Through ketamine fields

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CHAPTER 2

ORAL KETAMINE FOR THE TREATMENT OF PAIN AND TREATMENT-RESISTANT DEPRESSION

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Abstract

Background: Recent studies with intravenous application of ketamine show remarkable but short-term success in patients with major depressive disorder. Studies in patients with chronic pain have used different ketamine applications for longer time periods. This experience may be relevant for psychiatric indications.
Aims: To review the literature about the dosing regimen, duration, effects, and side effects of oral, intravenous, intranasal, and subcutaneous routes of administration of ketamine for treatment-resistant depression (TRD) and pain.
Method: Searches in PubMed with the terms "oral ketamine", "depression", "chronic pain", "neuropathic pain", "intravenous ketamine", "intranasal ketamine", and "subcutaneous ketamine" yielded 88 articles. We reviewed all papers information about dosing regimen, number of individuals who received ketamine, number of ketamine days per study, results, and side effects, as well as study quality.
Results: Overall, the methodological strength of studies investigating the antidepressant effects of ketamine was considered low, regardless of the route of administration. The doses for depression were in the lower range compared with studies that investigated analgesic use. Studies on pain suggested that oral ketamine may be acceptable for TRD in terms of tolerability and side effects.
Conclusions: Oral ketamine, given for longer time periods in the described doses, appears to be well tolerated, but few studies have systematically examined the longer-term negative consequences. The short- and longer-term depression outcomes, as well as side effects, need to be studied with rigorous randomised controlled trials.
Declaration of interest: None.

Introduction

The rapid antidepressant action of the glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist ketamine has kindled great interest and optimism among researchers, clinicians and patients (1,2). Both open-label studies and randomised controlled trials (RCTs) in treatment resistant unipolar or bipolar depression (TRD) have shown antidepressant effects occurring within hours of intravenous (IV) infusion with ketamine. This supports the idea that, besides the monoaminergic systems, the glutamatergic system may also be targeted for the treatment of major depressive disorder (MDD) (3). In patients with mood disorders, glutamate levels in serum and cerebrospinal fluid are altered (4). Ketamine increases the presynaptic release of glutamate, resulting in higher extracellular levels of glutamate by a combination of disinhibition of the neurotransmitter γ-aminobutyric acid (GABA) and blockage of the NMDA receptors at the phencyclidine binding site within the ion channel (5). This increase in extracellular glutamate release favours coexpressed α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), resulting in "an increased glutamatergic throughput of AMPA relative to NMDA" (5). The glutamatergic system is also fundamental for neuroplasticity, which is linked to mood disorders (6). NMDA receptor activation is part of the induction process for long-term potentiation, an important form of synaptic plasticity. Synapse-associated proteins and the number of dendritic spines then increase, for example, in the prefrontal cortex (7), thus reversing the structural and functional deficits resulting from long-term stress exposure (8).

In TRD studies, ketamine has mostly been administered intravenously (9). A rapid IV infusion of ketamine for TRD, usually at a dose of 0.5 mg/kg, leads to an immediate bioavailability of 100%. To date, six double-blind crossover RCTs have been published that compared a single dose of IV ketamine to placebo: five of them used an inactive placebo – saline (2,10-13) – and one used an active placebo – midazolam (14). Overall, these studies showed rapid initial effects (40 minutes after infusion) that increase to one day post-infusion, but overall the difference between ketamine and placebo (inactive or active) was no longer statistically significant at seven days post-infusion. A recent open-label study that compared ketamine with active placebo (midazolam) had a similar effect size of 0.81 at one day post-infusion, but again the effect did not last (15). The great challenge with ketamine as an antidepressant is to extend its duration of action.

To study the efficacy of repeated ketamine infusions, a non-blinded study provided six infusions over two weeks. After the last infusion eight of nine patients (89%) were in remission. The average time to relapse after the last infusion was

much longer than in single injection studies: nineteen days (SD=13) after the last infusion (16). Investigators reported no worsening of cognitive function during the follow-up period although this was not formally tested.

Other researchers (17,18) have sought to maintain the effect of IV ketamine by adding oral riluzole, a glutamatergic modulator with antidepressant and synaptic plasticity-enhancing effects, but this was unsuccessful. Future research should then explore new strategies to optimise the antidepressant response, including dosing regimens and routes of administration (9).

To date, the field of psychiatry has paid little attention to the experience with oral and other non-IV administrations of ketamine for chronic pain. Ketamine is a well-known anaesthetic, with analgesic effects that may be used to treat chronic pain in a range of disorders (19). In the field of pain management, there is ample experience with the oral, as well as IV application of ketamine. Indications for oral ketamine include neuropathic pain of various origins, complex regional pain syndrome, cancer pain, orofacial pain, and phantom limb pain. As in depression, the therapeutic effect is believed to be based on antagonism of the NMDA receptor (20).

