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The N-Methyl-D-Aspartate Receptor Antagonist d-Methadone Acutely Improves Depressive-Like Behavior in the Forced Swim Test Performance of Rats

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d-Methadone (dextromethadone) is a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist that binds to the dizocilpine (MK-801)-binding site of the receptor with an affinity comparable with that of well-established NMDAR antagonists. Considering the similar NMDAR activity of ketamine and d-methadone and the rapid and robust antidepressant effects of ketamine, we compared these 2 drugs in the forced swim test in Sprague-Dawley rats, which has been shown to be predictive of antidepressant activity for drugs with different mechanisms of action including ketamine. This study evaluated the antidepressant-like effect of d-methadone (10, 20, and 40 mg/kg) in the forced swim test 24 hr following a single-dose administration. At all doses, d-methadone significantly ($p < .05$) decreased immobility of rats compared with vehicle, suggesting antidepressant-like activity. In addition, the effect of d-methadone (20 and 40 mg/kg) on immobility was greater than the effect seen with ketamine (10 mg/kg). Importantly, there were no changes in locomotor activity of rats that could have confounded the immobility effects at all doses (10, 20, and 40 mg/kg) of d-methadone. This is the first demonstration that the NMDAR antagonist, d-methadone, exerts antidepressant-like activity in a preclinical animal model and that its efficacy is similar to or even stronger than that of ketamine, an antidepressant that demonstrates a rapid onset activity and robust efficacy in patients with treatment-resistant depression. d-Methadone is currently being evaluated in a Phase 2a clinical study for patients with treatment-resistant depression and could potentially represent a new effective antidepressant in the growing class of NMDAR antagonists.

Public Health Significance
d-Methadone is a noncompetitive N-methyl-D-aspartate receptor antagonist with an affinity comparable with that of well-established N-methyl-D-aspartate receptor antagonists. In this study, d-methadone significantly decreased immobility of rats compared with vehicle, suggesting antidepressant like-activity. The effect of d-methadone on immobility was larger than the effect seen with ketamine. d-Methadone may represent a new approach to treating depression.

Keywords: d-methadone, NMDAR antagonist, forced swim test, rapid-acting antidepressant, depression

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Dr. Paolo Manfredi and Dr. Charles Inturrisi are named inventors on patents for the use of d-methadone in neuropsychiatric diseases. These patents were licensed to Relmada Therapeutics, Inc.

The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Unipolar depression is the most common mental health condition with 12-month global prevalence rates averaging approximately 5.5% (Kessler & Bromet, 2013). The global burden of disease for patients with major depressive disorder is ranked as second only to chronic lower back pain and is associated with an estimated 54,700 years lived with disability per 1,000 persons (Global Burden of Disease Study 2013 Collaborators, 2015). Of note, the World Health Organization predicts that by 2030 unipolar depression will account for 6.2% of the total disability adjusted life years lost because of all diseases worldwide. Approximately 70% of patients do not fully remit symptomatically after a full course of monotherapy antidepressant treatment (Trivedi et al., 2006), and up to 85% of patients will relapse at least once (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). Other disadvantages of available treatments include the slow onset of action and side effects that compromise patient compliance (Dupuy, Ostacher, Huffman, Perlis, & Nierenberg, 2011), all of which translate to a clear unmet need for rapid acting and effective antidepressants.

d-Methadone (dextromethadone) is a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist that binds to the dizocilpine (MK-801)-binding site of the receptor with an affinity comparable with that of well-established NMDAR antagonists (Gorman, Elliott, & Inturrisi, 1997). In experimental studies, d-methadone was found to block morphine tolerance and N-methyl-D-aspartate (NMDA)-induced hyperalgesia (Davis & Inturrisi, 1999). In the rat formalin test, d-methadone was also found to be antinociceptive (Shimoyama, Shimoyama, Elliott, & Inturrisi, 1997), which was not blocked by naloxone, suggesting effects mediated by NMDAR antagonistic activity. Morgan and Nicholson (2011) found that d-methadone was 30- to 70-fold less potent in producing antinociception and concluded that d-methadone at these doses has partial μ-agonist activity. However, they also concluded that the contribution of NMDA antagonism versus μ-opioid receptor activation may vary, depending on the pain model used and the route of administration (i.e., intrathecal vs. systemic). The inhibitory activity of racemic methadone as well as its pure stereoisomers for various subtypes of NMDA receptor channels expressed in *Xenopus* oocytes were studied, and the d- and l-isomers exhibited different affinities for channel subtypes (Callahan, Au, Paul, Liu, & Yost, 2004). In vitro, the NMDAR antagonistic effects of racemic methadone, d-methadone, racemic ketamine, and [S]-ketamine have been demonstrated to be similar (low micromoles per liter range) using the electrophysiological response of human cloned NMDA NR1/NR2A, and NR1/NR2B receptors expressed in HEK293 cells (data on file, Relmada Therapeutics, Inc.; Bernstein et al., 2019).

