REVIEW ARTICLE

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Naldemedine for the Use of Management of Opioid Induced Constipation

By Ivan Urits, Anjana Patel, Hayley Cornwall Kiernan, Conner Joseph Clay, Nikolas Monteferrante, Jai Won Jung, Amnon A. Berger, Hisham Kassem, Jamal Hasoon, Alan D. Kaye, Adam M. Kaye, Omar Viswanath

ABSTRACT ~ Purpose of Review: *Opioid medications are a pillar of acute and chronic analgesia, though their use is often accompanied by side-effects, such as opioid-induced constipation. Unfortunately, tolerance rarely develops to this untoward side effect. This review presents the background, evidence, and indications for the use of Naldemedine (Brand name Symproic 0.2 mg tablets) to treat opioid-induced constipation.* ***Recent Findings:*** *Opioids are often used for the treatment of acute and chronic analgesia. Outside of the central effect they exert, they also interact with peripheral receptors, resulting in opioid-induced constipation, the commonest of side effects of chronic opioid usage. Complications include colonic distention, ileus, perforation, and can progress to other serious bowel complications, which can result in hospitalization and fatal events.*

For the most part, laxatives and other anti-constipation therapies are often inefficient and require intervention directed at the root cause, such as peripheral mu receptor agonists, including methylnaltrexone, naloxegol, and naldemedine. Naldemedine is the most recent to gain FDA approval of the group.

An antagonist of Mu, Kappa, and Delta peripheral receptors, Naldemedine, is the only drug to counteract all three receptor classes. It was shown to be both safe and effective when compared with placebo. No data exists to compare its efficacy to that of other members of the group.

Urits, Berger, Hasoon, Beth Israel Deaconess Medical Center, Department of Anesthesiology, Critical Care, and Pain Medicine, Harvard Medical School, Boston, MA. Patel, Jung, Georgetown University School of Medicine, Washington, DC. Cornwall Kiernan, Joseph Clay, Viswanath, University of Arizona College of Medicine – Phoenix, Department of Anesthesiology, Phoenix, AZ, Monteferrante, Viswanath, Creighton University School of Medicine, Department of Anesthesiology, Omaha, NE, Kassem, Mount Sinai Medical Center, Department of Anesthesiology, Miami Beach, FL, Kaye, Louisiana State University Shreveport, Department of Anesthesiology, Shreveport, LA, Kaye, Viswanath, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Department of Pharmacy Practice, Stockton, CA, Viswanath, Valley Anesthesiology and Pain Consultants – Envision Physician Services, Phoenix, AZ.

To whom correspondence should be addressed: Ivan Urits, Beth Israel Deaconess Medical Center, Department of Anesthesiology, Critical Care, and Pain Medicine 330 Brookline Ave, Boston, MA, 02215, Phone: 617 278 8000; E-mail: iurits@bidmc.harvard.edu

SUMMARY: *Opioids are frequently used in the management of acute and chronic pain. The most common of the side effects is opioid-induced constipation, secondary to the peripheral activity of opioids. Naldemedine is an FDA-approved, once-daily oral tablet that counteracts this side effect by antagonizing mu, kappa, and delta-opioid receptors and has been shown to be safe and effective. Further investigation including head-to-head clinical trials are required to evaluate the relative efficacy of naldemedine compare with other peripheral opiate receptor antagonists.* Psychopharmacology Bulletin. *2020;50(3):97–118.*

Introduction

Opioids are a large class of medications used for anesthesia, as well as the management of acute and chronic pain. In general, there are two classes of opioids, natural and synthetic. Natural derivatives include morphine and codeine, which are also referred to as opiates. Within the body, endogenous opioids are constantly released including endorphins dynorphins, and enkephalins. Synthetic derivates include heroin, fentanyl, and methadone and many others. Opioids act on opiate receptors located primarily in the brain and central nervous system to suppress painful signals. Opioids do not act to decrease or to treat the cause of the pain, but instead, alter the perception of pain.[1] Opioids also work on opiate receptors at other sites in the body such as smooth muscle, the adrenal gland, the myocardium, vascular beds, the gastrointestinal tract, and the lungs to cause respiratory depression, modulate fluid and hormonal effects, decrease gastrointestinal motility, increase urinary retention, and induce sedation.[1] Opiate receptors respond to endogenous opioid peptides as well as exogenous opioids and opiates. Related to the ability of opioids to provide pain relief, these substances can also be used to produce feelings of euphoria, which contributes to their addictive nature. Long term opioid use can lead to tolerance related to the desensitization of the opiate receptors, which then requires increased use of opioids to acquire the same euphoric sensation.[2] Uncontrolled intake and cravings are traditional symptoms of opioid addiction. Withdrawal symptoms can range from minor to severe and occur within several hours of the last dose, and most addicted individuals must continue to consume opioids to alleviate the unbearable side effects, which include muscle cramping, gastrointestinal discomfort, tachycardia, increased blood pressure and other signs and symptoms collectively known as a response to central nervous system hyperarousal state.[2]

The Center for Disease Control and Prevention (CDC) defines an epidemic as "the occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time".[3] The Opioid Epidemic is a multifaceted issue that has its origins in the 1990s when the pain was adopted as a 5th vital

sign, and strong efforts were made to minimize patient's pain, mostly chronic pain.[4] The push to combat chronic pain ultimately leads to more relaxed opioids prescription writing, which increased overall availability. Between 1997 and 2002, prescriptions for OxyContin to treat noncancer pain increased by about 10-fold.[4] During this period, significant increases were also seen in the prescribing of other opioids for the treatment of noncancer pain. Two hundred forty-five million prescriptions (not including refills) for opioids were dispensed in 2014, making them the most prescribed medication in the United States.[4] Ultimately, overprescribing and the misuse of prescription opioids have fueled the opioid epidemic and led to an exponential increase in patients dealing with a dependence on opioids.

