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Naldemidine (Symproic®): A New Treatment for Opioid-Induced Constipation

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Opioids are a class of analgesic drugs that play a major role in the management of chronic cancer and non-cancer pain. The use of opioids in the treatment of chronic pain has increased in the past decade. More than 650,000 opioid prescriptions are dispensed on an average day in the US, and in 2014, the CDC reported that 240 million prescriptions were written for opioids.[1] Over prescribing increases the risk for diversion and improper use of opioids. Although opioids are effective analgesic agents, their side effect profile limits their patient tolerability. With this in mind, this recent rise in opioid use will be associated with a concomitant increase in side effects, hence the need for effective treatment options to manage these adverse effects is essential.

Common side effects related to opioid use include respiratory depression, sedation, gastrointestinal problems, nausea and vomiting, pruritus, and motor and cognitive impairment.[2] Gastrointestinal problems are the most frequent side effect related to opioid use with opioid induced constipation (OIC) being the most common.[3] Studies have shown that up to 90% of patients on opioid therapy report dose-related constipation.[3,4] Compared to other side effects of opioids, patients rarely develop a tolerance to GI side effects which impacts quality of life, reduces work productivity, impairs effectiveness of pain management, and can lead to worsening bowel dysfunction.

Opioid induced constipation is caused by the peripheral agonistic action of opioids throughout the GI tract, predominantly on μ-receptors in the myenteric plexus. The effects of μ-receptor activation leads to decreased motility, decreased gastric, biliary, pancreatic and intestinal secretion, reduced fluid absorption into the bowels, lower blood flow, and causes delayed colonic transit and inhibited defecation.[3,5-7] Management of OIC involves the use of non-pharmacological measures (e.g. adequate hydration, increased dietary fiber), laxatives (e.g. Senna, docusate sodium), lubiprostone, linaclotide, and peripheral acting μ-opioid receptor antagonists (PAMORA).[8,9] Laxatives are most frequently used for the management of OIC, however like many current therapy options, they are only partially effective because they do not target the underlying mechanism of OIC. The PAMORAs, a relatively new class of medication used to target the main cause of OIC, are specifically designed to block μ-opioid receptors peripherally in the GI tract. These therapies have limited distribution through the blood brain barrier (BBB), thus theoretically offering no effect on central μ-receptors and no decrease in analgesic effects. Drugs currently available in this class include naloxegol (Movantik®); approved for the treatment of OIC in adults with chronic non-cancer pain, and methylnaltrexone (Relistor®); approved for the treatment of OIC in adults with non-cancer pain and in adults with advanced illness on palliative care when laxatives are ineffective. On March 23, 2017, naldemedine (Symproic®) received approval by the FDA for the treatment of OIC in patients with chronic non-cancer pain. Naldemedine is another PAMORA option for treatment of OIC offering a single therapeutic dose suitable for all patients regardless of renal function. The objective of this article is to review the pharmacology, clinical trials, dosing and administration, and adverse effects of naldemedine.

Clinical Pharmacology

Mechanism of Action

Naldemedine acts as an antagonist at μ, d, and k opioid receptors and inhibits μ-opioid receptors peripherally in the GI tract, thereby decreasing the constipating effects of opioids. Naldemedine is an amide derivative of naltrexone with addition of a side chain that increases its molecular weight and polarity compared to naltrexone, and thus prevents it from crossing the BBB. Naldemedine is a substrate for permeability glycoprotein 1 (P-gp) efflux transporters located in the BBB which also inhibits the penetration of this medication into the central nervous system (CNS). These structural features limit naldemedine's action on central μ-opioid receptor mediated analgesia.[10]

Pharmacokinetics

Naldemedine orally has a peak concentration occurring within 0.75 hours if fasting and slowed to 2.5 hours when taken with meals and even more so with high fatty meals. Despite changes in peak concentration, the extent of drug absorption is unchanged. It is highly protein bound at 94%, with a volume of distribution of 155 L and a half-life of 11 hours.[10]

Naldemedine is a substrate for CYP3A4 and should be used

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with caution when administered concurrently with CYP3A4 inducers or inhibitors. No drug interaction studies have been conducted with drugs that alter gastric pH (e.g. antacids, PPIs). Naldemedine is primarily metabolized by CYP3A to nor-naldemedine and to a lesser extent by UGT1A3 to naldemedine 3-G. Both metabolites are opioid receptor antagonists but have less activity than the parent compound. Naldemedine gets cleaved to form benzamidine and naldemedine carboxylic acid in the GI tract. Excretion of naldemedine and its metabolites is primarily via urine (57%) and feces (35%). Approximately 16% - 18% of the parent drug is excreted unchanged in the urine. Benzamidine is the predominant metabolite excreted in the urine (32%) and feces (20%), representing majority of the administered dose of the parent drug. Summary of the pharmacokinetic properties of naldemedine are summarized in Table 1.