Studies to evaluate the d-methadone stereoisomer in patients are very limited and suggest that the drug is well tolerated and may potentially exert antianxiety and antidepressant actions (Moryl et al., 2016). The predominant use of d-methadone is in the racemic form of methadone, which is a 50/50 mix of l-methadone and d-methadone. Although both d-methadone and l-methadone bind to the MK-801–labeled, noncompetitive site of the NMDAR (Dupuy et al., 2011), only l-methadone binds to opioid receptors with high affinity (Kristensen, Christensen, & Christrup, 1995) and is responsible for the opioid effects of the racemic form. Ketamine, another NMDAR antagonist, has been shown to have rapid antidepressant activity and to be efficacious in the treatment of individuals with treatment resistant depression (Lapidus et al., 2014; Murrough et al., 2013; Singh et al., 2016; Zarate et al., 2006).

Considering the similar NMDAR activity of ketamine and d-methadone, we compared the antidepressant activity of the two compounds with the forced swim test (FST) in Sprague-Dawley rats. The FST has been shown to be predictive of antidepressant activity for antidepressant drugs with different mechanisms of action including ketamine (Yuen, Swanson, & Witkin, 2017).

Method

Animals

All housing and testing of the animals was in accordance with the Principles of Laboratory Animal Care and the approval of the PsychoGenics, Inc. Institutional Animal Care and Use Committee in Association Assessment and Accreditation of Laboratory Animal Care–accredited facilities.

Male Sprague-Dawley rats (Envigo; Indianapolis, IN) weighing 240 g and 8 weeks of age were used in this study. Upon receipt, rats were assigned unique identification numbers (tail marked). Animals were housed three per cage in polycarbonate cages with microisolator filter tops and acclimated for 7 days. All rats were examined, handled, and weighed prior to the study to assure adequate health and suitability. Rats were maintained on a 6 a.m./6 p.m. light/dark cycle. The room temperature was maintained between 20°C and 23°C, with a relative humidity around 50%. Standard rodent chow and water were provided ad libitum for the duration of the study. Animals were randomly assigned across treatment groups with 10 rats per treatment group.

Drugs

The drug was d-methadone (Mallinckrodt), lot number 1410000367, dissolved in sterile water. The reference compound was ketamine (Patterson Veterinary, Greeley, CO), lot number AH013JC, dissolved in saline. d-Methadone dose formulations were prepared by dissolving a weighed amount of d-methadone in a measured volume of sterile injectable water to achieve concentrations of 10, 20, and 40 mg/mL. Ketamine dose formulations were prepared by dilution of a stock solution of ketamine at 100 mg/mL to obtain the desired dose of 10 mg/mL. Dose formulations were prepared shortly before use.

Dose and Administration

Rats were administered vehicle, ketamine or d-methadone 24 hr prior to forced swim and locomotor activity tests. Ketamine was administered intraperitoneally at a dose volume of 1 mL/kg. d-Methadone and saline vehicle were administered subcutaneously at a dose volume of 1 mL/kg.

Forced Swim Procedure

When rats are forced to swim in a small cylinder from which no escape is possible, they readily adopt a characteristic immobile posture and make no further attempts to escape except for small movements needed to prevent them from drowning. The immobility induced by the procedure can be reversed or largely decreased by a wide variety of antidepressants, suggesting that this test is sensitive to

