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Palonosetron and Hydroxyzine Pre-treatment Reduces the Objective Signs of Experimentally-Induced Acute Opioid Withdrawal in Humans: A Double-Blinded, Randomized, Placebo-Controlled Crossover Study

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Abstract

Background—Treatments for reducing opioid withdrawal are limited and prone to problematic side effects. Laboratory studies, clinical observations, and limited human trial data suggest 5-HT3-receptor antagonists and antihistamines may be effective.

Objectives—This double-blind, crossover, placebo-controlled study employing an acute physical dependence model evaluated whether (i) treatment with a 5-HT3-receptor antagonist (palonosetron) would reduce opioid withdrawal symptoms, and (ii) co-administration of an antihistamine (hydroxyzine) would enhance any treatment effect.

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Methods—At timepoint T=0, healthy (non-opioid dependent, non-substance abuser) male volunteers (N=10) were pre-treated with either a) placebo, b) palonosetron IV (0.75 mg), or c) palonosetron IV (0.75 mg) and hydroxyzine PO (100 mg) in a crossover study design. This was followed at T=30 by intravenous morphine (10mg/70kg). At T=165, 10mg/70kg naloxone IV was given to precipitate opioid withdrawal. The objective opioid withdrawal score (OOWS) and subjective opioid withdrawal score (SOWS) were determined 5 and 15 minutes after naloxone administration (T=170, 180, respectively). Baseline measurements were recorded at T=-30 and T=-15.

Results—Comparison of average baseline OOWS scores with OOWS scores obtained fifteen minutes after naloxone was significant (p=0.0001). Scores from fifteen minutes post-naloxone infusion showed significant differences in OOWS scores between treatment groups: placebo, 3.7 ± 2.4; palonosetron, 1.5± 0.97; and palonosetron with hydroxyzine, 0.2 ± .1333.

Conclusions—Pretreatment with palonosetron significantly reduced many signs of experimental-induced opioid withdrawal. Co-administration with hydroxyzine further reduced opioid withdrawal severity. These results suggest that 5-HT3 receptor antagonists, alone or in combination with an antihistamine, may be useful in the treatment of opioid withdrawal.

1. Introduction

Over 116 million adults suffer from chronic pain (1); 19% of US adults reported chronic pain and 34% reported recurrent pain in 2005 (2). It is estimated that the United States spends $560-635 billion annually as a result of chronic pain (1). In an effort to alleviate the suffering of those with chronic pain, use of opioid medications has dramatically increased over the past two decades (3). Subsequently, opioids have become the most highly prescribed class of medications in the United States, which has created a significant public health problem due to misuse. Although opioids are effective at managing moderate to severe pain, they possess maladaptive properties, including physical dependence and other associated sequelae including addiction, analgesic tolerance, and opioid-induced hyperalgesia. Difficulty in the cessation of opioid pain medications due to physical dependence is a contributing factor in opioid addiction and abuse. Unfortunately, the medications currently available to treat opioid withdrawal (clonidine, methadone, and buprenorphine) fail to adequately address this public health problem, and they carry their own drawbacks and adverse side effects. Methadone and buprenorphine have addiction potential and clonidine can induce potentially dangerous hemodynamic shifts (4). An ideal treatment modality to reduce opioid withdrawal would be a non-opioid medication with (i) a low liability for abuse and (ii) a benign side effect profile.

To address this need, we previously conducted murine haplotype-based computational mapping comparing withdrawal behavior between 16 strains of mice with genetic variation and SNPs, and identified involvement of the Htr3a gene coding for the 5-HT3 receptor to be implicated in the modulation of naloxone-induced opioid withdrawal and physical dependence (5). In this study, brainstem nuclei implicated in opioid physical dependence–the amygdala (6, 7), dorsal raphe (6, 8), and the periaqueductal gray (9)–showed reduction in the expression of Htr3a mRNA expression after morphine treatment (5). Subsequent 5-HT3 receptor protein expression was also significantly reduced (5). Systemic morphine induces

an increase in 5-HT in the dorsal raphe nucleus and amygdala, and morphine injected into the periaqueductal gray increased 5-HT release from spinal terminals (10). Thus, a medication that blocks the action of 5-HT on the 5-HT3 receptors implicated in morphine physical dependence prior to administration of morphine may be effective in reducing the progression of physical dependence if given prior to the administration of morphine.

