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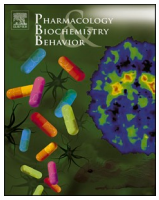

Rapastinel accelerates loss of withdrawal signs after repeated morphine and blunts relapse to conditioned place preference

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ABSTRACT

The purpose of the present study was to evaluate the efficacy of rapastinel, an allosteric modulator of NMDA receptor function, to accelerate the loss of opioid withdrawal symptoms and blunt or prevent relapse to morphine conditioned place preference (CPP) in rats. Two studies were conducted. In study 1, adult and adolescent male and female rats were treated with increasing doses of morphine (5 mg/kg, bid to 25 mg/kg bid) for 5 days. On day 6 animals were treated with naloxone (1 mg/kg) and withdrawal was assessed. They were then treated with saline or rapastinel (5 mg/kg) on days 6 and 8, and withdrawal was assessed on day 9. Rapastinel treated animals exhibited significantly lower levels of withdrawal signs on day 9. No sex or age differences were observed. In Study 2, CPP for morphine was established in adult rats (males and females) by 4 daily pairings with saline and morphine (am/pm alternation). They were tested for CPP on day 5, and then treated with rapastinel (5 mg/kg) or saline daily on days 6–10 of extinction. On day 11 they received a final dose of rapastinel or saline followed by extinction trial. On day 12, animals received 1 mg/kg of morphine and were tested for relapse. Rapastinel did not affect extinction of CPP, but rapastinel-treated animals spent significantly less time in the previously morphine-paired side than saline-treated animals during the relapse trial. These findings of accelerated loss of withdrawal signs and blunted relapse to CPP suggest that rapastinel could provide an adjunctive therapy for opioid dependence during initiation of pharmacotherapy for opioid dependence.

1. Introduction

The current opioid crisis has generated demand for additional therapeutic tools for treating opioid dependent patients. Treatment with the opioid drugs remains the current mainstay of pharmacotherapy of opioid dependence, but there are significant limitations to each of the FDA-approved pharmacotherapies. The opioid agonist methadone improves clinical outcomes but patients experience withdrawal symptoms if doses are lowered too quickly or the medication is stopped (Inturrisi, 2005; Inturrisi, 2002). The partial agonist buprenorphine can elicit withdrawal signs if patients use opioids during treatment and the opioid antagonist naltrexone requires an opioid-abstinent period before treatment begins (Maiti et al., 2020). Therefore, there is a pressing need for a non-opioid treatment to complement available pharmacotherapies. This need is especially critical for a rising population of adolescent opioid users. Adolescents and young adults (ages 18–25 especially) exhibit significant use of prescription opioids (143 % of high school seniors reported prescription opioid misuse use in the 2019 Youth Risk Behavior Study, and 1.8 % report heroin use) and this demographic has experienced an alarming increase in opioid use and overdose deaths, likely due to the presence of fentanyl and other opioids in the opioids they consumed (Bohm and Clayton, 2020; Friedman et al., 2022; Ford, 2019). Furthermore, there is only one medication approved for use in opioid-dependent adolescents (buprenorphine), which is effective, but retention of adolescents in buprenorphine treatment has been poor and they show a high relapse rate (Marsch et al., 2016; Marsch et al., 2005; Schuman-Olivier et al., 2014). Compulsive use of opioids results from neuroadaptation in many brain areas affecting reward-based behavior, autonomic function, and stress axes which lead ultimately to compulsive use despite negative consequences, and the symptoms both physiological and behavioral (withdrawal) which can be enduring after use stops (Kalivas and O'Brien, 2008; Koob, 2021).

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Neuroadaptation in the brain glutamate system represents a significant component of these changes, and demonstration of these changes has motivated interest in the potential of glutamate-modifying drugs as pharmacotherapies. Animal studies show that many aspects of glutamate transmission change during chronic exposure to opioids, including glutamate release and uptake as well as function of both AMPA and NMDA receptors (Neuhofer and Kalivas, 2018; Scofield et al., 2016; Medrano et al., 2015; Rawls et al., 2010; Hearing et al., 2018). Upregulation of NMDA receptor subunits (NR1) perseveres for weeks after chronic opioid exposure (Anderson et al., 2012; Anderson et al., 2015; Bajo et al., 2006; Oh et al., 2000; Murray et al., 2007). This neuroadaptation of NMDA receptors may be critical for the development of compulsive use of opioids (Hopf, 2017; Koob and Volkow, 2016; van Huijstee and Mansvelder, 2014). Research on the ability of NMDA receptor antagonists to treat both compulsive opioid self-administration and the symptoms of withdrawal support this possibility (Fluyau et al., 2020). In animal models, the prototype NMDA antagonist ketamine diminished heroin, methamphetamine and cocaine self-administration (Xi and Stein, 2002), the NMDA antagonist MK-801 blunted opioid withdrawal (Trujillo and Akil, 1991), and the NMDA antagonist memantine reduced opioid withdrawal symptoms in one human trial (Bisaga et al., 2014). Unfortunately, each of these pharmacologic approaches has significant limitations. Ketamine has a known human abuse and a serious side-effect profile, provoking dissociation and hallucinations at high doses (Liu et al., 2016). Memantine is a weak antagonist, and its clinical action is limited. Subtle modulation of NMDA receptor function has also been explored (Tomek et al., 2013). D-cycloserine, a glycine-site partial agonist, facilitated extinction of morphine CPP as well as naloxone conditioned place aversion (Lu et al., 2011; Myers and Carlezon, 2010a; Myers and Carlezon, 2010b), and another glycine-site antagonist felbamate diminished withdrawal severity in animals (Kosten et al., 1995). However, d-cycloserine has been unsuccessful in clinical studies of several psychiatric conditions including cocaine craving, which may be due to its narrow effective dose range, short duration of action and lack of efficacy with chronic treatment (Das and Kamboj, 2012; Hofmann, 2014; Johnson et al., 2020; Prisciandaro et al., 2013; Santa Ana et al., 2015).

The purpose of the present study was to investigate the possibility that rapastinel, a novel allosteric modulator of the NMDA receptor, might show efficacy in treating both acute withdrawal and the motivation to experience opioid reward without the limitations that other glutamate-targeted drugs have demonstrated. Rapastinel is a brain penetrant tetrapeptide derived from a monoclonal antibody to the NMDA receptor that recent findings show functions as a positive allosteric modulator of this receptor (Haring et al., 1991; Stanton et al., 2009; Moskal et al., 2005; Donello et al., 2019). It has shown potential efficacy against depression and PTSD, reversal of cognitive impairment and neuroprotection without the psychiatric side effects or reinforcing actions of ketamine (Moskal et al., 2005; Moskal et al., 2017; Garay et al., 2017; Newport et al., 2015; Zhang et al., 2008). Rapastinel may act in part through enhancement of NMDA receptor NR2B subunit action (Stanton et al., 2009; Burgdorf et al., 2015a; Burgdorf et al., 2011a; Moskal et al., 2014). Rapastinel has an additional benefit for treatment of psychiatric conditions: it initiates a sustained biologic effect that lasts from 5 days to a month after a single injection due to a sustained stimulation of NMDA receptor signaling (Zhang et al., 2008; Burgdorf et al., 2015a; Burgdorf et al., 2011a; Burgdorf et al., 2011b; Burgdorf et al., 2013; Burgdorf et al., 2015b). This feature introduces the possibility that weekly treatments might be adequate to sustain a clinical outcome. We hypothesized that rapastinel could suppress acute withdrawal signs, and perhaps prevent or blunt relapse. We used two well-characterized animal models to explore this possibility using investigator-administered opioid: the expression of acute withdrawal signs which occurred at the end of treatment, and the reinstatement of conditioned place preference, a measure of "motivated seeking" of a drug-associated environment (McKendrick and Graziane, 2020), a common trigger for relapse to drug use in abstinent opioid users.

The present study included both males and females to determine if there was a sex-specific sensitivity to treatment, as well as both adolescents and adults (Marsch et al., 2016; Marsch et al., 2005; Schuman-Olivier et al., 2014). Successful trial data with *N*-acetylcysteine against cannabis use disorder suggest that glutamate-targeted therapy may be effective in this undertreated disorder (Squeglia et al., 2019).

