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Abstract Text - 300 word maximum covering each of the following four categories. This version is about 307 words (not including the bold subheadings that are not counted)

Authors: Jack Henningfield, David Gauvin, Francesco Bifari, Reginald Fant*, Judy Caron, August Buchhalter, Judy Ashworth, Marco Pappagallo, Franco Folli, Paolo Manfredi

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Draft Title (200 characters): REL-1017 (esmethadone) Showed No Reinforcing Properties Compared to Oxycodone in Rat Self-Administration Study

Purpose: REL-1017 (esmethadone; dextromethadone) is an NMDAR channel blocker with a preference for hyperactive channels and has twenty-fold lower activity at the μ(mu)-opioid receptor than racemic methadone. REL-1017 is being developed for treatment of Major Depressive Disorder. The purpose of this study was to evaluate the potential reinforcing effects of REL-1017 compared to oxycodone in an intravenous (IV) rat self-administration study.

Methods: Rats were conditioned to self-administer oxycodone during daily access periods. Three-day substitution test sessions were instituted in rats trained to self-administer either oxycodone or saline vehicle (placebo) or four doses of REL-1017: 0.032, 0.056, 0.1 and 0.18 mg/kg. Measures of individual values for total number of infusions, total drug intake, and response rate (measured as number of drug-induced injection) were collected for three consecutive days. Linear regression functions (slopes) were calculated and fitted to the total number of injections during each three-day interval.

Results: Oxycodone maintained stable intake over a wide range of doses functioning as a robust reinforcer. Saline demonstrated a typical "extinction burst" pattern of response, in which initial exposure resulted in lever-pressing and several injections, followed by decreased responding across sessions as is typical of non-reinforcing stimuli in this assay (slope -28,25 vs 0.05; $p<0.05$, saline and oxycodone respectively). The day-to-day patterns of intakes during access to various doses of REL-1017 were statistically indistinguishable from the patterns engendered by saline in this study (p=ns). REL-1017 did not show evidence of reinforcing properties.

Conclusions and Discussion: REL-1017 did not produce reinforcing effects in this study, which suggests that it will not pose a risk for diversion or abuse. These results are consistent with the conclusion that REL-1017 differs substantially from methadone in its pharmacology and abuse potential.

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. All who had the opportunity to work with Reggie on this project came to appreciate him as a friend as well as a respected and invaluable colleague (see https://cpdd.org/membership/in-memoriam/).