2021 Issues

The Clinical Inquirer

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MONTHLY NEWSLETTER

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MedWise Matrix updates:

- Clindamycin noted as a low-affinity CYP3A4 substrate with an unknown MPC will now show as 85 percent
- Additional formulations (e.g., sublingual, IV, IM) of lorazepam have been added
- The bioavailability of abiraterone, a moderate CYP3A4 substrate and CYP2C8 and CYP2D6 inhibitor, increases 10 to 17 times in the presence of food, which is higher than that seen with the inhibition of CYP3A4

Monthly Clinical Inquiry highlight – Chandni Bardolia, PharmD, BCGP

Q: Is there literature that advises on the use of metformin on an as-needed (PRN) basis? Are there any safety concerns in using PRN metformin? Does PRN metformin provide A1c lowering benefits?

A: Metformin is the first-line medication for older adults with type 2 diabetes.[1] Metformin reduces blood glucose levels by decreasing the production of glucose in the liver, decreasing intestinal absorption, and increasing insulin sensitivity.[2,3] It decreases both the basal and postprandial blood glucose when used routinely.[3] A typical dosing regimen for metformin is initiated at 500mg once or twice daily and the dose is gradually titrated by 500mg every seven days.[2] The usual maintenance dose is 1g twice daily, with the maximum dose being 2.55g/daily.[2] Presently, there is a lack of evidence to support or refute the PRN use of metformin; however, the results from the two studies discussed below may build the case against PRN use of metformin.

Sambol et al. assessed whether or not metformin exhibited dose-dependent pharmacokinetics (PK) and studied the pharmacodynamic (PD) effects of single-dose versus multiple-dose metformin in individuals who are classified as noninsulin-dependent diabetics.[4] The authors noted no significant difference in PK parameters when comparing single-dose treatment to multiple-dose treatment.[4] With regards to PD of single versus multiple-dose metformin, single-dose metformin did not significantly influence pre- or postprandial insulin levels.[4] Additionally, single-dose metformin did not significantly decrease preprandial glucose levels, but at doses of 1.7-2.55g, it did significantly decrease postprandial glucose levels.[4] Although single metformin doses of 1.7g or higher decreased postprandial glucose levels in patients with diabetes, it is not until multiple doses are given that individuals show a clinically important decrease in glucose concentration.[4]

A second study demonstrated the varying PD effects of metformin with varying dosing regimens over 14 weeks.[5] Participants taking the lowest effective dose (500mg daily) reduced fasting plasma glucose by approximately 1.1 mmol/L and A1c by 0.6 percent; however, it was noted that more than 50 percent of metformin's efficacy is observed when taking 1000mg daily.[5] Safety was also assessed in this study. The majority of participants taking any dose of metformin experienced digestive disturbances, with the most prevalent being diarrhea. Metformin lowers glucose variables in a dose-related manner with daily use.[5]

Patient-specific factors should be considered, especially age, co-morbid conditions, and cognitive status. Based on the studies discussed and current ADA A1c goals, there is no clinical benefit to continued PRN metformin use. Both studies noted that metformin needs to be used on a regular basis to garner clinical benefit; therefore, utilizing metformin on an infrequent basis (e.g., PRN use) is unlikely to have clinically significant advantages. Due to a lack of evidence, it is difficult to state what adverse effects an individual may experience with PRN metformin use; however, gastrointestinal (GI) effects are likely, in addition to increased insulin sensitivity. The GI side effects of metformin are typically transient and resolve within a couple weeks on the designated maintenance dose, but may reoccur upon starting and stopping the medication.

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COVID-19 vaccine update references:

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COVID-19 vaccine update

Deepa Pednaker, PhD, RPh
APPE Student

Introduction

The novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) belongs to a family of common cold viruses and was identified in December 2019. The World Health Organization (WHO) designated the disease caused by the virus as COVID-19 and declared a global health emergency and pandemic on January 30, 2020 and March 11, 2020, respectively. Since its outbreak, COVID-19 has resulted in increased hospitalizations, mortality, and economic disruptions. As of December 14, 2020, there have been over 86.5 million cases worldwide, of which 21.1 million are from the United States.[1] COVID-19 has caused 1.61 million deaths worldwide, with higher mortality rates observed among older individuals and those with underlying comorbid conditions (e.g., diabetes, heart disease). At the time of writing, there is only one Food and Drug Administration (FDA) approved treatment: remdesivir.[2] Recently, several monoclonal antibodies have received emergency use authorization (EUA) for the treatment of COVID-19 with or without concomitant remdesivir use. Bamlanivimab, has received EUA for the treatment of mild to moderate COVID-19.[3] The combination of two monoclonal antibodies, casirivimab and imdevimab, have received EUA for the treatment of mild to moderate COVID-19. Additionally, an oral Janus Kinase (JAK) inhibitor, baricitinib, in combination with remdesivir, has received EUA to treat hospitalized patients with severe COVID-19. While treatments are emerging more frequently now, the purpose of this article is to discuss the emerging vaccinations.

Vaccines against SARS-CoV2

A safe and effective vaccine is crucial in combating COVID-19 and reducing the of morbidity and mortality of the disease. The ideal vaccine should produce balanced antibody mediated humoral responses as well as the cell mediated CD4+ T-cell response Th1 response.[4] Various vaccines are currently in progress at varied stages of development.[5,6] All vaccines that have advanced to late-stage clinical trials are administered intramuscularly; however, live intranasal vaccines have recently progressed as well. A variety of vaccine approaches are under study, including nucleic acid-based vaccines, protein subunit-based vaccines, live vaccine or whole inactivated virus vaccines, and vectored vaccines.[5]

Clinical trial update on select vaccine candidates

Pfizer and BioNtech (NCT04368728) developed two m-RNA vaccine candidates BNT162b1 and BNT162b2.[7,8] Participants included in the trials were healthy adults in the age group of 18 to 55 years and 65 to 85 years. The early phase 1 trial aimed at analyzing safety of three different doses (10ug, 30ug, or 100ug) as the primary outcome, while immunogenicity was the secondary outcome. The 10ug and 30ug doses were given as a two-dose series with an interval of 21 days between doses; the 100ug dose was administered as a single dose to the participants. Both vaccines reported mild to moderate local reaction, most common being pain at the injection site; however, patients administered BNT162b2 reported lower incidence and milder systemic side effects such as fatigue, headache, chills, muscle pain, and joint pain, especially in older adults. Both vaccines had similar immunogenicity in both younger and older adults at both 7 and 14 days. Results from the interim analysis of the BNT162b2 vaccine demonstrated 95 percent efficacy, well over the 50 percent efficacy benchmark required by the FDA, and demonstrated minimal serious safety concerns. Out of 44,000 participants in the study, 170 adults developed COVID-19; of these, 162 received placebo and 8 received the vaccine.[9] The Pfizer and BioNTech vaccine received EUA from the FDA on December 11, 2020. The vaccine may be administered to individuals 16 years of age or older for the presention of COVID-19. Pfizer will continue clinical trials and has expanded its inclusion criteria to involve children as young as 12 years for on-going phase 3 trials.

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The Pfizer vaccine is supplied as a preservative-free, multidose vial, which must be stored at ultra-cold temperatures (-70 to -100C). The vaccine requires reconsititution with 1.8 mL of 0.9 percent sodium chloride to provide 5 doses (0.3mL per dose). Once reconstituted the vaccine must be used within six hours and stored at room temperature.

Moderna (NCT04470427) was the first company to develop an m-RNA vaccine candidate and conduct phase 1 clinical trials in humans.[10,11] The phase 1 study, including healthy adults between the ages of 18 and 55, was a dose escalation study utilizing doses of 25ug, 100ug, and 250ug, administered four weeks apart.[10] The most common adverse effect was mild to moderate pain at injection site; no serious systemic adverse events were observed. The median magnitude of antibody responses after first vaccination in the 100ug and 250ug was comparable to that of median magnitude in convalescent serum samples from COVID-19 infected patients. Based on the promising results from this initial study, the trial was expanded to included older adults between the ages of 56 to 70 or ≥71 years at doses of 25ug or 100ug.[11] Similar to the study in younger adults, there were no serious adverse events and the 100ug dose was more efficacious in developing neutralizing antibody titers. The 100ug dose was used for further studies in the phase 2 and 3 trials. On November 16, 2020, Moderna announced, based on interim analysis, that their vaccine is over 94.5 percent efficacious. Of the 30,000 participants who participated in the clinical trial, there were 95 cases of COVID-19 and only five cases were in the vaccinated group.[12] Moderna applied for EUA on November 30, 2020 and received authorization on December 18, 2020.

Unlike the Pfizer vaccine, Moderna's vaccine is provided in ready-to-use vials (reconsititution not required). The vaccine can be stored in the freezer (-20C).

Janssen Research and Development (NCT04505722) is working on an adenovirus 26 (Ad26) vectored vaccine JNJ-78436735.[13] As the single dose was effective and well tolerated, this dose schedule was selected for study in a phase 3 ENSEMBLE clinical trial, which is currently in progress.

Novavax's (NCT04583995) vaccine candidate NVX-CoV2373 has also shown promising data in phase 1 trials and is currently in phase 3 trials.[14,15]

AstraZeneca's (NCT04516746) vaccine candidate AZD12222 is also in phase 3 trials in the UK and the United States.[16,17] AstraZeneca had stopped the trial due to safety concerns in one participant who experienced neurological symptoms due to a rare spinal inflammatory disorder transverse myelitis.[18] The trial was re-started after getting a green light to start the trial in the UK.[18] Interim analysis from AstraZeneca's trials indicate an average vaccine efficacy of 70 percent based on two different dosing regimens. When two full doses are given one month apart, 62 percent efficacy was noted; however, when half the dose is given followed by a full dose one month later, 90 percent efficacy was noted. The trial researchers noted that the difference in dosing regimen was actually an error; however, there is no rationale for why the two dosing regimens produced such different results. Full analysis of the results have not yet been published.

Conclusion

COVID-19 is a global health emergency. While accelerating vaccine development and production are key requirements, providing a vaccine that is both safe and efficacious is important in preventing the spread of the disease. The results from current clinical trials are very promising; however, additional research is necessary to determine long-term safety and efficacy. As of January 5, 2020, approximately 4.8 million people in the United States have received one dose of either the Pfizer or Moderna vaccine; this number is far less than officials had hoped for.

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13. Bos R, Rutten L, van der Lubbe JEM, Bakkers MJG et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. *NPJ Vaccines*. 2020 Sep 28;5:91.
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Pharmacogenomics corner

Projected utility of pharmacogenomic testing among individuals hospitalized with COVID-19: A retrospective multicenter study in the United States

Nicole Del-Toro Pagan, PharmD, BCPS PGY2

As of January 6, 2021, the novel coronavirus disease (COVID-19) has infected more than 21.1 million individuals and resulted in over 357,000 deaths within the United States. Patients diagnosed with COVID-19 and with a higher comorbidity burden are more likely to require hospitalization, which may prompt the prescribing of drugs with actionable pharmacogenomic (PGx) guidance for the treatment of acute symptoms and chronic conditions. Therefore, researchers of this study aimed to assess the possible benefit of preemptive PGx testing to improve therapy management of hospitalized patients diagnosed with COVID-19.

This study was a cross-sectional analysis of the JH-CROWN: The COVID-19 Precision Medicine Analytic Platform Registry, which collects electronic health record data on patients diagnosed with COVID-19 in a large, urban, tertiary academic medical center in the United States. The researchers developed a list of 122 drug/gene pairs with actionable PGx guidance. A drug/gene pair was deemed actionable if recommendations by the Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines were level A or B, or if the FDA table of pharmacogenetic associations classified it as "data supports therapeutic management recommendations" or "data indicates a potential impact on safety or response." Further, this list was limited to 14 commonly-assayed genes (e.g., CYP2C9, CYP2C19, CYP2D6) involved in drug metabolism and response.

Data collected included sociodemographic variables, baseline clinical characteristics, clinical outcomes, and medication orders for 1,852 consecutive hospitalized adult patients diagnosed with COVID-19. Patients had a median age of 60.1 years; a majority were male (53.3 percent) and primarily self-identified as Black non-Hispanic (35.3 percent), White non-Hispanic (29.2 percent), or Hispanic (28.6 percent). PGx testing was not completed; instead, a simulation analysis using estimated phenotype frequencies by ethnicity was performed to estimate how often PGx testing would lead to treatment modifications.

Since hydroxychloroquine is no longer recommended for routine use in the treatment of COVID-19, a second analysis was performed excluding this medication. A total of 64 drugs with actionable PGx guidance were ordered at least once. The majority of patients (87.9 percent) had at least one order for a drug with PGx guidance, while 18.7 percent were ordered four or more actionable drugs. CYP2D6 and CYP2C19 were responsible for the majority (74.0 percent) of the treatment modifications. The drugs most often affected were ondansetron, oxycodone, clopidogrel, citalopram, and pantoprazole. The researchers estimated that PGx testing would present 17 opportunities for genotype-guided treatment modifications per 100 patients tested.

This study only assessed the value of potential treatment modifications during the index hospitalization (i.e., patient's initial COVID-19 hospitalization) and failed to evaluate the impact after this period, which can vastly underestimate the lifelong utility of PGx testing. However, additional testing of this hypothesis is needed due to several study limitations. First, this simulation was established on the expected phenotype frequencies based on ethnicity and not on the actual PGx results for each patient. Second, this study evaluated opportunities for modification of medications for the treatment of chronic conditions, but information regarding the presence of lack of efficacy and/or adverse drug events was not available. Lastly, this study only assessed the potential number of PGx-guided recommendations, not the level of acceptance or readiness of the institution; therefore, assumptions regarding the impact on clinical outcomes cannot be made at this time.

In conclusion, the overwhelming majority of hospitalized patients diagnosed with COVID-19 are treated with multiple drugs with actionable PGx guidance. Preemptive PGx testing may benefit this population as it presents an opportunity to improve therapy management during hospitalization and intuitively for future outpatient care as well.

Pharmacogenomics corner references:

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2. Stevenson JM, Alexander GC, Palamuttam N, Mehta HB. Projected utility of pharmacogenomic testing among individuals hospitalized with COVID-19: A retrospective multicenter study in the United States. Clin Transl Sci. 2020.

December Clinical Inquiries

- COVID-19 and statins
- Topiramate and apixaban references
- Huntington disease chorea management
- Duration of benefit for anticoagulants

The DIRC would like to thank the Marketing department, specifically Amy Haines, for regularly reviewing the content of the Clinical Inquirer.

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MedWise Matrix updates:

- Azithromycin (oral and IV) information on QT prolongation was updated with a Long QT-JT index calculated at 1,514 and 450, respectively. The Adjusted Long QT-JT index has been set at 10 based on clinical observations. This drug is classified as Known Risk in CredibleMeds
- Desloratadine was updated. Information on QT prolongation was updated with a Long QT-JT index calculated at 88 (Intermediate Risk). This drug is not classified in CredibleMeds
- Famotidine was updated and is now listed as Conditional Risk in CredibleMeds

Monthly Clinical Inquiry highlight – Chandni Bardolia, PharmD, BCGP

Q: What is the indication for using tamsulosin in females? Is there any long-term data to support its use, in regards to efficacy and safety?

A: Tamsulosin antagonizes α-1A receptors and helps relax the smooth muscles in the prostate and bladder neck. It is commonly used in males for the management of benign prostatic hyperplasia (BPH). At this time, tamsulosin is not FDA approved for use in women and children; however, tamsulosin has been used off-label in females for lower urinary tract symptoms (LUTS) due to bladder outlet obstruction (BOO) or underactive detrusor muscle. It has also been used in women, acutely, to help pass kidney stones.[1]

Many females have reported a good clinical response and improved quality of life with tamsulosin use.[1] A recent meta-analysis looked at the safety and efficacy of tamsulosin for the treatment of LUTS in women.[2] LUTS was evaluated using a severity scoring system, International Prostate Symptom Score (IPSS). Tamsulosin improved the urodynamic parameters and post void residual volume when compared to its combination with prazosin and tolterodine. Tamsulosin was effective in treatment of LUTS in women when compared to the placebo; however, the authors were not able to provide much information about the safety of tamsulosin in females.[2]

A prospective study carried out from January 2005 to February 2007 enrolled patients with lower urethral stones <15mm diameter to be given tamsulosin once daily for two weeks.[3] Tamsulosin improved the mean score of urgency in IPSS as well as frequency of IPSS.[3] There was also an improvement in the Visual Analogue Scale (VAS) and voiding flank pain in the tamsulosin group compared to placebo.[3] The size of the urethral stone may determine whether tamsulosin should be used; Meltzer et al. noted for stones smaller than 9mm, tamsulosin does not significantly increase stone passage rate, when compared to placebo.[4]

A recent study reviewed the safety data from all the randomized clinical trials for tamsulosin use in females and children.[5] The most common adverse events in women and children were pain, asthenia, constipation, dizziness, dry mouth, drowsiness, dyspepsia, headache, incontinence, nasal congestion, nausea, orthostatic hypotension, and somnolence.[5] The overall safety profile in the female population was found to be similar to the safety profile in men.[5] The authors of the review noted that tamsulosin was fairly well tolerated and showed no acute urinary retention or serious adverse events.[2]

Urinary retention in females can impair quality of life and requires effective treatment. Evidence indicates that tamsulosin may be an effective therapy option to manage LUTS, BOO, and kidney stones and is generally well tolerated. The most common side effects reported were dry mouth, constipation, nausea, abdominal pain, dyspepsia, headache, asthenia, and dizziness. While tamsulosin may be used off-label to help manage LUTS or kidney stones in females, more randomized trials that involve more participants, and are adequately powered, are needed to support the current data.

Clinical Inquiry highlight references:

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2. Zhang HL, Huang ZG, Qiu Y et al. Tamsulosin for treatment of lower urinary tract symptoms in women: a systematic review and meta-analysis. Int J Impot Res. 2017; 29(4):148-56.
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4. Meltzer AC, Burrows PK, Wolfso AB, et al. Effect of tamsulosin on passage of symptomatic ureteral stones: a randomized clinical trial. JAMA Intern Med. 2018; 178(8): 1051-7.
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Additional data to support the Clinical Inquiry highlight:

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- Maiti K, Jaiswal A, Pal DK. A comparative study of alpha-1a blockers (tamsulosin) versus estrogens in the treatment of lower urinary tract symptoms in perimenopausal females. Indian J Pharmacol. 2020;52(1):9-9.
- Shalaby E, Ahmed AF, Maarouf A, Yahia I, Ali M, Ghobish A. Randomized controlled trial to compare the safety and efficacy of tamsulosin, solifenacin, and combination of both in treatment of double-j stent-related lower urinary symptoms. Adv Urol. 2013;752382

New drug update: Pizensy® (lactitol)

- Katie Pizzolato, PharmD
PGY1 Resident

Chronic idiopathic constipation and current treatment options:
Constipation is a term encompassing multiple symptoms, including difficulty passing stools, infrequent bowel movements, and excessive straining.[1] There are several causes of constipation, including particular medications (e.g., antihistamines, opioids), certain foods (e.g., dairy, alcohol), and underlying medical conditions (e.g., irritable bowel syndrome, diabetes). Individuals who have exhibited symptoms of constipation for at least three months, and have had a physician rule out all other potential causes, such as acute constipation or irritable bowel syndrome, may be diagnosed with chronic idiopathic constipation (CIC).[1,3,4] Approximately 35 million people in the United States are diagnosed with CIC.[1] Recent studies have indicated increased risk of CIC in women, the elderly, and those individuals with a sedentary lifestyle.[2] CIC is associated with side effects such as infrequent bowel movements, abdominal pain, and bloating, which affect an individual's quality of life, potentially leading to feelings of depression and mood disorders, particularly in the elderly.[2]

The primary goal of treatment for patients with CIC is to alleviate symptoms of constipation and regulate bowel movements to achieve a normal schedule.[3] The average individual with CIC tries four over-the-counter (OTC) and two prescription medications before discovering an effective treatment.[2] Nonpharmacologic treatment, such as increased fluid intake and regular exercise, has shown little efficacy in these patients. Pharmacologic treatment is often suggested for these patients, starting with OTC stool softeners or laxatives (e.g., docusate, biascodyl, polyethylene glycol), escalating to prescription medications (e.g., Amitiza®, Linzess®), if needed.[4] Currently, there are five medications on the market indicated for CIC, four of which are lubiprostone (Amitiza®), linaclotide (Linzess®), plecanatide (Trulance®), and prucalopraide (Motegrity®).[1] The fifth CIC prescription treatment was recently approved by the Food and Drug Administration (FDA).

