dc-ccp
District of Columbia
College of Clinical Pharmacy

The Lobbyist

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Inside This Issue

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An independent chapter of the American College of Clinical Pharmacy, the DC-CCP is dedicated to improvements in pharmacotherapy practice, education, and research in the District of Columbia, Maryland, and the Commonwealth of Virginia.

Pictured (from left to right): Chai Wang (Past President), Thao Tran (Immediate Past Secretary-Treasurer), Lisa Peters (Immediate Past President), Tim Rocafort (President)

President's Letter

Dear Members of the District of Columbia College of Clinical Pharmacy,

Happy New Year! Welcome to another exciting year for DC-CCP and the profession of clinical pharmacy!

I am very pleased to be elected president and cannot wait for what this year holds for our organization as we celebrate our 5th year anniversary. Looking ahead, we are anticipating more specialized continuing education programming for both practitioners and students, engaging networking opportunities for residents, strong advocacy effort for healthcare provider status at the Capitol, and philanthropic community service events.

Continued on page 2

Moreover, with our recent advancements in technology, web presence, and communication, we are aiming to better serve all of our members in the District of Columbia, Maryland, and Virginia regions.

With the enduring guidance of our past leadership and the enthusiasm of our new one, I am sure that this will be another successful year!

Best,

P. Tim Rocafort, PharmD, BCACP

DC-CCP President

Outgoing President's Letter

Dear Members of the District of Columbia College of Clinical Pharmacy,

I remember the first DC-CCP Business Meeting I attended in December 2011. I was a new clinical pharmacist and I had recently become board certified in Pharmacotherapy. I was excited to join a new local organization focused on clinical pharmacy; I was a member of ACCP and was impressed with the level of sophistication of their publications and their focus on excellence in clinical pharmacy and research. As we discussed who would take on leadership roles in the newly-established chapter, Richard Parrish, who did a heroic amount of legwork to establish the organization, nominated me for Secretary-Treasurer. My eyes widened as I thought, "I am one of the newest practitioners here; who am I to serve in the leadership?" I hesitated for a moment, then agreed to the nomination. Since then I have served as Secretary-Treasurer, President-Elect, and President of DC-CCP.

Our organization has expanded significantly since then, growing from 38 Founding Members to 158 Active Members. In 2013 when ACCP began recognizing student chapters DC-CCP developed key partnerships with local student chapters, including those at Howard University, Shenandoah, University of Maryland, and VCU. We cohosted many events and began having student co-chairs of our committees in 2014. We provided excellent pharmacist and student programming at our Spring and Fall Forums, and we began making our educational events accessible via webinar in 2015 to serve the needs of our geographically-dispersed membership. In 2014 and 2015 we organized Advocacy Days at the Capitol in Washington, D.C., to advocate for establishing payment under Medicare for Comprehensive Medication Management services. We organized outings to baseball games, state parks, and wine tastings to help pharmacists and student pharmacists network and get to know each other. This year we launched a new website to help us stay more connected and to better communicate our purpose and our accomplishments.

I know that through my participation in DC-CCP I have grown immensely as a practitioner and as a person and I greatly value the relationships I have gained with many amazing students and pharmacists. I thank all the people who have helped me to grow through this experience, and as we reach our fifth anniversary as an organization I celebrate all that we have accomplished together. I am eager to see what we will do in the years ahead as I remain an active member. I encourage all of you to take active roles in the chapter, whether as a member of the Education and Networking or Communications Committees or in the future as a leader in the Executive Board. I guarantee that if you take an active role, you will benefit in ways you never could have imagined.

Sincerely,

Lisa Peters, PharmD, BCPS

DC-CCP Immediate Past President

DC-CCP 2015 Year in Review

Students at the DC-CCP Transitions of Care Summit!

Second Annual Advocacy Day, 2015

Congratulations to **Dr. Cynthia Boyle**, recipient of the Richard Parrish Lecture Award!

Past President, Lisa Peters, and students at the DC-CCP Fall Forum!

Our excellent Fall Forum research panelists!

Dr. Cephas speaking to students at the Fall Forum residency networking session

Here's to an even better 2016!!

Naloxegol (Movantik® *[manufacturer]*)

Katelyn Smith, PharmD, BCPS, Notre Dame of Maryland University

David Lewis, PharmD Candidate, Notre Dame of Maryland University

Lindsey W. Crist, PharmD, BCPS, Notre Dame of Maryland University

Class: Peripherally-acting opioid antagonist

Indication: Opioid-induced constipation

Dose: 25 mg by mouth once daily in the morning on an empty stomach. Dosage adjustments should be made for renal dysfunction, poor tolerability, or concomitant administration of CYP3A4 inhibitors (details below).

