

Subjective Effects and Safety of Whole and Tampered Morphine Sulfate and Naltrexone Hydrochloride (ALO-01) Extended-Release Capsules versus Morphine Solution and Placebo in Experienced Non-Dependent Opioid Users

A Randomized, Double-Blind, Placebo-Controlled, Crossover Study

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Abstract

Background and Objective: Given the dual public health challenges of under-treated pain and opioid abuse, there is a need to reduce attractiveness of opioid analgesics to drug abusers. ALO-01 (morphine sulfate and naltrexone hydrochloride) extended-release capsules, indicated for treatment of chronic, moderate to severe pain, contain polymer-coated pellets of morphine, each with a core of sequestered naltrexone intended for release only upon tampering (crushing). The purpose of this study was to assess the pharmacodynamic effects (including drug-liking and euphoria) of whole and crushed ALO-01 versus morphine sulfate solution (MSS) and placebo.

Methods: This was a randomized, double-blind, placebo-controlled, triple-dummy, four-way crossover study carried out at a clinical research centre. Participants were experienced non-dependent opioid users. Subjects were given either two ALO-01 60 mg capsules, crushed pellets from two ALO-01

60 mg capsules, MSS 120 mg or placebo; there was a 14- to 21-day washout between treatments. The primary endpoints were drug-liking visual analogue scale score, scores on items from the Addiction Research Center Inventory (ARCI) and Cole/ARCI scales characterizing abuse potential and euphoria, and pupil diameter as measured by pupillometry.

Results: Morphine plasma concentrations were similar after ALO-01 crushed and MSS, with a median time to reach maximum plasma concentration (t_{\max}) of 1.1 and 1.2 hours, respectively; the plasma naltrexone median t_{\max} was 1.1 hours after ALO-01 crushed. By comparison, the median t_{\max} for morphine with ALO-01 whole was 8.1 hours. The maximum effect (E_{\max}) of MSS was significantly greater than placebo on pupillometry and the subjective measures (all $p < 0.001$). ALO-01 whole and crushed produced lower E_{\max} values and flatter effect-time profiles for subjective measures and caused less pupillary constriction than MSS.

Conclusions: The results of this study demonstrated that ALO-01, whether taken orally whole as intended or tampered with by crushing and taken orally, had reduced desirability compared with MSS.

Background

Opioids remain the gold standard for treating appropriately selected patients with moderate to severe pain, especially those for whom other interventions have been unsuccessful.^[1-3] Campaigns to address under-treatment of pain have raised awareness of the need for analgesics, including opioids; however, increased medical use of opioids has been paralleled by increased non-medical use and diversion.^[2,4]

Extended-release oral opioid formulations, which allow slow release of opioid to control pain for up to 12–24 hours, enable a constant plasma analgesic concentration without need for frequent dosing.^[2] Because rapid increases in plasma morphine concentrations contribute to the subjective experience of euphoria and drug-liking,^[2] it was once believed that extended-release technology, which yields less rapid rises in plasma drug concentrations and lower peak concentrations, had the potential to minimize opioid abuse compared with standard immediate-release formulations.^[5] Drug abusers, however, learned that tampering with extended-release formulations – by chewing, snorting crushed product or dissolving

crushed product and then injecting the solution – will release the full dose of opioid and provide the desired ‘high’.^[4]

Clinical management strategies for patients using opioids for chronic pain management include screening and monitoring for signs of misuse, abuse and diversion.^[6] In addition, various pharmaceutical formulation strategies have been proposed to make opioid abuse more difficult.^[5-7] Such strategies include physical barriers to make the product more resistant to crushing or extraction with common solvents, and addition of noxious agents or opioid antagonists that are released only upon product tampering.^[2,6] One opioid receptor antagonist, naltrexone, is rapidly absorbed from the gastrointestinal tract and effectively blocks the objective and subjective effects, including euphoria and drug-liking, of morphine and other opioids.^[8,9] This pharmacological profile is the basis for license of oral naltrexone in the UK to promote abstinence from opioid abuse.^[10]

ALO-01 (morphine sulfate and naltrexone hydrochloride) extended-release capsules, indicated for treatment of chronic, moderate to severe pain, contains polymer-coated pellets of

extended-release morphine sulfate, each with a sequestered core of naltrexone (figure 1). When ALO-01 is taken orally as directed, the extended release of morphine provides long-lasting analgesic activity, whereas naltrexone remains sequestered in the core and has no clinical effect.^[11] However, the pellets are designed such that tampering with ALO-01 (by crushing the pellets) will crush both the polymer outer coat surrounding the morphine layer and the inner coat surrounding the naltrexone core. This leads to release of naltrexone to counteract the effects of morphine. ALO-01 has been shown to provide analgesic efficacy and tolerability comparable to a marketed capsule formulation (KADIAN® Capsules; Actavis, Hafnarfjordur, Iceland) containing extended-release morphine pellets with an inactive inner core.^[11] The present study was designed to investigate the relative pharmacodynamic effects (including subjective effects of drug-liking and euphoria) and safety of whole and crushed ALO-01 compared with morphine sulfate solution (MSS) and placebo. These effects may serve as indicators of the attractiveness, or lack thereof, of this formulation for abuse by recreational opioid users.^[12,13]

Subjects and Methods

Design Overview

The study had a randomized, double-blind, placebo-controlled, triple-dummy, four-way crossover design and consisted of three periods: screening/qualifying period, double-blind treat-

ment sessions and post-treatment follow-up (figure 2).

