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Has psychiatry tamed the "ketamine tiger?" Considerations on its use for depression and anxiety

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ABSTRACT

Ketamine has been available for approximately 50 years as an anesthetic agent. It is known to have potent effects on the central nervous system glutamatergic system, in particular blockade of N-methyl-D-aspartate (NMDA) receptors. Based upon pre-clinical evidence of involvement of the glutamatergic system in mood disorders, studies have been undertaken to test the antidepressant properties of ketamine. Several well-controlled studies, along with open-label case series, have established that ketamine can have rapid antidepressant effects. Additionally, data exist showing benefits of ketamine in post-traumatic stress disorder as well as obsessive compulsive disorder. However, improvements in these conditions tend to be short-lived with single infusions of ketamine. Of concern, ketamine has been associated with neurotoxicity in pre-clinical rodent models and is well-known to cause psychotomimetic effects and addiction in humans. While ketamine has been proven safe for use in sub-anesthetic doses administered once or a few times, the safety profile of prolonged use has not been established. Aspects of safety, possible mechanisms of action, and future directions of ketamine research are discussed in addition to the clinical literature on its use in psychiatric conditions.

1. Introduction

Ketamine [2-(2 chlorophenyl)-2-(methylamino) cyclohexanone] was introduced as a better-tolerated anesthetic alternative to phencyclidine (PCP), which was associated with a high incidence of prolonged emergence psychotic reactions (Domino, 2010). First administered to humans in the early 1960's, ketamine was found to induce anesthesia reliably with minimal respiratory or circulatory depression, characteristics that were highly desired for certain clinical settings in anesthesiology practice. It was noted early on that unusual psychological reactions occurred with ketamine, notably, feelings of being disconnected with one's environment, leading to its being named a "dissociative" anesthetic (Domino, 2010). The name "ketamine" is a portmanteau of "ketone" and "amine," reflecting two of the moieties in its molecular structure.

Ketamine is a compound with a fascinating duality about it. It has been described as neuroprotective yet also neurotoxic (Olney et al., 1989, 1991). It has been studied as a model for induction of psychotic symptoms of schizophrenia (Olney et al., 1999) yet, as discussed in detail below, it is an antidepressant. It is implicated in addiction but yet has also been used to treat addictions. It is indispensable for anesthesia, yet some people are so traumatized by their experiences given this drug they never want to take it again (Johnstone, 1973). It is incumbent upon the field of psychiatry to balance risks with expected benefits as it embarks to investigate longer-term antidepressant and anti-anxiety effects of this drug.

The discovery that ketamine blocks N-methyl-D-aspartate (NMDA) receptors has fueled a new generation of research on the mechanisms of psychiatric illness, and new data collections on its use for depression and anxiety disorders are reported with dizzying frequency. Ketamine clinics are popping up in multiple American cities. Indeed, this drug is currently very much a hot topic in modern clinical and research psychiatry. However, in this author's view, there are aspects of this flurry of popularity that require caution, both in terms of the safety of this drug as well as the confidence with which its presumed NMDA-related mechanism of action can be deduced. There are lessons to be learned by a close examination of the currently available data on the use of ketamine for depression, obsessive compulsive disorder, and post-traumatic stress disorder that cast ambiguity on the "NMDA hypothesis" of its mechanism of action. In this paper, the author reviews the data on the use of ketamine in psychiatric conditions. Also discussed are perspectives on the safety issues pertinent to ketamine use as well as considerations on mechanisms of action alternative to the inherent biologic actions of the drug. Finally, some recommendations for further research are provided. Of note, to review the use of ketamine in psychiatric populations, an internet-based literature search was undertaken using search terms such as "ketamine" and "major depression,"

Abbreviations: NMDA, N-methyl-D-aspartate; PCP, phencyclidine; MDD, major depressive disorder; OCD, obsessive compulsive disorder; PTSD, posttraumatic stress disorder; ECT, electroconvulsive therapy; GABA, gamma amino butyric acid; AMPA, alpha amino three hydroxy five methyl four isoxazolepropionic acid; CSF, cerebrospinal fluid.

