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Prucalopride: The Only Prokinetic Chronic Idiopathic Constipation Treatment in the United States

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Currently, Chronic Idiopathic Constipation (CIC) ranks as the most prevalent GI issue presented to not only primary care physicians, but subspecialty physicians and surgeons as well.[1,2] In the United States, the prevalence of CIC is known to be 10.0%-14.9%, estimated 35 million patients, leading to GI complications such as rectal prolapse, diverticulitis, and fecal impaction.[1,2] There are currently a variety of non-pharmacological and over-the-counter (OTC) treatment options for the management of CIC, with the non-pharmacological options including exercise and high-fiber dietary modifications, and the OTC therapies including enema rinses and stool-softener, bulk-forming, osmotic, and stimulant laxatives. Despite this, patient dissatisfaction continues to rise with existing treatment modalities.[3] Many OTC and prescription options are within the same medication class which often means that treatment failure OTC bodes poorly for the use of a similar therapeutic prescription only agents, quickly causing patients to run out of options.

Currently prescription options include pro-secretory agents and prokinetic agents. The prosecretory agents include plecanatide (Trulance®), linaclotide (Linzess®), and lubiprostone (Amitiza®). These agents work by ultimately increasing the body's secretion of chloride and bicarbonate ions into the colon and thereby increase the water content of the stool in order to aid its passage through the bowels. In contrast, the prokinetic class of agents works by stimulating colonic serotonin (5-HT) receptors and includes only prucalopride (Motegrity®), as the previous agents, cisapride (Propulsid ©) and tegaserod (Zelnorm©) were withdrawn on July 14th, 2000 and March 30th, 2007, respectively, due to cardiovascular safety concerns.[4] The purpose of this article is to examine the clinical efficacy and safety of prucalopride in the treatment of CIC.

In This Issue

Clinical Implications

Mechanism of Action

Prucalopride is a selective serotonin 4 subtype (5-HT_4) receptor agonist which are found in smooth muscle cells throughout the GI tract.[3] Stimulation of 5-HT_4 receptors releases acetylcholine into the GI tract which enhances peristalsis and promotes propulsive motor patterns that produce bowel movements. Prucalopride has ~150 times greater affinity for the 5-HT_4 subtype compared to 5-$HT_{1,2}$ subtypes.[1-3] Previously, cross reactivity to other 5-$HT_{1,2}$ subtypes have been implicated in adverse cardiovascular outcomes.[4] There appears to be no information available regarding prucalopride with other 5-HT receptor subtypes.

Of note, prucalopride has no known activity for the HERG (the human Ether-à-go-go-Related Gene) channel.[4] The HERG channel was associated with adverse cardiac events in a previous 5 -HT_4 inhibitor, tegaserod, that has since been removed from the market.[5] However, prucalopride's interactions with the HERG channel were found to occur only at concentrations 1000-fold higher than prucalopride's therapeutic serum concentrations.[5]

Pharmacokinetics

Prucalopride reaches its peak plasma concentration 2-3 hours after oral dose and its absorption and is unaffected by food intake. Prucalopride has an oral bioavailability >90% and is 28-33% plasma protein bound.[6] In an open label study, 84.2% of the drug was found to be excreted in urine (60%-70% of the drug was excreted unchanged) and 13.3% was excreted in feces.[4] Renal excretion of prucalopride involves both passive filtration and active secretion.[7] The average half-life of prucalopride is 24 hours and steady state was achieved in 5 days of repeat once daily 2 mg doses; however in the 3 clinical trials examined in this paper, patients achieved their first spontaneous complete bowel movement (SCBM) after only 24-48 hours of their first dosage of prucalopride.[4] Hepatic impairment has not been shown to alter its pharmacokinetic parameters significantly.[8] Additionally, severe renal impairment (eGFR < 30 mL/min/1.73²) increase the $AUC_{0-\infty}$ of prucalopride 1.5-2.3 times higher with a resulting $t_{1/2}$ prolongation of 40-50%; therefore the recommended dose in severe renal impairment is 1 mg daily. Mild renal impairment (eGFR 60-89 mL/min/1.73²) resulted in no clinically relevant pharmacokinetic changes.[7] Prucalopride is metabolized by CYP3A4 into 8 distinct metabolites, with the most abundant metabolite being O-desmethyl prucalopride acid. At the time of writing, their activity has yet to be elucidated. The relevant pharmacokinetics data is summarized below in **TABLE 1**.

