day) should be cautioned about operating motorized vehicles the day after due to a higher risk of daytime somnolence.

Certain populations, such as the elderly, may benefit from suvorexant use in comparison to first-line therapy.[9] Benzodiazepines commonly cause loss of balance and vertigo, contributing to falls. However, suvorexant's mechanism of action does not cause vertigo; therefore, some detrimental falls in elderly patients could be avoided. Additionally, obese patients often suffer from insomnia. Interestingly, suvorexant is cleared more slowly, and achieves higher peak levels in obese women (BMI> 30 kg/m^2) compared to non-obese women. This may result in increased adverse effects in obese women compared to non-obese women. [8] Therefore, suvorexant therapy should be used with caution in obese patients, especially obese women.

Additionally, due to suvorexant's metabolism by cytochrome P450 (CYP) 3A4 enzymes, it should not be taken concurrently with CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) which will decrease clearance, or with strong CYP3A4 inducers (e.g. rifampin, carbamazepine, phenytoin) which will reduce efficacy.[16] If a patient is unable to

discontinue treatment with a CYP3A4 inhibitor, suvorexant should first be introduced at a reduced (5 mg) dose. Suvorexant is also not recommended for use in pregnancy; while no teratogenicity has been documented, suvorexant use was associated with decreased fetal body weight in animal models.[18] Because of the risk of accumulation, suvorexant is also not recommended for patients with severe hepatic impairment.[7]

Challenges and Unanswered Questions

Unfortunately, suvorexant is not covered by all insurance companies. In fact, one pharmacy benefit management company (Catamaran®) has suggested zolpidem as an alternative to suvorexant.[19] Without insurance, patients can expect to pay approximately $10.52 per tablet (regardless of dose).[8] This can result in significant financial burden on patients and can serve as a disincentive for suvorexant as a treatment option.

Due to limited post-marketing research, there are very few documented and substantiated contraindications to suvorexant use. Future research could provide a more thorough understanding and awareness of potential risk factors and contraindications associated with suvorexant, as well as safety and efficacy with long-term use. Furthermore, a greater understanding of when suvorexant is most and least effective would cement suvorexant's role in insomnia treatment going forward.

Conclusion

Suvorexant (Belsomra®) is a dual orexin receptor antagonist and is the first drug for insomnia acting via this mechanism. Findings from clinical studies suggest that suvorexant improves both sleep onset and total sleep time. In comparison with zolpidem, suvorexant has been found to significantly increase the quality and duration of sleep. In addition to improved efficacy, suvorexant does not result in withdrawal symptoms upon its discontinuation, which is commonly observed with many of the current insomnia treatments. However, one caveat is that long-term studies with suvorexant are currently unavailable. Cost of the medication may also be a problem for patients, as insurance companies and pharmacy benefit management companies may not include it on their formularies. In conclusion, suvorexant holds great promise due to its efficacy in insomnia patients and its potential to overcome some limitations associated with current first-line medications available for insomnia treatment.

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Assessment Questions

1. Which of the following is NOT a major adverse effect of suvorexant?
    A. Somnolence
    B. Nocturia
    C. Fatigue
    D. Dry mouth

2. Which of the following drug classes is NOT a current treatment option for insomnia?
    A. Benzodiazepine
    B. Anticonvulsant
    C. Tricyclic antidepressant
    D. Selective serotonin reuptake inhibitor

3. Which of the following is an advantage of suvorexant over benzodiazepines?
    A. Marked increase in rebound insomnia following suvorexant treatment as compared to benzodiazepines.
    B. No risk of withdrawal symptoms displayed upon abrupt discontinuation of suvorexant therapy.
    C. Marked increase in orexin neuron firing following suvorexant treatment.
    D. There is no significant advantage of suvorexant over benzodiazepines.

4. Which of the following patients would be the best candidate for suvorexant therapy?
    A. A well-managed insomnia patient who is struggling to afford his diazepam.
    B. An insomnia patient who has not experienced an increase in sleep time from treatment with a BZD.
    C. A patient without insomnia seeking relief from somnambulism.
    D. A narcoleptic patient who struggles to stay awake at work.

5. Which of the following medications would be safe to take in conjunction with suvorexant?
    A. Clarithromycin
    B. Carbamazepine
    C. Diazepam
    D. Methenamine

6. Which of the following counseling points would be appropriate when educating patients about suvorexant?
    A. Patients should only take suvorexant if they expect to receive at least seven hours of sleep.
    B. Patients taking high doses of suvorexant should not operate heavy machinery the following day until they know how the drug affects them.
    C. Patients who have consumed alcohol in an evening should still take their scheduled dose.
    D. Both A and B.
    E. All of the above.

7. At which receptor does suvorexant act? Does it act as an agonist or an antagonist at this receptor?
    A. Orexin; antagonist
    B. Gamma-amino butyric acid (GABA); agonist
    C. Orexin; agonist
    D. Gamma-amino butyric acid (GABA); antagonist

8. Suvorexant displays an onset of action in:
    A. 15 minutes
    B. 30 minutes
    C. One hour
    D. Two hours

9. Challenges to the use of suvorexant for treatment of insomnia include:
    A. The potential for rebound insomnia following suvorexant therapy.
    B. Few documented contraindications exist to suvorexant use.
    C. Limited coverage by insurance companies
    D. Both B and C.
    E. All of the above.

10. What specific sleep parameter(s) have demonstrated marked increase(s) following suvorexant treatment?
    A. sTST
    B. sTSP
    C. sTSA
    D. sTSS

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PCSK9 Inhibitors: A Novel Class of Pharmacotherapy for Hypercholesterolemia

Angela Chu, Austin Hilverding, Elizabeth Kramer, Brendan Rasor, Boyd Rorabaugh, BS, M.S., Ph.D.

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

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Objectives

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

1. Describe the mechanism of action of PCSK9 inhibitors.
2. Identify FDA approved indications for alirocumab (Praluent®) and evolocumab (Repatha®).
3. Review clinical trials involving PCSK9 inhibitors and identify potential adverse effects and significant clinical outcomes.
4. Explain the appropriate storage, use and administration of PCSK9 inhibitors for patient discussion.

Abstract

The recent U.S. Food and Drug Administration (FDA) approval of two new drugs, alirocumab (Praluent®) and evolocumab (Repatha®) is a breakthrough in the treatment of familial hypercholesterolemia. These drugs are a part of a new class called the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors that act by increasing the number of low density lipoprotein receptors (LDL-R) recycled to hepatocyte membranes. The increased density of LDL-R facilitates greater clearance of low density lipoproteins from the blood. Numerous clinical trials have demonstrated the efficacy of these agents, particularly for patients in whom standard cholesterol-lowering therapy is insufficient. However, data on long-term health outcomes in patients on PCSK9 inhibitors will not be known for several years. Opportunities for pharmacists include counseling on how to store and administer the medication, helping patients receive access to therapy and advocating for healthy lifestyle changes. Pharmacists should also be aware of insurance coverage and emerging indications for each agent in order to provide the best care for patients.

Key Terms

Antibodies; Cholesterol; Hypercholesterolemia; Human; Monoclonal; PCSK9 Protein

Introduction

Today's healthcare environment is dominated with concerns relating to obesity and high cholesterol. The current mainstays of therapy for these conditions are decades old and do not provide many patients with sufficient benefit to maximally reduce associated morbidity and mortality. Novel agents that affect lipid levels are necessary to improve outcomes, not only in patients with hyperlipidemia associated with a sedentary lifestyle and poor dietary habits, but also in patients with genetic conditions such as heterozygous and homozygous familial hypercholesterolemia (HeFH, HoFH). Many of these patients fail to reach or maintain sufficient reductions in cholesterol levels on standard lipid-lowering therapies, leading to increased morbidity and mortality. A new class of lipid-lowering agents, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, are able to induce significant reductions in low-density lipoprotein cholesterol (LDL-C) relative to statins and ezetimibe.[1,2] This article seeks to describe the mechanism and efficacy of these new agents as well as their future role in the management of patients with hypercholesterolemia.

Pharmacology

Both low density lipoprotein receptors (LDL-R) and PCSK9 are synthesized in hepatocytes under sterol regulatory element-binding protein 2.[3,4] The N-terminus of PCSK9, responsible for proper folding of the enzyme, is cleaved in the endoplasmic reticulum, but remains attached to PCSK9 in the catalytic site to inhibit other substrates from binding to it. The PCSK9 is then packaged and secreted by the golgi apparatus into the plasma, where it can bind LDL-R via the epidermal growth factor domain A (EGF-A). This initiates the endocytosis and lysosomal degradation of the PCSK9-LDL-R complex by an unknown mechanism (Figure 1a). When PCSK9 is overexpressed, this action results in fewer LDL-R recycled to the hepatocyte membrane, and a corresponding increase in LDL-C levels.

Alirocumab and evolocumab are monoclonal antibodies that bind to PCSK9 to inhibit its binding to the LDL-R (Figure 1b). They also allow the receptor to be recycled back to the surface of the hepatocyte membrane. Both drugs have been approved for the treatment of familial hypercholesterolemia and clinical atherosclerotic cardiovascular disease (ASCVD), in addition to a low fat diet and maximally tolerated statin therapy.[5,6] Both drugs have shown superior efficacy and safety profiles compared to the standard treatment, which includes a high dose statin (atorvastatin 80 mg or rosuvastatin 40 mg), ezetimibe and/or niacin with a low fat diet.[7]

In patients with familial hypercholesterolemia, LDL-C levels are commonly uncontrolled with high dose statins and adjunct therapy with a second cholesterol lowering agent, therefore, morbidity and mortality remain high. Statins work to inhibit cholesterol synthesis, but only modestly reduce LDL-C levels in some patients. Ezetimibe inhibits cholesterol absorption in the small intestine via inhibition of the Nie-

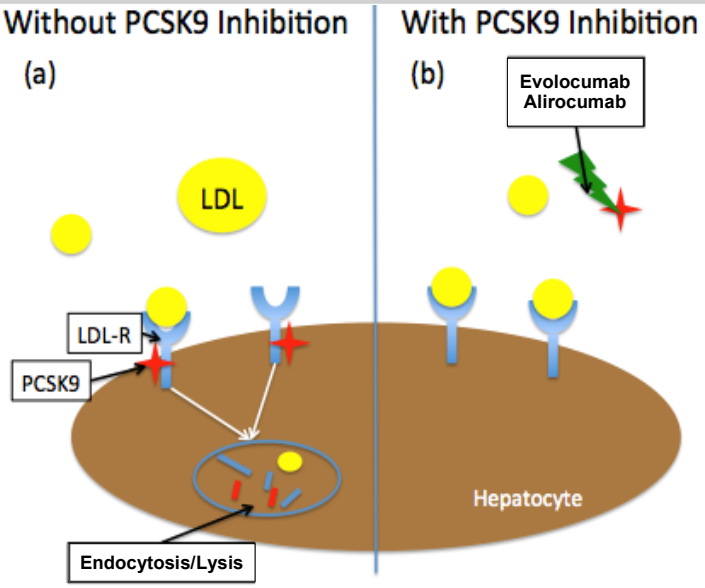

Figure 1.
(a) Proprotein convertase subtilisin/kexin type 9 (PCSK9) normally binds to the low density lipoprotein receptor (LDL-R) to induce its endocytosis and lysosomal degradation when LDL binds to the LDL-R.
(b) Evolocumab or alirocumab binds to PCSK9 extracellularly to inhibit PCSK9 from binding to the LDL-R.

mann-Pick C1-Like 1 transporter to prevent cholesterol from reaching the hepatic circulation.[8] Statins and ezetimibe are usually prescribed as dual therapy with the option of substituting niacin for ezetimibe. However, the mechanism of niacin is not well understood, and it is not as commonly prescribed. Newer treatments include lomitapide, a microsomal triglyceride transfer protein inhibitor and mipomersen, an inhibitor of mRNA coding of apolipoprotein B-100.[9] At over $34,000 and $6,000 per dose, respectively, the costs of lomitapide and mipomersen are far greater than either evolocumab and alirocumab, which each cost about $600 per dose.[10-13] These newer agents are also not as well studied as the PCSK9 inhibitors.

Trial Data: Alirocumab
Numerous studies have been conducted that illustrate the efficacy of PCSK9 inhibitors. The Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial examined the efficacy and safety of alirocumab in reducing lipids and cardiovascular events over a period of 78 weeks.[1] This trial included 2,341 patients who had LDL-C levels of greater than 70 mg/dl, at risk for cardiovascular events and receiving treatment with statins at the highest tolerated dose with or without other lipid-lowering therapy. Patients had coronary heart disease, a disease equivalent in cardiovascular risk, or HeFH.

The mean calculated LDL-C level was 122 mg/dL at baseline, with a goal LDL-C level of less than 70 mg/dL.[1] Subjects were randomly assigned to receive 150 mg subcutaneous injection of alirocumab or placebo every two weeks for 78 weeks with concomitant statin and other lipid-lowering therapy, if applicable, throughout the study. Follow ups were conducted at weeks 12, 24, 52 and 78 to assess safety and adherence and to perform lab tests to determine the efficacy of the drug. The primary endpoint was the change in calculated LDL-C levels from baseline to week 24. Safety endpoints were adverse events, including symptoms and laboratory abnormalities occurring up to week 10.