To test this hypothesis, this study utilized experimental designs that were intended to model treatment initiated at the beginning of abstinence, a situation analogous to the one that patients would experience. In experiment 1, we monitored opioid withdrawal symptoms with a well-characterized investigator-administered morphine treatment paradigm followed by assessment of naloxone-precipitated withdrawal at two time intervals. Rapastinel treatment was initiated at the start of opioid *abstinence*, after the first naloxone-precipitated withdrawal, to mimic clinical experience. Animals were treated with rapastinel or saline for three days, and naloxone-precipitated withdrawal was repeated to determine if rapastinel accelerated the loss of opioid dependence. The timing of the trial was based on substantial literature demonstrating that passive opioid withdrawal symptoms persist for at least a week in rats after a brief chronic treatment regimen (Villar and Bhargava, 1992; Kosersky et al., 1980; Yoburn et al., 1985). The second experiment evaluated the ability of rapastinel to blunt reinstatement after a brief (5 day) conditioned place preference paradigm. Rapastinel treatment was initiated during extinction from CPP, again paralleling potential clinical practice, and its effect on relapse after a probe dose of morphine was tested. A brief conditioning period and low dose of morphine were utilized to achieve extinction over a brief period. This facilitated timely assessment of rapastinel efficacy.

2. Materials and methods

2.1. Experimental subjects

Subjects were male and female adolescent and adult Sprague Dawley rats (PN 28–30 and PN 70–72) from Charles River Laboratories (Raleigh NC). This young adolescent age was selected based on earlier work by this laboratory that dopamine responsivity to many addictive drugs and their reinforcing effects are highest during this age range and that opioid withdrawal is robust (Schramm-Sapyta et al., 2011; Walker et al., 2009; Walker and Kuhn, 2008; Madison et al., 2020; Jiménez-Romero et al., 2020; Carpenter et al., 2020; Sanchez et al., 2016; Koek, 2016). Animals were grouped-housed in single sex groups in a 12/12 light/dark cycle with free access to water and standard lab chow.

2.2. Drug treatments

The basic treatment regimen is shown in Fig. 1. Rats were treated with a 5-day, increasing dose morphine regimen (5 mg/kg of the morphine salt s.c., bid, increasing 5 mg/kg/day to 25 mg/kg). Controls were treated with sterile 0.9 % saline bid. Adult male and female rats were randomized to saline or rapastinel post-morphine treatment groups before initiation of morphine treatment. All animals received saline or morphine on days 1–5, and a dose of naloxone (1 mg/kg, s.c.) on the morning of day 6 (12 h after the last morphine dose) to precipitate withdrawal. Withdrawal behaviors (wet dog shakes, diarrhea, mastication, salivation, ptosis and abnormal posture) were quantified as described by Gellert and Holtzman (1978) starting 10 min after naloxone. They were then treated with saline or rapastinel (5 mg/kg on day 6 and 8) according to group designation. The dose and alternate days of treatment are based on rat studies of rapastinel effects on depressive-like behavior which persisted for several days after a single injection (Burgdorf et al., 2015a; Burgdorf et al., 2013). On day 9 animals received a second naloxone challenge (1 mg/kg, s.c.) and withdrawal was scored again. One female was removed from the withdrawal cohort due to values triple that of other animals (excluded by Grubbs

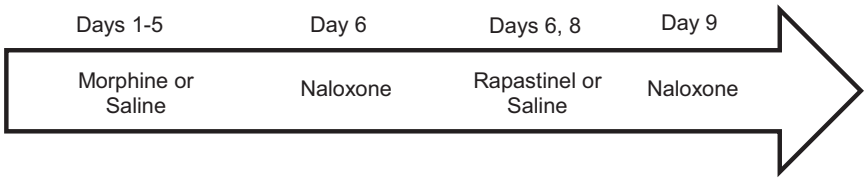

Fig. 1. Experiment 1.

test). Drug treatments and withdrawal assessments were conducted during the light phase.

2.3. CPP and extinction

Conditioned place preference (CPP) was conducted in adult male and female rats with a biased CPP procedure adapted from Mueller et al. (2002) (Fig. 2). Each rat was assigned to morphine on its nonpreferred side. CPP was conducted in a two-sided chamber. Side 1 had white walls and plexiglass flooring, and Side 2 had black walls and plastic mesh flooring (preferred side).

2.4. Acquisition

On habituation day (day 1), animals were allowed to explore the whole apparatus for 30 min. On days 2–4, rats were injected with morphine (2.5 mg/kg s.c.) or saline and immediately restricted to Side 1 for morphine or Side 2 for saline (alternated am and pm daily, 30 min). On test day 5, time on each side was monitored as animals explored the apparatus freely for 30 min.

2.5. Extinction

Extinction was conducted on days 6–10. Rats received saline pairings in both sides (AM and PM) for conditioning. During the extinction trial on day 10, animals could explore the entire chamber.

2.6. Relapse

Relapse was measured on day 11: animals were treated with saline or morphine (1 mg/kg) and allowed to explore both sides of the apparatus for 30 min. Animals were assigned to saline or rapastinel before the experiment started but were treated with saline or rapastinel (5 mg/kg) only during extinction in the morning on each day. Data are expressed as time on the drug-paired side. Four animals from each sex were excluded due to failure to develop a CPP (<100 s increase in time spent on drug-paired side), and so extinction and relapse were not tested. Two additional animals from each sex were eliminated because they did not extinguish CPP. Conditioning and testing were conducted during the light phase. AM testing took place 8–10, and PM testing from 4 to 6.

2.7. Materials

Morphine HCl was supplied by the National Institute for Drug Abuse. Naloxone was obtained from Sigma Chemical Company (St Louis, MO). Rapastinel was synthesized by the Duke Small Molecule Synthesis Facility and provided by Dr. David Gooden.

2.8. Statistics

Experimenters delivering naloxone and conducting the behavioral observations were blinded to the treatment. Withdrawal results were analyzed by 3-way repeated measures ANOVA (age, sex and treatment were the between subject variables and day was the within subject variable) followed by post-hoc Fishers LSD multiple comparison test to compare differences between groups. CPP data were analyzed by repeated measures ANOVA (treatment and sex were the between subject variables and day as within-subject variable). All experiments were approved by the Duke University IACUC and conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

3. Results

We conducted saline and rapastinel controls to verify that rapastinel did not affect the baseline behavioral assessments conducted in the withdrawal study and the CPP study. Fig. S1 shows that on day 9, the single day of the trial in which animals experienced rapastinel treatment, measurable withdrawal effects were not observed either in animals treated for 5 days with saline followed by naloxone on day 6, and saline control for rapastinel and a second passive withdrawal task on day 9 or in animals treated with saline for 5 days followed by naloxone on day 6 and then rapastinel. Saline-treated animals receiving naloxone on day 6 were not run on day 6 as a previous unreported study from this laboratory showed that withdrawal signs using our version of the withdrawal scale were very low (Fig. S2). Finally, Fig. S3 shows that animals treated with saline or rapastinel during extinction of the CPP task (the only time when CPP animals received rapastinel) showed identical total locomotion, suggesting that sedative effects of rapastinel did not influence behavior in this task. Concordant with published data (Burgdorf et al., 2013), rapastinel is not sedating nor does it demonstrate conditioned place preference or place aversion. Therefore, we omitted saline/rapastinel controls from subsequent experiments to minimize animal use.

Fig. 3 shows mean withdrawal scores of male and female adults on Day 6, and on day 9, after 2 treatments with saline or rapastinel. Day 6 data are shown with combined saline-rapastinel groups as these data were collected before cohorts were treated. Scattergram of data is shown in Fig. S4. Animals exhibited robust withdrawal signs which diminished by day (main effect of day, $F(1,47) = 122.2$, $p < 0.0001$ for effect of day). Animals treated with rapastinel had significantly lower withdrawal scores on day 9 (treatment × day interaction, $F(1,47) = 17.95$, $p < 0.0004$). There was a sex × day interaction ($F(1,47) = 12.00$, $p < 0.002$) but no interaction with treatment: males declined more than females from day 6 to day 9. Responses in adolescents were like those observed in adults.

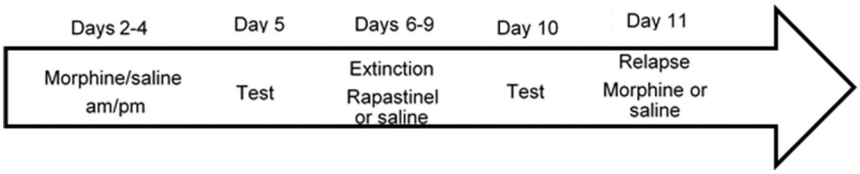

Fig. 2. Experiment 2.

