Desmetramadol Has the Safety and Analgesic Profile of Tramadol Without Its Metabolic Liabilities: Consecutive Randomized, Double-Blind, Placebo-and Active Comparator-Controlled Trials

John A. Zebala*, Shawn L. Searle†, Lynn R. Webster†, Matt S. Johnson‡, Aaron D. Schuler*, Dean Y. Maeda*, Stuart J. Kahn*

*Syntrix Pharmaceuticals, Auburn, Washington,
†PRA Health Sciences, Salt Lake City, Utah,
‡DF/Net Research, Seattle, Washington

Abstract

Desmetramadol is an investigational analgesic consisting of (+) and (−) enantiomers of the tramadol metabolite O-desmethyltramadol (M1). Tramadol is racemic and exerts analgesia by monoaminergic effects of (−)-tramadol and (−)-M1, and by the opioid (+)-M1. Tramadol labeling indicates cytochrome P450 (CYP) isozyme 2D6 ultrarapid metabolizer can produce dangerous (+)-M1 levels, and CYP2D6 poor metabolizers insufficient (+)-M1 for analgesia. We hypothesized that desmetramadol could provide the safety and analgesia of tramadol without its metabolic liabilities. We conducted consecutive double-blind, randomized, placebo-controlled, 3 segment cross-over trials A and B to investigate the steady-state pharmacokinetics and analgesia of 20 mg desmetramadol and 50 mg tramadol in 103 healthy participants without (n = 43) and with (n = 60) cotreatment with the CYP inhibitor paroxetine. In the absence of CYP inhibition (trial A), 20 mg desmetramadol and 50 mg tramadol dosed every 6 hours gave equivalent steady-state (+)-M1, similar adverse events, and analgesia significantly greater than placebo, but equal to each other. In trial B, CYP inhibition significantly depressed tramadol steady-state (+)-M1, reduced its adverse events, and led to insignificant analgesia comparable with placebo. In contrast, CYP inhibition in trial B had no deleterious effect on desmetramadol (+)-M1 or (−)-M1, which gave significant analgesia as in trial A and superior to tramadol (P = .003). Desmetramadol has the safety and efficacy of tramadol without its metabolic liabilities.

Keywords

Desmetramadol; tramadol; poor metabolizer; ultrarapid metabolizer; metabolism
It has been recommended that the morphine milligram equivalent dose in patients receiving opioid therapy be decreased to reduce opioid-related overdose and death.\textsuperscript{15,20,30} There are unfortunately limited pharmacologic options for patients seeking an alternative to schedule II opioids who still require effective analgesia. A critical challenge, therefore, exists to identify analgesic options for those suffering from pain that are safer and decrease the risk of treatment-related death.

Tramadol is approved in the United States for moderate to moderately severe pain and, as a schedule IV analgesic, is less prone to abuse than schedule II opioids, as well as being safer.\textsuperscript{10,86,87} Tramadol is extensively metabolized by CYP enzymes,\textsuperscript{88} and its analgesic activity in humans is thought to be due to a mixed mechanism of 1) norepinephrine reuptake inhibition by the negative enantiomers of tramadol and the O-desmethyltramadol metabolite ((−)-M1), and 2) agonism at the m-opioid receptor by the positive M1 enantiomer (+)-M1 (Fig 1).\textsuperscript{29,58} The (+)-tramadol enantiomer inhibits uptake by the serotonin transporter.\textsuperscript{16,58} It is thought to have a limited role in analgesia,\textsuperscript{1,58,73} but increases the potential for adverse effects and the serotonin syndrome when taken with serotonergic antidepressants that are also CYP2D6 inhibitors.\textsuperscript{53}

Schedule II opioid lethality is caused by a cessation in the drive to breathe mediated by agonism of m-opioid receptors in the brain stem.\textsuperscript{53} Tramadol is safer than schedule II opioids because it does not cause clinically significant respiratory depression at either therapeutic or supratherapeutic doses.\textsuperscript{3,29,34,39,48,66,67,75,76,83} Whereas a lethal oral dose of fentanyl, oxycodone, and hydrocodone in opioid-naïve and nontolerant participants can be 2, 40, and 90 mg, respectively,\textsuperscript{13,57,81} a lethal tramadol dose is >5 g.\textsuperscript{12,62,64} Reports of lethal overdoses owing to tramadol alone are, therefore, rare.\textsuperscript{11,12,62,64,69} It is not understood why tramadol spares respiration. The (+)-M1 metabolite has nearly the in vitro affinity of morphine at the human m-opioid receptor.\textsuperscript{29,58} Tapentadol is the only other marketed analgesic with the same mixed mechanism pharmacology as tramadol, but embodied in a single parent molecule. Tapentadol has no activity at the serotonin reuptake transporter, but has similar functional potency in vitro to the (+)-M1 and (−)-M1 enantiomers at the μ-opioid receptor (median effective concentration of .67 μmol/L vs .86 μmol/L) and norepinephrine transporter (K\textsubscript{i} of .48 μmol/L vs .86 μmol/L), respectively.\textsuperscript{58} However, clinically tapentadol causes similar respiratory depression to oxycodone and other schedule II agents.\textsuperscript{80,82} Metabolism acting as a possible protective saturable ceiling mechanism does not serve as an explanation for tramadol’s safety either, because systemic M1 is dose-proportional throughout the range from therapeutic to lethal, where lethal M1 blood concentrations have been found to exceed therapeutic levels (50–100 ng/mL) by ≤50-fold.\textsuperscript{11,35}

The U.S. Food and Drug Administration (FDA) recently amended the tramadol label to alert prescribers to the metabolic liabilities that can arise from unsafe M1 levels in patients who are CYP2D6 ultrarapid metabolizer,\textsuperscript{35,38,50} the lack of efficacy that can arise in patients who are metabolically deficient owing to either coprescribed inhibitors of CYP2D6 or suboptimal CYP2D6 genetics, and the excess adverse opioid effects that can arise if a coprescribed CYP2D6 inhibitor is discontinued without lowering the tramadol dose.\textsuperscript{35,55,70,71,84} The prevalence of the ultrarapid metabolizer genotype ranges from 4% in Caucasians to 11% in...
Middle Easterners.46 An analysis of >9,000 prescription claims found tramadol and CYP2D6 inhibitors coprescribed 21% of the time.65 In patients not coprescribed a CYP2D6 inhibitor, 5−10% are poor metabolizers and carry no functional CYP2D6 alleles, and another 2−11% are intermediate metabolizers who carry 1 reduced-function and 1 nonfunctional allele.9 Abnormal tramadol metabolism is, therefore, a common occurrence, likely affecting more than one-third of patients. The clinical impact is significant; tramadol was the second most prescribed opioid in the United States, with 41 million prescriptions dispensed in 2017.18,28 Eliminating the metabolic liabilities of tramadol could broadly expand its usefulness as a safer alternative to schedule II opioids.

Desmetramadol (Syntrix Pharmaceuticals, Auburn, Washington) is the racemic M1 tramadol metabolite formulated to orally deliver (+)-M1 and (−)-M1 into the systemic circulation with kinetics that replicate ideal tramadol metabolism but without requiring CYP enzymes.93 We hypothesized that desmetramadol could provide the safety and analgesic profile of tramadol without its metabolic liabilities. It was unknown if desmetramadol could provide this profile in metabolically unselected participants (ie, participants having any possible CYP2D6 genotype) and in metabolically deficient participants. The objectives of this first-in-man study were, therefore, to demonstrate that i) desmetramadol and tramadol doses giving equal plasma M1 yield equal analgesia in metabolically unselected participants, but that ii) the same doses in participants made metabolically deficient by the CYP enzyme inhibitor paroxetine yield greater plasma M1 and greater analgesia for desmetramadol than for tramadol. Paroxetine is a strong Zebala et al inhibitor of CYP2D6 and CYP2B6.33,79 The present study, is to our knowledge, the first human assessment of desmetramadol and the first to report its steady-state pharmacokinetics, efficacy, and safety versus placebo and versus tramadol in metabolically unselected and deficient populations.

Methods

Study Design

The study design consisted of 2 consecutive randomized, double-blind, 3-period cross-over, placebo-and active comparator-controlled, single-center trials A and B performed between August 2014 and October 2014 and between October 2017 and December 2017 and conducted in a clinical research unit in Salt Lake City, Utah (ClinicalTrials.gov Identifiers: and ). The study was approved by an independent ethics committee and was conducted in accordance with the Declaration of Helsinki and other applicable guidelines, laws, and regulations. Written informed consent was obtained from all participants.