In rats, this link was apparent in a report suggesting that the 5-HT3 antagonist ondansetron reduced naloxone-induced morphine withdrawal (11). Ondansetron is an FDA-approved medication commonly used to treat chemotherapy- and radiotherapy-associated nausea and vomiting (12). In a prior study, we observed in eight healthy male participants that pretreatment with ondansetron, using an experimental protocol design outlined by Compton et al., alleviated the objective symptoms of acutely-induced naloxone-precipitated opioid withdrawal by up to 76% on the OOWS scale (5, 13). Ondansetron itself, however, may not constitute optimal treatment for the prevention of withdrawal as it has a relatively low potency and short half-life. To investigate this possibility, therefore, we examined the effect of another 5-HT3 receptor antagonist with a different chemical structure on opioid withdrawal symptoms. The FDA-approved 5-HT3 antagonist palonosetron is similar to ondansetron, but is longer acting and more potent. Palonosetron's half-life (40.0 h) exceeds other 5-HT3-RAs: ondansetron (4.0 h), granisetron (9.0 h), and dolasetron (7.5 h) (14-16). Furthermore, among the 5-HT3 antagonist class, palonosetron has the highest binding affinity, uniquely displays allosteric effects on 5-HT3 receptor binding, and promotes the internalization of NK1 receptors linked to nausea, a problematic opioid withdrawal symptom (16).

Multiple signaling pathways are activated during opioid withdrawal (16). Therefore, co-administration of an inhibitor of other biological effector pathways with a 5-HT3 receptor antagonist could reduce opioid withdrawal symptoms further. There is evidence that histamine may mediate the pharmacologic effects of opioids and associated withdrawal symptoms. During chronic morphine administration and during morphine withdrawal there are changes in brain histamine levels and in brain histidine decarboxylase activity (17-19). Notably, Hauser et al. described anecdotal reports suggesting that hydroxyzine, a first-generation antihistamine, was effective in alleviating many of the symptoms of opioid withdrawal (20).

This double-blind, crossover, placebo-controlled pilot study evaluated the ability of palonosetron to reduce naloxone-precipitated withdrawal in healthy human subjects, and further evaluated whether the first-generation antihistamine hydroxyzine added to the effects of palonosetron in an acutely-induced opioid physical dependence and naloxone-precipitated withdrawal paradigm.

2. Methods

2.1 Study Design

This study was performed to assess the efficacy of pretreatment with palonosetron or with the combination of palonosetron and hydroxyzine in reducing the symptoms of opioid withdrawal in human subjects. An experimental protocol design, as detailed by Compton et

al., was used to precipitate acute opioid withdrawal after inducing acute opioid physical dependence to determine the efficacy of the 5-HT3 receptor antagonist, palonosetron, with and without hydroxyzine, in reducing the symptoms of opioid withdrawal in human study participants (13).

Analysis of the data obtained in our prior study (5) indicated that analysis of 10 individuals would provide 90% power to detect a treatment effect. Therefore, we examined the effect of three different pretreatments on naloxone-induced opiate withdrawal signs in 10 normal individuals.

In this randomized, double-blinded, placebo-controlled, crossover study, healthy male volunteers (N=10) aged 19-24 (21.5 ± 1.9), weight 78.4 ± 11.3 kg, with no prior history of opioid dependence or substance abuse, were pretreated with 0.9% normal saline placebo, IV palonosetron (0.05mg/cc at 15cc for a total of 0.75 mg), or IV palonosetron (0.05mg/cc at 15cc for a total of 0.75 mg) with hydroxyzine PO (100 mg) prior to induction of IV naloxone bolus (10mg/70kg) precipitated withdrawal following morphine (10mg/70g) exposure in three study sessions. Eligibility criteria for the study were: a) healthy, b) male, c) age 18-35, d) no allergies to morphine or palonosetron, e) no history of addiction or substance abuse. Female study participants were excluded from this study because of prior evidence that menstrual cycles can alter opioid responses (21). Three separate study sessions for each participant were scheduled one week apart from one another. The Institutional Review Board (Stanford University) authorized the human experimental protocol and the study was registered in the clinicaltrials.gov database (identifier NCT00661674). Prior to study enrollment, each individual participant freely provided informed written consent. All study sessions were conducted by a research assistant blinded to study group under the supervision of an unblinded physician; all drug treatment was provided by the unblinded physician. All data was collected in the Stanford Department of Anesthesiology Pain Lab.

All study sessions were closely monitored by research staff, including the physician (LC) and research nurse, to address any potential aforementioned adverse events, as well as unanticipated events.

2.2 Study Medications

The study medications were 0.9% normal saline placebo (Hospira Inc., Lake Forest, IL), IV palonosetron (0.05mg/cc at 15cc for a total of 0.75 mg) (Eisai Inc, Woodcliff Lake, NJ), or IV palonosetron (0.05mg/cc at 15cc for a total of 0.75 mg) with hydroxyzine PO (100 mg) (Teva Pharmaceuticals, North Wales, PA); IV naloxone bolus (10mg/70kg - 0.4 mg/cc) (Hospira Inc., Lake Forest, IL); IV morphine (10mg/70g - 10mg/cc) (Baxter Healthcare Corporation, Deerfield, Illinois, USA).