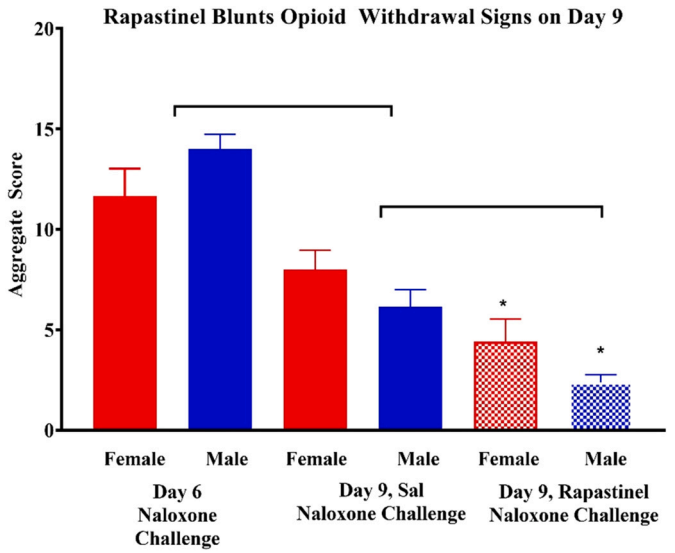

Fig. 3. Naloxone-precipitated withdrawal score on days 6 and 9 after 5 days of morphine treatment. Females indicated in red, males in blue. Rapastinel treatment indicated as cross-hatched. Results expressed as mean ± SEM. Brackets indicate that day 6 animals differed from day 9 Saline animals and Day 9 Saline differed from Day 9 Rapastinel by Fisher's LSD multiple comparison test. N's 5–7 for each experimental group. Asterisks indicate statistically different from animals that received saline not rapastinel.

Fig. 4 shows withdrawal on Day 9 after post-morphine saline or rapastinel in adult rats (adult data from Fig. 1) and a similar cohort of adolescents. Results are collapsed for sex, as no main effect of sex or interaction with treatment were observed. N's for the groups collapsed by sex were 12–14/group. Withdrawal on Day 6 was comparable in adolescents and adults (adult = 13.5 ± 0.9, N = 25, adolescent = 12.3 ± 0.7, N = 28). Scattergram of data is shown in Fig. S5. Naloxone treatment elicited a significant withdrawal response which declined with days after the end of morphine treatment ($F(1,58) = 201.9$, $p < 0.0001$ for effect of day). Animals treated with rapastinel had a lower response on day 9 compared to saline-treated animals ($F(1,58) = 31.1$, $p < 0.0001$ for interaction of day × treatment, testing on day 6 vs. day 9), suggesting that treatment with rapastinel accelerated the loss of dependence over this brief time in both adolescents and adults. There was no main effect of age or interaction or age × treatment.

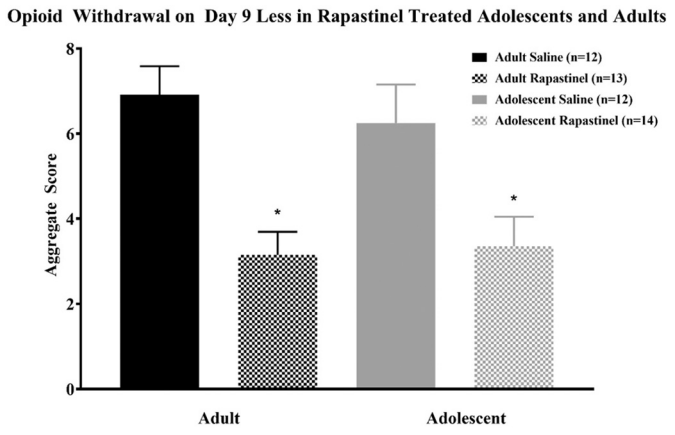

Fig. 4. Naloxone-precipitated withdrawal on Day 9 in adults and adolescents treated with saline or rapastinel from day 6 to day 9 after a 5-day morphine treatment. Results are expressed as mean ± SEM. * indicates different from age-matched saline treatment by Fisher's LSD multiple comparison test. N's for the groups collapsed by sex were 12–14/group.

CPP was conducted only in adults, as no age differences were observed in the withdrawal study. Repeated measures ANOVA including sex and treatment as between factors and time (1 = habituation, 2 = CPP and 3 = extinction) as within factors. Rapastinel was included as a treatment to indicate that there was no difference between animals assigned to saline or rapastinel BEFORE treatment started.

Fig. 5a shows habituation, CPP to morphine and Extinction in males and females. Scattergram of data is shown in Fig. S6. The repeated measures ANOVA indicated a significant effect of time indicating significant increase in time spent in the drug-paired side followed by decrease during extinction ($F(1,34) = 55.5$, $p < 0.0001$, N = 18 for saline, 17 for rapastinel). Time 1 (habituation) was significantly different from CPP and CPP was significantly different from Extinction by Fishers LSD multiple comparison test. No sex differences were observed, and no effects of rapastinel (as expected, as rapastinel treatment was initiated after CPP was established, and expected only in Time 3 (Extinction)).

Fig. 5b shows data by treatment (pooled by sex) to demonstrate that there was no difference in habituation or CPP times for animals pre-assigned to saline or rapastinel groups (treatment which began after assessment of CPP through extinction), indicating no baseline differences in the magnitude of CPP. Scattergram of data is shown in Fig. S7. Extinction values were slightly but significantly still elevated relative to habituation.

Fig. 6 shows extinction and reinstatement data collected after all

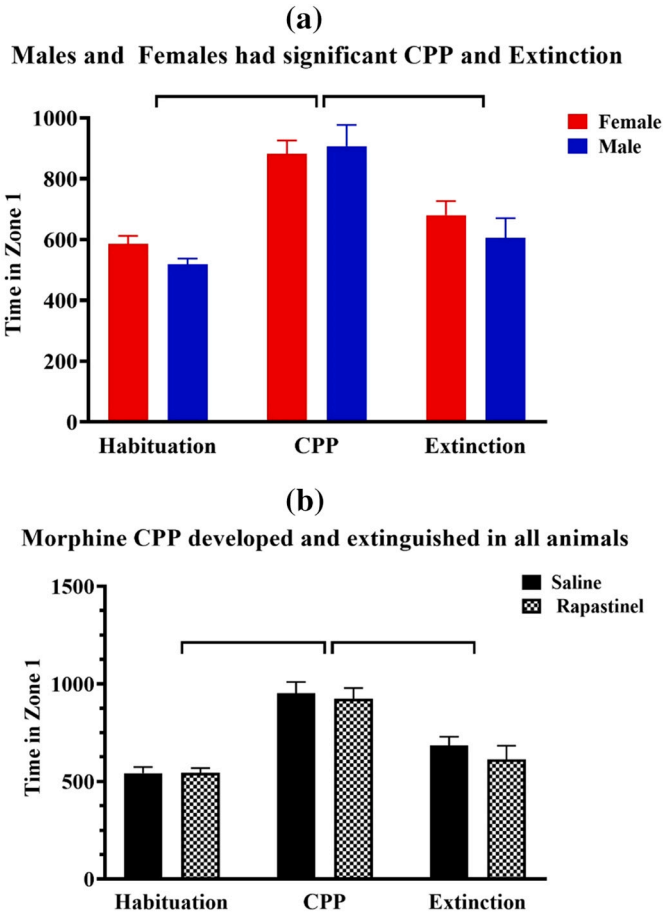

Fig. 5. a. Habituation, CPP and Extinction during morphine induced CPP by sex. Results are expressed as mean ± SEM. Brackets indicate CPP different from Habituation and from Extinction by Fishers LSD multiple comparison test. N = 19 for females and 16 for males. b. Results collapsed by treatment. Saline-treated animals are solid, rapastinel-treated animals are cross-hatched. N = 18 for saline, 17 for rapastinel.