Lactitol (Pizensy®), a drug formulated by Braintree Laboratories, Inc., was approved by the FDA on February 12, 2020 for CIC.[5] This article aims to provide an overview of lactitol and its place in therapy as another option for the treatment of CIC.

Pizensy® (lactitol):
Lactitol works as an osmotic laxative, producing an influx of water into the intestine. It is marketed as a dissolvable powder, meant to be dissolved in four to eight ounces of water, juice, or another beverage and fully consumed. The recommended starting dose for lactitol is 20 grams once daily with food, which can be reduced to 10 grams once daily if an individual is experiencing persistent loose stools. Administration of other medications should occur either two hours before or two hours after lactitol is taken. Commonly reported side effects include upper respiratory tract infection, flatulence, diarrhea, increased blood pressure, abdominal pain and distention, and urinary tract infection.[6,7]

Trials for lactitol:
The FDA utilized the evidence from three phase III clinical trials in their decision to approve lactitol for CIC. The first trial was a randomized, double-blind study that compared the use of lactitol 21mg and placebo in 594 constipated adults for six months, aiming to evaluate the daily dose of lactitol for safety and efficacy. The study population was primarily female (74 percent) with the majority of patients aged 50 years or older. The primary endpoint was to measure the number of subjects who had three or more complete spontaneous bowel movements (CSBMs) per week and an increase of baseline to more than one CSBM for at least 9 of the first 12 weeks. Patients using lactitol resulted in a 25 percent respondence rate as compared to 13 percent with placebo,

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demonstrating a treatment difference of 12 percent (CI 6.0-18.5; p-value <0.001).[8] In addition, of the patients taking lactitol, 74 were able to reduce their dose while still experiencing efficacy from the medication.[6,8] Regarding the safety of lactitol, this study reported three different incidents of serious adverse events in the lactitol arm: bile duct stone, blood pressure increase, and cerebrovascular accident. Additional adverse events with the use of lactitol and placebo included flatulence (8.03 percent and 2.63 percent, respectively) and urinary tract infections (6.69 percent and 8.55 percent, respectively).[8]

The second trial was a double-blind study aimed to compare the use of lactitol (20 grams once daily) to lubiprostone (24 mcg twice daily) in adult patients with CIC for a total of three months. Similar to the first study, the primary endpoint was to measure the number of patients who obtained three or more CSBMs per week and an increase of baseline tomore than one in the same week of that evaluation. The trial resulted in 25.1 percent of patients receiving lactitol meeting the primary endpoint, compared to 28.1 percent of patients receiving lubiprostone. A statistical analysis for this study proved non-inferiority of lactitol to lubiprostone (p-value = 0.016), indicating treatment with lactitol may have comparable efficacy to lubiprostone.[9] This analysis demonstrated the efficacy of lactitol, as it was compared to an FDA approved medication for CIC, resulting in similar patient outcomes regarding symptom improvement. Additionally, when analyzing the safety of lactitol compared to lubiprostone, one case of mortality and one case of cellulitis of the leg were observed in the lactitol group, both reported as unrelated to lactitol treatment; there were no incidents of mortality in the lubiprostone group. However, there was one case of stomach ulcers reported. Other adverse events following the administration of lactitol or lubiprostone include diarrhea (4.89 percent and 5.24 percent, respectively) and flatulence (7.56 percent and 1.31 percent, respectively).[9] Lastly, the third phase III trial was conducted with the intent to evaluate the safety of lactitol over the duration of one year. Following 305 patients taking lactitol, 23 (7.5 percent) experienced symptoms of diarrhea and 16 (5.2 percent) experienced symptoms of flatulence. There were no incidences of all-cause mortality; however, two serious adverse events occurred: one case of cirrhosis and one case of spondylolisthesis.[10]

Comparing lactitol to current treatment options:

Currently, the FDA-approved prescription medications for CIC act as either a guanylate cyclase-C agonist (linaclotide, plecanatide), 5-HT_4 receptor agonist (prucalopride), or a chloride channel activator (lubiprostone).[1] Considering most patients try two prescription medications before finding successful therapy, the approval of lactitol offers a new medication with a different mechanism of action to aid in treatment. In addition, lactitol is dosed once a day as opposed to lubiprostone, which is dosed twice a day, likely increasing adherence if it is an issue.

In addition, lactitol separates itself from its predecessors by being the only FDA approved product that the patient can self-titrate based on their personal stool consistency. Pizensy® will be supplied in 10-gram unit-dose packs, as well as in 280 grams and 560 grams multi-dose bottles with 10-gram measuring caps included.[6] Therefore, patients can adjust their medication to a lower effective dose of 10 grams daily, if they deem necessary. Lactitol also separates itself from other prescribed active comparators since it is formulated as a dissolvable powder, while all others are in tablet form. This dosage form may be ideal for patients who struggle with ingesting tablets.[6,7]

Unfortunately, the anticipated availability is currently unknown for lactitol and therefore cost data is unavailable at the moment. All of the approved prescription options for CIC are only available as brand name, ranging from $288 to $525 for a 30-day supply, independent of insurance coverage.[11] Thus, when more information is available, it will be very important to evaluate cost associated with lactitol.

Final considerations:

Overall, CIC affects millions of individuals, with geriatric patients being at an increased risk. Given the potential mental health-related implications associated with CIC, it is imperative to identify a successful treatment option to prevent negative outcomes. Although its place in therapy cannot be defined at this time, considering the low safety concerns and unique mechanism of action of this prescription product, lactitol can serve as an alternative therapy option in those individuals that have not been able to find medications to manage their CIC effectively.

Pizensy® references:

1. Lacy BE. Update on the Management of Chronic Idiopathic Constipation. Volume 25, Issue 4. Published March 27, 2019. Accessed December 1, 2020.
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10. Braintree Laboratories, Inc. An Open Label Study of Chronic Use of BLI400 Laxative in Constipated Adults. https://clinicaltrials.gov/ct2/show/results/NCT02819310. NCT02819310. Accessed December 1, 2020.
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Pharmacogenomics corner

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6, OPRM1, and COMT genotype and select opioid therapy

- Nicole Del-Toro Pagan, PharmD, BCPS PGY2

The purpose of this guideline update is to expand on the 2014 CPIC guidelines for *CYP2D6* genotype and codeine therapy. This update discusses the evidence on the impact of *CYP2D6* genotype for other opioids (e.g., tramadol, hydrocodone, oxycodone) and recommendations specific to indication for analgesia are provided. Additionally, evidence of opioid receptor μ1 (OPRM1) and catechol-O-methyltransferase (COMT) impact on pain control, risk for adverse drug events (ADEs), and opioid requirements is reviewed.

Currently, codeine and tramadol have the strongest level of evidence for the use of *CYP2D6* genotype results in clinical practice. Evidence for codeine has shown that poor metabolizers (PMs) achieve inadequate pain control and have reduced gastrointestinal side effects compared to normal metabolizers (NMs). However, central nervous system side effects (e.g., sedation, dry mouth) do not appear to be different among these two groups. Ultra-rapid metabolizers (UMs) have increased concentrations of the active drug (i.e., morphine) compared to NMs. For tramadol, PMs have reduced concentrations of the active metabolite (i.e., o-desmethyltramadol) compared to NMs; while UMs have increased concentrations. The latter has been associated with greater analgesia, increased miosis, and higher incidence of nausea. CPIC recommends avoiding codeine or tramadol therapy in UMs and PMs, due to a higher risk of toxicity and therapy failure, respectively. For NMs and intermediate metabolizers (IMs), guidelines recommend using label-recommended age- or weight-specific dosing.

Hydrocodone and oxycodone have a weaker level of evidence for the use of *CYP2D6* genotype results in clinical practice. Although hydrocodone has clinical analgesic activity, its active metabolite, hydromorphone, has a 100-fold higher affinity to the μ-opioid receptors. In individuals who are PMs, lower concentrations of hydromorphone have been reported; however, it is still unclear how this translates to pain control and risk for ADEs. For IMs and PMs, CPIC recommendations to follow label-recommended age- or weight-specific dosing, and if response is inadequate and opioid use is warranted, to use a non-codeine or non-tramadol opioid. For UMs, no recommendations are provided due to the lack of evidence. Similar to hydrocodone, oxycodone also has clinical analgesic activity and its active metabolite, oxymorphone, has a 60-fold higher affinity to the μ-opioid receptors. However, it is believed that oxycodone may be the major contributor to pain relief. Since studies have failed to demonstrate an impact of the *CYP2D6* genotype on pain control or risk for ADEs, there are no recommendations to guide clinical practice for oxycodone based on *CYP2D6* genotype at this time.

Evidence on the variant rs1799971 (A118G) of *OPRM1* has inconsistently been associated with altering opioid requirements. COMT is a regulator of pain perception and the variant rs4680 (p.Val158Met) has been evaluated for its influence on opioid response. At this time, there are no recommendations for dosing opioids based on either *OPRM1* or *COMT* genotype due to the lack of consistent evidence.

This updated guideline provides information to empower clinicians to use genetic results to guide opioid therapy. PGx-guided dosing can possibly improve therapeutic outcomes and decrease risk for ADEs for patients on opioid therapy. Although limited evidence exists to provide recommendations for hydrocodone and oxycodone based on *CYP2D6*, considering pain is highly subjective, a discussion with the patient to establish appropriate level of pain control without experiencing ADEs should be conducted. This discussion can assist the clinician to optimize therapy. Although *CYP2D6* genotype testing can provide valuable information to guide opioid therapy, when available, clinicians should still consider other genetic and clinical factors that may also influence the patient's response.

References:

1. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6, OPRM1, and COMT genotype and select opioid therapy. *Clin Pharmacol Ther*. 2021.

January Clinical Inquiries

- Metabolism pathway for eliglustat
- Switching between Trulicity® and insulin
- Depiection of P-gp in the MedWise Matrix
- Morphine ER vs. methadone for chronic pain
- PGx testing prior to initiation of clopidogrel

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MedWise Matrix updates:

- Betrixaban has been added to the Matrix as NON-CYP.
- Omadacycline, used for community-acquired pneumonia and skin infections, has been added to the Matrix as NON-CYP.
- Abemaciclib, approved for the treatment of advanced or metastatic breast cancers, has been updated with regards to information on QT prolongation. The long QT-JT index was calculated at 9.43 (high risk). This drug is not classified in CredibleMeds.

Monthly Clinical Inquiry highlight – Chandni Bardolia, PharmD, BCGP

Q: In terms of estimating a patient's renal function, is GFR or CrCl preferred?

A: It is common clinical practice to measure GFR via estimating creatinine clearance based on the serum creatinine level measured. Creatinine is filtered by the glomerulus; however, it is also actively secreted by the peritubular capillaries in small amounts leading to an overestimation of actual GFR by 10 to 20 percent. This margin of error is generally acceptable due to the ease of estimating creatinine clearance versus taking precise GFR measurements.

Actual GFR measurements involve constant infusion of inulin. Urinary inulin clearance is recognized as the gold standard for precise GFR measurements because inulin represents an ideal marker: it is freely filtered by the glomerulus, it is not secreted or reabsorbed in the tubules, and it is not synthesized or metabolized by the kidney. The measurement requires a constant intravenous infusion to maintain a constant level of inulin over 3 to 4 hours. Urine is then collected every 30 minutes and the urinary and plasma inulin are measured to calculate its clearance. The mean clearance of 4 or 5 measurements determines the patient's GFR. At this time, measuring inulin clearance remains the gold standard for assessing a patient's GFR; however, most laboratories cannot routinely measure inulin making the overall practice impractical.

With that being said, creatinine estimates of GFR have their limitations as well. All of the estimating equations depend on a 24 hour creatinine excretion rate, which is a function of muscle mass. Muscle mass from patient to patient may vary, which cause for inaccuracies with the CrCl measurement. With a higher muscle mass, serum creatinine will be higher for any given rate of clearance. One commonly used equation, the Cockcroft-Gault equation does not correct for race. Studies have demonstrated that serum creatinine concentrations tend to be higher in black patients versus non-black patients, potentially due to differences in body composition. Additionally, creatinine based equations should be used with caution in cachectic patients and patients with cirrhosis, due to their reduced muscle mass and lower creatinine excretion rate. In this case, equations like the Cockcroft-Gault may underestimate a patient's poor renal function.

Overall, GFR is considered a more accurate representation of patient's renal function and should be utilized if attainable. CrCl has been an acceptable estimation over the years; however, there are limitations to its use as discussed above.

Clinical Inquiry highlight references:

1. Kidney Disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management oc Chronic Kidney Disease. *Kidney Inter*. Suppl. 2013;3:1-150.

2. Hsu J, Johansen KL, et al. Higher serum creatinine concentrations in black patients with chronic kidney disease: beyond nutritional status and body composition. *Clin J Am Soc Nephrol*. 2008; 3(4): 992-997.

3. Langlois V. Laboratory evaluation at different ages. *Comp Ped Nephrol*. 2008. Available: https://www.sciencedirect.com/science/article/pii/B9780323048835500088?via%3Dihub Accessed May 2, 2019.

New and Approved Drugs

Meghan Ha, PharmD, PGY1 Resident

Bempedoic acid/ ezetimibe (NEXLIZET™, Esperion) $$$$

Nexlizet™ is a combination antilipidemic product consisting of 180mg bempedoic acid and 10mg ezetimibe. It was approved by the Food and Drug Administration (FDA) on February 26, 2020 for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of low-density lipoprotein-C (LDL-C). Use of this new combination medication is recommended as an adjunct to diet management and a maximally tolerated statin. While ezetimibe has been on the market since 2002, bempedoic acid was approved in February 2020. Bempedoic acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor that inhibits cholesterol synthesis in the liver. Bempedoic acid and ezetimibe decrease LDL-C by 19 percent and 25 percent, respectively. Phase 3 trial data showed that when combined, the combination lowered LDL-C by 38 percent compared to placebo.

The medication is available as oral tablets dosed once daily, without regard to meals. The most common adverse drug reactions with bempedoic acid/ezetimibe are constipation (5 percent), urinary tract infections (6 percent), and nasopharyngitis (5 percent). Hyperuricemia has occurred in patients (bempedoic acid 26 percent vs. placebo 9.5 percent), typically within the first weeks of initiating the medication and throughout treatment and may contribute towards gouty attacks. Patients, particularly those older than 60 years of age, should be counseled on the risk of tendon rupture when using this combination along with corticosteroid or fluoroquinolone drugs, or when experiencing renal failure.

Although this combination is recommended in use for patients who are maximally tolerated on statin therapy, bempedoic acid is not recommended to be used concomitantly with pravastatin doses exceeding 40mg and simvastatin doses exceeding 20mg. This is due to the fact that bempedoic acid can significantly increase the concentrations of these two statin agents and put the patient at higher risk for myopathy. Additionally, ezetimibe/ bempedoic acid should be administered either $\geq$2 hours before or $\geq$4 hours after bile acid sequestrants. The effect of bempedoic acid/ezetimibe on cardiovascular (CVD) morbidity and mortality has not been determined; however, clinical trials are currently in progress.

Vibegron (GEMTESA®, Urovant Sciences)

Gemtesa® is a beta-3 agonist that was approved in December 2020 for the treatment of adult patients with overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. The mechanism of action of vibegron involves selective activation of the beta-3 adrenergic receptor, which increases bladder capacity through relaxation of the detrusor smooth muscle during bladder filling. It is administered as a 75mg once-daily oral tablet and does not require a dose titration. Vibegron is generally well tolerated with a low risk of adverse reactions; some reported adverse reactions include hot flashes (<2 percent), gastrointestinal effects (2 percent), and headache (4 percent). Vibegron also does not increase risk of hypertension when compared to placebo, which is another advantage vibegron poses over the widely-used mirabegron.

Compared to the only other beta-3 agonist, mirabegron, vibegron does not interact with medications through the CYP2D6 pathway. This is significant because mirabegron is known to be a potent inhibitor of CYP2D6 and can perpetrate many drug interactions. While clinically significant interactions with vibegron are limited at this time, the manufacturers have reported it may increase serum concentrations of digoxin. Gemtesa should be available in the United States by the end of the first quarter of 2021. Pricing data is not currently available.

[con't p.2]

Ticagrelor (BRILINTA, Astra Zeneca) – Stroke Prevention $$$

Ticagrelor is a potent P2Y12 inhibitor that was initially approved in July 2011 for the treatment of acute coronary syndrome (ACS), which was expanded in 2015 to also reduce the rate of cardiovascular death, myocardial infarction (MI), and stroke in patients with ACS or a history of MI. In June 2020, ticagrelor received approval to reduce the risk of a first heart attack or stroke in high-risk patients with coronary artery disease (CAD) and most recently, in November 2020, it received the approval to reduce the risk of stroke in patients with an acute ischemic stroke (NIHSS score ≤5) or high-risk transient ischemic attack (TIA) (ABCD2 score ≥4), following the completion of the THALES trial. The NIHSS score quantifies stroke severity and the ABCD2 score estimates the risk of stroke after a suspected TIA.

While the THALES trial demonstrated clinically significant stroke prevention benefits of dual ticagrelor and aspirin therapy, the combination resulted in a number of severe bleeding events, including intracranial hemorrhages and fatal bleeding events [ticagrelor + aspirin group (n = 39) versus placebo + aspirin group (n=9)]. Ticagrelor is contraindicated in patients with active pathological bleeding (i.e. peptic ulcer, intracranial hemorrhages) and in patients with a history of intracranial hemorrhages. Ticagrelor is not subject to the same hepatic activation requirement as the P2Y12 inhibitor clopidogrel, which makes it favorable agent to meet the pharmacokinetic needs of most patients, if clinically appropriate.

Fluticasone/Umeclidinium/Vilanterol (TRELEGY ELLIPTA, GlaxoSmithKline) – Asthma $$$$

Trelegy Ellipta was appraised as the first once-daily, maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD) consisting of three medications—fluticasone (FF; inhaled corticosteroid), umeclidinium (UMEC; long-acting muscarinic antagonist), and vilanterol (VI; long-acting beta agonist)—during its initial approval back in September 2017. Three years later, in September 2020, the combination inhaler has now received an indication for the treatment of asthma in patients aged 18 years and older. This new approval for Trelegy Ellipta is at a strength that slightly differs from its COPD indication. For the indication of asthma, the component dosing is as follows: FF/UMEC/VI 200/62.5/25mcg, whereas in COPD it is dosed as FF/UMEC/VI 100/62.5/25mcg.

This new indication's approval was based on the results of the CAPTAIN study that showed that patients uncontrolled on ICS/LABA found significant improvements in lung function with the addition of on a long-acting muscarinic antagonist, in comparison to dual therapy with FF/VI. Of note, when used for asthma, FF/UMEC/VI is only approved for maintenance treatment in asthma and is not indicated for relief of acute bronchospasm. It should also not be initiated in patients experiencing significantly worsening, potentially life-threatening, or acutely deteriorating asthma.

Tramadol (QDOLO™, Athena Biosciences) - $$$$

Authorized in September 2020, the newly approved form of tramadol hydrochloride comes as a 5mg/mL oral solution and is sold in a 473mL stock bottle. This oral formulation contains notable ingredients such as propylene glycol, sodium benzoate, and grape flavoring, in addition to the active ingredient, tramadol hydrochloride. Propylene glycol toxicity, sodium benzoate-induced allergic dermatitis, and anaphylactic reactions to grapes should be considered with use of tramadol oral solution. Patients would be dosed to the equivalent strength as they would with the tablet form of tramadol, with 10mL being equivalent to the usual starting dose of 50mg. The liquid formulation provides two notable advantages: it addresses the needs of patients who have difficulties swallowing and allows for precision titration and dosing.

Similar to the tablet formulation, this formulation undergoes activation through CYP2D6 and its use should be cautioned in patients who are CYP2D6 ultra-rapid metabolizers. The same warnings and precautions apply to the new formulation, including but not limited to: serotonin syndrome, risk of seizure, risk of suicide, and severe hypotension. Treatment initiation should begin with 25mg/day of Qdolo with a 25mg incremental titration as separate doses every three days to reach 100mg/day (25mg four times a day). Afterwards, the total daily dose may be increased by 50mg every three days to reach 200mg/day. Post titration, Qdolo can be dosed 50 to 100mg every four to six hours and not to exceed 400mg/day. Geriatric patients older than 75 years should not exceed a total daily dose greater than 300mg/day. Doses should be limited to 50mg every 12 hours in patients with severe hepatic impairment and a maximum daily dose of 200mg with 12-hour dosing intervals in patients with a creatinine clearance less than 30mL/min. There is no available literature comparing the bioavailability of the oral solution to the extended-release oral tablet formulation, so conversion from solution to tablet should be accompanied with close observation for excessive sedation and respiratory depression.