This review describes the findings of these studies and combines the fields of pain management and depression, with special attention to safety, dosing regimen and treatment duration.

Method

We searched PubMed with the following terms: ["oral ketamine" AND "depression"], ["oral ketamine" AND ("chronic pain" OR "neuropathic pain")], ["intravenous ketamine" AND "depression"], ["intravenous ketamine" AND ("chronic pain" OR "neuropathic pain")], ["intranasal ketamine" AND "depression"], ["intranasal ketamine" AND ("chronic pain" OR "neuropathic pain")], ["subcutaneous ketamine" AND "depression"] and ["subcutaneous ketamine" AND ("chronic pain" OR "neuropathic pain")]. The final search date was 27 October 2014. Our searches yielded 112 studies. We excluded literature reviews, studies with animals and studies with healthy individuals, thereby yielding 88 studies. We scanned all papers for information about study type and size, dosing regimen, number of individuals who received ketamine, number of ketamine days per study, results and side effects. When these were described, we entered them into two tables: table 1 refers to the studies where ketamine was used to treat depression (appendix 1) and table 2 refers to the studies where ketamine was used to treat pain (appendix 2). We designed two graphs with the information provided by those tables (figures 2.1 and 2.2).

In total, for depression, four studies were found using oral ketamine (n=22), 43 studies used IV ketamine (n=763), two studies used intranasal ketamine (n=19), one study used sublingual ketamine (n=26), and two case reports concerned intramuscular (IM) ketamine (n=3). For pain, twelve studies used oral (n=76), 21 studies IV (n=553), two studies intranasal (n=21), and one study IM ketamine (n=35). We found only one study on subcutaneous ketamine for pain that met the inclusion criteria, but it presented insufficient data (no dose and no number of ketamine days described), so we excluded it from the analysis. We found no subcutaneous ketamine for depression study. One sublingual ketamine for depression study and three IM ketamine studies (one for pain and two for depression) were included in our analysis.

To compare dosing regimens across studies, we calculated the daily oral racemate equivalent dose (DORED), in mg/kg/day, by multiplying the IV dose by five to correct for the five times lower average oral bioavailability (21,22) and by multiplying the S-ketamine dose by two to correct for the double potency relative to racemate. For intranasal dosing regimens, we obtained the DORED by multiplying them by 2.25 to correct for the 2.25 times lower oral bioavailability (23). In the case of IM dosing regimens, we calculated the DORED by multiplying them by 4.65 to correct for the 4.65 times lower oral bioavailability (22). We multiplied the sublingual dose by 1.5 to obtain their DORED (23).

Results

Oral ketamine for depression

Five uncontrolled open-label studies were found that investigated the antidepressant properties of oral (including sublingual) ketamine (24-28). A small study (n=4) found depression relief in patients with TRD who were given up to 1.25 mg/kg oral S-ketamine for two weeks (24). In one study on palliative healthcare (25), the effects of ketamine on pain, anxiety and depression were assessed. This case report describes a hospice patient who was treated daily with 40 mg oral ketamine, which relieved all three complaints. Another hospice-based study described two severely ill and depressed patients who showed significant improvements lasting one or two weeks after a single oral dose of 0.5 mg/kg ketamine (27). A more recent hospice-based study administered daily oral ketamine (0.5 mg/kg) over a 28-day period to patients in hospice care who had depressive symptoms. Eight out of fourteen patients completed the trial and showed significant improvement in pain and depression with few side effects (26). De Gioannis and de Leo (2014) treated two patients with chronic suicidal ideation (and at least two significant past suicide attempts) with a

solution of ketamine ingested with a flavoured drink. The maximum dose used was 3 mg/kg of ketamine. Both patients achieved sustained remission from suicidal ideation (28).

Lara et al. (2013) reported on 10 mg sublingual ketamine, administered once, or every two, three or seven days for a total of up to twenty doses. They observed improved mood in 20 out of 26 patients with TRD. The antidepressant effects outlasted the acute side effects, which primarily concerned light-headedness, and did not include euphoria or dissociation (29).

Clearly, these are only first indications of possible antidepressant effects of oral ketamine, as all of these studies were very small and uncontrolled, and the quality of the evidence was low.

Dosing regimen and treatment duration of ketamine in chronic pain

Figures 2.1 and 2.2 show that both for depression and pain most studies used the IV route of application. Expressed in DORED, the doses for depression are in the lower range compared with studies that investigated analgesic use. Also, the graphs show that ketamine as an antidepressant is generally given for shorter durations (1 to 32 days) than ketamine as an analgesic. Finally, it shows that on average IV ketamine is given for a shorter duration than oral ketamine. Studies with oral ketamine, where pain was the primary indication, administered ketamine once (30) or for as long as 660 days (31), with most studies in the range of 20 to 80 days.