CLINICAL TRIALS

Since its inception to the global market, prucalopride has undergone a total of 76 clinical trials for safety and efficacy in the setting of CIC with roughly 46 Phase 1 studies, 14 Phase 2 studies, and 16 phase 3 and 4 studies.[4] With that said, the FDA ultimately based its approval decision on two sets of clinical trials for the indication of the treatment of CIC.[4] The efficacy data came from 6 double blind placebo-controlled trials and the safety data came from a combination of 16 phase 2, 3 and 4 trials. For the 6 efficacy trials (SPD555-401, SPD555-302, PRU-CRC-3001, PRU-INT-6, PRU-USA-11, and PRU-USA-13) only 3 are published in journals at the time of this manuscript writing. Therefore, the following section will discuss the published trials used for its FDA approval for the treatment of CIC.[4] A summary of the results from these three trials can be seen in **TABLE 2.**

The studies used ≥3 SCBMs/week as a primary endpoint. For secondary endpoints, all the trials used four groups of secondary outcomes: an increase of ≥1 SCBMs from baseline (deemed the key secondary endpoint), an assessment of CIC overall severity reported by the patient through the Subject's Global Assessment of Relief (SGA), an assessment of subjective CIC symptoms reported by the patient using the Patient Assessment of Constipation – Symptoms (PAC-SYM) questionnaire, and an assessment of the patients quality of life using the Patient assessment of Constipation—Quality of Life (PAC-QOL) questionnaire.[9-11] The SGA of Relief questionnaire was developed as a clinically validated survey to capture the relief of the patient's CIC symptoms provided by their CIC therapy.[12] The single question survey score ranges from 1 (completely relieved) to 5 (worse), with patients who reported a 1 or 2 experiencing clinically significant improvements.[12] The PAC-SYM questionnaire is a 12 item clinically validated questionnaire that assesses the severity of a patient's CIC symptoms with scoring range from 0 (absent) to 4 (very severe).[13] Historically, a reduction of one point has been used as the threshold to determine a positive response to the given treatment.[13] More recently however, the Minimal Important Difference (MID) for detecting clinically meaningful results has been shown to be on average -0.6.[13] The PAC-QOL questionnaire consists of 27 questions each pertaining to the quality of life of the patient. Each question can be answered with a rating of 0 to 4, with the higher the number meaning a worse quality of life.[14]

PRU-USA-13

Quigley et al. published a multicenter double blind placebo-controlled trial phase 3 (PRU-USA-13) that investigated the safety and efficacy of prucalopride in 641 patients.[9] Patients were randomized in a 1:1:1 ratio to either placebo (n = 212), prucalopride 2 mg (n = 214), or prucalopride 4 mg (n = 215) orally, administered once daily in the morning for 12 weeks. Baseline characteristics were similar between all three groups.[5] Patients recorded the frequency and details (straining, consistency, and feelings of incomplete evacuation) of their bowel movements in a daily diary.[9]

The study included men and women >18 years of age with a history of chronic constipation for ≥6 months not associated with drug-use, surgery, or congenital disorders of the large intestine.[9] Chronic constipation was defined using the modified ROME III chronic constipation criteria with 2 SCBMs/week over the past 6 months along with 2 of the following symptoms at least 25% of the time: very hard, pellet-like stool, sensation of incomplete evacuation, or straining during defecation.[9] The study excluded patients who were pregnant or breastfeeding and those with severe/clinically uncontrolled liver, cardiovascular, pulmonary, endocrine, renal, neurological, or psychiatric disorders, as well as acquired immunodeficiency syndrome (AIDS), cancer or previous treatment with prucalopride. The study also permitted patients that have gone 72 hours without a bowel movement to use 15 mg of Bisacodyl laxatives first and then a rescue enema treatment.[9] Rescue medications were not administered 48 hours before or after the first dose of prucalopride. After meeting the inclusion criterion, patients were put through a 2-week placebo run-in period where only those that confirmed their self-reported history of ≤2 SCBMs/week continued onto randomization