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with the ethical principles of Good Clinical Practice and all applicable regulatory requirements. The consent form and the protocol were approved by a central institutional review board (Institutional Review Board Services, Aurora, ON, Canada). All subjects provided written informed consent. Subjects were compensated for their time and travel based on a fee schedule outlined in the informed consent form, with subjects not completing the study being compensated on a *pro rata* basis.

Setting and Participants

Healthy men and women aged 18–55 years with a body mass index of 21–31 kg/m² and weight >55 kg were eligible if they were: opioid users, not currently physically dependent based on *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria,^[14] and had used opioids non-therapeutically for psychoactive effects on at least ten occasions within the previous year and at least once in the previous 12 weeks. Subjects with a positive urine drug screen for opioids, amphetamines, cocaine and benzodiazepines at screening were eligible if they subsequently tested negative at the qualifying session and all treatment sessions. Subjects testing positive for

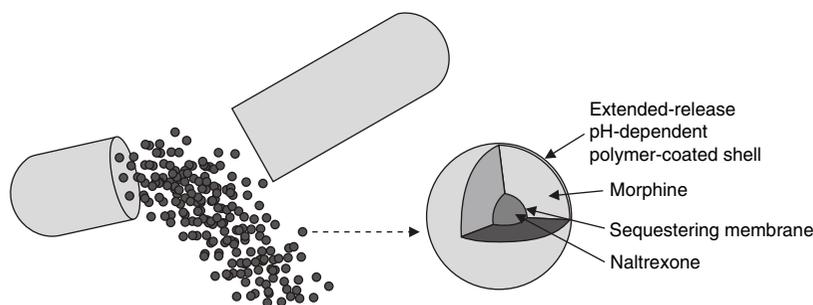


Fig. 1. Morphine sulfate and naltrexone hydrochloride (ALO-01) extended-release capsule.

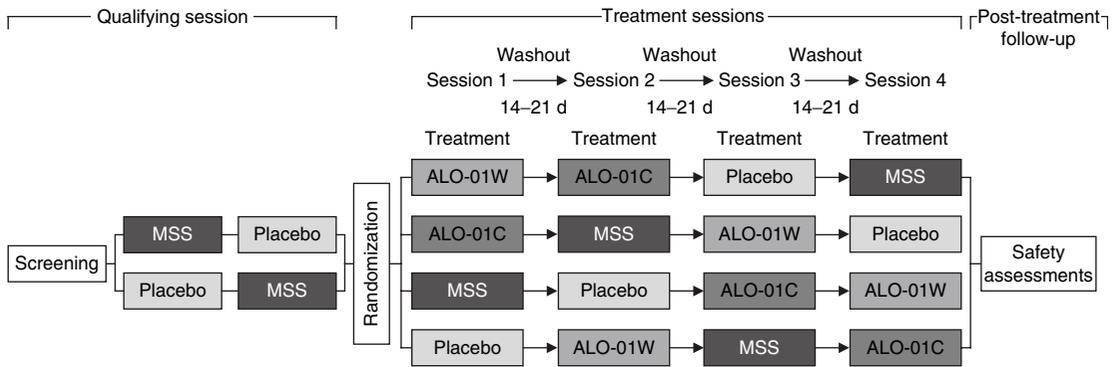


Fig. 2. Study design. **ALO-01C**=crushed pellets from two ALO-01 60 mg capsules; **ALO-01W**=two whole ALO-01 60 mg capsules; **MSS**=morphine sulfate solution.

tetrahydrocannabinol (THC) at screening were eligible if THC concentrations remained stable or decreased on testing at the qualifying session and all treatment sessions. Subjects agreed to use two medically acceptable methods of contraception throughout the study. Eligible women had negative pregnancy tests before each session and were not lactating.

Subjects with a history of drug or alcohol (ethanol) addiction or dependence, excluding nicotine and caffeine, were ineligible. Subjects with opioid addiction or dependence were excluded so as to not re-expose these individuals to opioids and because of the potential for naltrexone to precipitate withdrawal symptoms in subjects who might take opioids outside of the study. Subjects with current psychiatric illness, clinically significant medical or neurological conditions, or those who were currently receiving treatment that lowers seizure threshold, were ineligible. Additional exclusion criteria included haemoglobin <125 g/L (men) or <115 g/L (women), use of any prescription or non-prescription medication within 7 days before the qualifying session without evaluation and approval by the study investigator, and positive test or previous treatment for HIV or hepatitis B or C.

Participants resided at the clinical research centre during each of the treatment sessions. The first subject was enrolled on 2 March 2007; the last subject completed the study on 28 May 2007.

Randomization and Interventions

Subjects were screened for eligibility, and then participated in a 3-night inpatient double-blind, crossover, qualifying session to determine whether they could tolerate a single dose of morphine 120 mg and distinguish between morphine and placebo. Subjects were admitted to the clinical unit the evening prior to the first dosing. After an overnight fast they were randomized to receive single doses of morphine 120 mg in apple juice or placebo (apple juice) over two consecutive dosing days, with the alternate treatment being administered on the second dosing day. Subjects were discharged from the clinic approximately 24 hours following the second dosing. A subject was deemed eligible for participation in the study if he or she had a response to morphine that was greater than to placebo on at least four of the following six measures (see Assessments section): visual analogue scale (VAS) for drug-liking, VAS for overall drug-liking, VAS for feeling 'high', VAS for good effects, Addiction Research Center Inventory (ARCI)-Morphine Benzodrine Group (MBG)^[15] [reflecting euphoria] and subjective drug value (SDV).^[16]

