

Research Overview

Breaking Sad: Unleashing the Breakthrough Potential of Ketamine's Rapid Antidepressant Effects

David Feifel*

Department of Psychiatry, University of California, San Diego, School of Medicine, Gilman Drive, La Jolla, 9500, California, 92037 MC0957

Strategy, Management and Health Policy				
Enabling Technology, Genomics, Proteomics	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT The surprising results of a small clinical trial on the effects of low dose ketamine, a 65-year old anesthetic drug that is also used off-label for chronic pain and recreationally as a club drug, in eight depressed subjects unleashed the most significant advance in antidepressant drug development in decades. That study and subsequent ones have demonstrated that low dose, infused ketamine is able to induce a remission of depression in patients who have failed conventional medications, within 24 h. The apparent increased efficacy and rapid onset of effect of ketamine distinguish it from all other current antidepressant treatments. However, a single infusion of subanesthetic doses of ketamine produces benefits that typically last <3 weeks. The infusions are associated with a transient “psychedelic” experience and increased blood pressure that requires monitoring. There is also a theoretical potential to induce ketamine addiction. These features limit ketamine’s ability to be a widely used treatment for depression and thus limit its ability to have a meaningful impact on the heavy morbidity and mortality associated with this disorder, despite its “breakthrough” rate of efficacy and speed of action. While growing numbers of clinicians are using ketamine to treat treatment resistant depression, many in the depression field believe that the aforementioned limiting aspects need to be separated from its remarkable therapeutic effects in order to unlock the breakthrough potential of this agent. To that end, drug development efforts have focused on various features of ketamine as targets for optimization including its modulation of the NMDA receptor, its pharmacokinetics, its chirality and its active metabolites including HNK (2R, 6R)-hydroxynorketamine. *Drug Dev Res* 77 : 489–494, 2016. © 2016 Wiley Periodicals, Inc.

Key words: antidepressant; treatment resistant depression; ketamine; NMDA; AMPA; psychedelic

DRUG DISCOVERY DROUGHT

For several decades the landscape of novel psychotropic drug development has been bleak. In a 2013 op-ed in the *New York Times*, psychiatrist Robert Friedman sounded the alarm stating “we are facing a crisis in drug innovation” (Friedman, 2013). Friedman acknowledged that we have ample numbers of approved drugs, but the number was deceiving since, “each of these drug classes is filled with “me too” drugs, which are essentially just copies of one another.” Indeed, in the case of antidepressants, today there are over 30 drugs approved for

depression. They are categorized under various families but all share the mechanism of modulating one or more of the brain’s monoamine neurotransmitters, dopamine, noradrenaline, and serotonin. This led to

*Correspondence to: David Feifel, Department of Psychiatry, University of California, San Diego, School of Medicine, Gilman Drive, La Jolla, 9500, California, 92037 MC0957. E-mail: dfeifel@ucsd.edu

Received 0 Month 2016; Accepted 0 Month 2016

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ddr.21347

the “monoamine hypothesis of depression,” which avers that underactive monoamine neurotransmission is the cause of depression but for which there is, after 50 years of research, paltry evidence (Hirschfeld, 2000). One consequence of the lack of mechanistic heterogeneity among current antidepressants is the fact that one-third of depressed patients who seek treatment do not respond to, or do not tolerate, current antidepressants (Rush et al., 2004) and, as a result, end up categorized as having treatment-resistant depression (TRD).

Underscoring the urgency of this situation is statistics revealing that rates of major depression are on the rise globally and suicide, most often the direct result of clinical depression, is the tenth leading cause of death in the US. Moreover, rather than declining in frequency, as are many terminal diseases due to improvement in detection and treatment, the suicide rates in the US are on the rise (Harper, 2016).

It is against this gloomy backdrop that the recent, unexpected, discovery that a decade-old anesthetic may have unprecedented antidepressant efficacy has reinvigorated the field of psychotropic drug development.