Naldemedine does not require renal adjustment and is not cleared from the blood by hemodialysis due to its high protein binding. The effect of hepatic impairment on the pharmacokinetics of naldemedine 0.2 mg when studied in patients with Child-Pugh Class A and B, compared to healthy patients with normal hepatic function was found to be similar. No studies have evaluated the effects on patients with Child-Pugh class C.

Clinical Trials

Phase 2 trials

A phase 2b multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, aimed to evaluate the efficacy and safety of three different doses of oral naldemedine in patients with chronic non-cancer pain.[11] Patients were required to be on opioid therapy, have documented OIC, and maintain a stable laxative regimen throughout the study. Participants were identified from 24 states within the US with 49 sites participating in the study. Potential participants were screened for 15-28 days to determine eligibility. Patients were eligible if: they were 18 years of age or older; had a documented medical history of chronic non-cancer pain for at least three months before screening; had been taking a stable dose of a full opioid agonist equivalent to at least 30 mg oral morphine daily for one month or longer before screening; and had self-reported ongoing symptoms of OIC. Ongoing symptoms of OIC were defined as < 3 spontaneous bowel movements (SBMs) per week despite a stable regimen of laxatives along with straining, feeling of incomplete evacuation, and hard or small stools (defined as Bristol Stool Scale (BSS) score < 3) in at least 25% of bowel movements. Patients were required to maintain a stable laxative regimen (defined as any combination of laxatives that had been taken consistently in the 28 days before the start of the study) or not use any laxative during the study.

The exclusion criteria for the study were the following: evidence of clinically significant GI disease, dysfunction, obstruction, or pelvic disorder that may cause constipation; a history of chronic constipation before starting analgesic medication or non-opioid causes of bowel dysfunction that may have contributed to constipation; severe constipation that had not been appropriately managed, such that the patient was at immediate risk of developing serious related complications; initiation of a new treatment regimen for OIC or a prokinetic agent within 28 days of screening; cancer treatment within the past five years; history or presence of any clinically important abnormality, medical condition, or use of concomitant medication(s) that could have interfered with the study; medically significant cardiovascular, respiratory, hepatic, renal or thyroid dysfunction, or a history of HIV infection; any medical or psychiatric condition that may have compromised the ability of the patient to understand and comply with the study protocol; current use opioid receptor antagonists, partial agonists, fentanyl, or meperidine; the inability to take oral medication; any history of illegal drug use in the past five years; surgery within one month of screening or planned surgery during study treatment that would, in the opinion of the investigators, have affected the study results; any relevant allergies; treatment with an investigational study drug in the 30 days before screening; or previous exposure to naldemedine.

Overall, 244 patients were selected and randomized in a 1:1:1:1 ratio to receive naldemedine 0.1 mg, 0.2 mg, 0.4 mg or

Table 1 | Pharmacokinetics of Naldemedine[10]

Absorption		
C_{max}	0.75 hours fasting, 2.5 hours with meals	
Distribution		
Protein binding	94%	
V_d	155 L	
Metabolism		
Mechanism	**Metabolite**	**Activity**
CYP3A4	Nor-naldemedine (predominant in plasma)	Weak antagonist
UGT1A3	Naldemedine 3-G	Weak antagonist
GI Cleavage	Benzamidine	n/a
	Naldemedine carboxylic acid	n/a
Elimination		
Excretion (parent drug + metabolites)	Urine (57%) → 32% benzamidine Feces (35%) → 20% benzamidine	
Parent drug unchanged	Urine (16% - 18%)	
Half-life (parent compound)	11 hours	

C_{max} = maximum concentration; **CYP3A4** = Cytochrome P450 Enzyme 3A4; **GI** = gastrointestinal; **V_d**= volume of distribution; **L** = liter; **SubQ** = subcutaneous; **UGT1A3** = UDP Glucuronosyltransferase Family 1 Member A3

placebo for 4 weeks. Specific laxative regimens or percent use were not reported. Baseline patient characteristics were similar across the different treatment groups. The primary efficacy outcome was a change in weekly SBM frequency from baseline to the last 2 weeks of treatment. Secondary outcomes included the proportion of SBM responders defined as ≥ 3 SBMs/week and an increase of > 1 SMB/week from baseline (positive response week) over the last 2 weeks of treatment. Safety parameters evaluated included adverse events, effects on analgesia (assessed using numerical rating scale - NRS), and opioid withdrawal symptoms (assessed using clinical opiate withdrawal scale - COWS). Pharmacokinetic parameters were also assessed: maximum observed plasma concentration, time to attain this concentration, area under the curve, and elimination half-life.