Eligible subjects then entered the double-blind treatment period consisting of four 2-night inpatient treatment sessions, each separated by a 14- to 21-day washout period. Subjects were admitted to the clinic on the evening prior to dosing and remained confined until completion of the

24-hour post-dose assessments. During each session, subjects received one of the following treatments: two whole ALO-01 60 mg capsules (EMBEDA™, King Pharmaceuticals®, Inc., Bristol, TN, USA), crushed pellets from two ALO-01 60 mg capsules, MSS 120 mg (2.4 mL of Statex® oral drops 50 mg/mL; Pharmascience Inc., Montreal, QC, Canada) diluted in 148 mL of apple juice, or placebo in apple juice. When crushed ALO-01 was to be administered, the pellets from the capsules were manually crushed using a mortar and pestle for 2 minutes, after which the contents were dissolved in apple juice. To maintain blinding, subjects received two whole capsules (ALO-01 or matching placebo) and two apple juice beverages (one with crushed ALO-01 capsules or crushed placebo capsules; one with MSS or placebo) in each session. Each treatment was administered after an overnight fast of approximately 8 hours and was followed by an additional 4 hours of fasting. The post-treatment follow-up period consisted of safety assessments conducted 3–14 days after the last dose of study treatment.

Randomization was accomplished through computer-generated randomization sequences by DecisionLine Clinical Research Corporation. Two randomization sequences were generated for the study: one for the qualifying session and one for the treatment period. Neither the subject nor the clinic staff knew which treatment was being administered (i.e. active drug or placebo). Only the dispensing pharmacists or designee were unblinded, as this was necessary for the preparation of the study treatments. In the treatment period, the order of treatment sequence was according to Williams square design.

Assessments

Subjects underwent pharmacodynamic testing during each treatment session at approximately 1 hour before and approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after dosing. Each testing cycle lasted approximately 15 minutes and included evaluation on a series of rating scales and questionnaires in which subjects rated their

current perceptions of their subjective state and of the effects of treatment.

Primary outcomes included scores on a VAS for drug-liking, the ARCI-MBG scale,^[15] Cole/ARCI stimulation-euphoria and abuse potential scales,^[17] and SDV (assessed 12 and 24 hours after dosing).^[16] Pupillometry, an objective pharmacodynamic measure, was also assessed. Secondary endpoints, including additional subjective effects, will be detailed in a separate report.

The VAS for drug-liking consisted of a horizontal line with descriptive anchors at each end. Subjects used a computer mouse to position the cursor over the position on the line corresponding to how they felt at that moment regarding the statement “At this moment, my liking for this drug is...”. The scale was anchored by a score of 0 for ‘strong disliking’, 50 for ‘neutral’, and 100 for ‘strong liking’. Each response was captured electronically using proprietary software (Scheduled Measurement System, DecisionLine Clinical Research Corporation, Toronto, ON, Canada), and scored as an integer from 0 to 100.

The ARCI short form^[15] and the Cole-modified ARCI^[17] were based on a series of 77 questions derived from the larger 550-question ARCI. Each question was presented on a computer screen and subjects selected one of four possible responses (false, more false than true, more true than false, true). Responses were scored from 0 to 3 and were used to derive scores on several scales that were evaluated as primary outcomes, including the Cole/ARCI stimulation-euphoria, Cole/ARCI abuse potential and ARCI-MBG euphoria and well-being scales. Examples of questions related to these scales include “Things around me seem more pleasing than usual” and “My thoughts come more easily than usual”.

The SDV, adapted from Griffiths and colleagues,^[16] consisted of a series of independent, theoretical forced choices in which subjects were asked to choose between receiving another dose of study drug or an envelope containing a specified amount of money from \$Can0.25 to \$Can50.00. Depending on the answer, the monetary value in the next question was set higher or lower. At the end of six questions, the test estimated the crossover point at which the

subject was indifferent between choosing the drug or the money, which is a proxy of the reinforcing efficacy of the drug.

Pupillometry was used to measure pupillary constriction, an objective measure of opioid physiological effect. The evaluation was performed using a handheld optical scanner (Model 59001-IFU, NeurOptics, Inc., Irvine, CA, USA).

Safety Assessments

Vital signs were measured at the same times as pharmacodynamic assessments. In addition, subjects underwent continuous cardiac monitoring by telemetry for 8 hours after dosing, or longer if clinically required or indicated by the investigator. Adverse events were monitored throughout the study and solicited using a non-leading question. Clinical laboratory parameters and 12-lead ECG were obtained at screening and at follow-up.

Drug Concentration Measurements

Serial blood samples (10 mL each) were collected in tubes containing potassium ethylene diamine tetra-acetic acid (EDTA) at approximately 1 hour before and at approximately 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after study drug administration for measurement of plasma morphine, naltrexone and its metabolite 6- β -naltrexol. Samples were centrifuged at 3000 rpm for 15 minutes at 4°C, and plasma was transferred into polypropylene tubes and stored frozen until analysis. Pharmacokinetic parameters were calculated from plasma concentration data using non-compartmental methods. The limits of quantification were 0.0007 $\mu\text{mol/L}$ for morphine, 0.0104 nmol/L for naltrexone and 0.029 nmol/L for 6- β -naltrexol or 0.000725 nmol/L at the higher sensitivity working range.