antidepressant-like effect. However, because this test also detects many false positives (e.g., psychostimulants and antihistaminergics), locomotor activity was also measured to rule out hyperactivity. All experiments were carried out in ambient temperature under artificial lighting during the light cycle of the rat. Each forced swim chamber was constructed of clear acrylic (height = 40 cm; diameter = 20.3 cm). All rats were exposed to a swim test (habituation) prior to study drug administration (Detke & Lucki, 1996; Porsolt, Anton, Blavet, & Jalfre, 1978). This preadministration swim test consisted of one 15-min session in individual cylinders containing 23°C ± 1°C water, which was followed 24 h later by the experimental test of 5 min. The water level was 16 cm deep during habituation and 30 cm deep during testing. Immobility, climbing, and swimming behaviors were recorded every 5 s for a total of 60 counts per subject. The scoring was done every 5 s for the duration of the 300 s, and the number of the various behaviors was then summed over the 5 min test and presented as frequency of each behavior. In the event that an animal was unable to maintain a posture with its nose above water, it was removed immediately from the water and therefore eliminated from the study. The test and the analysis of the video files were performed by an observer blind to treatment. The observers were trained to score this test and only had animal identifications without any treatment codes. The success of the training depends on reproducibility of historical data for both control and following antidepressant treatment. Only one person scored a study. Data were represented as a frequency of total behavior over the 5-min trial.

Locomotor Activity Assessment

Locomotor activity was assessed using the Hamilton Kinder apparatus (Kinder Scientific, San Diego, CA). The test chambers were standard rat cages that fit inside two steel frames (24 × 46 cm) and are fitted with two-dimensional 4 × 8 beam grids to monitor horizontal and vertical locomotor activities. Photocell beam interruptions were automatically recorded by a computer system for 60 min in 5-min bins. Distance traveled was measured from consecutive horizontal beam breaks while rearing activity was measured from consecutive vertical beam breaks. Rats were brought to the experimental room for at least 1 hr of acclimation to the experimental room prior to the start of testing. A clean cage was used for each rat for testing.

Statistical Analysis

Data were analyzed by analysis of variance (ANOVA) followed by post hoc comparisons with Fisher's tests when appropriate (following significant main or interaction effects). An effect was considered significant if $p < .05$. Any rats that exhibited individual measures that fell above or below 2 *SD* from the mean were removed from the analysis. One rat was excluded from vehicle and one from the 20 mg/kg group for large variances.

Results

Forced Swim Test

The effects of ketamine and d-methadone on frequency of immobility, climbing, and swimming behavior are shown in Figure 1.

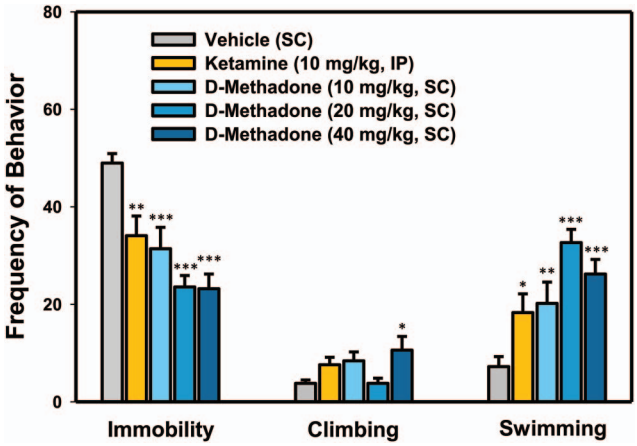

Figure 1. Effects of ketamine and d-methadone on immobility, climbing, and swimming counts. Data represent mean ± SEM. For immobility: ** $p < .05$ for ketamine versus vehicle, *** $p < .001$ for d-methadone 10 mg/kg, 20 mg/kg, and 40 mg/kg versus vehicle, Fisher's test. For climbing: * $p < .05$ for d-methadone 40 mg/kg versus vehicle. For swimming: * $p < .05$ for ketamine versus vehicle, ** $p < .01$ for d-methadone 10 mg/kg versus vehicle, and *** $p < .001$ for d-methadone 20 mg/kg and 40 mg/kg versus vehicle, Fisher's test.

Immobility

d-Methadone (10, 20, and 40 mg/kg) and ketamine significantly ($p < .05$) decreased the frequency of immobility compared with vehicle-treated animals. The magnitude of effect of d-methadone (20 and 40 mg/kg) on immobility was greater than that of ketamine (ANOVA: F value = 9.318, DF = 4 for d-methadone and 43 for ketamine, $p < .0001$).

Climbing

d-Methadone (40 mg/kg) significantly ($p < .05$) increased the frequency of climbing compared with vehicle-treated animals (ANOVA: F value = 2.736, DF = 4 for d-methadone and 43 for ketamine, $p = .0409$).