Common adverse effects: Abdominal pain, nausea, vomiting, diarrhea, headache

Approximately 41% of patients receiving opioid therapy suffer from opioid-induced constipation (OIC).[1] Not only is OIC associated with lower health-related quality of life (HRQOL) scores, but it also disproportionately affects work productivity and the utilization of healthcare resources.[2] Patient adherence to therapy is also negatively impacted. One study demonstrated that up to one third of patients may miss, decrease, or stop using their opioids to alleviate the burden of OIC.[3] While side effects such as somnolence and respiratory depression tend to abate with chronic opioid use, tolerance does not develop to OIC.[2] Opioids at any dose persistently inhibit GI motility and secretion via the activation of local μ-opioid receptors in the GI tract.

Traditional laxatives do not target the opioid-receptor mediated cause of constipation and thus have limited effectiveness for the management of OIC. One study showed that 94% of patients had an inadequate response to one laxative agent and 27% of patients still had an inadequate response to two or more agents from at least two different laxative classes.[4] Additional therapies for OIC include alvimopan, lubiprostone, methylnaltrexone, naloxone, and most recently, naloxegol (Table 1).[5-9] Naloxegol is a peripheral opioid antagonist that offers a promising alternative for the treatment of OIC.

The approval of naloxegol was based on two identical, phase 3, double-blind studies, KODIAC-04 (n=652) and KODIAC-05 (n=700).[10] Patients with non-cancer OIC were randomized to naloxegol 12.5 mg or 25 mg daily or placebo. The primary end point was response rate at 12 weeks, which was defined as ≥ 3 spontaneous bowel movements (BM) per week and an increase from baseline of at least one spontaneous BM for at least 9 of 12 treatment weeks and at least 3 of the 4 final weeks (patients had to meet all criteria to be classified as responders). When compared to placebo, naloxegol 25 mg demonstrated significantly higher response rates (study 04: 29.4% vs. 44.4%, P=0.001; study 05: 29.3% vs. 39.7%, P=0.02), a shorter time to the first spontaneous BM (P<0.001), and a higher mean number of days per week with ≥ 1 spontaneous BM (P<0.001). It is unclear why findings for naloxegol 12.5 mg were significant in study 04 only (response rates: 29.4% vs. 40.8%, P=0.02).

The long-term safety and tolerability of naloxegol was evaluated over 52 weeks in KODIAC-08.[11] Compared to standard laxatives (n=270), adverse events that occurred more frequently for naloxegol (n= 534) included abdominal pain (3.3% vs. 17.8%), diarrhea (5.9% vs. 12.9%), nausea (4.1% vs. 9.4%), headache (4.8% vs. 9.0%), and flatulence (1.1% vs. 6.9%). P values were not reported. Fifty-six (10.5%) patients discontinued therapy due to adverse effects. Two patients in each group experienced a major cardiovascular event that was unrelated to the study drug (which is important to note when considering the prohibitive cardiovascular profile of alvimopan). Per the manufacturer, no formal statistical comparisons were performed for any safety data. There is currently no data on the comparative efficacy of naloxegol versus standard laxatives. Naloxegol appears to be generally safe and well tolerated; however, caution should be exercised until results of post-marketing surveillance are available.

Naloxegol (Movantik® *[manufacturer]*)

Continued from *page 4*

Naloxegol is a derivative of naloxone, but has negligible CNS penetration due to structural pegylation and P-glycoprotein-mediated efflux across the blood brain barrier.[9] In contrast to oral naloxone which has been shown to adversely affect centrally-mediated analgesia, naloxegol was similar to methylnaltrexone in that it did not affect pain scores or daily opioid dose.[10,12-13]

Naloxegol is typically dosed 25 mg once daily in the morning.[9] The dose should be reduced to 12.5 mg once daily for patients with CrCl < 60 ml/min, poor tolerability to the 25 mg dose, or concurrent administration of moderate CYP3A4 inhibitors (e.g. diltiazem, verapamil). Concomitant use with strong CYP3A4 inhibitors is contraindicated. All maintenance laxatives should be discontinued prior to initiation of naloxegol and may be re-initiated after three days if there is suboptimal response. Patients should be counseled to take naloxegol on an empty stomach and to avoid consumption of grapefruit or grapefruit juice during treatment.

When considering the place of naloxegol in therapy, several factors should be considered. Similar to many conditions, the prevention of OIC is preferred to treatment.[14] Seventy-three percent of patients respond to two or more laxatives from at least two different classes, thus it is reasonable to initiate laxative therapy concurrently with opioid administration.[4] A well-tolerated regimen is the combination of a stool softener (e.g. docusate) with a stimulant laxative (e.g. senna or bisacodyl). Additional laxatives such as bulk forming agents, suppositories, or enemas may be considered based on patient tolerability and preference. In patients refractory to standard laxatives, targeted therapy should be pursued. Naloxegol offers a promising solution for patients who prefer affordable, oral therapy.