Statistical Analysis

Each pharmacodynamic measure was assessed using summary statistics by treatment group. When longitudinal measurements were taken, summary parameters were calculated: maximum effect (E_{max}), time to reach E_{max} , area under the

effect curve from dosing to 2 hours, 8 hours and 24 hours (AUEC_2 , AUEC_8 and AUEC_{24} , respectively). For the VAS for drug-liking and SDV, mean and peak responses were calculated. All summary parameters were evaluated as appropriate using descriptive statistics. Comparisons between pairs of treatment groups were made using contrasts from a linear mixed-effect analysis of covariance (ANCOVA) model, with fixed-effect terms for treatment, period and sequence, and a random effect term for subjects nested within sequence. For pharmacodynamic measures with pre-dose values, the model included pre-dose baseline value as a covariate. This model includes the response for each subject to each treatment, incorporating the within-subject nature of the crossover study design.

All safety parameters were summarized by treatment group using descriptive statistics. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 10.0) and their possible relationship to study treatment was evaluated by the investigator.

Planned sample size was approximately 64 subjects to yield a total of 24 completed subjects. This number had previously been determined to be an appropriate number for a bioequivalence study.^[18]

Results

Subjects

Although 73 subjects were eligible for the qualifying session, dosing was stopped after 58 subjects because 43 (74%) had already passed the qualifying session, exceeding the expected number, and continuation of the qualifying session was not necessary. Of these 43 subjects, 32 were randomized into the double-blind treatment period – consistent with the planned sample size of the study – and all 32 completed the four treatment sessions without major protocol violations (figure 3). The cohort had a mean age of 35 years, and included 26 men (81%) and 6 women (19%), most of whom were White (22 of 32; 69%) [table I].

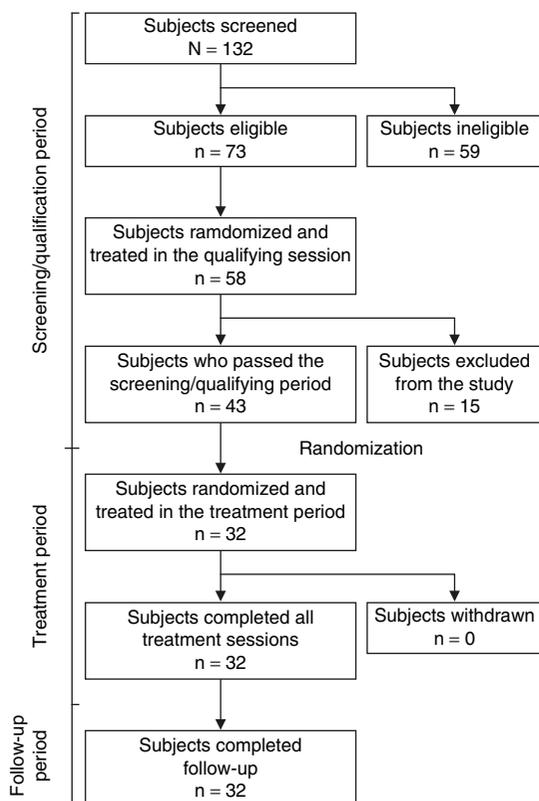


Fig. 3. Disposition of study participants.

Pharmacodynamics

Administration of MSS resulted in increases in scores on positive effect scales and produced characteristic decreases in pupil diameter (table II). As illustrated in figure 4, the mean effect of MSS for each measure peaked at approximately 1.5 hours after dosing and then declined over the next 3–4 hours. For each measure, the E_{\max} of MSS was significantly greater than that seen with placebo (all $p < 0.001$). The difference between MSS and placebo on each of these measures validates their use in the present study.

In comparison, administration of ALO-01 whole or crushed produced lower E_{\max} levels of response than MSS (all $p < 0.001$, except $p = 0.002$ for comparison between MSS and ALO-01 crushed on Cole/ARCI abuse potential scale) and flatter effect-time profiles (table II, figure 4). As expected, E_{\max} levels of response for pupillometry

and for all positive outcome measures with ALO-01 crushed and for most positive outcome measures with ALO-01 whole were also significantly greater than with placebo. The E_{\max} levels of response for ALO-01 whole and crushed did not differ significantly on any positive outcome measure or on pupil diameter.

At 1.5 hours, i.e. the first pharmacodynamic assessment after peak morphine concentrations were attained with MSS and ALO-01 crushed, these same effects of ALO-01, taken either whole or crushed, were also significantly lower than those with MSS ($p < 0.001$ for each comparison). Furthermore, the $AUEC_2$ for these subjective effects demonstrated significant differences between ALO-01 whole and crushed versus MSS ($p < 0.05$). The significant differences in AUEC continued through $AUEC_8$ (with the exception of Cole/ARCI abuse potential for ALO-01 crushed vs MSS) and $AUEC_{24}$ (with the exception of Cole/ARCI stimulation-euphoria for ALO-01 crushed vs MSS, and Cole/ARCI abuse potential for ALO-01 whole and crushed vs MSS).