At week 24, the mean percentage change in calculated LDL-C levels were -61.0 percent for the alirocumab group versus 0.8 percent in the placebo group ($p < 0.001$).[1] The mean absolute LDL-C level at week 24 was 48.3±0.9 mg/dL and 119±1.2 mg/dL in the alirocumab and placebo groups, respectively. Investigators also found that 79.3 percent of patients in the alirocumab group met the goal LDL-C level of less than 70 mg/dL versus only 8 percent of patients in the placebo group ($p < 0.001$). Reduction of the LDL-C levels in the alirocumab group persisted through the end of the trial.

The percentage of patients who experienced any adverse reactions was not found to be statistically significant.[1] Most of the reported reactions were related to pain at the injection site, or a general allergic reaction. Alirocumab had higher rates of injection-site reactions, myalgia, neurocognitive events and ophthalmologic events than placebo. In the alirocumab group, 18.7 percent of patients reported a serious adverse event versus 19.5 percent in the placebo group. However, most of the adverse events leading to subject dropout were not considered serious.

In conclusion, more evidence needs to be collected to determine alirocumab's impact on long-term risk of cardiovascular events. The ongoing trial ODYSSEY OUTCOMES is focused on providing these long-term cardiovascular outcome data and is expected to be completed near December of 2017.[14,15]

Trial Data: Evolocumab
Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS-2) assessed the efficacy and safety of evolocumab.[2] The study included 307 patients currently receiving no or low-dose statins who had previous intolerance to two or more statins. Subjects were divided into four groups with different medication regimens:

Group 1: Evolocumab 140 mg subcutaneous injection every two weeks with oral placebo.
Group 2: Evolocumab 420 mg subcutaneous injection every month with oral placebo.
Group 3: Ezetimibe once daily with subcutaneous injection of placebo every two weeks.
Group 4: Ezetimibe once daily with subcutaneous injection of placebo every month.

Primary endpoints were the change in LDL-C levels from baseline to the mean of weeks 10 and 12. The mean baseline LDL-C level was 193 mg/dL. Primary safety endpoints included serious adverse events and elevations in hepatic enzymes and creatinine kinase.

At weeks 10 and 12, the LDL-C reductions from baseline were 56.1 percent in group 1, 55.3 percent in group 2, 36.9 percent in group 3, and 38.7 percent in group 4.[2] More than 75 percent of the evolocumab-treated patients versus less than 10 percent of the ezetimibe-treated patients were able to achieve LDL-C levels of less than 100 mg/dL.

Additionally, this study did not find any significant elevations in liver enzyme tests or creatinine kinase levels.[2] Adverse events leading to treatment discontinuation occurred in 8 percent of evolocumab treated patients and 13 percent of ezetimibe treated patients. Only 6 percent of reported adverse events were considered serious. Myalgia was reported in 8 percent of evolocumab treated patients and 18 percent of ezetimibe treated patients. Patients taking low dose statins were more likely to report myalgia.

RedUction of LDL-C with PCSK9 InhibiTion in HEteRozygous Familial HyperchOlesteRolemia Disorder (RUTHERFORD-2) evaluated the effects of PCSK9 inhibition with evolocumab in subjects with HeFH.[16] All 331 patients had a clinical diagnosis of HeFH, had been on a statin with or without other lipid-lowering therapy for at least 4 weeks prior to the study and had a fasting LDL-C concentration of 2.6 mmol/L (100 mg/dl) or higher. The dosing was similar to the GAUSS-2 trial, except evolocumab was compared to placebo alone as shown in the following groups:

Group 1: Evolocumab 140 mg subcutaneous injection every two weeks.
Group 2: Evolocumab 420 mg subcutaneous injection every month.
Group 3: Subcutaneous injection of placebo every two weeks.
Group 4: Subcutaneous injection of placebo every month.

The primary endpoints were percentage change in plasma LDL-C from baseline to the mean of weeks 10 and 12, and to week 12. At the mean of weeks 10 and 12, patients in group 1 saw a mean reduction in LDL-C of 60.2 percent ($p < 0.0001$). Group 2 saw a mean reduction of LDL-C levels of 65.6 percent ($p<0.0001$). Also, rates of adverse events were similar to those seen in previous studies of evolocumab. Investigators did not see any serious adverse events that led to discontinuation of the study drug.

Evolocumab received additional approval for use in HoFH due to results from Trial Evaluating PCSK9 Antibody in Subjects with LDL-C Receptor Abnormalities (TESLA).[6] The ongoing trial Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) will provide additional information regarding the long-term efficacy of evolocumab plus statin therapy, and its overall impact on cardiovascular risks.[17]

Impact on Healthcare

Long-term data on the effects of PCSK9 inhibitors is several years away, but there is reason to believe that lowering patient LDL-C levels will improve a broad range of cardiovascular outcomes. Despite increasing research in the area, high cholesterol remains one of the largest nationwide health concerns with reports as recent as 2010 estimating that nearly 57 million adults in the United States have hypercholesterolemia.[18] The PCSK9 inhibitors will likely serve as efficacious adjuncts to statin therapy for those with FH or ASCVD. Furthermore, these drugs may potentially be useful as monotherapy for patients who cannot use or tolerate statins. While some patients may be deterred by having to inject the medication, these agents are proposed as high-compliance formulations. Two administrations per month from autoinjectors or prefilled syringes may be sufficient for therapy.[19,20]

Yet, there are numerous challenges healthcare professionals may face as they try to provide these medications to their patients. One of the greatest barriers to accessing PCSK9 inhibitors is cost. Upon approval of alirocumab, Sanofi-Regeneron announced a wholesale acquisition cost (WAC) of $40 a day, or $14,600 a year.[5,19] Subsequent approval of the competitor, evolocumab, was projected to considerably reduce the price of alirocumab, but Amgen announced the WAC at $14,100 a year.[20] Although the WAC does not include discounts or rebates, and serves merely as an estimate of the manufacturer's list price, each drug has entered the market well beyond its projected annual costs of $7,000 to $12,000.[19] Pharmacy benefit managers note that unlike many monoclonal antibodies used for terminal or curable diseases, PCSK9 inhibitors are currently indicated for indefinite use, and future pending studies could see routine use as a replacement for statins.[20] Approximately 71 million Americans at least 20 years of age have LDL-C levels that are borderline high or greater (>130 mg/dL).[18] Millions more have a history of coronary artery disease or previous cardiac event, suggesting that a wide range of patients beyond those with FH and ASCVD may benefit from PCSK9 inhibitors. Therefore, high healthcare costs may be a consequence of these medications if prices remain elevated.

Role of the Pharmacist

With the emergence of PCSK9 inhibitors, pharmacists have many opportunities for patient education. Patients prescribed these medications should be educated on proper aseptic and subcutaneous injection technique and disposal of used drug delivery devices. The most common adverse events leading to discontinuation in clinical trials included general allergic reactions, elevated liver enzymes and neurocognitive events. Other minor side effects include pain or irritation at the site of injection as well as flu-like symptoms. Patients should be counseled that rotating injection sites may help reduce skin irritation. As with all monoclonal antibodies, there is a potential for immunogenicity. Praluent® (alirocumab) and Repatha® (evolocumab) syringes should be stored under refrigeration and allowed to warm at room temperature approximately 30 minutes before use.[21,22] All storage, packaging and patient information provided by the manufacturers should be closely followed.

Additionally, pharmacy benefit managers that pay for these high-priced pharmaceuticals want evidence of efficacy and patient compliance to justify the use of PCSK9 inhibitors. They will likely require regular patient follow-up visits with

their prescriber and routine monitoring to determine baseline LDL-C levels. Pharmacists can assist patients in managing trips to multiple physicians, adherence to a list of medications and maintaining necessary lifestyle modifications. Engaging patients in comprehensive medication reviews and medication therapy management services will further improve adherence rates and overall patient outcomes.[23]

Patient assistance programs are currently available for those seeking financial support to cover the costs of these medications. Pharmacists can help patients acquire this information online at www.praluenthcp.com and www.repathahcp.com or by calling the support phone lines listed on each website.

Conclusion

The PCSK9 Inhibitors are a novel and highly efficacious class of lipid-lowering medications. These monoclonal antibodies facilitate the removal of LDL-C from the blood and have demonstrated superior changes from baseline compared to both placebo and standard lipid-lowering therapy. Neither alirocumab nor evolocumab are approved as monotherapy or first-line therapy, and trials on long-term cardiovascular outcomes are ongoing. While they have been on the market for only a few months, there is already much debate regarding the high financial costs and potential ramifications of these increasingly prescribed drugs. Despite this, the PCSK9 inhibitors present a new and efficacious pharmacotherapeutic option for patients with hypercholesterolemia.

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Assessment Questions

1. To what does proprotein convertase subtilisin/kexin type 9 bind?
    A. Epidermal growth factor domain A
    B. Low density lipoprotein cholesterol
    C. Hepatocyte membrane
    D. Apolipoprotein B-100

2. Inhibition of proprotein convertase subtilisin/kexin type 9 leads to increased recycling of _____?
    A. cholesterol
    B. triglycerides
    C. low density lipoprotein receptor
    D. hepatocytes

3. Alirocumab (Praluent®) is FDA approved to treat which conditions?
    A. Familial hypercholesterolemia
    B. Atherosclerotic cardiovascular disease
    C. Hypertension
    D. Both A and B

4. What is an additional approved indication for evolocumab (Repatha®)?
    A. Homozygous Familial Hypercholesterolemia
    B. Heterozygous Familial Hypercholesterolemia
    C. Clinical atherosclerotic cardiovascular disease
    D. Monotherapy treatment of hypercholesterolemia

5. What new information not addressed in completed clinical trials of PCSK9 inhibitors will be provided by the FOURIER and ODYSSEY OUTCOMES trials?
    A. Safety data
    B. Cardiovascular risk reduction data
    C. Efficacy of PCSK9 inhibitors with concomitant statin therapy
    D. Adverse effects when co-administered with ezetimibe

6. Which side effects were observed at a higher rate in the treatment group versus placebo group in the ODYSSEY LONG TERM trial?
    A. Myalgia and nausea
    B. Myalgia, neurocognitive effects and ophthalmologic events
    C. Injection site reactions, allergic reactions and GI upset
    D. Anaphylaxis requiring study discontinuation

7. Of the following options, which is the greatest barrier in preventing patient access to PCSK9 inhibitors?
    A. Compliance issues
    B. Lack of drug effectiveness data
    C. High medication costs
    D. Low product supply

8. Which of the following is an advantage to therapy with PCSK9 inhibitors?
    A. It is approved as monotherapy for patients with familial hypercholesterolemia.
    B. Dosing is once or twice monthly, which could improve adherence.
    C. Marked decreases in low density lipoprotein cholesterol for most patients.
    D. Both B and C.

9. What is a concern associated with long-term administration of monoclonal antibodies such as alirocumab (Praluent®) and evolocumab (Repatha®)?
    A. Immunogenicity
    B. A paradoxical increase in low density lipoprotein cholesterol
    C. Poor drug bioavailability
    D. Complex dosing regimens

10. Which of the following is an important step in the administration of alirocumab (Praluent®)?
    A. Keep injector pen frozen until ready to use.
    B. Patients should be counseled on proper intramuscular administration.
    C. Allow pen or syringe to warm at room temperature for 30 minutes prior to administration.
    D. Thoroughly shake the pen or syringe prior to use.

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Programmed Death Pathway Inhibition: Emerging Therapeutic Options for Treatment of Advanced or Refractory Cancers

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Abstract

The programmed death-1 (PD-1) pathway has a significant role in the promotion of immune tolerance. The PD-1 receptor ligands are normally expressed on various inactive immune cells. When cancer cells express these ligands, they are able to interact with active T and B lymphocytes to induce this tolerance. Nivolumab and pembrolizumab are two recently approved agents that act to disrupt this binding and facilitate an immune response against cancer cells. Numerous trials, including KEYNOTE-002 and CheckMate 063, have demonstrated the superior safety and efficacy of these drugs in patients with advanced or refractory cancers. Initially approved for the treatment of advanced or metastatic melanoma, both nivolumab (Opdivo®) and pembrolizumab (Keytruda®) have recently received expanded indications for the treatment of advanced squamous and non-squamous non-small cell lung cancer (NSCLC). However, both agents were granted accelerated approval and long-term studies evaluating their use are ongoing. Adverse drug events commonly associated with PD-1 inhibitors include fatigue, pruritus, decreased appetite and gastrointestinal disorders. More serious immune-mediated events such as hepatitis, colitis, hypophysitis, nephritis and thyroid disorders may also occur. The cost of therapy with anti-PD-1 drugs can reach upwards of $143,000 to $150,000 per year. Pharmacists should be familiar with current therapeutic recommendations regarding PD-1 targeted therapy. Pharmacists may also counsel patients on how to monitor for adverse reactions and common side effects associated with these medications.