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Naloxegol (Movantik® *[manufacturer]*)

Continued from *page 5*

	Lubiprostone[5]	Methylnaltrexone[6]	Alvimopan[7]	Naloxone[8]	Naloxegol[9]
Brand Name	Amitiza®	Relistor®	Entereg®	Evzio®	Movantik®
Approval Date for Indication	April 23, 2013	April 24, 2008	Non-FDA approved indication	Non-FDA approved indication	Sept. 16, 2014
Class	Chloride Channel Activator	Peripheral Opioid Antagonist	Peripheral Opioid Antagonist	Opioid Antagonist	Peripheral Opioid Antagonist
Dosing	24 mcg PO twice daily	12 mg SQ once daily*	12 mg PO twice daily	4 mg PO four times daily	Initial: 25 mg PO once daily If not tolerated, reduce dose to 12.5 mg once daily
Route	Oral	Subcutaneous	Oral	Oral (when compounded)	Oral
Adjustments	Hepatic	Renal	Avoid in ESRD Avoid in Child-Pugh class C	N/A	Renal Avoid use in severe hepatic impairment
Comments	Administer with food to reduce nausea Risk of acute onset dyspnea with first dose	Must be dispensed with an FDA-approved medication guide	U.S. Boxed Warning for myocardial infarction Use restricted to REMS program (max 15 doses) Hospital use only	Risk of systemic absorption and opioid withdrawal	Should be administered on an empty stomach Contraindicated with strong CYP3A4 inhibitors Avoid consumption of grapefruit & grapefruit juice during treatment
AWP	24 mcg (60): $377.45	**Kit** (Relistor SQ) 12 mg/0.6 mL (7): $500.22 **Solution** (Relistor SQ) 8 mg/0.4 mL (0.4 mL): $86.47 12 mg/0.6 mL (0.6 mL): $86.47	12 mg (30): $3899.38	**Solution** (Naloxone HCl Injection) 0.4 mg/mL (1 mL): $18.71 1 mg/mL (2 mL): $39.60 ***Compounding required, therefore final cost estimate not available*	12.5 mg (30) =$299.52 25 mg (30) =$299.52

*Dosing of methylnaltrexone is weight-based when used for cancer pain or advanced illness

Improving medication adherence through telemonitoring in patients initiating antidepressant therapy

Francoise Pradel, PhD; Professor, University of Maryland School of Pharmacy

Muhammad Sheheryar, PharmD Candidate 2016, University of Maryland School of Pharmacy

Adherence to antidepressant medications when initiating treatment for major depressive disorder (MDD) is often poor and early discontinuation rates are very high.[1] About one-third of patients discontinue antidepressant medications within 30 days and more than 40% stop treatment within 90 days.[2] The therapeutic effect of antidepressants is seen after 2 to 4 weeks of initiating therapy, however; it can take up to 8 weeks in some patients.[1, 2] Early discontinuation leads to high relapse rate and poor treatment ouctomes.[1, 2]

Studies have shown that some of the major reasons for nonadherence when initiating antidepressant medications include side-effects, patients feeling better and patients' fear of dependence on antidepressants.[2] Since MDD is a chronic condition and is managed in outpatient settings, community pharmacists frequently encounter and interact with patients with MDD.[3] This allows them to play an instrumental role by exploring barriers to adherence, clarifying common misconceptions and providing key educational messages about antidepressant medications.[3] They can serve as a valuable resource in helping patients overcome these barriers, such as by counseling patients how to manage side-effects or by making recommendations to the physician for dose adjustments, therapy change etc.

One of the ways that pharmacists can monitor patients who are starting antidepressant medications is through telemonitoring. Telemonitoring is defined as "the remote monitoring of patients, including the use of audio, video, and other telecommunications and electronic information processing technologies to monitor patient status at a distance".[4] The use of telemonitoring has been suggested to reduce chronic disease complications in outpatient settings due to a better follow-up, reduced patient travel, and time off from work and reduced overall costs.[4] Telemonitoring can be especially useful in patients who are unable to make frequent trips to the pharmacy due to a disability or those who are reluctant to visit the pharmacy often for follow-up.