The primary endpoint of the study was the proportion of patients that achieved ≥3 SCBMs/week, averaged over 12 weeks. For the primary endpoint, both prucalopride doses (2 mg or 4 mg) of were superior to placebo (2 mg = 23.9%; 4 mg = 23.5%; placebo = 12.1%; p ≤0.01).[9] For the key secondary endpoint, a higher proportion of patients in both the 2 mg and the 4 mg prucalopride groups experienced an increase of ≥1 SCBMs from baseline when compared to placebo (49% and 52% respectively vs 26% placebo; $p \leq 0.001$ for both cases).[9] For the other noteworthy secondary endpoints, the 2 mg and 4 mg prucalopride groups had a higher percentage of patients rate their treatment quite effective or extremely effective through the SGA of Relief questionnaire and also achieve a significant reduction in their overall PAC-SYM and PAC-QOL scores when compared to placebo, respectively (38.9% and 37.0% vs. 20.1% p ≤ 0.001 for both SGA of relief groups; -0.78 and -0.56 vs -0.45 p ≤ 0.05 for both PAC-SYM groups; -0.85 and -0.86 vs -0.47p ≤ 0.001 for both PAC-QOL groups). Additionally, patients in the 2 mg and 4 mg prucalopride groups reported significantly less days with bisacodyl use per week on average from baseline when compared to placebo (-0.3 and -0.4 vs -0.1; p ≤ 0.01, for both prucalopride groups for bisacodyl usage). See **Table 3** for summarized results of select secondary outcomes.

PRU-USA-11

Table 1 | Select Prucalopride Pharmacokinetics[7]

Parameters	Value
Absorption	
C_{max}	3.79 ng/mL
T_{max}	2-3 hours
Bioavailability	>90%
Distribution	
V_d	567 L
Plasma Protein Binding	30%
Metabolism	
Hepatic	CYP3A4
Metabolites	Unknown activity
Elimination	
Renal	~82%
Fecal	~13%
$T_{1/2}$	~31 days

Values represent reported means.
C_{max} = maximum plasma concentration of a single 2 mg oral dose; **CYP3A4** = Cytochrome P450 family 2, subfamily a, polypeptide 4; **L** = liter; **ml** = milliliter; **ng** = nanogram; **$T_{1/2}$** = half-life; **T_{max} =** time to maximum plasma concentration; **V_d** = volume of distribution;

Camilleri et al. conducted a multicenter, randomized, placebo -controlled, parallel-group, phase 3 trial (PRU-USA-11) to assess the safety and efficacy of prucalopride in patients with severe chronic constipation. Patients were randomly allocated in a 1:1:1 ratio to receive oral prucalopride 2 mg (n=207) once daily, prucalopride 4 mg (n=204) once daily, or placebo (n=209) for 12 weeks. Patients were instructed to take one dose daily of the treatment medication in the morning with breakfast and record the details and frequency of their bowl movements in a diary daily. Inclusion and exclusion criteria were identical to the trial by Quigley et al.[9,10] and baseline characteristics were homogenous for patients both within this trial and compared to the other two trials.

The results for primary endpoint, the proportion of patients that achieved ≥3 SCBMs/week averaged across 12 weeks, both prucalopride treatment groups had a significant increase in achieving ≥3 SCGM compared to placebo (2 mg = 30.9%; 4 mg = 28.4%; placebo = 12.0%; p < 0.001 for both active groups).[10] For the key secondary endpoint, a higher proportion of patients in both the 2 mg and the 4 mg prucalopride groups experienced an increase of ≥1 SCBMs from baseline when compared to placebo (47.3% and 46.6% respectively vs 25.8% placebo; $P \leq 0.001$ for both cases).[10] For the other noteworthy secondary endpoints, the 2 mg and 4 mg prucalopride groups had a higher percentage of patients rate their treatment quite effective or extremely effective through the SGA of Relief questionnaire and also achieve a significant reduction in their overall PAC-SYM and PAC-QOL scores when compared to placebo, respectively (33.3% and 37.7% vs. 17.0% p ≤ 0.001 for both SGA of relief groups; -0.6 and -0.7 vs -0.4 p ≤ 0.001 for both PAC-SYM groups; overall PAC-QOL scores not published but deemed significant; p ≤ 0.001 for both PAC-QOL groups). Additionally, patients in the 2 mg and 4 mg prucalopride groups reported significantly less days with bisacodyl use per week on average from baseline when compared to placebo (-1.0 and -0.8 vs -0.1; p ≤ 0.01, for both prucalopride groups for bisacodyl usage), which is consistent with the findings of Quigley et al.[9-10] See **Table 3** for summarized results of select secondary outcomes.