Key Terms

Antibodies; Carcinoma; Immune Tolerance; Melanoma; Monoclonal; Non-small-cell-lung Cancer; Programmed Cell Death-1 Receptor

The PD-1 Pathway

The programmed death-1 (PD-1) pathway serves as a protection against immune-mediated damage to healthy tissues, particularly by promoting T-cell tolerance.[1] The PD-1 receptor is located on the extracellular surface of activated T and B lymphocytes. Two endogenous ligands are known to bind PD-1 receptors: programmed death-1 ligand 1 (PD-L1) and programmed death-1 ligand 2 (PD-L2).[2,3] The PD-L1 is expressed by resting T and B lymphocytes, dendritic cells and macrophages, while PD-L2 expression has been observed only on dendritic cells and macrophages. Both PD-L1 and PD-L2 bind to the same PD-1 receptors located on T and B lymphocytes. Resting cells that express PD-L1 and PD-L2 may increase extracellular expression of PD-L1 or PD-L2 upon cell activation. When one of the ligands binds to the PD-1 receptor on T-cells, the resulting interaction inhibits signaling of T-cell receptors, leading to decreased T-cell proliferation and decreased cytokine production, thereby decreasing the immune response.[4,5] This pathway is important for promoting peripheral T-cell tolerance to minimize destruction of healthy cells.[1]

Some forms of cancer cells are known to overexpress PD-L1 or PD-L2, including melanoma cells and carcinoma cells of the ovary, breast and lung.[6] The expression of the ligands PD-L1 or PD-L2 by cancer cells may contribute to tumor evasion of the immune system. Anti-PD-1 drugs, including nivolumab and pembrolizumab, inhibit the PD-1 pathway and allow the immune system to recognize the cancer cells.[4,5] Inhibition of the PD-1 pathway represents a new mechanism for anticancer treatment by inhibiting T-cell tolerance and stimulating the body's intrinsic immune responses to kill cancer cells.

Anti-PD-1 Drugs

Therapeutic Indications

The two anti-PD-1 drugs currently approved by the U.S. Food and Drug Administration (FDA), nivolumab (Opdivo®) and pembrolizumab (Keytruda®), are fully humanized monoclonal immunoglobulin G4 (IgG_4) antibodies.[4,5] Both nivolumab and pembrolizumab are approved to treat unresectable or metastatic melanoma in patients who have experienced progression of the disease after treatment with ipilimumab and, if positive for BRAF V600 mutation, a BRAF inhibitor.[4,5,7] Pembrolizumab was approved for melanoma treatment in September 2014, and nivolumab was approved for advanced melanoma in December 2014.[8,9] On Nov. 24, 2015, the indication of nivolumab was expanded to include its use as a first-line treatment for unresectable or metastatic melanoma in patients with BRAF V600 wild-type melanoma.[10] As a first-line melanoma treatment in these patients, nivolumab may be used as monotherapy or in combination with ipilimumab.[4,7] Both drugs were approved under the FDA's Accelerated Approval Program.[8,9] This program fast-tracks approval for agents that treat serious and life-threatening disease states when there is justified clinical data for drug efficacy. For both nivolumab and pembrolizumab, continued approval for the treatment of melanoma is still pending additional proof of clinical benefits in various ongoing and future clinical trials.[4,5]

Nivolumab and pembrolizumab are also FDA-approved to treat patients with metastatic non-small cell lung cancer (NSCLC) who have experienced disease progression during or after platinum-based chemotherapy.[4,5,11] Nivolumab was approved in March 2015 for squamous NSCLC, and its indication was further expanded on Oct. 9, 2015, to include non-squamous NSCLC.[12] Pembrolizumab was approved by the FDA for advanced NSCLC in October 2015.[13] Administration of pembrolizumab for advanced NSCLC requires the use

of an FDA-approved test to show that the tumor expresses PD-L1.[5] This diagnostic test, called the PD-L1 IHC 22C3 pharmDx test, is the first tool that is able to detect whether a non-small cell lung tumor expresses PD-L1.[14]

On Nov. 23, 2015, the FDA announced that nivolumab was approved as a treatment for renal cell carcinoma, the most common form of kidney cancer in adults.[15] Use of nivolumab for renal cell carcinoma is intended for patients who have previously received anti-angiogenesis therapy, a type of treatment that disrupts tumor-mediated formation of new vasculature.[4,15] Additional clinical trials are ongoing for recruiting patients to study the effectiveness of nivolumab and pembrolizumab in treating many different cancer types including acute myeloid leukemia, chronic lymphocytic leukemia, glioblastoma and gliosarcoma.[16,17] Another anti-PD-1 agent currently being studied, but not yet FDA-approved is pidilizumab, a humanized monoclonal immunoglobulin G1 (IgG_1) antibody.[18]

Mechanism of Action

Nivolumab and pembrolizumab are specific for the human PD-1 receptor.[4,5] The monoclonal antibodies bind to PD-1 receptors, mainly located on T-cells, and prevent the receptor from interacting with its ligands, PD-L1 and PD-L2. Since ligand binding usually functions to inhibit T-cell receptor signaling and promote tolerance, use of nivolumab or pembrolizumab to block the ligand-receptor interaction results in increased T-cell receptor signaling. As a result, T-cells are activated and are able to participate in an anti-tumor immune response to target and kill cancer cells.

For melanoma patients with a BRAF V600 mutation, a BRAF inhibitor is needed in addition to anti-PD-1 therapy.[4,5] BRAF is a gene that encodes for the protein BRAF, which is involved in the mitogen-activated protein kinase (MAPK) signaling pathway.[19] The MAPK pathway is a kinase cascade needed for regulation of cell growth, proliferation, differentiation and survival. The most common BRAF gene mutation occurs at codon 600 of the BRAF gene, and results in an amino acid change from a non-polar valine to a polar glutamine in the BRAF protein. This mutated protein causes the pathway to be constitutively activated, leading to uncontrolled cell growth and proliferation. BRAF inhibitors, such as vemurafenib, are administered to patients with this mutation in addition to other antineoplastic therapies.

Literature Review

Pembrolizumab

The KEYNOTE-002 randomized controlled trial compared pembrolizumab to chemotherapy for ipilumumab-refractory melanoma.[20] The study enrolled 540 patients who had failed ipilimumab treatment, and randomized them 1:1:1 to 2 mg/kg every three weeks, 10 mg/kg every three weeks or investigator-choice chemotherapy (paclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine or oral temozolomide). Patients continued treatment until signs of disease progression were evident. After nine months, 24 percent (95% confidence interval (CI): 17-31) of the pembrolizumab 2 mg/kg group were progression free, as well 29 percent (22-37) of the pembrolizumab 10 mg/kg group. In comparison with the chemotherapy group, only 8 percent (4-14) were progression free. The pembrolizumab groups also experienced fewer grade 3 to 4 treatment-related adverse effects than the chemotherapy group. Though limited, the most common adverse effects reported with pembrolizumab were fatigue, generalized edema, myalgia, hypopituitarism, colitis, diarrhea, decreased appetite, hyponatremia and pneumonitis (1% each). In the chemotherapy group, the most common grade 3 to 4 treatment-related adverse effects reported were anemia (5%), fatigue (5%), neutropenia (4%) and leukopenia (4%). The pembrolizumab groups also showed some improvement in quality of life compared to chemotherapy as measured from Quality of Life Questionnaire C30 scores from the European Organization for the Research and Treatment of Cancer.

The KEYNOTE-006 study, a phase 3 clinical study, examined the efficacy of pembrolizumab versus ipilimumab in treating advanced melanoma.[21] The 834 patients enrolled were assigned to receive either pembrolizumab 10 mg/kg every two weeks, pembrolizumab 10 mg/kg every three weeks or four doses of ipilimumab 3 mg/kg given at three-week intervals. The overall progression free survival rates were greater for the pembrolizumab groups than for the ipilimumab group. The hazard ratio favoring pembrolizumab 10 mg/kg every two weeks over ipilimumab was 0.58 (95% CI: 0.46-0.72), and the hazard ratio favoring pembrolizumab 10 mg/kg every three weeks over ipilimumab was 0.58 (0.47-0.72). The pembrolizumab groups also experienced fewer treatment-related adverse effects. Grade 3 to 5 treatment-related adverse effects occurred in 13.3 percent, 10.1 percent, and 19.9 percent in the pembrolizumab every two weeks, pembrolizumab every three weeks and ipilimumab groups, respectively. The most common adverse events reported in the pembrolizumab groups were fatigue (20.9% and 19.1% in the two and three week groups, respectively), diarrhea (16.9% and 14.4%), rash (14.7% and 13.4%) and pruritus (14.4% and 14.1%). In the ipilimumab group, the reported adverse events were pruritus (25.4%), diarrhea (22.7%), fatigue (15.2%) and rash (14.5%).

Nivolumab

The efficacy of nivolumab in treating refractory squamous NSCLC was studied in the CheckMate 063 trial.[22] The investigators wanted to determine nivolumab's effect specifically for squamous NSCLC because this subtype has a very poor prognosis, and new potential treatments are often designed for non-squamous subtypes. Nivolumab 3 mg/kg every two weeks was administered to 117 patients with stage IIIB or IV squamous NSCLC until the disease progressed or until patients experienced unacceptable toxic effects. Of the 117 patients, 17 had a confirmed response and 11 showed a tumor reduction of at least 50 percent. Grade 3 to 4 treatment-related adverse events, more commonly fatigue, pneumonitis and diarrhea, were reported in 17 percent of patients.

Nivolumab was also compared to chemotherapy in patients with advanced melanoma in the CheckMate 037 trial.[23] A total of 405 patients with unresectable stage IIIC or IV meta-

static melanoma were randomized 2:1 to receive nivolumab 3 mg/kg every two weeks or investigator's choice of chemotherapy (dacarbazine or paclitaxel with carboplatin). The progression free survival at six months was 48 percent (95% CI: 38-56) and 34 percent (18-51) in the nivolumab and chemotherapy groups, respectively. Nine percent of nivolumab patients experienced a treatment-related adverse event of grade 3 to 4 as compared with 31 percent of the chemotherapy group. The most common grade 3 to 4 events reported in the nivolumab group were increased lipase, increased alanine aminotransferase, fatigue and anemia (1% each).

New Drugs on the Horizon

In a study conducted by Westin and associates, another monoclonal PD-1 inhibitor, pidilizumab, was examined in combination with the monoclonal ritixumab for treating follicular lymphoma.[24] Patients who had grade 1 to 2 follicular lymphoma and ritixumab-sensitive disease were administered 3 mg/kg of pidilizumab every four weeks for four infusions and 375 mg/m^2 of ritixumab weekly for four weeks, starting 17 days after the first pidilizumab infusion. Of the 29 patients enrolled, 25 (86%) experienced tumor regression. In addition, no grade 3 to 4 treatment-related adverse effects were reported. Although pidilizumab showed success in this trial, it is still awaiting approval from the FDA.

Adverse Drug Events

Adverse drug events commonly associated with PD-1 inhibitors include fatigue, pruritus, decreased appetite and gastrointestinal disorders.[4,5] The most common side effects associated with pembrolizumab and nivolumab plus ipilimumab during treatment of melanoma can be seen in Table 1.[25,26] Side effects from use of nivolumab in advanced squamous NSCLC include: cough, nausea, constipation, fatigue, muscle pain, dyspnea and decreased appetite.[4] Rare but serious side effects may result in the discontinuation of pembrolizumab and nivolumab. These side effects include: grade 3 or 4 pneumonitis, nephritis, infusion-related reactions, a five time increase in baseline AST and ALT levels and a bilirubin level greater than three times baseline.[4,5] Nivolumab should also be discontinued in patients with signs of hypophysitis, adrenal insufficiency, life-threatening rash and encephalitis.[4]

Anti-PD-1 drug actions on the immune system can lead to complications such as immune-mediated hepatitis, colitis, hypophysitis, nephritis and thyroid disorders. The development of these immune-mediated conditions may warrant the use of corticosteroids, with therapy ranging from three days up to 12 weeks.[4,5] In a phase I cohort study, Weber et al., evaluated the safety and tolerability of nivolumab in both ipilimumab-naïve and -refractory patients. Patients were started at a 60 mg prednisone dose and were tapered down to treat grade 3 bilateral optic neuritis, a dose-limiting toxicity. Two patients discontinued treatment of nivolumab due to high-grade fever and pneumonitis, resulting in a 60 mg and a 120 mg prednisone taper, respectively. Sixty-four patients were enrolled in the ipilimumab-refractory cohort, and one patient experienced intense rash, which resolved with a six-week prednisone taper starting from 60 mg.[27]

Currently, anti-PD-1 medications are not approved in pregnancy or breast-feeding. Endogenous PD-1 inhibitors are immunoglobulin IgG4, which crosses the placenta directly from the mother.[4] Immunoglobulin G (IgG) is the only member of the immunoglobulin class to cross the placenta, and therefore, is present in high concentration in newborns.[28] This implies that anti-PD-1 medications would also have the same effect, warranting caution with use in pregnancy. Although pembrolizumab has not undergone clinical animal reproduction studies with a focus on fetal development, nivolumab has been evaluated in cynomolgus monkeys. Nivolumab is currently listed as pregnancy category C and was found to cause fetal harm, higher incidence of stillbirth, premature delivery, infant mortality and abortion of the fetus.[4,5]

In recent studies, pembrolizumab has demonstrated a superior safety profile relative to previous chemotherapy treatments for advanced melanoma. A randomized controlled phase 3 study conducted by Robert et al., compared pembrolizumab and ipilimumab. Overall, ipilimumab was shown to cause a higher percentage of high-grade adverse events, which occurred in 19.9 percent of patients. Pembrolizumab was shown to have a more gradual onset of serious adverse events compared to ipilimumab. Additionally, the rate of permanent removal from the study was lower in pembroliza mab-treated patients.[21]

Table 1. Anti-PD-1 Agents Most Frequent Adverse Drug Events.[25,26]

Agent	Most Frequent Adverse Drug Events				
Pembrolizumab	Fatigue 19.4%	Pruritis 10.7%	Decreased Appetite 10.5%	Rash 9.7%	Arthralgia 9.1%
Nivolumab plus Ipilimumab	Diarrhea 45%	Rash 41%	Fatigue 39%	Pruritis 35%	Colitis 23%

Table 1 totals: obtained from pembrolizumab for non-small-cell lung cancer based on 495 treated patients from Garon et al., and nivolumab and ipilimumab vs. ipilimumab in untreated melanoma based on 94 patients from Postow et al.