KETAMINE: THE DRUG NEXT DOOR TURNED SUPERSTAR

Ketamine (Fig. 1) is a phencyclidine derivative first synthesized in 1962 and used widely as an intravenous anesthetic since 1970. It has several unique properties. When administered alone at anesthetic doses ($2\text{--}4\text{ mg kg}^{-1}$) it does not produce deep sedation or hypnosis, rather a “dissociative” anesthesia, a trance-like state in which patients may retain awareness of their environment but feel “disconnected” from it. Patients typically retain normal reflexes such as coughing and swallowing and, in contrast to opioids and other anesthetics, ketamine does not suppress respiration. It has a rapid onset of action (within minutes) and is metabolized quickly, so unless it is continually administered, patients typically regain full orientation within 30–40 min. The analgesic effect of ketamine, however, typically persists beyond the dissociative anesthesia. Pharmacologically, ketamine directly regulates glutamate neurotransmission, the primary excitatory neurotransmitter in brain. Ketamine binds to the NMDA receptor, where it acts as a noncompetitive antagonist.

In 2000, Berman et al. (2000) reported the results of a small ($n = 8$) crossover study conducted in depressed patients examining the effects of a subanesthetic ketamine dose (0.5 mg kg^{-1}) infused intravenously over 40 min. They found that half the subjects had an antidepressant response (defined as

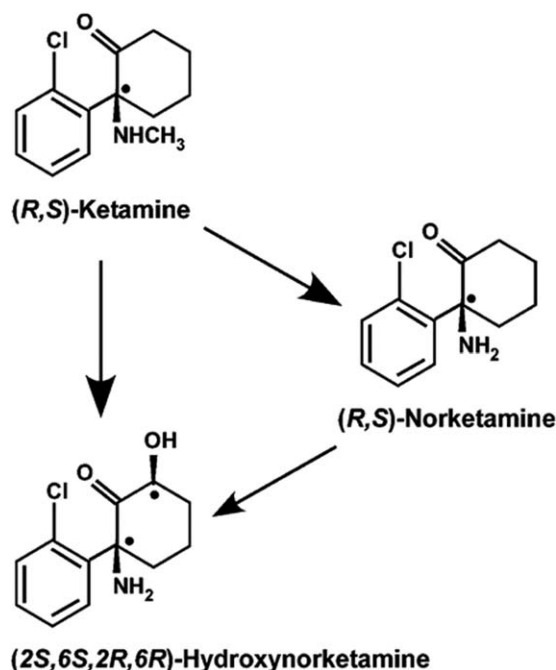


Fig. 1. Structures of ketamine and (2S, 6S, 2R, 6R)-hydroxynorketamine (HNK). (R,S)-KET is selectively demethylated to give (R,S)-norketamine (norKET) which is then hydroxylated to produce (2S, 6S, 2R, 6R)-hydroxynorketamine (HNK).

reduction in their depression rating score of at least 50%) within 4 days and some patients responded within 24 h. These results were so remarkable they largely garnered skepticism until another group (Zarate et al., 2006) replicated the findings in a somewhat larger sample ($n = 18$) of TRD patients, reporting even more positive ketamine outcomes—71% of TRD subjects responded to ketamine at 24 h and 30% had scores low enough to be considered in remission. None of the patients responded to saline infusions (Zarate et al., 2006). Since then, there have been at least six additional randomized controlled trials of subanesthetic IV ketamine in TRD patients, including studies of depression in patients diagnosed with bipolar disorder. There have also been at least 15 open label studies that have corroborated the remarkable antidepressant effects (for reviews see Ryan et al., 2014; Xu et al., 2016).

Subanesthetic ketamine has been reported to produce a therapeutic effect on several other psychiatric conditions including OCD (obsessive compulsive disorder) and PTSD (posttraumatic stress disorder) raising the possibility that there are other indications for which ketamine may contribute an important therapeutic option if appropriately developed (Bloch et al., 2012; Feder et al., 2014).

BREAKTHROUGH DRUG FEATURES OF KETAMINE'S ANTIDEPRESSANT EFFECTS

Two characteristics of ketamine's antidepressant effects, distinguish it from other antidepressants developed to date, greater apparent efficacy and faster onset.

Clinical Efficacy

Patients who continue to have significant depressive symptoms after trials of three antidepressants, have only an ~14% chance that they experience a remission of their depression upon trying a fourth antidepressant (Rush et al., 2006). In the ketamine trial by Zarate et al., (2006) patients had previously tried an average of 5.7 antidepressant medications. Despite this, 30% of them achieved a full remission of their depression after a single infusion of subanesthetic ketamine.