PRU-INT-6

Tack et al. completed a 12-week multicenter double-blind placebo-controlled phase 3 trial (PRU-INT-6) that assessed the safety and efficacy of prucalopride 2 mg and 4 mg doses in patients with CIC. Patients were randomly allocated in a 1:1:1 ratio to receive oral prucalopride 2 mg (n=238) once daily, prucalopride 4 mg (n=238) once daily, or placebo (n=240) for 12 weeks.[11] Patients were instructed to take their treatment medication each day in the morning with food and record the frequency and details of their bowel movements in a diary daily. The study had the same inclusion and exclusion criteria as the previously discussed trials, and baseline characteristics were homogenous for patients both within this trial and compared to the other two trials.[9-11]

A greater proportion of patients achieved ≥3 SCBMs/week averaged over 12 weeks, the primary endpoint, in the prucalopride treatment arms (2 mg = 19.5%; 4 mg = 23.6%) compared to placebo (9.6%; p ≤0.01 and p ≤0.001 respectively).[11] For the key secondary endpoint, a higher proportion of patients in both the 2 mg and the 4 mg prucalopride groups experienced an increase of ≥1 SCBMs from baseline when compared to placebo (2 mg =

Table 2 | Summary of Primary Outcomes for Prucalopride

Trial	Design	Intervention	Primary Endpoint	Results
PRU-USA-13[9]	12-week parallel group Double-blind multicenter, randomized placebo-controlled, meeting the modified ROME III chronic constipation criteria	Prucalopride 2 mg daily (n=214) Prucalopride 4 mg daily (n=215) Placebo (n=212)	Proportion of patients with an average of ≥ 3 SCBMs/week, weeks 1-12	Prucalopride 2 mg = 23.9% Prucalopride 4 mg = 23.5% Placebo = 12.1% (p < 0.01 both compared to placebo)
PRU-USA-11[10]	12-week parallel group Double-blind multicenter, randomized placebo-controlled, meeting the modified ROME III chronic constipation criteria	Prucalopride 2 mg daily (n=207) Prucalopride 4 mg daily (n=204) Placebo (n=209)	Proportion of patients with an average of ≥ 3 SCBMs/week, weeks 1-12	Prucalopride 2 mg = 30.9% Prucalopride 4 mg = 28.4% Placebo = 12.0% (p < 0.01 both compared to placebo)
PRU-INT-6[11]	12-week parallel group Double-blind multicenter, randomized placebo-controlled, meeting the modified ROME III chronic constipation criteria	Prucalopride 2 mg daily (n=238) Prucalopride 4 mg daily (n=238) Placebo (n=240)	Proportion of patients with an average of ≥ 3 SCBMs/week, weeks 1-12	Prucalopride 2 mg = 19.5% Prucalopride 4 mg = 23.6% Placebo = 9.6% (p ≤ 0.01 for 2 mg; p ≤ 0.001 for 4 mg)

SCBM = spontaneous complete bowel movement. **mg** = milligrams. Modified ROME III criteria for chronic constipation ≤ 2 SCBMs/week over the past 6 months with at least 2 of the following for the past 3 months for at least 25% of the time: very hard