Because this medication comes in the form of a solution and its strength is recorded in mg/mL, there is potential for medication dosing errors to occur as clinicians may overlook mg and mL when identifying orders. Healthcare providers should be aware that Qdolo is a part of the Opioid Analgesic REMS program to reduce the risk of abuse, misuse, addiction, overdose, and deaths due to prescription opioid analgesics.

Key: (Approximate cost per month supply)

¢	<$1
¢¢	$1 - $5
¢¢¢	$5 - $10
¢¢¢¢	$10 - $25
$	$25 - $75
$$	$75 - $150
$$$	$150 - $500
$$$$	>$500

Pharmacogenomics corner

Allopurinol therapy and HLA-B*58:01 genotype

- Rowyda Abdalla, 2021 PharmD Candidate -

Allopurinol, a xanthine oxidase inhibitor, is commonly used to manage hyperuricemia, gout, and tumor lysis syndrome. The human leukocyte antigen B (HLA- B) is a key factor in how the immune system responds to pathogens. The variant HLA-B*58:01 allele, most commonly seen in Asian populations, is associated with severe cutaneous adverse reactions (SCARs) during treatment with allopurinol. While rare, serious allopurinol-induced SCARs can lead to a mortality rate of up to 25 percent. Currently there is no mention of the HLA-B phenotype on the Food and Drug Administration (FDA) approved drug label for allopurinol, despite the high -prevalence of allopurinol-induced SCARs as well as the recommendation by the American College of Rheumatology (ACR) to test for HLA-B*58:01 before initiation of allopurinol in individuals of Southeast Asian descent and African Americans.

Two categories of drug reactions exist: Type A and Type B. Type A include adverse drug events (ADEs) that are predictable based on their drug properties and account for the majority (~85-90 percent) of all ADEs. Type B include hypersensitivity reactions that occur in susceptible individuals. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), as well as drug reaction with eosinophilia and systemic symptoms (DRESS), are examples of Type B allopurinol-induced SCARs. Although the specific cause is unclear, cytotoxic T-cells are known to be involved in eliciting a hypersensitivity reaction. The presence of HLA-B*58:01 does increase the risk of allopurinol-induced SCARs; however, it is not the only contributor to the etiology of SCARs.

In addition to the HLA-B*58:01 allele, risk factors for allopurinol-induced ADRs include other genetic risk factors (e.g., HLA-B75) and non-genetic risk factors (e.g., kidney impairment, allopurinol starting dose, and concomitant diuretic). The combination of genetic and non-genetic risk factors could contribute towards the development of allopurinol-induced ADRs. Genetic testing is available for HLA-B*58:01 as well as allopurinol response. The results can either be positive or negative; there is no intermediate phenotype as HLA-B is expressed in a codominant manner. Positive indicates HLA-B*58:01 is present in one or both copies of the HLA-B gene, whereas negative indicates there are no copies of the HLA-B*58:01 allele present.

Though not recommended by the FDA, testing for HLA-B*58:01 prior to initiation of allopurinol therapy is recommended and considered cost effective in individuals of southeast Asian descent or African American individuals by the ACR and the Clinical Pharmacogenetics Implementation Consortium (CPIC). Individuals that do possess HLA-B*58:01 should not start allopurinol therapy and should choose an alternative medication such as febuxostat. It is important to note, a negative test for HLA-B*58:01 does not completely eliminate the possibility of developing SCARs in populations such as Europeans.

Currently, the FDA-approved dose for the management of gout or hyperuricemia ranges from 100mg to a max daily dose of 800mg until the desired uric acid concentrations (6.0mg/dL) are achieved. Oftentimes, allopurinol is prescribed at lower doses to reduce the risk of hypersensitivity; however, the doses are too low to achieve therapeutic goal. A gradual dose escalation to achieve target serum urate levels is being studied based on renal function and should be avoided in individuals who experience hypersensitivity reactions to allopurinol therapy.

Given the high prevalence of allopurinol-induced SCARs, allopurinol should not be prescribed to individuals who have tested positive for HLA-B*58:01. To avoid the risk of developing SCARs, alternative treatment options should be considered for these individuals. For additional information and complete therapeutic recommendations, please review the following links: FDA, ACR, and CPIC.

Reference:
Dean L, Kane M. Allopurinol therapy and HLA-B*58:01 genotype. U.S. National Library of Medicine. 2021.

February Clinical Inquiries

- Metered dose inhalers vs. dry powder inhalers
- Trulicity for individuals with thyroidectomy
- Concomittant naltrexone and buprenorphine for pain
- Switching between anticonvulsant therapies
- Natural remedies for insomnia
- As needed use of gabapentin
- Managing bloot clots in patient with Factor V Leiden mutations

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MedWise Matrix updates:

- Information on the QT prolongation for amoxapine was updated with a Long QT-JT index calculated at 16 (High Risk)
- Information on the QT prolongation for atazanavir was updated with a Long QT-JT index calculated at 1.43 (High Risk)
- Information on the QT prolongation for cilostazol was updated with a Long QT-JT index calculated at 15.3 (High/Intermediate Risk)

Monthly Clinical Inquiry highlight – Briana Skalski, PharmD, BCGP

Q: Is there a preferred loop diuretic in chronic kidney disease?

A: Pharmacokinetic parameters and concomitant disease states are factors one can consider when selecting the appropriate loop diuretic for their patient. Loop diuretics are variably metabolized. Torsemide is approximately 80 percent cleared by the cytochrome P450 (CYP450) system, whereas approximately 50 percent of bumetanide is metabolized by the CYP450 system. Differentially, only 10 percent of furosemide is metabolized by the CYP450 system. Both bumetanide and torsemide are better absorbed than furosemide. Moreover, the consistency of torsemide's absorption and its longer duration of action are two features that may be favorable in a patient with chronic heart failure and chronic kidney disease (CKD).

As the most widely used loop diuretic, furosemide's pharmacokinetic profile is more significantly altered in CKD compared to that of torsemide or bumetanide. Approximately 50 percent of a dose of furosemide is excreted unchanged, while the remainder is conjugated to glucuronic acid in the kidney. Because furosemide is metabolized by the kidney, both its renal metabolism (conjugation) and clearance are reduced in CKD, prolonging its half-life. Bumetanide and torsemide undergo significant metabolism by the CYP450 system; thus, in CKD their pharmacokinetic profiles change as a result of decreased kidney clearance only.

Regardless of the loop diuretic, the renal clearance of these drugs is reduced in parallel to the level of change in renal function. They are particularly useful in CKD stage 4 or 5 patients for treating edema or high blood pressure in addition to a thiazide diuretic, especially if the thiazide diuretic has lost its ability to overcome fluid retention. When selecting a loop diuretic, physicians may want to address significant drug interactions involving the CYP450 system or concomitant disease states in their patient that may benefit from a loop diuretic with a prolonged half-life.

Reference:

Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Inter. Suppl. 2013;3:1-150.

New and approved drugs

Aashish Sreeram, PharmD, PGY1 Resident

Newly approved medications:

Vericiguat (*VERQUVO™*, Merck Sharp and Dohme Corp) $$$$
Vercuvo™ was approved by the U.S. Food and Drug Administration (FDA) in January 2020 for use in adults with symptomatic chronic heart failure (CHF) and ejection fraction (EF) <45 percent who are already on other optimized CHF therapy. Vericiguat is a soluble guanylate cyclase (sGC) stimulator that works to increase activity of sGC to improve smooth muscle relaxation and vasodilation. While it is the second sGC stimulator on the U.S. market, it is the first one to be approved for CHF patients. In the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA), vericiguat demonstrated a reduction in the incidence of mortality from cardiovascular causes. The starting dose for vericiguat is 2.5mg by mouth daily with food; this dose is doubled every two weeks to reach the maintenance dose of 10mg once daily, as tolerated. Vericiguat is supplied in doses of 2.5mg, 5mg, and 10mg tablets. Vericiguat does not require dosage adjustment in patients with renal or hepatic impairment. Additionally, vericiguat does not require dosage adjustments in geriatric patients; however, older adults may be sensitive to the effects of vericiguat. Vericiguat is contraindicated in patients using other sGC stimulators (e.g., riociguat) and use should be avoided in individuals using phosphodiesterase 5 inhibitors. The most commonly reported adverse drug effects are hypotension and anemia. Vericiguat is metabolized primarily through glucuronidation by UGT1A9, while CYP450-mediated metabolism is a minor clearance pathway (<5 percent). Vericiguat is also a substrate of BCRP/ABCG2 and a minor substrate of P-glycoprotein. The launch date for vericiguat has yet to be determined.

Cabotegravir/rilpivirine (*CABENUVA*, Viiv Healthcare) $$$$
Cabenuva is a two-drug, co-packaged medication containing cabotegravir and rilpivirine. Cabotegravir is an integrase strand transfer inhibitor (INSTI) and rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Cabotegravir/rilpivirine was approved by the FDA in January 2020 as a complete regimen for human immunodeficiency virus type-1 (HIV-1) in adults. Cabotegravir/rilprivirine is indicated to replace an antiretroviral regimen for those who are virologically suppressed (HIV RNA <50 copies/mL) with no history of treatment failure or resistance to either cabotegravir or rilpivirine. This combination marks the first approved extended-release injectable drug regimen for adults with HIV-1. Prior to initiating the injection, a patient must first be treated with oral cabotegravir and rilpivirine for approximately one month to assess tolerability of this combination. The lead-in dosing schedule is one 30mg tablet of cabotegravir and one 25mg tablet of rilpivirine by mouth daily with food. Initiation of injection occurs on the final day of oral therapy with a starting dose of 600mg cabotegravir and 900mg rilpivirine injected intramuscularly into the gluteus. Following this initiation dose, individuals tolerating therapy will be injected once monthly moving forward. These injections are administered by a healthcare professional; therefore, it is important that patients remain adherent with scheduled visits. If a patient misses a scheduled injection by more than seven days, daily oral therapy of cabotegravir and rilpivirine can replace up to two consecutive months of missed visits. No dosage adjustment is required for patients with renal or hepatic impairment. However, patients with severe renal impairment (creatinine clearance <30mL/min) may require increased monitoring for adverse effects. It is also important to note that the effect of severe hepatic impairment (Child-Pugh C) on pharmacokinetics of cabotegravir/rilpivirine is unknown. Commonly reported adverse effects pertaining to the injectable formulations include pyrexia, fatigue, and headache. Additionally, cabotegravir is primarily metabolized by UGT1A1 along with minor involvement of UGT1A9, while rilpivirine is primarily metabolized by CYP3A4. Strong inducers of UGT1A9 and CYP3A4 (e.g., rifampin, carbamazepine, phenytoin) are contraindicated with cabotegravir and rilpivirine. Cabenuva is available as of February 2021.

Sodium sulfate/magnesium sulfate/potassium chloride (*SUTAB*®), Braintree Laboratories) $$
Sutab® was approved by the FDA in November 2020 for use as an osmotic laxative to cleanse the colon in preparation for a colonoscopy in adults. This mechanism of action occurs due to the osmotic action of sodium sulfate and magnesium sulfate. This results in water retention in the lumen of the colon resulting in loose stools. Sutab joins Osmoprep® as the second tablet formulation for colonoscopy preparation. Unlike Osmoprep, Sutab is dosed with 24 tablets rather than 32. The dosing regimen begins the day prior to a colonoscopy with 12 tablets by mouth with a sip of water, drinking the full 16oz over a period of 15 to

[con't p.2]

20min. One hour after the last tablet is ingested, another 16oz of water should be consumed over a 30min period. After another 30min, 16oz should be consumed over another 30min period, one last time; thus, a total of 48oz of water should be consumed. On the day of the colonoscopy, the patient should repeat the entire regimen a second time five to eight hours before the colonoscopy. All water should be consumed at least two hours before the procedure. This medication does not have any dosing adjustments for patients with renal or hepatic impairment; however, it is important to ensure adequate hydration is observed especially in renally impaired patients. Sutab is contraindicated in patients with ileus, bowel perforation, toxic colitis/megacolon, and gastric retention. Commonly reported adverse effects of Sutab are nausea, abdominal distension, vomiting, and upper abdominal pain. Additionally, avoiding solid food, red and purple liquids, milk, and alcoholic beverages should be observed during the administration period. A low residue breakfast such as eggs, white bread, or cottage cheese is allowed on the day before the colonoscopy. Afterwards, a clear liquid diet should be followed through the day prior and day of the colonoscopy. Sutab has been available on the market as of January 2021.

Newly approved indication:

Liraglutide (*SAXENDA*®) Novo Nordisk $$$$
Liraglutide was originally approved in 2010 as Victoza® for use in adults with type 2 diabetes mellitus to improve glycemic control. Following this indication, liraglutide was approved for adjunctive treatment for chronic weight management in adults as Saxenda®. In December 2020, the FDA extended the approval for Saxenda to be used in the adolescent population (12 to 17 years). Liraglutide has various mechanisms through which it promotes its weight loss effect. It is a glucagon-like peptide 1 analog, which increases postprandial insulin levels, decreases glucagon secretion, reduces gastric emptying, and reduces appetite. In a randomized controlled trial of liraglutide for adolescents with obesity, results revealed an average decrease in the standard deviation score of body mass index (BMI) (-0.22). The dosing regimen for the pediatric population is the same as adults: 0.6mg subcutaneously once daily and increase by 0.6mg/day weekly up to a target dose of 3mg/day. There are no dosing adjustments to consider for patients with renal or hepatic impairment. Contraindications to liraglutide include any previous hypersensitivity to liraglutide, history or family history of medullary thyroid cancer, history of multiple endocrine neoplasia syndrome type 2 (MEN2), or pregnancy. Common adverse effects with liraglutide are nausea, vomiting, headache, tachycardia, hypoglycemia, and constipation/diarrhea. Common drug interactions of Saxenda are mainly with medications that may enhance the hypoglycemic effect (e.g., sulfonylureas, insulin,selective serotonin reuptake inhibitors).

Newly approved biosimilar:

Insulin glargine (*SEMGLEE™*, Mylan Pharmaceuticals) $-$$
Semglee™ cleared FDA approval in June 2020. It joins two other insulin glargine biosimilar products, Lantus® and Basaglar®, as a long-acting insulin option for patients with diabetes (types 1 and 2). Semglee is available in both vial and injectable pen formulation like Lantus, whereas Basaglar is only available as an injectable pen formulation. All three products are equivalent in insulin conversion (1:1) and are each dosed once daily. Although insulin products are biosimilar, patients may have differences in response when switching between the products. It is important to monitor a patient's blood glucose and A1c for continued safety and efficacy. The most notable feature of Semglee is cost; currently, Semglee costs less than Lantus and Basaglar.

Key:
(Approximate cost per month supply)

₵	<$1
₵₵	$1 - $5
₵₵₵	$5 - $10
₵₵₵₵	$10 - $25
$	$25 - $75
$$	$75 - $150
$$$	$150 - $500
$$$$	>$500

Pharmacogenomics corner

A hybrid implementation-effectiveness randomized trial of CYP2D6 -guided postoperative pain management: A summary

- Scott Jacobs, 2021 PharmD Candidate

Recent studies show that Americans suffer from pain more than heart disease, lung disease, and cancer combined. Opioid prescription medications play a large role in acute and post-operative pain management in the United States. According to the Center for Disease Control, 153 million opioid prescriptions were written by prescribers in 2019, resulting in a 46.7 percent opioid dispensing rate per 100 Americans. Several opioid medications (e.g., codeine, hydrocodone, oxycodone, tramadol) require metabolic conversion by the body's CYP2D6 enzyme into potent active metabolites. The CYP2D6 gene contains over 130 different alleles, resulting in multiple variations that can cause a multitude of responses specific to the individual. These different enzyme responses are often categorized into poor, intermediate, normal, and ultra-rapid metabolizers. If a patient is deemed a CYP2D6 poor metabolizer, then they can expect inadequate analgesic effects from the opioid medication. If a patient is found to be a CYP2D6 ultra-rapid metabolizer, then they may experience toxic concentration of the active metabolite, which can result in death. Currently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines recommend the use of a CYP2D6 genotype guide when prescribing opioid medications for a patient; however, adoption in practice has been scarce.

A study was conducted to evaluate the feasibility of implementing a CYP2D6-guided postsurgical pain management protocol and determine if this approach would not worsen pain control. The study was a randomized, open label, type 2 hybrid implementation effectiveness trial that took place between 2018 to 2019. A total of 260 participants participated from two different University of Florida orthopedic clinic sites. All participants were adults (>18 years old) that underwent unilateral joint arthroplasty and received long-term opioid therapy, defined as use on most days for more than three months. Participants were randomized into two different treatment arms labeled "genotype-guided" (n= 173) and "usual pain management" (n=87). Each patient's CYP2D6 genotype and phenotype was determined at the start of the trial. In the genotype-guided treatment arm, 20 percent of its participants were found to carry the poor, intermediate or ultra-rapid metabolizer phenotype. This resulted in 72 percent of participants to receive an alternative opioid other than codeine, tramadol, hydrocodone, or oxycodone compared to zero percent of participants in the usual pain management treatment arm ($p<.0.001$). Hydromorphone was the most commonly prescribed alternative opioid for participants with a high-risk phenotype in the CYP2D6-guided arm (69 percent). The most commonly prescribed therapy for high-risk phenotypes in the usual treatment care arm was tramadol + hydrocodone (82 percent). There was a decrease in opioid consumption in the genotype-guided treatment arm ($p< 0.047$) while the pain intensity between the two groups remained similar (2.6 ± 0.8 vs. 2.5 ± 0.7; $p = 0.638$).

Researchers concluded that the implementation of CYP2D6 genotype-guided therapy when prescribing opioids is not only feasible but may also lead to lower opioid use without negatively affecting patients' pain control.

Reference:
Thomas CD, Parvataneni HK, Gray CF, et al. A hybrid implementation-effectiveness randomized trial of CYP2D6-guided postoperative pain management.*Genet Med*. 2021. PMID: 33420349

March Clinical Inquiries

- Oculogyric crisis causes and treatment
- Basal insulin conversion to Semglee
- Atrial fibrillation and hyperthyroid management
- Pharmacological treatment for obesity
- Insulin and diabetic medications reference sheet
- Pantoprazole and iron absorption
- Avycaz shelf-life
- Anti-epileptics for rectal administration
- Prostate cancer treatment

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MedWise Matrix updates:

Earlier in April, TRHC's Precision Pharmacotherapy Research and Development Institute, in collaboration with others, published a study that demonstrated mortality risk is associated with higher medication risk scores (MRS). The study used electronic health record data for over 427,000 patients from multiple U.S. healthcare organizations to calculate medication risk scores, using MedWise® technology. The results revealed that MRS is associated with death after adjusting for confounding variables. This suggests that interventions made to a medication regimen for those with an elevated MRS could significantly improve medication safety. Additionally, the results provide further evidence to support that the MRS is correlated with poor health outcomes.

- Ratigan AR, Michaud V, Turgeon J, et al. Longitudinal association of a medication risk score with mortality among ambulatory patients acquired through electronic health record data. Journal of Patient Safety. 24 March 2021.

Monthly Clinical Inquiry Highlight – Chandni Bardolia, PharmD, BCGP

Q: What factors make a drug more dialyzable?

A: When a patient is on dialysis, pharmacists must consider the amount of medication cleared during dialysis in order to recommend the correct dose and interval. Medications that are removed during dialysis must be given after dialysis or may require a supplemental dose following dialysis.

Drug removal during dialysis depends primarily on the factors noted below:

Factor (Drug Characteristics)	Effect
Molecular weight/size	Smaller molecules tend to be more readily removed by dialysis
Volume of distribution	Drugs with large Vd are less likely to be significantly removed by dialysis
Protein-binding	Highly protein-bound drugs are less likely to be removed by dialysis

Factor (Dialysis)	Effect
Membrane	High-flux (large pore size) and high-efficiency (large surface area) HD (hemodialysis) filters remove substances more than conventional/low-flux filters
Blood flow rate	Higher dialysis blood flow rates increase drug removal during dialysis over a given time interval

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New Drug Update: Vibegron (Gemtesa®)

Meghan Ha, PharmD, PGY1 Resident

Introduction:
Approximately 400 million people suffer from overactive bladder (OAB) worldwide, with roughly 30 to 40% of patients older than 75 years old.[1,2] OAB occurs when there is a presence of urinary urgency, usually accompanied by frequency and nocturia, with or without urinary incontinence in the absence of urinary tract infections.[3] On average, patients experience up to seven micturition episodes during waking hours.[5] It is considered nocturia if the patient experiences two or more awakenings in the night to urinate.[5] With OAB, urinary incontinence can occur in the forms of urge, stress, mixed, functional, and overflow incontinence.