Recent studies have shown that telemonitoring can be a very effective tool for pharmacists to monitor patients on antidepressant medications and increase adherences to therapy. In 2004, Rickles et al. conducted a randomized controlled study to explore the impact of telephone-based education and monitoring on adherence by community pharmacists in patients starting antidepressant medications.[1]The intervention group received three monthly calls from pharmacists providing education and monitoring for their antidepressant regimen. The control group received no special counseling, monitoring of adherence or telephone follow-up. During the first telephone call, which took place around 3 weeks after the patient picked up initial antidepressant prescription, the pharmacist assessed the patient's antidepressant knowledge and beliefs, adverse effects and other concerns and treatment goals or areas in which they hoped the medication would help. The second and third telephone calls, which took place approximately 1 and 2 months, respectively, after the initial call, the pharmacist continued to review current adherence and identified whether the patient has experienced any new adverse effects and made new recommendations to patients as needed. Adherence was measured using pharmacy records at 3 and 6 months of starting the antidepressant therapy. There were no significant group differences in patient adherence at 3 months; however, adherence was higher in the treatment group at 6 months and the rate of missed doses was significantly lower in the treatment group than the control group (30% versus 49%, $p<0.05$).[4]

A particular barrier to the implementation of telemonitoring is lack of reimbursement mechanisms for pharmacists.[5] Additionally, there is a lack of information about the long-term return on investment on implementing pharmacist-let telemonitoring programs.[5] This is especially crucial because community pharmacies, where pharmacists frequently encounter patients with MDD, often struggle with a lack of staffing resources.[3]

Improving medication adherence through telemonitoring in patients initiating antidepressant therapy

Continued from *page 7*

Telemonitoring can be an effective strategy for increasing adherence in patients starting antidepressant therapy by allowing pharmacists to monitor and counsel patients, especially those patients who are either unable or reluctant to visit the pharmacy for follow-up. Telemonitoring will allow pharmacists to become more involved in patient care and identifying any barriers to adherence early on. However, it will require further training for pharmacists in community pharmacies in order to successfully plan and implement the integration of telemonitoring in patient care plans and pharmacy workflow.

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Preoperative Warfarin Management

Muna Chemali, B.S.Pharm

Should warfarin be stopped in patients undergoing a procedure? A question that emerges with a clinical dilemma since on one hand, warfarin plays an essential role in reducing the risk of thromboembolic events but on the other hand it would predispose the patient to an increased bleeding risk during an invasive procedure/surgery. Hence, it's important to reach a comprehensive approach towards the appropriate decision on the use of warfarin in patients undergoing a procedure.

First, **estimate the patient's thromboembolic risk** which is variable among patients and depends on the clinical indication of warfarin and the associated comorbidities , which mainly include: atrial fibrillation, prosthetic heart valves, and a recent thromboembolism. Depending on many factors, patients –of these conditions- can be further classified into a high, medium or low thromboembolic risk groups "1"; (1) *Atrial Fibrillation (AFib)* which is considered to be heterogeneous due to variable risk rates depending on the associated comorbidities. CHADS2 score and -more recently- CHADS2VAS score are clinical prediction rules used to estimate the risk for developing thromboembolic events in patients with non-rheumatic atrial fibrillation **Table 1**. AFib patients with CHADS2 score=(5-6) or CHADS2VAS score≥6 are considered to be in a high risk category, which also applies to patients with a recent onset of atrial fibrillation of 3 months. Meanwhile, a medium risk category includes Afib patients with CHADS2 score=(3-4) or CHADS2VAS score=(4-5) and finally, low thromboembolic risk category includes Afib patients with CHADS2 score=(0-2) or CHADS2VAS score=(2-3) respectively."4"

Table 1 Scoring Differences Between CHADS2 and CHA2DS2-VASc

	CHADS2	CHA2DS2-VAS
Cognitive heart failure	1	1
Hypertension	1	1
Age≥75	1	2
Diabetes	1	1
Stroke	2	2
Vascular Disease	N/A	1
Age 65-74	N/A	1
Sex: Female	N/A	1

(2) **Patients with** *prosthetic heart valves (PHV)*- the rate of thromboembolism during the first three months (particularly the first 10 to 30 days) after prosthetic valve replacement is significantly higher than after that period of time. Patients with aortic or mitral valve prosthesis, caged-ball or tilting disk are considered to be in a high risk category for thromboembolism. Having a prosthesis with no other risk factor (Diabetes, HTN, AFib or age>75) put the patient at a low risk of thrombosis. But, if having at least one of the previous factors predispose the patient to a medium risk "4"and (3) **patients with** *a recent thromboembolism*- the risk is greater in the immediate period following a thromboembolic event and declines over time, mostly 3 months after the incident, patients of a high thromboembolic risk also include those with a severe thrombophilia such as deficiencies in protein C, protein S or antithrombin. It's good to mention that even if the incident is not recent, the patient would still be at risk of thrombosis but it's considered a low risk if the incident occurred longer than 12 months, and a medium risk if thrombosis occurred in the past 3-12 months or if it's recurrent. "4"