After screening, participants in both trials A and B were randomized to 1 of 6 possible treatment sequences of placebo, 50 mg tramadol (Ultram; Janssen Ortho, LLC, Gurabo, Puerto Rico) and 20 mg desmetramadol (Syntrix Pharmaceuticals; Fig 2). Nine doses of each study drug were given every 6 hours in each of the 3 treatment segments, with segments separated by 1 week in trial A and 2 weeks in trial B. Participants stayed at the clinical research unit during the entirety of each treatment segment and were discharged during the time between segments and at the end of the third segment. For 1 hour before and 1 hour after doses 8 and 9, the participant’s diet (oral intake) was limited to clear liquids only. Participants in trial B also received 3 consecutive 20 mg daily doses of paroxetine
beginning 1 day before each treatment segment. Paroxetine levels were quantified by sampling blood immediately before the ninth dose of study drug in each treatment segment (Quest Diagnostics, West Valley City, Utah). Blood was collected to test the CYP2D6 genotype after the ninth dose of study drug of the first segment in trial A and at screening in trial B. The end of the study in both trials consisted of a telephone follow-up 1 week after the end of the third segment.

Randomization to the 6 treatment sequences was in a ratio of 1:1:1:1:1:1 using a computer-generated random list of permuted blocks of 6. Blinding of study drug was by overencapsulation.

Measurements were made to quantify steady-state plasma M1 and tramadol enantiomers by sampling blood immediately before and after the ninth dose of study drug. Cold-induced pain was measured in the cold pressor test after the ninth dose of study drug. Pupil diameter and abuse liability measures were assessed after the seventh dose of study drug in trial A. Adverse events (AEs) and vital signs were collected throughout each trial.

**End Points and Formal Study Hypothesis**

**Trial A**—The primary end point consisted of the steady-state minimum (C_{ss_{min}}) and maximum (C_{ss_{max}}) plasma concentrations of (+)-tramadol, (−)-tramadol, (+)-M1, and (−)-M1. Secondary end points consisted of cold-induced pain, safety, abuse liability, pupil diameter, and CYP2D6 genotype.

**Trial B**—The primary end point consisted of cold-induced pain perception or tolerance. Secondary end points consisted of C_{ss_{min}} and C_{ss_{max}}, and safety.

The formal study hypothesis was that bioequivalent and equianalgesic doses of tramadol and desmetramadol in trial A will produce significantly greater plasma (+)-M1 and superior analgesia for desmetramadol compared with tramadol in trial B, where participants are metabolically deficient.

**Participants**

Eligible participants were aged 18 to 55 years, of general good health, had a tolerance to cold-induced pain of ≥20 seconds and ≤120 seconds, and in trial B had a CYP2D6 genotype consistent with an intermediate metabolizer phenotype or normal metabolizer phenotype. Each participant’s CYP2D6 genotype was determined using a multiplex PCR and allele-specific primer extension assay (xTAG Mutation Detection, Luminex Molecular Diagnostics, Austin, Texas) that identifies 17 variants (*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *41, and gene duplication) and 2 gene rearrangements (Genelex, Inc., Seattle, Washington). The assay covers >93–97% of poor metabolizer phenotypes and has an analytical specificity and sensitivity for detection of these mutations of >99%. Trial A conserved statistical power to detect tramadol and desmetramadol analgesia by enrolling only males because females exhibit large variation and temporal instability to repeated cold-induced pain. Further criteria for key inclusion and exclusion criteria are presented in Table 1.
Designation of CYP2D6 Phenotype

Each participant’s CYP2D6 genotype was reported using the star (*) allele nomenclature and used to predict metabolizer phenotype. Each star (*) allele or haplotype is defined by the presence of a specific combination of single-nucleotide polymorphisms and/or other sequence alterations within the CYP2D6 gene locus. The *1 allele is defined as wild type (see www.pharmvar.org for other alleles). Each CYP2D6 genotype is reported as a diplotype, which includes 1 maternal and 1 paternal allele (e.g., *1/*4). Participants with >2 copies of the CYP2D6 gene are denoted by an “xN” after the allele designation; for example, a *2 × 2 haplotype is a duplication of the *2 allele. Each CYP2D6 allele designation was translated into an activity score, that is, 0 for nonfunctional (e.g., *3, *4, or *5), .5 for reduced function (e.g., *9, *10, or *17), or 1.0 for fully functional (e.g., *1, *2, or *27). The sum of the activity scores for each allele in the diplotype determines the participant’s overall CYP2D6 activity score; for example, a *1/*1 genotype has an activity score of 2.0, a *3/*9 genotype has an activity score of .5, and a *3/*5 genotype has an activity score of .0 (www.pharmgkb.org/vip/PA166170264). Participants with an activity score of 0 were designated poor metabolizers (individuals carrying no functional alleles), those with a score of .5 or 1.0 were designated intermediate metabolizers, those with a score of 1.5 or 2.0 were designated normal metabolizers (individuals carrying 2 alleles with full function or 1 full function and 1 reduced function allele), and those participants with a score of >2.0 were designated as ultrarapid metabolizers (individuals carrying >2 copies of functional alleles).

Assessments

Steady-State Pharmacokinetics—The Css_{min} and Css_{max} of (+)-tramadol, (−)-tramadol, (+)-M1, and (−)-M1 were measured by collecting blood immediately before the ninth study drug dose and at 1.0, 1.5, 2.0, 2.5, and 4.0 hours afterward. An additional sample was taken at 8.0 hours in trial B to measure the half-life (t_{1/2}). The tramadol and M1 enantiomers were quantified using a chiral liquid chromatography mass spectroscopy method using a Lux Cellulose-2 (Phenomenex, California) chromatographic column and positive atmospheric pressure chemical ionization mode while operating the instrument in the multiple reaction monitoring mode. The assay was validated in accordance with FDA guidance. The lower limit of quantification for each enantiomer was 5.0 ng/mL. The calibration range was 5−1,000 ng/mL for each enantiomer. Assay accuracy for (+)-M1 was 99.3−103% and the precision (relative standard deviation [SD]) was 8.8−3.6%. Assays were conducted in the bioanalytical laboratories of IITRI Life Sciences Group (Chicago, Illinois).

Pupillometry—Pupillary contraction measured by pupillometry is a pharmacodynamic marker of target engagement by opioids including tramadol. Pupil diameter was measured with a NeurOptic VIP 200 pupillometer (Laguna Hills, California) before the first dose and after the seventh dose of each treatment segment. Pupillometry was not performed in trial B because paroxetine causes pupil dilation that confounds the contractionary effect of opioids.

Abuse Liability—Opioids induce positive responses in subjective measures of abuse in healthy participants who are not abusing drugs. Abuse liability assessments
were performed in trial A after the seventh dose that consisted of a 100-mm visual analog scale (VAS) for each of drug liking–disliking, take drug again, and strength of drug effect measures.

**Analgesia**—The cold pressor test is an established test model for evaluating opioid induced analgesia including tramadol. Pain intensity (0–10 VAS) at 30 seconds and at first perception, and time (seconds) to hand withdrawal and first pain were determined at 1, 2, and 3 hours after the ninth dose of each study drug and averaged.

**Safety and Tolerability**—Assessments of the safety and tolerability of desmetramadol and tramadol included 1) AEs and serious AEs, 2) vital signs, 3) laboratory analyses, and 4) study drug discontinuation. AEs were allocated to a study drug if they occurred after its first dose and before either the first dose of the next study drug or the end of the study. The AE relationship to blinded study drug was assessed by the investigator as either not related, unlikely related, possibly related, probably related, or definitely related. An AE was drug-related if it was designated as possibly, probably, or definitely related. The severity of AEs were graded on an FDA-specified scale for healthy adult and adolescent volunteers. Vital signs included systolic and diastolic arterial blood pressures, pulse, and respiratory rate. Vital signs were obtained at screening baseline and before and after each study drug administration in trial A. In trial B, baseline vital signs were obtained once for each segment before paroxetine administration and then once after each paroxetine and study drug administration. Vital signs were obtained in trials A and B at the end of each treatment segment and before discharge.