Opiate use disorder (OUD) occurs in 16 million people worldwide, and over 2.1 million people in the U.S.[5] Opioid use disorder consists of an overpowering desire to use opioids, increased opioid tolerance, and withdrawal syndrome when discontinued. Opioid use disorder results in over 47,000 deaths per year in the U.S.[5] Opioid-related death is the most lethal drug epidemic in American history.[5] In 2017, the opioid epidemic was declared a national emergency by Health and Human Services, and safeguards have been put in place in an attempt to rectify the situation, such as improved physician education and prescription drug monitoring programs.[6] Opioid prescriptions were reduced by 13.1% from 2012 to 2015 as a result of physician awareness and implementation of new policies.[7] One particular study displayed a 30% reduction in opioid prescriptions for pain management as a result of these efforts.[8]

Opioid-Induced Constipation – Background

Opioid-induced bowel dysfunction (OIBD) is a pharmacologically induced condition that presents with a variety of different symptoms including as dry mouth, gastroesophageal reflux, vomiting, bloating, abdominal pain, anorexia, hard stools, constipation and incomplete evacuation.[9] The mechanism behind opioid-induced constipation is a result of opioid receptors also being present in the gastrointestinal tract.[9] Delta- (δ-), kappa- (κ-), and mu- (μ-) opioid receptors have been identified in the gastrointestinal tract.[10] In humans, μ- receptors contribute the most to the mechanism of OIBD as they have been identified in neuronal cells of submucosal and myenteric neurons and on mononuclear cells in lamina propria.[10] While endogenous ligands typically influence normal regulation of gastrointestinal function, opioid receptors are also activated by exogenous opioids.[11] All opioid receptors belong to the G-protein-coupled receptor family and activate

intracellular signaling through direct activation of K+-channels (membrane hyperpolarization) and inhibition of Ca2+-channels (decreased neurotransmitter release); it may also involve Na+-channels.[12] The main effect, however, is likely decreased formation of cyclic adenosine monophosphate, which subsequently activates several target molecules and leads to decreased neuronal excitability with an overall inhibitory effect on the cells.[13]

Opioid receptor activation in the gut has three main effects: (i) a change in gut motility, (ii) decreased gut secretion, and (iii) increased sphincter tone.[14] Gut motility is controlled from the myenteric plexus via neurotransmitters released onto the smooth muscle cells, and since opioid administration inhibits the release of these neurotransmitters, it directly causes abnormal coordination of gut motility as reflected by an increased tone and decreased propulsive activity.[14] Opioids cause motility changes that cause the slowing of normal motility, segmentation, increased tone, and disrupted motility. Opioids decrease gut fluid secretion, causing dry feces and less propulsive motility as well as increase sphincter tone, which may lead to defecation difficulties, including opioid-induced constipation (OIC).[15]

Traditionally there has not been a generally accepted definition of OIC with different methods of definition across disciplines and studies.[16] However, OIC was formally defined by a panel of the American Academy of Pain Medicine Foundation (AAPMF) in 2015.[17] The panel concluded with a definition consisting of reduced bowel movement frequency, development, or worsening of straining to pass stool, a sense of incomplete rectal evacuation, and harder stool consistency.[17] OIC is the most common OIBD with up to one-half of patients on long-term opioids experiencing OIC, and, of those, fewer than half get adequate relief from conventional treatment with laxatives.[17] In a survey of patients with noncancer pain taking a median daily dose of 127.5 mg morphine-equivalent (range 7.5–600 mg), the most commonly reported G.I. side effect was constipation (46.9%; 95 % CI 36.8–57.3).[18] A multi-national study involving 322 patients taking oral opioids and laxatives found that OIC was most often characterized as severe, with 45% reporting < 3 bowel movements per week with nearly a third of patients altered their doses of opioid therapy in an attempt to mitigate the constipating side effects of these medication.[19] The frequency of OIC varies depending on both the types of opioids used and the total amount of opioids used. OIC can become an even more important issue when opioids are used in terminally ill patients, who will poorly tolerate increased gastrointestinal side effects.[20] The development of chronic constipation due to opioid treatment may cause serious long-term consequences such as

obstipation, colonic distension, ileus, and perforation.[21] Constipation may also lead to increased health resource use, decreased quality of life, and increased mortality.[21]

Currently, there are no available tools to assess OIBD, but many rating scales have been developed to assess constipation, and a few specifically address OIC. Two constipation-specific instruments that are available to assess impact and severity are the Patient Assessment of Constipation Quality of Life (PAC-QOL) and the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaires.[17] The AAPMF consensus panel also endorsed the Bowel Function Index (BFI), a patient-reported outcome tool containing only three items (pertaining to ease of defecation, incomplete evacuation, and patients' judgment of constipation) as the method best suited for assessing OIC in most clinical settings.[17]

Current Treatment of Opioid-Induced Constipation

Prophylactic Approaches

Clinical guidelines recommend the use of prophylactic nonpharmacological and pharmacological approaches for the initial management of opioid-induced constipation (OIC).[22] Nonpharmacological approaches include increasing dietary fiber, fluid intake, and physical activity.[23] Pharmacological approaches include the use of over-the-counter laxatives such as stool softeners, stimulants, osmotic, and bulk laxatives. The evidence behind these methods is largely anecdotal, and while they do not address the underlying physiology, their low cost and favorable safety profile make them first-line agents for OIC.[24,25] A survey of 198 UK patients who had taken opioid analgesics for at least one month showed the ineffectiveness of over-the-counter laxatives for treating OIC with 75% of patients reporting persistent constipation based on the Bowel Function Index (BFI) and was associated with unfavorable side effects including flatulence, bloating, and the sudden urge to defecate in 75% of patients.[25]