Cost Implication

A barrier of any new medication, especially monoclonal antibodies, is cost. On average, pembrolizumab will cost $12,500 per cycle of treatment. Treatment can range from two to 12 months, resulting in a cost of over $150,000 for many patients. A year of treatment for nivolumab can reach $143,000.[29] Before the initiation of treatment, patients must undergo genetic testing as well. The FDA-approved genetic test known as the Cobas® 4800 test used to detect the BRAF V600 mutation gene represents an additional cost.[30]

Pharmacists' Role

Recommendations

As with any new drugs, pharmacists bear the responsibility as drug experts to understand the drugs well enough to be able to educate and advise not only patients, but also prescribers on their appropriate use in therapy. The guidelines provided by the National Comprehensive Cancer Network (NCCN) are helpful when trying to decide the best course of treatment for cancers. The following is a summary of NCCN recommendations that pharmacists may consider during nivolumab and pembrolizumab therapy in relation to comparable therapies.

According to the NCCN guidelines for the treatment of metastatic or unresectable melanoma, anti-PD-1 monotherapy (pembrolizumab or nivolumab) is an appropriate first-line therapy for patients with a BRAF V600 wild-type mutation.[11] Alternative first-line therapies for metastatic or unresectable melanoma include nivolumab/ipilimumab, dabrafenib/trametinib, vemurafenib or dabrafenib. Nivolumab or pembrolizumab can also be used as second-line therapy in the case of treatment failure or disease progression after trial with another first-line treatment, as long as the patient has a performance status of 0 to 2.[21]

The NCCN NSCLC guidelines state that nivolumab and pembrolizumab can be used as subsequent therapy for patients with a performance scale of 0 to 2 following a progression of the disease after first-line therapies have been attempted for large cell adenocarcinoma and squamous cell carcinoma.[11] First-line therapies for NSCLC include doublet chemotherapy, bevacizumab or chemotherapy based on a patient's performance score.

For kidney cancer, nivolumab is also indicated as subsequent therapy in the treatment of renal cell carcinoma specifically in the case of disease relapse and stage IV or unresectable renal carcinoma according to the NCCN guidelines.[31] After first-line therapy such as participation in a clinical trial, sunitinub, temsirolimus, bevacizumab/IFN, pazopanib, high dose IL-2, axitinib, or sorafenib, nivolumab may be used if a patient requires follow-up therapy.

Patient Education

Pharmacists should advise patients to contact their healthcare provider if they experience adverse reactions such as a fever of 100.4° F or higher, difficulty breathing, or if they exhibit any signs of an allergic reaction such as hives, red or blistered skin, swelling of the mouth or tongue or tightness in the chest.[32] Pharmacists should also inform patients of common side effects such as diarrhea, nausea, vomiting, fatigue and dizziness. For these reasons, patients should be instructed to drive or operate machinery with caution during treatment periods. While taking anti-PD-1 medications it is pertinent that patients are aware of the embryonic hazards of these medications, and utilize barrier methods such as condoms for at least five months after discontinuation. Pharmacists should also encourage patients to drink plenty of fluids, wash their hands often, eat small frequent meals and rest during treatment with these medications.

Conclusion

The PD-1 pathway plays an important role in the normal functioning of the immune system. This pathway also presents a means of treatment against cancer cells expressing the PD-1 ligands, especially in tumors that fail to fully respond to traditional treatments. Monoclonal antibodies directed against the PD-1 receptor are able to elicit an immune response against such cells. Anti-PD-1 drugs, nivolumab (Opdivo®) and pembrolizumab (Keytruda®), were granted accelerated approval by the FDA. Both drugs are indicated in treatment of advanced melanoma and NSCLC, as well as tumors refractory to treatment that have BRAF mutations. Trials are ongoing to determine long-term efficacy of these agents, as well as exploring additional cancer types. Further research into anti-PD-1 drugs has already produced at least one new member of this class, which shows promising results in early clinical trials. As more trial data becomes available, and nivolumab and pembrolizumab continue to receive FDA approval for new indications, pharmacists in all practice settings should be aware of the appropriate use and adverse effects of anti-PD-1 drugs.

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Improving Healthcare Costs and Patient Outcomes Across Healthcare Professions

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Abstract
Healthcare professionals must be aware of the importance of preventive medicine and the responsibility they have in contributing to it. There are three levels of preventive medicine that a healthcare professional can provide based on the patient population that is receiving care and the goals of the particular service. Preventive medicine has the ability to improve both overall healthcare costs and have a positive impact on a patient's quality of life. All healthcare professionals have the potential to fulfill a role in each level of preventive medicine, and should understand the role of each member of the healthcare team, to ensure that preventive medicine can be effectively provided.

Key Terms
Healthcare Costs; Individualized; Patient Care Team; Population-based; Preventive Measures; Preventive Medicine; Quality of Life; Screening

Introduction
The importance of preventive medicine in patient health is often overlooked. In some cases, medical concerns can be prevented by changing lifestyle habits, limiting exposure to risk or catching disease states at early stages via routine screenings.[1] Medical professionals must work together to provide education and guidance for patients in order to prevent major events from occurring.

Preventive medicine leads to an improved quality of life, early detection of disease and increased direct and indirect healthcare cost savings. Emphasizing the importance of all levels of preventive medicine affects patients, society and overall healthcare costs. Pharmacists, exercise physiologists and other healthcare professionals can perform vital roles in patient interventions. The routine patient interactions in all stages of health provide unique opportunities to ensure appropriate screenings and lifestyle choices are taking place. Therefore, there are numerous benefits of preventive medicine which include opportunities for patient and healthcare savings.

Levels of Preventive Medicine
Preventive medicine is a broad topic that can be subdivided into three different levels: primary prevention, secondary prevention and tertiary prevention. These levels are categorized by the target population and associated with specific goals.

Primary prevention includes the total population with a focus on healthy individuals.[2] The goals of primary prevention are to limit the rate of a disease by reducing its risk in the total population and to promote overall good health. Primary prevention can be achieved by lifestyle modifications, such as consuming a healthier diet, administering vaccinations or making positive environmental changes.[1]

Secondary prevention targets asymptomatic individuals who either have high risk factors or are in the early stages of a particular disease state.[2] The main goal of this level is to reduce the progression of the disease. This is accomplished through methods of early detection (e.g., hypertension screenings).[1]

Tertiary prevention focuses on patients with an established disease state and the goals are to limit the impact of the disease and improve the patient's quality of life after diagnosis.[2] Examples include rehabilitation after a stroke or injury and prescribing proper medications for chronic disease states.

Healthcare Cost Improvements
In addition to improving patients' quality of life, one of the best measures to explain the impact of preventive medicine is to examine the costs associated with and saved from each prevention measure.[3] Preventive care that decreases costs is referred to as cost savings. If an intervention has benefits that extensively outweigh the associated costs, the measure is referred to as cost-effective, regardless of whether it saves money. Often, cost-savings interventions slow the growth of healthcare costs.

To simplify, an intervention's cost and the health impact it delivers is summarized in the cost-effectiveness ratio which is equal to the intervention's incremental cost divided by its incremental health benefits.[3] A small cost-effectiveness ratio favors intervention, while a large ratio is unfavorable due to high incremental costs compared to the incremental health benefits.

Health benefits are often expressed in the number of quality adjusted life years (QALYs) saved.[3] One year of perfect health is represented by one QALY, whereas a year with an adverse condition is worth between zero and one QALY. Economists disagree on the value contained in a QALY; it is usually estimated between $50,000 and $100,000, though it has been argued that one QALY could be worth up to $430,000.

Targeting high risk populations for preventive measures typically improves cost-effectiveness by increasing the proportion of individuals in good health.[3] High risk populations usually encounter more health problems, which costs more money. Therefore, targeting them for preventive measures saves more money compared to non-high risk populations in the long run. How cost-effective a measure is also depends

on what it is compared with and the assumptions made about how people who develop the targeted disease will be treated. For example, comparing a preventive measure to no intervention will show a greater cost-effectiveness ratio than comparing one preventive measure to another. Also, the availability of preventive treatments can the cost-effectiveness of a measure. However, preventive measures can cause people to live longer, which can in turn increase lifetime healthcare costs because people have more time to develop additional illnesses.

There are a variety of preventive measures, all of which have varying cost-effectiveness ratios.[3] An example of a secondary prevention measure is screening for diabetes in patients with hypertension, which has been shown to be a cost-effective preventive health measure. When screening 75- and 35-year-olds with hypertension, the cost-effectiveness ratio is $38,000/QALY and $87,000/QALY, respectively. This compares to all 35-year-olds who have a cost-effectiveness ratio when screened for diabetes of $130,000/QALY. This shows a substantial savings for diabetes screenings for hypertension patients because a lower cost-effectiveness ratio is preferred. Another example of a cost-effective secondary prevention is screening for hypertension in any adult which has an estimated cost-effectiveness range of $29,000/QALY to $38,000/QALY. An example of a primary preventive measure is counseling adult and adolescent women to use calcium supplements to prevent bone fracture. This shows a cost-effectiveness ratio of between $17,000/QALY and $42,000/QALY. Additionally, the frequency of the intervention can have an impact on cost-effectiveness. For example, a colonoscopy every three years is estimated at a cost-effectiveness ratio of $22,000/QALY while every 10 years is approximately $11,000 to $27,000.

Health Benefits

While preventive medicine is associated with significant healthcare cost improvements, it has significant impact on improving overall health. Chronic diseases, such as cardiovascular disease (CVD), cancer, chronic respiratory disease and diabetes, are the primary cause of death in almost all countries worldwide, resulting in about 36 million deaths annually.[2] With the exception of the African region, chronic noncommunicable diseases have been found to cause significantly more deaths than communicable diseases. Furthermore, chronic, noncommunicable diseases occur more commonly in low- and middle-income countries as opposed to high-income countries; 80 percent of deaths due to chronic diseases occur in low- and middle-income countries while 20 percent occur in high-income countries.

There are two approaches that are utilized to implement prevention strategies: an individual-based approach and a population-based approach.[4] Individual-based prevention

Table 1. Trends in primary and secondary intervention and their potential to save lives.[5]

	Population analyzed	Current % engaged in given activity	Lives saved annually if current % increased to 90%
Daily aspirin use	Males 40+ Females 50+ (Reported in 2005)	40%	45,000
Smoking cessation advice and help quitting	Adult smokers (Reported in 2005)	28%	42,000
Colorectal cancer screening	Adults 50+ (Reported in 2005)	48%	14,000
Influenza vaccination	Adults 50+ (Reported in 2005)	37%	12,000
Pneumococcal vaccination	Adults 65+ (Reported in 2005)	54%	800
Cervical cancer screening	Females 18-64 (Screened between 2002-2005)	83%	620
Cholesterol screening	Males 35+ Females 45+ (Screened between 1998-2003)	79%	2,450
Breast cancer screening	Females 40+ (Screened between 2003-2005)	67%	3,700
Chlamydia screening	Females 16-25 (Screened in 2005)	40%	30,000

*All statistics above extrapolated according to National Health Interview Survey done by the National Center for Health Statistics within the CDC (Partnership for Prevention. Preventive care: a national profile on use, disparities and health benefits. Washington, DC: Partnership for Prevention; 2007.)

strategies focus on high-risk or susceptible individuals by providing direct intervention. In contrast, population-based prevention strives to control determinants of health in the population as a whole by promoting healthy behavior to lower the overall risk within a population.

