

## Plecanatide (Trulance®): A New Guanylate Cyclase-C Agonist for CIC and IBS-C

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**C**hronic idiopathic constipation (CIC) is a very common gastrointestinal disorder which affects 15-25% of people in North America.<sup>1,2</sup> This disorder is more common in woman, lower socioeconomic status, and older populations.<sup>1,2</sup> CIC has been linked to a lower quality of life, especially in the elderly.<sup>1</sup> Constipation is classified as CIC if any of the following symptoms occur for  $\geq 3$  months: difficult stool passage, prolonged time to stool, hard/lumpy stools, straining, incomplete evacuation, a sense of difficulty of passing stool, or need to manual maneuvers to pass stool.<sup>1</sup> Along with CIC, other conditions such as irritable bowel syndrome (IBS), specifically irritable bowel syndrome with constipation (IBS-C) which affects 5-15% of the global population, can cause long sustaining constipation. IBS may cause both constipation and loose stools which makes it a difficult disease to control. It has a considerable socioeconomic impact associated with both indirect and direct medical costs, including medical diagnostic tests and medical treatments.<sup>1</sup>

The 2014 American College of Gastroenterology Monograph on Management of IBS-C and CIC recommends pharmacologic treatment with agents such as fiber, 5-HT<sub>4</sub> agonists (prucalopride), probiotics, bile acid transporter inhibitors, osmotic and stimulant laxatives (lactulose, sodium picosulfate, bisacodyl), and prosecretory agents (lubiprostone, and linaclotide).<sup>1</sup> Guanylate cyclase (GC-C) receptors are a promising target for constipation because of their critical role in electrolyte homeostasis and maintenance of intestinal fluid. GC-C agonist can be an effective

option with the convenience of once-daily dosing unlike agents like bisacodyl which can sometimes require multiple doses in a day. There is currently only one GC-C agent available, linaclotide, however, out of all currently available treatment options this agent has high incidence of patient reported diarrhea (16-22%).<sup>1,3</sup> Due to this high incidence of unwanted adverse effects (ADE), an agent with the same efficacy as linaclotide but with less adverse effects would be of great benefit to patients. In January 2018, a new GC-C agent, Trulance® (plecanatide) was approved for treatment of CIC in adults and IBS-C a few weeks after. The purpose of this article is to review the safety and efficacy of plecanatide for the treatment of CIC.

### PHARMACOLOGY

#### *Mechanism of Action*

Plecanatide is a GC-C agonist. It is related structurally to uroguanylin which is an endogenous GC-C agonist. Plecanatide and its active metabolites increase cyclic guanosine monophosphate (cGMP) concentrations extracellularly and within cells that line the luminal surface of the intestinal epithelium by binding and activating GC-C. Increased levels of cGMP stimulate secretion of bicarbonate and chloride into the intestinal lumen by the activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. In animal models, plecanatide has been shown to increase fluid secretion into the GI tract, accelerate transit of the intestine, and cause stool consistency changes.<sup>4</sup>

#### *Pharmacokinetics*

Plecanatide is minimally absorbed systemically after oral administration and stays at the site of action within the GI tract.<sup>4</sup> Plasma concentrations of plecanatide and its active metabolite are below the limit of detection after the approved 3 mg oral dose. Because of its minimal absorption, the AUC, maximum concentrations and half-life are unable to be calculated. In a crossover study, a single dose of plecanatide 9 mg, 3x the approved dose, resulted in a detectable plasma concentration, but only in one study subject.<sup>4</sup> Plecanatide exhibits little to no binding to human alpha-1 glycoprotein or serum albumin. It is metabolized in the GI tract to an active metabolite but both the metabolite and plecanatide are degraded within the intestinal lumen to smaller peptides and amino acids. Because of its minimal absorption, the excretion of plecanatide has not been studied in humans.