Lubiprostone

Lubiprostone (Brand name: Amitiza 8 mcg and 24 mcg capsules) was the first approved treatment for OIC in patients with noncancer pain (CNCP) refractory to laxative prophylaxis. Lubiprostone targets chloride channels to increase intestinal fluid secretion and improve gastrointestinal (G.I.) transit time and is indicated for chronic idiopathic constipation in adults and irritable bowel syndrome with constipation.[26]

Two 12-week randomized, double-blinded, placebo-controlled trials that evaluated the efficacy and safety of oral lubiprostone showed an increase in spontaneous bowel movement frequency compared to placebo with side effects including diarrhea, nausea, abdominal pain, and distention and no serious adverse events.[26,27] A 36-week open-label extension study to determine the long-term safety and efficacy of lubiprostone mirrored the data found in the short terms trials.[28] Adverse events were common, with almost 1 in 4 patients experiencing at least one treatment-related adverse event.[28]

Peripherally Acting Mu-Opioid Receptor Antagonists (PAMORA)

A new class of peripherally acting mu-opioid receptor antagonists (PAMORA) has emerged over the past decade with the intent of targeting the underlying mechanism of OIC. By selectively inhibiting the action of opioids in the G.I. tract, PAMORAs allow for the preservation of bowel function without compromising pain control. Approved PAMORAs for the treatment of OIC include methylnaltrexone, naloxegol, and naldemedine.[29]

Methylnaltrexone (Brand name: Relistor 150 mg Tablets, 8 mg/0.4 ml vial, 12 mg/0.6 ml vial)

A handful of RCTs have been conducted to evaluate the efficacy of methylnaltrexone for the management of OIC in patients with CNCP. Iyer et al. conducted a 28-day phase 3 trial, which showed improved patient-reported symptoms of OIC following both daily and every other day injections of methylnaltrexone 12 mg.[30] Michna et al. used the same sample population as Iyer et al. and showed improvement in rescue-free bowel movements within 4 hours of the first dose as well as an increased percentage of injections that led to a rescue-free bowel movement (RFBM) compared to placebo.[31] A study by Rauck et al. found that oral methylnaltrexone is an efficacious alternative to SubQ methylnaltrexone, particularly at higher doses with minimal differences in side effects.[32]

Naloxegol

Naloxegol (Brand name: Movantik 12.5 mg and 25 mg tablets) is another PAMORA evaluated for efficacy for OIC in CNCP in the last decade. Two 12-week parallel-group trials by Chey et al. reported improved response rate (44.4%, P = 0.001 and 39.7%, P = 0.02) to

oral naloxegol 25 mg, defined as three or more spontaneous bowel (SBM) movements per week. At a dose of 12.5 mg, one trial reported significantly improved rate response or 40.8% (P = 0.02) versus 34.9% (P = 0.2) in the other. The placebo response rate was 29.4% and 29.3% for the studies. Adverse events occurred most commonly in the oral naloxegol 25 mg group and included abdominal pain, diarrhea, nausea, and vomiting. All adverse events were considered mild to moderate, and neither trial found reduced efficacy of opioid-mediated analgesia.[33] Webster et al. conducted a 4-week double-blinded dose-escalation study with naloxegol 5 mg (n = 33), naloxegol 25 mg (n = 30), and naloxegol 50 mg (n = 35) with placebo for OIC in CNCP. They found that higher doses of naloxegol have a stronger effect than the lower doses compared to placebo, with no significant result in the 5 mg cohort. The 50 mg cohort experienced the highest rate of adverse effects, including mild to moderate abdominal pain, diarrhea, and nausea, with 11 patients in the 50 mg cohort dropping out of the study due to gastrointestinal A.E.[34] Webster et al. additionally conducted a 52-week open-label safety and tolerability study for patients with OIC in CNCP comparing 25 mg (n = 534) and usual care (n = 281) defined as non-PAMORA laxatives. In the naloxegol arm, 81% experienced an A.E., of which 9.6% were considered serious, and 10.5% led to discontinuation of the naloxegol therapy. The incidence and severity of A.E.s were consistent with a longer duration of treatment. In the usual care arm, 72.2% of patients experienced an A.E., 11.1% were deemed serious, and 1.8% led to discontinuation of the study.[35]

Systematic Reviews

A systematic review and network meta-analysis of twenty-seven eligible RCTs of pharmacological therapies consisting of 9149 patients found naloxone and naldemedine to be the most efficacious and naloxone to be the safest for treatment of OIC in CNCP.[36] Another review showed a benefit for methylnaltrexone, naloxegol, naldemedine, and lubiprostone in treating OIC in CNCP, with conflicting evidence for alvimopan after assessment of 16 RCTs.[29] Alvimopan is not approved by the FDA for the treatment of OIC but has been studied for its effectiveness.[29] Due to its risk for myocardial infarction, alvimopan is only indicated for the use in the hospital setting to accelerate the time to upper and lower G.I. recovery following partial or small bowel resection surgery. A review by Bowers and Crannage sought to evaluate the efficacy and safety of approved pharmacological therapies for OIC for CNCP beyond the 12-week period of most short-term trials

and determined that while treatment remains very patient-specific, there is a stronger recommendation for lubiprostone, and tentatively naldemedine.[24]

Naldemedine Drug Information

Naldemedine (SYMPROIC R) is the newest FDA-approved PAMORA for the treatment of OIC in adult patients with CNCP. It is currently available in 0.2 mg tablets with a once-daily recommended dose. Previously a schedule II controlled substance, the Drug Enforcement Administration removed naldemedine from the schedules of the Controlled Substance Act in September 2017.[37] Serious adverse effects of the drug include gastrointestinal (G.I.) perforation and opioid withdrawal. Naldemedine is contraindicated in patients with known or suspected G.I. obstruction or at increased risk for recurrent obstruction due to the risk for G.I. perforation. Additionally, patients with disruption to the blood-brain barrier may have increased risk for opioid withdrawal or reduced analgesia so the cluster of symptoms consistent with opioid withdrawal should be monitored for (hyperhidrosis, chills, increased lacrimation, flushing, pyrexia, sneezing, feeling cold, nausea, vomiting, abdominal pain, and diarrhea). Less serious adverse reactions include abdominal pain, diarrhea, and nausea (SYMPROIC FDA Label).