Speed of Onset

Another unique feature of ketamine's antidepressant effect is its speed of onset. Among patients who respond to 12 weeks of conventional antidepressant treatment, ~60% did so after the fourth week (Rush et al., 2006). In contrast, the response and remission rates noted above for a single ketamine infusion were observed at 24 h. This rapid onset of efficacy is unprecedented among current antidepressant drugs.

FLIES IN KETAMINE'S ANTIDEPRESSANT OINTMENT

Considered in isolation, ketamine's level and speed of efficacy in TRD patients would qualify it as a "breakthrough" drug. Although increasing numbers of psychiatrists and anesthesiologists, the author included, are offering ketamine in clinical settings to patients with TRD, most pundits in the mental health and drug development establishment do not view ketamine administered in the manner currently associated with the rapid antidepressant effects reported in the literature, as an effective tool to make a dent in the formidable morbidity and mortality currently associated with clinical depression. Rather, they view it as a beacon pointing the way to a potential future class of breakthrough antidepressants that will likely tip the scales in the battle against depression; One could say that for most pundits in this field, intravenous administration of ketamine is not the long awaited psychotropic "messiah," rather a pharmacological "John the Baptist." The reason for their lack of enthusiasm for ketamine itself are several features associated with the current paradigm of ketamine treatment for

depression. The most problematic of these features are the acute dissociative and psychedelic effects, the hemodynamic effects, therapeutic durability, and potential for abuse. In the following section each of these are discussed.

Dissociative/Psychedelic Effects

The subanesthetic IV ketamine doses which have been reported to produce rapid antidepressant effects produce a transient state in patients characterized by dissociative and "psychedelic" features. Patients commonly report feeling their consciousness separating from their physical bodies, often they experience visual imagery and sometimes ineffable insights into reality among other experiences. These effects are short-lived, dissipating quickly once the infusion of ketamine is stopped and in the author's experience, patients usually find the experience enjoyable, or at least interesting and frequently deeply profound. It is important to note that the experience differs dramatically from the psychosis associated with schizophrenia spectrum disorders, mainly in the maintenance of insight into the subjective nature of their perceptions, (preserved reality testing). Nevertheless, during this ketamine "trip," patients have a reduced awareness and ability to effectively respond to the environment leaving them vulnerable. As a result, treatments need to take place in an environment where they can be monitored and remain safe for the duration of the trip. This requirement represents a unique restriction that has no counterpart among current antidepressant medication.

Hemodynamic Effects

In the parenteral doses associated with its antidepressant effects, ketamine is a sympathomimetic and will produce an increase in blood pressure and heart rate. Although this effect is typically modest in degree and transient, medical standards of care recommend monitoring patients vitals during subanesthetic ketamine treatments. The major contribution to the increase in these vitals may not be a direct pressor effect, rather a consequence of the highly salient "trip" patients experience, much as increases in blood pressure and heart rate are expected when watching any "edge of your seat" movie or sporting event. In this regard, the hemodynamic effects of ketamine may not be a distinct fly in ketamine's antidepressant ointment.

Duration of Antidepressant Effect

The antidepressant effect produced by a single infusion of ketamine typically lasts 3–14 days (Ryan

et al., 2015). This therapeutic duration precludes ketamine infusions as a viable treatment for many depressed patients whose symptoms do respond to this intervention since it would require repeated infusions daily to biweekly, with the associated logistical limitations, to maintain the therapeutic effect.

Some authors have interpreted this as ketamine's antidepressant effect being shorter than conventional antidepressants, but closer examination reveals this is an inaccurate interpretation when one keeps in mind that duration of benefit requires only a single dose of ketamine. After a single infusion, ketamine and its metabolites are eliminated from the body within 24 h. Therefore, any ketamine-induced antidepressant effect is 200–1,300% longer than the duration of ketamine exposure. In contrast, antidepressant effects from existing orally administered antidepressants typically require at least 6 weeks of daily dosing to produce an therapeutic effect. If an approved antidepressant drug were to be discontinued immediately upon inducing an antidepressant effect (e.g., after 4–6 weeks), the therapeutic effect would need to persist for an additional 8–78 weeks in order to match ketamine's drug exposure to therapeutic duration ratio. From this perspective, ketamine's antidepressant effects are not only faster in onset than conventional antidepressants, they also generally persist longer comparatively, requiring less exposure to the drug.