The doses used in the analysed pain studies differed from 0.1 DORED via oral administration (30) to 62.5 mg/kg/day intravenously (32). It is not possible to establish a dose-response association, but the majority of the analysed pain studies describe ketamine as effective in reducing pain, even in low oral doses. The exceptions are six studies that used IV ketamine (33-38), which did not lead to any reduction in the pain scores. Although the study conducted by Kapural et al. (2010) used a high dose (DORED of 21.5 mg/kg/day), it did not achieve an improvement in long-term pain scores in patients with high opioid requirements (33).

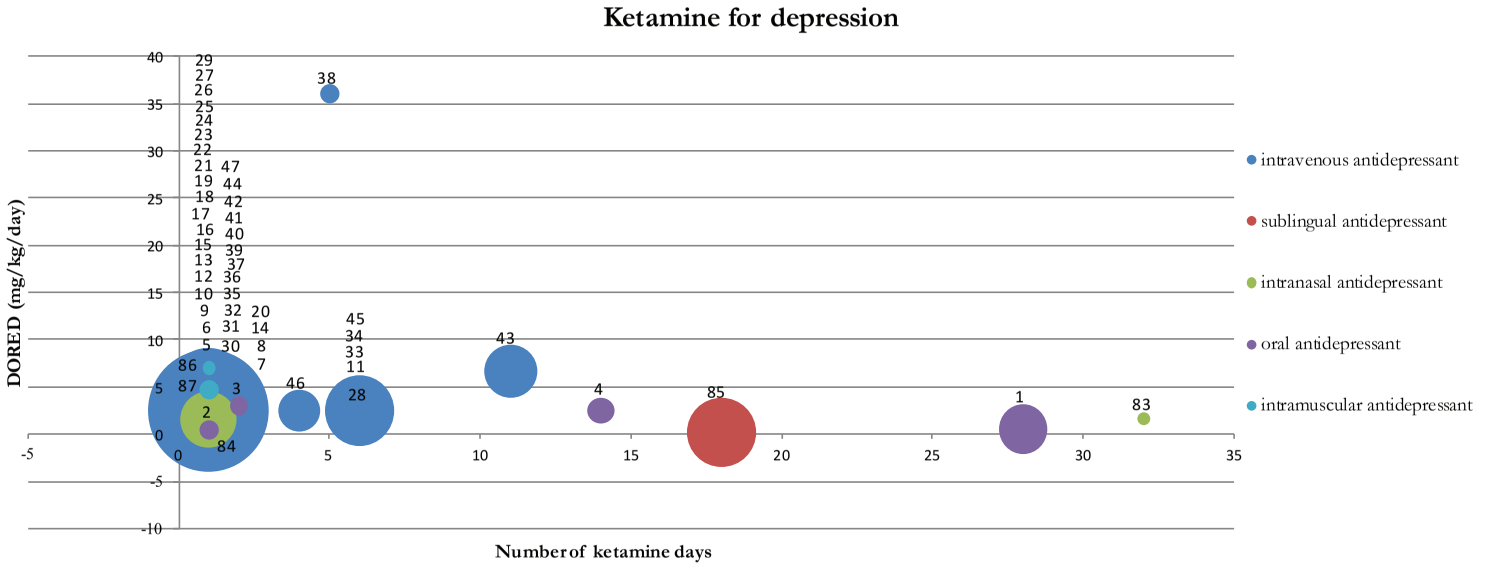

Figure 2.1: Overview of daily dose of ketamine for treating depression and number of ketamine days. Fifty-two studies about ketamine used to treat depression were included. The x-axis represents the number of ketamine days, which is different from the study duration (in some studies, only one or few doses were given during a long follow-up time) The size of the bubbles represents the sample size (number of individuals who received ketamine). The numbers close to the bubbles refer to the study identification, which can be found in table 1 (appendix 1).