Mechanism of Action

Naldemedine is a peripheral antagonist of mu-, delta-, and kappa-opioid receptors. Common in both the central and peripheral nervous system, their interaction with opioids peripherally leads to non-peristaltic contraction of the esophagus, decreased G.I. secretions, inhibited intestinal propulsion, and ultimately greater absorption of water from bowel contents resulting in symptoms of constipation.[38] Antagonism of these receptors peripherally is responsible for reducing the constipating effects of opioids. Unlike the other PAMORAs previously described, naldemedine antagonizes all three of these peripheral receptors, with delta- and kappa-receptors primarily being found in the proximal stomach and colon and mu-receptors being widely distributed through the G.I. tract.[39] In vitro studies have determined that naldemedine is a non-competitive antagonist of mu-opioid receptors, while naloxegol and naloxone (a central-acting opioid antagonist) are competitive antagonists.[39] In vivo studies of the effect of naldemedine and naloxegol on morphine-induced small intestinal transit (SIT) inhibition

determined the dose-response curve of naldemedine was unchanged at 1 and 3 mg/kg morphine, while that of naloxegol was significantly shifted to the right from 1 to 3 mg/kg morphine. This indicates the insurmountable antagonism of morphine-induced inhibition of SIT.[39] Additionally, as a substrate of the P-glycoprotein efflux transporter, naldemedine is excluded from the central nervous system at the blood-brain barrier limiting unwanted side effects.[40,41]

Pharmacokinetics/Pharmacodynamics

Absorption and Distribution

Naldemedine is absorbed through the G.I. tract with peak concentration (C_{max}) occurring approximately 0.75 hours (T_{max}) after administration in the fasted state.[42] A high-fat meal decreases C_{max} by approximately 35%, and T_{max} is extended to approximately 2.5 hours when taken with food. Trials recognize a near-dose proportional increase in C_{max} and the area-under the plasma-concentration-time curve (AUC) without significant change when taken with a high-fat meal as this lowers the degree but not the speed of naldemedine absorption. Multiple daily doses of naldemedine show minimal accumulation. The volume of distribution of naldemedine is 155 L and is 93% to 94% bound to human plasma proteins when taken orally.[40,43]

Metabolism

Naldemedine undergoes metabolism via the CYP3A system of the liver to form nor-naldemedine, and to a lesser degree, through UGT1A3 to form naldemedine 3-G. Naldemedine is additionally cleaved to benzamidine and naldemedine carboxylic acid in the G.I. tract. Radiolabeled naldemedine taken orally showed nor-naldemedine as the primary metabolite in plasma with a concentration of 9% to 13% relative exposure compared to naldemedine, and naldemedine 3-G with a relative exposure of less than 3%.[44] Given this metabolic profile, various drug interactions are observed. The use of drugs, which are strong CYP3A inducers, is contraindicated as increased hepatic metabolism leads to significant reductions in plasma concentration and may reduce efficacy. Additionally, the use of CYP3A inhibitors decreases hepatic metabolism and may be leading to increased drug plasma concentrations and greater risk of A.E. For these reasons, drugs with these characteristics are contraindicated, or dosing must be considered to limit A.E.[40]

Elimination

When taken orally, 57% of radiolabeled naldemedine was excreted in the urine, and 35% was excreted in the feces. Approximately 16% to 18% of the administered dose excreted in the urine as unchanged. Benzamidine is the primary metabolite excreted in the urine and feces and represents approximately 32% and 20% of the administered dose, respectively.[40,43]

Hepatic and Renal Impairment

The pharmacokinetic properties of oral naldemedine given once at a dose of 0.2 mg in subjects with normal hepatic and renal (estimated creatinine clearance $\geqslant$ 90 mL/min) function were similar to those in subjects with mild (estimated glomerular filtration rate [eGFR] of 60 to 89 mL/min/1.73 m^2), moderate (eGFR of 30 to 59 mL/min/1.73 m^2), or severe renal impairment (eGFR of $<$ 30 mL/min/1.73 m^2), subjects with an end-stage renal disease requiring hemodialysis, and subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Pharmacokinetic assessments indicate there is no necessary dose adjustment for patients with any degree of renal impairment or for patients with mild to moderate hepatic impairment. To date, the effect on pharmacokinetic properties in patients with severe hepatic impairment has not been studied.[40,43,45]

Clinical Studies: Safety and Efficacy

Phase I Studies

Two-phase I, randomized, double-blind, placebo-controlled (RDBPC) studies demonstrated the safety of naldemedine in healthy individuals. The single ascending dose (SAD) study compared a single dose of naldemedine (0.1 to 100 mg) to a placebo. The multiple ascending dose (MAD) study compared a 10-day daily dose of naldemedine (3 to 30 mg) to a placebo. No safety concerns or significant vital signs or electrocardiogram abnormalities were found either study; however, in both trials, G.I. adverse-events (A.E.s) were more frequent with naldemedine than a placebo (SAD: 16.7% versus 0%; MAD: 14.8% versus 11.1%). A.E.s were not dose-dependent.[42]

Another phase 1 studies investigated the safety of naldemedine 0.2 mg in patients with opioid-induced constipation (OIC) and renal (mild to end-stage renal disease) or hepatic (mild or moderate) impairment. For renal impairment, no notable difference in treatment-emergent adverse events (TEAEs) were found between participants with impairment and those with normal renal function, while patients with mild and