The study showed a significant increase in the primary endpoint of mean weekly SBM frequency from baseline to the last 2 weeks of treatment, total of 4 weeks, in the naldemedine 0.2 mg group (3.37 ± 0.43 SBM/week for naldemedine vs. 1.42 ± 0.42 for placebo; P = 0.0014) and the 0.4 mg group (3.64 ± 0.44 SBM/week for naldemedine vs 1.42 ± 0.42 for placebo; P = 0.0003). The difference in mean weekly SBM frequency between the 0.2 mg (3.37 ± 0.43 SBM/week) and 0.4 mg (3.64 ± 0.44 SBM/week) doses was not significant (P = 0.6657). There was also no difference found between the naldemedine 0.1 mg (1.98 ± 0.42 SBM/week) group compared with placebo (P = 0.3504). For the secondary endpoints, the proportion of SBM responders was significantly higher with naldemedine 0.2 mg (71.2% for naldemedine vs 39.3% for placebo; p = 0.0005) and naldemedine 0.4 mg (66.7% for naldemedine vs 39% for placebo; p = 0.003). The difference in the proportion of SBM responders between the naldemedine 0.2 mg and 0.4 mg doses was not significant (P = 0.5989). Also, the naldemedine 0.1 mg group was not different from placebo (52.5% for naldemedine vs 39.3% for placebo; p = 0.1461). The most common adverse effects reported were abdominal pain, diarrhea, flatulence, and nausea. Of note, the incidence of treatment related adverse effects with naldemedine was dose dependent. The 0.2 mg dose showed a better safety profile than the 0.4 mg dose but with the same efficacy; hence, naldemedine 0.2 mg once daily was the chosen dose in phase 3 trials. There were no significant changes in effects on analgesia or opioid withdrawal symptoms from baseline in any of the naldemedine groups compared to placebo.

Phase 3 trials

Two phase 3 trials evaluating the safety and efficacy of naldemedine 0.2 mg vs placebo have been completed to date and published; the naldemedine in the treatment of opioid-induced constipation in subjects with non-malignant chronic pain receiving opioid therapy (COMPOSE-1 and COMPOSE-2) trial. Another phase 3 trial (COMPOSE-3) evaluating the long-term safety of naldemedine was completed in 2016 but data from this trial is yet to be published.

COMPOSE-1 and COMPOSE-2

The COMPOSE-1 and COMPOSE-2 trials are identical, phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies that compared the efficacy and safety of naldemedine with those of placebo over a 12-week treatment period.[12] The objective of both trials was to assess the efficacy and safety of naldemedine 0.2 mg orally once a day versus placebo for the treatment of OIC in patients with chronic non-cancer pain. The definition of OIC was similar to that used in the phase 2 trial with the addition of "no more than 4 SBM over a 14-day qualifying period; and at least 78% compliance with daily completion of diary entries during the 14-day qualifying period in a 28-day screening period." Unlike the phase 2 trials which allowed for participants to use laxatives, these trials included those who did not currently use laxatives. In both studies, all participants were enrolled, treated and monitored in an outpatient setting. COMPOSE-1 was done in 68 outpatient clinical research facilities in seven countries (USA, Austria, Czech Republic, Germany, Poland, Spain, and the UK) and COMPOSE-2 was done in 69 outpatient sites in the seven countries as COMPOSE-1 except the UK.

Patients were eligible if they were aged 18 – 80 years, had chronic non-cancer pain treated with opioids for at least 3 months, and had a stable opioid regimen for a total daily dose averaging at least 30 mg equivalents of oral morphine for at least 1 month before screening. Patients were required to not be using laxatives at the time of screening or agree to stop their use at the time of enrollment. Optional rescue laxatives were provided and allowed if a patient had not had a bowel movement for a period of 72 hours.