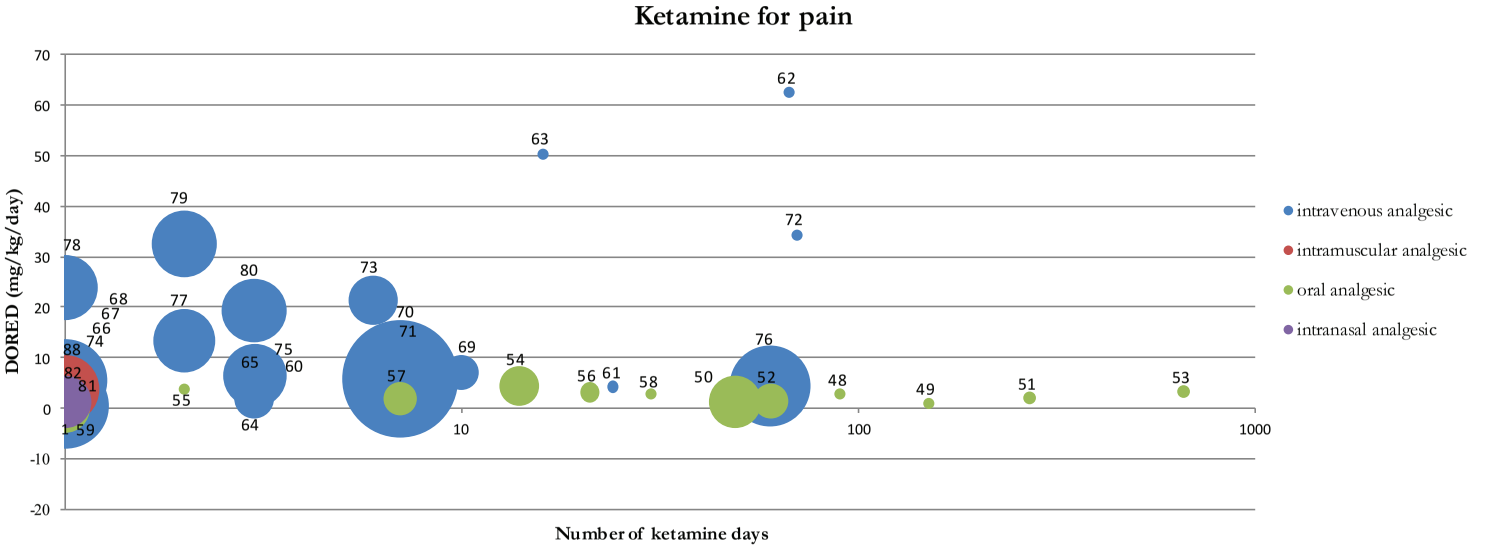

Figure 2.2: Overview of daily dose of ketamine for treating pain and number of ketamine days. Thirty-six studies about ketamine used for treating pain were included. The x-axis represents the number of ketamine days, which is different from the study duration (in some studies, only one or few doses were given during a long follow-up time). The size of the bubbles represents the sample size (number of individuals who received ketamine). The numbers close to the bubbles refer to the study identification, which can be found in table 2 (appendix 2).

Some studies in patients with chronic pain (that could be progressive and/or related to terminal illness) showed that patients required higher doses over time. For instance, Villanueva-Perez et al. (2007) administered 30 mg of oral ketamine every eight hours to a patient with complex regional pain syndrome type 1, increasing this dose weekly in 5 mg until a maximum dose of 60 mg/6 hours was reached. This patient kept this last dose for more than two years with significant improvement mainly in the first seventeen months (31). Vick and Lamer (2001) achieved significant improvement in pain, allodynia and hyperalgesia in one patient with central post-stroke pain at the dose of 50 mg oral ketamine three times per day. This treatment lasted three months (39). This is in line with preclinical and clinical studies on anaesthesia and studies on ketamine misuse, that suggest that tolerance may develop (40-45).

Clearly, the dosage is directly related to the bioavailability of ketamine. With oral administration, the bioavailability is generally low, because of extensive first-pass metabolism (22). Reported values of oral ketamine in adults are in the range of 17 to 24% (21-23,46). A study by Brunette et al. (2011) in children showed the highest bioavailability (45%), and used a nasogastric tube and a 10 mL water flush (47), but Yanagihara et al. (2003) also used a water flush (100 mL) and found a bioavailability of only 20% in adults (23). Other factors underlying the variability after oral dosing may include the formulation (tablet or solution, ketamine concentration), state of the stomach, dietary enzyme induction, and individual differences in cytochrome phenotype. It should be noted that interindividual pharmacokinetic variability is common to oral administration in general (48-50) and has also been described for currently prescribed antidepressants (51). Intranasal and sublingual ketamine administration have been reported to yield 45% and 30% bioavailability, respectively (23), but interindividual variability has been described for these routes of ketamine administration as well (52,53). Ketamine absorption after IM injection has been described as more rapid, with a bioavailability of 93% (22).

Safety and abuse potential

The most common side effects of IV ketamine are psychotomimetic effects and dissociative symptoms (54,55), which correlate with high initial plasma levels and may thus be less pronounced in oral administration (56). Feeling "high" after ketamine is also dependent on plasma levels (56). Other known side-effects are confusion, dizziness, euphoria, elevated blood pressure and increased libido, although all of these usually dissipate within two hours of IV infusion (57).