**Statistical and Computational Methods**

The reported peak mean pain perception to cold before and after a single 50 mg dose of tramadol was used to power the first-in-man trial A (mean [SD] pain intensity before and after tramadol of 6.3 [2.0] and 5.0 [2.3] cm on a VAS, respectively). To provide ≥80% power in trial A to detect a −1.3-cm change in pain perception between desmetramadol and placebo, a sample size of 39 participants was planned. To provide ≥97% power in trial B to detect a −.5-cm change in pain perception between desmetramadol and tramadol at 30 seconds, a sample size of 60 participants was planned, as informed by trial A data. Formal statistical analysis plans were developed before unblinding trials A and B. All descriptive and inferential statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina) or R version 3.0 (The R Foundation, Vienna, Austria). Continuous end points were analyzed using mixed-effects linear models. The appropriate covariance structure was selected using graphical tools and information criteria. In trial B, the overall analgesic analysis used a backward selection approach to determine the significant effects with treatment, segment, sequence, and gender as fixed effects and participant as a random effect nested within sequence. Segment was added as a fixed effect to find any significant first-order crossover effects. Otherwise, analyses used mixed effects linear models with treatment, segment, and sequence as fixed effects and participant as a random effect nested within sequence. Segment was again added as a fixed effect to find any significant first-order crossover effects. If significant treatment effects were present, least-squares means were compared between desmetramadol and placebo, or tramadol and placebo, using Dunnett’s
procedure, and between desmetramadol and tramadol using a paired t-test. In addition to overall analyses, separate analyses for measures of analgesia were performed for males and females. The \( \text{Css}_{\text{min}} \) was specified as the smallest and the \( \text{Css}_{\text{max}} \) as the largest value for each analyte in a segment. Bioequivalence was computed using the log-transformed \( \text{Css}_{\text{min}} \) and \( \text{Css}_{\text{max}} \) values for each enantiomer and claimed when the 90% confidence interval (CI) of their ratio was 0.8 to 1.25.\(^\text{22,59}\) The \( t_{1/2} \) in trial B was computed using the elimination rate constant (\( k_e \)) and analyte concentrations \( C_4 \) and \( C_8 \) at hour 4 (\( t_4 \)) and hour 8 (\( t_8 \)), respectively, where \( k_e = (\ln C_4 - \ln C_8)/(t_8 - t_4) \) and \( t_{1/2} = 0.693/k_e \).

Missing data were confirmed to be missing completely at random and excluded without imputation. The hypothesized superior analgesia of desmetramadol to tramadol in trial B was tested using a 1-sided test at the 5% significance level. All other statistical comparisons were made using 2-sided tests at the 5% significance level and all CIs for bioequivalence were calculated with a 2-sided 90% confidence level.

The intention-to-treat (ITT) population included all participants who were randomized to treatment, and was stipulated to be the primary dataset for analysis and statistical conclusions of significance. The per-protocol population was composed of a subset of participants from the ITT population who completed the study with no major protocol deviations. A major protocol deviation was one that could adversely affect the rights, safety, or well-being of the participants and/or the quality and integrity of data. Protocol deviations were assigned as being major or minor before unblinding. The efficacy population in trial B constituted participants who received all drug doses and had cold pressor efficacy data from all 3 segments. A sensitivity analysis was performed by conducting the analyses for the ITT, per-protocol, and efficacy populations as defined. All results presented are for the ITT population; unless otherwise specified, results from the per-protocol and efficacy population analyses supported those for the ITT population. The safety population included all patients who received study drug. All safety analyses were performed on the safety population.

**Results**

**Participant Disposition and Demographics**

Of the 300 participants screened, 103 participants were randomized in consecutive trials A and B at 1 clinical research unit in the United States (Fig 3). All participants who were randomized (the ITT population) received treatment with study drug and 96 participants (93%) completed the study. A total of 7 of the 103 participants discontinued from the study after treatment was initiated. In the trial A cohort, 4 participants discontinued; 1 discontinued owing to AEs (grade 1 nausea, vomiting, and dizziness after 4 doses of desmetramadol in segment 1; no blood samples were collected and the participant did not advance to the remaining segments with placebo and tramadol) and 3 were lost to follow-up. In the trial B cohort, 1 participant was withdrawn because of a major protocol violation involving a urine test positive for a substance of abuse (cocaine) and 2 participants were lost to follow-up. Participants received 1,111 doses (96%) of 1,161 possible study drug doses in trial A, and received 1,575 doses (97%) of 1,620 possible study drug doses in trial B. Participants with missing study drug doses were evenly distributed across placebo (A, B = 2, 2), desmetramadol (A, B = 1, 1), and tramadol (A, B = 3, 2). All participants in trial B
received all planned paroxetine doses while on study, or 525 of 540 (97%) possible doses. Most participants were Caucasian (92%) and baseline demographic characteristics such as age and body mass index were similar in both trial A and B cohorts (Table 2). Normal and intermediate CYP2D6 metabolizers constituted 96% and 100% of the trial A and B cohorts, respectively (for individual CYP2D6 genotypes, see Supplementary Table 1).

**Steady-State Pharmacokinetics**

In the absence of paroxetine (trial A), 20 mg desmetramadol dosed every 6 hours replicated the mean steady-state plasma profile of (+)-M1 produced by 50 mg tramadol dosed at the same frequency (Fig 4A). The desmetramadol and tramadol mean C\textsubscript{SS\textsubscript{min}} and C\textsubscript{SS\textsubscript{max}} for (+)-M1 were statistically bioequivalent (mean [SD] = 28 [7] ng/mL vs 26 [6] ng/mL and 37 [10] ng/mL vs 36 [10] ng/mL; 90% CIs, .85–1.08 and .88 –1.13, respectively; Table 3). The C\textsubscript{SS\textsubscript{min}} and C\textsubscript{SS\textsubscript{max}} for (−)-M1 were 30% lower for desmetramadol compared with tramadol and just outside statistical bioequivalence (mean [SD] = 30 [6] ng/mL vs 21 [5] ng/mL and 42 [9] ng/mL vs 30 [9] ng/mL; 90% CIs, .69–.76 and .67 –.76, respectively; Fig 4B and Table 3). Desmetramadol produced no circulating tramadol enantiomers, as expected (Fig 4C and 4D).

Paroxetine given in 3 daily 20-mg doses in trial B produced a similar level of circulating paroxetine in tramadol and desmetramadol dosed segments (mean [SD] = 11 [8] ng/mL vs 12 [9] ng/mL, respectively; Table 3). Compared with trial A, paroxetine in trial B depressed tramadol (+)-M1 C\textsubscript{SS\textsubscript{min}} (−61%) and C\textsubscript{SS\textsubscript{max}} (−62%), but increased desmetramadol (+)-M1 C\textsubscript{SS\textsubscript{min}} (46%) and C\textsubscript{SS\textsubscript{max}} (41%; Fig 4E vs Fig 4A and Table 3). The paroxetine-induced changes in trial B caused desmetramadol C\textsubscript{SS\textsubscript{min}} and C\textsubscript{SS\textsubscript{max}} for (+)-M1 to each significantly exceed by 3.5-fold the corresponding tramadol C\textsubscript{SS\textsubscript{min}} and C\textsubscript{SS\textsubscript{max}} (mean [SD] = 38 [9] ng/mL vs 11 [6] a ng/mL and 51 [11] ng/mL vs 14 [8] ng/mL, respectively; P < .001; Table 3). The (+)-M1 t\textsubscript{1/2} after tramadol dosing was double the t\textsubscript{1/2} after desmetramadol dosing (mean [SD] = 18 [39] hours vs 8 [6] hours; P = .065).

Paroxetine resulted in comparatively smaller changes for (−)-M1 (Fig 4F vs Fig 4B). Compared with trial A, the (−)-M1 C\textsubscript{SS\textsubscript{min}} and C\textsubscript{SS\textsubscript{max}} were decreased 17% for tramadol and increased 14–16% for desmetramadol in the presence of paroxetine (Table 3). The paroxetine-induced changes in trial B had the net effect of making desmetramadol and tramadol C\textsubscript{SS\textsubscript{min}} and C\textsubscript{SS\textsubscript{max}} for (−)-M1 statistically bioequivalent (mean [SD] = 25 [7] ng/mL vs 25 [8] ng/mL and 35 [10] vs 35 [10] ng/mL; 90% CIs, .95–1.09 and .93–1.07; Table 3). Like the positive enantiomer, the t\textsubscript{1/2} of (−)-M1 in trial B was greater for tramadol compared with desmetramadol (mean [SD] = 12 [8] hours vs 7 [5] hours; P < .001).

As in trial A, desmetramadol produced no circulating tramadol enantiomers in trial B (Fig 4G and 4H). However, compared with trial A, the mean steady-state (+)-tramadol and (−)-tramadol plasma concentration profiles after tramadol dosing were increased 2-fold in the presence of paroxetine, as were the C\textsubscript{SS\textsubscript{min}} and C\textsubscript{SS\textsubscript{max}} (Fig 4G vs Fig 4C and Fig 4H vs Fig 4D; Table 3).

The C\textsubscript{SS\textsubscript{min}}, C\textsubscript{SS\textsubscript{max}} and t\textsubscript{1/2} had no statistically significant sequence or segment effects in either trial A or trial B. There was no carryover from segment to segment in either trial A or
trial B, as evidenced by no detectable M1 or tramadol enantiomers in placebo-treated segments, and no detectable tramadol enantiomers in desmetramadol treated segments.