TABLE 1

Clinical Efficacy and Safety

AUTHOR (YEAR)	GROUPS STUDIED AND INTERVENTION	RESULTS AND FINDINGS	CONCLUSIONS
Webster et al. (2017)[46]	Phase 2b, double-blinded placebo-controlled trial on long-term opioid therapy for chronic noncancer pain with OIC. 4 different groups, naldemedine (0.1 mg, 0.2 mg, and 0.4 mg) or placebo. The primary efficacy endpoint was changed in weekly spontaneous bowel movement. Secondary endpoints were the portion of SBM responders.	Weekly SBM frequency was higher, with naldemedine 0.2 mg (3.37) and 0.4 mg (3.64). The proportion of SBM responders was significantly higher in 0.2 mg and 0.4 mg groups.	Naldemedine 0.2 mg once daily was concluded to offer the most favorable benefit-risk profile and was chosen as the dose for future trials.
Katakami et al. (2017)[47]	Phase 2b, double-blind study with patients with cancer receiving an opioid analgesic for at least two weeks with OIC and no more than 5 SBM during 14 days were assigned to naldemedine (0.1, 0.2, or 0.4) or placebo. The primary endpoint was a change in SBM frequency, and secondary endpoints were a change of frequency from baseline of SBM.	SBM frequency was higher with all naldemedine doses compared to placebo ($p < 0.5$). SBM frequency without straining was significantly improved with 0.2 and 0.4 mg of naldemedine.	Naldemedine 0.2 mg was selected for phase 3 studies.
Hale et al. (2017)[48]	Randomized, placebo-controlled trials in adults with chronic noncancer pain and OIC. Patients were either on naldemedine 0.2 mg or placebo for 12 weeks. (COMPOSE 1 and COMPOSE 2). The primary endpoint was the proportion of responders (at least 3 SBM per week and increase from baseline for at least nine weeks of 12-week treatment).	The proportion of responders in both trials was significantly higher with naldemedine than the placebo. COMPOSE 1, 47.6% vs. 34.6% ($p = .0002$) and COMPOSE 2, 52.5% vs. 33.6% ($p = .0001$). The incidence of adverse events was similar to placebo.	Naldemedine had a higher response rate than the placebo and was well tolerated.

(*Continued*)

TABLE 1 (Continued)

Clinical Efficacy and Safety

AUTHOR (YEAR)	GROUPS STUDIED AND INTERVENTION	RESULTS AND FINDINGS	CONCLUSIONS
Katakami et al. (2017)[50]	Randomized, double-blinded, placebo-controlled study (COMPOSE 4), an open-label, 12-week extension study (COMPOSE 5) were done. Naldemedine 0.2 mg or a placebo was given to the randomized group. The primary endpoint was the proportion of SBM responders for COMPOSE 4. The primary endpoint for COMPOSE 5 was safety.	COMPOSE-4, the proportion of SBM responders was significantly greater with naldemedine than the placebo. (71.1% vs. 34.4%, respectively, $p < .0001$). More patients reported treatment-emergent adverse effects with naldemedine than placebo; diarrhea was the most common TEAE.	Once-daily oral naldemedine 0.2 mg effectively treated OIC and was well tolerated.
Fukumura et al. (2018)[42]	Two randomized, double-blind, placebo-controlled, phase 1 studies: single ascending dose study and multiple ascending dose study of naldemedine. Primary end	Maximum plasma concentration levels of the single ascending study and the multiple ascending studies of naldemedine were 1.98 to 2510 ng/ml and 73.8 to 700 ng/ml, respectively. There were no major safety or tolerability concerns at doses up to 500 times the therapeutic dose of .2 mg.	The incidence of adverse events for naldemedine is not dosing dependent.
Saito et al. (2018)[52]	Patients with chronic noncancer pain with OIC took oral naldemedine 0.2 mg for 48 weeks. Primary endpoints were treatment-emergent adverse events (TEAEs), pain intensity, and opioid withdrawal. Secondary efficacy endpoints were Patient Assessment of Constipation Symptoms (PAC-SYM) and Quality of Life (PAC-QOL) scores.	OIC patients using regular opioid use (COMPOSE 6) or prolonged-release oxycodone (COMPOSE 7) reported 88% and 90% TEAEs, respectively. Pain intensity and opioid withdrawal symptoms remained stable for 48 weeks. PAC-SYM and PAC-QOL were significantly improved and sustained.	Most side effects of naldemedine were mild or moderate in severity. Naldemedine can improve bowel function and QOL.

Katakami et al. (2018)[51]	Double-blind study (COMPOSE-4), patients with OIC and cancer were randomized to receive naldemedine 0.2 mg or placebo for two weeks, and those who continued on to COMPOSE-5 received naldemedine for 12 weeks. Spontaneous bowel movement (SBM) and complete SBM (CSBM) were assessed, and QOL using PAC-SYM and PAC QOL were evaluated.	Naldemedine improved bowel function compared to placebo ($P < .0002$). The time of onset of the first SBM was 4.7 hours for the naldemedine group and 26.6 hours for the placebo. For CSBM, it was 24 hours and 218.5 hours, respectively. PAC-SYM and PAC-QOL scores showed significant improvement.	Naldemedine provided effective and timely relief from OIC and improved QOL of subjects with OIC and cancer.
Webster et al. (2018)[49]	Patients with OIC and chronic noncancer pain were randomized into double-blind, phase 3 study. Patients were randomized to naldemedine 0.2 mg or placebo. The primary endpoint was treatment and emergent adverse events. Opioid withdrawal, pain intensity, frequency of bowel, and QOL were measured as well.	Treatment-emergent adverse events were similar, 68% and 72.1% for naldemedine and placebo, respectively. Diarrhea was more frequent with the naldemedine group. Bowel movement frequency and overall QOL due to OIC was significantly better in the naldemedine group ($p < .0001$).	Naldemedine significantly increased bowel movement frequency, OIC symptoms, and QOL compared to placebo.
Osaka et al. (2019)[55]	Data from patients of Phase IIb and Phase 3 studies with spontaneous bowel movement (SBM) and diarrhea were assessed for each treatment group.	Three hundred seven patients were in the analysis in two groups naldemedine ($n = 155$) and placebo ($n = 152$). There was a significant increase in SBM with naldemedine versus placebo. More patients experienced diarrhea with naldemedine compared to the placebo as well.	Naldemedine seems to benefit patients with opioid-induced constipation (OIC) and cancer.