Swimming

d-Methadone (10, 20, and 40 mg/kg) and ketamine significantly ($p < .05$) increased the frequency of swimming compared with vehicle-treated animals. Compared with ketamine, rats treated with d-methadone (20 mg/kg) showed increased swimming behavior (ANOVA: F value = 7.556, DF = 4 for d-methadone and 43 for ketamine, $p = .0001$).

Locomotor Activity

Total distance traveled. The time course for the effects of ketamine and d-methadone on locomotor activity is shown in Figure 2. Two-way, repeated-measures ANOVA found no significant treatment effect and no significant Treatment × Time interaction. Total distance traveled was calculated by summing the data during the 60-min test (see Figure 3). One-way ANOVA found no significant effect of either ketamine or d-methadone on this measure (ANOVA: F value = 1.740, DF = 4 for d-methadone and 25

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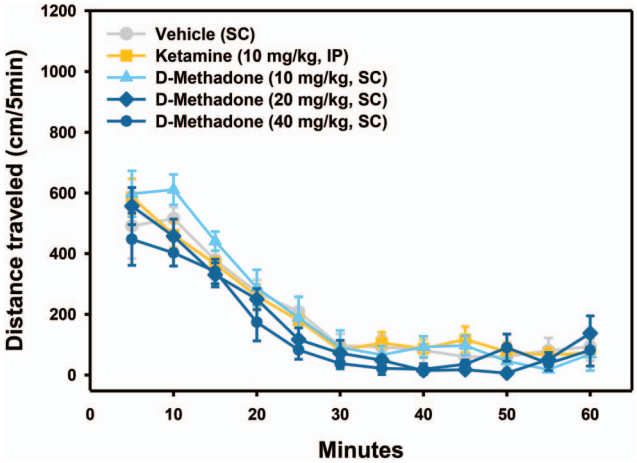

Figure 2. Time course of the effects of ketamine and d-methadone on locomotor activity. Data represent mean ± SEM.

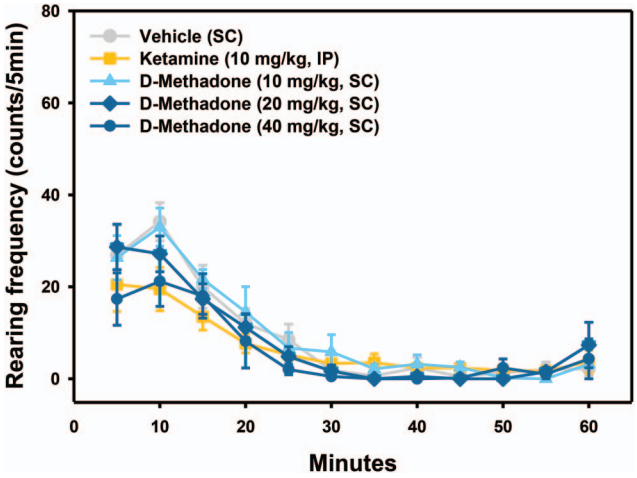

Figure 4. Time course of the effects of ketamine and d-methadone on rearing activity. Data represent mean ± SEM.

for ketamine, $p = .1728$). In addition, distance traveled during the first 5 min of the test, which corresponds to the FST time, revealed no significant treatment effect (ANOVA: F value = 0.644, DF = 4 for d-methadone and 25 for ketamine, $p = .6365$).

Rearing. The time course for the effects of ketamine and d-methadone on rearing activity is shown in Figure 4. Two-way, repeated-measures ANOVA found no significant treatment effect and no significant Treatment × Time interaction. Total rearing frequency was summed during the 60-min test (one-way ANOVA), and no significant effect of ketamine and d-methadone (ANOVA: F value = 0.994, DF = 4 for d-methadone and 25 for ketamine, $p = .429$) was observed on this measure (see Figure 5). In addition, rearing during the first 5 min of the test, which corresponds to the FST time, found no significant treatment effect (ANOVA: F value = 0.730, DF = 4 for d-methadone and 25 for ketamine, $p = .580$).