Potential for Misuse

Shortly after its introduction as an anesthetic, ketamine began to be used illicitly for recreational purposes, especially among “rave” partygoers. Such users find the dissociative state desirable due to a sense of relaxation, well-being and heightened spiritual awareness. In animal studies, ketamine produces reinforcing effects, a predictive feature of a drug's abuse potential in humans. Because of its emergence as a club drug, in 1991 the DEA classified ketamine under schedule III of the Controlled Substance Use Act, a category designated for substances with a moderate to low potential for physical and psychological dependence (de la Pena and Cheong, 2016).

One of the most often cited concerns voiced by critics of the expanding clinical use of ketamine to treat depression is the possibility that repeated administration of this drug to sustain its antidepressant effect, will induce an addiction for ketamine, especially among those patients with a history of substance use. Unlike the limitations described above which are well established features of subanesthetic ketamine infusion, the liability of medically

supervised ketamine infusion to induce an addiction to the drug is currently only speculative.

HACKING KETAMINE TO DEVELOP A MORE VIABLE DEPRESSION TREATMENT

The perception of that the above described features associated with subanesthetic ketamine infusions are a significant barrier to the widespread use of this intervention to treat depression has spurred significant efforts to separate these undesirable features—in particular the acute dissociative/psychedelic effects—from subanesthetic ketamine's breakthrough antidepressant actions by modifying its pharmacokinetics, pharmacological effects, chirality, and metabolism.

Pharmacokinetics

Because all the published randomized trials demonstrating the rapid antidepressant effects of infused ketamine's have utilized a similar dose and infusion rates (0.5 mg kg^{-1} over 40–60 min), it is not known whether the dissociative effects produced in patients receiving ketamine are inherently yoked with the antidepressant effect, for example, due to strongly overlapping dose-response curves (negligible therapeutic window) for both phenomenon, or whether there is a yet to be determined therapeutic window, e.g., a ketamine blood level range which is therapeutic for depression but below the threshold of inducing dissociative effects. If the existence of such a therapeutic window could be established, it would be possible to develop ketamine delivery strategies that target this therapeutic window. Such strategies may involve non-IV routes of administration and/or formulations of ketamine (e.g., controlled release). A few studies examining delivering ketamine via oral, intranasal, and sublingual routes demonstrated that repeated administration via these routes produces antidepressant effects despite the lower ketamine bioavailability associated with these routes. Thus a strategy in which lower ketamine blood levels than those produced by the standard 0.5 mg kg^{-1} IV infusion but more frequently than intermittent infusions, e.g., daily ingestion of an oral formulation, may achieve antidepressant effects without the acute dissociative/psychedelic effects. Elucidating the blood levels associated with ketamine's antidepressant and psychedelic effects will be important in order to identify a potential exploitable therapeutic window.

Chirality

Ketamine, is a racemic mixture containing equal amounts of the two enantiomers, (S)- and (R)-ketamine.

(S)-ketamine binds to the NMDA receptor with three-fold higher affinity than (R)-ketamine. (S)-ketamine is also eliminated faster in humans than (R)-ketamine and thus patients recover faster from its effects. Based on this, it would be natural to assume that the development of formulations containing only (S)-ketamine would be more potent as an antidepressant with fewer or shorter, of the dissociative and hemodynamic changes (Muller et al., 2016) associated with racemic ketamine. However, surprisingly, a recent study in mice found that (R)-ketamine produced a more pronounced and longer lasting antidepressant-like effect. (R)-ketamine also produced a stronger increase in signs of neural plasticity, which is a proposed mechanism by which ketamine produces its antidepressant effects. In contrast (S)- but not (R)- ketamine produced effects in mice that are predictive of mind altering effects and abuse potential (Yang et al., 2015). These results await human confirmation, but if validated in humans, it will provide a potential way of optimizing ketamine antidepressant effect by developing selective (R)-ketamine formulations.