Pharmacokinetics

Mean plasma morphine concentrations increased sharply within the first hour after administration of MSS and ALO-01 crushed (median time [t_{\max}] to reach maximum plasma concentration [C_{\max}] 1.2 [range 0.6–2.1] and 1.1 [range 0.6–2.2] hours, respectively) followed by a gradual decline over the next 5 hours (figure 5a). In comparison, plasma concentrations of morphine rose in a slow and steady manner, with ALO-01 whole reaching C_{\max} after a median time of 8.1 (range 4.1–12.2) hours. Following administration of ALO-01 crushed, mean naltrexone concentrations also rose sharply over the first hour, followed by a decline over the next 5 hours (figure 5b). Naltrexone reached C_{\max} (mean \pm SD 3.29 ± 1.84 nmol/L) at a median of 1.1 (range 0.6–1.2) hours following administration of ALO-01 crushed. In addition, only trace amounts of naltrexone were present in five subjects after administration of ALO-01 whole (each had one concentration just above the limit of quantification). Naltrexone is rapidly metabolized to

Table I. Subject demographics

Characteristic	Men (n=26)	Women (n=6)	All subjects (n=32)
Age (y)			
mean (SD)	34.5 (7.8)	37.3 (6.9)	35.0 (7.6)
range	23–47	25–46	23–47
Race [n (%)]			
White	19 (73)	3 (50)	22 (69)
Black/African American	2 (8)	1 (17)	3 (9)
Hispanic/Latino	2 (8)	0	2 (6)
Asian	1 (4)	0	1 (3)
multiracial or other	2 (8)	2 (33)	4 (13)
Bodyweight (kg)			
mean (SD)	84.0 (10.3)	75.7 (12.3)	82.4 (11.0)
range	60.7–105.2	56.7–87.5	56.7–105.2
BMI (kg/m ²)			
mean (SD)	26.4 (2.7)	26.5 (3.2)	26.4 (2.8)
range	21.7–31.0	22.1–30.6	21.7–31.0

BMI = body mass index.

6- β -naltrexol; after administration of ALO-01 crushed, mean 6- β -naltrexol concentrations also rose rapidly (figure 5c), with median t_{\max} again being 1.1 hour (mean \pm SD C_{\max} 20.2 \pm 6.90 nmol/L). Trace amounts of 6- β -naltrexol were present in 14 subjects taking ALO-01 whole during at least one timepoint, with mean concentrations shown in figure 5c.

The highest individual C_{\max} for quantifiable 6- β -naltrexol following ALO-01 whole administration was 0.13 nmol/L, which was 70-fold lower than the lowest individual C_{\max} for quantifiable 6- β -naltrexol following administration of ALO-01 crushed (range 9.28–32.2 nmol/L). Eight subjects had at least three quantifiable concentrations of 6- β -naltrexol following administration of ALO-01 whole; the median t_{\max} in this limited sample was 2.7 hours.

Safety

Most subjects experienced treatment-emergent adverse events following administration of each active agent, including 28 subjects (88%) after MSS and ALO-01 whole, and 23 subjects (72%) after ALO-01 crushed (table III). Fifteen subjects (47%) had adverse events after administration of placebo. All adverse events reported were mild to moderate in intensity, most commonly the typical morphine-associated effects of euphoric mood,

pruritus, somnolence and vomiting. There were no severe or serious adverse events reported and no discontinuations due to adverse events. Other safety assessments, including vital sign assessments and continuous cardiac monitoring, revealed no differences among ALO-01 whole or crushed and MSS.

Discussion

The results of this study suggest that ALO-01, whether taken orally whole, or taken orally after product tampering by crushing, has a lower potential for abuse than MSS in non-dependent subjects who commonly abuse opioids. Administration of MSS produced the characteristic and expected increases in scores on positive effect scales measuring drug-liking and euphoria. For each scale, the responses to MSS were significantly greater than those to placebo (all $p < 0.001$), thereby confirming the validity of each outcome measure.

Administration of ALO-01 whole produced a lower level of positive response as measured by E_{\max} values and a flatter, more gradual effect over time. This profile is consistent with the extended-release characteristics of ALO-01. Measurement of plasma morphine concentrations showed that C_{\max} occurred at a median of 8.1 hours after ALO-01 whole compared with

1.2 hours after MSS. The slower systemic absorption of morphine and lower levels of response attained after ALO-01 whole account for the reduction in euphoria, a key factor that influences drug-seeking behaviour and abuse.^[2]

When crushed, ALO-01 also produced a lower level of response and flatter, more gradual effects on all primary outcome measures compared with MSS. The differences between ALO-01 crushed and MSS in the E_{\max} values for each outcome measure were statistically significant. In this case, the profile reflects the release of sequestered naltrexone from the core of the extended-release pellets and its subsequent absorption into the systemic circulation. Plasma morphine concentrations after ALO-01 crushed and MSS were generally comparable. Plasma naltrexone concentrations peaked approximately 1 hour after administration of ALO-01 crushed. These findings suggest that the release and absorption of naltrexone effectively mitigated the positive effects of morphine.

The subjective measures used in this study were confirmed by the objective assessment of pupil diameter by pupillometry. The characteristic morphine-induced miosis^[19] was evident following administration of MSS. The reduction in pupil diameter with ALO-01 whole and crushed was significantly less than with MSS. Again, ALO-01 whole produced less miosis presumably due to the slow morphine release and absorption from the extended-release formulation, and ALO-01 crushed produced less miosis due to the blocking effects of naltrexone.