Ketamine neurotoxicity has been described in preclinical studies (58), but this was suggested to be due to the presence of the preservative chlorobutanol rather than

to the ketamine itself (59). Without preservative, ketamine can induce neurotoxicity when injected in very high doses into the subarachnoid space (60). The study of Sun et al. (2014) showed that IV ketamine given to adolescent cynomolgus monkeys at a dose of 1 mg/kg in saline for six months might also produce permanent and irreversible deficits in brain function through the neurotoxic effect caused by the activation of apoptotic pathway in the prefrontal cortex (61). This appears to be in contrast with studies in humans where ketamine was given in similar or higher doses with few mentions of cognitive problems (10,11). It should be noted that currently available clinical studies with IV ketamine used only one or few applications. In the studies involving pain, patients were given ketamine more often, but mostly did not have the "peak effect" of IV application. Prolonged ketamine misuse has been associated with white matter changes (62), memory changes (63), neurocognitive impairment (55,64), and reduced well-being (55). Finally, inflammation and damage to the ureters and bladder are well documented in very heavy ketamine users who consume daily amounts of one gramme by inhalation and for prolonged periods of months or even years (65,66). Notably, in these studies, daily doses were substantially higher than those used in clinical studies. Calculated in DORED, these users had approximately 80 mg/kg/day, which is 2.2 times higher than the highest DORED found in a study where ketamine was used to treat depression (67).

The majority of the pain and depression studies retrieved by our search did not report the side effects of oral ketamine as a major burden in treatment maintenance. Side effects commonly mentioned were dizziness, hallucinations, nausea, vomiting, drowsiness, confusion, light-headedness, headache, somnolence, and anxiety. An exception to this is the study by Kannan et al. (2002) involving nine patients with neuropathic pain, which stated that the beneficial effects in the management of intractable neuropathic pain were limited in some patients by the adverse effects such as nausea, vomiting, loss of appetite, drowsiness, sedation, and feeling of unreality (68). Haines and Gaines (1999) found that ketamine caused an analgesic response in only 14% of individuals and described that the adverse events (light-headedness, dizziness, tiredness, headache, nervous floating feeling, and bad dreams) limited the use of ketamine in almost half of their patients (69). Hallucinations and paranoid feelings were reported in only one patient (31); memory impairment and dysuria were reported in one study on twelve patients (70).

Very low dose sublingual administration of 10 mg (approximately equivalent to 0.036 mg/kg IV) was not associated with euphoria or psychotic and dissociative symptoms (29). In some studies, increased blood pressure was controlled with the concomitant administration of a benzodiazepine (71,72). The reported adverse events were usually limited to the ketamine treatment phase and did not persist after

ketamine discontinuation (see tables 1 and 2 in appendices 1 and 2, respectively, for more details about side effects per study).

Another concern with ketamine is its misuse potential, which has been demonstrated in both animals and humans (73,74). Ketamine has been used as a street drug since the 1960's, probably because of its rapid effects, its low cost and its specific psychotropic effects such as hallucinatory and dissociative experiences (e.g. "melting into the surrounding", "out-of-body" experiences), as well as "giggliness" (75,76). Multi-drug users who have used ketamine in large doses recreationally have also expressed concerns about its addictive properties (75). No studies have compared different routes of ketamine administration directly, but the misuse potential is generally found to be higher with IV administration or inhalation that produces much more rapid and intensive effects compared to oral administration (77). In line with this, the psychedelic effects of ketamine are directly related to plasma concentrations (56). Importantly, in the pain studies mentioned earlier, addiction or misuse were not described as side effects. Still, it is clear that these unwanted effects should be balanced against the possible beneficial properties of ketamine.

Discussion

Overall, the results suggest that oral ketamine in the described doses may be well tolerated. However, few studies have systematically studied its possible longer-term consequences. In comparison with studies of patients with pain, treatment duration in the currently available studies of depression is at the lower end of the spectrum. Further research is needed including basic science, acceptability and feasibility studies, ethical perspectives, and ultimately building to randomised trials designs. A number of issues need to be addressed. First, ketamine raises concerns, such as its potential for misuse, that warrant solid monitoring. Even though our review did not show such problems to be very important in studies on depression and pain, this may be much more of a problem if ketamine were to be used on a broader basis in clinical practice. We agree with the statement made by Caddy et al. (2015), in a Cochrane review about ketamine for depression in adults, that there is a need for studies examining the longer-term effects of repeated use of ketamine that also take into account oral and IM routes (78).

Second, even though the side effect profile of oral ketamine seems to be milder than that reported in IV studies and in severe drug misusers, the overall safety profile would warrant that ketamine should be provided in a hospital setting. After an initial inpatient phase, oral ketamine might, however, be prescribed to depressed

patients outside the hospital environment for maintenance purposes, depending on an assessment of risk for each individual patient. Furthermore, side effects should systematically be monitored using an instrument, such as the SAFTEE, the "systematic assessment for treatment emergent events" (79).

Third, oral bioavailability of ketamine is rather low and variable; studies should take into account blood levels of active metabolites and ketamine formulation. Fourth, as the antidepressant effects of ketamine may partially be related to its anaesthetic potential, especially in depressed patients with pain, a thorough assessment of both depressive symptoms and pain needs to be incorporated into upcoming trials.