### CLINICAL TRIALS

The following section will review plecanatide in a phase I trial and two phase III trials that evaluated plecanatide safety and efficacy in the treatment of CIC.<sup>5,6,7</sup> Plecanatide has also been studied in two additional phase III trials in patients with IBS-C; however, at the time of this manuscript writing these studies have yet to be published. Additionally, there is no evidence currently to suggest

### IN THIS ISSUE

**Plecanatide (Trulance®): A New Guanylate Cyclase-C Agonist for CIC and IBS-C**

**Personalized Medicine: Genotype-Guided Opioid Prescribing**



that plecanatide would be effective in opioid induced constipation.

A summary of plecanatide efficacy for the treatment of CIC can be found in **Table 1**, safety data is presented in **Table 2**. Both phase III trials inclusion criteria required patients to meet modified ROME III functional constipation criteria to participate in the trial. The modified ROME III criteria is defined as patients reporting loose stools that are rarely present without use of laxatives, a history of <3 defecations per week, and not using manual maneuvers to facilitate defecations.<sup>7</sup> In addition, patients are required to report at least 2 of the following: straining, sensation of incomplete evacuation, lumpy or hard stool, or sensation of anorectal blockage/obstruction for at least 25% of defecations.<sup>7</sup> Patients also could not meet ROME III criteria for IBS-C which is defined as recurrent abdominal pain, 3 days per month in the last 12 weeks associated with  $\geq 2$  of the following criteria: improvement with defecation, onset associated with change in stool form, or onset associated with change in frequency of stool. The Bristol stool form scale (BSFS) is also used in the phase III trials which evaluates the feces of patients on a scale of 1-7; a score of 1 indicates severe constipation and 7 indicates severe diarrhea.<sup>6,7</sup>

#### Phase I Trial

A Phase I trial for plecanatide conducted by Shailubhai et al. was a single-site, first-in-human, double-blind, randomized, placebo-controlled, single ascending-dose trial and investigated plecanatide safety, tolerability, pharmacokinetics, and pharmacodynamics.<sup>5</sup> It included 72 healthy volunteers that were male or post-menopausal females between the ages of 18-64 years old with a body mass index between 18-29 kg/m<sup>2</sup>. Blood samples were taken at specific time intervals from 0 hours to 48 hours post-dose and patients kept daily stool diaries for 7 consecutive days during the 14-day screening period. Volunteers were either given concentrated stock solution of plecanatide in phosphate-buffered saline (PBS) or placebo. There were 9 different plecanatide dose strengths given as a single oral dose: 0.1, 0.3, 0.9, 2.7, 5.4, 8.1, 16.2, 24.3, and 48.6 mg. Of the 53 volunteers that were given plecanatide, 18 volunteers were given placebo, and one did not receive either due to meeting exclusion criteria. Of these participants, 13 (24.5%) had at least one treatment-emergent adverse events (TEAE). Of the 13 patients with reported TEAEs, 8 patients (15.1%) had diarrhea, 3 patients (5.7%) had abdominal discomfort, 3 patients (5.7%) had nausea, and 2 patients (3.8%) had vomiting. In comparison to placebo, all doses of plecanatide demonstrated no clinically significant changes to vital signs, hematology, urinalysis, chemistry, ECG, or physical exam. Plecanatide was not detected in any plasma samples (0.1 mg to 48.6 mg) which indicates that there were no measurable systemic exposure of drug in a single dose. Because of this, pharmacokinetic and pharmacodynamics parameters were not able to be calculated. The authors concluded that oral treatment of plecanatide was well tolerated and safe.

#### Phase III Trials

The first phase III trial conducted by DeMicco et al. examined the efficacy and safety of plecanatide in CIC over 12 weeks in a randomized, parallel-group, double-blind, placebo-controlled study that included 1,410 patients.<sup>6</sup> The objective of the study was to evaluate safety and efficacy of once-daily plecanatide tablets (3 mg and 6 mg) when compared to placebo over 12 weeks in patients with CIC. The primary endpoint was the percentage of patients achieving durable overall complete spontaneous bowel