Preventive measures that are individual-based are most effective for people with the greatest risk of developing a specific disease.[2] The main disadvantage of a personalized approach is that it usually requires screening programs to identify high-risk groups, which are often difficult and expensive. Screening programs do not serve to establish diagnoses, but are used to identify the presence or absence of an identified risk factor. However, such information is very valuable in that identified risk factors make individuals aware of their likelihood of developing a given disease. This encourages monitoring for early diagnosis and increases the chance of a full recovery. As a result, this correlates with improved quality of life and increased life expectancy because of decreased morbidity and mortality.

Health screenings provide an opportunity to identify disease states at a stage that can be addressed by lifestyle modifications alone. Healthcare professionals can influence the course of a patient's disease development through monitoring values such as blood pressure. Heart disease is the number one cause of death, regardless of gender, resulting in over 610,000 deaths in the United States each year.[6] An indicator of heart health is blood pressure, a value that is easily measured. Hypertension is indicated by a reading greater than 140/90 mmHg, and often requires two or more types of antihypertensive medications to keep blood pressure within the normal range.[7] Preventive screenings can identify patients who are at risk for developing hypertension, which allows healthcare professionals to advise diet and exercise changes to positively affect these values. Small lifestyle changes can have a large impact overall, for instance, losing 10 pounds will show reductions in a patient's blood pressure.[8] A dose-response relationship has also been identified between physical activity and health. As levels of activity increase, the rates of premature mortality, cardiovascular disease, hypertension, type 2 diabetes, obesity and many other disease states decrease.[9] Identifying patients at risk for high blood pressure and implementing diet and exercise changes may prevent the need for future medications and decrease healthcare costs. Lifestyle changes can lower a patient's chance of developing heart disease, stroke and kidney failure; helping to increase their quality and length of life.[8] Some other benefits of lifestyle changes include improved cognitive function, prevention of limitations and a higher sense of well-being.[9] Primary intervention has the greatest impact on prevention of disease development, but lifestyle changes after risk of a disease state is identified are also important. Secondary interventions can help prevent the progression of a disease, and tertiary interventions reduce the chances of recurrence. As a result, patients will be able to have more independence and live more satisfied lives when they are in good health. As medical professionals, our help in identifying risks and support through lifestyle changes can save lives.

Combining individual-based preventive actions with a population-based strategy has been shown to be a more effective approach than solely focusing on high-risk individuals.[2] This principle is based on improving the health of individuals as a means of improving the health of general populations. This is especially applicable to communicable diseases, which are responsible for 14.2 million deaths annually, and are most prevalent in low-income countries. The most widespread communicable diseases include human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis and malaria. One of the most effective preventive measures in a population-based strategy includes immunizations which serve as a powerful tool in the management and control of infectious diseases. Systematic immunization programs have been proven to be very effective in controlling transmission. An example of this is the eradication of smallpox. In 1967, 10 to 15 million new cases of smallpox were reported annually in 31 countries while 2 million deaths occurred annually. As a result, the World Health Organization (WHO) established a 10 year eradication program for smallpox. After effective vaccination, this disease was declared eradicated on May 8, 1980. On the other hand, HIV/AIDS has no definitive treatment even though it is one of the most destructive infectious disease epidemics in recorded history. In this instance, preventive action stresses identifying risk factors and social determinants, as well as promoting safe practices to control the spread of the disease.

Role of Healthcare Professionals

There are many roles that healthcare providers can fulfill in preventive medicine. It is important that each professional is aware of their own role and the role of other healthcare professionals due to the nature of the work across disciplines and in interprofessional teams.[10] Each healthcare professional has a different skill set that allows them to perform a unique role in the three levels of preventive medicine. Every member of the healthcare team must work together to provide the best care available for all patients, especially for the prevention of chronic healthcare concerns and costs.

Roles in Primary Prevention

Primary prevention can be accomplished through a variety of services and healthcare providers. Pharmacists are very accessible healthcare professionals in the community which allows them to have a large opportunity to provide preventive services.[11] One primary preventive medicine service is education on various over-the-counter products that patients seek when going to a pharmacy. A study showed that some of the top ranked preventive services include educating men over the age of 40 and women over the age of 50 on the use of aspirin to prevent heart disease, and counseling patients on the importance of smoking cessation and helping them through the process of quitting.[5] Rankings are based on clinically preventable burden (CPB), or how likely providing the service is to prevent a disease state or premature death and promote cost-effectiveness. Educating women of childbearing age on the use of folic acid and elderly women about calcium supplementation are also in the rankings of preventive services that pharmacists can focus on to help improve the quality of life for patients. Pharmacists can also provide a

cost-effective, primary preventive service through administering immunizations to prevent the spread of diseases. The importance of pharmacists in this role has been noticed. In Ohio, House Bill 394 was passed in the spring of 2015, which lowered the age that a pharmacist or pharmacy intern can administer a Centers for Disease Control and Prevention (CDC) recommended vaccine to patients seven years old and older.[12] While pharmacists are one of the most accessible healthcare providers to administer vaccines, they can also be provided by other healthcare professionals including doctors and nurses.

Another primary preventive service that can benefit patients is supporting lifestyle modifications such as a healthier diet and participation in an exercise program. Physical activity has been found to reduce the rates of premature mortality, cardiovascular disease, hypertension, obesity, functional health and many other disease states.[9] Exercise physiologists are in a unique position to develop and guide a patient through the implementation of an exercise program. After the identification of a need for an exercise prescription, a doctor will clear the patient for participation depending on their risk stratification. While some risks are associated with exercise, the benefits of exercise for patients at all levels of preventive medicine are extensive. Benefits include lower incidence rates of cardiovascular disease, stroke, type 2 diabetes mellitus, osteoporotic fractures and cancers of the colon and breast. Patient education is the most important role an exercise physiologist has throughout program development and progression. Individual-based prevention embodies exercise programming. Each prescription is created with respect to the client's goals, disease states and capabilities according to the criteria found in the American College of Sports Medicine Guidelines for Exercise Testing and Prescription.[9] Inclusion of exercise in a patient's healthcare plan can prevent a deviation from optimal health, including the prevention of an initial cardiovascular event. Overseeing the patient's program and helping them prevent disease state development is an important role exercise physiologists play in primary prevention.

An additional primary preventive service that healthcare professionals can fulfill is being a legal advocate and impacting public policy. As drug experts, pharmacists should have a large impact on legislation that affects healthcare and medications. Pharmacists may be employed by organizations, such as the U.S. Food and Drug Administration, that help pass laws concerning drugs.[11] There are many other ways that a pharmacist can become involved in advocacy, such as through their local board of health or state board of pharmacy. It has also been noted that pharmacists in underserved areas have become proponents for various environmental programs including water pollution control and sanitation. Again, many other healthcare professionals can be legal advocates for many different causes. Dentists have taken public policy advocacy roles to help with water fluoridation efforts to improve oral health.[10] Also, nurses who have graduate-level public health training can help plan and implement public health initiatives on the local, state and national level.

Roles in Secondary Prevention

Secondary preventive medicine focuses on patients who are at high risk for a particular disease and can be achieved through screenings to detect these diseases in their early stages. These screenings can be completed by various healthcare professionals. One of the main focuses of primary care physicians is to provide preventive screening services to patients.[10] Dentists also provide secondary preventive medicine by checking their patients for dental caries and oral cancer. Pharmacists can also provide many screening services such as hypertension screenings.[5] Some patients identified by these screenings will benefit from professional assistance in making the lifestyle changes necessary to prevent the development of a disease. For example, exercise physiologists can help patients understand their own risks and the benefits of physical activity, while helping them increase their sense of self-efficacy.[9] Including high-risk patients in exercise programs can reduce the risk of symptom development of chronic diseases. An exercise physiologist must act as a patient advocate to inform, develop and motivate patients through an exercise program to help them improve their level of risk.

Roles in Tertiary Prevention

Tertiary prevention is important in limiting the impact of a disease on a patient's quality of life.[2] While doctors diagnose and prescribe medications for chronic diseases, pharmacists educate patients on how to most efficiently manage their medication regimen to control their disease states.[10] One example would be a patient diagnosed with diabetes and prescribed medication by a physician, In addition, this patient is taught by a pharmacist on how to check their blood sugar and use their medications properly to best control their diabetes. Community pharmacies that have incorporated diabetes management programs have shown to increase patient satisfaction while also reducing overall healthcare costs. Patients diagnosed with disease states will collaborate with their healthcare team to develop the best treatment plan for them. In combination with drug intervention, exercise is beneficial to this population as well. Exercise programming can change a patient's prognosis, including improving glucose tolerance, increased insulin sensitivity and improvement in cardiovascular risk factors.[9] These advancements can reduce a patient's need for exogenous insulin and combat the need for weight loss and maintenance in these patients.

Conclusion

Preventive medicine plays a crucial role in reducing healthcare costs. Through routine screenings and immunizations, medical professionals can support healthy lifestyle choices. Intervention during good health can prevent the onset of most disease states, and has the greatest impact on patients' lives. Secondary and tertiary interventions also provide opportunities to increase a patient's overall health and sense of well-being. Prevention of chronic disease states can eliminate the need for some medications and future hospital stays to reduce the amount of money spent on healthcare. Exercise is also a key component of any healthcare plan, and requires patient effort and professional support. Every mem-

ber of the healthcare team must participate in methods of prevention. As a result, the opportunity to influence patients through preventive medicine can last a lifetime and may extend a patient's length of life.

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The Effect of CYP3A5 Polymorphism on Kidney Transplant Recipients Given Tacrolimus

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Abstract
Tacrolimus, an immunosuppressant agent indicated for organ transplants, is commonly administered to reduce the risk of renal graft rejection in patients with chronic kidney disease (CKD) and end stage renal disease (ESRD). Due to its narrow therapeutic index and high inter-patient variability, studies have suggested that CYP3A5-based dosing provides specialized regimens which may significantly improve the chances of achieving therapeutic concentrations. According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendations, extensive (CYP3A5*1/*1) and intermediate metabolizers (CYP3A5*1/*3) require a higher initial dose while poor metabolizers (CYP3A5*3/*3) require a lower initial dose in order to achieve target tacrolimus concentrations. Studies concluded that CYP3A5 expressers present a greater risk for chronic nephrotoxicity and acute transplant rejection, supporting the need to closely monitor patients for severe adverse events. Further trials considering CYP3A5 polymorphisms are needed to determine whether this genotype dosing improves clinical outcomes, which includes reducing rejection and toxicity, before testing can be recommended.

Key Terms
Cytochrome P-450; CYP3A; Genotype; Graft Rejection; Immunosuppressive Agents; Chronic Kidney Failure; Pharmacogenetics; Chronic Renal Insufficiency; Tacrolimus

Introduction

According to the Centers for Disease Control and Prevention (CDC), chronic kidney disease (CKD) is a top 10 cause of mortality in the United States, and approximately 20 million American adults have some level of CKD.[1] While the prevalence of CKD is highest in patients older than 60 years (24.5%), CKD is burdensome and costly to patients, healthcare providers and payers.[2] Chronic kidney disease can potentially progress to end stage renal disease (ESRD), resulting in irreversible kidney damage with significantly impaired ability to properly regulate fluid balance, waste excretion, acid-base chemistry, blood pressure and other metabolic functions. According to the 2014 United States Renal Data System annual data report, in 2012 there were 636,905 prevalent cases of ESRD in the United States, which includes 114,813 new cases. The highest rates of ESRD occurred in populations greater than 45 years old and in the Ohio/Mississippi Valley.

Currently, there are three treatment options available for patients with ESRD: hemodialysis (HD), peritoneal dialysis (PD) or kidney transplant. Among patients with ESRD in the United States, 402,514 utilize HD, 40,605 utilize PD and 175,978 have a functioning renal graft.[2] In 2012, there were 17,305 kidney transplants performed, marking a 2 percent decline from 2011. Although the majority of organs came from deceased donors (11,535), live donors were preferred due to increased post-transplantation functionality and longer survival rates. By the end of 2012, there were 81,982 patients on the waiting list to receive a transplant, with 46,693 classified as status 1a (urgent), 1b (stable on medical device) or 2 (stable on oral medications). The remaining patients were classified as status 7 (inactive due to change in condition).

Unfortunately, the demand for kidneys is 2.7 times higher than the supply with an average patient wait time of five years before receiving a kidney. Patients aged 17 years and younger in need of a transplant are most likely to receive a kidney while patients aged 65 to 74 years are least likely based on the Organ Procurement and Transplantation Network Policies. As with many solid organ transplantation procedures, a major concern for kidney transplant is host rejection of the graft. The advent of the immunosuppressive calcineurin inhibitor (CNI) class, consisting of cyclosporine and tacrolimus, helped revolutionize organ transplantation therapeutics by reducing host rejection, thereby cutting the cost of treating a rejection and allowing hospitals to perform transplants at higher rates. Because of these immunosuppressive agents, there is only a 7 to 9 percent chance that an acute rejection will occur. These agents also reduced long-term graft failure rates to 7.7 percent, with only 3.7 percent of those failures resulting in fatality.