Based on the above, we believe it is time to conduct rigorous RCTs that determine the benefits, as well as possible unsolicited consequences of oral ketamine, given for weeks rather than days, for patients with TRD.

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References

1. Vollenweider FX, Kometer M. The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. Nat Rev Neurosci 2010 Sep;11(9):642-651.
2. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000 Feb 15;47(4):351-354.
3. Hashimoto K. Emerging role of glutamate in the pathophysiology of major depressive disorder. Brain Res Rev 2009 Oct;61(2):105-123.
4. Murrough JW. Ketamine as a novel antidepressant: from synapse to behavior. Clin Pharmacol Ther 2012 Feb;91(2):303-309.
5. Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci 1997 Apr 15;17(8):2921-2927.
6. Zarate C,Jr, Machado-Vieira R, Henter I, Ibrahim L, Diazgranados N, Salvadore G. Glutamatergic modulators: the future of treating mood disorders? Harv Rev Psychiatry 2010 Sep-Oct;18(5):293-303.
7. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 2010 Aug 20;329(5994):959-964.
8. Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, et al. Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biol Psychiatry 2011 Apr 15;69(8):754-761.
9. aan het Rot M, Zarate CA, Jr., Charney DS, Mathew SJ. Ketamine for depression: where do we go from here? Biol Psychiatry 2012 10/01; 2019/09;72(7):537-547.
10. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry 2010 Aug;67(8):793-802.
11. Zarate CA,Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry 2012 Jun 1;71(11):939-946.
12. Zarate CA,Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006 Aug;63(8):856-864.
13. Sos P, Klirova M, Novak T, Kohutova B, Horacek J, Palenicek T. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. Neuro Endocrinol Lett 2013;34(4):287-293.
14. Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety 2014 Apr;31(4):335-343.

15. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 2013 Oct;170(10):1134-1142.
16. aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry 2010 Jan 15;67(2):139-145.
17. Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology 2012 May;37(6):1526-1533.
18. Mathew SJ, Murrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial. Int J Neuropsychopharmacol 2010 Feb;13(1):71-82.
19. Blonk MI, Koder BG, van den Bemt PM, Huygen FJ. Use of oral ketamine in chronic pain management: a review. Eur J Pain 2010 May;14(5):466-472.
20. Fisher K, Coderre TJ, Hagen NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management: preclinical animal studies, recent clinical experience and future research directions. J Pain Symptom Manage 2000 Nov;20(5):358-373.
21. Chong C, Schug S, Page-Sharp M, Ilett K. Bioavailability of ketamine after oral or sublingual administration. Pain Medicine 2006;7(5):469-469.
22. Clements JA, Nimmo WS, Grant IS. Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. J Pharm Sci 1982 May;71(5):539-542.
23. Yanagihara Y, Ohtani M, Kariya S, Uchino K, Hiraishi T, Ashizawa N, et al. Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. Biopharm Drug Dispos 2003 Jan;24(1):37-43.
24. Paslakis G, Gilles M, Meyer-Lindenberg A, Deuschle M. Oral administration of the NMDA receptor antagonist S-ketamine as add-on therapy of depression: a case series. Pharmacopsychiatry 2010 Jan;43(1):33-35.
25. McNulty JP Hahn K. Compounded oral ketamine. Int J Pharm Compd 2012 Sep-Oct;16(5):364-368.
26. Irwin SA, Iglewicz A, Nelesen RA, Lo JY, Carr CH, Romero SD, et al. Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. J Palliat Med 2013 Aug;16(8):958-965.
27. Irwin SA, Iglewicz A. Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care. J Palliat Med 2010 Jul;13(7):903-908.
28. de Gioannis A, de Leo D. Oral ketamine augmentation for chronic suicidality in treatment-resistant depression. Aust N Z J Psychiatry 2014 Jan 22;48(7):686.
29. Lara DR, Bisol LW, Munari LR. Antidepressant, mood stabilizing and procognitive effects of very low dose sublingual ketamine in refractory unipolar and bipolar depression. Int J Neuropsychopharmacol 2013 Oct;16(9):2111-2117.

