REL-1017 (esmethadone) Demonstrates No Physical Dependence and No Withdrawal Effects in a Rat Study

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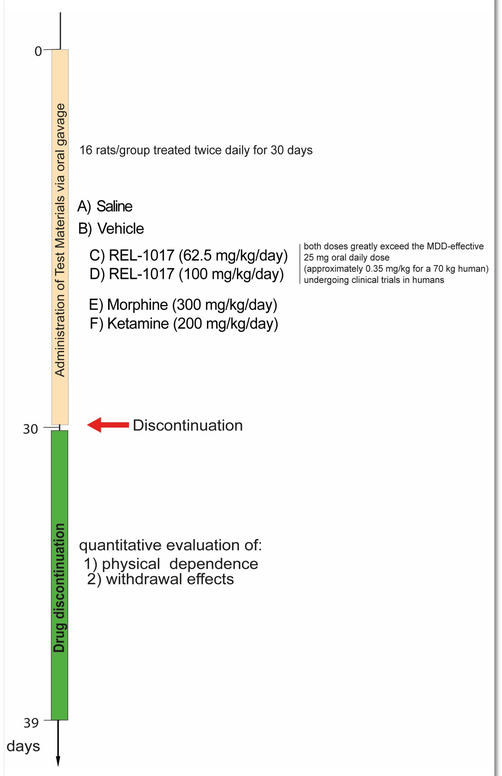
BACKGROUND AND AIM

REL-1017 (esmethadone; dextromethadone) is currently in Phase 3 trials for major depressive disorder[1]. REL-1017 is a novel NMDAR channel blocker[2] with GluN1-GluN2D subtype preference[3] devoid of meaningful opioid agonist effects[4-6]. REL-1017 retains potential neuroplasticity and therapeutic effects without dissociative effects[1-8] and does not cause potentially neurotoxic Olney's brain lesions, unlike higher potency NMDAR blockers[9].

Physical dependence is an adaptive process in response to chronic exposure to drugs. This study, designed and conducted in accordance with the 2017 FDA Guidance on the Assessment of Abuse Potential of Drugs, assessed the potential of REL-1017 to engender physical dependence and withdrawal. The active comparators morphine and ketamine were also evaluated. All drugs in this study were administered via oral gavage.

STUDY DESIGN

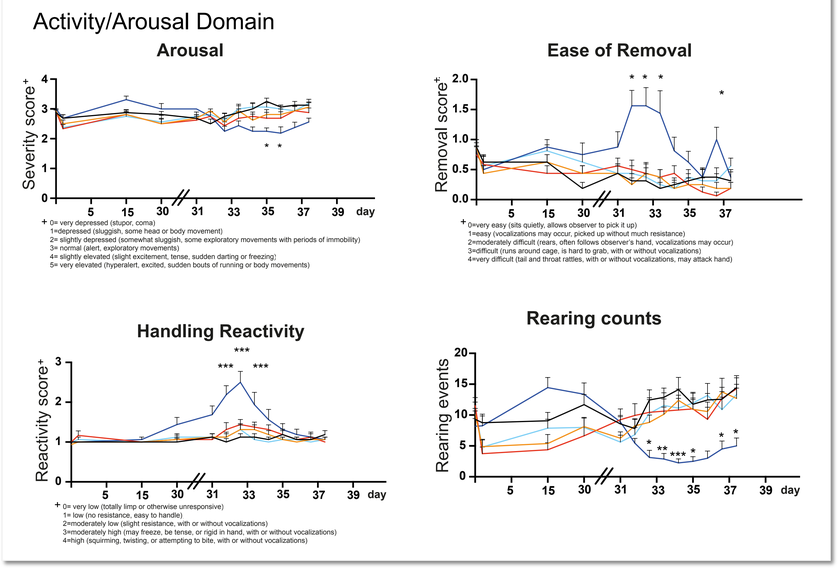


RESULTS

Vehicle — Morphine (300 mg/kg/day) — Ketamine (200 mg/kg/day) — REL-1017 (100 mg/kg/day) — REL-1017 (62.5 mg/kg/day)

Figure 1

Following abrupt cessation after 30 consecutive days of drug administration, measures of excitability (top panels), including arousal, ease of removal, handling reactivity, and rearing counts were significantly different in morphine-treated animals compared to vehicle and REL-1017-treated animals (*=p<0.05; **=p<0.01; ***=p<0.001;****=p<0.0001). Furthermore, vehicle and REL-1017 differed significantly from morphine on tested autonomic and physiological measures (bottom panel), including defecation and body weight.