Compared with mean tramadol (+)-M1 in the poor metabolizer and ultrarapid metabolizer of trial A, the mean desmetramadol (+)-M1 was increased 650% (41 ng/mL vs 6.3 ng/mL) and decreased 40% (22 ng/mL vs 36 ng/mL), respectively (Supplementary Fig 1).

### Pupillometry and Abuse Measures

The mean predose pupil diameter in trial A was similar in the placebo, tramadol, and desmetramadol dosed segments (mean [SD] = 6.1 [.9], 6.1 [.9], and 6.0 [1.1] mm, respectively; Table 4). After dosing, tramadol and desmetramadol each caused a significant decrease in pupil diameter compared with placebo (mean paired reduction [SD] = −.7 (.6) and −1.1 (.8) mm; each < .0001).

Tramadol and desmetramadol dosing did not cause mean responses in the drug liking −disliking and take drug again VASs to differentiate from placebo (Table 4). There was a significant treatment effect (P < .0001) in the strength of drug effect VAS and mean responses after tramadol and desmetramadol dosing were significantly elevated compared with placebo (mean [SD] = 32 [29] mm vs 12 [8] mm and 29 [28] mm vs 12 [8] mm; P < .001 and P = .0004, respectively). There were also significant segment (P = .004) and sequence (P = .034) effects in the strength of drug effect VAS (Supplementary Table 2).

### Analgesia

In the male population of trial A (n = 43), there was a similar and statistically significant decrease in average cold-induced pain perception at 30 seconds in participants treated with tramadol and desmetramadol compared with placebo (mean and standard error [SE] = −.46 [.19] and −.60 [.15]; P = .022 and P = .0005, respectively; Fig 5). There was no significant difference between tramadol and desmetramadol in trial A (P = .47). In the male population of trial B (n = 42) treated identically as trial A, except for the inclusion of paroxetine, tramadol failed to statistically differentiate from placebo (P = .90). In contrast, desmetramadol provided pain relief that was statistically superior to both placebo (P = .036) and tramadol (P = .003). The average change in paired pain scores between desmetramadol and placebo, and between desmetramadol and tramadol were similar (mean [SE] = −.75 [.28] and −.62 [.20], respectively; Fig 5). There was no significant treatment effect in the intensity of pain at first perception by participants in either trial A or trial B (Supplementary Table 3).

The average duration of tolerance to pain in trial A was similar for desmetramadol (63 seconds) and tramadol (62 seconds), and each was significantly greater than placebo (mean paired increase relative to placebo [SE] = 12.6 [3.8] and 12.4 [4.4] seconds; P = .006 and P = .0076, respectively; Supplementary Table 3). In the presence of paroxetine, male participants in trial B tolerated pain 44% longer after desmetramadol than after tramadol (mean paired increase relative to placebo [SE] = 9.9 [1.9] seconds vs 6.9 [1.6] seconds; P < .001 and P = .001, respectively). In both trials, the average time to the first perception of pain was similar for tramadol and desmetramadol, and each was significantly greater than placebo.
There was no significant treatment effect in the trial B female population (see Discussion and Supplementary Table 3). There was no significant sequence or segment effect in any pain measure in either trial A or trial B. Results from the sensitivity analyses were consistent with the primary analgesic analyses.

Safety and Tolerability

AEs—One participant in trial A discontinued owing to AEs after administration of desmetramadol in the first segment. No participants discontinued from trial B owing to AEs.

After dosing with tramadol and desmetramadol in trial A, participants reported a similar qualitative and quantitative profile of drug-related AEs (Table 5). AEs were reported in 49% and 44% of participants after tramadol and desmetramadol, respectively, compared with 24% of participants after placebo. The 5 most common drug-related AEs after desmetramadol and tramadol in trial A were nausea, dizziness, headache, somnolence, and pruritus. The severity of drug-related AEs in trial A were all grade 1 except for a single participant who reported grade 2 headache and dizziness after tramadol.

Drug-related AEs were reported in 27%, 50%, and 67% of participants in trial B after placebo, tramadol and desmetramadol, respectively (Table 5). Compared with the desmetramadol AE profile in trial B, the tramadol AE profile in the same participants featured less nausea (−50%), somnolence (−60%), headache (−40%), vomiting (−78%), presyncope (−83%), and pruritus (−75%). The tramadol AE profile resembled placebo except for an increased incidence of dizziness (8-fold placebo) and muscle spasticity (absent from placebo). The incidence of muscle spasticity after tramadol was the same as after desmetramadol. Female participants in trial B made up 30% of the safety population and 43% of the specified AEs. Drug-related AE severity in trial B was all grade 1 except for 5 participants who had grade 2 drug-related AEs after placebo (somnolence), tramadol (asthenia), and desmetramadol (nausea/vomiting, feeling hot, hypotension).

Less common drug-related AEs reported by participants in trial A and trial B are provided in Supplementary Table 4. No deaths or serious AEs were reported in either trial A or trial B.

Respiration and Other Vital Signs—Respiration was assessed 1,744 times in trial A and 2,510 times in trial B. In trial A, respiratory rate was assessed before and after each of the 9 study drug doses in each of the 3 treatment segments (Fig 6). Desmetramadol and tramadol had no discernable predose versus postdose effect on respiratory rate compared with placebo, or compared with each other. Compared with baseline screening assessments in trial A, there was no effect of placebo, tramadol, or desmetramadol on the systolic or diastolic blood pressure, pulse, or respiration at the end of each treatment segment (Supplementary Table 5). Paired comparisons of respiration were made between tramadol and placebo, desmetramadol and placebo, and desmetramadol and tramadol with respect to the average postdose respiration. Average respiration after tramadol and desmetramadol were minimally reduced compared with placebo, and this decrease was statistically significant in the presence of paroxetine, but not in its absence (trial B mean paired difference [SD] = −.34 [.99] and −.30 [.90] breaths per minute; \( P = .004 \) and \( P = .012 \), respectively; Table 6). In addition to a significant treatment effect (\( P = .004 \)), there was a
significant segment effect ($P < .001$). There was no significant difference in respiration between desmetramadol and tramadol.

### Discussion

#### Key Findings and Clinical Significance

Desmetramadol provided superior analgesia to tramadol in metabolically deficient participants, the same group in which tramadol efficacy was lost. Desmetramadol provided the same qualitative and quantitative safety profile as tramadol in metabolically unselected participants and the same as described in the FDA-approved tramadol label.\(^{35}\)

Desmetramadol thus obviates the metabolic liabilities of tramadol while preserving its safety profile, because it does not rely on the activity of CYP enzymes for its activity. This property of desmetramadol is significant because tramadol is widely used globally with 41 million prescriptions dispensed in 2017 in the United States alone,\(^{18,28}\) and an estimated one-third or more of patients treated with tramadol fail to metabolize it to its active metabolite with optimal kinetics.\(^9,35,46,50,56,65\)

The metabolic liabilities of tramadol could explain the misalignment between U.S. prescriber perceptions in the United States of modest efficacy and its approved indication for treating moderate to moderately severe pain.\(^{35,87}\)

#### Pharmacologic Underpinnings

Tramadol is racemic, and the negative and positive enantiomers are metabolized in vivo to (−)-M1 and (+)-M1, respectively.\(^{29,58}\)

The in vitro $\mu$-opioid receptor binding affinity ($K_i$) is dominated by (+)-M1 (.0034 $\mu$mol/L), compared with substantially weaker affinities for (−)-tramadol (25 $\mu$mol/L), (+)-tramadol (1.3 $\mu$mol/L), and (−)-M1 (.24 $\mu$mol/L). The in vitro inhibition ($K_i$) of serotonin uptake is dominated by (+)-tramadol (.5 $\mu$mol/L), whereas the inhibition of norepinephrine uptake is mediated by the similarly potent (−)-tramadol (.5–1.6 $\mu$mol/L) and (−)-M1 (.9–1.4 $\mu$mol/L).\(^{16,58}\)

The analgesia of tramadol is thought to arise from a combination of $\mu$-opioid receptor binding and inhibition of norepinephrine uptake in the descending pain inhibitory system.\(^{58}\) Serotonin is a transmitter in descending inhibitory and excitatory projections and causes antinociceptive and pronociceptive effects, respectively, leading some investigators to question its role in mediating tramadol analgesia.\(^{1,58,73}\)

The role played by the enantiomers of tramadol and M1 in human analgesia has been the subject of investigation. Controlled trials in metabolically deficient patients demonstrated that M1 is necessary for analgesia in both experimental and surgical pain.\(^{43,55,70,71,84}\)

Other trials used opioid and $\alpha_2$-adrenoceptor antagonists to demonstrate that human tramadol analgesia is mediated by both opioid receptor agonism and monoaminergic modulation.\(^{14}\)

The specific contribution of the tramadol enantiomers to human tramadol analgesia has not been investigated. To our knowledge, this is the first human study to ask whether the tramadol parent enantiomers can be discarded and tramadol analgesia replicated by (−)-M1 and (+)-M1 alone; that is, whether M1 is not only necessary, but sufficient, to replicate tramadol analgesia in both metabolically unselected and deficient participants.
A distinguishing feature of this study from single-dose trial designs was that participants were on the study drug for >2 days (54 hours, 9 doses). This duration allowed systemic concentrations, including central nervous system concentrations, to equilibrate before key assessments were made. It also allowed for the collection of safety information that more faithfully reflects actual clinical use.