30. Kaviani N, Khademi A, Ebtehaj I, Mohammadi Z. The effect of orally administered ketamine on requirement for anesthetics and postoperative pain in mandibular molar teeth with irreversible pulpitis. J Oral Sci 2011 Dec;53(4):461-465.
31. Villanueva-Perez VL, Cerda-Olmedo G, Samper JM, Minguez A, Monsalve V, Bayona MJ, et al. Oral ketamine for the treatment of type I complex regional pain syndrome. Pain Pract 2007 Mar;7(1):39-43.
32. Klepstad P, Borchgrevink P, Hval B, Flaat S, Kaasa S. Long-term treatment with ketamine in a 12-year-old girl with severe neuropathic pain caused by a cervical spinal tumor. J Pediatr Hematol Oncol 2001 Dec;23(9):616-619.
33. Kapural L, Kapural M, Bensitel T, Sessler DI. Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic-pain patients with high opioid requirements. Pain Physician 2010 Jul-Aug;13(4):389-394.
34. Joseph C, Gaillat F, Duponq R, Lieven R, Baumstarck K, Thomas P, et al. Is there any benefit to adding intravenous ketamine to patient-controlled epidural analgesia after thoracic surgery? A randomized double-blind study. Eur J Cardiothorac Surg 2012 Oct;42(4):e58-65.
35. Hu J, Liao Q, Zhang F, Tong J, Ouyang W. Chronic postthoracotomy pain and perioperative ketamine infusion. J Pain Palliat Care Pharmacother 2014 Jun;28(2):117-121.
36. Barreveld AM, Correll DJ, Liu X, Max B, McGowan JA, Shovel L, et al. Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: results of a prospective, randomized, double-blind study. Pain Med 2013 Jun;14(6):925-934.
37. Yazigi A, Abou-Zeid H, Srouji T, Madi-Jebara S, Haddad F, Jabbour K. The effect of low-dose intravenous ketamine on continuous intercostal analgesia following thoracotomy. Ann Card Anaesth 2012 Jan-Mar;15(1):32-38.
38. Tena B, Gomar C, Rios J. Perioperative epidural or intravenous ketamine does not improve the effectiveness of thoracic epidural analgesia for acute and chronic pain after thoracotomy. Clin J Pain 2014 Jun;30(6):490-500.
39. Vick PG, Lamer TJ. Treatment of central post-stroke pain with oral ketamine. Pain 2001 May;92(1-2):311-313.
40. Stevens RW, Hain WR. Tolerance to rectal ketamine in paediatric anaesthesia. Anaesthesia 1981 Dec;36(12):1089-1093.
41. Pouget P, Wattiez N, Rivaud-Pechoux S, Gaymard B. Rapid development of tolerance to sub-anaesthetic dose of ketamine: an oculomotor study in macaque monkeys. Psychopharmacology 2010 May;209(4):313-318.
42. Rocha BA, Ward AS, Egilmez Y, Lytle DA, Emmett-Oglesby MW. Tolerance to the discriminative stimulus and reinforcing effects of ketamine. Behav Pharmacol 1996 Mar;7(2):160-168.
43. Byer DE, Gould AB,Jr. Development of tolerance to ketamine in an infant undergoing repeated anesthesia. Anesthesiology 1981 Mar;54(3):255-256.
44. Cumming JF. The development of an acute tolerance to ketamine. Anesth Analg 1976 Nov-Dec;55(6):788-791.

45. Livingston A, Waterman AE. The development of tolerance to ketamine in rats and the significance of hepatic metabolism. Br J Pharmacol 1978 Sep;64(1):63-69.
46. Chong C, Schug SA, Page-Sharp M, Jenkins B, Ilett KF. Development of a sublingual/oral formulation of ketamine for use in neuropathic pain: preliminary findings from a three-way randomized, crossover study. Clin Drug Investig 2009;29(5):317-324.
47. Brunette KEJ, Anderson BJ, Thomas J, Wiesner L, Herd DW, Schulein S. Exploring the pharmacokinetics of oral ketamine in children undergoing burns procedures. Pediatric Anesthesia 2011;21(6):653-662.
48. Di WL, Kadva A, Johnston A, Silman R. Variable bioavailability of oral melatonin. N Engl J Med 1997 Apr 3;336(14):1028-1029.
49. Harvey VJ, Slevin ML, Joel SP, Smythe MM, Johnston A, Wrigley PF. Variable bioavailability following repeated oral doses of etoposide. Eur J Cancer Clin Oncol 1985 Nov;21(11):1315-1319.
50. Zimm S, Collins JM, Riccardi R, O'Neill D, Narang PK, Chabner B, et al. Variable bioavailability of oral mercaptopurine: is maintenance chemotherapy in acute lymphoblastic leukemia being optimally delivered? N Engl J Med 1983 Apr 28;308(17):1005-1009.
51. Lund J, Thayssen P, Mengel H, Pedersen OL, Kristensen CB, Gram LF. Paroxetine: pharmacokinetics and cardiovascular effects after oral and intravenous single doses in man. Acta Pharmacol Toxicol 1982 Oct;51(4):351-357.
52. Weber F, Wulf H, Gruber M, Biallas R. S-ketamine and s-norketamine plasma concentrations after nasal and i.v. administration in anesthetized children. Paediatr Anaesth 2004 Dec;14(12):983-988.
53. Rolan P, Lim S, Sunderland V, Liu Y, Molnar V. The absolute bioavailability of racemic ketamine from a novel sublingual formulation. Br J Clin Pharmacol 2014 Jun;77(6):1011-1016.
54. Caddy C, Giaroli G, White TP, Shergill SS, Tracy DK. Ketamine as the prototype glutamatergic antidepressant: pharmacodynamic actions, and a systematic review and meta-analysis of efficacy. Ther Adv Psychopharmacol 2014 Apr;4(2):75-99.
55. Morgan CJ, Muetzelfeldt L, Curran HV. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. Addiction 2010 Jan;105(1):121-133.
56. Bowdle TA, Radant AD, Cowley DS, Kharasch ED, Strassman RJ, Roy-Byrne PP. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anesthesiology 1998 Jan;88(1):82-88.
57. Liebrenz M, Borgeat A, Leisinger R, Stohler R. Intravenous ketamine therapy in a patient with a treatment-resistant major depression. Swiss Med Wkly 2007 Apr 21;137(15-16):234-236.
58. Malinovsky JM, Cozian A, Lepage JY, Mussini JM, Pinaud M, Souron R. Ketamine and midazolam neurotoxicity in the rabbit. Anesthesiology 1991 Jul;75(1):91-97.
59. Malinovsky JM, Lepage JY, Cozian A, Mussini JM, Pinaudt M, Souron R. Is ketamine or its preservative responsible for neurotoxicity in the rabbit? Anesthesiology 1993 Jan;78(1):109-115.