Cyclosporine was previously the drug of first choice, but it has since been replaced by tacrolimus which is now used to treat 91.8 percent of patients receiving a transplant because of its greater potency.[2,3] While tacrolimus is considered highly efficacious, recent studies suggest that tacrolimus levels may have inter-patient variability based on previously unknown pharmacogenetic influences on drug metabolism. This could potentially alter current renal transplant treatment guidelines for tacrolimus in terms of genetic testing and dosing.

Tacrolimus

Pharmacokinetics

Tacrolimus is a macrolide isolated from Streptomyces tsukubaesis that binds to FK506 binding proteins (FKBP12 and FKBP52) on the glucocorticoid receptor complex.[4] Once bound to the FK506 proteins, the complex binds to the calcium/calmodulin dependent phosphatase, calcineurin. Without active calcineurin, T cell transduction signaling is inhibited because nuclear translocation does not occur, disallowing cytokine gene transcription. The cytokines inhibited are interleukin 2, interferon gamma and tumor necrosis factor alpha.

Tacrolimus has a bioavailability of about 25 percent, but may range from 5 to 93 percent, reaching its peak concentration in 30 minutes to one hour.[5] Decreased bioavailability is attributed to poor gut motility or poor solubility in the gut, therefore, oral doses must be three to four times greater than that of intravenous solutions to reach equivalent serum levels. African-Americans and non-Caucasian populations achieve lower bioavailability, possibly due to genetic variations in metabolism.[6] Once absorbed, tacrolimus binds extensively to red bloods cells which helps protect the drug from hepatic metabolism.[7] In the intestines and liver, CYP3A4 and CYP3A5 enzymes metabolize tacrolimus by o-demethylation, hydroxylation and oxidation.[8] After metabolism, 95 percent is excreted via the biliary route and 2.5 percent is excreted in the urine.[9]

For the prophylactic treatment of renal graft rejection following kidney transplantation, the standard dose is 0.1 to 0.2 mg/kg/day divided into two doses taken every 12 hours.[10] Guidelines also suggest a target trough concentration of 15 to 20 ng/ml be evaluated daily once steady-state has been reached post transplantation until hospital discharge, as tacrolimus causes nephrotoxicity in 50 percent of patients.[10,11] Tacrolimus levels can then be titrated to desired levels based on tolerability and clinical outcomes. Pediatric and African-American patients often need two to four times higher doses of tacrolimus to maintain therapeutic trough levels compared to other populations because of genetic and metabolic variations.[12] Even though tacrolimus therapy alone can cause nephrotoxicity, it is difficult to determine whether the incidence of nephrotoxicity is caused by tacrolimus therapy, comorbid medical conditions or drug interactions.[13] Because of the high inter-patient variability in bioavailability and potential risk of nephrotoxicity, determining the right dose of tacrolimus is essential to graft survival. Recent studies reveal a genetic element to dosing that has helped patients achieve a therapeutic level of tacrolimus more consistently than before.

Pharmacogenetics

Evidence suggests that initial dosing of tacrolimus should be dependent on the CYP3A5 genotype instead of an entirely weight-based dosing regimen.[14] In a 2010 study conducted by Zhang et al., Chinese renal transplant patients who received tacrolimus based on genotype efficiently achieved therapeutic concentrations in the blood in a shorter time. Within the CYP3A5*1/*3 genotype group, 46.7 percent of patients achieved the therapeutic range of 6 to 12 ng/ml when standard tacrolimus weight-based dosing of 0.1 mg/kg was initially administered post-transplant. However, 46.7 percent of CYP3A5*1/*3 patients had blood concentrations that were below therapeutic range, indicating that a higher dose was needed (P=1.000). When dosing was determined by genotype, 81.8 percent of CYP3A5*1/*3 patients were in therapeutic range while only 9.1 percent of CYP3A5*1/*3 were below therapeutic range (P=0.674). It is evident that dose adjustments based on genotype decreased the number of patients that were outside the therapeutic range and increased the number of patients that were within range (Table 1). Administration of the initial 0.1 mg/kg in CYP3A5*3/*3 patients led to a greater percentage of patients who had tacrolimus blood concentrations exceeding the therapeutic range; however, the percentage of patients outside the range significantly decreased once dosing was determined by genotype (46.2% P=0.021 versus 11.5% P=1.000).

Table 1. Tacrolimus blood concentrations of CYP3A5*1/*3 patients on weight-based and genotype-based dosing regimens.[14]

	Subtherapeutic (< 6 ng/ml)	Therapeutic (6-12 ng/ml)
Weight-based dosing	46.7% (7/15)	46.7% (7/15)
Genotype-based dosing	9.1% (2/22)	81.8% (18/22)

Tacrolimus blood concentrations were measured on the third day after kidney transplant. The weight-based dosing group consisted of Chinese adults (median age 33.5 years) who received 0.1 mg/kg/day. The genotype-based dosing group consisted of Chinese adults (median age 32 years) who received 0.15 mg/kg/day based on their CYP3A5*1/*3 genotype. When dosing was based on genotype, the percentage of patients having subtherapeutic levels decreased, and the percentage of patients having therapeutic levels increased supporting the use of genotype-based dosing for tacrolimus.

The prevalence of tacrolimus toxicity among the different CYP3A5 variants is still being studied (Table 2).[15] A meta-analysis performed by Rojas et al., concluded that CYP3A5 expressers (CYP3A5*1/*1 and CYP3A5*1/*3) present a greater risk for chronic nephrotoxicity (OR=2.42, 95% CI 1.51-3.90, I2=0%), and a greater risk for acute transplant

Table 2. Risk of adverse events between CYP3A5 expressers and non-expressers.[15]

	Odds Ratio (OR)	95% Confidence Interval (CI)	Heterogeneity (I^2)
Chronic nephrotoxicity	2.42	1.51-3.90	0%
Acute transplant rejection	1.32	1.02-1.71	3%

rejection (OR=1.32, 95% CI 1.02-1.71, I2=3%) than CYP3A5 non-expressers (CYP3A5*3/*3). Furthermore, the use of tacrolimus results in neurotoxic effects such as tremor, headaches, and insomnia, in addition to its known nephrotoxic effects.[16]

A systematic review and meta-analysis analyzed five studies for chronic nephrotoxicity (n=867), excluding one study in the post hoc sensitivity analysis, and 21 studies for acute transplant rejection (n=2185). The CYP3A5 expressers included patients with CYP3A5*1/*1 and CYP3A5*1/*3 genotype. The CYP3A5 non-expressers included patients with CYP3A5*3/*3 genotype. The elevated odds ratio indicated that patients had a higher risk of chronic nephrotoxicity and acute transplant rejection.

In a study conducted by Thölking et al., the tacrolimus metabolism rate expressed as the blood concentration normalized by the dose (C/D ratio) was used as a predictor to identify at risk patients for developing CNI toxicity: [17]

*C/D ratio (ng/mL * 1/mg) = blood tacrolimus trough level (ng/ml)/daily tacrolimus dose (mg)*

In this study, renal function was analyzed one, two, three, six, 12 and 24 months after renal transplantation in patients prescribed tacrolimus. The patients were divided into three groups: fast (CYP3A5*1/*1), moderate (CYP3A5*1/*3) and slow metabolizers (CYP3A5*3/*3). Fast metabolizers of tacrolimus had a C/D ratio <1.05 ng/mL*1/mg while slow metabolizers had a C/D ratio of ≥1.55 ng/mL*1/mg. Intermediate metabolizers typically had a mean C/D ratio value of 1.05 to 1.54 ng/mL*1/mg. Fast metabolizers had lower estimated glomerular filtration rates (eGFR) at all time points when compared with slow metabolizers. At the 24-month point, fast metabolizers versus slow metabolizers had a change in mean eGFR (ml/min/1.73 m^2) of -8.8 with a 95 percent confidence interval from -14.7 to -2.8 (p=0.0039). Also, patients classified as fast metabolizers were shown to have lower renal function and a higher mortality within two years (mortality rates: fast 7.4% versus intermediate 4.4% versus slow 4.9%). In addition, 5 percent of the fast metabolizers died from infections, which was a common reason for mortality, while none occurred in slow metabolizers (p=0.111). Fast metabolizers also had a higher incidence of CNI nephrotoxicity (p=0.015). In this study, 9 percent of fast metabolizers switched therapy from tacrolimus due to CNI toxicity, while only 1 percent of slow metabolizer switched (p=0.047). The mean daily dose (mg) of tacrolimus required was higher in fast metabolizers than that in the intermediate and slow metabolizers (11 mg (range: 6.3-26.7), 7.5 mg (range: 4-14) and 5.5 mg (range: 2.33-11.5) respectively) (p<0.001). Thus, genotyping for the CYP3A5 gene is not only helpful in predicting response to tacrolimus, but also is a valuable predictor of adverse events.

Furthermore, the polymorphism of CYP3A5 explains not only the wide variability of the drug's pharmacokinetics but also its interaction with other medications such as diltiazem. A patient's CYP3A5 genotype can possibly be used to predict whether tacrolimus can be co-administered with such medications in an individual patient. A randomized, parallel-controlled study completed in Chinese renal transplant patients in 2013 by Chen et al., reported that the tacrolimus dose necessary to reach the target level trough concentration (C0), which is comparable to a $C_{ss,\,min}$, is associated with the CYP3A5 genotype.[18] Expressers of CYP3A5 (CYP3A5*1/*1 and *1/*3) needed higher doses of tacrolimus than CYP3A5 non-expressers (CYP3A5*3/*3) to reach a comparable C0 level. It was also found that when diltiazem was not used with tacrolimus, CYP3A5 expressers required a significantly higher dose of tacrolimus to reach a target C0 level as seen in the day 14 post-transplant analysis between the expresser group that received diltiazem and the expresser group without diltiazem, 0.06 mg/kg ± 0.01 mg/kg versus 0.09 mg/kg ± 0.02 mg/kg (p= 0.017), respectively. Diltiazem could reduce tacrolimus dose in the CYP3A5 non-expressers as seen in the day 14 post-transplant analysis between the non-expresser group that received diltiazem versus the non-expresser group that did not receive diltiazem, although the dose was not significantly reduced (0.05 mg/kg ± 0.01 mg/kg versus 0.09 mg/kg ± 0.06 mg/kg, respectively) (p= 0.017). Thus, the results suggest that a single nucleotide polymorphism in CYP3A5 can change the metabolic interaction between tacrolimus and diltiazem. More specifically, the results show that diltiazem can act as a tacrolimus-saving agent in CYP3A5 expressers.

There are demonstrated potential benefits for CYP3A5 genotype testing, but evidence is inconclusive whether genotype-based dosing is superior to standard therapeutic drug monitoring at achieving clinical end points. A 2010 study by Thervet and colleagues found genotype dosing had significantly lower time needed to achieve target tacrolimus concentrations (p=0.001) and fewer dose adaptations compared to therapeutic drug monitoring (p=0.004).[19] However, there was no difference between treatment groups in delayed graft function, acute rejection, occurrence of tacrolimus-related nephrotoxicity or renal function. The study design introduced tacrolimus seven days post-transplant following biological therapy with either basiliximab or rabbit thymocyte antiglobulin; the authors acknowledged that clinical outcome effects may be more significant when tacrolimus is initiated on the day of transplant.

Clinical Applications

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is neither for nor against CYP3A5 genotype testing for transplants, but does advise modifications for initial tacrolimus treatment using the CYP3A5 genotype if known (Table 3).[20]

Conclusion

While tacrolimus is a standard immunosuppressant for nearly all kidney transplant recipients, it has a narrow therapeutic index, high inter-patient variability, significant drug interactions, and major risks for severe adverse events including rejection and nephrotoxicity. The presence of genetic polymorphisms in the CYP3A5 enzyme can affect tacrolimus metabolism and, consequently, blood levels, contributing to patient variability in response. Determining the genotype of

Table 3. Dosing recommendations for tacrolimus based on CYP3A5 genotype.[20]

CYP3A5 phenotype [a]	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations[b]	Classification of recommendations[c]
Extensive Metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus, and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose to 1.5 to 2 times of the recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate Metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus, and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose to 1.5 to 2 times of the recommended starting dose.[a] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor Metabolizer (CYP3A5 non-expresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus, and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

[a]Typically with other CYP enzymes, an extensive metabolizer would be classified as a "normal" metabolizer, and therefore, the drug dose would not change based on the patient's genotype. However, in the case of tacrolimus and the CYP3A5 genotype, a CYP3A5 expresser (i.e., CYP3A5 extensive metabolizer or intermediate metabolizer) would require a higher recommended starting dose, and the CYP3A5 non-expresser (i.e., poor metabolizer) would require the standard recommended starting dose.

[b]This recommendation includes the use of tacrolimus in kidney, heart, lung and hematopoietic stem cell transplant patients, and liver transplant patients where the donor and recipient genotypes are identical.

[c]Rating scheme is described in Supplementary Data online.

[d]Further dose adjustments or selection of alternative therapy may be necessary because of other clinical factors (e.g., medication interactions or hepatic function).