In trial A, 50 mg tramadol and 20 mg desmetramadol dosed every 6 hours gave systemic (+)-M1 levels that were bioequivalent and (−)-M1 levels there were nearly bioequivalent. In the absence of circulating tramadol enantiomers, desmetramadol produced similar responses as tramadol with respect to analgesia, pupil constriction, abuse measures, AE profile, and vital signs. If tramadol enantiomers contributed to analgesia, participants should have experienced greater analgesia after tramadol, but they did not. Serotonergic agents have been reported to cause mydriasis,\textsuperscript{49} and both pronociceptive and antinociceptive effects.\textsuperscript{1,58,73}

Compared with desmetramadol, tramadol exhibited relative pupil dilation (−.4 mm; post hoc $P = .0017$) and muted analgesia, possibly suggestive of the serotonergic effects of (+)-tramadol. The most straightforward interpretation of these findings is that circulating M1 enantiomers as provided by desmetramadol are not only necessary, but are also sufficient to replicate the therapeutic pharmacology of tramadol. In this interpretation, tramadol provides superfluous enantiomers with (+)-tramadol contributing unwanted metabolic liabilities related to the under or over production of the (+)-M1 opioid, and unwanted serotonergic activity that may negatively influence analgesia and potentially contribute to the risk of seizure and serotonin syndrome (discussed elsewhere in this article).

The doses of tramadol and desmetramadol in trial A were advanced into trial B, where participants were made metabolically deficient by coadministration of paroxetine, a strong inhibitor of CYP2D6 and CYP2B6.\textsuperscript{33,79} Studies in human liver microsomes indicate that tramadol is metabolized to M1 by CYP2D6 and to N-desmethyltramadol by CYP2B6 and CYP3A4; M1 is metabolized to O,N-didesmethyltramadol (M5) by CYP2B6 and CYP3A4 (Fig 7).\textsuperscript{72,88} Although racemic M5 does bind to the $\mu$-opioid receptor with substantial affinity in vitro ($K_i = .10 \mu$mol/L), it is highly polar and neither crosses the blood–brain barrier nor contributes to analgesia or centrally mediated AEs in vivo.\textsuperscript{29} Metabolism of tramadol to M1 by CYP2D6 favors the positive enantiomer.\textsuperscript{55} Consistent with these transformations, the presence of paroxetine in trial B depressed tramadol plasma (+)-M1 by approximately 60% and increased desmetramadol plasma (+)-M1 by approximately 40%. The effect of paroxetine on (−)-M1 levels was less pronounced, with tramadol plasma (−)-M1 decreased and desmetramadol plasma (−)-M1 increased by approximately the same amount. The net paroxetine effect in trial B caused tramadol and desmetramadol (−)-M1 to assume bioequivalent levels, and for tramadol (+)-M1 to be depressed to less than one-third of the desmetramadol (+)-M1 level. Consistent with a paroxetine block on tramadol metabolism by CYP2D6 and CYP2B6, (−)-tramadol and (+)-tramadol levels in trial B increased to 200% of their levels in trial A in the absence of paroxetine. Despite the elevated levels of tramadol enantiomers and bioequivalent (−)-M1, the depression of (+)-M1 in trial B was sufficient to cause the analgesic activity of tramadol to collapse to that of placebo. This finding is consistent with prior studies that demonstrated that M1 is necessary for tramadol
analgesia in both experimental and surgical pain.\textsuperscript{43,55,70,71,84} The finding underscores the actual role tramadol enantiomers play in mediating analgesia, because even elevated levels could not compensate for the loss of (+)-M1. In contrast, desmetramadol had no corresponding metabolic liability; in metabolically deficient participants of trial B, it produced therapeutic levels of both M1 enantiomers and analgesia as effective as in the metabolically unselected participants of trial A. Desmetramadol also normalized the abnormal levels of tramadol M1 seen in genetic poor metabolizers and ultrarapid metabolizers. As seen in trial A, desmetramadol returned M1 to therapeutic levels in a poor metabolizer and reduced M1 exposure in an ultrarapid metabolizer. Mechanistically, because desmetramadol does not depend on CYP2D6 for its plasma level, it obviates the metabolic liabilities of tramadol, regardless of whether the metabolic defect is due to inhibition of CYP2D6 (eg, by paroxetine in trial B) or CYP2D6 genetics.

The lack of statistically significant analgesia in the trial B female population dosed with either tramadol or desmetramadol was expected a priori, because normally menstruating women exhibit a variable and increasing cold-induced pain tolerance and threshold over repeated stimulation.\textsuperscript{41} Females were enrolled in trial B to collect data for the secondary safety and pharmacokinetic end points in both sexes. To ensure sufficient males would be enrolled to test the formal hypothesis and primary pain end point, trial B was intentionally overpowered to 97%.

Desmetramadol had the same safety profile in trial B as in the approved tramadol label.\textsuperscript{35} Consistent with selective reduction of the (+)-M1 opioid, participants in trial B dosed with tramadol exhibited a safety profile that resembled placebo except for dizziness and muscle spasticity. The latter AEs likely resulted from persistent monoaminergic activity. Desmetramadol had the same incidence of muscle spasticity in trial B as tramadol. Muscle spasticity was more common in trial B than trial A, possibly owing to the additive effect of paroxetine.

**Role of Metabolism in Desmetramadol Elimination**

The major route of excretion for tramadol and its metabolites is through the kidneys, with >90% of a tramadol dose appearing in the urine.\textsuperscript{29,45} Inhibition of CYP2B6 by paroxetine in this study increased steady-state desmetramadol levels—approximately 40% for (+)-M1 and approximately 15% for (−)-M1—consistent with a role for CYP2B6 in desmetramadol elimination by its transformation to M5 (Fig 7). A cross-over study in 12 participants administered tramadol with either placebo, ticlopidine (CYP2B6 and CYP2D6 inhibitor), or ticlopidine with itraconazole (CYP3A4 inhibitor) demonstrated the following.\textsuperscript{31} Ticlopidine alone decreased the formation rate of M1 consistent with inhibition of CYP2D6. The addition of itraconazole had no effect on tramadol pharmacokinetics or the rate of M1 formation rate compared with ticlopidine alone, suggesting that CYP3A4 is of limited importance in the metabolism and elimination of tramadol or desmetramadol in vivo.

Another crossover study pretreated 12 participants for 5 days with placebo or rifampicin, an inducer of CYP2B6 and CYP3A4, before the administration of 100 mg oral tramadol.\textsuperscript{61} Induction decreased the tramadol and M1 AUC by nearly the same amount (59% and 54%) and increased the M1 formation rate by only 12%, consistent with less available CYP2D6.
substrate proportionally forming less M1 as the major cause of decreased plasma M1 and to a lesser extent enhancement of the M1 to M5 reaction.

M1 is glucuronidated in vitro most actively by the UDP-glucuronosyltransferases 2B7 and 1A8, with 2B7 having a slight preference for (−)-M1 over (+)-M1 and 1A8 exhibiting strict stereoselectivity for (+)-M1.44 Previous human studies have reported that an oral dose of tramadol is excreted in the urine in the following forms and approximate quantitative ranges: unchanged tramadol (12−32%), unchanged M1 (>10%), M1 glucuronide (2−5%, 24%, 30%, 31%, and 48%), M1 sulphate (2−5%), unchanged N-desmethyltramadol (>10%), unchanged M5 (5−10%), M5 sulphate (5−10%), and M5 glucuronide (2−5%, 10%, 15%, and 16%).31,45,51,52,68,88 These data collectively suggest that the glucuronidation of desmetramadol, and conversion of desmetramadol to M5 by CYP2B6 are metabolic transformations involved in the in vivo elimination of desmetramadol in the urine, together with unchanged desmetramadol.