First-line therapy options for OAB involve behavioral therapies such as bladder training, pelvic floor muscle training (i.e., Kegel exercises), and fluid management.[6] Oral antimuscarinics (e.g., oxybutynin, tolterodine, darifenacin, fesoterodine) are designated as the second-line treatment, but are commonly used in combination with behavioral therapy to optimize symptom management. The class effect is heavily anticholinergic, resulting in side effects such as dry eyes, dry mouth, constipation, and blurred vision.[7] Approximately 50% of patients discontinue treatment with antimuscarinics at three months.[8] When urinary antimuscarinics cannot be tolerated, the second-line pharmacological therapy option is mirabegron, a beta-3 adrenergic agonist.[6] Mirabegron (Myrbetriq®) is not typically preferred due to its relatively higher cost compared to antimuscarinics, although it has a significantly lower anticholinergic burden.[6,9] Last-line recommendations include OnabotulinumtoxinA, nerve stimulation, surgical correction, and indwelling catheters.[6]

The second beta-3 adrenergic receptor agonist:
In December 2020, the Food and Drug Administration approved a new drug for the treatment of adult patients with OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.[10] Vibegron (Gemtesa®) is a selective beta-3 adrenergic receptor agonist that activates beta-3 adrenergic receptors in the bladder, resulting in the relaxation of the detrusor smooth muscle and an increase in bladder capacity.[11] In this manner, vibegron is able to improve clinical symptoms by increasing the interval between voids without impacting bladder contraction.[10] Clinical studies indicate that vibegron's effect on functional bladder volume is dose-dependent.[10,12]

Vibegron is available as a 75mg oral tablet and is dosed once daily.[13] It can be administered with or without food. Vibegron should be swallowed whole with a glass of water or crushed and mixed with a tablespoon of applesauce and swallowed immediately, followed by a glass of water.[14] Use of vibegron in end-stage kidney disease (eGFR <15 mL/minute/1.73 m^2) with or without hemodialysis and in severe hepatic impairment (Child-Pugh class C) is not recommended as these patient populations were not studied in clinical trials.[14] Vibegron should be used with caution in patients with bladder outlet obstruction and in patients using concomitant muscarinic antagonists as it can increase the risk of urinary retention.[14]

Adverse reactions are minimal for vibegron, at this time. Current evidence dicatates that vibegron does not penetrate the blood-brain barrier, which reduces its risk for central nervous system (CNS) toxicity.[15] The most common side effects are hot flash (<2%), constipation (<2%), diarrhea (2%), nausea (2%), xerostomia (<2%), increased post-void residual urine volume and urinary retention (<2%), and headaches (4%).[13] Post-marketing reported side effects include eczema, pruritis, and skin rash.[13]

Comapred to mirabegron, vibegron is less likely to be associated with drug-drug interactions (DDIs) because it does not inhibit CYP2D6 metabolism.[10] This gives vibegron a clear advantage in treating patients who are on multiple chronic medications and at a higher risk for DDIs. It undergoes minor metabolism though CYP3A4 and is excreted in both feces (54% unchanged) and urine (19% unchanged).[13] A notable DDI does occurs when vibegron is used with alongside digoxin therapy, as vibegron may increase serum concentrations of digoxin, requiring close monitoring of digoxin concentrations.[13]

The average wholesale price (AWP) of vibegron is estimated to be $18.34 per 75mg oral tablet.[13] The most commonly prescribed urinary antimuscarinic, oxybutynin, has an AWP of $1.86 to $6.24 per 5mg tablet and is priced similarly for 10mg and 15mg tablets.[17] On the other hand, mirabegron costs $16.69 per 25mg and 50mg tablets.[18] With a stronger selectivity for beta-3 receptors and reduced risk of drug interactions compared to mirabegron, vibegron has the potential for cost benefits even at its higher price, but further studies are warranted.

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Vibegron clinical trials

There were several notable trials that demonstrated vibegron's safety and efficacy in the treatment of OAB.The EMPOWUR trial was an international, randomized, double-blind, placebo- and active-controlled multicenter phase III study that evaluated the safety and efficacy in vibegron in patients with OAB.[22] A total of 1,518 adult patients with OAB were assigned to be treated with vibegron 75mg once daily, placebo, or tolterodine ER 4mg once daily in a 5:5:4 ratio for a 12-week treatment period. Patients enrolled were categorized as wet OAB or dry OAB based on their preceding run-in diary entries. The stratification of treatment groups was based off of wet/dry OAB categories and sex. Most were Caucasian (78%) and female (85%) with a mean age of 60 (range 18 to 93) years.

There were two primary end-points for the EMPOWUR trial: 1) change from baseline to week 12 in the average daily number of micturitions and 2) change from baseline to week 12 in the average daily number of urge urinary incontinence (UUI) episodes for patients with wet OAB.

The results of the study found that statistically significant reductions occurred in the number of micturitions and number of UUI episodes per day in patients receiving vibegron 75mg once daily versus placebo. These two co-primary endpoints were met as early as week two of the 12-week treatment period. Secondary endpoints such as change in the number of urgency episodes, change in volume per micturition, and the proportion of wet OAB cases with a ≥75% reduction in UUI episodes per day were also observed at week two and well maintained through week 12. Adverse events of blood pressure elevation were more common in the tolterodine group (1.7%) than in the vibegron group (0.7%). The results of the EMPOWUR study confirmed similar efficacy and safety findings from a Japanese vibegron phase III study that evaluated a total of 1,232 patients randomly assigned to vibegron, placebo, or imidafenacin.[23]

An extension study was made available to those enrolled in the EMPOWUR study to lengthen their overall treatment period by 40 weeks, bringing the total treatment duration to 52 weeks.[24] In the extension trial, patients continued to receive their assigned medication from the previous 12 weeks. If a patient was assigned to placebo, they were randomized in the extension arm in a 1:1 ratio to vibegron or tolterodine. At 52 weeks, vibegron showed a mean change from baseline in the average daily number of micturitions of -2.4 compared with -2.0 with tolterodine and a mean change from baseline in the average number of UUI episodes of -2.2 compared with -1.7 with tolterodine. The extension results also showed that adverse event-related treatment discontinuations occurred in 1.5% versus 3.4% of patients in the vibegron and tolterodine groups, respectively.

The patient reported QOL outcomes in the original 12-week EMPOWUR study were evaluated only for those taking vibegron and placebo.[25] It was found that at 12 weeks of vibegron treatment, patients had greater improvements in the OAB questionnaire areas of coping, concern, sleep, health-related QOL total, and symptom bother. A greater number of patients receiving vibegron achieved the best response on the patient global impression scale at week 12 and were classified as responders to treatment, when compared to placebo. It can be concluded that vibegron treatment is associated with clinically meaningful improvement in QOL compared with placebo.

Geriatric considerations

There was a subgroup analysis completed within the EMPOWUR trial that assessed the efficacy and safety of patients that were older than 65 and 75 years.[26] In this trial, 628 patients were ≥ 65 years and 179 patients were ≥ 75 years. Patients who received once-daily vibegron 75mg for 12 weeks in both age subgroups showed significant improvements in all three documented symptoms of OAB: daily micturitions, UUI episodes, and urgency episodes compared to placebo. Rates of cardiovascular-associated adverse events were <2% in both age subgroups and similar to that of patients taking placebo. The percentage of hypertension occurring in patients ≥65 receiving vibegron, placebo, and tolterodine was 1.2%, 3.1%, and 2.8%, respectively; in patients ≥75 it was reported to be 1.3%, 3.3%, and 2.1%, respectively. This study indicates that the use of vibegron 75mg in older patients is considered safe, well-tolerated, and efficacious.

Final considerations

Overall, vibegron is a useful addition to the OAB treatment arsenal.[15] Its approval may increase the overall popularity of the beta-3 agonist drug class, given that vibegron's safety and tolerability profile is much favorable over the adverse effects of traditional urinary anti-muscarinics. Unlike its predecessor, mirabegron, vibegron is less likely to cause a DDIs. It also has a place in treatment for OAB patients with cognitive impairment, as vibegron does not penetrate the blood-brain barrier.[15] These characteristics justify the choice of vibegron as a popular treatment for patients with OAB, particularly in the elderly.

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Pharmacogenomics Corner

Integrating Pharmacogenetic Testing via Medication Therapy Management in an Outpatient Family Medicine Clinic

- Michelle Farrell, 2021 PharmD Candidate -

Brown *et al*. performed a prospective study that evaluated 91 patients in a single outpatient family medical clinic to assess the integration of pharmacogenomic (PGx) testing with interpretation by medication therapy management (MTM) pharmacists. Patients were eligible to be included if they were on medications with approved PGx recommendations, had the potential to be on medications in the future with PGx recommendations, and completed a capacity to consent assessment. Samples were self-collected via buccal swabs. Participants enrolled in the study were educated on how the results of the PGx test could help their medical care and optimize their medications. Upon receiving PGx results, two pharmacists who specialized in PGx evaluated the results and focused on genes that were represented in the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, such as CYP2D6, CYP2C19, CYP2C9, and HLA. Demographics, diagnosis, current medications, failed medications, PGx results, Patient Health Questionnaire (PHQ-9), and Generalized Anxiety Disorder (GAD-7) scores were collected before study period, at first follow-up, and at second follow-up. A paired t-test with an □ of <0.05 was used to analyze baseline PHQ-9 and GAD-7 scores to those reported at follow up visits.

At baseline, 83.5% of participants had a mean PHQ-9 score of 13.9 and 77% of participants had a mean GAD-7 score of 14.1, representing moderate depression and moderate anxiety, respectively. Most were CYP2D6 normal metabolizers (49.5%), followed closely by intermediate metabolizers (42.9%). CYP2C9 normal metabolizers and CYP2C19 normal metabolizers made up 61.5% and 41.8% of the population, respectively. After participant's medications were analyzed, the frequency of CYP2D6 poor metabolizers increased from 6.6% to 34.1% due to phenoconversion. Additionally, 15.4% of the population were positive for the HLA-A*31:01 allele, while none were positive for the HLA-B*1502 allele. Per the CPIC guidelines, there were about two actionable genotypes per participant. In this scenario, genotypes were deemed actionable if CPIC provided recommendations supported by strong levels of evidence. On average, there was one recommendation (e.g., initiate new medication, stop medication, increase monitoring) made per participant based on PGx results. MTM pharmacists made a total of 85 interventions for 67% of participants. Almost all (90.6%) of the recommendations resulted in a change to the medication regimen. The most common perpetrator drugs associated with causing phenoconversion were fluoxetine (n=14) between drugs metabolized by CYP2C19 or CYP2D6, as well as bupropion (n=5) between drugs metabolized by CYP2D6. Participants' median depression score per the PHQ-9 did not show a statistically significant difference between baseline (17.1) and second follow up (13.5) (n=15; p=0.20). For GAD-7 scores, there was a significant difference (n=13; p=0.04) seen for participants at baseline (17.3, severe anxiety) compared to second follow up (13.2, moderate anxiety).

The authors concluded that integrating PGx testing into MTM services provided by pharmacists is feasible and actionable recommendations can be provided. This study also highlights the role of MTM pharmacists and PGx experts in interpreting PGx results to optimize patients' medication regimens.

Reference:
Brown JT, MacDonald D, Yapel A, Luczak T, Hanson A, Stenehjem DD. Integrating pharmacogenetic testing via medication therapy management in an outpatient family medicine clinic. Pharmacogenomics. 2021 Jan 20.

April Clinical Inquiries

- Literature search on nutrition and medication effectiveness
- References to support an interaction between losartan and rosuvastatin
- Evidence for sacubitril and valsartan in heart failure with reduced ejection fraction

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MedWise Matrix Updates:

- Tucatinib will be added to the Matrix as a CYP2C8 strong substrate and mechanism-based inhibitor of CYP3A4; it is a low-risk Long QT prolonging drug
- Capmatinib will be added to the Matrix as a CYP3A4 substrate (weak 35%). It inhibits CYP1A2 and ABCG2; its Long QT JT index is moderate risk

Monthly Clinical Inquiry Highlight – Chandni Bardolia, PharmD, BCGP

Q: Should ACE inhibitors be started and/or continued in end-stage kidney disease?

A: Studies have shown the majority of patients who are on hemodialysis develop hypertension (HTN) due to fluid overload secondary to sodium retention.[1,2] In these cases, the goal is to render the patient euvolemic and normotensive. Often times, this goal cannot be achieved without the use of antihypertensives. A 2009 meta-analysis of eight randomized controlled trials (RCTs) performed in dialysis patients determined there were no differences in benefits between antihypertensive medication classes; thus, compelling indications should be considered when selecting an antihypertensive for patients with end-stage kidney disease (ESKD).[3]

When looking to start an angiotensin-converting enzyme (ACE) inhibitor for HTN in patients with ESKD, there are several considerations to account for including, but not limited to, residual renal function (RRF), proteinuria, hyperkalemia, and cardiovascular (CV) mortality. Several studies have shown that ACE inhibitors preserve RRF.[1] A 2012 study concluded that ACE inhibitors, as well as angiotensin receptor blocker, were independently associated with RRF preservation after one year of hemodialysis, especially if patients were at least 80% adherent to the regimen.[1]

A recent study looked at the risk of stopping renin-angiotensin system (RAS) inhibitor therapy in Swedish patients with advanced kidney disease.[4] Compared with continuing RAS therapy, stopping therapy was associated with a higher five-year risk of death (40.9% versus 54.5%) and major adverse CV events (47.6% versus 59.5%).[4] There was, however, a lower risk of renal replacement therapy.[4] These findings suggest continuing RAS therapy in individuals with advanced kidney disease may confer significant benefits.[4]

The UK STOP-ACEi trial is an on-going trial that aims to answer the question: should ACE inhibiors be stopped in advanced kidney disease.[5] Specifically, the authors of this trial hope to strengthen the evidence base and shed light on the potential merits and dangers of RAS therapy in advanced CKD on renal function and cardiovascular outcomes.[5] Until these results are published, initiation and continuation of ACE inhibitors must be determined on a case by case basis.

Though guidelines do not have explicit recommendations for the management of HTN in ESKD, the use of ACE inhibitors in this patient population has shown a positive impact on CV outcomes and RRF. Patients who develop ESKD while on ACE inhibitors should be continued on the medication, if tolerated. Furthermore, for patients with existing ESKD and development of other compelling indications (e.g., HTN, HF), prescribers should consider initiating ACE inhibitors, as this class is still a viable first-line treatment option; however, when initiating ACE inhibitors, prescribers should remain vigilant in monitoring for acute kidney injury, serum creatinine levels, potassium levels, and adherence.

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Using Low-dose Naltrexone for Chronic Pain

Chandni Bardolia, PharmD, BCGP

Studies cite pain as the most common reason patients with inflammatory arthritis seek appointments with rheumatologists.[1] While treatment with disease-modifying antirheumatic drugs (DMARDs) is effective in reducing pain symptoms, observational studies indicate that many patients continue to experience pain despite optimized DMARD therapy.[1] Even though the evidence is weak, guidelines continue to recommend opioids as the third-line option for the treatment of pain, if patients fail treatment with NSAIDs or acetaminophen.[1] Opioids for this indication are often recommended to be used for a short duration, particularly due to the potential for opioid-induced hyperalgesia, which results in heightened pain sensitivity and an increased clinical pain intensity.[1] To counter these effects of opioids, clinical experts recommend the use of very-low-dose naltrexone (vLDN) in combination with opioids.[3-6]

Naltrexone, available as a 50mg tablet, is an opioid receptor antagonist.[2] The U.S. Food and Drug Administration (FDA) has approved naltrexone for the treatment of opioid-use disorder[2]; however, emerging evidence is showing support for the use of low-dose naltrexone (LDN) for pain management.[3-7] Naltrexone, in low (1-6mg/day) to very-low doses (1-8mcg/day), exhibits paradoxical mechanisms which result in analgesia and anti-inflammatory actions.[2-4,11] This mechanism is termed hormesis, which occurs when low doses of an antagonist results in effects typically seen with an agonist.[10] In the absence of an opioid, LDN can activate glial cells.[2-4] Toll-like receptors, found on glial cells, are spread across the central and peripheral nervous systems.[2-4] Through animal studies, researchers have found that opioids induce these Toll-like receptors which lead to pro-inflammatory effects (e.g., production of interleukin-6, tumor necrosis factor, nitric oxide).[3] LDN attenuates the pro-inflammatory response initiated by the Toll-like receptors, specifically Toll-like receptor-4, and inhibits the production of the inflammatory factors, mentioned previously.[3] Another proposed mechanism of LDN may involve upregulation of basal opioid receptor signaling.[10]

While studies have not been conducted with LDN or vLDN with all available opioids, a few studies have been conducted with vLDN and morphine and oxycodone.[5-7] Preclinical studies with morphine demonstrated that vLDN enhanced opioid analgesia with morphine and attenuated tolerance/dependence by selectively antagonizing excitatory opioid receptor functions.[5] Pain Therapeutics, a pharmaceutical company, was in the process of gaining FDA approval for their oxycodone plus naltrexone combination, Oxytrex®, but due to high dropout rates in their phase III trial, the approval was never granted.[6-7] Oxytrex® contained vLDN in combination with therapeutic doses of oxycodone.[6-7] Though the primary objective of the phase III trial was unmet, the secondary objective was met: Oxytrex® was shown to be statistically non-inferior to oxycodone during the three-month period.[7] It also reduced physical dependency by 75% in patients older than 50.[7] Available data from the Oxytrex® trials have shown that very-low-dose opioid antagonists may enhance and prolong opioid analgesia while reducing analgesic tolerance and physical dependence.[7] Table 1 below depicts the differences in naltrexone dosing ranges, and various indication that may benefit from the specific doses.

[con't p.2]

Table 1: Naltrexone Dosing Ranges[11]		
Category	**Dose**	**Indication**
Pico-dose	1 trillionth of a gram	Currently, only used for abuse-deterrent formulations
Ultra-low-dose ***(Very-low-dose)***	1 to 8 mcg/day	May result in enhanced pain control. Typically used in preventing the development of opioid tolerance and excitatory adverse effects (e.g., hyperalgesia, GI spasm, euphoria, nausea/vomiting, hallucinations, agitation)
Low-dose	1 to 6 mg/day	Use has been studied in the management of fibromyalgia, Crohn's disease, abdominal pain, multiple sclerosis, and interstitial cystitis. This dose may precipitate opioid withdrawal.
High-dose	25 to 200 mg/day	Use without concurrent opioid for the management of post-traumatic stress disorder, borderline personality disorder, central neuropathic pain syndromes (e.g., fibromyalgia and chronic headaches). This dose precipitates opioid withdrawal if used concurrently.

Hay et al. discussed the use of buprenorphine plus naltrexone for pain management.[8] This study demonstrated that the dose ratio between the two drugs greatly influences analgesia, specifically when buprenorphine and naltrexone are administered in a 166:1 ratio.[8] The study by Hay et al. was small in sample size (n=10) and noted a statistically significant, yet clinically insignificant, increase in respiratory depression with the combination when compared to buprenorphine alone.[8]

As monotherapy, LDN has demonstrated benefit in reducing symptom severity for fibromyalgia, Crohn's disease, multiple sclerosis, and complex regional pain syndrome.[3,9,11] Though inflammatory processes are at play in the development of fibromyalgia, this condition does not typically respond well to anti-inflammatory medications or opioids.[3,9] However, due to the anti-inflammatory mechanism(s) of LDN, it has been shown to be a potential treatment option for this condition.[9] One study showed that 57% of the participants (n=30) diagnosed with fibromyalgia reported a significant reduction of pain after treatment with LDN.[8] The current condition with the most evidence to support the use of LDN is Crohn's disease.[9] LDN has demonstrated reduction in self-reported pain, as well as reductions in objective markers of pain (e.g., severity scores and scales).[9] Studies indicate over 80% of participants exhibiting significant improvements with LDN therapy.[9]

While the current evidence is not strong to support the use of LDN in combination with and opioid agonist, LDN **monotherapy** is showing benefit for chronic pain management, especially for pain associated with immune and inflammatory conditions. The use of vLDN, in combination with opioid agonists, for chronic pain management, is supported based on emerging evidence. Due to the diffiuclties with compounding vLDN, patients may be prescribed LDN in combination with an opioid agonist. In these scenarios, it should be validated that all providers are aware of this combination and the patient should be monitored closely for withdrawal effects.