This study also provides evidence that naltrexone remains sequestered when ALO-01 is taken orally as directed. Trace amounts of naltrexone were present in only five of 32 subjects, and in each case, measurable naltrexone concentrations above the lower limit of quantification (0.0104 nmol/L) occurred at only one timepoint. Trace concentrations of the 6- β -naltrexol metabolite, which is more bioavailable but has little antagonist activity, were present in 14 (43.8%) of

Table II. Subjective effects and pupillometry at time of maximum effect (n=32)

Pharmacodynamic assessment	Range of scale	Effects of treatment [mean (SD)]			
		placebo	ALO-01 whole	ALO-01 crushed	MSS
VAS for drug-liking ^{a,b}	0–100	52.2 (4.5)	67.6 (13.1)	68.1 (17.5)	89.5 (12.6)
Cole/ARCI abuse potential ^{c,d}	–18 to 18	3.4 (2.9)	5.9 (3.7)	6.3 (4.7)	8.7 (4.0)
Cole/ARCI stimulation-euphoria ^{a,f}	0–45	6.9 (8.2)	10.8 (11.2)	11.9 (11.3)	18.4 (11.6)
ARCI-MBG ^{g,h}	0–51	9.4 (9.8)	13.4 (12.5)	15.7 (13.5)	23.0 (12.8)
Subjective drug value (\$Can) ^{b,i}	0.25–50.00	2.73 (7.08)	14.22 (15.46)	13.72 (16.98)	28.85 (14.55)
Pupil diameter ^b PC _{min} (mm)		4.71 (0.92)	3.20 (0.81)	3.43 (0.81)	2.70 (0.64)

a Response to question "At this moment, my liking for this drug is..." on VAS anchored by 'strong disliking' at 0, 'neutral' at 50, and 'strong liking' at 100.

b $p < 0.001$, all comparisons except ALO-01 whole vs ALO-01 crushed ($p = \text{NS}$).

c Derived from 12 questions scored on a scale of 0–3, of which six questions are weighted positive and six questions are weighted negative; score reflects a net balance between positive and negative effects.^[17]

d $p < 0.001$, all comparisons except ALO-01 whole vs ALO-01 crushed ($p = \text{NS}$) and ALO-01 crushed vs MSS ($p = 0.002$).

e Derived from answers to 15 questions scored on a scale of 0–3.

f $p < 0.001$, all comparisons except ALO-01 whole vs ALO-01 crushed ($p = \text{NS}$), ALO-01 crushed vs placebo ($p = 0.007$) and ALO-01 whole vs placebo ($p = \text{NS}$).

g Derived from answers to 17 questions scored on a scale of 0–3.

h $p < 0.001$, all comparisons except ALO-01 whole vs ALO-01 crushed ($p = \text{NS}$), ALO-01 crushed vs placebo ($p = 0.002$) and ALO-01 whole vs placebo ($p = \text{NS}$).

i Derived from answers to six questions; crossover point at which subject is indifferent between choosing drug and choosing money.

ARCI = Addiction Research Center Inventory; **MBG** = Morphine Benzodrine Group; **MSS** = morphine sulfate solution; **NS** = non-significant; **PC_{min}** = minimum pupil diameter; **VAS** = visual analogue scale.