Seizures and Serotonin Syndrome

Impact on Respiration—Seizures and serotonin syndrome after normal doses of tramadol alone are exceedingly rare.26,27,36,53 The risk for seizure and serotonin syndrome increases with the concomitant use of serotonergic drugs, although on an absolute basis the risk remains rare and it is common clinical practice to coprescribe tramadol and serotonergic antidepressants in pain disorders.53 Coprescribing antidepressants that are also CYP2D6 inhibitors (eg, bupropion, duloxetine, fluoxetine, or paroxetine) was among several factors associated with enhanced risk of tramadol-induced serotonin syndrome.53 As shown in this study, CYP2D6 inhibition decreased tramadol clearance and exposed a participant to the combined serotonergic effect of the antidepressant and markedly elevated levels of the serotonergic (+)-tramadol enantiomer, which may reach supratherapeutic levels. Desmetramadol may have a lower risk of serotonin syndrome when combined with antidepressants because the serotonergic (+)-tramadol enantiomer is absent, and because plasma levels of its active enantiomers undergo clinically insignificant changes in response to CYP2D6 and CYP2B6 inhibition.

A major cause of schedule II opioid lethality is respiratory depression mediated by agonism of μ-opioid receptors.63 Participants with respiratory depression (oxygen saturation of <94%) after tramadol overdose had ingested a median dose of 2,500 mg (range = 500−4,000 mg), or 25 times the maximum approved therapeutic dose, compared with participants with no respiratory depression who had ingested a median dose of 1,000 mg (range = 450−6,000 mg).60 These properties explain why lethal overdoses owing to tramadol alone are rare.11,12,62,64,69 Achiral analyses of blood from fatal intoxications with tramadol and M1 found mean blood M1 levels of 1,900 and 1,300 ng/mL, or 38-fold and 26-fold the mean M1 level in this study, respectively.11,42 Even at therapeutic doses, schedule II opioids and the biased opioid receptor ligand TRV130 caused clinically significant respiratory depression, whereas tramadol does not.3,29,34,39,48,66,67,75,76,83 Tramadol is reported to cause a minimal and clinically insignificant decrease in respiration in healthy participants and patients at therapeutic doses.3,48,83 In 1 study, the decrease in respiration was associated with an increase in plasma epinephrine.48 It is unknown whether
this respiratory depression by tramadol is mediated by its opioid or monoaminergic mechanism, because adrenergic agents also cause respiratory depression and naloxone failed to fully reverse it. The effect of serotonin on ventilatory control is more uncertain and depends on the types of respiratory neuron and 5-hydroxytryptophan receptor. In this study, mean respiration after tramadol and desmetramadol were minimally decreased compared with placebo, and this decrease was statistically significant in trial B, but not in trial A. To the extent this represents a bone fide phenomenon in this study, it is most likely attributable to the monoaminergic activities of tramadol and desmetramadol rather than their opioid activities, because the paroxetine-induced depression of the (+)-M1 opioid in trial B had no effect on its magnitude.

Abuse Potential—Consistent with its mixed mechanism pharmacology, tramadol is less prone to abuse and diversion than schedule II opioid analgesics and was made a schedule IV controlled substance in 2014 in the United States. The abuse potential of tramadol is attributed to the (+)-M1 opioid, which exhibits rate-limited and delayed transport into the central nervous system. It has been suggested that experienced drug abusers are the most sensitive clinical population for assessing abuse liability. However, studies have consistently shown that opioids elicit similar signals of abuse-related subjective effects in non–drug abusers and drug abusers. Morphine, oxycodone, and hydrocodone all elicit robust and statistically significant responses in non–drug abusers in one or all of the measures for drug liking–disliking, take drug again, and strength of drug effect (Table 7). In trial A of this study, 50 mg tramadol and 20 mg desmetramadol exhibited similar and statistically significant responses for strength of drug effect, but were indistinguishable from placebo for drug liking–disliking and take drug again. Strength of drug effect seems to be the more sensitive of the 3 measures in other studies of opioids as well. Absent signals for drug liking–disliking and take drug again are unlikely to be due to insufficient statistical power, because the present study (trial A) distinguishes itself with a sample size that is 2–5 times larger than the size of a typical human abuse liability study. The lack of responses for these abuse measures is likely the result of dose. In recreational drug users (n = 22) who were not opioid experienced, 50 mg tramadol caused no significant subjective effects, but 100 mg caused significant responses in all 3 abuse measures.

In nondependent recreational opioid users (n = 8) trained to discriminate hydromorphone and methylphenidate, tramadol exhibited a positive dose-dependent trend in drug liking–disliking and strength of drug effect between 100 mg and 400 mg. No dose attained statistical significance, likely because of the small sample size. Lower doses of tramadol (50 mg and 100 mg) were identified as placebo, whereas 200 mg and 400 mg doses were identified as hydromorphone. The 400 mg dose also increased scores on a stimulant scale, consistent with the monoaminergic activity of tramadol.

Conclusions

For prescribers seeking to decrease the morphine milligram equivalents in their patients who require effective analgesia, tramadol is a viable option to the schedule II opioids. Tramadol provides analgesia for moderate to moderately severe pain but, compared with the schedule II opioids, has a lower abuse potential and a substantially wider margin of safety with
respect to respiratory depression and lethality in overdose. Critical shortcomings of tramadol relate to its metabolic liabilities. The findings from this study indicate that desmetramadol offers the safety and analgesia of tramadol, but without its metabolic liabilities and related drug–drug interactions. Desmetramadol could, therefore, offer expanded safety and usefulness for clinicians who prescribe tramadol as an alternative to schedule II opioids.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

The authors thank Nathaniel Katz of Analgesic Solutions, Natick, Massachusetts, for his valuable comments and suggestions. The authors also thank the patients who participated in this study.

Supported by a National Institute on Drug Abuse grant DA027304 to Syntrix. Syntrix developed the protocols in conjunction with the clinical investigators and provided the study drug. The article was prepared by Syntrix. The authors are fully responsible for all content and editorial decisions for this report. There was no editorial support from other parties. J.A.Z. was an employee of Syntrix during the execution of the reported study, and an owner of Syntrix stock. S.L.S. and L.R.W. were employees of PRA Health Sciences during the conduct of the study. M.S.J was an employee of DF/Net Research during the study and its analysis and received standard compensation. A.D.S, D.Y.M. and S.J.K. were employees of Syntrix during the execution of the study and its analysis.

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Perspective:

To our knowledge, this is the first study of desmetramadol in humans and the first to show it provides the same safety and analgesia as tramadol, but without tramadol’s metabolic liabilities and related drug–drug interactions. Desmetramadol could potentially offer expanded safety and usefulness to clinicians seeking an alternative to schedule II opioids.
Figure 1.
Chemical structure and dominant pharmacology of each enantiomer of tramadol and the M1 metabolite. An enantiomer is each of a pair of molecules that are mirror images of each other.
Figure 2.
Study design. Participants were randomized in trials A and B to all 6 possible treatment sequences with each segment separated by 1 week (trial A) or 2 weeks (trial B). Nine doses of each study drug were given every 6 hours in each segment to reach steady-state levels and then cold-induced pain was assessed after the ninth dose. All participants in trial B additionally received daily paroxetine beginning 1 day before each treatment segment. S, participants randomized.
Figure 3.
Participant flow and disposition.
Figure 4.
Mean steady-state plasma levels of (+)-M1 (A, E), (−)-M1 (B, F), (+)-tramadol (C, G), and (−)-tramadol (D, H) in trials A (n = 43) and B (n = 60). Bars are for SD and shown in 1 direction. Baseline points all below the quantitation limit.
Figure 5.
Cold-induced pain at 30 seconds in trial A and trial B. Bars are SE of the mean.
Abbreviation: NS, not statistically significant. *$P < .05$; **$P < .01$; ***$P < .001$. 
Figure 6.
Mean respiratory rate before and after each study drug administration in trial A. Bars are for SD for desmetramadol (up bars) and placebo (down bars). The horizontal separation of data points at each dose (ie, before and after dosing) are exaggerated to allow adequate visualization of the respiration rate before and after each dose.
Figure 7.
Tramadol and desmetramadol metabolism catalyzed by CYPs in vitro.
Table 1.