Discussion

This study evaluated the antidepressant-like effect of d-methadone (10, 20, and 40 mg/kg) in the FDT 24 hr following a single-dose administration. At all doses, d-methadone significantly decreased immobility of rats compared with vehicle, suggesting antidepressant-like activity. In addition, the effect of d-methadone (20 and 40 mg/kg) on immobility was greater than the effect seen with ketamine (10 mg/kg). Importantly, there were no changes in locomotor activity of rats that could have confounded the effects at all doses tested (10, 20, and 40 mg/kg) of d-methadone (see Figure 3). Typically increases in swimming behavior is seen with selective serotonin reuptake inhibitors and increases in climbing is seen with norepinephrine reuptake inhibitors. Because all doses increased climbing, this could suggest that the effects could involve increases in norepinephrine. The highest dose also increased swimming, which may also suggest increases in 5-hydroxytryptamine at this dose.

Of note, the findings on the behavioral effect of ketamine are in agreement with effects previously observed in forced swim test studies (Garcia et al., 2008). In particular, Garcia et al. (2008) found that acute ketamine infusion at 10 and 15 mg/kg doses

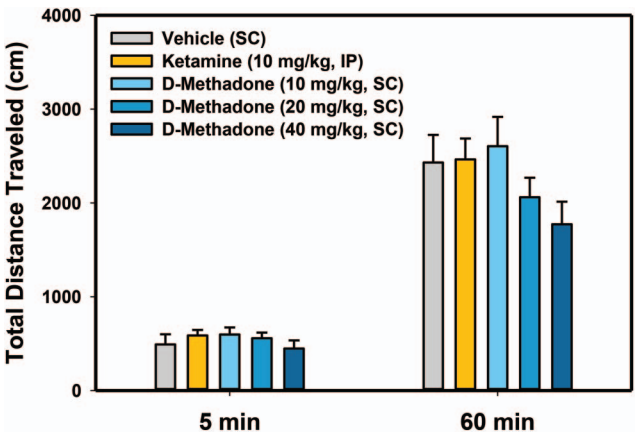

Figure 3. Effects of ketamine and d-methadone on total distance traveled during the first 5 min of the test and during the whole 60-min test period. Data represent mean ± SEM.

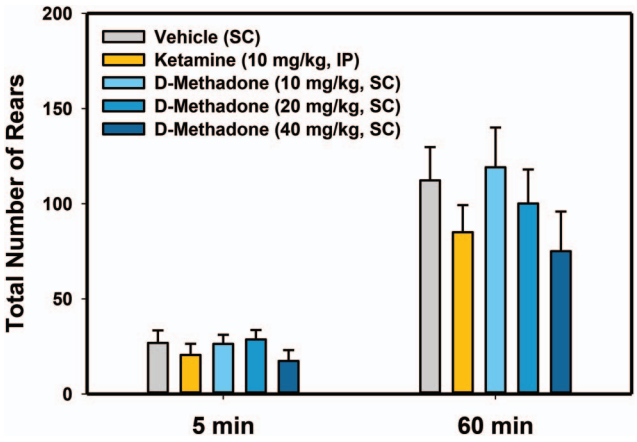

Figure 5. Effects of ketamine and d-methadone on rearing during the first 5 min of the test and during the whole 60-min test period. Data represent mean ± SEM.

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significantly decreased the immobility time of tested rats. The dose of ketamine we selected for this study has been established as the standard to study antidepressant effects in rats. In fact, it has been shown to improve the performance in the FST test in rats without affecting locomotor activity (Garcia et al., 2008) while inducing mechanistic target of rapamycin–dependent synaptic formation (Li et al., 2010). We acknowledge that the use of only one dose of ketamine does not allow to compare the dose-response curves of d-methadone and ketamine. Nonetheless, the main objective of this study was to establish whether d-methadone improves performance on the FST in a dose dependent fashion using ketamine, a known antidepressant and NMDAR antagonist, as a positive control.

Previous studies showed that d-methadone does not significantly contribute to the opioid effect of racemic methadone and that it has a 10-fold lower affinity for the mu_1, mu_2, and delta receptors compared with the l-methadone isomer (Kristensen et al., 1995). In another study, racemic methadone and its stereoisomers were evaluated in competition binding assays (Gorman et al., 1997). Racemic methadone and its d- and l-isomers exhibited low micromolar affinities for the [^{3}H]MK-801–labeled noncompetitive site of the NMDAR in both rat forebrain and spinal cord synaptic membranes, with inhibition constant (K_i) values and displacement curves similar to those of dextromethorphan, an established NMDAR antagonist. The isomers lacked affinity at the [^{3}H]CGS-19755–labeled competitive site of the NMDA receptor (Gorman et al., 1997).