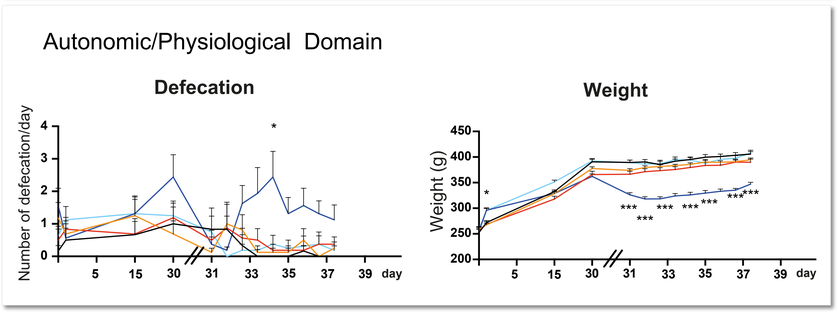


Figure 2

Morphine- and ketamine-treated rats demonstrated statistically significant changes in measurements of neuromuscular functions, including hindlimb and forelimb grip strength, compared to vehicle and REL-1017 (*=p<0.05; **=p<0.01; ***=p<0.001;****=p<0.0001).

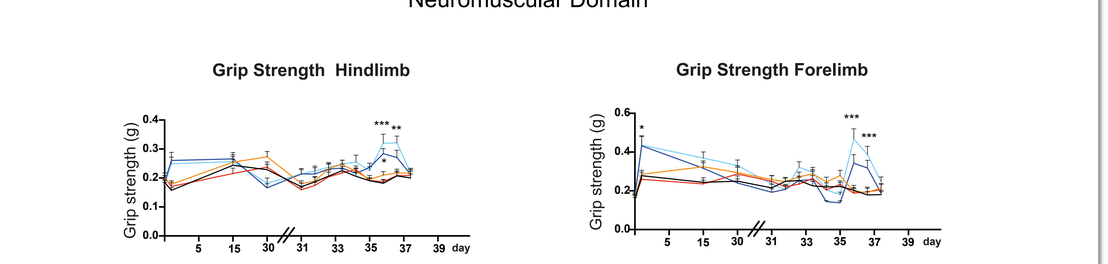


Figure 3

Following abrupt cessation after 30 consecutive days of drug administration, measures related to sensorimotor functions, including non-threatening approach response, tail pinch, and simple body-touch were significantly different in morphine-treated animals compared to vehicle and REL-1017-treated animals (*=p<0.05; **=p<0.01; ***=p<0.001;****=p<0.0001).

CONCLUSION

Upon abrupt discontinuation following 30 days of 300 mg/kg/day morphine, rats exhibited changes characteristic of the classic opioid withdrawal syndrome reported in the peer-reviewed scientific literature. As expected, the withdrawal syndrome engendered by morphine spanned across multiple domains. Upon abrupt discontinuation following 30 days of 200 mg/kg/day ketamine, rats exhibited a mild cluster of changes, as expected for this agent. The testing batteries performed in this study were adequate to identify opiate-type and PCP-type physical dependence and withdrawal.

Upon abrupt discontinuation following 30 days of 62.5 and 100 mg/kg/day REL-1017, REL-1017-treated rats did not engender either morphine-type or ketamine-type discontinuation syndromes. This study confirms earlier data indicating that REL-1017 lacks meaningful opioid agonist effects[4-6]. Additionally, this study further differentiates REL-1017 from the more potent and dissociative NMDAR blocker ketamine. The differentiation of REL-1017 from ketamine had been anticipated by human trials[1,7] showing that REL-1017 lacks dissociative effects at all tested doses.

In conclusion, these data in rodents add to the growing body of evidence signaling that the opioid-inactive dextro-isomer of methadone and NMDAR channel blocker, REL-1017 lacks clinically meaningful opioid agonist effects and PCP-like effects, supporting a recent DEA statement on methadone: *The d-isomer lacks significant respiratory depressant action and addiction liability*[10].

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DISCLOSURES

This research was performed at Charles River Laboratories and was sponsored by Relmada Therapeutics. Dr Gauvin is an employee at Charles River Laboratories. Drs. Manfredi, Pappagallo, Caron, Folli, Henningfield, Ashworth, Lanier are paid consultants of Relmada Therapeutics. Dr. Manfredi is an inventor on esmethadone patents and other patents and patent applications. We are grateful for the contributions of *Dr. Reginald ("Reggie") V. Fant in our efforts to study and understand the potential of REL-1017 for abuse. We were deeply saddened by his unexpected death in September 2020.

Relmada THERAPEUTICS

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