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11. Table adapted from Practical Pain Mangement

Pharmacogenomics Corner

Prevalence of predicted gene-drug interactions for anti-depressants in the treatment of major depressive disorder in the PRecision Medicine In MEntal Health (PRIME) Care Study[1]

- Nicole Del Toro-Pagan, PharmD, BCPS, PGY2 Resident -

Major depressive disorder (MDD) is a leading cause of disability among adults. Because limited guidance is available for antidepressant selection, the treatment approach for MDD relies on clinician's preference. By utilizing this approach, antidepressant treatment response and remission rates are approximately 50% and 37%, respectively.[2] Pharmacogenomic (PGx)-guided antidepressant care may be a promising tool that can support antidepressant selection through a precision medicine approach.

The PRecision Medicine In MEntal Health (PRIME) Care study was a pragmatic multi-site, randomized, controlled trial conducted across 22 U.S. Department of Veteran Affairs (VA) medical centers. Researchers evaluated the clinical utility of PGx-guided care in adult patients with symptomatic MDD, whose physician was starting *de novo* or switching to a new antidepressant therapy due to lack of adequate response. The prevalence of current and next-intended antidepressant therapy classified as moderate and clinically significant drug-gene interaction (DGI) predicted potential was estimated. Additionally, demographic characteristics and antidepressant treatment histories were evaluated to determine the likelihood of being prescribed an antidepressant with clinically significant DGI predicted potential. PGx results included phenotypes for eight genes associated with antidepressant pharmacokinetic or pharmacodynamic response. The final report included an analysis based on the DGI predicted potential (i.e., none, moderate, or significant) for 22 antidepressants.

For those patients experiencing insufficient response, approximately 20% with clinically significant and more than 50% with moderate DGI predicted potential were prescribed an antidepressant. . The next-intended treatment was documented for patients starting *de novo* and those switching to a new antidepressant. Approximately 20% and 45% of patients had a next-intended treatment with clinically significant or moderate DGI predicted potential, respectively. PGx results showed that nearly 15% of patients had a significant DGI predicted potential for 11 or more of the 22 antidepressants analyzed. Likelihood of next-intended antidepressant treatment to have clinically significant DGI predicted potential was found to increase if the patient was prescribed one or more antidepressants in the past two years.

The researchers stated that this is the first study to the evaluate clinical utility of antidepressant PGx-guided care in patients starting *de novo* antidepressant treatment. They concluded that PGx-guided care may be beneficial for patients that have experienced antidepressant treatment failure and for those who are starting antidepressant therapy. However, additional testing of this hypothesis is needed due to several limitations. First, these results are based on a sample of veterans seeking medical therapy in the VA and represented reduced ethnic diversity, which limits generalizability. Second, PGx test and interpretation algorithm utilized will vary across institutions; therefore, results may differ. Third, this analysis did not consider concomitant medications and possible drug-drug interactions that can impact the predicted pharmacokinetic response. Lastly, the researchers did not assess the patients' antidepressant response in their treatment history or after PGx-guided interventions were implemented; therefore, no conclusions on the impact in care can be drawn.

In conclusion, this study demonstrated that between 20% to 50% of patients seeking antidepressant treatment may benefit from antidepressant PGx-guided care, with individuals having a prior antidepressant therapy history being more likely to benefit.

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- Medications that can cause long competitive inhibition
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- Mirtazapine causing insomnia
- Dulaglutide in chronic kidney disease

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- Binimetinib, an antineoplastic drug with an active metabolite, was recently added to the Matrix as a CYP1A2 and CYP2C19 weak substrate
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- Gilteritinib, an antineoplastic drug, was added to the Matrix as a CYP3A4 weak substrate (MPC 20%)

Monthly Clinical Inquiry Highlight – Chandni Bardolia, PharmD, BCGP

Q: What evidence is available to support or refute the use of dulaglutide (Trulicity®) in patients with chronic kidney disease (CKD)?

A: Type 2 diabetes (T2D) is the leading cause of chronic kidney disease (CKD) throughout the world. Previously, a decline in kidney function limited the selection of antidiabetic treatment options, as many of these options are eliminated through the kidneys. Not too long ago, all sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) required renal dose adjustments or were contraindicated, depending on the stage of CKD. Recently, renal outcome studies have demonstrated benefits of both SGLT2 inhibitors, as well as GLP-RAs.[1]

In 2017, Tuttle et al. evaluated the effects of dulaglutide on estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR), and kidney adverse events in the AWARD-7 trial. The AWARD-7 study was an international trial conducted at 99 sites across nine countries and included 577 participants. Individuals were randomized to receive dulaglutide or to insulin glargine plus prandial insulin lispro. The average age of participants was 65 years. The mean HbA1c level at study entry was 8.6%. The majority of participants included had an eGFR of less than 45mL/min per 1.73 m2, about 30% of participants had stage 4 CKD, about 45% had macroalbuminuria, and approximately one-third of the participants had microalbuminuria.[2]

Focusing on the endpoints dealing with CKD, albuminuria was reduced in all study groups, but at 26 weeks, a greater reduction was observed in the dulaglutide group. The mean change in UACR from baseline to week 26 was -27.7 for the 1.5mg dose of dulaglutide, -26.7 for the 0.75mg dose, and -16.4 for glargine. Additionally, eGFR decline at week 26 was also lower with dulaglutide 1.5mg and 0.75mg than with glargine.[2]

Several sub-analysis of the AWARD-7 study have been conducted since 2017. In February 2021, an exploratory sub-analysis of the AWARD-7 trial was published that aimed to determine the risk of clinical event outcomes between treatment groups (dulaglutide and glargine-lispro). Results indicated that patients receiving dulaglutide weekly had reduced risk of ≥40% eGFR decline or endstage kidney disease over 1 year when compared to those individuals receiving glargine-lispro. This effect was primarily observed in participants presenting with macroalbuminuria and the authors suggest this may indicate possible beneficial effects of dulaglutide among patients with stage 3-4 CKD. This sub-analysis was the first to demonstrate a reduced risk of 40% eGFR decline and end-stage renal events by GLP-1 receptor agonists in patients who have established moderate-to-severe CKD.[3]

While the evidence to support the use of dulaglutide in patients with CKD is fairly new, the strength and level of evidence is strong. In fact, the product labeling has been updated to include the data from the AWARD-7 trial stating dulaglutide is an effective treatment option in patients with T2D and moderate to severe CKD; however, at this time, the FDA has not granted dulaglutide a CKD approval.

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Modafinil for Narcolepsy in the Older Adult

Chandni Bardolia, PharmD, BCGP

Patients with excessive daytime sleepiness (EDS) have difficulty maintaining wakefulness or alertness at appropriate times during the day.[1] EDS is important to recognize because it can indicate a potential undiagnosed sleep disorder or other treatable conditions (e.g., sleep apnea, restless leg syndrome).[1] One such sleep disorder could be narcolepsy. Narcolepsy is a clinical syndrome consisting of daytime sleepiness with cataplexy, hypnagogic hallucinations, and sleep paralysis.[1,2] Narcolepsy can be managed with several non-pharmacologic interventions[1,2]:

- Napping and sleep hygiene
- Psychosocial support
- Exercise

While non-pharmacologic interventions provide some benefits to patients, most will require medications to reduce sleepiness.[2] When medications are prescribed for narcolepsy, goals of therapy should be clearly defined, including a timeframe for expected benefit. Typical goals of therapy are to achieve alertness during conventional waking hours or during activities of daily living.[2] Thereafter, treatment should be individualized and selection of medication driven by the degree of daytime sleepiness, the presence/absence of cataplexy, and the severity of sleep disruption.[3] Available medications to manage narcolepsy without cataplexy include: modafinil, solriamfetol, pitolisant, methylphenidate, and amphetamines.[2]

Of the medications listed above, modafinil is designated as the first-line medication. The largest randomized controlled trial to date of modafinil included 285 narcoleptic patients.[4] Patients were randomly assigned to receive 200 mg/day of modafinil, 400 mg/day of modafinil, or placebo over nine weeks, followed by an open-label period.[4] Subjective sleepiness was measured with the Epworth Sleepiness Scale.[4] Objective sleepiness was assessed with the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test.[4] Results revealed that modafinil significantly reduced all measures of sleepiness and patients reported lower likelihood of falling asleep during daily activities compared to patients in the placebo group.[4] Of note, the mean age of patients enrolled in the study was approximately 42 years (range 18-68 years).[4] Additionally, patients with severe cataplexy were excluded.[4] With regards to safety, headache was the only statistically significant adverse event between the three groups, with higher rates in the two modafinil groups.[4] Laboratory measures (e.g., body weight, vital signs, electrocardiogram) were also collected; there were no clinically meaningful differences between groups.[4] Overall, it was concluded that modafinil demonstrated a tolerable safety profile over the course of 40 weeks, and the efficacy was maintained into the prolonged open-label period.[4] The same research group completed a second trial including 271 participants.[5] They noted similar clinical results over the course of nine weeks; however, in this study they also looked at the effects of discontinuing modafinil.[5] Following discontinuation of modafinil, patients did not experience withdrawal symptoms, but patients did

[con't p.2]

experience a return of EDS to baseline levels.[5]

Modafinil is typically initiated at 200mg once daily in the morning and the effects should last into the evening without interfering with "normal" sleep time.[2] The medication may be titrated to 400mg daily as needed.[2] Though modafinil is generally well tolerated, common side effects include headache, nausea, dry mouth, anorexia, and diarrhea.[2] Since modafinil has fewer sympathomimetic effects compared to amphetamines, it is often the drug of choice for older adults.[2] The medication should be used cautiously in individuals with arrhythmias and/or heart disease as it may increase blood pressure (dose dependent).[2] Of note, few reports have been made of arrhythmic events associated with modafinil use.[6] Additionally, the most common treatment-related cardiovascular events in a cohort of 478 patients were palpitations (1.5%), hypertension (1.0%), and tachycardia (1.0%).[6] Modafinil may perpetrate drug-drug interactions as it is an inducer of CYP3A4, and therefore may increase clearance of CYP3A4 substrates. If opting to initiate modafinil in this patient population, routine follow-up and careful monitoring are highly recommended.[2]

Other first-line medications include armodafinil, pitolisant, and sodium oxybate.[2] Pitolisant and sodium oxybate are also beneficial options in patients presenting with cataplexy.[2] Pitolisant has demonstrated efficacy in a study with 95 participants and improved frequency of hallucinations, when present.[2] Lehert *et al*. demonstrated that pitolisant is non-inferior to modafinil in relieving EDS, but superior to modafinil in reducing cataplexy.[7] However, for patients presenting with narcolepsy without cataplexy, both drugs perform equally.[7] When looking at safety, pitolisant may be involved in more drug-drug interactions as it is a substrate of CYP3A4 and CYP2D6, as well as an inducer of CYP3A4.[2] Additionally, pitolisant is associated with dose-dependent QT prolongation, and it requires dose reductions in renal and hepatic impairment.[2]

While pitolisant can be used in patients presenting with/without cataplexy, sodium oxybate is reserved for patients presenting with cataplexy.[2,8] The onset of action for this medication is slow, and patients should be counseled that it may take several weeks of treatment before a reduction in cataplexy rate is noticed.[2] Side effects of sodium oxybate is dose-dependent and typically include nausea and dizziness, weight loss, urinary incontinence, mood swings, and worsening of depression, sleepwalking, and psychosis.[2] Combined use with alcohol, sedatives, or hypnotics is contraindicated as it may result in respiratory depression, coma, and/or death.[2] Prescribers must enroll in a Risk Evaluation and Mitigation Strategies (REMS) program in order to prescribe this medication.[2]

Current evidence is limited to assist prescribers in selecting narcolepsy treatment options for the older adult patient population. Treatment should be individualized and selection of medication driven by the degree of daytime sleepiness, the presence/absence of cataplexy, and the severity of sleep disruption. For most patients, modafinil would be the first-line treatment option due to its demonstrated safety and efficacy, as well as its low abuse potential. However, routine cardiovascular monitoring may be require for patients with heart conditions (e.g., atrial fibrillation).

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Pharmacogenomics Corner

Pharmacogenomics guided vs standard antidepressant treatment in a community pharmacy setting: A randomized controlled trial

- Jessica Prevete, 2021 PharmD Candidate -

Oftentimes, antidepressant therapy is started in a primary care setting as a first-line treatment option for major depressive disorder (MDD) and generalized anxiety disorder (GAD). However, many antidepressants are linked to suboptimal therapeutic response and there is evidence to support that two-thirds of patients do not achieve remission, despite several adequate trials of medications.[1] Patient response to antidepressant medications is proposed to be a polygenic trait, with common genetic variants accounting for over 40% of the variability in response. The evidence supporting the use of pharmacogenomics (PGx) to guide antidepressant drug selection has flourished in recent years. Further, it has been argued that pharmacists should have a more active role in PGx, with both pharmacists and physicians perceiving pharmacist-led interpretation a valuable method to scale this innovation for depression treatment.

In this prospective, randomized controlled design, the impact of PGx-guided versus standard antidepressant therapy for depression and anxiety was studied in three large community pharmacies in Ontario.[2] A total of 213 patients were enrolled in the trial. All patients were over 18 years of age, prescribed one or more antidepressant, and diagnosed with MDD or GAD. Patients were either newly initiated on therapy or had a recent change in therapy, and were experiencing adverse drug events, suboptimal response, or dissatisfaction with therapy. Non-adherence, recipients of liver transplant, or diagnoses of bipolar disorder, schizophrenia or dementia, resulted in exclusion from the study.

Participants were randomly assigned to either a PGx-guided group or control group through a randomizer tool. A Pillcheck portal was used to create patient profiles. Pharmacists facilitated and supervised the buccal swab DNA collection process. Pharmacists received the Pillcheck report two weeks after swab collection for patients in the PGx-guided group, which allowed them to provide recommendations for optimizing antidepressant drug therapy.

Recommendations that were accepted included dose adjustments (e.g., increased dosages due to ultra-rapid metabolism), change to alternative medication (e.g., to mitigate adverse events as a result of poor metabolism), addition of a new medication as adjunctive therapy, and establishing medication adherence when continuing a medication. Pharmacists provided at least one or two recommendations per patient. Due to these recommendations provided by pharmacists, participants with MDD or GAD that received PGx-guided treatment reported greater improvements in depression severity and generalized anxiety over a six-month period compared to those that only received guideline directed therapy in the control group. Various questionnaires, such as the Patient Health Questionnaire (PHQ-9), Sheehan Disability Scale (SDS), and Treatment Satisfaction with Medicines Questionnaire (SATMED-Q), were used to assess treatment success.

Overall, this trial supports pharmacist-led PGx testing in the treatment of mental health. The results of this trial demonstrate that pharmacists can provide meaningful interventions considering PGx, which further improves patient care and personalizes patient treatment plans. Current and future research on PGx will continue to show the benefit of PGx-guided therapy for patients.

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MedWise Matrix Updates:

- Pitolisant was added to the Matrix as a CYP2D6 medium affinity substrate with moderate impact on QT prolongation
- Rimegepant was added to the Matrix as a CYP3A4 medium affinity substrate (MPC 17.5%); this medication is a P-gp substrate
- Ubrogepant was added as a CYP3A4 low affinity substrate (MPC 45%); P-gp plays a significant role in its elimination

Monthly Clinical Inquiry Highlight – Chandni Bardolia, PharmD, BCGP

Q: Is CYP2C9 inducible?

A: CYP2C9 is the most prevalent CYP2C subfamily enzyme in human livers.[1] It is well known that polymorphisms may occur that result in decreased function of this enzyme.[1] The most common variant alleles are *CYP2C9*2* and **3*, which both result in decreased activity of CYP2C9.[1] To date, there have been no reports of variant alleles resulting in increased activity of CYP2C9.[1]

While, there are no known genotypes that would result in increased activity of CYP2C9, this enzyme may be induced by extrinsic factors (e.g. medications).[1,2] Inducers of CYP2C9 include, but are not limited to, barbiturates, carbamazepine, phenytoin, primidone, rifampin, and St. John's Wort.[2,3] Individuals who have a reported phenotype of normal or intermediate metabolizer may be **phenoconverted** to a rapid or normal metabolizer, respectively, if using these CYP2C9 inducers regularly. This may be of particular concern when patients are concomitantly taking CYP2C9 substrates (e.g., warfarin, most NSAIDs, sulfonylureas). In these situations, monitoring the patient for appropriate response and obtaining therapeutic drug levels, if applicable, may be warranted.

The CYP2C9 enzyme is inducible by a variety of medications. Healthcare providers may use pharmacogenomic information, as well as knowledge of medication pharmacokinetic properties, to help guide therapy for individuals.

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Adjusting Clopidogrel Dosing in CYP2C19 Intermediate or Poor Metabolizers

Adriana Matos, PharmD, BCGP
Nicole Del Toro-Pagan, PharmD, BCPS
Sally Luvsantseren, PharmD

Current clinical practice guidelines[1] recommend dual antiplatelet therapy (DAPT), a $P2RY_{12}$ inhibitor (i.e., clopidogrel, prasugrel, or ticagrelor) and aspirin, for acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI). Clopidogrel is the most commonly prescribed $P2RY_{12}$ inhibitor due to its lower cost and bleeding risk compared with alternatives.[1,2]

Clopidogrel, a thienopyridine prodrug, requires biotransformation into an active metabolite by cytochrome P-450 (CYP) enzyme CYP2C19. The active metabolite selectively and irreversibly inhibits the $P2RY_{12}$ receptor, preventing platelet activation and aggregation. Polymorphisms in the *CYP2C19* gene encoding for loss-of-function (LOF) alleles reduce an individual's antiplatelet response to clopidogrel. Among patients prescribed clopidogrel, *CYP2C19* LOF allele carriers (i.e., intermediate metabolizers (IMs), poor metabolizers(PMs)) have an increased risk for major adverse cardiovascular events (MACE; i.e., composite of cardiovascular death, myocardial infarction, or stroke) post PCI as compared with **1* homozygotes.[3] In contrast, *CYP2C19* genotype does not affect clinical response to prasugrel or ticagrelor. For this reason, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend using one of these alternative antiplatelet agents over clopidogrel in CYP2C19 IM/PMs without contraindications in the ACS post-PCI setting.[4] In 2017 the Food and Drug Administration (FDA) included a boxed warning regarding the concern for diminished antiplatelet activity of clopidogrel in individuals that are CYP2C19 PMs. The warning advised clinicians to consider the use of another platelet $P2RY_{12}$ inhibitor amongst CYP2C19 PMs.[5] Prasugrel and ticagrelor have demonstrated superior outcomes compared to clopidogrel in clinical trials; however, they carry increased bleeding risk and higher medication cost.[2,6,7] As a result, there is a subset of patients who may not be eligible to receive ticagrelor or prasugrel. The Dutch Pharmacogenetics Working Group (DPWG) recommends clopidogrel dose escalation (150 mg daily with 600mg loading dose) as an alternative strategy in CYP2C19 IMs.[8] CPIC and the French National Network (Réseau) of Pharmacogenetics (RNPGx) do not support the practice of clopidogrel dose escalation due to insufficient clinical outcomes data.[4,9]

In the ELEVATE-TIMI 56 trial[10], Mega *et al*. established the pharmacodynamic association of *CYP2C19*2* LOF allele carriers and platelet function in patients with stable cardiovascular disease (N = 333). Overall, carriers of *CYP2C19*2* had higher platelet reactivity to clopidogrel 75mg daily than noncarriers. In heterozygotes, increasing clopidogrel to 225mg daily resulted in a similar degree of platelet reactivity as noncarriers with clopidogrel 75mg daily. In homozygotes, a high degree of platelet reactivity was maintained despite clopidogrel 300mg daily. A meta-analysis by Zhang L. *et al*.[11] further demonstrated the relationship between *CYP2C19* LOF alleles and higher platelet reactivity on standard (75mg daily) and high-dose (150mg daily) clopidogrel in patients undergoing PCI (N = 10,960). Six studies in the meta-analysis reported clinical outcomes data (N = 6,811): *CYP2C19*2* carriers treated with high-dose clopidogrel were at higher risk for MACE and urgent coronary revascularization (RR 1.68, 95% CI: 1.19-2.37, P = 0.003) and stent thrombosis (RR 1.75, 95% CI: 1.31-2.34, P = 0.0001) when compared with non-carriers on the standard clopidogrel dose. Compared with previous reports[3], the results from this study suggest risk for MACE may be similar in *CYP2C19*2* carriers treated with high-dose or standard dose clopidogrel. In summary, clopidogrel 150mg daily dose does not seem to overcome the variability of clopidogrel antiplatelet effect between *CYP2C19 *2* carriers and non-carriers in patients treated with PCI.[10]

Shen *et al*.[12] studied MACE outcomes (i.e., composite of death from any cause, myocardial infarction, or target vessel revascularization) of four different antiplatelet strategies in Chinese patients with coronary artery disease after PCI (N = 628). Patients randomized to the routine group were treated with clopidogrel 75mg daily without *CYP2C19*

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[con't p.2]

testing (N = 319), whereas patients randomized to the individual group received *CYP2C19* testing and were further allocated into three treatment strategies based on CYP2C19 phenotype: CYP2C19 normal metabolizers (NMs) received clopidogrel 75mg daily (N = 133), IMs received clopidogrel 150mg daily (N = 139), and PMs received ticagrelor 90mg twice daily (N = 37). Patients in the routine group were at higher risk for MACE at 1 month (OR 4.92, P = 0.009), 6 months (OR 2.48, P = 0.042), and 12 months (OR 2.36, P = 0.027) in comparison to the individual group, without significant differences in bleeding risk. Within the individual group, MACE and bleeding events were similar among CYP2C19 NMs on clopidogrel 75mg daily, IMs on clopidogrel 150mg daily, and PMs on ticagrelor 90mg twice daily. Although the study was not powered to detect differences within the individual group, the results of this study suggest that clopidogrel 150mg daily may have clinical utility in CYP2C19 IMs.[12]

Xie *et al*.[13] conducted a similar single-site randomized control trial in Chinese patients with ACS post PCI (N = 600). In the genotype-guided arm, CYP2C19 IMs received clopidogrel 150mg daily (N = 128), PMs received clopidogrel 150mg daily plus cilostazol 100mg twice daily (N = 30), and NMs received clopidogrel 75mg daily (N = 143). Patients in the routine therapy arm did not receive CYP2C19 testing and received clopidogrel 75mg daily (N = 299). Patients randomized to routine therapy had a higher risk of MACE at 6 months compared to genotype-guided therapy (9.0% vs 2.7%; P = 0.001), without significant differences in bleeding risk. The study, however, did not genotype patients in the routine therapy arm after study completion to analyze difference in event rates among CYP2C19 IMs receiving clopidogrel 75mg daily and 150mg daily; therefore, strength of this study is somewhat limited in supporting the practice of clopidogrel dose escalation in CYP2C19 IMs.