Preoperative Warfarin Management

Continued from *page 9*

An overview of perioperative management of warfarin therapy and heparin bridging before and after a sugery or a procedure was published in "Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach" article, Blood journal 2011. Although the overview categorizes patients based on their risk for bleeding/thromboemblism, the article states that "There are no validated risk stratification schemes to estimate risk for perioperative stroke or thromboembolism as is the case with the $CHADS_2$ and CHA_2DS_2VASc prediction guides." Douketis J D et al, suggest an empiric formulation of perioperative thrombotic risk stratification based mainly on the urgent of the surgery and on the estimated bleeding and thromboemblic risk of the patient. In case of an elective surgery, the decision of keeping or discontinuing warfarin is made based on the associated bleeding risk. If the bleeding risk is low, there's no need to stop warfarin, whereas if the bleeding risk is not low, stopping warfarin is recommended five days before surgery and then to be continued in the evening following surgery if the patient is drinking fluids, otherwise resume warfarin on the first or third day following surgery as soon as the patient start drinking fluids again. If warfarin is suspended, a further decision concerning bridging with a therapeutic dose of LMWH should be made based on the thromboembolic risk; if the patient is at a low thromboembolic risk, there's no need to bridge, whereas if at a moderate or high risk, bridging is recommended and is usually stared three days before the surgery and suspended in the morning of surgery day and then is resumed on the 1st or 3rd day after surgery once hemostasis is secured, to be finally stopped on the fifth or sixth day after surgery once INR is therapeutic. "4"

In the case of a reversal of the anticoagulant effect is required for an urgent surgical or other invasive procedure in patients receiving VKAs, ACCP recommends treatment with low-dose (2.5 to 5.0 mg) IV or oral vitamin K (Grade 1C). For more immediate reversal of the anticoagulant effect, ACCP suggests the use of the four-factor prothrombin complex concentrate rather than with plasma (Grade 2C). They also suggest the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (Grade 2C). "1"

According to the American College of Chest Physicians (ACCP) Guidelines of Antithrombotic and Thrombolytic Therapy, 9th edition for patients with PVT, AFib or VTE; if they are at high risk for thromboembolism, ACCP recommends bridging anticoagulation with therapeutic-dose subcutaneous (SC) LMWH or IV UFH over no bridging during temporary interruption of VKA therapy (Grade 2C). According to the guidelines, If they are at moderate risk for thromboembolism, ACCP recommends that bridging or no-bridging approach is chosen based on an assessment of individual patient- and surgery-related factors; if they are at low risk for thromboembolism, ACCP recommends no bridging instead of bridging (Grade 2C). In patients who have had temporary interruption of a VKA before surgery or a procedure, ACCP recommends resuming VKAs approximately 12 to 24 h (the evening of or the next morning) after surgery and when there is adequate hemostasis over later resumption of VKAs (Grade 2C). "1"

Second, the patient's **procedural bleeding risk** is estimated, usually based on the type of the surgery; in major surgeries it ranges between 2-4%, meanwhile in minor procedures it's estimated between 0-2% "**7**". Hence, bleeding risk is dominated by the type and urgency of surgery; some patient comorbidities also contribute. Procedures with a low bleeding risk often can be performed without interruption of anticoagulation. Examples of high risk procedures are –but not limited to- heart valve replacement, coronary artery bypass, kidney biopsy and bilateral knee replacement. Examples of low risk bleeding procedures are –but not limited to- simple dental extractions and Cholecystectomy "5".

Preoperative Warfarin Management

Continued from *page 10*

According to ACCP Guidelines of Antithrombotic and Thrombolytic Therapy, 9th edition In patients receiving VKAs and undergoing (1) minor dental procedures ACCP recommends continuing warfarin around the time of the procedure and co-administering an oral prohemostatic agent or stopping warafarin 2 to 3 days before the procedure (Grade 2C); (2) minor dermatologic procedures ACCP recommends continuing warfarin around the time of the procedure and optimizing local hemostatsis (Grade 2C); (3) cataract removal ACCP recommends continuing VKAs around the time of the procedure (Grade 2C). "1"

After estimating both thromboembolic and bleeding risk, a decision on bridging anticoagulation can be approached to reduce the clotting risk specially in patients with high thrombolic risk with an extended suspension of their anticoagulation medication.

