# Remoxy™, A Novel Drug Candidate, Deters Oxycodone Abuse in Humans

Pain Therapeutics, Inc.

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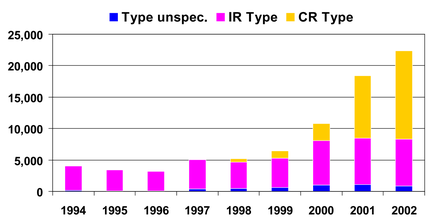
## INTRODUCTION

Abuse of controlled-release (CR) formulations of oxycodone and other prescription opioids is a large, fast-growing problem in the US. Simply crushing and dissolving these formulations can yield the full 12-hr dose to produce an immediate, large spike in opiate blood levels and a powerful morphine-like high, as well as the potential for respiratory depression and death. This problem and associated addictions have attracted a substantial amount of media attention in recent years[1-5]. In the U.S., oxycodone abuse resulted in over 20,000 Emergency Room (ER) visits, according to the Drug Abuse Warning Network (DAWN), a division of the Substance Abuse and Mental Health Services Administration (SAMHSA). Abuse of oxycodone comprised nearly 20% of all ER visits involving abuse of narcotic analgesics in 2002. The majority of oxycodone abuse resulting in ER visits may be due to the introduction of CR formulations, as the increase in ER visits related to oxycodone abuse is coincident with the 1996 introduction and marketing of the initial CR oxycodone formulation (Fig. 1; Source: DAWN).

**Fig. 1. Emergency Room Visits Involving Oxycodone Abuse, 2002**




Remoxy is a novel long-acting oxycodone formulation designed to deter oxycodone abuse. When taken whole as directed, Remoxy and a commercial CR oxycodone formulation result in a similar Cmax and AUC[6]. *In vitro* tests of abuse deterrence show that Remoxy cannot be fragmented by forceful crushing, even after freezing at –80°C, and that its long-acting properties are preserved after crushing or attempts to extract in alcohol. The abuse deterrent properties of Remoxy are demonstrated here in clinical pharmacokinetic studies. Healthy male volunteers ingested Remoxy or a commercial CR formulation subjected to common methods of abuse: crushing followed by extraction in water or alcohol.

## METHODS

These studies received IRB approval, and all subjects gave their written informed consent. Subjects were 18- to 45-year-old healthy male volunteers. In the first study, the pharmacokinetics of Remoxy were compared to those of a commercial CR oxycodone after ingesting whole as intended a 10 mg formulation of each, with both fed and fasted conditions for Remoxy. In the second study, a 10 mg Remoxy and a 10 mg commercial CR oxycodone were subjected to crushing challenge before consuming with water or 80 proof alcohol. In this study, a 10 mg immediate-release (IR) oxycodone formulation was included as a comparator. In each study, blood samples were taken prior to dosing and at specified intervals for 48 hrs post-dosing to determine oxycodone plasma concentrations. In all cases, doses were separated by a washout of 2-3 days.

Study 1:
Oxycodone plasma levels were measured in 5 subjects in a 2-way cross-over of:

1) Remoxy after overnight fasting, and swallowing whole with water.
2) Commercial CR after overnight fasting, and swallowing whole with water.

Three of the 5 subjects subsequently returned to receive:

3) Remoxy after eating a full breakfast.

Study 2:
Two groups of 5 subjects were randomly assigned to receive either Remoxy or the commercial CR oxycodone as well as an IR oxycodone for comparison in a 4-way crossover of:

1) Swallowing whole with water.
2) Swallowing the IR formulation whole with water.
3) Crushing and dissolving in water, then drinking the mixture.
4) Crushing and dissolving in 80 proof alcohol, then drinking the mixture.

## RESULTS

Study 1
In fasted subjects, the absorption of oxycodone from Remoxy was significantly less than that of the commercial CR (Fig. 2). Since the pharmacokinetics for Remoxy and the commercial CR were very similar in preclinical studies, this first clinical PK study suggested that the Remoxy formulation might require GI peristalsis or blood flow for optimal oxycodone absorption. To test this hypothesis, we measured oxycodone plasma levels in 3 of the 5 original subjects after the ingested Remoxy following a meal. Indeed, mean oxycodone plasma levels after this test were equivalent to the previous levels obtained for the commercial CR (Fig.3). The commercial CR is not reported to be affected by food.