A retrospective cohort study conducted by Zhang M. *et al.*[14] aimed to analyze the impact of *CYP2C19* polymorphisms on clopidogrel dosing on in-stent restenosis (ISR) after coronary stenting in Chinese patients (N = 111). All patients underwent PCI with drug-eluting stent. CYP2C19 NMs received 75mg of clopidogrel daily (N = 51), while IMs received 75mg of clopidogrel daily (N = 27) or twice a day (N = 33). ISR rate was significantly higher in the once daily IM group compared to the EM group (40.7% and 11.8%, respectively). Among IMs, ISR occurred more often in the patients receiving clopidogrel daily when compared to those who received clopidogrel twice a day (40.7% vs. 6.1%; P = 0.004). These results suggest that increasing the dose of clopidogrel in patients with a LOF allele can result in lower risk of ISR; however, this study had a small sample size.

The clinical outcomes evidence does not support the practice of doubling the clopidogrel dose (150mg daily) in patients who are CYP2C19 PMs and there is limited evidence available to support this practice in CYP2C19 IMs in the ACS post-PCI setting. The data is scarce for the clinical value of clopidogrel 225mg daily dose, which was shown to overcome *CYP2C19*2* related clopidogrel resistance in *CYP2C19*2* heterozygotes in the ELEVATE-TIMI 56 trial.[10] At this time, we recommend utilizing alternative $P2RY_{12}$ inhibitors, ticagrelor or prasugrel, in patients without contraindications who are CYP2C19 IM/PM as directed by the CPIC guideline for ACS patients undergoing PCI.[4] For CYP2C19 IMs/PMs who have contraindications to alternative antiplatelet therapy (e.g., history of stroke/transient ischemic attack limits prasugrel use and history of intracranial hemorrhage limits ticagrelor use), treatment strategy is ultimately left to clinical judgement. Clinicians must consider the age, history of cardiovascular disease (e.g., history of myocardial infarction, ischemic/hemorrhagic stroke, transient ischemic attack), certain comorbidities that may affect alternative antiplatelet use (e.g., diabetes), and risk of MACE and bleeding for each of these patients. Clinician's may potentially consider using an increased clopidogrel dose (e.g., 150 or 225mg daily) for CYP2C19 IMs in light of limited options.

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Pharmacogenomics Corner

Supporting pharmacogenetic-guided opioid prescriptions for post-operative pain - Nicole M. Del Toro-Pagán, PharmD, BCPS, PGY2 -

Genetic variants can significantly contribute to interpatient variability in opioid disposition and response, which increases the complexity of developing protocols on standard opioid dose recommendations. Pharmacogenomic (PGx)-guided opioid therapy may be a promising tool to support opioid dose selection in the post-operative setting. This approach may reduce the risk of opioid misuse.

The pharmacogenetics of **o**pioid **t**reatment for acute post-operative **p**ain (OTP) was an exploratory, pilot study conducted in three oral surgery offices of the Centre for Addiction and Mental Health in Ontario, Canada. Researchers aimed to identify genes that impact opioid effectiveness, adverse drug event (ADE) profiles, and the risk of dependence. The study included 72 patients, ages 16 to 44, who underwent a third molar extraction procedure and were prescribed at least one opioid (i.e., codeine, hydrocodone, morphine, oxycodone, tramadol) for post-operative pain management. Of note, patients were excluded if they were on a medication (e.g., antidepressant, diuretic) that could interfere or influence analgesic response to opioid and non-opioid analgesic medications.

Patients completed PGx testing prior to the surgery and three questionnaires during post-operative days 1, 3, and 7, regarding pain severity and interference, presence of ADEs, and risk of dependence. Overall, patients were prescribed more opioids than consumed. Pain severity, interference, and the average number of ADEs (e.g., fatigue, drowsiness) declined across the seven-day post-operative period. Considering an association has been demonstrated regarding pain severity and interference, multiple genes associated to opioid response were analyzed. The genes analyzed that can impact pharmacodynamic response were opioid receptor μ1 (OPRM1) and δ1 (OPRD1). Polymorphisms in these genes can impact the sensitivity to certain opioids, while the ATP binding cassette transporter subfamily B member 1 (ABCB1), encodes for an efflux transporter that functions at the blood-brain barrier, impacting clearance of certain opioids from the brain and into the blood. The genes analyzed that can impact pharmacokinetic response were: cytochrome P450 2D6 (CYP2D6; the major metabolizing enzyme for codeine, tramadol hydrocodone and oxycodone) and UDP glucuronosyltransferase 2B7 (UGT2B7; impacts phase II clearance mechanism for morphine and hydromorphone).[2] The OPRD1 T921C variant was significantly associated with enhanced pain relief (P = 0.02), the ABCB1 C3435T variant was significantly associated with decreased pain relief (P = 0.02), and CYP2D6 metabolizer status was associated with impacting pain severity (P = 0.01). No associations were found between OPRM1 A118G variant and or UGT2B7 C802T variant and pain severity.[3]

The researchers concluded that patients undergoing third molar extraction may benefit from PGx-guided opioid therapy to optimize pain management efficacy, and potentially decrease the risk of ADEs and dependence. A strength of this study is that the researchers performed population stratification via principal component analysis to determine the ancestry of the patients. It was noted that the cohort had a diverse ethnic background, which may make the results of the study more generalizable. However, additional testing of this hypothesis is needed due to several limitations. First, these results are based on a small sample of relatively young healthy patients undergoing a specific type of surgery, which may limit external validity of this study. Second, these patients underwent third molar extraction with surgeons with different levels of experience and the number of teeth extracted differed between patients. Lastly, only 10 percent of participants were prescribed an opioid, exclusively, whereas 75 percent were prescribed an additional analgesic medication (i.e., acetaminophen, non-steroidal anti-inflammatory drug). Therefore, it is difficult to determine the amount of pain relief that was attributed to the opioid when used in combination with other analgesics.

In conclusion, PGx-guided opioid therapy can potentially aid in the development of protocols to prescribe opioids and strategies to tackle the opioid epidemic. Results of the OTP study may further support these findings. Future randomized controlled trials incorporating PGx, should include specific genetic markers (e.g., *OPRD1, ABCB1, CYP2D6)* to support individualized opioid recommendations for post-operative pain.

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MedWise Matrix Updates:

- Solriamfetol was added to the Matrix as a non-CYP metabolized medication with a high QT risk
- Brigatinib has been added to the Matrix as a CYP3A4 substrate (MPC 50%) with a low potential for QT prolongation
- Glasdegib was added as a CYP3A4 intermediate substrate (MPC 70%); it has a known risk of QT prolongation, with a Long QT-JT index

Monthly Clinical Inquiry Highlight – Chandni Bardolia, PharmD, BCGP

Q: What are the treatment options and duration of therapy for a patient with the Factor V Leiden mutation who has a previous history of a provoked blood clot? Is therapy necessary to continue lifelong for all patients with this mutation?

A: Factor V Leiden (FVL) results from a point mutation in the F5 gene, which encodes the factor V protein in the coagulation cascade. The mutation renders factor V insensitive to the actions of activated protein C (aPC), a natural anticoagulant. As a result, individuals who carry the FVL variant are at an increased risk of venous thromboembolism (VTE). Though VTE is the major clinical manifestation of FVL, only 5% to 10% of individuals with this mutation will experience a VTE in their lifetime.

The initial treatment of VTE in individuals with the FVL mutation is the same as that of the general population: anticoagulants. Direct oral anticoagulants (DOACs) are initiated for individuals with typical VTE presentation. Warfarin is reserved for individuals with extreme body weights, those taking medications with major drug interactions with DOACs, renal impairment, and/or for those with adherence concerns. The duration of anticoagulation therapy depends on the risk of recurrent VTE. In the case of a single, provoked VTE, indefinite anticoagulation is generally not required after the initial three to six months of treatment. Indefinite anticoagulation is recommended for those whose experience a VTE that is unprovoked, life threatening, or at an unusual site (e.g., the mesenteric or portal vein). Additionally, patients with a history of multiple VTEs, and/or additional risk factors (e.g., obesity, cancer, immobility, surgery) may warrant indefinite anticoagulation. There is no evidence that dictates benefits of long-term anticoagulation in individuals with FVL, and it is not recommended to anticoagulate these individuals in the absence of VTE.

Individuals with FVL mutations are treated with DOACs or warfarin; the selection depends on patient specific factors. Duration for a provoked VTE is limited to the initial three to six months. Indefinite anticoagulation should be reserved for specific patient populations (e.g., unprovoked VTE).

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Extended-release Morphine Versus Methadone for Long-term Pain Control

Chandni Bardolia, PharmD, BCGP

Chronic pain is one of the most common indications for opioid prescriptions. In the United States, 27.6% of individuals aged 65 to 84 years and 33.6% of individuals aged 85 years and older had chronic pain in 2016. Because chronic pain is highly prevalent and has negative consequences in older adults, it is vital to adequately manage it to prevent further disability; however, chronic pain is difficult to manage because healthcare professionals must balance pain control as well as opioid risks (e.g., adverse drug reactions, abuse potential).[1]

The selection of an opioid should be based on a variety of factors, including renal and hepatic function, presence of comorbidities, as well as concomitant medications. For older individuals with chronic non-cancer pain (CNCP), strong opioids like morphine, buprenorphine, oxycodone, and hydromorphone are equally recommended to control pain; however, methadone is typically not an early option.[1] Prescribing methadone is complex due to its unique pharmacokinetic (PK) properties (e.g., extensive bioavailability, long elimination half-life), ability to prolong the QT interval, and its potential for toxicity.[1,2]

Very few researchers have compared morphine and methadone for the management of CNCP. Those that have studied the two medications utilized very small sample sizes or had incomplete outcome reporting. Ray *et al*. studied outpatient mortality (due to overdose death or sudden cardiac death) in patients receiving methadone or sustained-release morphine. The authors' results demonstrated that the risk of mortality in methadone users was 46% greater than that of morphine users. Furthermore, individuals taking 20mg/day or less of methadone were at higher risk of mortality versus those receiving a comparable dose of morphine (HR 1.59, 95% CI 1.01-2.51; p-value = 0.046). The authors contribute the increased mortality to the highly variable half-life of methadone resulting in possible drug accumulation.[3]

A recent narrative review, authored by Hanna *et al*., investigated the effectiveness of methadone for the management of pain, in relation to other pain medications. The authors noted that methadone is effective for various types of pain, with the exception of post-procedural pain or cancer-related pain. Though methadone provided similar pain relief as buprenorphine/naloxone for individuals with opioid addiction, methadone provided additional advantages, namely the lack of adjuvant opioid use. The authors concluded that methadone should be considered as a low-cost alternative in individuals requiring CNCP management; however, high-quality, large-scale randomized controlled trials are lacking and are required prior to determining its exact place in managing CNCP.[4]

Since limited literature exists comparing the effectiveness of methadone to morphine in the CNCP setting, the following references will compare the use of these two opioids in patients with cancer-related pain. Bruera *et al*. randomized 103 individuals to the methadone (7.5mg orally every 12 hours and 5mg every 4 hours as needed) or morphine (15mg sustained release every 12 hours and 5mg every 4 hours as needed) group. The results indicated that the methadone group saw a higher dropout rate compared to the morphine group; however, this finding was not considered statistically significant. After four weeks, similar proportions of individuals reflected a 20% or more improvement in pain (0.49 vs 0.56 in the methadone and morphine group, respectively). The researchers concluded that, in individuals with cancer-related pain, methadone was not superior to morphine when comparing efficacy or tolerability. Of note, the study did not achieve sufficient power to detect a difference of 30% or greater in the response proportions.[5]

A second study, conducted by Mercadante *et al*., also evaluated pain management and safety of methadone compared to morphine in forty patients with cancer.[6] The patients who were assigned to the methadone group reported lower opioid escalation indices compared to those treated with morphine.[6] More patients in the methadone group maintained dosing (as opposed to dose

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escalation requirements).[6] The group of authors conducted another study comparing sustained-release morphine 60mg, transdermal fentanyl 25mcg/h, and methadone 15mg in 2008.[7] They recruited 70 patients with cancer diagnoses; among these patients, no differences in pain and symptom intensity were observed.[7] Similar to their previous findings, the researchers noted the opioid escalation index was significantly lower in patients receiving methadone ($p<0.0001$); however, patients in the methodone group did require dose decreases and subsequent increases for reasons not explained.[7] The use of supportive drugs (e.g., laxatives, non-opioid analgesics) were similar between all groups.[7] The researchers concluded that all three opioids were equally effective, well-tolerated, and required similar supportive or adjunct treatments.[7] Methadone was found to be significantly less expensive, but did require more dose titrations suggesting a need for clinical experience with this drug.[7]

Looking at abuse potential for methadone and morphine, methadone is involved in one-fourth of opioid-related deaths[8], while morphine has been cited as the third-leading drug-related cause for emergency room admissions.[9] When reviewing the FDA's Adverse Event Reporting System (FAERS) dashboard, morphine accounts for 4.68% of overdoses reported, whereas methadone accounts for 1.74% of overdoses reported to the FAERS database.[10] Of note, the FAERS database is limited to individual reportings.

Drug companies and opioid manufacturers are taking steps to produce abuse-deterrent formulations of various opioids.[11] Extended-release morphine, available as MorphaBond™ ER, is formulated using these abuse-deterrent methods.[11] Specifically, the formulation makes it difficult to abuse via injection and intranasal routes.[11] While the new formulation may reduce abuse potential in theory (real-world evidence is lacking at this time), the novel formulation increases production costs, resulting in a higher out-of-pocket cost.[11]

While the majority of the studies reviewed above mention no difference in safety when comparing these two opioids[5-7], Ray *et al.,* demonstrated an increased risk of mortality in individuals utilizing methadone which is important to keep in mind.[3] The safety of both medications also depends on specific PK parameters and patient status, see table 1 for information on how these medications should be adjusted based on the presence of renal or hepatic impairment, as well as information on the metabolism of these two medications.[12] Two additional characteristics of methadone that are important to consider include its ability to prolong the QT interval and its propensity to cause respiratory depression. If an individual is prescribed medication that may prolong the QT interval, adding methadone to the list may further increase risk. Routine EKGs would be recommended. Additionally, the FDA has noted that methadone's respiratory depressants effects occur after and persist longer than its peak analgesic effects, which may result in unintentional overdoses, especially in the early initiation phase.[13] In order to decrease the risk of respiratory depression, methadone requires careful initiation and monitoring by experienced healthcare providers knowledgeable about its PK properties.

Ultimately, due to the lack of clinical studies demonstrating long-term efficacy and safety for methadone, sustained release morphine may be considered the more viable option for individuals experiencing CNCP. Patient specific factors (e.g., renal function, hepatic function, concomitant medications) should be considered when selecting the optimal opioid. Additionally, a plan should be drafted for continuous reevaluation of pain and routine reassessment for the need for the selected opioid should be performed.

Table 1: Key Factors to Consider when Selecting Between Morphine and Methadone[12]

	Formulations	Hepatic Impairment	Renal Impairment	Metabolism
Morphine	IV, oral, rectal	Dose decrease recommended	Dose decrease recommended	UGT2B7, UGT1A3
Methadone	IV, oral	No dose adjustment required	Dose decrease recommended	CYP2D6, CYP2B6

Morphine and Methadone References (cont'd):

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Pharmacogenomics Corner

Patients with geographic barriers to healthcare access are prescribed a higher proportion of drugs with pharmacogenetic testing guidelines[1]

- Nicole M. Del Toro-Pagán, PharmD, BCPS -

Drugs with available pharmacogenomics (PGx) guidelines are generally off-patent and less expensive compared to alternatives. Utilizing PGx testing may be a promising approach to support healthcare providers to optimize therapy of these drugs in fewer encounters. This approach may be especially valuable to medically underserved populations, who often experience geographic and socioeconomic barriers to health care access.

A retrospective chart review study was conducted at the University of Florida Health (UF Health) system. Researchers aimed to evaluate whether prescribing patterns for drugs with available Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines (e.g., clopidogrel, citalopram, simvastatin) varied between medically underserved and served patients within the UF Health system. The study included a total of 67,753 patients. These patients were: (1) 18 years of age or older, (2) had a home address in Florida, and (3) had at least one outpatient prescription recorded between 2016 and 2018.

Results from this study revealed that patients with poor geographic healthcare access had fewer encounters with their providers and fewer unique drug prescriptions. Drugs with available PGx guidelines are currently being prescribed in a higher proportion to patients with poor geographic healthcare access when compared with populations with higher geographic healthcare access in the UF Health system; (Q3 IRR 1.1, 95% [CI] 1.05–1.15; Q4 IRR 1.08, 95% [CI] 1.04–1.13). Additionally, Black race and poor geographic health care access scores were found to have even lower number of encounters with providers and total drugs, but were prescribed a much higher proportion of drugs with available PGx guidelines. These results suggest that poor geographic healthcare access may be a contributor to racial healthcare disparities.

The authors were able to use geographic healthcare access status data in conjunction with patient-specific data to identify populations most likely to be prescribed drugs with available PGx guidelines. The use of PGx testing may allow providers to make more efficient use of limited opportunities (e.g., encounters) to improve drug therapies for various disease states. This approach may be particularly beneficial for patients with certain conditions, such as depression, which is more common among poor healthcare access populations. Currently, the standard depression treatment consists of a trial-and-error approach, which may result in the need for several follow-up appointments. The implementation of PGx testing may help reduce the number of appointments required to optimize drug therapy for patients that have poor geographic health care access. However, additional testing of this hypothesis is needed. Only patient-data from visits with UF Health system providers was included in this study, which limits generalizability. However, the authors completed a secondary analysis and confirmed that state-wide results were consistent with those of the UF Health system catchment area.

In conclusion, improved access to PGx testing may allow providers to make more efficient use of limited encounter opportunities to optimize therapy for medically underserved patients. As PGx implementation increases, there is an opportunity to reorient research and allocate resources in alignment with public health care priorities.

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1. Dalton R, Brown JD, Duarte JD. Patients with geographic barriers to health care access are prescribed a higher proportion of drugs with pharmacogenetic testing guidelines. *Clin Transl Sci*. 2021.

August Clinical Inquiries

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MedWise Matrix Updates:

- Selpercatinib was added as a CYP3A4 (MPC 74%) intermediate substrate; it is not classified by Credible Meds but has a high risk of drug-induced LQTS by Long QT-JT index
- Dextromethorphan was updated to show an MPC of 55% at CYP2D6 and an MPC of 35% at CYP3A4
- Voxetotor was added to the MRM Matrix as a major CYP3A4 substrate

Monthly Clinical Inquiry Highlight – Chandni Bardolia, PharmD, BCGP

Q: At what point does sedative burden warrant concern?