movement (CSBM) (weekly responders for  $\geq 9$  of 12 treatment weeks, including  $\geq 3$  of the last 4 weeks). A CSBM was defined as an SBM (spontaneous bowel movement), a bowel movement (BM) occurring without laxative use within 24 hours, and a sense of complete evacuation. Inclusion criteria included age between 18-80 years, a BMI between 18-40 kg/m<sup>2</sup>, a modified ROME III functional constipation criteria for  $\geq 3$  months before the screening visit with symptoms for  $\geq 6$  months before the diagnosis. Exclusion criteria were, but not limited to, a history or presence of disease associated with constipation other than CIC (originating from central nervous system, GI system, collagen vascular disease, etc...), post-surgical or structural GI disorders, conditions or diseases that could affect GI motility or defecation, history of cancer in the past 5 years, or presence of any other medical condition that is uncontrolled. The study prohibited the use of laxatives that included lubiprostone, prucalopride, linaclotide, stool softeners, lactulose, osmotic laxatives, and stimulant laxatives. Patients were randomly allocated 1:1:1 to receive a once-daily dose of oral plecanatide 3 mg (n=467), 6 mg (n=469) or a placebo (n=466) for 12 weeks. Baseline characteristics were similar among all three treatment groups. Study medication was dosed in the morning with or without food and patients returned to clinic at weeks 4, 8, and 12 with a follow-up visit 2 weeks after treatment ended (week 14). Patients were permitted to use bisacodyl 5 mg tablets as rescue medication, but only if they did not have a BM in the past 72 hours and recorded its use in their BM diary.

The primary outcome, the percentage of patients with durable overall CSBM after 12 weeks of treatment, was significantly greater with plecanatide 3 mg and 6 mg when compared to placebo (3 mg = 20.1%; 6 mg = 20.0%; placebo = 12.8%; p=0.004 for both comparisons). Secondary outcomes included mean weekly CSBM frequency and stool consistency based on BSFS score. In terms of secondary outcomes, both doses of the treatment drug showed significant increases from baseline in mean weekly CSBM frequency when compared to placebo (plecanatide 3 mg = 1.49 CSBMs/week; 6 mg = 1.5 CSBMs/week; placebo = 0.87 CSBMs/week; p<0.001 for both comparisons). Also, both doses of plecanatide demonstrated improvements in stool consistency with improvements from baseline BSFS score after treatment (3 mg = 1.49 points increase; 6 mg = 1.50 points increase; placebo = 0.87 points increase; p< 0.001 for both comparisons). The most common TEAEs were diarrhea (plecanatide 3 mg = 3.2%; 6 mg = 4.5%; and placebo = 1.3%) and headache (plecanatide 3 mg = 2.1%; 6 mg = 2.1%; and placebo = 1.9%). There were no unexpected safety signals observed in the study and no deaths reported. Laboratory values, vitals, and physical examination were all unremarkable. The authors concluded that plecanatide appeared to be well tolerated with low adverse effect profile and increased CSBM, frequency, and stool consistency over placebo.

Miner et al. completed a second phase III trial to assess the efficacy and safety of plecanatide in the treatment of CIC.<sup>7</sup> This study was a randomized, double-blinded, 12-week, placebo-controlled trial that included 1,394 CIC patients. Like the previous clinical trial, the primary efficacy endpoint was the percentage of patients who were durable overall CSBM responders (weekly responders for  $\geq 9$  of 12 treatment weeks, including  $\geq 3$  of the last 4 weeks). Participants reported all BMs in an electronic diary in real time or daily. The inclusion and exclusion criteria were identical as the previous phase III trial discussed with minor additional exclusion criteria discussed in the trial's supplemental material. Patients were randomly assigned in a 1:1:1 ratio into one of three treatments groups, plecanatide 3 mg (n=453), 6 mg (n=441), or placebo