**Key Inclusion and Exclusion Criteria**

| Key Inclusion Criteria                                                                 | Key Exclusion Criteria                                                                 |
|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Healthy male and female (trial B) adults ≤55 years old with normal blood pressure, pulse, and respiration | History of seizures, epilepsy, or recognized increase risk of seizure                   |
| Tolerance to cold-induced pain of ≥20 and ≤120 seconds                                   | History of cirrhosis or laboratory evidence of liver disease                            |
| Negative urine for substances of abuse                                                 | Known or suspected alcohol or drug abuse within the past 6 months                       |
| Normal or intermediate CYP2D6 metabolizer (trial B)                                     | Inhibitors of monoamine oxidase, serotonin and/or norepinephrine reuptake, and other medications or supplements known to induce or inhibit drug metabolism or that may affect the serotonergic neurotransmitter system |
| Adequate hematologic and liver function per predefined limits                           | Ethanol, grapefruit, grapefruit-related citrus fruits (eg, Seville oranges, pomelos), grapefruit-related juices or other new medication |
| Cockcroft-Gault glomerular filtration rate of ≥60 mL/min and urinalysis with ≥1 glucose, +1 ketones, and +1 protein | Pregnant or breast feeding (trial B)                                                    |
| Body mass index of 18.0–32 kg/m²                                                        |                                                                                        |
| If female of childbearing potential, must use adequate contraception                   |                                                                                        |
| Electrocardiogram without clinically significant changes                               |                                                                                        |
| Negative serology for HIV, hepatitis B surface antigen, and hepatitis C virus antibody |                                                                                        |
Table 2.

Demographics and CYP2D6 Phenotype

| Characteristics                                   | Trial A (n = 43) | Trial B (n = 60) |
|--------------------------------------------------|-----------------|-----------------|
| Age, years                                       | 28.4 ± 8.0      | 28.0 ± 6.8      |
| Age range, years                                 |                 |                 |
| Minimum                                          | 21              | 18              |
| Maximum                                          | 53              | 45              |
| Sex                                              |                 |                 |
| Male                                             | 43 (100)        | 42 (70)         |
| Female                                           | 0 (0)           | 18 (30)         |
| Race                                             |                 |                 |
| Caucasian                                        | 39 (91)         | 56 (93)         |
| Asian                                            | 3 (7)           | 0 (0)           |
| Black or African American                        | 0 (0)           | 3 (5)           |
| American Indian or Alaska Native                 | 1 (2)           | 1 (2)           |
| Ethnicity                                        |                 |                 |
| Hispanic or Latino                               | 6 (14)          | 7 (12)          |
| Not Hispanic or Latino                           | 37 (86)         | 53 (88)         |
| BMI, kg/m²                                       | 25.5 ± 3.1      | 24.8 ± 3.4      |
| BMI range, kg/m²                                 |                 |                 |
| Minimum                                          | 19.5            | 18.9            |
| Maximum                                          | 31.8            | 31.7            |
| CYP2D6 activity score, phenotype *               |                 |                 |
| 0.0, Poor metabolizer                            | 1 (2)           | 0 (0)           |
| 0.5, Intermediate metabolizer                    | 0 (0)           | 3 (5)           |
| 1.0, Intermediate metabolizer                    | 17 (41)         | 19 (32)         |
| 1.5, Normal metabolizer                          | 7 (17)          | 9 (15)          |
| 2.0, Normal metabolizer                          | 16 (38)         | 29 (48)         |
| 3.0, Ultrarapid metabolizer                      | 1 (2)           | 0 (0)           |

NOTE: values are mean ± SD or number (%) unless otherwise noted.

*Predicted from genotype. See Supplementary Table 1 for participant genotypes.
### Table 3.

Steady-State Pharmacokinetics and Paroxetine Levels

| Analyte       | Trial A (n = 43) | Trial B (n = 60) |
|---------------|------------------|------------------|
|               | Tramadol         | Desmethyltriamidol | Tramadol | Desmethyltriamidol |
| (+)-M1        |                  |                  |          |                  |
| C_{ss, min}, ng/mL, M (SD) | 28 (7)          | 26 (6)           | 11 (6)   | 38 (9)           |
| 90% CI       |                  |                  |          |                  |
|              | .85 - 1.08       |                   |         |                  |
| P value      |                  |                  |          |                  |
|              | <.001            |                   |         |                  |
| C_{ss, max}, ng/mL, M (SD) | 37 (10)         | 36 (10)          | 14 (8)   | 51 (11)          |
| 90% CI       |                  |                  |          |                  |
|              | .88 - 1.13       |                   |         |                  |
| P value      |                  |                  |          |                  |
|              | <.001            |                   |         |                  |
| t_{1/2}, h, M (SD) | 18 (39)         |                   | 8 (6)   |                  |
| P value      |                  |                  |          |                  |
|              | .065             |                   |         |                  |
| (−)-M1       |                  |                  |          |                  |
| C_{ss, min}, ng/mL, M (SD) | 30 (6)          | 21 (5)           | 25 (7)   | 25 (8)           |
| 90% CI       |                  |                  |          |                  |
|              | .69 - 7.6        |                   | .95 - 1.09 |                  |
| P value      |                  |                  |          |                  |
|              | .64              |                   |         |                  |
| C_{ss, max}, ng/mL, M (SD) | 42 (9)          | 30 (9)           | 35 (10) | 35 (10)          |
| 90% CI       |                  |                  |          |                  |
|              | .67 - 7.6        |                   | .93 - 1.07 |                  |
| P value      |                  |                  |          |                  |
|              | .79              |                   |         |                  |
| t_{1/2}, h, M (SD) | 12 (8)          |                   | 7 (5)   |                  |
| P value      |                  |                  |          |                  |
|              | <.001            |                   |         |                  |
| (+)-triamidol|                  |                  |          |                  |
| C_{ss, min}, ng/mL, M (SD) | 85 (33)         | ND               | 183 (49) | ND               |
| C_{ss, max}, ng/mL, M (SD) | 143 (36)        | ND               | 295 (62) | ND               |
| t_{1/2}, h, M (SD) | 8.6 (2.5)       | ND               |         | ND               |
| (−)-triamidol|                  |                  |          |                  |
| C_{ss, min}, ng/mL, M (SD) | 68 (27)         | ND               | 140 (41) | ND               |
| C_{ss, max}, ng/mL, M (SD) | 122 (32)        | ND               | 242 (56) | ND               |
| t_{1/2}, h, M (SD) | 7.2 (2.3)       | ND               |         | ND               |
| Analyte                  | Trial A (n = 43) | Trial B (n = 60) |
|-------------------------|------------------|------------------|
| Paroxetine, ng/mL, M (SD) | NA               | NA               |
|                         | 11 (8)           | 12 (9)           |

Abbreviations: M, mean; NA, not applicable; ND, not detected.

*The pharmacokinetic parameter is statistically bioequivalent if the 90% CI is within the range of 0.80 to 1.25.
### Table 4.

**Pupil Diameter and Abuse Measures**

|                       | Trial A (n = 43) |       |       |
|-----------------------|------------------|-------|-------|
|                       | Placebo          | Tramadol | Desmetramadol |
| Pupil diameter, mm, M (SD) | 6.1 (.9)        | 6.1 (.9) | 6.0 (1.1)   |
| Predose               | 6.2 (1.0)        | 5.5 (1.1) | 5.1 (1.2)   |
| After seventh dose    | <.0001           | <.0001   |       |
| Abuse Measures, 0–100 mm, M (SD) | 49(14)         | 48(15)   | 47 (25)   |
| Drug liking-disliking | NS               | NS      |       |
| Take drug again       | 49 (19)          | 47(18)   | 43 (26)   |
| Strength of drug effect | 12(18)         | 32 (29)  | 29 (28)   |
|                        | <.0001           | .0004    |       |

Abbreviations: M, mean; NS, not significant.
Table 5.

Summary of Drug-Related AEs (Safety Population)