Table 3 | Select Secondary Outcomes for Prucalopride

Secondary Outcome	PRU-USA-13[9]	PRU-USA-11[10]	PRU-INT-6[11]
Number of patients with an average increase ≥1 SCBM/week, *n*/*N* (%)	Placebo = 57/207 (27.5) P 2 mg = 89/209 (42.6)[a] P 4 mg = 95/204 (46.6)[a]	Placebo = 54/209 (25.8) P 2 mg = 98/207 (47.3)[a] P 4 mg = 95/204 (46.6)[a]	Placebo = 23/240 (9.6) P 2 mg = 86/226 (38.1)[a] P 4 mg = 94/213 (44.1)[a]
Average SCBM/week, mean (mean change from baseline)	Placebo = 1.2 (0.8) P 2 mg = 1.9 (1.5)[a] P 4 mg = 2.0 (1.5)[a]	Placebo = 1.2 (0.8) P 2 mg = 2.6 (2.2)[a] P 4 mg = 3.0 (2.5)[a]	Placebo = 1.0 (0.6)[a] P 2 mg = 1.6 (1.2)[a] P 4 mg = 1.9 (1.4)[a]
Number of bisacodyl tablets taken/week, mean (mean change)	Placebo = 1.7 (−0.1) P 2 mg = 1.4 (−0.7)[a] P 4 mg = 1.2 (−1.0)[a]	Placebo =1.9 (-0.1) P 2 mg = 0.9(-1.0)[a] P 4 mg = 1.0 (-0.8)[a]	Placebo = 0.8 (-0.2) P 2 mg = 0.4(-0.4)[a] P 4 mg = 0.5 (-0.3)[a]
Number of patients rating treatment quite a bit or extremely effective[b], *n*/*N* (%)	Placebo = 37/184 (20.1) P 2 mg = 75/193 (38.9)[a] P 4 mg = 67/181 (37.0)[a]	Placebo = 35/207(17.0) P 2 mg = 67/201(33.3)[a] P 4 mg = 75/199(37.7)[a]	Placebo = 38/209 (18.1) P 2 mg = 71/205 (34.6)[a] P 4 mg = 65/180 (36.1)[a]

All values are presented as an average across 12 weeks.
a = Ratings obtained through the SGA of Relief questionnaire; **b** = p ≤0.001 for prucalopride compared to placebo; **P** = prucalopride; **SCBM** = spontaneous complete bowel movement. mg = milligram

38.1%; 4 mg = 44.1%; placebo = 20.9%; p < 0.001 for both doses).[11] For the other noteworthy secondary endpoints, the 2 mg and 4 mg prucalopride groups had a higher percentage of patients rate their treatment quite effective or extremely effective through the SGA of Relief questionnaire and also achieve a significant reduction in their overall PAC-SYM and PAC-QOL scores when compared to placebo, respectively (34.6% and 36.1% vs. 18.7% p ≤ 0.001 for both SGA of relief groups; -0.66 and -0.71 vs -0.37 p ≤ 0.001 for both PAC-SYM groups; -0.65 and -0.66 vs -0.38p ≤ 0.001 for both PAC-QOL groups). Additionally, patients in the 2 mg and 4 mg prucalopride groups reported significantly less days with bisacodyl use per week on average from baseline when compared to placebo (-0.3 and -0.4 vs -0.1; p ≤ 0.01, for both prucalopride groups for bisacodyl usage), which is consistent with the findings from both Quigley et al. and Camilleri et al.[9-11] See **Table 3** for summarized results of select secondary outcomes.

Adverse Effects and Precautions

In the trials discussed above, the most common side effects (>10% frequency) with prucalopride were headache, nausea, and generalized abdominal pain or discomfort.[9-11] The most common side effects are summarized in **Table 4**. Of note, most adverse events were experienced on the first day of treatment. Other than the first day of treatment, the incidences of adverse events were nearly identical between placebo and prucalopride. Only one patient withdrew from a study between all 3 trials due to cardiac adverse effects in the study conducted by Camilleri et al.[10] This patient had known history of supraventricular mitral-valve prolapse and supraventricular tachycardia discontinued treatment due to a supraventricular tachycardia exacerbation.[10] There were no deaths in any of the 3 trials reviewed nor any abnormal hematological findings, metabolic chemistry panels, urinalysis, and vital signs in the treatment arms.[9-11] Additionally, the QT interval corrected by Fredericia (QTcF) were recorded for all patients to detect possible QT interval prolongation (QTc > 470 ms), however in all three studies, no differences were observed between both treatment and placebo groups.[9-11]

Dosing and Administration

Prucalopride (Motegrity®) is not currently available, but will be manufactured as 1 mg and 2 mg tablets. The usual starting doses is 2 mg daily.[7] In the clinical trials examined in this paper, the 4 mg dose did not offer any additional benefit over the 2 mg dose.

For patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) 1 mg QD is the recommended dose.[4,7] Patients with severe hepatic impairment (Child-Pugh class C) start with 1 mg once daily which may be increased to 2 mg if required to improve efficacy and if the 1 mg dose is well tolerated.[4,7] If a dose is missed, skip the missed dose and proceed by taking the next dose at its scheduled time.[7]

Prucalopride should be avoided in pregnant and patients < 18 years of age as safety data is limited. Prucalopride should also be avoided in lactating patients as it is present in breast milk and no data has determined its safety in breastfed children.[4,7]

Discussion

Throughout the trials examined in this paper, prucalopride was ultimately shown to cause more SCBM's than placebo and resulted in a statistically significant reduction in laxative usage. Additionally, patients reported greater satisfaction with the prucalopride than they did with placebo or placebo plus a laxative. However, it is worth noting that throughout all three trials, prucalopride was not compared directly head to head with current OTC or prescription CIC therapies, so no direct comparisons of efficacy can be made. Patients were instructed to record their laxative usage throughout the study, and bowel movements were only recorded as SCBMs if they occurred >24 hours after the last laxative use of the patient; however, this is not the same as directly comparing prucalopride once daily to bisacodyl once daily. All three trials were consistent in their primary endpoints as well as their secondary endpoints, only differing in the p-values that they

Table 4 | Summary of Common Day 1 Prucalopride Adverse Effects

Trial	PRU-USA-13[9]			PRU-USA-11[10]			PRU-INT-6[11]		
Treatment	2 mg (n = 214)	4 mg (n = 215)	Placebo (n = 212)	2 mg (n = 207)	4 mg (n = 204)	Placebo (n = 209)	2 mg (n =238)	4 mg (n = 238)	Placebo (n = 240)
Headache	25%	25%	15%	26%	29%	12%	26%	29%	17%
Abdominal pain	18%	16%	10%	19%	22%	19%	23%	18%	17%
Nausea	13%	23%	7.5%	22%	21%	8%	24%	24%	14%
Diarrhea	12%	13%	3%	13%	18%	5%	13%	13%	5%

Prucalopride dose represented in mg above given orally daily.

used to determine statistical significance among certain endpoints (as reviewed in Table 3), making the comparisons between these trials straight-forward.

From a patient perspective, the largest drawback to prucalopride therapy will undoubtedly be the high anticipated cost that comes with a newly approved therapy. Prucalopride is currently only intended to treat patients whom have already failed the current standard of care of OTC medications such as bisacodyl or docusate, which come in several dosage forms and can often be purchased extremely cheaply depending on the retailer and the quantity. Despite the increase in subjectively reported quality of life from the patients in the aforementioned studies, to date, no pharmacoeconomic analysis has been published to determine how much patients are willing to pay for the benefits they received from prucalopride.

From a safety perspective, prucalopride does not currently present with the rare yet severe adverse effects, including cathartic colon syndrome or enteric nerve damage, that are presently, yet controversially, thought to be associated with long-term stimulant laxative therapy use, such as bisacody.[15] In fact, excluding the first day of therapy, prucalopride appears to possess no more adverse effects than placebo over a 12 week interval.[9-11]

Conclusion

Prucalopride has over 10 years' worth of sufficient safety and efficacy data worldwide to meet the needs of patients dissatisfied with current prescription or OTC CIC therapies. Unlike the previous member of the Prokinetic class, tegaserod, which was withdrawn from the market due to cardiovascular concerns, prucalopride has demonstrated a higher specificity for its therapeutic target resulting in no known cardiovascular harm.[16]

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Personalized Medicine Corner