2.3 Data collection

During each study session, the following study measures were recorded by the blinded research assistant: sedation score, euphoria score, pruritus score, pruritus location, nausea score, objective opioid withdrawal scale, and vitals–including respiratory rate, heart rate, blood pressure and O_2 saturation. The blinded research participant completed the subjective opioid withdrawal scale.

2.4 Opioid Withdrawal Assessments

Two validated rating scales given in conjunction, assessed by Handelsman et al., were implemented to assess the efficacy of the pretreatment drug on acutely induced opioid physical dependence and withdrawal: the objective opioid withdrawal scale (OOWS), completed by a blinded research assistant, and the subjective opioid withdrawal scale (SOWS), completed by the blinded research participant (22). The same blinded research assistant completed all OOWS measurements. The OOWS comprises 13 physical signs that can be observed during a 5-minute observation period, rated on a binary scale of present (1) or absent (0) (22). The total OOWS score is the sum of the physically observable signs rated present by the blinded research assistant during the observation period. The SOWS comprises 16 symptoms reported by the participant during the 5-minute observation period used for OOWS rating. The symptoms are rated on a scale of 0 (not at all) to 4 (extremely). The total SOWS score is the sum of physical and emotional responses to opioid withdrawal as self-reported by the research participant (22).

2.5 Study Timeline

Each participant completed three study sessions, separated by an interval of at least 7 days, and each study session had an identical structure. At the beginning of each study session the participant was weighed to determine dosing protocols. Research staff re-evaluated medication use and ensured that the participant obtained at least 6 hours of sleep, as a lack of sleep can interfere with perception of pain (23, 24). Following the check-in period, the participant received an intravenous catheter in their non-dominant arm, and was connected to a pulse oximeter. Before any medications were given baseline measurements (sedation score, euphoria score, pruritus score, pruritus location, nausea score, objective opioid withdrawal scale, subjective opioid withdrawal scale, and vitals) were recorded twice to ensure data reliability (T=-30 and T=-15).

Study interventions were administered prior to morphine infusion to examine treatment effect on the prevention of acutely induced physical dependence in accordance with methodology previously described by Compton et al. (13).

After the two baseline measurements, the study session was organized according to the following time points where T=0 designates the first medication infusion. At T=0 the participant was given a pretreatment infusion of either IV palonosetron, IV palonosetron and PO hydroxyzine, or IV and oral placebo according to their study randomization schedule. After a 30-minute rest (T=30), participants were given a morphine infusion over a 10-minute period followed by 105 minutes of rest. Following this rest period (T=145), study measures were recorded. At T=165 naloxone was administered, and study measures were recorded at 5 and 15 minutes later (T=170, T=180 respectively). Once participants were deemed medically stable and free of opioid effects, the physician or research nurse discharged them.

Palonosetron was administered 30 minutes prior to morphine infusion in accordance with clinical guidelines for palonosetron administration based on onset of action and half-life (40-hours) in patients undergoing chemotherapy induced nausea and vomiting (CINV) (25). Hydroxyzine was administered 30 minutes prior to morphine infusion as the onset of action

of PO Hydroxyzine is 15-30 minutes with a duration of action between 4 and 6 hours (26). Compton et al. demonstrated in healthy male subjects that IV morphine (10mg/70kg) bolus reliably induces acute physical dependence in an experimental model validated two hours after morphine infusion by naloxone challenge (13). Naloxone-precipitated withdrawal in those with IV morphine induced opioid physical dependence is first observable within a period of 5 minutes and is greatest within a period of 15 minutes after administration; therefore, the 15-minute post-naloxone administration interval represented the primary outcome measure of this study in accordance with an established experimental procedure (13).

2.6 Statistical analysis

The focus in the analysis was data for primary outcome measures (OOWS and SOWS) from all participants that completed the study. All participants completed the study. Because each participant underwent the same protocol in three different conditions, and the specific OOWS and SOWS variables were assessed over three timepoints and compared to baseline, a Friedman test was used. The test was first used to determine if there were any differences at all between pretreatment groups (a) placebo, b) palonosetron, c) palonosetron with hydroxyzine). Follow-up pairwise comparisons utilized the Wilcoxon signed-rank test with Bonferroni correction for multiple comparisons. Further analysis utilized the Friedman test to compare baseline OOWS and SOWS scores with OOWS and SOWS scores after morphine administration (T=145) and after naloxone administration (T=180). A Friedman test was also used to analyze individual SOWS symptom scores. A Wilcoxon matched-pairs signed rank test was used to test the reliability of the OOWS measures by comparing baseline OOWS scores. Overall, BMI, age, and other factors were not adjusted for in statistical analyses. $P<0.05$ was defined as statistically significant during statistical analysis with GraphPad Prism 6 (La Jolla, CA).