It's good to mention, that some recent studies compared the use of LMWHs to UFHs in periprocedural bridging therapy and found that although they result in similar efficacy and safety, there was an association between the use of LMWH and lower rates of thromboembolism, besides of showing significant cost savings compared with the use of inpatient UFH "**3**". However, both LMWH and UFH are used in bridging in perioperative settings and following are some of the ACCP 9th guideline recommendation concerning bridging with heparin.

If a therapeutic dose of SC LMWH is used in bridging, ACCP recommendation is to administer the last pre-operative dose of LMWH 24 hours before surgery or a procedure over administering LMWH 12 hours prior to surgery (Grade 2C); After a minor surgical or other invasive procedure ACCP recommends resuming the LMWH regimen approximately 24 hours after (ex. the day after) the procedure when there is adequate hemostasis instead of later resumption of VKAs (Grade 2C). **.** In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery, we suggest resuming therapeutic-dose LMWH 48 to 72 hours after surgery instead of resuming LMWH within 24 hours after surgery (Grade 2C)**.** If a therapeutic dose of IV UFH is used in bridging, ACCP recommendation is to stop UFH approximately 4 to 6 hours before surgery over stopping UFH closer to surgery (Grade 2C). "**1**"

Finally, we can conclude that for patients on warfarin and undergoing invasive surgery/procedure, reaching a decision regarding keeping or suspending warfarin should be tailored to each patient based on their estimated risk of bleeding and thrombosis, taking into consideration, their risk factors, comorbidities and the type and urgency of surgery, in order to decrease bleeding incidents and to prevent clotting events at the same time. In the same manner, deciding on anticoagulation bridging in those patients, should also be individualized, to reach the best clinical and economic outcomes.

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Possible Benefits of Ezetimibe as Adjunctive Therapy

Sheeva Chopra, PharmD, Parkland Hospital

The use of statins has been proven through various clinical trials and meta-analyses to significantly reduce low-density lipoprotein cholesterol (LDL-C) levels and has demonstrated a benefit in lowering rates of cardiovascular events. The most recent ACC/AHA lipid guidelines place preference on the use of statins when treating hyperlipidemia.[1] However, current guidelines suggest the use of non-statin therapy only in high-risk patients with insufficient response to statin therapy, who display an intolerance to lower intensity statin than what is recommended, or have a general intolerance to statin therapy. High-risk patients were defined by the guidelines as those with atherosclerotic cardiovascular disease, an LDL-C greater than 190 mg/dl, or aged 40 to 75 with diabetes.[1] When considering non-statin therapy, the use of ezetimibe has been of much debate. Ezetimibe inhibits the intestinal absorption of cholesterol, resulting in a reduction of LDL-C in the serum due to an upregulation of LDL receptors in the liver. This medication has been used in combination with statins to assist in further lowering of LDL-C levels.[2]

Much controversy related to the benefits of ezetimibe came about following the Ezetimibe and simvastatin in hypercholesterolemia enhances atherosclerosis regression (ENHANCE) trial. Despite its primary outcome not being associated with cardiovascular risk, this trial assessed the progression of atherosclerosis in patients receiving the combination of ezetimibe 10 mg in combination with simvastatin 80 mg.[3] Unfortunately the ENHANCE trial did not find a significant difference in the primary endpoint, mean change in carotid intima-thickness, between randomized patients receiving the combination of ezetimibe and simvastatin versus simvastatin as monotherapy (p= 0.29). On the other hand, the combination did provide a significant decrease in LDL cholesterol after 24 months (58% vs. 42%, $p < 0.01$).[3] This trial further supported that the use of ezetimibe is clearly a second line agent for patients with hyperlipidemia following statins as first line therapy. The reaction to the ENHANCE trial was a significant decrease in this medications growth and sales and an outbreak of criticism and concern related to its benefits.[3]

A recent trial, the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), was developed to evaluate the potential benefits of combination therapy between ezetimibe 10 mg and simvastatin 40 mg in the reduction of cardiovascular events.[2] The population analyzed were patients who presented with acute coronary syndromes and had a LDL-C less than 125 mg/dL or less than 100 if already on a medication for hyperlipidemia.[2,4,5] 18,144 patients were randomized to receive either combination therapy or simvastatin alone.[2, 5] Patients were enrolled from 2005 to 2010.[2, 5] Just recently, the results of this trial were presented at the annual American Heart Association meeting. During the presentation, it was stated that the addition of ezetimibe to simvastatin "reduced LDL-C levels by an average of 17 mg/dL" and the rate of cardiovascular events by 2% (34.7% vs. 32.7%).[5] Since this meeting, much discussion has occurred regarding the current lipid guidelines and what place in therapy non-statins, such as ezetimibe, should have.[6, 7] Some argue that adjunctive use of non-statin therapy should be considered for treatment of hyperlipidemia due to the fact that more intensive treatment can have greater clinical benefits.[6, 7] It is important to note that the results provided are considered preliminary results until the final results are published.[6] The provided results seem promising and could push towards a more aggressive treatment of hyperlipidemia with the addition of non-statin therapy in the future.