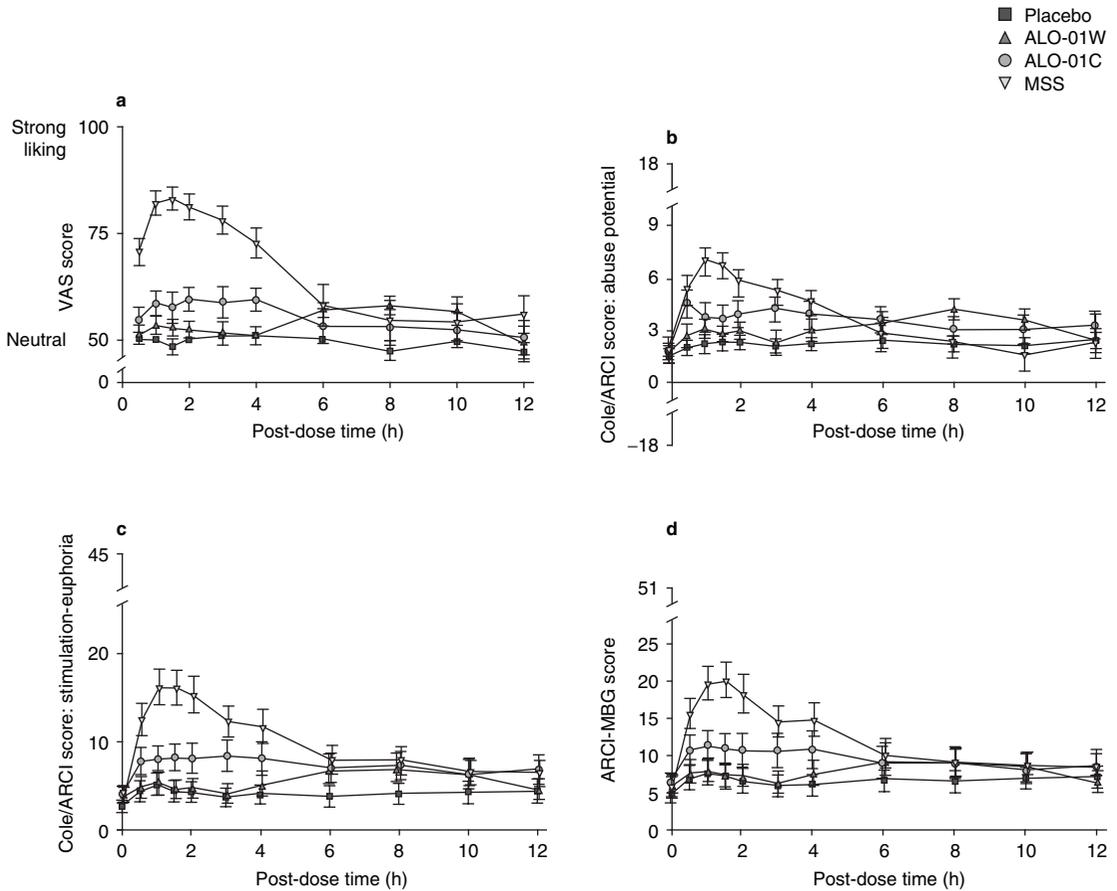


Fig. 4. Effect-time profiles of mean \pm standard error of the mean scores on subjective effects of morphine following administration of ALO-01 whole (ALO-01W; two whole ALO-01 60 mg capsules), ALO-01 crushed (ALO-01C; crushed pellets from two ALO-01 60 mg capsules), morphine sulfate solution (MSS) and placebo ($n=32$ for each) for (a) drug-liking; (b) abuse potential; (c) stimulation-euphoria; and (d) euphoria. **ARCI**=Addiction Research Center Inventory; **MBG**=Morphine Benzidine Group; **VAS**=visual analogue scale.

32 subjects, indicating exposure to minimal quantities of naltrexone.

Similarly, a study that assessed pharmacokinetics of ALO-01 at steady state demonstrated only trace concentrations of naltrexone and 6- β -naltrexol in some patients.^[11] The results of that study also demonstrated that these concentrations did not affect analgesic activity, with no correlation between presence of naltrexone in plasma and pain score. Furthermore, patients in that study reported equivalent pain relief when taking ALO-01 and when taking an extended-release morphine product with no sequestered naltrexone (KADIAN[®]).^[11]

Conversely, the presence of systemic concentrations of naltrexone in subjects in this study when they took crushed ALO-01 confirms that tampering with ALO-01 by crushing the pellets alters the extended-release characteristics and leads to the release of sequestered naltrexone. In a recent bioavailability study of ALO-01 crushed in the same manner (at least 2 minutes with a mortar and pestle) and a naltrexone oral solution of the same dose sequestered in ALO-01 administered to healthy subjects, naltrexone area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) and C_{max} with ALO-01 crushed were bioequivalent to those with the oral

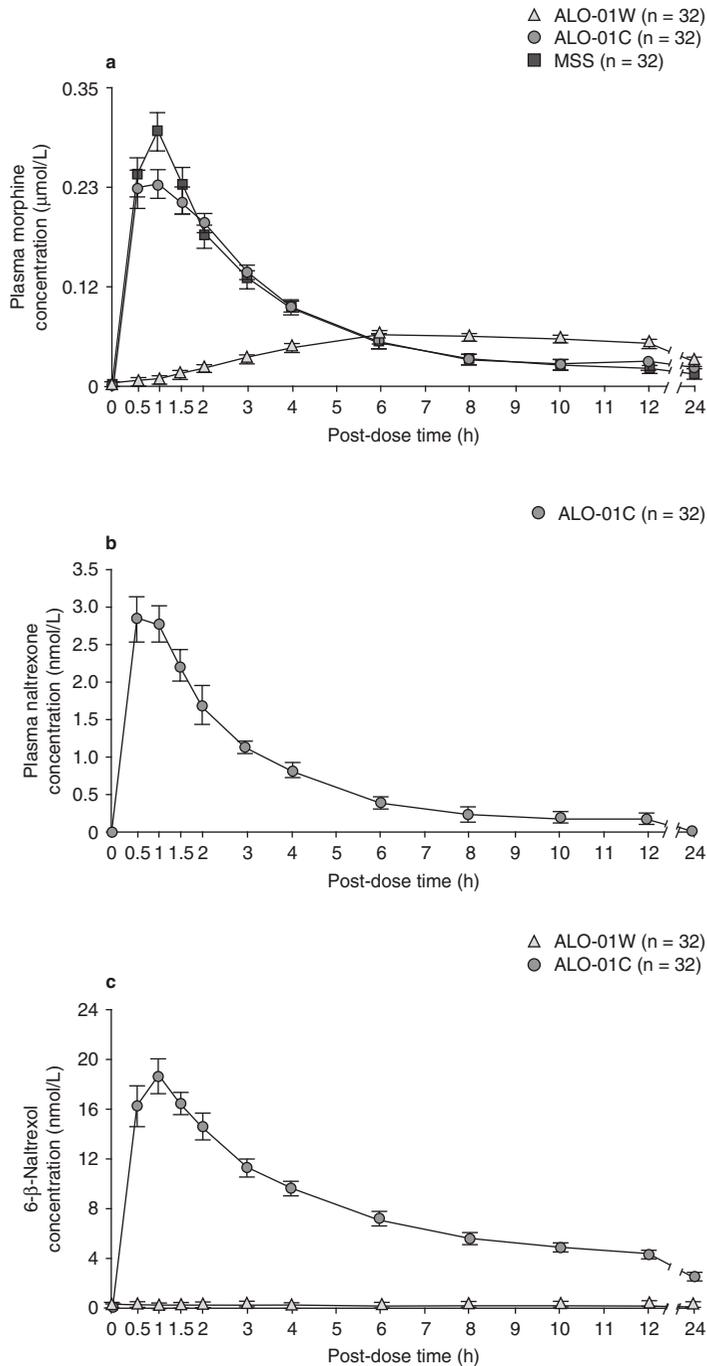


Fig. 5. Mean \pm standard error of the mean plasma concentrations of (a) morphine, (b) naltrexone and (c) 6- β -naltrexol following administration of ALO-01 whole (ALO-01W; two whole ALO-01 60 mg capsules), ALO-01 crushed (ALO-01C; crushed pellets from two ALO-01 60 mg capsules), and morphine sulfate solution (MSS).