3. Results

There was a significant difference ($p=0.0001$) between average baseline OOWS scores compared to scores 15 minutes post-naloxone (T=180) for all treatment groups. OOWS scores measured 15 minutes after naloxone administration were then analyzed with the same test, and were significant ($p=0.0001$) between pretreatment groups (a) placebo, b) palonosetron, and c) palonosetron with hydroxyzine). Mean post-naloxone OOWS scores (±SEM) were determined for pretreatment groups, and are presented in Figure 1. Table 1 contains median OOWS and SOWS scores (±SEM). Eight of the ten participants developed objective signs of opioid withdrawal after naloxone administration; palonosetron treatment alone reduced the severity of these signs in seven of eight participants. Palonosetron with hydroxyzine treatment reduced objective withdrawal signs in all of the participants (Fig. 2B).

Analysis of baseline scores with the Wilcoxon matched-pairs signed rank test demonstrated reliability, as there was not a significant difference between measures taken at time T=-30 and T=-15 (OOWS, $p>0.9999$; SOWS, $p>0.05$). Comparison of OOWS scores between

baseline and post-morphine administration (T=145) did not show significance either (p=0.7407).

SOWS scores at baseline and after naloxone administration (T=180) were also analyzed using the Friedman test. An analysis of total post-naloxone SOWS score differences between groups did not reach statistical significance (p=0.5189) (Fig. 4). There was not a significant difference between baseline measures of SOWS at T=-30 and T=-15 (p>0.05), demonstrating testing reliability. Comparison of SOWS scores between baseline and post-naloxone administration (T=180) with a Friedman test did not show a significant difference, p=0.2244. Mean post-naloxone SOWS scores (±SEM) were computed for pretreatment groups, and are presented in Figure 3.

There were no adverse or unanticipated events over the course of the study.

4. Discussion

Our results suggest that pretreatment with palonosetron reduces the severity of objective signs, but not self-reported symptoms, of experimentally-induced opioid withdrawal measured using the OOWS and SOWS scales. These signs were reduced most effectively when treatment with palonosetron was co-administered with hydroxyzine. To our knowledge, this is the first clinical trial to investigate a 5-HT3-receptor antagonist and hydroxyzine in combination for the treatment of acute opioid withdrawal after acutely induced opioid physical dependence.

Taken together, these data are consistent with the findings of our pilot study in which healthy volunteers receiving a similar opioid infusion followed by IV naloxone showed reduced signs of withdrawal when the 5-HT3-receptor antagonist ondansetron was pre-administered (5). The efficacy of both ondansetron and palonosetron in this regard suggests that the reduction in opioid withdrawal symptoms is a class effect of 5-HT3 receptor antagonists and not specific to a particular drug in this family. Pre-clinical work also strongly suggests that it is the 5-HT3 receptor itself that constitutes the target for reducing the physiological manifestations of naloxone-precipitated opioid withdrawal (5, 11, 27). While the pre-clinical studies did not find an effect of the study drugs on opioid withdrawal symptoms, one 5-HT3 antagonist, tropisetron, was observed to reduce a naloxone-induced place aversion behavior in rats more akin to some of the experiences assessed by the SOWS scale. That effect, however, is believed to be mediated by an off-target interaction with alpha7 nicotinic receptors (28). Cui et al. found that tropisetron-induced reduction of naloxone-precipitated place aversion in rats given a single dose of morphine could be completely reversed in a dose-dependent fashion with methyllcaconitine (an alpha7 nicotinic receptor antagonist) but was not reversed with dihydroxy-beta-erithroidine (an alpha4-beta2 nicotinic receptor antagonist) (28-30). Notably, the 5-HT3 receptor and the alpha7 nicotinic receptor are both part of the ligand-gated ion channel superfamily and display the greatest similarity within the superfamily with approximately 30% sequence homology (31). The prior studies strongly suggest that the 5HT-3 receptor antagonist, tropisetron, attenuated place aversion through off-target interactions with alpha7 nicotinic receptors and not merely interaction with the 5HT-3 receptor.

Two other α2-adrenergic receptor agonists have shown promise in reducing opioid withdrawal–clonidine and lofexidine (32). Walsh et al. evaluated the modulation effects on opioid withdrawal of clonidine and lofexidine, finding that both drugs reduced the objective sympathomimetic response to naloxone-precipitated withdrawal but with little effect on subjective measures of opioid withdrawal (33). The prior findings are compounded in a 2014 review of several clinical trials by Albertson et al, where in addition, lofexidine was found to be more effective in reducing the symptoms of opioid withdrawal than placebo and reduced the number of days required for detoxification when compared to methadone (32).