Possible Benefits of Ezetimibe as Adjunctive Therapy

Continued from *page 12*

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Painless Prandial Insulin: Could Afrezza® Be the Answer?

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Diabetes mellitus (DM) includes endocrinologic diseases that are characterized by hyperglycemia. The most common forms of DM include type 2 DM, followed by type 1 DM. Hyperglycemia in type 2 DM is a result of insulin resistance and the inability of the pancreas to produce insulin, whereas hyperglycemia in type 1 DM is a result of absolute insulin deficiency.[1] The Center for Disease Control and Prevention estimates that 29.1 million people in the United States have DM.[2] Insulin therapy is a mainstay treatment in patients with DM. While evidence supporting the benefits of insulin therapy in managing DM is well known, insulin therapy continues to be underutilized; especially in type 2 DM despite its efficacy in attaining recommended glycemic targets. Approximately 45% of patients with type 2 DM are not at the goal hemoglobin A1c (HbA_{1c}) target of less than 7%, as recommended by the American Diabetes Association (ADA), yet, only 29% of patients are on insulin.[3]

Many barriers deter patients from initiating insulin therapy or result in noncompliance to insulin therapy. According to a 2010 survey conducted by Karter *et al*, in patients with noninsulin-dependent DM, misconceptions regarding insulin risk, fear of injection, and inconvenience were found to be important barriers to initiating insulin.[4] Effective DM management is essential to prevent the microvascular and macrovascular complications that arise from this disease.

Insulin in the form of an inhalation powder has been developed as an alternative to subcutaneous insulin injections. In 2006, the United States Food and Drug Administration (FDA) approved the first insulin inhalation product marketed as Exubera®.[5] It was available for 13 months before being withdrawn from the market due to poor sales.[5] Some of the reasons for its failure were linked to the size of the device, difficult dose adjustment, dosage form inconsistencies, and risk of lung disease.[5] The inhaler was complex and very large, making it more of an inconvenience for patients. Additionally, Exubera® was never proven to be more effective than subcutaneous insulin, although it cost 30% more.[5]

Afrezza® (insulin human inhalation powder), a dry-powder formulation of recombinant human regular insulin, is a newly approved, innovative, rapid-acting inhalation insulin, developed to manage post-prandial blood glucose in adults ≥ 18 years of age with type 1 and type 2 DM.[6] This medication provides the millions of patients with DM an alternative method of prandial insulin administration with a smaller and more convenient delivery system. The FDA reports that insulin human inhalation powder is not designed to substitute long-acting insulin, however, it can be used in combination with basal insulin to improve blood glucose control in patients with DM.[6]

In an open-label, prospective, non-inferiority randomized controlled trial consisting of 539 adult patients with type 1 DM and a HbA_{1c} >7.0% and ≤11.0%, patients were randomized to receive 52 weeks of treatment with insulin human inhalation powder or insulin aspart prior to meals. All patients received a once daily dose of basal insulin in addition to the study or control treatment. The primary endpoint was the change in HbA_{1c} from baseline to the end of treatment. The results indicated no statistically significant difference in reduction of HbA_{1c} between insulin human inhalation powder and insulin aspart. The 95% CI for the difference in change from baseline was 0.11 to 0.38. This met the pre-specified non-inferiority margin of a 0.4% reduction in HbA_{1c}. Patients randomized to receive insulin human inhalation powder had a statistically significant reduction in the incidence of mild/moderate (odds ratio (OR): 0.474; confidence interval [CI]: 0.0271, 0.831; p=0.0091) and total hypoglycemia (OR: 0.488; CI: 0.278, 0.856; p=0.0124). Patients receiving insulin human inhalation powder experienced weight loss, whereas, patients receiving insulin aspart gained weight (p<0.0001).[7]

Painless Prandial Insulin: Could Afrezza® Be the Answer?