**Table 1 | Summary of Clinical Trials for Plecanatide**

Trial	Design	Interventions	Primary Endpoint	Results
Phase 1; Shailuhai et al. <sup>5</sup>	Phase I, single-site, double-blind, randomized, placebo-controlled, single ascending-dose trial	Plecanatide single dose (n=6 per treatment arm) <ul style="list-style-type: none"> <li>0.1 mg, 0.3 mg, 0.9 mg, 2.7 mg, 5.4 mg, 8.1 mg, 16.2 mg, 24.3 mg, 48.6 mg</li> </ul> Placebo (n=18)	Percentage of TEAEs	<ul style="list-style-type: none"> <li>≥1 TEAE: <ul style="list-style-type: none"> <li>PBO: 22.2%</li> <li>Plecanatide (all doses): 24.5%</li> </ul> </li> <li>Diarrhea: <ul style="list-style-type: none"> <li>PBO: 16.7%</li> <li>Plecanatide (all doses): 15.1%</li> </ul> </li> <li>Abdominal Discomfort <ul style="list-style-type: none"> <li>PBO: 0%</li> <li>Plecanatide (all doses): 5.7%</li> </ul> </li> </ul>
Phase 3; DeMicco et al. <sup>6</sup>	Phase 3, 12 week, randomized, parallel-group, double-blind, placebo-controlled trial in patients with Rome III functional constipation criteria <sup>a</sup>	<ul style="list-style-type: none"> <li>Plecanatide 3 mg daily (n=467)</li> <li>Plecanatide 6 mg daily (n=469)</li> <li>PBO daily (n=466)</li> </ul>	Percentage of patients with durable overall CSBM (≥9 of 12 treatment weeks, including ≥3 of the final 4 weeks)	<ul style="list-style-type: none"> <li>Plecanatide 3 mg: 20.1%</li> <li>Plecanatide 6 mg: 20.0%</li> <li>PBO: 12.8% (p=0.004 for both plecanatide comparisons)</li> </ul>
Phase 3; Shailuhai et al. <sup>7</sup>	Phase 3, 12 week, randomized, parallel-group, double-blind, placebo-controlled trial in patients with Rome III functional constipation criteria <sup>a</sup>	<ul style="list-style-type: none"> <li>Plecanatide 3 mg daily (n=467)</li> <li>Plecanatide 6 mg daily (n=469)</li> <li>PBO daily (n=466)</li> </ul>	Percentage of patients with durable overall CSBM (≥9 of 12 treatment weeks, including ≥3 of the final 4 weeks)	<ul style="list-style-type: none"> <li>Plecanatide 3 mg: 21.0%</li> <li>Plecanatide 6 mg: 19.5%</li> <li>PBO: 10.2% (p&lt;0.001 for both plecanatide comparisons)</li> </ul>

**BMI:** body mass index (kg/m<sup>2</sup>); **CSBM:** complete spontaneous bowel movement; **kg:** kilogram; **m:** meter; **mg:** milligram; **PBO:** placebo; **TEAE:** treatment-emergent adverse events

<sup>a</sup>ROME III functional constipation criteria: patients reporting loose stools that is rarely present without use of laxatives, not meeting ROME III criteria for IBS-C, reporting a history of <3 defecations per week, not using manual maneuvers to facilitate defecations, and reporting at least 2 of the following: straining, sensation of incomplete evacuation, lumpy or hard stool, or sensation of anorectal blockage/obstruction for at least 25% of defecations.

bo (n=452) each given once daily orally for 12 weeks. The demographic characteristics were balanced across all three treatment groups for the study population. Patient compliance was assessed by pill count and required at least 80% of assigned doses to be taken to be considered compliant. Compliance was comparable across the three groups (plecanatide 3 mg, 96.5%; 6 mg, 96.6%; and placebo, 98.0%).