These results are somewhat consistent with our present findings on palonosetron for opioid withdrawal symptoms while notably, palonosetron does not have the same hemodynamic shift potential as the alternative therapies discussed previously.

Our results concerning the use of hydroxyzine are further consistent with a previous report by Hauser et al. in which hydroxyzine did not affect overall subjective symptom-oriented SOWS scores but did alleviate a multitude of symptoms associated with opioid withdrawal such as: lacrimation, rhinorrhea, diarrhea, abdominal pain, nausea, vomiting, diaphoresis, anxiety, irritability, muscle spasm, arthralgia, and insomnia (20). To our knowledge, no randomized clinical trials have studied the effects of hydroxyzine in the treatment of opioid withdrawal. In our study hydroxyzine clearly added to the OOWS reducing effects of palonosetron, though the mechanism remains enigmatic. As a first-generation antihistamine, it is possible that the effect of hydroxyzine on opiate withdrawal may be mediated by its activity on other (non-histamine) pathways due to its lack of specificity for histamine receptors. Future studies could address this question by testing the effect of more recently developed antihistamine agents, which have greater histamine receptor selectivity.

It is noteworthy that this is our second study (5) where there was a statistically significant treatment effect on the physiologically observable objective opioid withdrawal score (OOWS) in the absence of a significant effect on the participant rated subjective opioid withdrawal score (SOWS). This may be due to i) mechanistic differences associated with the factors being rated between the objective opioid withdrawal scale (OOWS) and subjective opioid withdrawal scale (SOWS), ii) objective rating between subjects by trained research assistants for OOWS vs. independent participant rating for SOWS compounded with the subjective interpretation of SOWS criteria between participants, and iii) withdrawal criteria being applied to an opioid naive study population in an acute physical dependence model. It is notable that the lack of significant alleviation of subjective opioid withdrawal symptoms may limit the clinical utility of such treatment. We did not include any assessment of global perceived effects of the treatment drug combinations that might have been useful in further characterizing the subjective responses.

There are some important limitations to this study. This study evaluates the efficacy of a 5-HT3 receptor antagonist and non-selective antihistamine to reduce symptoms of opioid withdrawal within the confines of an acute opioid exposure and subsequent naloxone-precipitated opioid withdrawal model. Participants in this study were opioid naïve at the time of the study; they were not dependent on opioids and had no prior history of substance abuse. We cannot say with certainty that these results will be generalizable to a population

with chronic opioid exposure and/or pre-existing physical dependence. If the pretreatment mechanism of palonosetron and/or palonosetron with hydroxyzine functions by blocking the progression of physical dependence and not merely attenuating the symptoms, it logically follows that this treatment would not be effective for those with chronic opioid exposure. Presumably, the majority of patients requiring rapid opioid dose reductions will have sustained periods of opioid exposure prior to withdrawal. Furthermore, palonosetron is currently only available as an IV injection, which may limit the feasibility and accessibility for treatment of opioid withdrawal in the clinical setting.

Overall, our results suggest that 5-HT3-receptor antagonists in combination with hydroxyzine may be useful in attenuating the expression of opioid withdrawal and may further have a role in regulating the development of opioid dependence. This and other combination therapies could be subsequently examined to develop new strategies to address the growing public health problem associated with opioid dependence.

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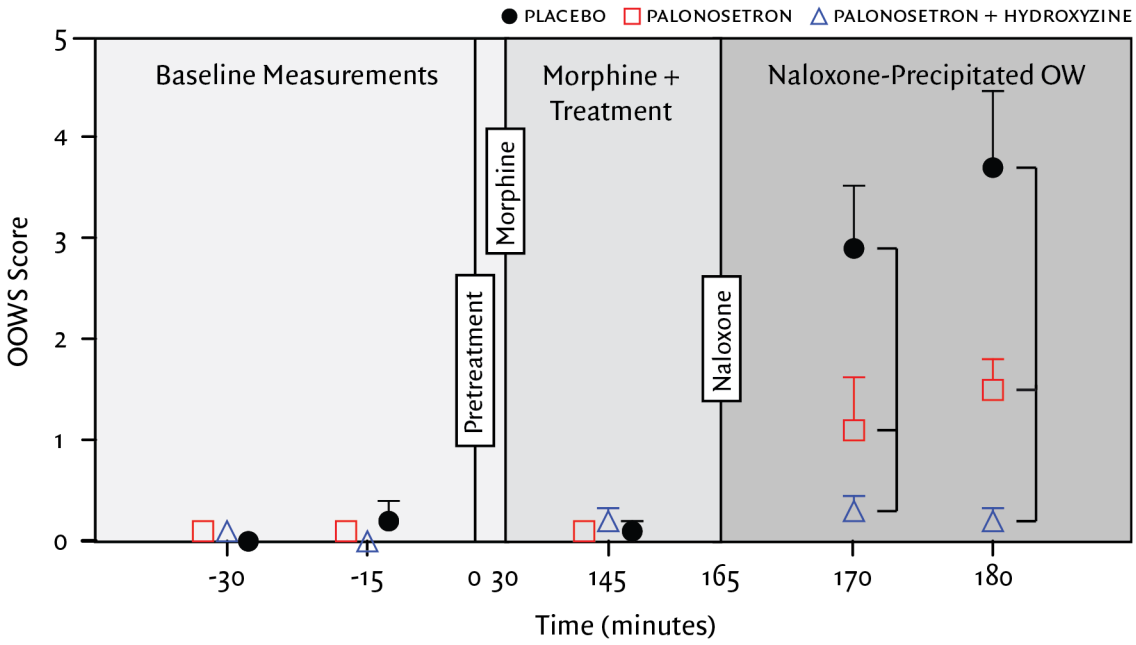