Patients were excluded if they had significant structural gastrointestinal abnormalities and other conditions or circumstances that might have affected bowel transit; had potential conditions not related to opioid use that might have caused or contributed to constipation, including pelvic disorders; had never taken laxatives for the treatment of opioid-induced constipation; and had comorbidities or other medical conditions that might have interfered with study completion. Women who were pregnant or lactating were also excluded. The primary efficacy endpoint in both trials was the proportion of responders defined as a participant having ≥ 9 positive response weeks out of the 12-week treatment period and ≥ 3 positive response weeks out of the last 4 weeks of the 12-week treatment period. A positive response week was defined as ≥ 3 SBMs/week and an increase from baseline of ≥ 1 SMB/week for that week. A SBM was defined as a bowel movement occurring without the use of rescue laxative medication in the previous 24 h. A bowel movement occurring within 24 h of an optional rescue laxative therapy was not considered to be a SBM. The secondary efficacy endpoints were the following: the least squares mean change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period, change in the frequency of SBMs per week from baseline to week 1; change in the frequency of complete SBMs (defined as an SBM with the feeling of complete evacuation) per week from baseline to the last 2 weeks of the treatment period; and change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period.

In COMPOSE-1, 547 patients were randomized in a 1:1 ratio to receive naldemedine 0.2 mg (n=274) or placebo (n=273). Similarly, in COMPOSE-2, there were 553 patients randomized in a 1:1 ratio to receive naldemedine 0.2 mg (n=277) or placebo (n=276). Baseline characteristics of patients in both studies were generally similar between the treatment groups. During the 12-week treatment period, naldemedine 0.2 mg tablets or placebo were administered orally once a day with or without food. Dosing time was left to patients to decide but they were encouraged to take the drug at the same time each day. After the 12-week treatment period or early termination of treatment, patients entered a 4 -week follow-up period after the last dose of naldemedine or placebo in which safety was assessed with both clinical and subjective opiate withdrawal scale scores.

Table 2 | Summary of Clinical Trials

Trial	Design	Intervention	Primary Outcome	Results
Webster et al[11]	12-week, Phase 2b RCT	Naldemedine 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg daily or placebo	Change in weekly SBM frequency from baseline to the last 2 weeks of treatment	Naldemedine vs placebo (1.42 ± 0.42) • 0.1 mg vs placebo (1.98 ± 0.42), p = 0.3504 • 0.2 mg vs placebo (3.37 ± 0.43), p = 0.0014 • 0.4 mg vs placebo (3.64 ± 0.44), p = 0.0003
Hale et al[12]	12-week Phase 3 RCT	Naldemedine 0.2 mg daily or placebo	Proportion of responders[a]	**COMPOSE-1:** Naldemedine 0.2 mg (47.6%) vs placebo (34.6%); difference = 13.0% [95% CI, 4.8 – 21.3, p =0.002] **COMPOSE-2:** Naldemedine 0.2 mg (52.5%) vs placebo (33.6%); difference = 18.9% [95% CI, 10.8 – 27.0, p<0.0001]

[a]Responder defined as a participant having ≥ 9 positive response weeks out of the 12-week treatment period and ≥ 3 positive response weeks out of the last 4 weeks of the 12-week treatment period. A positive response week was ≥ 3 SBMs/week and an increase from baseline of ≥ 1 SMB/week for that week.
95% CI = 95% confidence interval, **mg =** milligram, **RCT =** randomized controlled trial, **SMB** = spontaneous bowel movement

The primary outcome of proportion of responders from both studies was significantly higher in the naldemedine group than in the placebo group (See Table 2). COMPOSE-1 showed an increase in SBM of 47.6% in the naldemedine 0.2 mg daily group vs. an increase of 34.6% in the placebo group with a difference of 13.0% (95% CI, 4.8 – 21.3%, p = 0.002). Similarly, the COMPOSE-2 study found an increase of 52.5% in the naldemedine 0.2 mg daily group vs 33.6% in the placebo group, a slightly higher difference of 18.9% (95% CI, 10.8 – 27.0%, p<0.0001). The differences in the proportion of responders between naldemedine and placebo groups were similar across baseline opioid dose strata.