(*Continued*)

TABLE 1 (Continued)

Clinical Efficacy and Safety

AUTHOR (YEAR)	GROUPS STUDIED AND INTERVENTION	RESULTS AND FINDINGS	CONCLUSIONS
Wild et al. (2020)[54]	Patients age 18–80 with chronic noncancer ⩾ 3 months treated with opioids for ⩾ 3 months in COMPOSE -1 and COMPOSE – 2 with opioid-induced constipation (OIC) received 0.2 mg naldemedine or placebo. Safety was assessed by treatment-emergent adverse events (TEAEs), and efficacy was based on spontaneous bowel movements (SBM).	The incidence of TEAEs with naldemedine was 1.1% in older patients above the age of 65, 1% overall. The incidence of TEAEs of possible opioid withdrawal was 1.1% in patients above the age of 65, 1.7% overall. There was a greater proportion of SBM responders with naldemedine than with placebo in patients ⩾ 65 (51.8% versus 37.6%).	OIC treatment with naldemedine 0.2 mg was tolerated well in patients ⩾ 65 years with chronic noncancer pain.
Takagi et al. (2020)[57]	A multi-center retrospective study of patients who had cancer and was under palliative care and was prescribed regular opioids with at least one dose of naldemedine. 2 groups was studied, the early group that started naldemedine within three days of starting opioids and the others were considered the late group. The primary endpoint was the incidence of diarrhea.	The incidence of diarrhea in the early group was significantly lower than in the late group ($p = 0.02$).	Early administration of naldemedine reduces adverse events, such as diarrhea.

moderate hepatic impairment experienced a numerically greater incidence of TEAEs (37.5% and 50.0% respectively versus 12.5% in healthy individuals) compared to those with normal function.[45]

Phase II Studies

A phase IIb RDBPC trial investigated the efficacy and safety of a single daily-dose of naldemedine (0.1 mg to 0.4 mg) for the treatment of OIC in chronic noncancer pain patients. The study found a significantly greater frequency of weekly SBMs from baseline to the last two weeks of treatment with both naldemedine 0.2 mg (3.37, $p = 0.0014$) and 0.4 mg (3.64, $p = 0.0003$); but, not for 0.1 mg ($p = 0.3504$) versus a placebo. There was no difference in weekly SBMs between 0.2 mg and 0.4 mg ($p = 0.66557$). The proportion of SBM responders (defined as $\geqslant 3$ SBMs/week with increase of $\geqslant 1$ SBMs from baseline over the last 2 weeks of the trial) were also greater for 0.2 mg (71.2%, $p = 0.0005$) and 0.4 mg (66.7%, $p = 0.003$), but not for 0.1 mg ($p = 0.1461$) than a placebo (39.3%). TEAEs were mild to moderate in severity and AEs increased with naldemedine dosage (0.1 mg: 41%; 0.2 mg: 50%; 0.4 mg: 55.7%), with GI disorders being the most common TEAE (0.1 mg: 21.3%; 0.2 mg: 25.0%; 0.4 mg: 34.4%). Naldemedine 0.2 mg once daily was concluded to offer the most favorable benefit-risk profile and was chosen as the dose for future trials.[46]

Another phase 2b trial investigated the safety and efficacy of a single daily-dose of naldemedine (0.1 mg to 0.4 mg) in cancer patients. In this study, all doses had a greater change in SBM frequency (0.1 mg: 3.43, $p = 0.0465$; 0.2 mg: 4.75, $p < .001$; 0.4 mg: 7.29, $p < 0.001$) versus a placebo (1.50). Additionally all doses had a greater proportion of SBM responder (56.4%, $p = 0.0464$; 77.6, $p = 77.6\%$, $p < 0.001$; 82.1%, $p < 0.001$ respectively) versus a placebo (37.5%), as well as greater change in complete SBM (CSBM) frequency ($p = 0.0021$, < 0.001, 0.10 respectively) versus a placebo. 0.2 mg (3.32, $p = 0.0021$) and 0.4 mg (5.11, $p < 0.001$) also had a greater change in SBM frequency without straining versus placebo. There were a greater incidence of TEAEs at all doses (0.1 mg: 66.1%; 0.2 mg: 67.2%; 0.4 mg: 78.6%) versus a placebo (51.8%), with diarrhea being the most common TEAE. The trial concluded that 0.2 mg naldemedine had the most favorable risk-benefit profile in treating OIC in cancer patients.[47]

COMPOSE Trials

A series of phase III RDBC trials (COMPOSE) investigated both the efficacy and safety of naldemedine in patients with OIC.