Figure 1.

Objective opioid withdrawal score (OOWS) before and after precipitated opioid withdrawal. Composite participant OOWS scores as mean (standard error bar) are shown for palonosetron with hydroxyzine (combo), palonosetron, and placebo according to study time points.

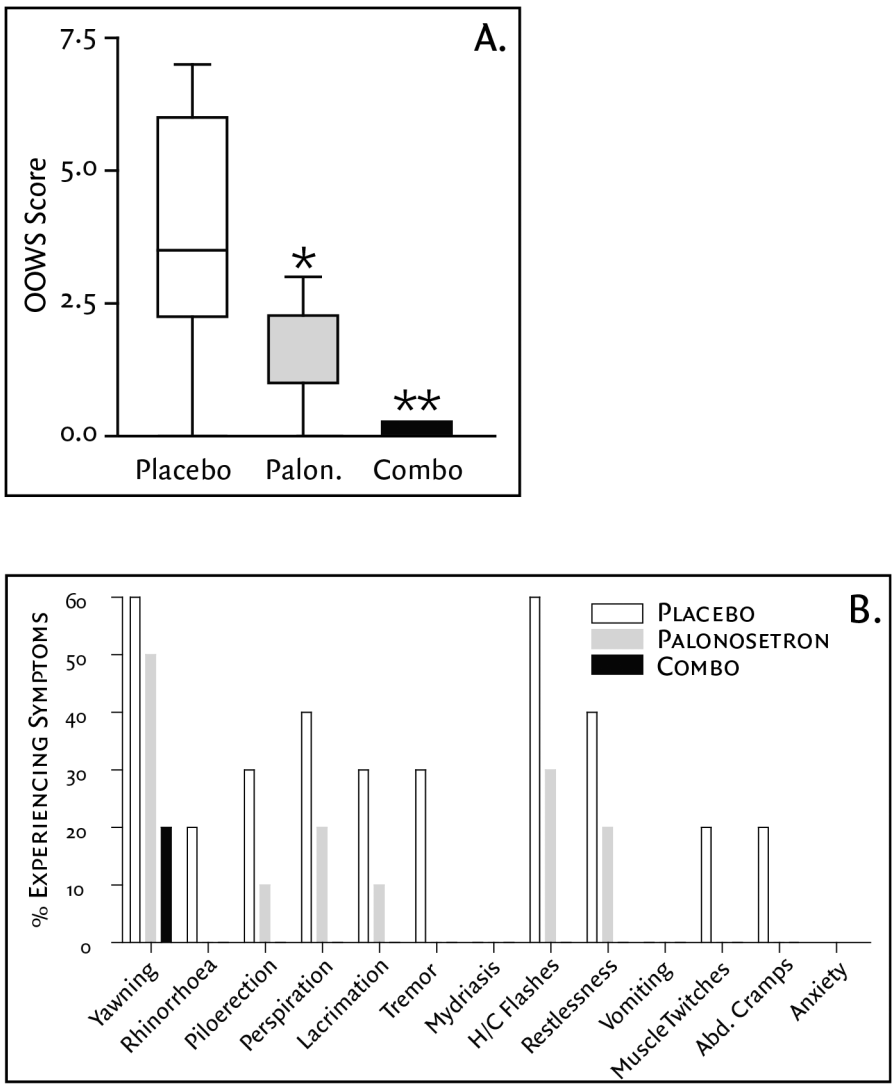

Figure 2.