**Fig. 2 Plasma Oxycodone Levels in Fasted Subjects**

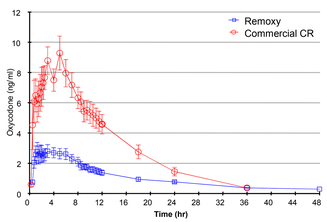
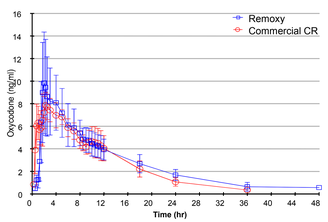
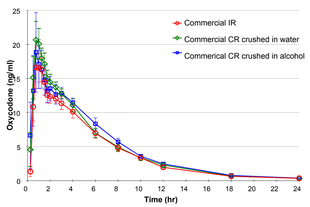



**Fig. 3 Plasma Oxycodone Levels in Fed Subjects**



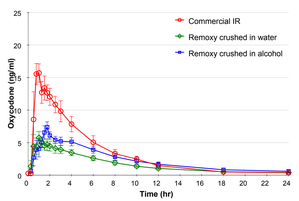

Study 2
This study assessed pharmacokinetics of Remoxy vs. the commercial CR following abuse by crushing and consumption with water or alcohol. For comparison, subjects also took a commercial IR oxycodone formulation of the same dose strength. When crushed and taken with water or alcohol, the commercial CR produced plasma oxycodone levels very similar to the commercial IR formulation. In fact, the Cmax values resulting from crushing the commercial CR formulation in water (21.8 ng/ml) or in alcohol (21.0 ng/ml) were slightly higher than the Cmax of the commercial IR formulation (18.9 ng/ml) (Fig. 4).

**Fig. 4 Plasma Oxycodone Levels after Crushing Commercial CR**



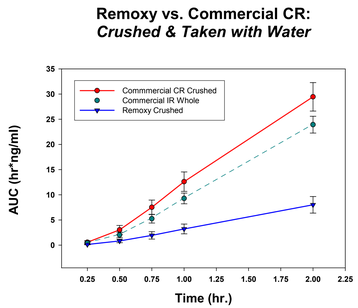

In contrast, the oxycodone Cmax for Remoxy after crushing and taking with water (6.2 ng/ml) or alcohol (7.7 ng/ml) was significantly lower than the Cmax produced by the commercial IR formulation (18.2 ng/ml) ($P$<0.001 for Remoxy with water; $P$<0.001 for Remoxy with alcohol; Fig. 5).

**Fig. 5 Plasma Oxycodone Levels after Crushing Remoxy**



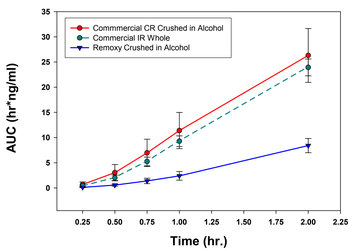

The abuse-deterrent properties of Remoxy are also seen by comparing oxycodone AUCs after crushing each formulation with AUCs after ingesting the IR formulation. Since different subjects took Remoxy versus the commercial CR formulation but all took a commercial IR formulation, data for the IR formulations were pooled after establishing the lack of group differences. Crushing and taking the commercial CR formulation with water resulted in oxycodone AUCs that were slightly higher than AUCs produced by the IR formulation. In contrast, crushing Remoxy and taking it with water produced AUCs that were significantly lower than the commercial IR formulation ($P$=0.03 at 45 min; $P$=0.003 at 1 hr; $P$<0.001 at 2 hr.; Fig. 6).

**Fig. 6**




Crushing and taking each formulation with alcohol produced similar results (Fig. 7). Oxycodone AUCs after taking the crushed commercial CR formulation in alcohol did not differ from those produced by an IR formulation. In contrast, taking crushed Remoxy in alcohol produced AUCs significantly lower than the IR formulation ($P$=0.01 at 45 min; $P$=0.001 at 1 hr; $P$<0.001 at 2 hr).

**Fig. 7**




No adverse events were reported after taking either formulation whole with water except one report of dizziness in the Remoxy group. Crushing and taking Remoxy with water resulted in one report of lethargy. In contrast, crushing and taking the commercial CR formulation with water produced dizziness (4 subjects), a feeling of relaxation (3 subjects), a euphoric mood, fatigue and somnolence (2 reports, each) and nausea, decreased blood pressure, bradycardia, both increased and decreased heart rate, both increased and decreased respiration, dyspnea, pruritis, feeling hot and diaphoresis (a single report of each). The decrease in blood pressure was clinically significant, i.e. a drop from 114/66 pre-dosing to 78/39 one hour later, but recovered within 2 hrs. Crushing and taking with alcohol instead of water did not notably change the incidence of reported side effects for either formulation other than an increase in lethargy or somnolence.

## DISCUSSION

Remoxy is highly resistant to abuse by crushing and dissolving in water or alcohol, in contrast to the commercial CR oxycodone formulation. Crushing the commercial CR oxycodone formulation and taking it with water or alcohol resulted in oxycodone blood levels that were not significantly different than those produced by a commercial IR formulation. The crushing challenges to Remoxy produced oxycodone plasma levels that were significantly lower than those resulting from the commercial IR or crushed CR formulations. The resultant lower blood levels of oxycodone may represent decreased opioid-related side effects, including the euphoric effect sought by abusers and the respiratory depression that has caused many abuse-related fatalities.

## CONCLUSION

**Remoxy is a novel 12-hr oxycodone formulation that is highly resistant to abuse. Crushing Remoxy produced oxycodone plasma concentrations that were significantly lower than both the IR and crushed CR commercial formulations. Remoxy therefore represents a safer alternative to currently marketed CR oxycodone formulations.**

## REFERENCES

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