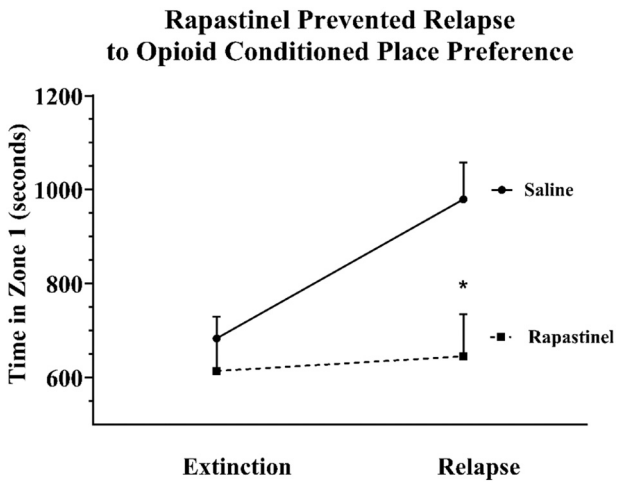

Fig. 6. Reinstatement to CPP with morphine challenge in animals treated with saline (solid line) or rapastinel (dotted line). Results are expressed as mean ± SEM. * indicates different from saline treatment by Fisher's LSD multiple comparison test. N = 18 for saline and 17 for rapastinel.

animals were treated with morphine following extinction is shown in Fig. 2. Scattergram of data is shown in Fig. S8. Repeated measures ANOVA was conducted with sex and treatment as between factors, and time (time 1 = extinction, time 2 = reinstatement) as within factors, as indicated above. ANOVA indicated a significant effect of day ($F = (1,33) = 9.97$, $p < 0.003$), a significant effect of treatment and a significant time × treatment interaction ($F(1,33) = 6.55$, $p < 0.02$) indicating that rapastinel blunted reinstatement. There was no effect of sex on any of the measures.

4. Discussion

The main findings of this study are that rapastinel, the novel allosteric modulator of NMDA receptors for glutamate rapastinel can accelerate the loss of opioid dependence in animals that have become morphine-dependent through investigator-administered drug and can blunt reinstatement to morphine conditioned-place preference. Rapastinel treatment initiated at the start of withdrawal (as would occur for a clinically useful pharmacotherapy) resulted in lower withdrawal signs on day 9 in both sexes and ages and treatment begun during extinction of CPP resulted in blunted reinstatement to morphine CPP. We speculate that these changes may represent a more rapid reversal of neuroplastic changes that contribute to opioid dependence. These two findings suggest that it could potentially be useful in treatment of opioid dependence.

The rapastinel dosing strategies utilized in this study were based on two considerations. First, previous reports demonstrated that rapastinel has a brief half-life, but its behavioral effects reflect a combination of acute and prolonged biological/behavioral effects after a single dose. This has been demonstrated in numerous studies of its effect on pain, and in animal models of depression (Donello et al., 2019; Moskal et al., 2017; Ghoreishi-Haack et al., 2018; Khan et al., 2017). Second, we initiated treatment *after* the development of dependence or CPP to evaluate its potential therapeutic utility without interference from its potential to blunt the development of dependence or place preference. A slightly different regimen (daily not alternate days) was chosen for the CPP study to guarantee coverage of both extinction and reinstatement in the absence of any previous research on this agent in this behavioral protocol. This approach models how rapastinel might be used in a clinical context, in which patients are already drug dependent, but could benefit from treatments which ameliorate withdrawal or lower the chance of reinstatement.

All animals, regardless of sex or age, demonstrated marked and comparable signs of naloxone precipitated withdrawal 12 h after the last morphine treatment, and smaller but still statistically significant signs on day 9, after 3 days of passive withdrawal. The fall in withdrawal signs from day 6 to day 9 is consistent with an abundant literature on opioid withdrawal in adults which shows that withdrawal signs are typically observed for up to 8–10 days after cessation of a treatment regimen (Kandasamy et al., 2017; Cicero et al., 2002; Kelsey et al., 1990).

The lack of sex or age differences in the magnitude of withdrawal could reflect the increasing dose regimen of morphine and the large dose of naloxone used which resulted in high withdrawal scores. Exaggerated naloxone-precipitated withdrawal has been reported in males compared to females (Craft et al., 1999) as has the absence of sex differences (Cicero et al., 2002; Towers et al., 2019). Opioid withdrawal occurs even in infancy in humans (McQueen and Murphy-Oikonen, 2016) and rats (Barr et al., 1998; Ceger and Kuhn, 2000), but behavioral manifestations differ and mechanisms differ from adults (Barr et al., 2011). We showed that behavioral and hormonal withdrawal responses increased from postnatal day (PN) 10 to PN 26 (juvenile, pre-adolescent age) (Windh et al., 1995). The data in adolescents here is consistent with the increasing pattern with age observed in our previous study (Windh et al., 1995). There are few other studies of opioid dependence in adolescent rats and these involve other dependent measures, and no comparison to adults (Jiménez-Romero et al., 2020). The one study using comparable behavioral measures surprisingly reported no withdrawal signs in adolescents after heroin exposure (Doherty and Frantz, 2013), a finding that contradicts the literature reporting withdrawal signs at earlier ages.

The lack of sex differences in morphine CPP is consistent with several studies which reported comparable morphine CPP in male and female rats at the dose used in the present study, although females have been reported to acquire CPP at lower doses than males (Karami and Zarrindast, 2008; Cicero et al., 2000; Timar et al., 2010). These CPP findings are consistent with the conflicting literature about sex differences in opioid self-administration and dependence in rodents. Sex differences (with females acquiring faster and taking more drug) have been reported (Towers et al., 2019; Lynch and Carroll, 1999; Cicero et al., 2003) as has the absence of sex differences (Hempel et al., 2020; Venniro et al., 2017).

Withdrawal signs decreased significantly more in rapastinel-treated animals than in saline-treated animals from day 6 to day 9, although the distribution of specific withdrawal signs did not differ (data not shown). The physiologic basis of the signs tracked by Gellert and Holtzman (wet-dog shakes, diarrhea, mastication, salivation, ptosis and abnormal posture) are skewed toward peripheral autonomic effects likely mediated by increased activation of descending noradrenergic function by afferent input (Caille et al., 1999; Frenois et al., 2002; Nestler, 2016; Rasmussen et al., 1990). The effects of rapastinel observed in the present study are consistent with studies by Rasmussen which have shown that NMDA antagonists may blunt physical signs of withdrawal through actions in the locus coeruleus (Rasmussen et al., 1990; Rasmussen, 1995; Rasmussen et al., 1995; Rasmussen et al., 1991).

Rapastinel also significantly decreased reinstatement of CPP following extinction, which likely was mediated by neural circuits distinct from those mediating the naloxone-precipitated withdrawal signs. The dose of morphine used in CPP studies was considerably lower than that used in the withdrawal study (4 daily doses of 2.5 mg/kg vs twice daily dosing increasing from 5 to 25 mg/kg/injection and animals experienced 5 days before the relapse study). Multiple previous studies show that NMDA antagonists memantine and MK801 blunt reinstatement of morphine CPP (Aguilar et al., 2009; Popik et al., 2006; Ribeiro Do Couto et al., 2005) although negative findings with d-cycloserine have been reported (Lu et al., 2011). Rapastinel values did not differ from controls after extinction, in contrast with a recent study which showed that spermidine both enhanced extinction and prevented reinstatement in mice through an action the authors speculated reflected its modulatory action on NMDA receptors (Girardi et al., 2020). Although

we avoided preventing CPP by delaying rapastinel treatment, it is possible that rapastinel itself could cause a conditioned place aversion that could appear to be a blunting of relapse. It is also possible that rapastinel relieved withdrawal symptoms and thereby reduced the negative reinforcement value of morphine causing animals to spend less time in the drug-paired zone in the CPP test (Ahmed et al., 2000). While these preliminary data are promising, potential clinical utility of rapastinel in preventing relapse should be followed up by a more definitive method like self-administration.