Objective opioid withdrawal score (OOWS) after precipitated opioid withdrawal. (Fig. 2A) Standard box plot (with mean standard error bars) showing participant response to acutely induced naloxone-precipitated withdrawal after pretreatment with palonosetron with hydroxyzine (combo), palonosetron, and placebo is shown (T=180) (Fig. 2B). Percentage of participants experiencing individual OOWS components. Participant OOWS responses to acutely induced naloxone-precipitated withdrawal after pretreatment with palonosetron with hydroxyzine (combo), palonosetron, and placebo at T=180 are displayed as individual OOWS components. The OOWS scale consists of 13 physical human responses that were objectively observed and recorded by a trained research assistant.

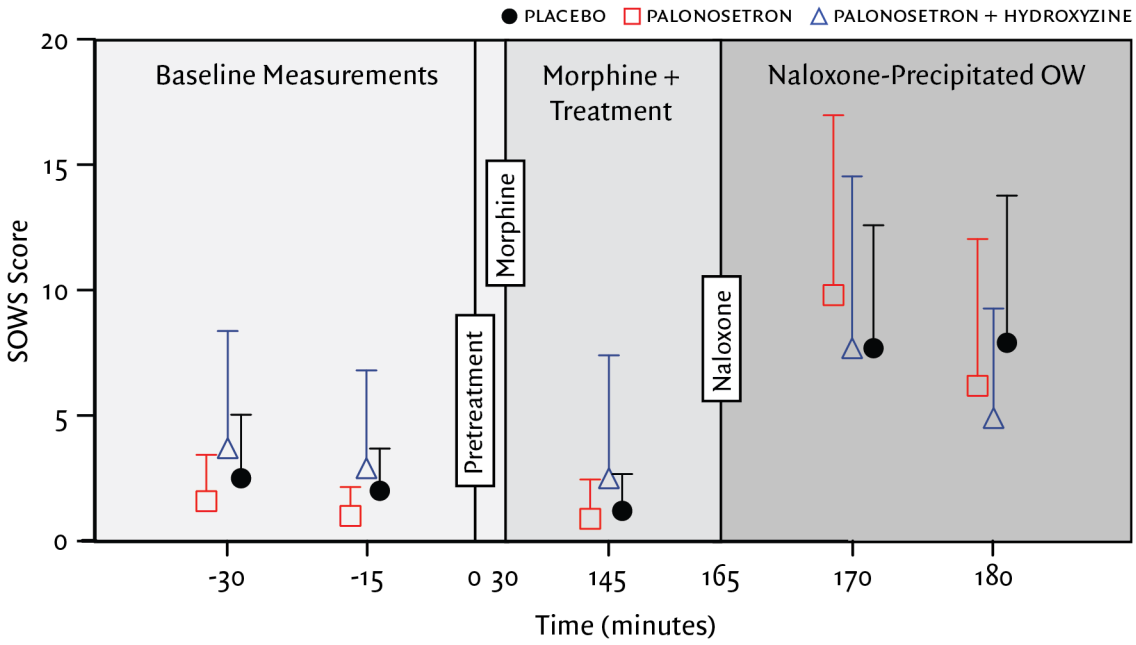

Figure 3.

Subjective opioid withdrawal score (SOWS) before and after precipitated opioid withdrawal. Composite participant SOWS scores as mean (standard error bar) are shown for palonosetron with hydroxyzine (combo), palonosetron, and placebo according to study time points.