COMPOSE-1 and COMPOSE-2 investigated the efficacy and safety of 0.2 mg naldemedine in OIC patients with chronic noncancer pain. The primary endpoint of the studies was the proportion of SBM responders (defined as ⩾ three SBMs/week with an increase of ⩾ 1 SBM/week from baseline for at least 9 of 12-weeks and for at least 3 of the last four weeks). In both studies, the naldemedine group had a greater proportion of SBM responders than the placebo group (COMPOSE-1: 47.6% versus 34.6%, $p = 0.002$; COMPOSE-2: 52.5% versus 33.6%, $p < 0.0001$). Incidence of AEs were similar between the two treatment groups (COMPOSE-1: naldemedine, 49% versus placebo, 45%; COMPOSE-2: 50% [n = 271] versus 48% [n = 132]). Gastrointestinal AEs were more common with naldemedine than a placebo (COMPOSE-1: naldemedine, 15% versus placebo, 7%; COMPOSE-2: 16% versus 7%).[48]

COMPOSE-3 evaluated the long-term safety of once-daily naldemedine 0.2 mg in patients with OIC and chronic noncancer pain. In the study, the incidence of TEAEs was similar between the two treatment groups (68.4%, naldemedine versus 72.1%, placebo), with diarrhea (11.0% versus 5.2%), abdominal pain (8.2% versus 3.1%), and vomiting (6.0% versus 3.1%) occurring more frequently with naldemedine than a placebo. TEAEs leading to study discontinuation were also similar between the groups (naldemedine, 6.3% versus placebo, 5.8%). Additionally, opioid withdrawal and pain intensity scores were similar between the groups as well.[49]

COMPOSE-4 was a 2-week study that evaluated the efficacy of 0.2 mg naldemedine in OIC patients with cancer, while COMPOSE-5 evaluated the safety of naldemedine over a 12-week period. The primary endpoint for COMPOSE-4 was the proportion of SBM responders, which was found to be significantly greater for naldemedine than a placebo (71.1% versus 34.4%, $p < 0.0001$). Additionally, naldemedine had a greater change in frequency of SBMs/week (5.16 versus 1.54, $p < 0.0001$), CSBM/week (2.76 versus 0.71, $P < .0001$), and SBMs without straining/week (1.29 versus 2.81, $P < .0001$) compared to a placebo.[50] The time of onset to first SBM (4.7 versus 26.6 hours, $p < 0.0001$) and CSBM (24.0 versus 218.5 hours) were also significantly lower for the naldemedine group than the placebo group.[51] For safety, naldemedine was associated with significantly more TEAEs than the placebo in COMPOSE-4 (44.3% versus 26.0%, $p = .01$), and in COMPOSE-5, 80.2% of patients were found to have experienced a TEAE, with diarrhea being the most common A.E. in both studies (COMPOSE-4: naldemedine, 19.6% versus placebo, 7.3%; COMPOSE-5: 18.3%). TEAEs led to study discontinuation of 9.3% of patients in COMPOSE-4 (versus 1.0% in the placebo group, $p = 0.0184$),

and 9.2% of patients in COMPOSE-5. Opioid-withdrawal and pain intensity scores were similar between the two treatment groups.[50]

Additionally, naldemedine was found to improve the quality of life (QOL), evaluated through the Patient Assessment of Constipation Symptoms (PAC-SYM) and PAC-QOL surveys, of patients with OIC and cancer. In COMPOSE-4, both the PAC-SYM stool domain ($p = 0.045$) and PAC-QOL dissatisfaction domains ($p = 0.015$) were improved for patients taking naldemedine compared to a placebo. Likewise, in COMPOSE-5, the PAC-SYM and PAC-QOL scores were significantly improved for naldemedine compared to a placebo.[51]

COMPOSE-6 and COMPOSE-7 evaluated the safety and efficacy of naldemedine 0.2 mg in patients with OIC and chronic non-caner pain receiving either regular-use opioids (COMPOSE-6) or prolonged-release oxycodone (COMPOSE-7). TEAEs were reported in 88% of patients in COMPOSE-6 and 90% in COMPOSE-7, with diarrhea (COMPOSE-6: 14%; COMPOSE-7: 40%) and nasopharyngitis (26% and 30%) being the most common reported TEAEs. Opioid withdrawal and pain intensity scores remained stable over the course of the treatment period. In both studies, there was an increase in the frequency of weekly SBMs (5.42 and 5.45 respectively), CSBMS (2.74 and 3.55), and SBMs without straining (2.86 and 4.35) with naldemedine. Furthermore, improvements in PAC-SYM and PAC-QOL scores were seen in both of the studies (all $p < 0.05$).[52]

Other Studies

The data from COMPOSE-1 and COMPOSE-2 was used to investigate the time it took for naldemedine to lead to SBMs, as well as A.E.s. In both trials, a greater proportion of patients with naldemedine experienced an SBM and CSBM at 4, 8, 12, and 24 hours after the initial dose of medication than a placebo (all $p < 0.0001$). The median time to first SBM was also shorter with naldemedine than a placebo (COMPOSE-1: 16.1 versus 46.7 hours, $p < 0.0001$; COMPOSE-2: 18.3 versus 45.9 hours, $p < 0.0001$), and a greater proportion of patients in the naldemedine group experienced an SBM on day 1 of treatment compared to a placebo in both trials (45–47% versus 16–19% in the placebo group). Furthermore, the incidence of gastrointestinal A.E.s was most frequent on day 1 (6%–7%) and then decreased over the next six days (0%–3%) with naldemedine in both trials.[53]

A subgroup analysis of the data from the COMPOSE-1, COMPOSE-2, and COMPOSE-3 was used to investigate the safety and efficacy of naldemedine in patients $\geqslant 65$ years ($n = 344$). The incidence of TEAEs was similar in patients $\geqslant 65$ receiving naldemedine

(45.9%) and in patients ⩾ 65 receiving placebo (51.6%), as well as in the overall patient population (47.1%). Incidence of GI TEAEs was also comparable between the groups (⩾ 65: naldemedine, 20.2%; overall: naldemedine, 21.8%; placebo: ⩾ 65: 16.1%). Furthermore, the incidence of opioid withdrawal was similar between treated patients ⩾, 65 (1.1%), and overall treated patients (1.0%). Additionally, there was a greater proportion of SBM responders with naldemedine than with placebo in patients ⩾ 65 (51.8% versus 37.6%).[54]