A: It is well recognized that some drugs (e.g., alprazolam, morphine, amitriptyline) have strong sedative properties. However, providers may not be aware of other drugs (e.g., lisinopril, cetirizine) with weaker sedative properties. Multiple drugs with weaker sedative activity can have additive effects leading to a growing sedative load. Sedative load refers to the cumulative exposure to drugs with sedative activity.[1] Risks associated with high sedative load include, but are not limited to, daytime sleepiness, memory impairment, depression, and dizziness.[1] These sedative effects of drugs may be pronounced among older people due to aging and the changes in the central nervous system (CNS) that alter the pharmacokinetics and pharmacodynamics of various medications.[2]

Patients with a high sedative burden are at risk of "sedative morbidity."[3] A high sedative burden can cause or worsen physical inactivity, leading to a decline in muscle strength, balance, and mobility.[1-4] This may potentially result in falls and fractures.[1-4] A study in older Veterans Affairs adults with a history of falls or hip fracture demonstrated that patients receiving three or more CNS medications were more likely to have another serious fall than those taking no CNS medications.[4] It has also been demonstrated that high sedative load can cause or contribute to motor vehicle accidents.[3]

Several scales (e.g., Sedative Load Model (SLM), Sloane Model) and tools (e.g., Drug Burden Index) have been developed to quantify sedative activity of individual drugs and sedative load of drug regimens.[1] Individual drugs are assigned sedative scores using the Sedative Load and Sloane Models. The Drug Burden Index provides an equation to measure the total anticholinergic and sedative burden but does not provide categorizations or ratings similar to the SLM. It is worthwhile to note that all the scales and tools take into account dose with the exception of the SLM.[1] The two scales discussed typically categorize drugs into one of three score classes based on their sedative activity: (1) weak, (2) moderate, and (3) strong. **The summative sedative score reflects the cumulative load contributed by the combination of all drugs with sedative activity, with a score greater than 3 generally considered clinically relevant.[1]**

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A Brief Commentary on the Canadian Biomarker Integration Network in Depression (CAN-BIND) Study of Treatment Outcomes of Adding Adjunct Aripiprazole to Escitalopram

Chandni Bardolia, PharmD, BCGP

Depressive disorders, including major depressive disorder (MDD), are highly prevalent and disabling conditions. Treatment of depressive disorders is typically based on empirical data and evidence-based guidelines, but treatment selection remains more of an art. The Canadian Biomarker Integration Network in Depression (CAN-BIND) is a program of research and learning that discovers ways to identify the right treatment for the right person in order to help individuals with depression get well quickly and stay well. CAN-BIND recently conducted a series of research studies (CAN-BIND-1) that analyzes the impact of adding on aripiprazole therapy to patient regimens of those who do not respond to escitalopram as their first antidepressant.[1]

The objective of the CAN-BIND-1 study was to present treatment outcomes for clinical and functional measures of MDD and to estimate the value of early improvement after two weeks of treatment with escitalopram or escitalopram plus aripiprazole to predict symptom outcomes. The researchers recruited 211 participants who were followed for 16 weeks. The average participant age was 35 years (range: 18–61). Participants were treated with open label escitalopram (10–20mg) for eight weeks (Phase 1). If participants responded to escitalopram, they were continued on therapy for an additional eight weeks. Those deemed non-responders after Phase 1 received adjunct aripiprazole (2–10mg) for an additional eight weeks (Phase 2).[2]

At the end of Phase 1, 47% of patients taking escitalopram were considered responders based on the Montgomery-Asberg Depression Rating Scale (MADRS) and continued therapy with escitalopram. From this responder group, 91% maintained response at week 16. The remission rate after Phase 1 was 31% for escitalopram monotherapy. Of those who received adjunct aripiprazole, 61% were considered MADRS responders at week 16. The Phase 2 remission rates were 80% and 42% for those continued on escitalopram and those receiving adjunct aripiprazole, respectively. The authors presented four key findings from this study in their discussion[2]:

1. Response and remission rates were modest following eight weeks of escitalopram therapy and comparable to other studies
2. Response rates to escitalopram were maintained by week 16
3. More than half of the non-responders at week eight had a positive response to adjunct aripiprazole therapy at week 16
4. In both phases, early symptomatic change (after two weeks) provided modest value in predicting subsequent response rates

The CAN-BIND-1 study found that participants treated with escitalopram followed by adjunctive aripiprazole can achieve reasonable rates of symptomatic, functional, and combined response; however, rates of remission remained low.[2] Safety information

[con't p.2]

revealed that the most frequently reported side effects of escitalopram were drowsiness (23%), nausea and headache (16%), weakness and fatigue (14%), nervousness/agitation (14%), and delayed ejaculation (14%). The majority of these side effects waned as escitalopram treatment continued with the exception of drowsiness and delayed ejaculation. The most frequently reported side effects of the combination group were weakness (24%), drowsiness (21%), decreased libido (14%), delayed ejaculation (16%), nervousness/agitation (15%), and decreased sleep (12%).

A secondary analysis of the participants was conducted to see if the addition of aripiprazole resulted in changes in the interest-activity score in patients with MDD. This symptom was the focus of this study because evidence indicates that it is a strong predictor of poor outcomes with antidepressant treatment.[3] The results demonstrated that individuals with MDD, profound loss of interest, and reduced activity had poorer response to escitalopram monotherapy. However, these same individuals benefited from adjunctive aripiprazole therapy, which preserved interest and activity levels. The authors concluded that loss of interest and reduction of activity reported among patients with MDD are predictive of a poor response to antidepressant monotherapy with escitalopram and are indicative of the need for aripiprazole augmentation.[3]

The same group of researchers conducted another analysis to study the cognitive impact of antidepressant and aripiprazole therapies when used for MDD. Results from baseline characteristics demonstrated that participants with MDD display poorer global cognition, composite memory, and psychomotor speed compared to healthy participants. No significant changes were observed in neurocognitive index, reaction time, complex attention, cognitive flexibility, memory or psychomotor speed for individuals taking escitalopram monotherapy during Phase 1 and 2; however, reaction time worsened for participants in the aripiprazole group.[4]

The CAN-BIND-1 study and the sub-analyses demonstrate that aripiprazole can be an effective adjunct treatment option for individuals not responding to first-line selective serotonin reuptake inhibitors (SSRIs: e.g., escitalopram). These studies show that participants can achieve modest improvements in their interest and activity levels with add-on aripiprazole, but remission rates were low. These generally positive results may be explained by the mechanism of aripiprazole. Aripiprazole is a partial dopamine agonist. Studies have suggested that substances that enhance dopamine neurotransmission may be useful in treatment-resistant depression. Previous studies have demonstrated that dopamine agonists (e.g., pramipexole, aripiprazole) have been used in combination with other antidepressants (e.g., bupropion, SSRIs) and have proven to be effective in managing MDD.[5,6] As noted in the VAST-D trial, the effects of adjunct aripiprazole are not only limited to use with escitalopram, but any SSRI. While evidence to support adjunctive aripiprazole therapy is available, a significant limitation to implement in our practice would be patient age. The researchers for the CAN-BIND-1 studies excluded individuals older than 60. Additionally, the dosage of escitalopram used in the study (20mg) is higher than what we would recommend for those in the PACE setting. Furthermore, the studies demonstrated worsening reaction time with adjunctive aripiprazole use. Therefore, if the CAN-BIND-1 approach is used, the patient should be monitored closely and if remission is not achieved within 16 weeks, aripiprazole should be discontinued.

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Pharmacogenomics Corner

A prospective study to determine the clinical utility of pharmaco-genetic testing of veterans with treatment-resistant depression

- Katie Pizzolato, PharmD, PGY2 Resident -

McCarthy et al. conducted a prospective study that aimed to determine the efficacy of pharmacogenomic (PGx) guided treatment in veterans with treatment-resistant depression (TRD). TRD was defined as patients having past treatment failure with at least one trial of an antidepressant or mood stabilizer. Individuals with other psychiatric disorders, such as bipolar depression (BD) and post-traumatic stress disorder (PTSD), were included, making this study unique as most PGx studies focus on patients diagnosed with major depressive disorder (MDD). The 182 eligible patients were randomly assigned to either the PGx-guided group or the treatment-as-usual (TAU) group. For those in the PGx group, a personalized report was prepared that included 15 genes (e.g., CYP2D6, CYP2C19, CYP2B6) and 53 medications (e.g., venlafaxine, risperidone, citalopram), with the latter classified into one of four categories based upon the individual's genetics: preferential use, use as directed, may have significant limitations, and may cause serious adverse events. Meanwhile, the clinician for the TAU group was provided a similar report without PGx driven suggestions. Patients were seen at weeks zero, four and eight by their treating clinicians, at which time mood symptoms were reported on a seven-point scale using the Clinical Global Impression (CGI). Additionally, subjects used the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR) to report their symptoms of depression and side effects.

Upon evaluation, the CGI results demonstrated that subjects in both groups significantly improved over the eight-week trial, with a mean improvement of approximately one point in each group ($p < 0.001$). A faster trend of improvement was observed in the PGx group compared to the TAU group, though not statistically significant ($p=0.08$). Overall, both groups demonstrated significant symptom and side effect improvement based on completed QIDS-SRs ($p<0.001$); however, a significant difference was not observed between the two groups. At week eight, remission rate was 21% in the TAU group and 29% in the PGx-guided group (OR 1.54, 95% CI 0.26-1.63). The clinicians found the PGx test report to be useful in 57% of the patient interactions, primarily reducing side effects rather than improving efficacy of medications, which is in line with clinical literature. The baseline level of depression reported by the patients significantly correlated positively with perceived utility of the test ($r = 0.27$, $p < 0.05$), as did the number of high-risk and moderate-risk drug warnings included in the test ($r = 0.37$, $p < 0.01$).

Test performance was also evaluated by diagnosis and examined the outcomes of the three most common diagnoses (i.e., MDD, BD, PTSD). Patients with BD did poorly in the trial, which could be due to the lack of PGx-guided recommendations available for medications utilized in BP; however, after excluding the BD patients, a significant difference was observed in the CGI favoring the PGx group ($p = 0.02$), which was largely driven by patients with PTSD. This study did observe differences in several aspects favoring the PGx-guided treatment; however, many endpoints were not statistically significant. These results may be partially attributed to the small sample size of the study. Additionally, phenoconversion was not assessed prior to formulating these recommendations, potentially underestimating drug-gene interactions that could alter the recommendations in these personalized reports.

Overall, McCarthy et al. found limited evidence for the utility for PGx testing in a transdiagnostic sample of TRD veterans with MDD, BD, and PTSD.

Reference:
McCarthy MJ, Chen Y, Demodena A, et al. A prospective study to determine the clinical utility of pharmacogenetic testing of veterans with treatment-resistant depression. *Journal of Psychopharmacology*. 2021.

September Clinical Inquiries

- Discontinuing VMAT2 inhibitors
- Changes in pharmacokinetics of medications due to autoimmune diseases
- Alternate-day aspirin dosing
- Association between joint injections and leg tremors
- Continuous glucose moniting in patients with type 2 diabetes
- Interaction between famotidine and tizanidine

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TRHC Publication Updates:

Our PGY2, Katie Pizzolato, along with key individuals from the OTRRP and PPRDI departments, recently published a case report where a PACE participant's hallucinations were potentially caused by cannabis use. It was determined that the participant was experiencing hallucinations from cannabis use likely due to a combination of the participant's *COMT* genotype, diagnosis of Parkinson's disease, and concomitant dopamine-promoting medications. The participant was advised to discotinue cannabis use, which resulted in dissipation of his hallucinations. The clinical pharmacist provided additional medication recommendations to further improve the participant's tremor symptoms, as well as reported pain. For more information on the case, read the full publication here.

Monthly Clinical Inquiry Highlight – Chandni Bardolia, PharmD, BCGP

Q: Do all doses of Cogentin® (benztropine) contribute to altered mental status (e.g., confusion, psychosis) or only doses higher than 1mg BID?

A: Benztropine antagonizes acetylcholine and histamine receptors and is indicated for the treatment of Parkinson's disease and drug-induced extrapyramidal symptoms (EPS; acute treatment only). Geriatric patients are generally more sensitive to the anticholinergic effects and may have a relatively intense response to benztropine compared to younger adults. Common side effects of benztropine in the geriatric population are delirium, confusion, drug-induced dementia, urinary tract problems, and benign prostatic hyperplasia in males. The confusion and mental status changes seen with benztropine are associated with relatively higher doses or higher patient susceptibility (e.g., geriatric patients, patients on antipsychotics).[1]

Manufacturer information indicates that the typical dose to manage Parkinsonism is 1 to 2mg/day, with the maximum recommended dose being 6mg/day.[2] For the acute treatment of EPS, the manufacturer recommends 1–2mg once or twice daily.[2] The manufacturer goes on to state that confusion, visual hallucinations, or excitement may occur, but this is seen at higher doses.[2] Current evidence does not clearly define "higher doses" of benztropine; however, being that benztropine is highly anticholinergic, long-term exposure at any dose, especially in the geriatric population, can contribute significantly to a decline in cognitive status. Therefore, no matter the dose, patients should be monitored for changes in cognition and mental status following initiation of benztropine. If being used for Parkinsonism, benztropine should be discontinued if cognitive dysfunction occurs at any dose and should not be reintroduced. If being used for EPS, the cognitive effects of benztropine should be closely monitored. Additionally, the lowest effective dose of the EPS-inducing antipsychotic drugs should be used to avoid or reduce the need for benztropine.

Clinical Inquiry Highlight Reference:

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Salvage Treatment for *H. Pylori* and Antibiotic Resistance Considerations

Chandni Bardolia, PharmD, BCGP

The *helicobacter pylori* (*H. pylori*) infection is a common worldwide infection that is an important cause of peptic ulcer disease and gastric cancer.[1] While choosing a treatment regimen for *H. pylori*, patients should be asked about previous antibiotic exposure and this information should be incorporated into the decision-making process.[1,2] Patients will typically be initiated on clarithromycin triple therapy or bismuth quadruple therapy as first-line treatment.[1,2] Of note, clarithromycin triple therapy should be reserved for patients with no previous history of macrolide exposure (for any reason) and those who reside in areas where clarithromycin resistance is known to be low (<15%).[1-3] If patients do not meet this criteria, bismuth quadruple therapy should be initiated.[1-3]

Despite the efficacy of these regimens, approximately 20% of patients will fail initial treatment.[3] The top two reasons for therapy failure include noncompliance and antibiotic resistance.[3] When a patient fails initial therapy, a salvage regimen is required.[1-3] Following the initial treatment failure it is not recommended to conduct cultures and antibiotic sensitivity testing.[1,3] Since cultures and sensitivity testing is expensive and not routine in the U.S., such testing is typically reserved for patients who have failed two prior treatment regimens.[1,3]

Salvage regimen should avoid including antibiotics that were previously used, with the exception of amoxicillin, as resistance rarely develops.[3] Of note, for indivduals with a reported penicillin allergy, an allergist should determine if the penicillin allergy is true or more of an intolerance.[3] If a patient happen to receive a first-line treatment containing clarithromycin, bismuth quadruple therapy or levofloxacin salvage regimens should be the preferred treatment options (**Figure 1**).[1] If a patient received first-line clarithromycin triple therapy, bismuth quadruple therapy or levofloxacin-containing salvage regimens would be the preferred treatment options.[1] Clarithromycin salvage regimens should be avoided in locations where resistance is greater than 15% and in patients with any previous macrolide exposure.[2] Levofloxacin-based triple therapy has demonstrated efficacy as a salvage regimen in patients who have failed initial clarithromycin triple therapy or bismuth quadruple therapy.[3] Levofloxacin triple therapy has also demonstrated efficacy in patients who have failed two prior attempts at treatment.[3] Ultimately, the selection of the best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics.[1-3]

Data on resistance patterns in North America are scarce. More research is needed to determine local, regional, and national patterns of *H. pylori* resistance to antibiotics to guide the choice of regimen.[2] Healthcare providers should generally assume clarithromycin resistance rates are greater than 15%, unless local data indicate otherwise.[3] Additionally, Savoldi et al. noted that between 2006 and 2016, resistance rates were 21% to 30% for clarithromycin and levofloxacin in the U.S. and 10% to 20% for metronidazole in the US and Canada.[4] More recently, Hulten et al. revealed that the proportion of US *H. pylori* isolates with resistance to clarithromycin (17.6%), metronidazole (43.6%), and levofloxacin (57.8%) were higher compared with previous reports (**Table 1**).[5] The authors noted that the recently

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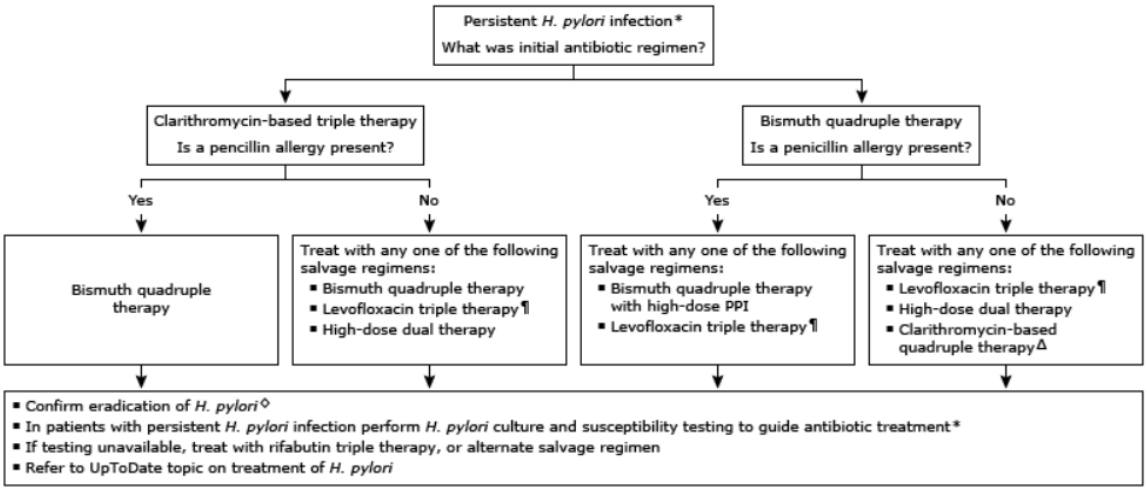
Figure 1: Approach to antibiotic treatment in patients with persistent Helicobacter pylori infection



* Confirmed by a urea breath test, stool antigen test, or upper endoscopy-based testing; ¶ If known levofloxacin sensitive strain or the population levofloxacin resistance rates are known to be less than 15%; Δ This regimen should be avoided if local clarithromycin resistance is unknown; ◊ Confirmed with a urea breath test, stool antigen testing, or upper endoscopy-based testing.

introduced rifabutin triple therapy (Talicia®) and bismuth quadruple therapy are the only currently available regimens in the U.S. for which *H. pylori* resistance is rare.[5]

The rifabutin regimen is the first and only FDA-approved rifabutin-based *H. pylori* therapy designed to address the "high and growing bacterial resistance and diminished efficacy of clarithromycin-based standard-of-care therapy".[5] The rifabutin regimen, which consists of omeprazole magnesium (120mg), amoxicillin (3g), and rifabutin (150mg) for 14 days, demonstrated 84% eradication of *H. pylori* infections compared with 58% in the active comparator arm.[6] With regards to safety, adverse events were similar between treatment groups.[6] The most commonly reported adverse events with the rifabutin regimen and the active comparator were diarrhea (10.1% vs. 7.9%, respectively), headache (7.5% vs. 7.0%), and nausea (4.8% vs. 5.3%).[6]

One other option for salvage therapy is the "high-dose dual therapy" regimen.[3] This regimen consists of amoxicillin (at least 2g divided three or four times per day) and a PPI for 14 days.[3] This option may be considered in patients for whom dual metronidazole/ clarithromycin resistance or levofloxacin resistance is suspected.[3] While studies have demonstrated a pooled eradication rate of 78% with this regimen, the role of high-dose dual therapy as first-line treatment is conflicting and unclear.[6]

Overall, there is a lack of knowledge on *H. pylori* resistance in the U.S., which creates a significant barrier to evidence-based treatment recommendations. It is known, however, that the resistance profiles are increasing for some of the mainstay antibiotics used to manage *H. pylori*. If clarithromycin and levofloxacin resistance is of significant concern, there are other options available with little to no resistance issues for salvage therapy, such as the rifabutin regimen or the high-dose dual therapy regimen.