There has been significant research interest in the possibility that antagonists of NMDA receptor function might prove clinically useful in treating opioid dependence, as outlined above. Many aspects of glutamate transmission change during repeated opioid exposure, including glutamate release and uptake as well as both expression and function of AMPA and NMDA receptors (Neuhofer and Kalivas, 2018; Scofield et al., 2016; Medrano et al., 2015; Rawls et al., 2010; Hearing et al., 2018). Neuroadaptation of NMDA receptors may be critical for the development of compulsive use of opioids (Hopf, 2017; Koob and Volkow, 2016; van Huijstee and Mansvelder, 2014). Upregulation of NMDA receptor subunits (NR1) perseveres for weeks after chronic opioid exposure (Anderson et al., 2012; Anderson et al., 2015; Bajo et al., 2006; Oh et al., 2000; Murray et al., 2007). The ability of rapastinel to blunt opioid withdrawal signs and relapse to CPP is consistent with studies of other NMDA receptor antagonists which blunt other behaviors reflective of opioid reinforcement. However, rapastinel has recently been shown to be a positive allosteric modulator of the NMDA receptor at antidepressant doses (Wang et al., 2022), and has been proposed to work through a "metaplasticity" that can include complex modulation of various aspects of glutamate transmission (Burgdorf et al., 2015a). The present findings indicate that more subtle modulation of glutamate function may provide better clinical outcomes and lack the side effects associated with negative modulators of NMDA function. Rapastinel may serve as a first-in-class of a family of NMDA receptor modulators which lack ketamine-like side effects that are being explored for treatment of depression, pain and other conditions that may also prove useful in treating drug dependence. These include apimostinel, a more potent analogue of rapastinel and CP-101,606 (traxoprodil), which also targets NR2B receptors (Fasipe, 2019; Wilkinson and Sanacora, 2019).

The present study utilized two rapid screens for pharmacologic action against opioid dependence (withdrawal, reinstatement of CPP) to determine whether this drug had potential efficacy as a medication. There are limitations to this study. First, we did not exhaustively assess the locomotor effects in the study, as published research on rapastinel has yielded only negative data on this measure. The comparable basal activity during the reinstatement trial and activity during extinction when rapastinel treatments were given suggests that our conclusions are not invalidated by locomotor effects of rapastinel. Second, the use of a biased design in the CPP study could artificially inflate drug preference. Third, it is not possible to differentiate between the immediate effects of rapastinel and its persevering effects: multiple studies have shown that effects on NMDA receptor function as well as its behavioral effects are observed immediately but last over a period of at least days (Zhang et al., 2008; Burgdorf et al., 2015a; Burgdorf et al., 2011a; Burgdorf et al., 2011b; Burgdorf et al., 2013; Burgdorf et al., 2015b). The termination of clinical trials for depression suggest caution about its potential utility in treating opioid dependence, although one factor in the failure of depression trials was the well-known robust placebo effects in depression trials. In addition, it is likely that rapastinel has actions in different cell populations in exerting the effects noticed in this study.

Future work which clarifies the dose and frequency of rapastinel treatment and its site of action are needed to resolve some of these limitations. Understanding these limits is especially important as the peptide structure of rapastinel imposes limits on acceptable routes of administration. In addition, approaches to studying opioid dependence that include extended-access opioid self-administration followed by abstinence and reinstatement trials will provide better evidence of clinical potential. Investigation of its mechanism and location of action and assessment of its efficacy in blunting opioid-induced hyperalgesia and prolonged abstinence signs like "craving" and anxiety which are thought to play a significant role in relapse to opioid use will also provide substantial information about the utility of this therapeutic approach (Towers et al., 2019; Koob, 2020; Kenny et al., 2018).

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Declaration of competing interest

Drs. Kuhn and Patkar have a patent pending on use of rapastinel in treating drug dependence. The other authors have no interests to declare.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pbb.2022.173485.

References

Aguilar, M.A., Rodriguez-Arias, M., Minarro, J., 2009. Neurobiological mechanisms of the reinstatement of drug-conditioned place preference. Brain Res. Rev. 59 (2), 253–277. https://doi.org/10.1016/j.brainresrev.2008.08.002. Mar.

Ahmed, S.H., Walker, J.R., Koob, G.F., 2000. Persistent increase in the motivation to take heroin in rats with a history of drug escalation. Neuropsychopharmacology 22 (4), 413–421. https://doi.org/10.1016/S0893-133X(99)00133-5. Apr.

Anderson, E.M., Del Valle-Pinero, A.Y., Suckow, S.K., Nolan, T.A., Neubert, J.K., Caudle, R.M., 2012. Morphine and MK-801 administration leads to alternative N-methyl-D-aspartate receptor 1 splicing and associated changes in reward seeking behavior and nociception on an operant orofacial assay. Neuroscience 214, 14–27. https://doi.org/10.1016/j.neuroscience.2012.04.032.

Anderson, E.M., Reeves, T., Kapernaros, K., Neubert, J.K., Caudle, R.M., 2015. Phosphorylation of the N-methyl-d-aspartate receptor is increased in the nucleus accumbens during both acute and extended morphine withdrawal. J. Pharmacol. Exp. Ther. 355 (3), 496–505. https://doi.org/10.1124/jpet.115.227629. Dec.

Bajo, M., Crawford, E.F., Roberto, M., Madamba, S.G., Siggins, G.R., 2006. Chronic morphine treatment alters expression of N-methyl-D-aspartate receptor subunits in the extended amygdala. J. Neurosci. Res. 83 (4), 532–537. https://doi.org/10.1002/jnr.20756. Mar.

Barr, G.A., Zmitrovich, A., Hamowy, A.S., Liu, P.Y., Wang, S., Hutchings, D.E., 1998. Neonatal withdrawal following pre- and postnatal exposure to methadone in the rat. Pharmacol. Biochem. Behav. 60 (1), 97–104. May.

Barr, G.A., McPhie-Lalmansingh, A., Perez, J., Riley, M., 2011. Changing mechanisms of opiate tolerance and withdrawal during early development: animal models of the human experience. ILAR J. 52 (3), 329–341. https://doi.org/10.1093/ilar.52.3.329.

Bisaga, A., Sullivan, M.A., Glass, A., et al., 2014. A placebo-controlled trial of memantine as an adjunct to injectable extended-release naltrexone for opioid dependence. J. Subst. Abus. Treat. 46 (5), 546–552. https://doi.org/10.1016/j.jsat.2014.01.005. May-Jun.

Bohm, M.K., Clayton, H.B., 2020. Nonmedical use of prescription opioids, heroin use, injection drug use, and overdose mortality in U.S. adolescents. J. Stud. Alcohol Drugs 81 (4), 484–488. Jul.

Burgdorf, J., Zhang, X.L., Weiss, C., et al., 2011. The N-methyl-D-aspartate receptor modulator GLYX-13 enhances learning and memory, in young adult and learning impaired aging rats. Neurobiol. Aging 32 (4), 698–706. https://doi.org/10.1016/j.neurobiolaging.2009.04.012. Apr.

Burgdorf, J., Kroes, R.A., Weiss, C., et al., 2011. Positive emotional learning is regulated in the medial prefrontal cortex by GluN2B-containing NMDA receptors. Neuroscience 192, 515–523. https://doi.org/10.1016/j.neuroscience.2011.05.001.

Burgdorf, J., Zhang, X.L., Nicholson, K.L., et al., 2013. GLYX-13, a NMDA receptor glycine-site functional partial agonist, induces antidepressant-like effects without ketamine-like side effects. Neuropsychopharmacology 38 (5), 729–742. https://doi.org/10.1038/npp.2012.246. Apr.

Burgdorf, J., Zhang, X.L., Weiss, C., et al., 2015. The long-lasting antidepressant effects of rapastinel (GLYX-13) are associated with a metaplasticity process in the medial prefrontal cortex and hippocampus. Neuroscience 308, 202–211. https://doi.org/10.1016/j.neuroscience.2015.09.004.

Burgdorf, J., Kroes, R.A., Zhang, X.L., et al., 2015. Rapastinel (GLYX-13) has therapeutic potential for the treatment of post-traumatic stress disorder: characterization of a NMDA receptor-mediated metaplasticity process in the medial prefrontal cortex of rats. Behav. Brain Res. 294, 177–185. https://doi.org/10.1016/j.bbr.2015.07.039.

Caille, S., Espejo, E.F., Reneric, J.P., Cador, M., Koob, G.F., Stinus, L., 1999. Total neurochemical lesion of noradrenergic neurons of the locus ceruleus does not alter either naloxone-precipitated or spontaneous opiate withdrawal nor does it influence ability of clonidine to reverse opiate withdrawal. J. Pharmacol. Exp. Ther. 290 (2), 881–892. Aug.