| Event, n (%) | Trial A (n = 43; M = 43) | Trial B (n=60; M = 42, F=18) |
|--------------|--------------------------|-------------------------------|
|              | Placebo | Tramadol | Desmetramadol | Placebo | Tramadol | Desmetramadol |
| All AEs      |          |          |             |          |          |             |
|              | 10 (24)  | 20 (49)  | 19 (44)     | 16(27)   | 30 (50)  | 40 (67)     |
| Specified AEs |          |          |             |          |          |             |
| Nausea       | 3(7)     | 5(12)    | 8(19)       | 7(12)    | 8(13)    | 16(27)      |
| M            | 3(7)     | 5(12)    | 8(19)       | 4(10)    | 6(14)    | 11(26)      |
| F            |          |          |             | 3(17)    | 2(11)    | 5 (28)      |
| Dizziness    | 1 (2)    | 5(12)    | 6(14)       | 1(2)     | 8(13)    | 12 (20)     |
| Male         | 1 (2)    | 5(12)    | 6(14)       | 1(2)     | 4(10)    | 7 (17)      |
| Female       |          |          |             | 0(0)     | 4(22)    | 5 (28)      |
| Somnolence   | 0 (0)    | 2 (5)    | 3 (7)       | 2(3)     | 4(7)     | 10(17)      |
| Male         | 0 (0)    | 2 (5)    | 3 (7)       | 1(2)     | 2 (5)    | 4 (10)      |
| Female       |          |          |             | 0(0)     | 4(22)    | 5 (28)      |
| Headache     | 0 (0)    | 7(17)    | 3 (7)       | 3 (5)    | 6 (10)   | 10(17)      |
| Male         | 0 (0)    | 7(17)    | 3 (7)       | 0(0)     | 0(0)     | 4(10)       |
| Female       |          |          |             | 3(17)    | 6(33)    | 6(33)       |
| Vomiting     | 0 (0)    | 1(2)     | 1 (2)       | 1 (2)    | 2 (3)    | 9(15)       |
| Male         | 0 (0)    | 1 (2)    | 1(2)        | 1 (2)    | 2 (5)    | 6(14)       |
| Female       |          |          |             | 0(0)     | 0(0)     | 3 (17)      |
| Presyncope   | 0 (0)    | 0(0)     | 0(0)        | 0(0)     | 1 (2)    | 6(10)       |
| Male         | 1 (2)    | 0 (0)    | 0(0)        | 0(0)     | 1 (2)    | 3 (7)       |
| Female       |          |          |             | 0(0)     | 0(0)     | 3 (17)      |
| Pruritus     | 0 (0)    | 4(10)    | 3 (7)       | 1(2)     | 1 (2)    | 4 (7)       |
| Male         | 0 (0)    | 4(10)    | 3(7)        | 0(0)     | 0(0)     | 1 (2)       |
| Female       |          |          |             | 1(6)     | 1 (6)    | 3 (17)      |
| Spasticity   | 0 (0)    | 1(2)     | 0 (0)       | 0(0)     | 3 (5)    | 3 (5)       |
| Male         | 0 (0)    | 1 (2)    | 0 (0)       | 0(0)     | 3 (7)    | 3 (7)       |
| Female       |          |          |             | 0(0)     | 0(0)     | 0 (0)       |
| Feel abnormal| 0 (0)    | 1 (2)    | 0 (0)       | 0(0)     | 2 (3)    | 3 (5)       |
### Event, n (%)

| Event  | Trial A (n = 43; M = 43) | Trial B (n=60; M = 42, F=18) |
|--------|--------------------------|-------------------------------|
|        | Placebo                  | Tramadol                      | Desmetramadol                | Placebo | Tramadol | Desmetramadol |
| Male   | 0 (0)                    | 1 (2)                         | 0 (0)                        | 0 (0)   | 2 (5)    | 2 (5)         |
| Female | —                        | —                             | —                            | 0 (0)   | 0 (0)    | 1 (6)         |
| Feel hot | 0 (0)                   | 0 (0)                        | 0 (0)                        | 1 (2)   | 0 (0)    | 3 (5)         |
| Male   | 0 (0)                    | 0 (0)                        | 0 (0)                        | 1 (2)   | 0 (0)    | 2 (5)         |
| Female | —                        | —                             | —                            | 0 (0)   | 0 (0)    | 1 (6)         |
| Euphoria | 0 (0)                  | 0 (0)                        | 0 (0)                        | 0 (0)   | 1 (2)    | 2 (3)         |
| Male   | 0 (0)                    | 0 (0)                        | 0 (0)                        | 0 (0)   | 1 (2)    | 1 (2)         |
| Female | —                        | —                             | —                            | 0 (0)   | 0 (0)    | 1 (6)         |
| Sweating | 0 (0)                 | 0 (0)                        | 0 (0)                        | 1 (2)   | 1 (2)    | 2 (3)         |
| Male   | 0 (0)                    | 0 (0)                        | 0 (0)                        | 1 (2)   | 1 (2)    | 2 (5)         |
| Female | —                        | —                             | —                            | 0 (0)   | 0 (0)    | 0 (0)         |
| Severe AEs | 0 (0)            | 0 (0)                        | 0 (0)                        | 0 (0)   | 0 (0)    | 0 (0)         |
| Deaths | 0 (0)                    | 0 (0)                        | 0 (0)                        | 0 (0)   | 0 (0)    | 0 (0)         |

* AE incidence of ≥3% of participants dosed with desmetramadol in trial B. See Supplementary Table 4 for drug-related AEs of lower incidence.
### Table 6.

#### Average Postdose Respiratory Rate

|                      | Tramadol Versus Placebo | Desmetramadol Versus Placebo | Desmetramadol Versus Tramadol |
|----------------------|-------------------------|-----------------------------|-----------------------------|
| **Trial A, n = 43**  |                         |                             |                             |
| Respiratory rate, min⁻¹, MPD (SD) | - .24 (.97)             | - .14 (.87)                 | .11 (.91)                   |
|                      | NS                      | NS                          | NS                          |
| **Trial B, n = 60**  |                         |                             |                             |
| Respiratory rate, min⁻¹, MPD (SD) | - .34 (.99)             | - .30 (.90)                 | .05 (.85)                   |
|                      | P = .004                | P = .012                    | P = .345                    |

Abbreviations: MPD, mean paired difference; NS, no significant treatment effect.
Table 7.
Abuse Measures in Opioid Studies in Drug Abusers and Non-Drug Abusers

| Opioid, Oral Route | N | Drug Liking-Disliking | Take Drug Again | Strength of Drug Effect | Study |
|-------------------|---|-----------------------|-----------------|-------------------------|-------|
| Drug abusers      |   |                       |                 |                         |       |
| Morphine          |   |                       |                 |                         |       |
| 25 mg             | 12| 8                     | 6               | 35†                     | Zacny 2005 |
| Oxycodone         |   |                       |                 |                         |       |
| 15 mg             | 9 | 21†                   | 35†             | 43†                     | Comer 2010 |
| 30 mg             | 9 | 19†                   | 33†             | 50†                     | Comer 2010 |
| Hydromorphone     |   |                       |                 |                         |       |
| 4 mg              | 8 | 29                    | —               | 19                      | Duke 2011 |
| 8 mg              | 8 | 44†                   | —               | 32†                     | Duke 2011 |
| Tramadol          |   |                       |                 |                         |       |
| 50 mg             | 22| 3                     | 5               | 5                       | Zacny 2005 |
| 100 mg            | 22| 10†                   | 9†              | 20†                     | Zacny 2005 |
| 50 mg             | 8 | 1                     | —               | 0                       | Duke 2011 |
| 100 mg            | 8 | 6                     | —               | 4                       | Duke 2011 |
| 200 mg            | 8 | 15                    | —               | 19                      | Duke 2011 |
| 400 mg            | 8 | 24                    | —               | 19                      | Duke 2011 |
| Non-drug abusers  |   |                       |                 |                         |       |
| Morphine          |   |                       |                 |                         |       |
| 30 mg             | 20| 12†                   | 12†             | 28†                     | Zacny 2008 |
| 40 mg             | 18| 12†                   | 12†             | 33†                     | Zacny 2003 |
| Oxycodone         |   |                       |                 |                         |       |
| 10 mg             | 18| 13†                   | 15†             | 30†                     | Zacny 2003 |
| 15 mg             | 9 | 19†                   | 18†             | 45†                     | Comer 2010 |
| 20 mg             | 18| 20†                   | 21†             | 48†                     | Zacny 2003 |
| Opioid, Oral Route | N   | Drug Liking- Disliking | Take Drug Again | Strength of Drug Effect | Study         |
|-------------------|-----|------------------------|----------------|--------------------------|---------------|
| 20 mg             | 20  | 16$^\dagger$           | 17$^\dagger$   | 53$^\dagger$             | Zacny 2008    |
| 30 mg             | 9   | 18$^\dagger$           | 15             | 53$^\dagger$             | Comer 2010    |
| 30 mg             | 18  | 21$^\dagger$           | 20$^\dagger$   | 58$^\dagger$             | Zacny 2003    |
| Hydrocodone       |     |                        |                |                          |               |
| 15 mg$^\dagger$   | 20  | 4                      | 4              | 33$^\dagger$             | Zacny 2009    |
| 30 mg$^\dagger$   | 20  | 8                      | 6              | 50$^\dagger$             | Zacny 2009    |
| Tramadol          |     |                        |                |                          |               |
| 50 mg             | 43  | -1                     | -2             | 20$^\dagger$             | This study    |
| Desmetramadol     |     |                        |                |                          |               |
| 20 mg$^\dagger$   | 43  | -2                     | -6             | 17$^\dagger$             | This study    |

$^\dagger$ Difference between peak drug and placebo value, normalized to 100 point scale where required. Data collated from Comer 2010,$^6$ Duke 2011,$^19$ Zacny 2003,$^89$ Zacny 2005,$^88$ Zacny 2008,$^91$ and Zacny 2009.$^90$

$^\ddagger$ Statistically significant compared with placebo.

$^\ddagger$ Acetaminophen combination.