Another study evaluated baseline characteristics, such as age, body mass index, sex, prior opioid or laxative usage, history of cancer therapy, and brain metastasis, that might impact the efficacy and safety of naldemedine in patients with cancer. The analysis found that, overall, proportion of SBM responders (difference [95% CI] 38.0% [27.6% to 48.4%], $p < 0.0001$), and incidence of diarrhea (37.5% [27.1% to 47.9%], $p < 0.0001$) were greater with naldemedine than a placebo (73.5% versus 35.5%, $p < 0.0001$); results that held consistent regardless of baseline characteristics analyzed. Additionally, regardless of potential brain metastases, naldemedine was found to not reduce the analgesic effect of opioids nor precipitate opioid withdrawal symptoms.[55]

Another meta-analysis looked at six randomized control trials ($n = 2{,}762$) to evaluate the safety and efficacy of naldemedine 0.2 mg in treating OIC. The study reaffirmed that the proportion of SBM responders was greater with naldemedine than a placebo (56.4% versus 34.7%, $p < 0.00001$), as changed in SBM frequency and CSBM frequency greater (both $p < 0.00001$). Additionally, no significant difference in TEAEs was found between the two groups ($p = 0.25$).[56]

Another study looked into management and prevention strategies of one of the most common reported A.E.s of naldemedine. In the study, participants either received naldemedine within three days of taking opioids (early group) or more than three days (late group). A lower proportion of patients in the early group experienced diarrhea than in the late group (3.9% versus 22.2%, $p = 0.02$). Furthermore, constipation occurred in 53% of all patients after diarrhea resolved, and in 78% of the patients that discontinued naldemedine. 92% of participants noticed an improvement of diarrhea within three days after stopping other laxatives, but continuing naldemedine. The study concluded that the early administration of naldemedine could decrease the A.E. of diarrhea and that diarrhea could be managed by stopping other laxatives, but continuing naldemedine.[57]

Another study suggested that using naldemedine (within two days of opioid therapy) could improve opioid-induced nausea and committing (OINV). In the study, the incidence of OINV was significantly lower in

patients that used naldemedine versus those that did not (36.0% versus 47.2%, p = 0.0426).[58]

Comparison Study

To date, no head-to-head comparison of the therapeutic options used to manage OIC has been conducted; however, in a meta-analysis comparison study, all of the available interventions, including lubiprostone, prucalopride, naldemedine, naloxegol, alvimopan, senna, and subcutaneous and oral methylnaltrexone, were found to improve rescue-free bowel movements (RFBM) compared to a placebo, with subcutaneous methylnaltrexone having the highest odds ratio (OR [95% CI] 7.02 [4.26, 11.57]) and naldemedine having the second-highest ratio (5.77 [2.54, 13.11]). All of the treatments, except senna and lubiprostone, reduced the usage of rescue laxatives, with naldemedine performing the best (0.23 [0.10, 0.53]). Additionally, only naldemedine (3.42 [1.58, 7.39]) and lubiprostone (1.35 [1.03, 1.77]) had a significant increase in A.E.s compared to a placebo.[59]

Conclusion

Opioid medications are fundamental in anesthesia and analgesia and are often used to treat acute and chronic pain. They achieve their desired effects by modulating pain perception in the central nervous system; however, they also act on opioid receptors in the periphery, causing many undesirable effects, such as respiratory depression, sedation (which rarely continues after a few days or weeks), and chronic G.I. dysmotility leading to opioid-induced constipation (OIC).

OIC is part of a spectrum of OIBD that presents with various G.I., including reflux, vomiting, bloating, abdominal pain, anorexia, hard stools, constipation, and incomplete evacuation caused by overstimulation of opioid receptors in the G.I. tract. These G-protein coupled receptors lead to decreased excitability, leading to decreased motility and increased sphincter tone. OIC is defined clinically as a combination of reduced bowel movement frequency, straining to pass stool, harder stools, and incomplete evacuation. It is the most common side-effect of opioid consumption, affecting close to 50% of chronic users. Complications can lead to ileus, distention, perforation, and even death.

Treatment starts with nonpharmacological measures, such as increased fiber consumption, fluid intake, and physical activity. First-line pharmacological interventions include OTC laxatives, but those are largely inefficient.

PAMORA are a class of drugs that treat the cause of OIC by targeting peripheral mu-opioid receptors. They include methylnaltrexone, naloxegol, and naldemedine. Methylnaltrexone was originally proven to be more effective than placebo with subcutaneous injections, but recently also using an orally available formulation. Naloxegol is orally available and also effective compared with placebo; however, it also has more common side effects reported.

Naldemedine is a once-daily tablet. It is a peripheral mu, delta, and kappa receptor antagonist. It is the only of its class to target all three receptors. It was evaluated in several clinical trials and was shown to be both effective and safe when compared to placebo, and shown to improve the quality of life of users through the alleviation of symptoms. Unfortunately, no head-to-head data exists to compare the efficacy of naldemedine to that of the other members of the group and other anti-constipation drugs.

The chronic use of opioids has seen a constant decrease, mostly owing to the associated risks of dependence and addiction; however, opioids remain a cornerstone of analgesia and anesthesia. OIC is the commonest of side effects of chronic opioid use, and non-specific interventions are usually ineffective. Naldemedine is an FDA-approved, once-daily, orally available peripheral opioid receptor antagonist that specifically treats OIC. It has been shown to be relatively safe and effective when compared with placebo. Further studies are required to estimate its efficacy when compared with other available therapies. ✤

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