Carpenter, M.D., Manners, M.T., Heller, E.A., Blendy, J.A., 2020. Adolescent oxycodone exposure inhibits withdrawal-induced expression of genes associated with the dopamine transmission. Addict. Biol., e12994 https://doi.org/10.1111/adb.12994. Dec 15.

Ceger, P., Kuhn, C.M., 2000. Opiate withdrawal in the neonatal rat: relationship to duration of treatment and naloxone dose. Psychopharmacology 150 (3), 253–259. Jun.

Cicero, T.J., Ennis, T., Ogden, J., Meyer, E.R., 2000. Gender differences in the reinforcing properties of morphine. Pharmacol. Biochem. Behav. 65 (1), 91–96. https://doi.org/10.1016/s0091-3057(99)00174-4.

Cicero, T.J., Nock, B., Meyer, E.R., 2002. Gender-linked differences in the expression of physical dependence in the rat. Pharmacol. Biochem. Behav. 72 (3), 691–697. https://doi.org/10.1016/s0091-3057(02)00740-2. Jun.

Cicero, T.J., Aylward, S.C., Meyer, E.R., 2003. Gender differences in the intravenous self-administration of mu opiate agonists. Pharmacol. Biochem. Behav. 74 (3), 541–549. Feb.

Craft, R.M., Stratmann, J.A., Bartok, R.E., Walpole, T.I., King, S.J., 1999. Sex differences in development of morphine tolerance and dependence in the rat. Psychopharmacology 143 (1), 1–7. Mar.

Das, R.K., Kamboj, S.K., 2012. Maintaining clinical relevance: considerations for the future of research into D-cycloserine and cue exposure therapy for addiction. Biol. Psychiatry 72 (11), e29–e30. https://doi.org/10.1016/j.biopsych.2012.05.030 author reply e31–2.

Doherty, J.M., Frantz, K.J., 2013. Attenuated effects of experimenter-administered heroin in adolescent vs. adult male rats: physical withdrawal and locomotor sensitization. Psychopharmacology (Berl) 225 (3), 595–604. https://doi.org/10.1007/s00213-012-2847-1. Feb.

Donello, J.E., Banerjee, P., Li, Y.X., et al., 2019. Positive N-methyl-D-aspartate receptor modulation by rapastinel promotes rapid and sustained antidepressant-like effects. Int. J. Neuropsychopharmacol. 22 (3), 247–259. https://doi.org/10.1093/ijnp/pyy101.

Fasipe, O.J., 2019. The emergence of new antidepressants for clinical use: agomelatine paradox versus other novel agents. IBRO Rep. 6, 95–110. https://doi.org/10.1016/j.ibror.2019.01.001. Jun.

Fluyau, D., Revadigar, N., Pierre, C.G., 2020. Clinical benefits and risks of N-methyl-D-aspartate receptor antagonists to treat severe opioid use disorder: a systematic review. Drug Alcohol Depend., 107845 https://doi.org/10.1016/j.drugalcdep.2020.107845, 2020/01/11/.

Ford, J.A., 2019. Prescription opioid misuse among adolescents. Pediatr. Clin. N. Am. 66 (6), 1099–1108. https://doi.org/10.1016/j.pcl.2019.08.005. Dec.

Frenois, F., Cador, M., Caille, S., Stinus, L., Le Moine, C., 2002. Neural correlates of the motivational and somatic components of naloxone-precipitated morphine withdrawal. Eur. J. Neurosci. 16 (7), 1377–1389. Oct.

Friedman, J., Godvin, M., Shover, C.L., Gone, J.P., Hansen, H., Schriger, D.L., 2022. Trends in drug overdose deaths among US adolescents, january 2010 to june 2021. JAMA 327 (14), 1398–1400. https://doi.org/10.1001/jama.2022.2847.

Garay, R.P., Zarate Jr., C.A., Charpeaud, T., et al., 2017. Investigational drugs in recent clinical trials for treatment-resistant depression. Expert. Rev. Neurother. 17 (6), 593–609. https://doi.org/10.1080/14737175.2017.1283217. Jun.

Gellert, V.F., Holtzman, S.G., 1978. Development and maintenance of morphine tolerance and dependence in the rat by scheduled access to morphine drinking solutions. J. Pharmacol. Exp. Ther. 205 (3), 536–546. Jun.

Ghoreishi-Haack, N., Priebe, J.M., Aguado, J.D., et al., 2018. NYX-2925 is a novel N-methyl-d-aspartate receptor modulator that induces rapid and long-lasting analgesia in rat models of neuropathic pain. J. Pharmacol. Exp. Ther. 366 (3), 485–497. https://doi.org/10.1124/jpet.118.249409. Sep.

Girardi, B.A., Fabbrin, S., Wendel, A.L., Mello, C.F., Rubin, M.A., 2020. Spermidine, a positive modulator of the NMDA receptor, facilitates extinction and prevents the reinstatement of morphine-induced conditioned place preference in mice. Psychopharmacology 237 (3), 681–693. https://doi.org/10.1007/s00213-019-05403-z. Mar.

Haring, R., Stanton, P.K., Scheideler, M.A., Moskal, J.R., 1991. Glycine-like modulation of N-methyl-D-aspartate receptors by a monoclonal antibody that enhances long-term potentiation. J. Neurochem. 57 (1), 323–332. Jul.

Hearing, M., Graziane, N., Dong, Y., Thomas, M.J., 2018. Opioid and psychostimulant plasticity: targeting overlap in nucleus accumbens glutamate signaling. Trends Pharmacol. Sci. 39 (3), 276–294. https://doi.org/10.1016/j.tips.2017.12.004. Mar.

Hempel, B.J., Crissman, M.E., Imanalieva, A., et al., 2020. Cross-generational THC exposure alters heroin reinforcement in adult male offspring. Drug Alcohol Depend. 212, 107985 https://doi.org/10.1016/j.drugalcdep.2020.107985. Jul 1.

Hofmann, S.G., 2014. D-cycloserine for treating anxiety disorders: making good exposures better and bad exposures worse. Depress Anxiety. 31 (3), 175–177. https://doi.org/10.1002/da.22257. Mar.

Hopf, F.W., 2017. Do specific NMDA receptor subunits act as gateways for addictive behaviors? Genes Brain Behav. 16 (1), 118–138. https://doi.org/10.1111/gbb.12348. Jan.

van Huijstee, A.N., Mansvelder, H.D., 2014. Glutamatergic synaptic plasticity in the mesocorticolimbic system in addiction. Front. Cell. Neurosci. 8, 466. https://doi.org/10.3389/fncel.2014.00466.

Inturrisi, C.E., 2002. Clinical pharmacology of opioids for pain. Clin. J. Pain 18 (4 Suppl), S3–S13. https://doi.org/10.1097/00002508-200207001-00002. Jul-Aug.

Inturrisi, C.E., 2005. Pharmacology of methadone and its isomers. Minerva Anestesiol. 71 (7–8), 435–437. Jul-Aug.

Jiménez-Romero, F., Bis-Humbert, C., García-Fuster, M.J., 2020. Adolescent morphine induces emotional signs of withdrawal paired with neurotoxicity selectively in male rats: female resilience. Neurosci. Lett. 715, 134625 https://doi.org/10.1016/j.neulet.2019.134625. Jan 10.

Johnson, M.W., Bruner, N.R., Johnson, P.S., Silverman, K., Berry, M.S., 2020. Randomized controlled trial of d-cycloserine in cocaine dependence: effects on contingency management and cue-induced cocaine craving in a naturalistic setting. Exp. Clin. Psychopharmacol. 28 (2), 157–168. https://doi.org/10.1037/pha0000306. Apr.

Kalivas, P.W., O'Brien, C., 2008. Drug addiction as a pathology of staged neuroplasticity. Neuropsychopharmacology 33 (1), 166–180. https://doi.org/10.1038/sj.npp.1301564, 2008/01/01.

Kandasamy, R., Lee, A.T., Morgan, M.M., 2017. Depression of home cage wheel running is an objective measure of spontaneous morphine withdrawal in rats with and without persistent pain. Pharmacol. Biochem. Behav. 156, 10–15. https://doi.org/10.1016/j.pbb.2017.03.007. May.

Karami, M., Zarrindast, M.R., 2008. Morphine sex-dependently induced place conditioning in adult wistar rats. Eur. J. Pharmacol. 582 (1–3), 78–87. https://doi.org/10.1016/j.ejphar.2007.12.010.