NMDA Receptor Modulation

Notwithstanding a recent finding regarding ketamine metabolites (*vide infra*), the prevailing hypotheses regarding ketamine's mechanism of action was blockade of NMDA receptors on cortical GABAergic interneurons. The NMDA receptor is a complex structure offering numerous targets for selective modulation that may preserve the antidepressant effects produced by ketamine but not its undesirable ones. In addition to the glutamate receptor, the NMDA receptor complex has a coagonist binding site, allosteric binding sites and a phencyclidine (PCP) binding site within the ion channel (Paoletti et al., 2013). Ketamine binds to the latter.

Several investigational drugs which modulate the NMDA receptor complex in various ways have been investigated as potential rapid antidepressants, inspired by the antidepressant effects of ketamine (Newport et al., 2015). Drugs which bind with the same or greater affinity as ketamine to the PCP binding site (e.g., memantine, AZD6765), and to the allosteric sites (traxoprodil, MK-0657) or bind to the coagonist site (D-cyloserine, rapastinel) have been evaluated in preliminary trials but none of these produced the robust and rapid antidepressant effect with the consistency of ketamine. While disappointing, these findings raise questions about the importance of the NMDA receptor in mediating ketamine's antidepressant effects.

Ketamine Metabolites

Ketamine has a complex metabolism *in vivo*, resulting in some 18 metabolites (Zanos et al., 2016). Recent findings have shifted the focus of ketamine's antidepressant effects from ketamine itself to its metabolites. Most notably, Zanos et al. (2016), recently proposed that ketamine metabolite (2R,6R)-hydroxynorketamine (HNK; Fig. 1) is the compound primarily responsible for ketamine's antidepressant effects and that ketamine serves mainly as a prodrug. This claim is based on a series of experiments performed using animal models of depression that have a degree of predictive validity for antidepressant efficacy in humans. In one experiment, inhibition of the conversion of racemic ketamine to its respective stereoisomeric HNK metabolites, (2R, 6R)-HNK and (2S, 6S)-HNK, abolished ketamine's sustained antidepressant-like effects in mice. Furthermore, peripheral administration of (2R, 6R)-HNK produced a potent and sustained antidepressant-like effect at 24 h, whereas (2S, 6S)- HNK was much less potent in this respect. Importantly, neither stereoisomer of HNK had a marked affinity for NMDA receptors, whereas these metabolites effectively activate another glutamate receptor, the AMPA receptor. In concordance with this, the same group found that the uncompetitive NMDA receptor inhibitor, MK-801 did not produce the sustained antidepressant effects seen with ketamine. In a final study, Zanos et al. (2016) found that the AMPA receptor antagonist, NBQX (2,3-dihydroxy-6-nitro-7-sulfamoylbenzo[f]quinoxaline-2,3-dione) administered in conjunction with ketamine blocked its antidepressant-like effects. Taken together, the findings from these preclinical experiments suggest that the AMPA receptor, and not the NMDA receptor, mediates the antidepressant effects ketamine.

Making these finding more exciting is the group's finding that (2R, 6R)- HNK did not produce the animal model equivalents of many of the side effects associated with ketamine including drug seeking behavior, psychotomimetic effects and impaired motor function, holding out the possibility that AMPA agonists can be developed to produce the antidepressant-like effects of ketamine without its limiting side effects.

While the findings by Zanos et al. (2016) represent a potential major discovery, it must be kept in mind that they are based on animal models of antidepressant efficacy which historically have been imperfect predictive tools. Confirmation of these important findings awaits testing in humans.

CONCLUSION

The discovery of the rapid and highly efficacious antidepressant effect of parenterally administered

subanesthetic dose of ketamine represents a major development in the last 20 years of antidepressant drug discovery. However, the impact of this discovery is not likely to have a major impact on the morbidity and mortality associated with depression unless the features associated with the current standard IV delivery of ketamine that preclude ketamine's widespread use for depression are addressed. Considerable efforts are being directed toward dissociating these features from ketamine's impressive antidepressant effects.

Elucidating the specific mechanism of action responsible for ketamine's antidepressant effect is likely to be the most facile pathway to accomplish this while reducing the undesirable side effects. Good progress is being made towards this goal as evidenced by the recent preclinical findings implicating AMPA receptors in the antidepressant effects of ketamine and the finding that that ketamine may be a prodrug, with the active entity being HNK, a metabolite of ketamine.

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