Table 1: Geographic distribution of antimicrobial resistance patterns per US region, 2017-2018

Antibiotic	All Isolates (n=345)	West (n=108)	Central (n=86)	East (n=151)
Amoxicillin	6.4 (22)	8.3 (9)	5.8 (5)	5.3 (8)
Clarithromycin	17.4 (60)	11.1 (12)	15.1 (13)	23.2 (35)
Metronidazole	43.6 (150)	35.5 (38)	43.0 (37)	49.7 (75)
Rifabutin	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
	Limited Analysis (n=71)	**(n=19)**	**(n=19)**	**(n=33)**
Tetracycline	2.8 (2)	5.3 (1)	5.3 (1)	0.0 (0)
Levofloxacin	57.8 (41)	57.8 (11)	68.4 (13)	51.5 (17)

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Pharmacogenomics Corner

Determining the potential clinical value of panel-based pharmacogenetic testing in patients with chronic pain or gastro-esophageal reflux disease - Joshua Russell, PharmD, PGY2 Resident -

Panel-based pharmacogenomic (PGx) testing is the assessment of two or more genes. Results from this type of PGx test can be utilized to guide current and future treatment decisions. Having PGx results for patients diagnosed with chronic pain and/or gastroesophageal reflux disease (GERD) can be beneficial because these individuals are generally treated with drugs that have high level of evidence as it relates to PGx (e.g., *CYP2D6*—opioids and *CYP2C19*—proton pump inhibitors (PPIs)). Panel-based testing provides an additional layer of benefit for these patients because medications used to treat common comorbidities (e.g., anxiety, depression) have high level of evidence for their gene-drug pairs (*CYP2D6/CYP2C19*—antidepressants, anti-anxiolytics). This study aimed to assess the potential clinical utility of panel-based testing in patients with chronic pain or GERD who complete PGx testing.[1]

This was a retrospective study of patients previously enrolled in two pragmatic trials assessing genotype-guided management of chronic pain or GERD at the University of Florida (UF). The chronic pain and GERD cohorts were genotyped for *CYP2D6* and *CYP2C19*, respectively. Following PGx testing, a 12-month evaluation was conducted to assess the utilization of other medications that can be impacted by PGx results. The analysis included the addition of the following medications: Level A evidence (e.g., antidepressants, simvastatin), select Level B* evidence (e.g., PPIs, celecoxib), and CYP2D6-guided opioids that were not categorized as Level A or B (e.g., oxycodone).

Initially, 500 patients were enrolled in the chronic pain or GERD trials. From there, 52 were excluded and of the 448 participants remaining, 337 were included from the chronic pain analysis and 111 from the GERD analysis. Of the patients included from the chronic pain study, 76.6% (n=259) were prescribed one additional medication with available PGx information and 52% (n=175) were prescribed two or more additional medications with PGx recommendations. Of the medications added (e.g., PPIs, selective serotonin receptor inhibitors (SSRIs)), 50% were metabolized by CYP2C19 and would have benefited from panel-based testing. In the GERD population, 71.2% (n=79) were prescribed one additional drug with PGx data of interest and 40% (n=44) were prescribed two or more medications with gene-drug pairs of interest. Of the medications added (e.g., opioids, antiemetics), 75% were metabolized by CYP2D6 and would have benefited from panel-based testing. The average number of additional PGx medications per patient was 1.7 and 1.6, for the chronic pain and GERD cohorts, respectively. Of the additional medications prescribed in the pain cohort, the most common were PPIs (67%), antiemetics (40%), and SSRIs (16%). In the GERD cohort, the most common medications were opioids (62%), antiemetics (49%), and SSRIs (22%).

The frequency of additional PGx medications in patients with chronic pain or GERD can be explained by the prevalence of comorbidities with each of these disease states. Panel testing may have a greater benefit then this study demonstrated if some limitations were addressed, such as, over the counter medications (PPIs) and medications prescribed outside of the UF study site missing from the electronic health record. This study supports the use of panel-based testing in patients receiving PGx testing for chronic pain or GERD. As other gene-drug pairs are evaluated, and more drugs acquire higher level of evidence grades regarding PGx, we can assume the utility and value of panel-based testing will only increase.

*Level of evidence by Clinical Pharmacogenetics Implementation Consortium in 2019

Reference:
Elchynski AL, Cicali EJ, Ferrer Del Busto MC, et al. Determining the potential clinical value of panel-based pharmacogenetic testing in patients with chronic pain or gastroesophageal reflux disease [published online ahead of print, [2021 Jun 1]. *Pharmacogenomics J*. 2021.

November Clinical Inquiries

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TRHC Publication Update:

Our very own members of the PPRI department published a systematic review of 13 anticholinergic and sedative burden risk scales and models used in older adults. This patient population is at higher risk for poor cognitive and physical outcomes with the use of medications that carry high anticholinergic and sedative properties. Our researchers noted that there is considerable variability among risk scales and models used to categorize drugs with anticholinergic and sedative properties. They proposed a new way to categorize drugs with these properties. The proposed table combines information about 642 drugs and categorizes 44, 25, 99, and 474 drugs as high, moderate, low, or no anticholinergic and sedative activity, respectively. To read more and to view the table, please click here.

Monthly Clinical Inquiry Highlight – Chandni Bardolia, PharmD, BCGP

Q: Is there an expert consensus on which triple-inhaler therapy (Breztri Aerosphere™ or Trelegy Ellipta®) is recommended for chronic obstructive pulmonary disease (COPD) management?

A: Per the 2021 edition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, triple therapy with a long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS) has been shown to improve lung function and reduce exacerbations when compared to monotherapy and/or dual therapy.[1] Additionally, fixed-dose triple inhaled therapy versus fixed-dose LABA/LAMA combinations have demonstrated a beneficial effect on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations who were previously receiving maintenance therapy with triple therapy, LABA/ICS or single or dual long-acting bronchodilators.[1]

Breztri was approved approximately one year ago. To date, there have not been any head-to-head comparisons between Breztri and Trelegy. While these data may be lacking, there are a few differences between both inhalers that can guide product selection: first is dosing. Breztri is dosed as two inhalations twice daily. Trelegy is dosed as one inhalation once daily. Additionally, the delivery device differs between both products. Breztri is a metered-dose inhaler (MDI), whereas Trelegy is a dry-powder inhaler (DPI). MDIs require the user to coordinate pressing down the canister and inhaling the medication while DPIs do not; however, the inspiratory flow rate is a drawback of DPIs.[2] Using DPIs also requires the patient to be careful not to disperse medication via exhalation into the device prior to using.[2] MDIs have a high percentage of patients misusing them, which can lead to inhaler overdose or can cause the patient to receive less than the proper amount of medication.[2] DPIs are more susceptible to contamination because of their design and drug delivery; MDIs can easily be dissembled and cleaned.[2] Of note, the Ellipta device has previously been characterized as having the highest usability of various DPI devices (e.g., Turbohaler, Diskus).[3] Cost may also be an important factor to consider when choosing between the two inhalers. The average whole price (AWP) for Trelegy per the Red Book is $722.23 and the AWP for Breztri is $708.48.[4,5] While the pricing may be similar (difference of $13.75/month and $165.00/year), insurance coverage may vary between companies.

In conclusion, the guidelines do not state a preference for which triple therapy product should be used in COPD patients. Various factors, including dosage, device, and price, should guide the selection of the product. Patient-specific factors should be accounted for as well, including mental status and co-morbid conditions (e.g., rheumatoid arthritis).

Clinical Inquiry Highlight Reference:

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2. How to Use Inhalers Interactive Guidance and Management. Comparative studies on Metered dose inhalers and Dry powder inhalers. 2020. Accessed October 21, 2021. https://use-inhalers.com/comparative-studies-on-mdi-and-dpi.
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New and Approved Drugs

Selina Muhn, PharmD, PGY1 Pharmacy Resident

Newly approved medications:

Ruxolitinib (Opzelura™, Incyte)

In September 2021, the Food and Drug Administration (FDA) granted approval for the first topical Janus kinase (JAK) inhibitor for atopic dermatitis (AD), ruxolitinib. JAK inhibitors inhibit JAK1 and JAK2, which mediate the signaling of cytokines and growth factors that are important for hematopoiesis and immune function. Ruxolitinib 1.5% cream received approval for short-term, non-continuous treatment of moderate-to-severe AD that has not been adequately controlled with topical prescription therapies. Ruxolitinib can be used in non-immunocompromised patients ages 12 and older. Approval was based on the randomized, phase III TRuE-AD1 and TRuE-AD2 clinical trials, which involved more than 1,200 adults and adolescents with moderate-to-severe AD. Of the 1,249 total patients, 115 were 65 years of age and older, and there were no clinically meaningful differences in safety or efficacy between younger and older patients. The primary endpoint was Investigator's Global Assessment (IGA) of Treatment Success at week 8. More than half of patients randomized to ruxolitinib met the primary endpoint as compared with 15.1% and 7.6% of patients in the control groups (P<0.0001). Additionally, more than half of the patients randomized to ruxolitinib had clinically meaningful reductions in itch as compared with 15 to 16% of patients randomized to placebo (P<0.0001).

The cream is applied as a thin layer twice daily to affected areas of up to 20% body surface area. More than 60g/week is not recommended. The most common adverse events (1 to 3%) in ruxolitinib treated patients were nasopharyngitis, diarrhea, increased eosinophil count, urticaria, folliculitis, tonsillitis, and rhinorrhea. As with some other medications in its class, ruxolitinib carries boxed warnings for serious infections, mortality, cancer, major adverse cardiovascular events, and thrombosis. Ruxolitinib cream is projected to be available by the end of 2021.

Atogepant (Qulipta™, Abbvie)-$$$$*

With FDA approval granted in September 2021, atogepant became the first oral calcitonin gene-related peptide (CGRP) receptor antagonist specifically developed for migraine prevention. The approval of atogepant was supported by data from the phase III ADVANCE study, which included participants aged 18 to 74 years old. In ADVANCE, participants were assigned to receive a once-daily dose of atogepant (10mg, 30mg, or 60mg) or placebo. After 12 weeks, the mean number of migraine days per month dropped from baseline by 3.7 days with atogepant 10mg, 3.9 days with 30mg, 4.2 days with 60mg, and 2.5 days with placebo (P< 0.0001 for all doses). In addition, more than half of patients in each atogepant arm achieved a reduction in mean monthly migraine days of ≥50% (P<0.001 for all doses). Approximately 29% patients who received placebo achieved this outcome.

Atogepant is available as tablets, and the recommended dosage is 10mg, 30mg, or 60mg taken orally once daily with or without food. The most common adverse events (at least 4%) with atogepant were constipation and nausea. In patients with pre-existing mild, moderate, or severe hepatic impairment, the total atogepant exposure was increased by 24%, 15%, and 38% respectively. Due to the potential for liver injury, atogepant should be avoided in patients with severe hepatic impairment. Although, there is no significant difference in the pharmacokinetics of atogepant in patients with mild or moderate renal impairment relative to those with normal renal function, patient with severe renal impairment have not been studied. Therefore, the lowest effective dose (10mg) is recommended in patients with severe renal impairment. Since clinical studies did not include enough patients aged 65 years and over, it is recommended to start at a low dose for elderly patients. Manufacturer packaging suggests dose reductions when atogepant is taken concomitantly with strong or moderate CYP3A4 inhibitors/inducers or OATP inhibitors; however, atogepant is not presently mapped in MedWise™.

Difelikefalin (Korsuva™, Vifor)

In August 2021, the FDA approved difelikefalin for the treatment of moderate to severe pruritus in patients on hemodialysis. Difelikefalin is an injectable kappa opioid receptor agonist that targets the peripheral nervous system. By avoiding receptors in the brain and spinal cord, patients are less likely

[con't p.2]

to experience nausea, respiratory depression, and abuse potential. Difelikefalin is the only medication with FDA approval for the treatment of chronic kidney disease associated pruritus. The approval for difelikefalin was granted based on two phase III trials, KALM-1 and KALM-2. These studies involved a total of 1,300 chronic kidney disease dialysis patients with moderate-to-severe pruritus. Of the difelikefalin recipients, 40% and 37% had a four-point improvement from baseline on a measure of their most severe itch compared to 21% and 26% for those who received placebo.

The recommended dosage of difelikefalin is 0.5mcg/kg administered by an intravenous bolus injection into the venous line of the dialysis circuit at the end of each hemodialysis treatment. Difelikefalin may cause dizziness, sleepiness, mental status changes, and gait disturbances. It may also cause impairment when driving a car or operating machinery. However, none of these side effects were evident in more than 7% of patients who received difelikefalin in the trials. Difelikefalin has not been studied in patients on peritoneal dialysis and is not recommended for use in this population. In clinical studies, no overall differences in safety or effectiveness of difelikefalin have been observed between patients 65 years of age and older and younger adult patients, except for the incidence of somnolence which was higher in elderly patients (7% compared to 2.8%). Difelikefalin is expected to be available in the first quarter of 2022.

Dihydroergotamine mesylate (Trudhesa™, Impel) - $$$$

The FDA-approved dihydroergotamine mesylate nasal spray in September 2021 to treat acute migraines with or without aura in adults. Dihydroergotamine mesylate is not indicated for the preventative treatment of migraines. In 1946, dihydroergotamine mesylate was one of the first synthetic medications developed for treating migraine, and it has been administered intravenously. The approval of dihydroergotamine mesylate was supported by data from the open-label phase III STOP 301 study. During the trial, more than 5,650 migraine attacks were treated over 52 weeks. Of the patients receiving the experimental treatment, 52% no longer experienced their most bothersome migraine symptom two hours after the first dose. For 16% of patients, relief was experienced as quickly as 15 minutes. For patients who were pain-free two hours after taking the medication, 93% were still pain-free 24 hours later and 86% were pain-free two days later.

The recommended dose of dihydroergotamine mesylate is 1.45mg (one spray of 0.725mg into each nostril), and the dose may be repeated at least one hour after the first dose. However, more than two doses should not be used within a 24-hour period, and patients should not exceed three doses within seven days. Overuse of dihydroergotamine mesylate may lead to exacerbation of headache. The most common adverse effects are nasal congestion (17.8%), nausea (6.8%), nasal discomfort (6.8%), abnormal olfactory test (6.8%), and vomiting (2.7%). Serious and life-threatening peripheral ischemia has been associated with the co-administration of strong CYP3A4 inhibitors, according to the package insert. Patients with ischemic heart disease, coronary artery vasospasm, uncontrolled hypertension, peripheral arterial disease, sepsis, vascular surgery, severe hepatic/renal impairment, or hypersensitivity to ergot alkaloid should not use dihydroergotamine mesylate. Concomitant use of other 5-HT1 agonists (e.g., sumatriptan), ergotamine containing or ergot-type medications within 24 hours is contraindicated. Dihydroergotamine mesylate should not be used with peripheral and central vasoconstrictors.

Newly approved indication:

Empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly)-$$$$

First approved in 2014 for glucose lowering in type 2 diabetes, in September 2021, the FDA added a new indication for empagliflozin for treating heart failure with reduced ejection fraction (HFrEF). Empagliflozin is now the second sodium-glucose co-transporter-2 (SGLT2) inhibitor to be FDA approved for both type 2 diabetes and heart failure after dapagliflozin (Farxiga®) was approved for HFrEF in 2020. SGLT2 inhibitors lower glucose through a unique mechanism that targets SGLT2 in the proximal convoluted tubule, allowing glucose to be excreted through the urine. Although the mechanism by which SGLT2 inhibitors confer cardiovascular benefits remains unclear, it has been suggested that these medications are involved in changes of epicardial fat and myocardial metabolism. The 10mg once-daily dose of empagliflozin was approved for the reduction of risk of cardiovascular death and hospitalization for heart failure based on the EMPEROR-Reduced trial, which had a mean patient age of 67 years. In that study, empagliflozin reduced cardiovascular deaths and hospitalizations for heart failure by approximately 25% for HFrEF patients over 16 months, regardless of diabetes status. A key secondary endpoint demonstrated approximately a 30% reduction in the first or recurrent hospitalization for heart failure, compared to placebo.

The most common adverse events (5% or greater incidence) associated with empagliflozin are urinary tract infection (UTI) and female genital mycotic infection. Elderly patients may be more prone to adverse drug events (e.g., hypotension, UTI) due to volume depletion. No dosage adjustment is necessary for hepatic impairment or eGFR ≥ 30 mL/minute/1.73 m^2. Empagliflozin should not be used when eGFR is persistently < 30 mL/minute/1.73 m^2. In addition, empagliflozin is not indicated for use in patients with type 1 diabetes, diabetic ketoacidosis, end stage kidney disease, or dialysis. In vitro studies suggest that the primary route of metabolism of empagliflozin is glucuronidation. However, at this time, no significant drug interaction is anticipated when concomitantly administer with substrates of UDP-glucuronosyltransferase (UGT) or major CYP450 isoforms. Currently, a generic product is not available and empagliflozin is packaged as either 10mg or 25mg tablets.

***Key**: (Approximate cost per month supply)

₵		<$1
₵₵		$1 - $5
₵₵₵		$5 - $10
₵₵₵₵		$10 - $25
$		$25 - $75
$$		$75 - $150
$$$		$150 - $500
$$$$		>$500

Pharmacogenomics Corner

Pharmacogenomics guided prescription changes improved medication effectiveness in patients with mental health-related disability: A retrospective cohort analysis

- Katie Pizzolato, PharmD, PGY2 Resident -

The leading cause of disability among working individuals in Canada results from mental health problems. Approximately 70% of total disability costs can be attributed to mental illness claims (i.e., depression, bipolar disorder, anxiety, post-traumatic stress disorder). Additionally, only an estimated 50% of the individuals prescribed psychotropic medications will respond to their initial medication. In this retrospective study out of Canada, Ahmed *et al*. sought to assess whether pharmacogenomic (PGx)-guided therapy improved antidepressant effectiveness in patients on mental health-related disability. The study included 84 participants, with an average age of 35, who completed an individual medication history review with a licensed pharmacist. During the review, the pharmacist utilized a pre-defined questionnaire to evaluate the effectiveness of each participant's treatment. This was measured on a numerical scale that accounted for the presence of medication-related side effects (maximum score = 5) and the individual's feelings towards work tasks and quality of life (maximum score= 5). Adding these scores together resulted in the total treatment effectiveness score, ranging from 0 (good) to 10 (worst). Following this review, each participant was asked to complete a PGx test from Rx Report®. The Rx Report® analyzed 54 genes, which included pharmacokinetics (PK) genes that can affect drug metabolizing enzymes (e.g., *CYP2C19, CYP2D6*) and pharmacodynamics (PD) genes that can alter brain receptors (e.g., *HTR2A, DRD2*). Upon receiving the PGx results, the pharmacist developed individualized recommendations utilizing a proprietary software containing an algorithm of 104 key genetic variants. Afterwards, the pharmacist sent these recommendations to the participant's physician. After three months, the pharmacist contacted each participant to complete another medication review to evaluate for medication changes and to reevaluate treatment effectiveness with the same questionnaire used during the first encounter.

Out of the 84 participants, the most common mental health conditions were depression (~90%) and anxiety (~50%). The most common medication-related side effects were fatigue (32%), dizziness (17%), and insomnia (17%). It was found that all of the tested individuals had at least one genetic mutation, with approximately 66% of them having a mutation in both PK and PD genes. Follow-up assessment data was available for 46 participants, and all but one participant had a pharmacist-recommended prescription change implemented (e.g., alternative medication, dosage change, adjunct medication). At baseline, the average effectiveness score was 8.39 (SD=1.22); however, at the 3-month follow-up and after the prescription changes, the average medication effectiveness scores significantly improved to 2.30 (SD=1.01) ($p \leq 0.001$). A supplementary analysis discovered a significant correlation between genetic mutation and baseline treatment effectiveness scores for the initial 84 participants (Spearman's correlation coefficient=0.281, $p=0.01$), as well in the smaller cohort of participants that completed the follow-up questionnaire (Spearman's correlation coefficient=0.375, $p=0.01$).

Limitations of the study include the small sample size and study design. This study did have a high rate of medication changes; however, the authors did not mention if phenoconversion was accounted for, which could have altered the recommendations. Another limitation to note is that acceptance and implementation of the pharmacist's recommendations was solely dependent on successful contact with each study participant. Overall, the results from Ahmed *et al.* suggest that PGx results can aid pharmacists in generating recommendations that can improve outcomes in patients with mental health-related disabilities and reduce medication-related side effects.

Reference:
Ahmed S, Tahir R, Akhtar U, Faiz M. Pharmacogenomics guided prescription changes improved medication effectiveness in patients with mental health-related disability: A retrospective cohort analyses. Front Genet. 2021;12:644-694.

November Clinical Inquiries

- Ergocalciferol vs. cholecalciferol use for vitamin D deficiency
- P-gp interaction between carvedilol and apixaban
- Cannabis metabolism pathways
- Alternatives to vismodegib for metastatic basal cell carcinoma

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