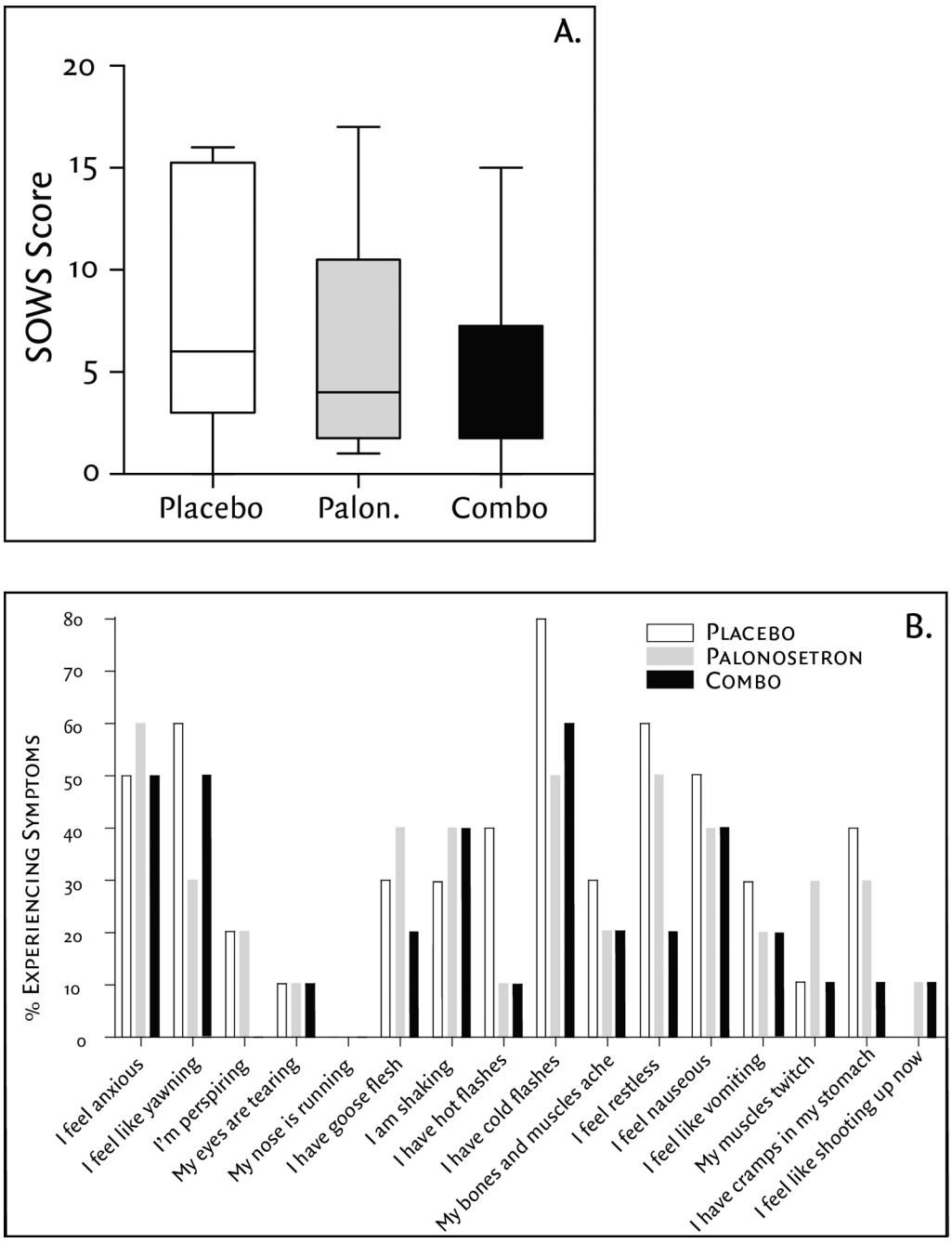

Figure 4.

Subjective opioid withdrawal score (SOWS) after precipitated opioid withdrawal. (Fig. 4A) Standard box plot (with mean standard error bars) showing participant response to acutely induced naloxone-precipitated withdrawal after pretreatment with palonosetron with hydroxyzine (combo), palonosetron, and placebo (T=180). (Fig. 4B) Percentage of participants experiencing individual SOWS components. Participant SOWS responses to acutely induced naloxone-precipitated withdrawal after pretreatment with palonosetron with hydroxyzine (combo), palonosetron, and placebo at T=180 are displayed as individual

SOWS components. The SOWS scale is composed of 16 subjective symptoms that are rated independently by study participants. Symptoms are rated as not at all (0), a little (1), moderately (2), quite a bit (3), and extremely (4).

Table 1

Patient demographics and objective and subjective opioid withdrawal scores (OOWS and SOWS). Demographic data is shown as mean ± SD. Median (and SEM) scores are shown based on pretreatment group (palonosetron and hydroxyzine (combo), palonosetron, or placebo) and timepoint (T = -30, -15, 145, 170, 180).

		All	Placebo	Palonosetron	Combo
Sex (no.)					
	Male	10	-	-	-
Age (yr)		21.5 ± 1.9	-	-	-
Weight (kg)		78.4 ± 11.3	-	-	-
T = -30 (baseline)					
	OOWS		0 (0)	0 (0.1)	0 (0.1)
	SOWS		1.5 (0.81)	1 (0.58)	3 (1.48)
T = -15 (baseline)					
	OOWS		0 (0.2)	0 (0.1)	0 (0)
	SOWS		1.5 (0.54)	1 (0.37)	2 (1.23)
T = 145 (morphine)					
	OOWS		0 (0.1)	0 (0.1)	0 (0.13)
	SOWS		1 (0.47)	0 (0.50)	1 (1.55)
T = 170 (naloxone)					
	OOWS		2.5 (0.62)	0 (0.53)	0 (0.15)
	SOWS		6.5 (1.55)	8 (2.27)	6 (2.17)
T = 180 (naloxone)					
	OOWS		3.5 (0.76)	1 (0.37)	0 (0.13)
	SOWS		6 (1.86)	4 (1.86)	3.5 (1.39)