Kelsey, J.E., Aranow, J.S., Matthews, R.T., 1990. Context-specific morphine withdrawal in rats: duration and effects of clonidine. Behav. Neurosci. 104 (5), 704–710. https://doi.org/10.1037//0735-7044.104.5.704. Oct.

Kenny, P.J., Hoyer, D., Koob, G.F., 2018. Animal models of addiction and neuropsychiatric disorders and their role in drug discovery: honoring the legacy of athina markou. Biol. Psychiatry 83 (11), 940–946. https://doi.org/10.1016/j.biopsych.2018.02.009.

Khan, M.A., Houck, D.R., Gross, A.L., et al., 2017. NYX-2925 is a novel NMDA receptor-specific spirocyclic-beta-lactam that modulates synaptic plasticity processes associated with learning and memory. Int. J. Neuropsychopharmacol. https://doi.org/10.1093/ijnp/pyx096. Nov 1.

Koek, W., 2016. Morphine-induced conditioned place preference and effects of morphine pre-exposure in adolescent and adult male C57BL/6J mice. Psychopharmacology 233 (11), 2015–2024. https://doi.org/10.1007/s00213-014-3695-y. Jun.

Koob, G.F., 2020. Neurobiology of opioid addiction: opponent process, hyperkatifeia, and negative reinforcement. Biol. Psychiatry 87 (1), 44–53. https://doi.org/10.1016/j.biopsych.2019.05.023.

Koob, G.F., 2021. Drug addiction: hyperkatifeia/negative reinforcement as a framework for medications development. Pharmacol. Rev. 73 (1), 163–201. https://doi.org/10.1124/pharmrev.120.000083. Jan.

Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 3 (8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8. Aug.

Kosersky, D.S., Kowolenko, M.D., Howes, J.F., 1980. Physical dependence and tolerance development after chronic exposure to low levels of morphine in the rat. Pharmacol. Biochem. Behav. 12 (4), 625–628. https://doi.org/10.1016/0091-3057(80)90199-9. Apr.

Kosten, T.A., DeCaprio, J.L., Rosen, M.I., 1995. The severity of naloxone-precipitated opiate withdrawal is attenuated by felbamate, a possible glycine antagonist. Neuropsychopharmacology 13 (4), 323–333. https://doi.org/10.1016/0893-133X(95)00065-L. Dec.

Liu, Y., Lin, D., Wu, B., Zhou, W., 2016. Ketamine abuse potential and use disorder. Brain Res. Bull. 126 (Pt 1), 68–73. https://doi.org/10.1016/j.brainresbull.2016.05.016. Sep.

Lu, G.Y., Wu, N., Zhang, Z.L., Ai, J., Li, J., 2011. Effects of D-cycloserine on extinction and reinstatement of morphine-induced conditioned place preference. Neurosci. Lett. 503 (3), 196–199. https://doi.org/10.1016/j.neulet.2011.08.034.

Lynch, W.J., Carroll, M.E., 1999. Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats. Psychopharmacology 144 (1), 77–82. May.

Madison, C.A., Wellman, P.J., Eitan, S., 2020. Pre-exposure of adolescent mice to morphine results in stronger sensitization and reinstatement of conditioned place preference than pre-exposure to hydrocodone. J. Psychopharmacol. 34 (7), 771–777. https://doi.org/10.1177/0269881120926675. Jul.

Maiti, T., Das, S., Ramasamy, A., Stanley Xavier, A., Kumar Behera, S., Selvarajan, S., 2020. An overview on medication-assisted treatment (MAT) for opioid dependence. J. Opioid Manag. 16 (2), 141–149. https://doi.org/10.5055/jom.2020.0560. Mar/Apr.

Marsch, L.A., Bickel, W.K., Badger, G.J., et al., 2005. Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. Arch. Gen. Psychiatry 62 (10), 1157–1164. https://doi.org/10.1001/archpsyc.62.10.1157. Oct.

Marsch, L.A., Moore, S.K., Borodovsky, J.T., et al., 2016. A randomized controlled trial of buprenorphine taper duration among opioid-dependent adolescents and young adults. Addiction 111 (8), 1406–1415. https://doi.org/10.1111/add.13363. Aug.

McKendrick, G., Graziane, N.M., 2020. Drug-induced conditioned place preference and its practical use in substance use disorder research. Front. Behav. Neurosci. 14, 582147 https://doi.org/10.3389/fnbeh.2020.582147.

McQueen, K., Murphy-Oikonen, J., 2016. Neonatal abstinence syndrome. N. Engl. J. Med. 375 (25), 2468–2479. https://doi.org/10.1056/NEJMra1600879.

Medrano, M.C., Mendiguren, A., Pineda, J., 2015. Effect of ceftriaxone and topiramate treatments on naltrexone-precipitated morphine withdrawal and glutamate receptor desensitization in the rat locus coeruleus. Psychopharmacology 232 (15), 2795–2809. https://doi.org/10.1007/s00213-015-3913-2. Aug.

Moskal, J.R., Kuo, A.G., Weiss, C., et al., 2005. GLYX-13: a monoclonal antibody-derived peptide that acts as an N-methyl-D-aspartate receptor modulator. Neuropharmacology 49 (7), 1077–1087. https://doi.org/10.1016/j.neuropharm.2005.06.006. Dec.

Moskal, J.R., Burch, R., Burgdorf, J.S., et al., 2014. GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces antidepressant effects without the psychotomimetic side effects of NMDA receptor antagonists. Expert Opin. Investig. Drugs 23 (2), 243–254. https://doi.org/10.1517/13543784.2014.852536. Feb.

Moskal, J.R., Burgdorf, J.S., Stanton, P.K., et al., 2017. The development of rapastinel (Formerly GLYX-13); a rapid acting and long lasting antidepressant. Curr. Neuropharmacol. 15 (1), 47–56.

Mueller, D., Perdikaris, D., Stewart, J., 2002. Persistence and drug-induced reinstatement of a morphine-induced conditioned place preference. Behav. Brain Res. 136 (2), 389–397.

Murray, F., Harrison, N.J., Grimwood, S., Bristow, L.J., Hutson, P.H., 2007. Nucleus accumbens NMDA receptor subunit expression and function is enhanced in morphine-dependent rats. Eur. J. Pharmacol. 562 (3), 191–197. https://doi.org/10.1016/j.ejphar.2007.01.027.

Myers, K.M., Carlezon Jr., W.A., 2010. D-cycloserine facilitates extinction of naloxone-induced conditioned place aversion in morphine-dependent rats. Biol. Psychiatry 67 (1), 85–87. https://doi.org/10.1016/j.biopsych.2009.08.015.

Myers, K.M., Carlezon Jr., W.A., 2010. Extinction of drug- and withdrawal-paired cues in animal models: relevance to the treatment of addiction. Neurosci. Biobehav. Rev. 35 (2), 285–302. https://doi.org/10.1016/j.neubiorev.2010.01.011. Nov.

Nestler, E.J., 2016. Reflections on: "A general role for adaptations in G-proteins and the cyclic AMP system in mediating the chronic actions of morphine and cocaine on neuronal function". Brain Res. 1645, 71–74. https://doi.org/10.1016/j.brainres.2015.12.039.

Neuhofer, D., Kalivas, P., 2018. Metaplasticity at the addicted tetrapartite synapse: a common denominator of drug induced adaptations and potential treatment target for addiction. Neurobiol. Learn. Mem. https://doi.org/10.1016/j.nlm.2018.02.007. Feb 9.

Newport, D.J., Carpenter, L.L., McDonald, W.M., et al., 2015. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am. J. Psychiatry 172 (10), 950–966. https://doi.org/10.1176/appi.ajp.2015.15040465. Oct.

Oh, S., Kim, J.I., Chung, M.W., Ho, I.K., 2000. Modulation of NMDA receptor subunit mRNA in butorphanol-tolerant and -withdrawing rats. Neurochem. Res. 25 (12), 1603–1611. Dec.

Popik, P., Wrobel, M., Bisaga, A., 2006. Reinstatement of morphine-conditioned reward is blocked by memantine. Neuropsychopharmacology 31 (1), 160–170. https://doi.org/10.1038/sj.npp.1300760. Jan.