Table III. Frequency of treatment-emergent adverse events (TEAEs) during or after treatment periods^{a,b} (n=32)

Variable	Placebo	ALO-01 whole	ALO-01 crushed	MSS
Subjects with TEAEs	15 (47)	28 (88)	23 (72)	28 (88)
Euphoric mood	3 (9)	9 (28)	9 (28)	18 (56)
Pruritus	0 (0)	9 (28)	9 (28)	17 (53)
Somnolence	4 (13)	14 (44)	8 (25)	11 (34)
Vomiting	0 (0)	6 (19)	1 (3)	11 (34)
Nausea	1 (3)	4 (13)	1 (3)	9 (28)
Headache	3 (9)	3 (9)	5 (16)	5 (16)
Dizziness	1 (3)	5 (16)	3 (9)	4 (13)

a Events occurring at a frequency >10% during or after any treatment.

b Data are given as n (%).

MSS = morphine sulfate solution.

naltrexone solution.^[20] Therefore, it can be assumed that approximately 100% of the naltrexone was systemically available in the current study. The degree of morphine receptor antagonism produced by the liberated naltrexone was evidenced by the significant decreases observed in the subjective abuse liability measurements compared with MSS.

The most common adverse events observed during this study were consistent with the safety profile of morphine, i.e. euphoric mood, pruritus, somnolence and vomiting. The reduction in frequency of euphoric mood and most other adverse events with ALO-01 whole compared with MSS is again consistent with its extended-release characteristics. However, somnolence was more common with ALO-01 whole, possibly reflecting the persistence of lower morphine concentrations over time. A further reduction in some adverse events, particularly vomiting and nausea, was seen with ALO-01 crushed, presumably reflecting the opioid receptor antagonist effects of the released naltrexone.

Those who misuse and abuse drugs do so in a multitude of ways, using various techniques and methodologies. The current study examined the attractiveness of ALO-01 when crushed and taken orally. The practice of crushing tablets or capsule content is a simple and convenient method used by drug abusers to prepare a drug

for various routes of administration, including oral ingestion, snorting and intravenous use (by solubilizing crushed material). While this study did not assess other means of abuse, it is important to recognize that study designs testing tampered products in human subjects are subject to practical and ethical constraints that are different from studies in which a product is used as directed.^[21] A separate study in which recreational opioid users were given intravenous doses of morphine and naltrexone, in the ratio present in ALO-01 capsules to simulate intravenous use of the tampered product, yielded similar results, whereby the morphine and naltrexone combination was less attractive than morphine alone.^[22] While additional studies may be considered to simulate other modes of abuse or attempts at opioid extraction, the full impact of these formulations may not be known until they are monitored in the community.

The need for extended-release opioids with reduced abuse potential evolved from the dual obligations to provide pain management while deterring misuse, abuse and diversion. The goal of such a formulation is to provide optimal pain management by allowing slow release of opioid and a constant plasma concentration of analgesic over 12–24 hours, while minimizing the potential for abusers to tamper with these formulations to release the opioid rapidly and attain a desired ‘positive’ euphoric effect. Studies have demonstrated the analgesic efficacy and safety of ALO-01 used as directed in patients with chronic, moderate to severe pain.^[11,23,24] However, use of formulations such as ALO-01 for pain management must be considered within the context of the comprehensive treatment plan. Such a plan should include a detailed medical history and physical examination, screening for history of substance abuse, a written treatment plan with agreed treatment goals (such as functional improvement), guidelines for opioid use, and monitoring for signs of misuse, abuse or diversion, as well as for addiction.^[25] It is important to note that, while development of iatrogenic addiction is rare when opioids are carefully prescribed to appropriate patients,^[25,26] formulations with reduced attractiveness for abuse are not designed

to directly reduce the potential for addiction in patients with a predisposition toward this disorder.

Conclusion

Our study results demonstrate that ALO-01 whole or crushed produced less euphoria, drug-liking and other subjective effects than MSS when taken orally by non-dependent subjects who commonly abuse opioids. This profile indicates that tampering by crushing does not increase the desirability of ALO-01 when taken orally, suggesting that ALO-01 has a lower abuse potential than MSS.

Healthcare providers play a critical role in ensuring the appropriate use of opioid analgesics for patients who need them and in monitoring for signs of aberrant use. As ALO-01 and other products with features that may minimize abuse potential gain regulatory approval, it will be important to assess their impact by monitoring the frequency of misuse, abuse and diversion in the community. If results from this clinical research setting are mirrored in the setting of society, such formulations may assist in the goal of enabling all patients with chronic pain to attain relief using opioid analgesics if needed, while minimizing the attractiveness of these formulations to people who misuse, abuse or divert opioids.

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Joseph Stauffer and Franklin Johnson were responsible for the study design, analysis and interpretation of data, and planning, critical review and approval of manuscript drafts. Marta Sokolowska, Beatrice Setnik, Myroslava Romach (chief investigator) and Edward Sellers (chief scientific advisor) were responsible for protocol development and implementation, study assessments, data entry and transfer, analyses and interpretation of data, writing the clinical study report and critical review of outlines and manuscript drafts. All authors had full access to all data, including statistical reports and tables, and take responsibility for the integrity of the data and the accuracy of the data analysis. Beatrice Setnik is guarantor.

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