60. Gomes LM, Garcia JB, Ribamar JS,Jr, Nascimento AG. Neurotoxicity of subarachnoid preservative-free S(+)-ketamine in dogs. Pain Physician 2011 Jan-Feb;14(1):83-90.
61. Sun L, Li Q, Li Q, Zhang Y, Liu D, Jiang H, et al. Chronic ketamine exposure induces permanent impairment of brain functions in adolescent cynomolgus monkeys. Addict Biol 2014;19(2):185-194.
62. Edward Roberts R, Curran HV, Friston KJ, Morgan CJ. Abnormalities in white matter microstructure associated with chronic ketamine use. Neuropsychopharmacology 2014 Jan;39(2):329-338.
63. Freeman TP, Morgan CJ, Pepper F, Howes OD, Stone JM, Curran HV. Associative blocking to reward-predicting cues is attenuated in ketamine users but can be modulated by images associated with drug use. Psychopharmacology 2013 Jan;225(1):41-50.
64. Morgan CJ, Curran HV, Independent Scientific Committee on Drugs. Ketamine use: a review. Addiction 2012 Jan;107(1):27-38.
65. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. Urology 2007 May;69(5):810-812.
66. Tsai TH, Cha TL, Lin CM, Tsao CW, Tang SH, Chuang FP, et al. Ketamine-associated bladder dysfunction. Int J Urol 2009 Oct;16(10):826-829.
67. Correll GE, Futter GE. Two case studies of patients with major depressive disorder given low-dose (subanesthetic) ketamine infusions. Pain Med 2006 Jan-Feb;7(1):92-95.
68. Kannan TR, Saxena A, Bhatnagar S, Barry A. Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. J Pain Symptom Manage 2002 Jan;23(1):60-65.
69. Haines DR, Gaines SP. N of 1 randomised controlled trials of oral ketamine in patients with chronic pain. Pain 1999 Nov;83(2):283-287.
70. Bredlau AL, McDermott MP, Adams HR, Dworkin RH, Venuto C, Fisher SG, et al. Oral ketamine for children with chronic pain: a pilot phase 1 study. J Pediatr 2013 Jul;163(1):194-200.e1.
71. Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. J Pain Symptom Manage 2000 Oct;20(4):246-252.
72. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo-controlled study. Pain 2009 Dec 15;147(1-3):107-115.
73. Beardsley PM, Balster RL. Behavioral dependence upon phencyclidine and ketamine in the rat. J Pharmacol Exp Ther 1987 Jul;242(1):203-211.
74. Klein M, Calderon S, Hayes B. Abuse liability assessment of neuroprotectants. Ann N Y Acad Sci 1999; 890:515-525.
75. Muetzelfeldt L, Kamboj SK, Rees H, Taylor J, Morgan CJ, Curran HV. Journey through the K-hole: phenomenological aspects of ketamine use. Drug Alcohol Depend 2008 Jun 1;95(3):219-229.

76. Corazza O, Assi S, Schifano F. From special K to special M: the evolution of the recreational use of ketamine and methoxetamine. CNS Neuroscience & Therapeutics 2013;19(6):454-460.
77. Argoff CE, Stanos SP, Wieman MS. Validity testing of patient objections to acceptance of tamper-resistant opioid formulations. J Pain Res 2013 May 16; 6:367-373.
78. Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R, et al. Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database of Systematic Reviews 2015(9).
79. Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacol Bull 1986;22(2):343-381.