The trial results demonstrated a greater percentage of patients achieving the primary efficacy endpoint for both the plecanatide 3 mg and 6 mg compared to placebo (plecanatide 3 mg = 21.0%; 6 mg = 19.5%; placebo = 10.2%; p<0.001 for both comparisons). The secondary endpoints included frequency of weekly CSBM, stool consistency using the BSFS, and TEAE. There was a greater percentage of weekly CSBM responders in both treatment groups within the first week when compared to placebo (plecanatide 3 mg = 35.8%; 6 mg = 29.3%; placebo = 16.6%; p<0.001 for both comparisons). Frequency of weekly CSBM also increased with plecanatide 3 mg and 6 mg doses (2.5 CSBMs and 2.2 CSBMs/week, respectively) when this was compared to placebo (1.2/week; p<0.001 for each dose). Stool consistency, based off the BSFS, improved with both doses of plecanatide by 1.5 points compared with 0.8 points for placebo (p<0.001 for each comparison). About a third of patients experienced ≥1 adverse effect dur-

ing the 12-week period (plecanatide 3 mg = 35.4%; 6 mg = 33%; and placebo = 32.8%). A majority of TEAEs were mild to moderate with the most common TEAE being diarrhea (5.9% for plecanatide 3 mg; 5.7% for 6 mg; and 1.3% in placebo). A total of 15 patients (1.1% of total trial population) experienced a serious adverse effect (serious effect was undefined in article) across all three treatment groups. Only one serious adverse effect occurred, diverticulitis, but this was in the placebo group. There were low rates of patient discontinuation due to TEAE, 5.1% in the plecanatide 3 mg group, 2.6% in the 6 mg group, and 1.3% in the placebo group. With the AE occurrence similar in both doses of plecanatide, there seems to be no dose dependency for any of the reported adverse effects, which is most likely because of the small difference in treatment doses of 3 mg and 6 mg. Vitals, laboratory values, and physical examination differences were unremarkable, with low incidence of any changes with clinical importance. The authors concluded that plecanatide is well tolerated with a limited adverse effect profile and also was effective at increasing the overall CSBM response in patients with CIC.

### ADVERSE EFFECTS AND PRECAUTIONS

The most common adverse reaction was diarrhea which was

**Table 2 | Averse Effects of Plecanatide in Phase 3 Clinical Trials**

Trial	Phase 3; DeMicco et al. <sup>6</sup>			Phase 3; Shailuhai et al. <sup>7</sup>		
	Placebo (n=466)	Plecanatide 3 mg (n=467)	Plecanatide 6 mg (n=469)	Placebo (n=458)	Plecanatide 3 mg (n=474)	Plecanatide 6 mg (n=457)
<b>Diarrhea</b>	1.3%	3.2%	4.5%	1.3%	5.9%	5.7%
<b>Headache</b>	1.9%	2.1%	2.1%	—	—	—
<b>Nasopharyngitis</b>	—	—	—	1.7%	0.8%	2.4%
<b>Sinusitis</b>	—	—	—	0.7%	2.1%	0.7%

mg: milligram

reported in approximately 5% of the total 1,733 patients who were given plecanatide in the two studies (Table 2).<sup>6,7</sup> The majority of reported cases of diarrhea occurred within 4 weeks of the initiation of treatment. Severe diarrhea was reported in 0.6% of patients treated with plecanatide compared to the 0.3% in patients treated with placebo, all of which occurred within the first 3 days of treatment.<sup>4</sup> Other adverse reactions reported in less than 2% of patients with plecanatide included upper respiratory tract infection, flatulence, sinusitis, abdominal tenderness, abdominal distension, and an elevated liver biochemical test (ALT and AST values that were anywhere from 5-15 times greater than the normal upper limit).

There is lack of clinical data to support plecanatide use in pregnancy or lactation.<sup>4</sup> Because plecanatide is negligibly absorbed systemically it is not expected to have fetal exposure in pregnancy. There is no information regarding plecanatide in human milk or in the infant or milk production. Plecanatide is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and in pediatric patients who are under the age of 6 years old because they are more likely to develop diarrhea and are at risk of serious dehydration.<sup>4</sup> It should be avoided in patients between 6 to 18 years old because of lack of clinical data.<sup>4</sup> There were insufficient patients over 65 years old in clinical trials to determine if their response would significantly differ from patients between 18 to 65 years old.<sup>4</sup> Plecanatide currently has no known drug interactions. Plecanatide and its active metabolites do not inhibit cytochrome P450 (CYP) enzymes 3A4 and 2C9 because they are not systemically absorbed and likely do not inhibit other CYP450 enzymes.<sup>4</sup> There are currently no specific guidelines for hepatic and/or renal impairment dose adjustment, so there are no renal or hepatic dose adjustment that are needed currently.<sup>4</sup> This is most likely because plecanatide is minimally absorbed but there is currently limited clinical data to confirm the suspicions.