Prisciandaro, J.J., Myrick, H., Henderson, S., et al., 2013. Impact of DCS-facilitated cue exposure therapy on brain activation to cocaine cues in cocaine dependence. Drug Alcohol Depend. 132 (1–2), 195–201. https://doi.org/10.1016/j.drugalcdep.2013.02.009.

Rasmussen, K., 1995. The role of the locus coeruleus and N-methyl-D-aspartic acid (NMDA) and AMPA receptors in opiate withdrawal. Neuropsychopharmacology 13 (4), 295–300. https://doi.org/10.1016/0893-133X(95)00082-O. Dec.

Rasmussen, K., Beitner-Johnson, D.B., Krystal, J.H., Aghajanian, G.K., Nestler, E.J., 1990. Opiate withdrawal and the rat locus coeruleus: behavioral, electrophysiological, and biochemical correlates. J. Neurosci. 10 (7), 2308–2317. Jul.

Rasmussen, K., Fuller, R.W., Stockton, M.E., Perry, K.W., Swinford, R.M., Ornstein, P.L., 1991. NMDA receptor antagonists suppress behaviors but not norepinephrine turnover or locus coeruleus unit activity induced by opiate withdrawal. Eur. J. Pharmacol. 197 (1), 9–16. https://doi.org/10.1016/0014-2999(91)90358-w.

Rasmussen, K., Brodsky, M., Inturrisi, C.E., 1995. NMDA antagonists and clonidine block c-fos expression during morphine withdrawal. Synapse 20 (1), 68–74. https://doi.org/10.1002/syn.890200110. May.

Rawls, S.M., Baron, D.A., Kim, J., 2010. Beta-lactam antibiotic inhibits development of morphine physical dependence in rats. Behav. Pharmacol. 21 (2), 161–164. https://doi.org/10.1097/FBP.0b013e328337be10. Mar.

Ribeiro Do Couto, B., Aguilar, M.A., Manzanedo, C., Rodriguez-Arias, M., Minarro, J., 2005. NMDA glutamate but not dopamine antagonists blocks drug-induced reinstatement of morphine place preference. Brain Res. Bull. 64 (6), 493–503. https://doi.org/10.1016/j.brainresbull.2004.10.005.

Sanchez, V., Carpenter, M.D., Yohn, N.L., Blendy, J.A., 2016. Long-lasting effects of adolescent oxycodone exposure on reward-related behavior and gene expression in mice. Psychopharmacology 233 (23–24), 3991–4002. https://doi.org/10.1007/s00213-016-4425-4. Dec.

Santa Ana, E.J., Prisciandaro, J.J., Saladin, M.E., et al., 2015. D-cycloserine combined with cue exposure therapy fails to attenuate subjective and physiological craving in cocaine dependence. Am. J. Addict. 24 (3), 217–224. https://doi.org/10.1111/ajad.12191. Apr.

Schramm-Sapyta, N.L., Cauley, M.C., Stangl, D.K., et al., 2011. Role of individual and developmental differences in voluntary cocaine intake in rats. Psychopharmacology 215 (3), 493–504. https://doi.org/10.1007/s00213-011-2216-5. Jun.

Schuman-Olivier, Z., Weiss, R.D., Hoeppner, B.B., Borodovsky, J., Albanese, M.J., 2014. Emerging adult age status predicts poor buprenorphine treatment retention. J. Subst. Abus. Treat. 47 (3), 202–212. https://doi.org/10.1016/j.jsat.2014.04.006. Sep.

Scofield, M.D., Heinsbroek, J.A., Gipson, C.D., et al., 2016. The nucleus accumbens: mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. Pharmacol. Rev. 68 (3), 816–871. https://doi.org/10.1124/pr.116.012484. Jul.

Squeglia, L.M., Fadus, M.C., McClure, E.A., Tomko, R.L., Gray, K.M., 2019. Pharmacological treatment of youth substance use disorders. J. Child Adolesc. Psychopharmacol. 29 (7), 559–572. https://doi.org/10.1089/cap.2019.0009. Aug.

Stanton, P.K., Potter, P.E., Aguilar, J., Decandia, M., Moskal, J.R., 2009. Neuroprotection by a novel NMDAR functional glycine site partial agonist, GLYX-13, 20 (13), 1193–1197. https://doi.org/10.1097/WNR.0b013e32832f5130.

Timar, J., Sobor, M., Kiraly, K.P., et al., 2010. Peri, pre and postnatal morphine exposure: exposure-induced effects and sex differences in the behavioural consequences in rat offspring. Behav. Pharmacol. 21 (1), 58–68. https://doi.org/10.1097/FBP.0b013e3283359f39. Feb.

Tomek, S.E., Lacrosse, A.L., Nemirovsky, N.E., Olive, M.F., 2013. NMDA receptor modulators in the treatment of drug addiction. Pharmaceuticals (Basel) 6 (2), 251–268. https://doi.org/10.3390/ph6020251.

Towers, E.B., Tunstall, B.J., McCracken, M.L., Vendruscolo, L.F., Koob, G.F., 2019. Male and female mice develop escalation of heroin intake and dependence following extended access. Neuropharmacology 151, 189–194. https://doi.org/10.1016/j.neuropharm.2019.03.019. Jun.

Trujillo, K.A., Akil, H., 1991. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science 251 (4989), 85–87.

Venniro, M., Zhang, M., Shaham, Y., Caprioli, D., 2017. Incubation of methamphetamine but not heroin craving after voluntary abstinence in male and female rats. Neuropsychopharmacology 42 (5), 1126–1135. https://doi.org/10.1038/npp.2016.287. Apr.

Villar, V.M., Bhargava, H.N., 1992. Pharmacodynamics and kinetics of loss of tolerance and physical dependence on morphine induced by pellet implantation in the rat. Pharmacology 45 (6), 319–328. https://doi.org/10.1159/000139017.

Walker, Q.D., Kuhn, C.M., 2008. Cocaine increases stimulated dopamine release more in periadolescent than adult rats. Neurotoxicol. Teratol. 30 (5), 412–418. https://doi.org/10.1016/j.ntt.2008.04.002. Sep-Oct.

Walker, Q.D., Schramm-Sapyta, N.L., Caster, J.M., Waller, S.T., Brooks, M.P., Kuhn, C.M., 2009. Novelty-induced locomotion is positively associated with cocaine ingestion in adolescent rats; anxiety is correlated in adults. Pharmacol. Biochem. Behav. 91 (3), 398–408. https://doi.org/10.1016/j.pbb.2008.08.019. Jan.

Wang, Y.T., Zhang, N.N., Liu, L.J., et al., 2022. Glutamatergic receptor and neuroplasticity in depression: implications for ketamine and rapastinel as the rapid-acting antidepressants. Biochem. Biophys. Res. Commun. 594, 46–56. https://doi.org/10.1016/j.bbrc.2022.01.024.

Wilkinson, S.T., Sanacora, G., 2019. A new generation of antidepressants: an update on the pharmaceutical pipeline for novel and rapid-acting therapeutics in mood disorders based on glutamate/GABA neurotransmitter systems. Drug Discov. Today 24 (2), 606–615. https://doi.org/10.1016/j.drudis.2018.11.007. Feb.

Windh, R.T., Little, P.J., Kuhn, C.M., 1995. The ontogeny of mu opiate tolerance and dependence in the rat: antinociceptive and biochemical studies. J. Pharmacol. Exp. Ther. 273 (3), 1361–1374. Jun.

Xi, Z.X., Stein, E.A., 2002. Blockade of ionotropic glutamatergic transmission in the ventral tegmental area reduces heroin reinforcement in rat. Psychopharmacology 164 (2), 144–150. https://doi.org/10.1007/s00213-002-1190-3. Nov.

Yoburn, B.C., Chen, J., Huang, T., Inturrisi, C.E., 1985. Pharmacokinetics and pharmacodynamics of subcutaneous morphine pellets in the rat. J. Pharmacol. Exp. Ther. 235 (2), 282–286. Nov.

Zhang, X.L., Sullivan, J.A., Moskal, J.R., Stanton, P.K., 2008. A NMDA receptor glycine site partial agonist, GLYX-13, simultaneously enhances LTP and reduces LTD at schaffer collateral-CA1 synapses in hippocampus. Neuropharmacology 55 (7), 1238–1250. https://doi.org/10.1016/j.neuropharm.2008.08.018. Dec.