Compounds with NMDAR antagonistic activity have emerged as a promising new class of antidepressants. In particular, in clinical studies, ketamine produces antidepressant effects as early as 2 hr after a single infusion, which can last up to 7 days (Zarate et al., 2006). In addition, ketamine appears to be efficacious in relieving depression in patients who failed to respond to several adequate antidepressant trials (Zanos & Gould, 2018). This rapid onset of action appears to involve intracellular pathways distinct from the ones underlying the activity of typical monoamine reuptake inhibitors (Duman, Aghajanian, Sanacora, & Krystal, 2016; Zanos & Gould, 2018). In particular, NMDAR antagonists seem to increase the expression of brain-derived neurotrophic factor and activate the mechanistic target of rapamycin complex 1 (Dwyer, Lepack, & Duman, 2012; Li et al., 2010; Voleti et al., 2013), thus promoting protein synthesis important for strengthening both synaptic structure and function, which are negatively affected in the brain of depressed individuals (Duman et al., 2016; Zanos & Gould, 2018).

This is the first demonstration that the NMDAR antagonist d-methadone exerts antidepressant-like activity in a preclinical animal model of depressed behavior and that its efficacy is similar to or greater than that of ketamine, an antidepressant that demonstrates a rapid onset activity and robust efficacy in patients with treatment-resistant depression (Lapidus et al., 2014; Murrough et al., 2013; Singh et al., 2016).

d-Methadone has been tested in healthy, opioid-naïve subjects in single ascending and multiple ascending dose studies, which demonstrated an acceptable safety and tolerability profile (Bernstein et al., 2019). In addition, d-methadone is currently being evaluated at 25 and 50 mg/day doses in Phase 2a clinical study for patients with treatment-resistant depression (REL-1017; ClinicalTrials.gov identifier: NCT03051256). d-Methadone could potentially represent a new effective antidepressant in the growing class of NMDAR antagonists.

References

Bernstein, G., Davis, K., Mills, C., Wang, L., McDonnell, M., Oldenhof, J., . . . Vitolo, O. V. (2019). Characterization of the safety and pharmacokinetic profile of d-methadone, a novel N-methyl-D-aspartate receptor antagonist in healthy, opioid-naive subjects: Results of two Phase 1 studies. *Journal of Clinical Psychopharmacology, 39,* 226–237. http://dx.doi.org/10.1097/JCP.0000000000001035

Callahan, R. J., Au, J. D., Paul, M., Liu, C., & Yost, C. S. (2004). Functional inhibition by methadone of N-methyl-D-aspartate receptors expressed in Xenopus oocytes: Stereospecific and subunit effects. *Anesthesia and Analgesia, 98,* 653–659. http://dx.doi.org/10.1213/01.ANE.0000099723.75548.DF

Davis, A. M., & Inturrisi, C. E. (1999). d-Methadone blocks morphine tolerance and N-methyl-D-aspartate-induced hyperalgesia. *Journal of Pharmacology and Experimental Therapeutics, 289,* 1048–1053.

Detke, M. J., & Lucki, I. (1996). Detection of serotonergic and noradrenergic antidepressants in the rat forced swimming test: The effects of water depth. *Behavioural Brain Research, 73,* 43–46. http://dx.doi.org/10.1016/0166-4328(96)00067-8

Duman, R. S., Aghajanian, G. K., Sanacora, G., & Krystal, J. H. (2016). Synaptic plasticity and depression: New insights from stress and rapid-acting antidepressants. *Nature Medicine, 22,* 238–249. http://dx.doi.org/10.1038/nm.4050

Dupuy, J. M., Ostacher, M. J., Huffman, J., Perlis, R. H., & Nierenberg, A. A. (2011). A critical review of pharmacotherapy for major depressive disorder. *International Journal of Neuropsychopharmacology, 14,* 1417–1431. http://dx.doi.org/10.1017/S1461145711000083

Dwyer, J. M., Lepack, A. E., & Duman, R. S. (2012). mTOR activation is required for the antidepressant effects of mGluR2/3 blockade. *International Journal of Neuropsychopharmacology, 15,* 429–434. http://dx.doi.org/10.1017/S1461145711001702

Garcia, L. S., Comim, C. M., Valvassori, S. S., Réus, G. Z., Barbosa, L. M., Andreazza, A. C., . . . Quevedo, J. (2008). Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 32,* 140–144. http://dx.doi.org/10.1016/j.pnpbp.2007.07.027

Global Burden of Disease Study 2013 Collaborators. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet, 386,* 743–800.