### DOSING AND ADMINISTRATION

The current recommended dose of plecanatide is 3 mg taken orally once daily.<sup>4</sup> It can be taken with or without food and can be crushed and mixed with soft foods or water. The maximum daily limit is 3 mg and if a dose is missed, skip the missed dose and take the next dose at the next regular time.<sup>4</sup>

### COST

The average retail cash price of Trulance® is \$410 for a 30 day supply.<sup>8</sup> The average cash price for Linzess® (linaclotide) is \$410 for 30 day supply and \$290 for Amitiza® (lubiprostone), the other prosecretory agent.<sup>9,10</sup> However, pricing is subject to change based on individual insurance coverage. The manufacturer for Trulance®, Synergy Pharmaceuticals™, offers patient assistance

programs for patients with commercial insurance. Patients with commercial insurance can pay no more than \$25 per 90-day supply of Trulance®. Patients with public or any federally or state funded healthcare program are not eligible for the manufacturer savings.<sup>11</sup>

### CONCLUSIONS

Overall, it appears that plecanatide is both safe and effective in the treatment of CIC according to the available trials. A possible advantage of plecanatide could be its low incidences of diarrhea, especially when compared to the incidences of diarrhea with other GC-C agents. Efficacy was not directly compared between already known treatment options so choice in therapy will be determined by cost and SE profile. Based off the current data, Trulance® (plecanatide) is an effective agent with a minimal adverse effect profile for patients over the age of 18 with CIC or IBS-C.

### REFERENCES

1. Ford A, Moayyedi P, Lacy B, et al. American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation. *The American Journal of Gastroenterology*. 2014; 109(S1): S2-S26.
2. Tse Y, Armstrong D, Andrews C, et al. Treatment Algorithm for Chronic Idiopathic Constipation and Constipation-Predominant Irritable Bowel Syndrome Derived from a Canadian National Survey and Needs Assessment on Choices of Therapeutic Agents. *Canadian Journal of Gastroenterology and Hepatology*. 2017; 2017: 1-11.
3. Linzess (linaclotide) package insert. Cambridge, MA: Ironwood Pharmaceuticals, Inc.; 2017 Jan.
4. Trulance (Plecanatide) package insert. New York, New York: Synergy Pharmaceuticals Inc.; 2017 Jan.
5. Shailubhai K, Comiskey S, Foss JA, et al. Plecanatide, an Oral Guanylate Cyclase C Agonist Acting Locally in the Gastrointestinal Tract, Is Safe and Well-Tolerated in Single Doses. *Digestive Diseases and Sciences*. 2013; 58(9): 2580-2586.
6. DeMicco M, Barrow L, Hickey B, et al. Randomized clinical trial: efficacy and safety of plecanatide in the treatment of chronic idiopathic constipation. *Therapeutic Advances in Gastroenterology*. 2017; 10(11): 837-851.
7. Miner Jr P, Koltun W, Wiener G, et al. A Randomized Phase III Clinical Trial of Plecanatide, a Uroguanylin Analog, in Patients With Chronic Idiopathic Constipation. *The American Journal of Gastroenterology*. 2017; 112(4): 613-621.
8. GoodRx. Trulance. Savings-to-Go Card for Trulance (plecanatide). Available from: <https://www.trulance.com/>



savings/. Accessed June 28, 2018.