These trials also found that the secondary outcome of mean frequency of SBMs per week from baseline to the last 2 weeks of treatment was improved with the naldemedine 0.2 mg group compared to placebo group. The COMPOSE-1 secondary outcome difference in mean frequency of SBMs between the naldemedine and placebo groups was 1.30 SBM/week (95% CI, 0.77–1.83 SBM/week, p<0.0001) and the difference between groups in the COMPOSE-2 trial was 1.40 SBM/week (95% CI, 0.92–1.88 SBM/week, p<0.0001). At week 1 of the treatment period, the mean increase in frequency of SBMs/week from baseline was 3.48 SBM/week for naldemedine vs 1.36 SBM/week for placebo (difference 2.11 SBM/week, 95% CI, 1.60-2.71 SBM/week, p<0.0001) in COMPOSE-1 and 3.86 SBM/week for naldemedine vs 1.69 SBM/week for placebo (difference 2.17 SBM/week, 95% CI, 1.63-2.63 SBM/week, p<0.0001) in COMPOSE-2. Similarly, the mean increase in the frequency of complete SBM (CSBM) per week from baseline to the last 2 weeks of the 12-week treatment period was higher at 2.58 CSBM/week for naldemedine vs 1.57 CSBM/week for placebo (difference 1.01 CSBM/week, 95% CI 0.54-1.48 CSBM/week, p<0.0001) in COMPOSE-1 and 2.77 CSBM/week for Naldemedine vs 1.62 CSBM/week for placebo (difference 1.15 CSBM/week, 95% CI 0.70-1.61 CSBM/week, p<0.0001) in COMPOSE-2. Also, change in the frequency of SBMs without straining (SBMws) per week from baseline to the last 2 weeks for the treatment period was higher at 1.46 SBMws/week for naldemedine vs 0.73 SBMws for placebo (difference 0.73 SBMws/week, 95% CI 0.34-1.12 SBMws/week, p=0.0003) for COMPOSE-1 and 1.85 SBMws/week for naldemedine vs 1.10 SBMws/week for placebo (difference 0.75 SBMws/week, 95% CI 0.30-1.19 SBMws/week, p=0.0011). Both studies noted a trend of improvement in mean frequency of SBM from baseline every week, starting from week one, in all categories of the secondary endpoint.

In COMPOSE-1, the median exposure to naldemedine (84.0 days, IQR 83.0–85.0) was similar to placebo (84.0 days, 84.0–85.0), which was similar to that observed in COMPOSE-2 (84.0 days [IQR 84.0–86.0] for the naldemedine group vs 85.0 days [83.0–86.0] for the placebo group). The proportion of patients in both treatment groups for whom treatment-emergent adverse events were reported were similar in both studies (COMPOSE-1: 49% in the naldemedine group vs 45% placebo group; COMPOSE-2: naldemedine 50% vs placebo 48%).

The mean clinical and subjective opiate withdrawal scale scores decreased slightly from baseline in a similar proportion in both treatment groups. No meaningful differences between groups were observed at any of the assessed time points in either COMPOSE-1 or COMPOSE-2 according to the investigators. The change in numerical rating scale score for pain intensity remained stable from baseline and no meaningful difference between the treatment groups was observed at any time point in either of the two studies.

Adverse Effects

From the COMPOSE-1 and COMPOSE-2 trials, the most frequently reported adverse events in the naldemedine group, and were observed more frequently than in the placebo group, were diarrhea (COMPOSE-1: 7% in naldemedine group vs 3% in the placebo group; COMPOSE-2: 9% in naldemedine group vs 2% in

Table 3 | Prevalence of common AEs from phase 3 clinical trials[12]

Adverse Effect	COMPOSE-1		COMPOSE-2	
	Naldemedine 0.2 mg (N = 271)	Placebo (N = 274)	Naldemedine 0.2 mg (N = 271)	Placebo (N = 274)
Abdominal pain	17 (6%)	5 (2%)	14 (5%)	3 (1%)
Diarrhea	18 (7%)	8 (3%)	24 (9%)	5 (2%)
Flatulence	3 (1%)	4 (2%)	6 (2%)	9 (3%)
Nausea	13 (5%)	7 (3%)	13 (5%)	9 (3%)

Data presented represents adverse event incidence with percent of study population

placebo group) and abdominal pain (COMPOSE-1: 6% for naldemedine vs 2% for placebo; COMPOSE-2: 5% for naldemedine vs 1% for placebo).[12] Treatment-emergent adverse events that were adjudicated as a major adverse cardiovascular events (MACE) were reported in < 1% of patients in the naldemedine group in COMPOSE-1 and < 1% in placebo group in COMPOSE-2.[12] There were no deaths reported in COMPOSE -1 and COMPOSE-2. One patient in the naldemedine group in COMPOSE-2 died due to cardiopulmonary arrest caused by opioid overdose but was not considered related to the study drug.12 In the COMPOSE-1 trial, 3 patients had at least one treatment-emergent adverse event of opioid withdrawal (2 in the naldemedine group vs 1 in placebo), but none were reported in COMPOSE-2.