Continued from *page 14*

In another open-label, non-inferiority, randomized controlled trial, 677 insulin-dependent adult patients with poorly controlled type 2 DM, defined as a HbA_{1c} > 7.0% and ≤11.0%, were randomized to receive 52-weeks of treatment with either insulin human inhalation powder plus bedtime insulin glargine or twice daily premixed biaspart insulin (70% insulin aspart protamine suspension and 30% insulin aspart of rDNA origin). The primary endpoint was the change in HbA_{1c} from baseline to week 52. Patients receiving insulin human inhalation powder plus insulin glargine (standard error [SE] 0.077, CI: -0.83, -0.53) experienced a change in HbA_{1c} similar to and non-inferior to patients receiving biaspart insulin (SE: 0.071, CI: -0.90, -0.62). The difference between the groups was 0.07% (SE: 0.102, CI: -0.13, 0.27). Weight gain occurred less in patients randomized to receive insulin human inhalation powder plus insulin glargine as compared to those randomized to receive insulin biaspart (p =0.0002). Hypoglycemia was the most frequent adverse event reported, occurring in 31% of patients receiving insulin human inhalation powder plus insulin glargine and 49% in patients receiving biaspart insulin. Patients receiving insulin human inhalation powder plus insulin glargine experienced an increased occurrence of cough (32% vs. 4%) and a small decrease in pulmonary lung function, as measured by forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and diffusing capacity (DL_{CO}).[8]

The dry-powder formulation of recombinant human regular insulin is available as either 4-unit or 8-unit single-use cartridges to be used only with the provided inhaler via inhalation.[6] The cartridges are color-coded for convenience and safety, blue for the 4-unit and green for the 8-unit cartridge. The cartridges should be kept refrigerated, however, should be left at room temperature for 10 minutes before use. If cartridges are left at room temperature, they must be used within 10 days. The insulin human inhalation powder inhaler can be used for up to 15 days, then discarded and replaced with a new inhaler. Insulin human inhalation powder should be administered via the Afrezza® inhaler at the beginning of each meal or within 20 minutes after starting a meal. For insulin-naïve patients, the initial dose is 4 units. Information regarding dose conversion from prandial subcutaneous insulin to insulin human inhalation powder can be found in table 1. After inhalation, the powder is aerosolized and delivered to the lungs via Technosphere® Insulin particles and absorbed systemically. The medication has an onset of action of 12-15 minutes, with a peak of approximately 60 minutes and duration of action of approximately 2.5-3 hours.

Prandial Insulin Conversion Table

Converting from subcutaneous prandial insulin to Afrezza®

Subcutaneous Prandial Insulin Dose	Afrezza®
Up to 4 units	4 units [One 4 unit cartridge]
5-8 units	8 units [One 8 unit cartridge]
9-12 units	12 units [One 4 unit and one 8 unit cartridge]
13-16 units	16 units [Two 8 unit cartridges]
17-20 units	20 units [Two 8 unit cartridges and one 4 unit cartridge]
21-24 units	24 units [Three 8 unit cartridges]

Table 1: Conversion of subcutaneous prandial insulin to insulin human inhalation powder Afrezza® [package insert]. Danbury, CT: MannKind Corporation; 2014.

Painless Prandial Insulin: Could Afrezza® Be the Answer?

Continued from *page 15*

The FDA issued a Risk Evaluation and Mitigation Strategy (REMS) program upon approval of Afrezza®. Before administration of insulin human inhalation powder, lung function assessment including spirometry for evaluation FEV_1 is required. Insulin human inhalation powder carries a black box warning of acute bronchospasm in patients with chronic lung disease.6 Insulin human inhalation powder is contraindicated in patients with asthma, chronic obstructive pulmonary disease, or other chronic lung conditions, secondary to studies resulting in pulmonary function decline in this subset of patients. Insulin human inhalation powder is not recommended for the treatment of diabetic ketoacidosis. There are currently no clinical trials that determine the safety of this medication in patients with renal or hepatic dysfunction, therefore, use in this population is not recommended at this time. When using insulin human inhalation powder, it is not recommended to drink alcohol or take medications that contain alcohol. It is not recommended in patients that are pregnant, plan to become pregnant, or are breastfeeding. Common adverse effects associated with the use of insulin human inhalation powder include hypoglycemia, cough, and throat irritation.[6]

Notable drug-drug interactions with insulin human inhalation powder involve medications that may increase the risk of hypoglycemia, medications that may increase or decreased the blood glucose lowering effect of insulin human inhalation powder or medications that may affect hypoglycemia signs and symptoms.[6] It is important for patients to discuss their medication regimen with their pharmacist or provider to ensure that there are no pertinent interactions.

Insulin human inhalation powder is not yet available in pharmacies and the cost is unknown. Post-marking studies are required by the FDA to evaluate the safety and efficacy of this medication in pediatrics, potential pulmonary malignancy risks, long-term effects on pulmonary function, and other pharmacokinetic and pharmacodynamic characteristics associated with this medication. The approval of insulin human inhalation powder may help to improve adherence in patients currently prescribed subcutaneous prandial insulin. This medication may also help to increase the use of prandial insulin in patients with an elevated HbA1c, yet are reluctant to initiate insulin therapy.

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