Gorman, A. L., Elliott, K. J., & Inturrisi, C. E. (1997). The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neuroscience Letters, 223,* 5–8. http://dx.doi.org/10.1016/S0304-3940(97)13391-2

Hardeveld, F., Spijker, J., De Graaf, R., Nolen, W. A., & Beekman, A. T. (2010). Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatrica Scandinavica, 122,* 184–191. http://dx.doi.org/10.1111/j.1600-0447.2009.01519.x

Kessler, R. C., & Bromet, E. J. (2013). The epidemiology of depression across cultures. *Annual Review of Public Health, 34,* 119–138. http://dx.doi.org/10.1146/annurev-publhealth-031912-114409

Kristensen, K., Christensen, C. B., & Christrup, L. L. (1995). The mu1, mu2, delta, kappa opioid receptor binding profiles of methadone stereoisomers and morphine. *Life Sciences, 56,* PL45–PL50. http://dx.doi.org/10.1016/0024-3205(94)00937-6

Lapidus, K. A., Levitch, C. F., Perez, A. M., Brallier, J. W., Parides, M. K., Soleimani, L., . . . Murrough, J. W. (2014). A randomized controlled trial

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of intranasal ketamine in major depressive disorder. *Biological Psychiatry, 76,* 970–976. http://dx.doi.org/10.1016/j.biopsych.2014.03.026

Li, N., Lee, B., Liu, R.-J., Banasr, M., Dwyer, J. M., Iwata, M., . . . Duman, R. S. (2010). mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science, 329,* 959–964. http://dx.doi.org/10.1126/science.1190287

Morgan, R. W., & Nicholson, K. L. (2011). Characterization of the antinociceptive effects of the individual isomers of methadone after acute and chronic administrations. *Behavioural Pharmacology, 22,* 548–557. http://dx.doi.org/10.1097/FBP.0b013e328349ab0d

Moryl, N., Tamasdan, C., Tarcatu, D., Thaler, H. T., Correa, D., Steingart, R., . . . Obbens, E. (2016). A phase I study of D-methadone in patients with chronic pain. *Journal of Opioid Management, 12,* 47–55. http://dx.doi.org/10.5055/jom.2016.0311

Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M., . . . Mathew, S. J. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. *American Journal of Psychiatry, 170,* 1134–1142. http://dx.doi.org/10.1176/appi.ajp.2013.13030392

Porsolt, R. D., Anton, G., Blavet, N., & Jalfre, M. (1978). Behavioural despair in rats: A new model sensitive to antidepressant treatments. *European Journal of Pharmacology, 47,* 379–391. http://dx.doi.org/10.1016/0014-2999(78)90118-8

Shimoyama, N., Shimoyama, M., Elliott, K. J., & Inturrisi, C. E. (1997). d-Methadone is antinociceptive in the rat formalin test. *Journal of Pharmacology and Experimental Therapeutics, 283,* 648–652.

Singh, J. B., Fedgchin, M., Daly, E. J., De Boer, P., Cooper, K., Lim, P., . . . Van Nueten, L. (2016). A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. *American Journal of Psychiatry, 173,* 816–826. http://dx.doi.org/10.1176/appi.ajp.2016.16010037

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., . . . the STAR*D Study Team. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *American Journal of Psychiatry, 163,* 28–40. http://dx.doi.org/10.1176/appi.ajp.163.1.28

Voleti, B., Navarria, A., Liu, R. J., Banasr, M., Li, N., Terwilliger, R., . . . Duman, R. S. (2013). Scopolamine rapidly increases mTORC1 signaling, synaptogenesis, and antidepressant behavior. *Biological Psychiatry, 74,* 742–749. http://dx.doi.org/10.1016/j.biopsych.2013.04.025

Yuen, E., Swanson, S., & Witkin, J. M. (2017). Prediction of human efficacious antidepressant doses using the mouse forced swim test. *Pharmacology, Biochemistry, and Behavior, 161,* 22–29. http://dx.doi.org/10.1016/j.pbb.2017.09.002

Zanos, P., & Gould, T. D. (2018). Mechanisms of ketamine action as an antidepressant. *Molecular Psychiatry, 23,* 801–811. http://dx.doi.org/10.1038/mp.2017.255

Zarate, C. A., Jr., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., . . . Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry, 63,* 856–864. http://dx.doi.org/10.1001/archpsyc.63.8.856

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