Dosing and Administration

The recommended dose of naldemedine for OIC in adult patients taking opioids for non-cancer pain is 0.2 mg administered orally as a once daily dose with or without food. Safety and efficacy has not been established in the pediatric population. Alteration of analgesic dosing regimen prior to initiating naldemedine is not required and patients receiving opioids for less than 4 weeks may be less responsive to this medication.[10] When opioid therapy is no longer required, naldemedine should be discontinued as well. No dose adjustment is required in patients with renal impairment. Naldemedine should be avoided in hepatic impairment patients with Childs-Pugh class C due to lack of data.[10] Based on animal data, naldemedine may cross the placenta and cause opioid withdrawal in the fetus if administered during pregnancy.[10] It is not known if naldemedine is present in breast milk and so the decision to breastfeed during therapy should be based on the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Breastfeeding may be resumed 3 days after the discontinuation of naldemedine.[10] Naldemedine should be stored at room temperature and protected from light.

Conclusion

Opioid induced constipation is a frequent adverse effect of opioid treatment and standard interventions have limited or inconsistent efficacy because they do not target the underlying mechanism. PAMORAs target the mechanism of OIC, and naldemedine was shown to be a safe and effective treatment option for patients using opioids for chronic non-cancer pain; however, no high-quality data is available yet regarding concomitant use with laxatives or in comparison to laxatives. Naldemedine is administered once daily and does not require dose adjustments for renal function and offers another alternative to current therapy. Results from a randomized, controlled, multicenter, 52-week phase 3 study (COMPOSE-3) evaluating the long-term safety of naldemedine for the treatment of OIC in subjects with non-malignant chronic pain receiving opioids will be published soon and aim to provide information about long term safety and benefits of use in combination with laxatives.

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PERSONALIZED MEDICINE CORNER

Patient Case: Pharmacogenetics in Primary Care

The University of Florida established a pilot pharmacogenetics consult service (PGx-CS) in September 2017 with the UF Health Internal Medicine Clinic at Tower Hill. The goal of this innovative service is to have a pharmacogenetics-trained pharmacist provide primary care providers with detailed, customized drug therapy plans for their referred patients based on pharmacogenetic test results. Herein, we describe a representative case for a consult clinic patient.

A 70 yo male with a history of GERD, anxiety, and depression treated with pantoprazole 40 mg every morning and alprazolam 0.5 mg twice daily, was referred by her primary care physician for pharmacogenetic testing to assist with his drug therapy management. The patient reported taking fluoxetine, amitriptyline, and paroxetine in the past but discontinued these because of adverse effects (agitation with fluoxetine, insomnia and severe nightmares with amitriptyline, and nausea with paroxetine). He also reported no relief of GERD symptoms with pantoprazole. CYP2C19 and CYP2D6 genetic testing was ordered with the following results:

- CYP2D6*2/*4 (Normal metabolizer phenotype; normal CYP2D6 activity)
- CYP2C19*17/*17 (Ultra-rapid metabolizer phenotype; significantly increased CYP2C19 activity)

Escitalopram, citalopram, and sertraline undergo inactivation via the CYP2C19 enzyme, and the CYP2C19 ultra-rapid metabolizer phenotype is associated with greater inactivation of these drugs and risk of treatment failure.[1] Similarly, PPIs undergo inactivation by the CYP2C19 enzyme, which occurs to a greater extent with first generation PPIs (i.e., omeprazole, lansoprazole, pantoprazole).[2] Paroxetine and fluvoxamine undergo inactivation via the CYP2D6 enzyme, and CYP2D6 activity is normal in this case.[1]

The UF Health Personalized Medicine Program recommended a trial of venlafaxine ER 37.5 mg daily for depression/anxiety based on genotype (i.e., increased risk of treatment failure with escitalopram, citalopram, and sertraline) and patient-specific (e.g., past adverse effects with SSRIs, potential for increased agitation with buproprion) factors. The pharmacist also recommended a 50% to 100% increase in the patient's pantoprazole dose based on CYP2C19 genotype and insufficient relief of GERD symptoms.[3]

Pharmacogenetics is only one chapter of the patient's story. This representative patient case illustrates the potential use of pharmacogenetics in routine clinical practice to optimize drug therapy, with consideration of the patient's medication history and concerns.

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