Using Pharmacogenetic Testing to Guide Antidepressant Selection: A Patient Case

Selective serotonin reuptake inhibitors (SSRIs) are metabolized by the cytochrome P450 enzymes, including the CYP2C19 and/or CYP2D6 enzymes. CYP2C19 genotype can affect the plasma concentration of citalopram, escitalopram, and sertraline while CYP2D6 genotype can affect the plasma concentration of paroxetine and fluvoxamine. Genetic variability in CYP2C19 and CYP2D6 are associated with differences in toxicity and/or efficacy of SSRIs.1

Approximately 5-30% of the general population have a CYP2C19 genotype associated with increased metabolism of citalopram, escitalopram, and sertraline while 1-2% have a CYP2D6 genotype associated with increased metabolism of paroxetine. These "rapid" or "ultrarapid" metabolizers are at increased risk for treatment failure because of lower drug concentrations. The effect of CYP2D6 ultrarapid metabolism on fluvoxamine is still unknown. About 2-15% of individuals have a CYP2C19 genotype that can lead to a loss of CYP2C19 function and decreased metabolism of citalopram, escitalopram, and sertraline. Similarly, 5-10% of patients have a CYP2D6 genotype that can lead to a loss of CYP2D6 function and decreased metabolism of paroxetine and fluvoxamine. Patients who are CYP2C19 or CYP2D6 "poor" metabolizers are at increased risk for adverse drug effects because of higher plasma drug levels.1

The UF Health Precision Medicine Program (PMP) implemented CYP2C19 and CYP2D6 genotyping for SSRIs in 2016. Clinical pharmacogenetics guidelines recommend using alternative therapy or decreasing the dose by 50% for affected SSRIs in patients who are poor metabolizers of CYP2C19 (citalopram, escitalopram, sertraline) or CYP2D6 (paroxetine, fluvoxamine). In patients who are CYP2C19 rapid or ultrarapid and/or CYP2D6 ultrarapid metabolizers, guidelines recommend avoidance of the affected SSRIs when possible.1

Genotype-guided SSRI therapy can help decrease the risk for adverse effects and increase the chances of a positive response.2 In this article, we present a case for a patient who underwent CYP2C19 and CYP2D6 genotyping to guide antidepressant therapy.

Patient Presentation

A 19 year-old male with a history of major depressive disorder (MDD), hyperlipidemia, hypertension, and obesity presented with complaints of lethargy, hopelessness, and apathy. The patient had tried sertraline, aripiprazole, and lamotrigine without significant symptom control. His medications at presentation included lisinopril 10 mg daily. The UF Health PMP was consulted to assist in providing an interpretation and accompanying antidepressant recommendation for his CYP2C19 and CYP2D6 genotype results.

Pharmacogenetic Test Result

CYP2C19*17/*17; Ultrarapid metabolizer phenotype (Increased CYP2C19 activity)
CYP2D6*1/*4; Normal metabolizer phenotype (Normal CYP2D6 activity)

Drug Therapy Recommendation provided by the PMP Team

This patient's CYP2C19 ultrarapid metabolizer status is associated with significantly increased CYP2C19 activity and increased risk for pharmacotherapy failure with citalopram, escitalopram, and sertraline. His CYP2D6 normal metabolizer status is associated with typical response to paroxetine and fluvoxamine.1 Based on his pharmacogenetic results and other clinical factors we recommended to initiate fluoxetine 10 mg and titrate to response.

Discussion

At the time of presentation this patient was concerned about further weight gain with SSRI use. We recommended avoiding citalopram, escitalopram, and sertraline based on pharmacogenetic test results because the patient is less likely to achieve a therapeutic benefit with standard doses of these CYP2C19-mediated SSRIs, and the efficacy of higher than standard dosing is unknown. While paroxetine and fluvoxamine were appropriate options based on his CYP2D6 genotype, fluoxetine was ultimately chosen because it is less likely to cause weight gain.3

References

1) Hicks JK, et al. Clin Pharmacol Ther. 2015 Aug;98(2):127-34.
2) Bradley P, et al. J Psychiatr Res. 2018 Kan;96:100-107.
3) Ferguson JM. Companion J Clin Psychiatry. 2001 Feb;3(1):22-27.

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