CYP3A5 can allow for initial dose adjustments, and improve the ability to reach and maintain target tacrolimus concentrations. Further trials considering CYP3A5 polymorphisms are needed to determine whether this genotype dosing improves clinical outcomes such as reducing rejection, toxicity and drug interactions before testing can be recommended. Additionally, other dynamics contribute to the inter-individual differences to drug response, and CYP3A5 genotype alone cannot fully account for variability in tacrolimus metabolism. Despite these limitations, CYP3A5 genotyping has the potential to improve post-transplant therapy outcomes and help prevent the occurrence of serious adverse effects.

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Health Risks and Emerging Trends with the Use of Electronic Cigarettes

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Abstract
Cigarette smoking is associated with many health risks and complications. Despite smokers' strong desire to quit, most battle with nicotine withdrawal and relapse. Because electronic cigarettes (e-cigarettes) do not contain tobacco, some believe them to be safer than traditional cigarettes and have used them as a replacement or adjunct nicotine source to prevent withdrawal symptoms. Electronic cigarettes are designed to mimic traditional cigarettes and expel a vapor composed of nicotine, water, glycerol, propylene glycol and other flavorings. Many e-cigarette companies use appealing platforms, which promise smoking cessation and harm reduction, to attract consumers; however, several studies have found e-cigarettes actually contain ingredients that are harmful to one's health. Studies have demonstrated that the use of e-cigarettes can be toxic to patients' health if patients do not research the products they intend to purchase. The flavoring of e-cigarettes may be a major contributor to e-cigarette cytotoxicity. If flavoring and other cytotoxic contents of e-cigarettes can be eliminated, e-cigarettes may be useful in smoking reduction and cessation. Many clinicians today support traditional forms of nicotine replacement therapy for smoking cessation rather than e-cigarettes. Due to the lack of regulation and studies by the U.S. Food and Drug Administration, e-cigarettes may not be as safe as users may perceive and should not be a preferred product for smoking cessation therapy until they are further studied and regulated.

Key Terms
Electronic Cigarettes; Nicotine; Pharmacies; Safety; Smoking Cessation

Introduction

Cigarette smoking is linked to multiple, serious health risks. Smoking impairs almost every organ in the body, causes several diseases, increases healthcare costs and negatively impacts the overall health of people who choose to use these products.[1] While only 18 percent of the U.S. population were smokers in 2012 compared to 42 percent in 1965, there are still about 42 million Americans who continue to smoke.[2] In 2012, about 21 percent of all American men and about 16 percent of all American women smoked. Furthermore, smoking is a problem among adolescents, and it is estimated that each day more than 3,200 teenagers smoke for the first time.[3] This results in nearly 14 percent of high school students and 4 percent of middle school students being considered as current cigarette smokers.

Smoking not only impacts a person's health but also affects the public environment.[4] Smoke contains carcinogens, toxic metals and poisonous gases that are harmful to not only the smoker but also to the people around the smoker. Additionally, second-hand smoke harms the atmosphere by degrading air quality and significantly contributes to littering, where cigarette butts are listed as the most littered item. It is also extremely costly to clean up littering related to smoking.[5] For example, in places like San Francisco, it costs up to $10.7 million to remove cigarette butts from public spaces each year. The production of cigarettes alone is also detrimental to the environment, as for every 300 cigarettes that are produced, one tree is consumed.[5,6] Improper discarding of cigarettes has been found to cause destructive wildfires which leads to damaged properties, vegetation, forestry, animal habitats and death.[6]

Smoking cessation can help decrease the risk of smoking-related diseases and add years to past-smokers' lives.[7] According to a survey by the Centers for Disease Control and Prevention (CDC) in 2010, almost 70 percent of adult smokers said they wanted to quit smoking completely. Smokers in the beginning stages of quitting often experience severe withdrawal symptoms due to nicotine addiction.[8] Nicotine, the primary psychoactive chemical in tobacco, is highly addictive, and smokers who quit often experience intense withdrawal symptoms including extreme nicotine cravings, depression, anxiety, difficulty sleeping, nightmares, headaches, increased appetite and weight gain.[9] Medications containing nicotine such as lozenges, gums and patches can help to decrease the withdrawal symptoms and cigarette cravings, when used correctly, and could potentially double a smoker's chances of quitting.[8] Some people have turned to e-cigarettes as a nicotine replacement or adjunct therapy option for smoking cessation.[10] Electronic cigarettes provide patients with the sensation of smoking; however, what most people do not know is that e-cigarettes have not been proven safe or effective in smoking cessation.

Hon Lik, a pharmacist and smoker in China, developed e-cigarettes in 2003 after his father died of lung cancer.[11] Electronic cigarettes were later introduced to the United States in late 2006 and early 2007. However, e-cigarettes did not become popular until 2013 when a number of large tobacco companies invested in their production.[12] As a two-packs-per-day smoker, Hon Lik developed e-cigarettes in hopes of producing a method that would help himself quit. In the past he had tried nicotine patches, but they failed to give him the "rush" associated with smoking cigarettes he enjoyed. Thus, e-cigarettes were designed to imitate "smoke without fire."[13]

Electronic cigarettes vaporize a mixture of liquid nicotine, water, glycerol, propylene glycol and other flavorings.[12] They consist of an atomizer, which heats the liquids into a vapor; a

cartridge, which holds the e-liquids; and a rechargeable battery, which powers the atomizer. Electronic cigarettes contain no tobacco, odor or smoke. Most are designed to be used and appear as a cigarette so that when a user draws on it, visible vapor is produced while a light-emitting diode (LED) portrays a real cigarette glow. Aside from the traditional tobacco and menthol flavors, more than 200 other flavors, such as bubblegum and cherry, exist. Before using an e-cigarette, the user must first attach the cartridge.[14] Most e-cigarettes are activated when a user inhales, causing the atomizer to heat the liquid and turn it into a vapor, while other e-cigarettes are activated with a switch. Inhalation of the vapor through the mouthpiece delivers nicotine to the user's lungs and, upon exhalation, gives an appearance similar to a cloud of smoke.

Emerging Trends

Electronic cigarette use has risen rapidly over the last few years. The number of adults in the United States who used an e-cigarette rose from 3.3 percent in 2010 to 8.5 percent in 2013, and the number of current cigarette smokers who have used e-cigarettes has risen from 9.8 percent to 36.5 percent.[15] From 2013 to 2014, the number of high school students who used an e-cigarette in the past month tripled to 13.4 percent, and the number of high school students that have never used cigarettes, but have used e-cigarettes, increased to an estimated 250,000.[16] Marketing of e-cigarettes by tobacco companies is extensively aimed at youth under the age of 21 years, specifically high school students, where companies invest in advertising their products through magazines, movies, sponsorship of concerts and auto races, and celebrity endorsements and researching youth behaviors to generate attracting themes.[16-18]

Currently, only e-cigarettes marketed for therapeutic purposes are regulated by the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER).[19] Other tobacco products, such as cigarettes, smokeless tobacco and roll-your-own tobacco are currently regulated by the FDA Center of Tobacco Products (CTP). However, to address the public issue of unhealthy tobacco use, a rule named "Tobacco Products Deemed To Be Subject to the Food, Drug & Cosmetic Act" has been proposed by the FDA to expand its authority to regulate all products that are considered tobacco products, including e-cigarettes.[20] State and local governments also have laws about tobacco products, which include prohibiting smoking and tobacco in public places, taxing tobacco products, enforcing Medicaid to cover smoking cessation programs and prohibiting the sale of flavored tobacco products.[21] In 2006, Ohio instituted a statewide ban against tobacco requiring businesses and organizations to prohibit smoking.[22]

Electronic Cigarettes: Cytotoxicity and Other Health Risks

While e-cigarettes are becoming a popular alternative to tobacco cigarettes, many health professionals are wary in recommending these products to their patients primarily because e-cigarettes have not been proven safe for long-term use.[23] Common complaints from e-cigarette users are headache, respiratory tract infection and changes in appetite. Upon initial investigation of e-cigarettes, they may appear to be a good alternative to traditional cigarettes. Most e-cigarette companies use the appealing platform of promising smoking cessation and harm reduction to attract consumers.However, without knowing the long-term health risks associated with e-cigarettes, it can be difficult for a healthcare professional to provide any recommendation of e-cigarettes to both tobacco and non-tobacco users.[24]

Farsalinos and colleagues performed a study to determine whether or not e-cigarettes are less harmful than tobacco cigarettes.[25] They measured and compared the cytotoxic potential of cigarette smoke and e-cigarette vapor extract on cultured myocardial cells. Additionally, they measured whether or not using a higher voltage (3.7 volts versus 4.7 volts) has an effect on cytotoxicity of e-cigarette agents. Electronic cigarette and cigarette smoke samples were tested in vapor form, as this is the form most used by consumers. Cytotoxicity was defined as viability less than 70 percent based on a specific protocol (ISO 10993-5). This was only done on low voltage e-cigarette samples due to an insufficient number of high voltage samples to demonstrate a significant difference.

The authors tested the vapor cytotoxicity of one cigarette smoke sample, 20 e-cigarette liquid samples and an e-cigarette base sample at five different concentrations: 100 percent, 50 percent, 25 percent, 12.5 percent and 6.25 percent.[25] Table 1 demonstrates the myocardial cell viability at low voltage of the cigarette smoke sample, base sample and the four e-cigarette vapor extracts that demonstrated a cytotoxic effect. Most tobacco producing samples exhibited the lowest survival rates. The base sample, containing 50 percent propylene glycol, 50 percent glycerol and no nicotine or flavoring, was considered non-cytotoxic at any extract concentration. Cigarette smoke was significantly more cytotoxic than e-cigarette samples with cytotoxicity exhibited at all concentrations above 6.25 percent. The most cytotoxic of the four samples was "El Toro Puros." Results of high voltage samples above 6.25 percent were not considered statistically significant due to the small amount of samples tested. The authors admitted the need to perform further studies, using more samples and more efficient atomizers, to determine the viability of e-cigarette use in higher voltage samples. Farsalinos and colleagues also suggested that flavoring, and the varying quantities of flavorings in liquids, may be a major contributor to e-cigarette cytotoxicity. Some flavorings are approved for use in food, but their effects when heated or evaporated are unknown.

A study by Romagna and colleagues also suggested flavoring as a cause of cytotoxicity in e-cigarettes liquid.[26] In the study, 21 e-cigarette liquids were tested, and only one out of the 21 liquids had cytotoxic properties when exposed to cultured mammalian fibroblasts. All samples were produced by the same manufacturer and had the same main ingredients (propylene glycol, glycerol and nicotine) in similar concentrations, leaving flavoring as the only contributor to varying cell viability.

Table 1. Myocardial Cell Viability in Cigarette Smoke and Electronic Cigarette Vapor Extracts at 3.7 volts (low voltage).[25]

	Dilutions				
Samples	100%	50%	25%	12.50%	6.25%
Cinnamon-Cookies	64.8± 2.5%	100.8±2.0%	97.2± 2.9%	99.3± 1.7%	99.2± 3.8%
El Toro Cigarillos-1	39.1±1.2%	52.5±1.8%	81.0± 2.0%	92.6± 0.4%	99.2± 1.0%
El Toro Cigarillos-2	22.3±4.0%	66.9± 6.2%	104.1± 5.8%	109.9±6.0%	112.0± 8.8%
El Toro Puros	2.2± 0.6%	7.4± 3.9%	84.5±6.5%	115.3±11.7%	111.9±7.4%
Base Sample	105.1± 1.2%	103.5± 1.9%	101.3± 4.2%	100.7± 3.4%	100.4± 2.3%
Cigarette smoke	3.9± 0.2%	5.2 ± 0.8%	3.1± 0.2%	38.2± 0.6%	76.9 ± 2.0%

Data comparing cytotoxicity between e-cigarettes and cigarette smoke was reported using mean ± standard deviation. Data comparing e-cigarette samples was reported using a paired t-test. Among e-cigarette samples, an independent t-test was used to assess whether nicotine levels played a role in viability. A two tailed p value < 0.05 was considered statistically significant. All samples, besides the base, had p values <0.001 and were considered statistically significant.