9. GoodRx. Linzess Prices and Linzess Coupons. Available from: <https://www.goodrx.com/linzess>. Accessed June 28, 2018.
10. GoodRx. Amitiza Prices and Amitiza Coupons. Available from: <https://www.goodrx.com/> <https://www.goodrx.com/amitiza>. Accessed June 28, 2018.
11. Trulance® (plecanatide) patient assistance program. Accessed June 28, 2018. Available from: <https://www.trulance.com/savings/>

## PERSONALIZED MEDICINE CORNER

### Genotype-Guided Opioid Prescribing

Chronic pain affects approximately 100 million American adults, with an estimated total cost of \$560 to \$635 billion annually. This alarming cost and the negative impact on patients' quality of life of poor pain control highlight the need for better methods to improve chronic pain management.<sup>1</sup>

Providers need to prescribe the optimal opioid regimen that allows adequate pain control with minimal adverse effects. However, due to the subjective nature of pain tolerance and variability of opioid response, selection of the right drug, right dose, and right frequency can be challenging. These challenges can be overcome with clinical pharmacogenetics by helping providers predict the expected responses to certain opioids and provide a personalized pain regimen based on the patient's genetics. As genetic testing costs and regulation restrictions decrease, we expect more institutions to apply pharmacogenetics clinically with increasing evidence and access to testing.<sup>2</sup>

Codeine, tramadol, and, to a lesser extent, oxycodone and hydrocodone are biotransformed by CYP2D6 to metabolites with greater affinity for the opioid *mu* receptor. One to two percent of individuals have the *CYP2D6* genotype associated with ultra-rapid metabolism. Ultra-rapid metabolizers are at risk for toxic concentrations of the active metabolites of codeine and tramadol and serious adverse effects, including respiratory depression and even death. In contrast, five to ten percent of individuals are CYP2D6 poor metabolizers with no enzyme activity. Another 2 to 11% are intermediate metabolizers with significant reductions in CYP2D6 activity. Poor and intermediate metabolizers have impaired ability to biotransform codeine and tramadol to their active metabolites and may attain little to no analgesic effect from these drugs. In addition to genotype, a number of medications inhibit the CYP2D6 enzyme, which can lead patient conversion to a poor or intermediate metabolizer CYP2D6 phenotype. The Clinical Pharmacogenetics Implementation Consortium recommends use of opioids that are not primarily metabolized by CYP2D6 or non-opioids in ultra-rapid and poor metabolizers because of the risk for toxicity and non-response, respectively.<sup>3</sup>

A pilot study from the UF Health Personalized Medicine Program compared a *CYP2D6* genotype-guided approach to pain management versus usual care in adult patients with chronic pain. For patients in the genotype-guided arm with the poor, intermediate, or ultra-rapid metabolizer phenotype based on *CYP2D6* genotype and concomitant use of any CYP2D6 inhibitors, recommendations were made to avoid codeine, tramadol, and to a lesser extent, hydrocodone and oxycodone. Among poor and intermediate metabolizers treated with codeine or tramadol at baseline, a significant reduction in pain intensity was observed in the genotype-guided arm compared to the usual care arm. These data

suggest that a genotype-guided approach to opioid prescribing may lead to better pain control.<sup>4</sup>

Personalizing pain management based on patient genetics and other patient-specific factors can move the healthcare system closer achieving optimal pain regimens that provide patients with adequate pain relief and limited adverse effects on a larger scale.

For questions about this guideline contact the UF Health Personalized Medicine Program. Please send an email to [PMP-HELP@ctsi.ufl.edu](mailto:PMP-HELP@ctsi.ufl.edu).

#### References:

1. Gaskin DJ, Richard P. The Economic Costs of Pain in the United States. *J Pain*. 2012;13(8):715-724.
2. Smith DM, Weitzel KW, Cavallari LH, et al. Clinical Application of pharmacogenetics in pain management. *Per Med*. 2018;(Epub ahead of print)
3. Crews KR, Gaedigk A, Dunnenberger DM, et al. CPIC guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther*. 2014;95:376-82.
4. Smith DM, Weitzel KW, Elsey AR, et al. Outpatient CYP2D6 Genotype-Supported Opioid Therapy: A Prospective Trial. Poster presented at: American Society for Clinical Pharmacology and Therapeutics; 2018 Mar 21-24; Orlando, FL.

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