Studies evaluating the cytotoxicity of individual flavors in vapor form and the cytotoxicity of flavors at different concentrations may be essential in the production of safe e-cigarettes.[27] Bahl and colleagues completed a study using embryonic and adult cells to compare the cytotoxicity of various e-cigarette refill fluid flavors. They used three cell types: cells modeling the epiblast stage of human embryonic development (hESC), mouse neural stem cells (mNSC) isolated from the brain of a newborn and human pulmonary fibroblasts (hPF) representing adult cells from one of the initial points of contact of inhaled e-cigarette aerosol. Thirty-four refill fluid samples of varying doses, flavorings and nicotine concentrations were compared in all cell types, and found to differ significantly in potency. Refill fluids used were obtained from popular companies whose products are easily accessible to e-cigarette users online. Ninety-six well plates were filled with negative controls and refill solutions of various doses (0.001%, 0.01%, 0.03%, 0.1%, 0.3% and 1%). Table 2 shows the half maximal inhibitory concentration (IC_{50}) of the refill fluid product flavors that produced the most significant results and are the most common humectants used in refill fluid. Vegetable glycerin (VG) and propylene glycol (PG) are the two humectants most often used in refill solutions, and these were considered non-cytotoxic for both cell types. Menthol Artic (Freedom Smoke USA) and Caramel #40 (Global Smoke) demonstrated the strongest cytotoxic effects on hPF cells. Cinnamon Ceylon was found to be the most potent sample and the only one that produced strong cytotoxic effects on all three types of cells. The Bubblegum sample was tested and found to be non-cytotoxic. The authors warned that the cytotoxicity results achieved were potentially inaccurate. This is because the study used doses of vapor that were 100 times lower than the actual doses consumers would use. Therefore, a flavor demonstrating no toxicity at a 1 percent concentration, which was used in this study, may actually exhibit cytotoxicity when consumed at normal high doses such as 10 percent.

The study then used high pressure liquid chromatography spectra and found that products of the same flavor varied in flavor peaks and cytotoxicity.[27] For example, Butterscotch #30 and Butterscotch #29 had low toxicity and had fewer and shorter flavoring peaks (low chemical concentrations). In contrast, Butterscotch #20, which demonstrated cytotoxicity, had greater and higher flavor peaks (high chemical concentrations). These results demonstrate that companies are not always consistent with the contents of their products. Products of the same flavor from one manufacturer can vary in the amount of chemicals and, therefore, the levels of cytotoxicity. Additionally, stem cells from embryos and newborns were found to be more sensitive to refill solution than differentiated adult lung cells; consequently, it will be essential in future studies for e-cigarette cytotoxicity to be tested during pregnancy and in multiple cell types.

This study also examined the effects of nicotine on the cytotoxicity of e-cigarettes.[27] In Table 2, the nicotine levels of the refill fluids and humectants are shown. Samples containing nicotine concentrations ranging from 0 to 24 mg/mL were used. Propylene glycol, VG, Caramel #26, Butterscotch #30, Menthol Artic, Butterscotch #20, Cinnamon Ceylon and Caramel #21 contained 0 mg nicotine/mL; however, they differed in cytotoxicity. Propylene glycol, VG, Caramel #26, Butterscotch #30 and Menthol Artic were non-cytotoxic/low cytotoxicity while Butterscotch #20, Cinnamon Ceylon and Caramel #21 were considered toxic. Bubblegum and Butterfinger #19 were considered to have no cytotoxicity or low cytotoxicity but contained 24 mg nicotine/ml.

This study demonstrates that in order to truly confirm the cytotoxicity of e-cigarettes additional studies will need to be completed with great caution.[27] As this study only examined the end result of exposure, studies evaluating the reason for differences in cell survival may be beneficial. The results also demonstrate that high levels of nicotine do not correlate with high cytotoxicity in e-cigarettes, leaving the flavoring of e-cigarettes as the main cause of e-cigarette toxicity.

Aside from flavoring, there are several other toxic substances present in e-cigarette cartridges at low levels.[28] These substances include carbonyl compounds, volatile organic compounds, nitrosamines, ultrafine particulate matter and heavy metals. Performing studies on the cytotoxicity of these additional agents is important because they are known to contribute to various disease processes. Even the humectant propylene glycol, which is not cytotoxic in liquid form, has been found to contribute to allergic respiratory symptoms, and the safety of inhaling its vaporized form has not been tested in humans. By eliminating their cytotoxic flavors and other cytotoxic component, e-cigarettes may be able to contribute safely to tobacco reduction and cessation.

Table 2. Cytotoxic Levels and Nicotine Content of Various Refill Fluid Product Flavors.[27]

Refill fluid (Company)	Nicotine (mg/ml)	Cell Type		
		hESC[c]	mNSC[d]	hPF[e]
Propylene glycol (FS-USA)[a]		Low	Low	Low
Vegetable Glycerin (FS-USA)		Low	Low	Low
Bubblegum #18 (FS-USA)	24	Low	Low	Low
Butterscotch #30 (FS-USA)	0	Low	Low	Low
Butterscotch #29 (FS-USA)	6	Low	Low	Low
Caramel #26 (Freedom Smoke)	0	Low	Low	Low
Caramel #27 (Freedom Smoke)	6	Low	Low	Low
Caramel #28 (Freedom Smoke)	6	Low	Low	Low
Caramel #40 (Global Smoke)	18	Moderate	Low	Moderate
Butterfinger #19 (FS-USA)	24	Moderate	Low	Low
Menthol Arctic (Freedom Smoke)	0	Moderate	Low	Moderate
Vanilla Tahity (FS-USA)	0	Moderate	Moderate	Moderate
Pure nicotine (FS-USA)	100	Moderate	Moderate	Moderate
Caramel #21 (Freedom Smoke)	0	Moderate	Moderate	Moderate
Arctic Menthol (Johnson Creek)	18	High	Moderate	Low
Butterscotch #20 (FS-USA)	0	High	Moderate	Moderate
Cinnamon Ceylon (FS-USA)	0	High	High	High
Butterscotch #41 (Freedom Smoke)[b]	0	----	Moderate	Moderate

Refill products were considered to be non-cytotoxic or have low cytotoxicity if IC_{50}>1%, moderate toxicity if IC_{50} was 0.1-1%, and high cytotoxicity if IC50<0.1%.

[a]Freedom Smoke USA

[b]Butterscotch #41 was only tested in mNSC and hPF because it was ordered and arrived from the manufacturer later in the experiment.

[c]Cells modeling the epiblast stage of human embryonic development

[d]Mouse neural stem cells isolated from the brain of a newborn

[e]Human pulmonary fibroblasts

Electronic Cigarettes: Examining Utility for Smoking Cessation Therapy

In a prospective proof of concept six-month pilot study, Polosa and colleagues examined the effect of e-cigarettes on smoking reduction and cessation.[29] Forty regular smokers (unwilling to quit) were invited to attend five study visits (baseline, week 4, week 8, week 12 and week 24) and follow-up appointments at each visit. Adverse events and participants' opinions and acceptance of the product were also monitored. Smokers ranged from 18 to 60 years of age, smoked greater than or equal to 15 factory made cigarettes per day for at least the past 10 years and were not currently trying to quit smoking or hoping to do so in the next 30 days. At the baseline visit, participants were given a free e-cigarette kit and were instructed on how to use, charge and activate the e-cigarette. A four-week supply of 7.4 mg nicotine cartridges was also provided, and participants were trained on how to load them into the e-cigarette atomizer. Participants were allowed to use the e-cigarette at their own convenience throughout the day up to a maximum of four cartridges per day as recommended by the manufacturer. They were also instructed to complete a four-week study diary to record their use, the number tobacco cigarettes smoked and any adverse events. Subjects were invited to subsequent visits to receive more free supplies of cartridges and study diaries, to record their exhaled carbon monoxide (eCO) levels and to give back completed study diaries and unused products. At the final follow-up visit, participants reported product usage (cartridges/day), number of tobacco cigarettes, and eCO levels and rated the degree of usefulness of the product.

The product ratings of satisfaction, helpfulness in keeping them from smoking and whether they would recommend to a friend who wants to quit or reduce smoking were measured using a visual analogue scale (0 = completely unsatisfied, 10 = fully satisfied). Patients who spontaneously asked for assistance in quitting were provided with smoking cessation services but were excluded from the study. The majority (67.5%) of participants were able to adhere to the program and returned for the final follow-up visit with an overall quit rate of 22.5 percent. There was at least a 50 percent reduction in cigarette smoking in 32.5 percent of participants.

Overall 55 percent of participants exhibited reduction or smoking cessation.[29] The study suggested that the positive effect of e-cigarettes could have been due to their ability to replace some of the rituals associated with smoking (e.g., hand-to-mouth action of smoking). E-cigarette use was not found to produce increased CO levels. Serious adverse events or events causing unscheduled visits to a healthcare provider did not occur. The most frequent adverse events were mouth irritation (20.6%), throat irritation (32.4%) and dry cough (32.4%) possibly due to the low toxicity of propylene glycol. However, these adverse events subsided with time, and participants were satisfied with the product. Side effects such as depression, anxiety, insomnia, irritability, hunger and constipation that are normally present in smoking cessation trials with drugs for nicotine dependence were absent.

The authors admitted that the study was small and uncontrolled; therefore, the results could have been due to chance and should be interpreted with caution.[29] Additionally, the study's design should not be considered as an ordinary cessation study because the design included smokers who were unwilling to quit and used e-cigarettes. Based on this study, e-cigarettes should not be compared to other smoking cessation products, and the absence of withdrawal symptoms and adverse effects should be considered with caution, given that the authors did not study these variables rigorously.

Conclusion from Selected Studies on Electronic Cigarettes

These five studies demonstrate that the use of e-cigarettes is not yet safe and healthy for the public.[25-29] There are still many factors including toxicity and efficacy in smoking cessation that need to be studied further. An article by Simon Chapman, professor of public health at the University of Sydney, stresses many mistakes have been made with the way tobacco has been sold and marketed.[23] In order to avoid the same mistakes with e-cigarettes, early caution should be taken. Chapman suggests scheduling e-cigarettes and creating access through pharmacies with a permit or prescription as a way for them to be overseen for quality and safety. This tighter control would allow e-cigarettes to be carefully monitored through research, and their availability to be relaxed or tightened as evidence of benefits and/or harms develop.

Clinical Applications and the Role of the Pharmacist

As of now the FDA has not completely studied and evaluated e-cigarettes and cannot state if there is any therapeutic benefit from the use of these products. Currently, only e-cigarettes that are marketed for or claim a therapeutic purpose such as smoking cessation are being regulated.[30] The FDA issued a proposition that would allow the agency's tobacco authority to cover additional products that meet the legal definition of a tobacco product, such as e-cigarettes and any other products containing tobacco derivatives such as nicotine.[30,19]

Before initiating any form of smoking cessation, pharmacists should consider using the "5As" approach. This involves **asking** the patient about his or her current tobacco use, **advising** them on the importance of quitting and the health benefits that come with smoking cessation, and **assessing** if the patient is willing and ready to quit. Once the patient is ready, the pharmacist should **assist** the patient in selecting and beginning smoking cessation therapy and **arranging** follow-up sessions to help monitor and encourage the patient's progress. A first-line treatment to smoking cessation for most patients is nicotine replacement therapy (NRT).[31] Other first-line treatments include prescription products such as varenicline and bupropion SR. On the market, there are a number of NRT products designed to help patients end their need for nicotine. Available NRT products include gums, lozenges, nasal sprays, inhalers and patches. Each of these products have advantages and disadvantages which the patient should discuss with a pharmacist in order to determine which product is right for them.[32] As of now, e-cigarettes have not been formally classified as a NRT product, but there is continuing research to determine if e-cigarettes would qualify.[19]

From the presented studies and evidence, the use of e-cigarettes can be toxic to the health of patients, and without regulation to standardize e-cigarettes, it may be difficult to discern which products are safe.[30] Although, there are no official counseling guidelines for e-cigarettes, it is still important that pharmacists use available knowledge to inform patients on the effects of e-cigarettes. Most e-cigarettes do not contain a tamper resistant mechanism, which has resulted in children overdosing on nicotine by consuming the concentrated nicotine liquid. Likewise, various liquids cause damage to cells, and certain e-cigarette devices, especially ones that are higher in voltage, can contribute additional harm.[25] In comparison to traditional tobacco based cigarettes, it is not accurate to say that e-cigarettes are better or worse. This is because e-cigarettes are not being formally regulated in the same way.[19] Patients who are looking to switch from traditional tobacco cigarettes to e-cigarettes as a form of NRT should be informed about the consequences of using e-cigarettes and their effects on health; an example being that certain nicotine liquids and e-cigarettes can cause more cytotoxicity when compared to other brands of e-cigarettes.[27,30,32] If a patient wants to quit smoking cigarettes, pharmacists should make recommendations on safer established methods, such as NRT products, before suggesting e-cigarettes. Patients already using e-cigarettes as a form of smoking cessation should be encouraged to switch to established methods or, at a minimum, invest in products that progressively contain less and less nicotine, eventually seceding from all nicotine and tobacco containing products.[25,30,31] Utilizing the above counseling points, regulated forms of NRT, or referral to a physician who can prescribe a prescription based smoking cessation therapy, would all be safer options than using an e-cigarette.[27,30]

Conclusion

Presently, there have been studies to show that certain e-cigarette and nicotine liquid brands are safer than the traditional e-cigarette, but that does not mean e-cigarettes in general are completely safe. The FDA has listed a number of adverse effects that have been attributed to the chronic use of e-cigarettes including, but not limited to, chronic heart failure, pneumonia and seizures. Additional studies, the creation of standards and regulating e-cigarettes like tobacco are important next steps. Unfortunately, the FDA has not instituted such regulations but is currently working on extending the e-cigarette classification to be in the same category as traditional tobacco products. If a standard and safe e-cigarette is created, this could add another potentially safer NRT option for smoking cessation.

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