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"obsessive compulsive disorder," and "post-traumatic stress disorder." All relevant papers and the bibliographies of these were reviewed and are discussed below.

2. Ketamine for depression

Berman et al. (2000) first postulated, based upon data of glutamatergic dysfunction in animal models of depression and outcome with NMDA receptor blocking drugs in such models, that ketamine may have antidepressant effects in humans. Thus far, there have been seven randomized, controlled single-infusion trials of ketamine versus another treatment, details of which are presented in Table 1. Five of these studies involved intravenous ketamine versus saline, two in patients with bipolar depression (Diazgranados et al., 2010a; Zarate et al., 2012) and the rest in unipolar depressives (Berman et al., 2000; Sos et al., 2013; Zarate et al., 2006a). In all these studies, saline infusions were associated with essentially no antidepressant response at 24 h post-infusion while ketamine was associated with strong responding which generally abated by a few days to a week or two following the infusions. Dissociative effects, as measured by a dissociative states scale (Bremner et al., 1998) and psychotomimetic effects as measured by the Brief Psychiatric Rating Scale (Overall and Gorham, 1988), were common with ketamine in these studies during the infusions but disappeared within 20–30 min post-infusion. Generally, the depressed patients in these studies were chronically ill, highly medication refractory and were not acutely ill or psychotic. Rise in psychotomimetic effects during ketamine infusions did weakly correlate with degree of reductions in depression scores at day 3 following the infusions in the Sos et al. (2013) study.

In a study providing an alternative to the inconvenience of intravenous ketamine administration, Lapidus et al. (2014) randomized 18 depressed patients to 50 mg intranasal ketamine versus intranasal saline, again in a crossover design, and found 24 hour response rates of 44% with ketamine and no response with saline. There was a higher rise in dissociative scores in ketamine responders versus non-responders. By day 7 following the dosing, ketamine responses had dissipated.

Responding to criticisms that ketamine versus saline studies are not truly blind given the dramatic side effects to ketamine and none with saline, Murrough et al. (2013a) used the short-acting benzodiazepine midazolam as "active placebo." Midazolam was chosen because it is available intravenously and has pharmacokinetics similar to ketamine. As can be seen in Table 1, response rates were greater with ketamine but also quite high in the midazolam-treated group, a surprising finding considering the highly chronic, medication-refractory nature of the patients.

In addition to these randomized, controlled comparisons, there are several case studies (reviewed in detail in aan het Rot et al., 2012) and open-label single-infusion ketamine studies documenting rapid antidepressant response, generally with return to baseline severity within days to two weeks or so of the infusion (Diazgranados et al., 2010b; Duncan et al., 2013; Ibrahim et al., 2011, 2012; Mathew et al., 2010; Phelps et al., 2009; Salvadore et al., 2010; Thakurta et al., 2012; Valentine et al., 2011). Additionally, Chilukuri et al. (2014) randomized depressed patients to ketamine 0.5 mg/kg intravenously over 40 min versus 0.5 mg/kg or 0.25 mg/kg intramuscularly and found similar reductions in depression ratings at 2 h and 3 days post-dosing. However, there was no non-ketamine control group in that study.

As this single-infusion literature suggests impressive acute antidepressant responses to ketamine, a logical next question is whether multiple infusions in a series could result in greater response rates. Thus, this would be analogous to a course of electroconvulsive therapy (ECT) in which case a patient receives a series of ECT treatments, typically twice or thrice weekly, until maximal symptomatic improvement occurs. There are currently three data sets shedding light on multiple-infusion ketamine therapy for depression. Murrough et al. (2013b) and aan het Rot et al. (2010), reporting two phases of a single study, administered six thrice weekly ketamine infusions (i.e., two weeks of infusions) to depressed patients, each infusion being 0.5 mg/kg over 40 min. Analysis of the graphically-displayed depressive severity scores in each cohort reveals that the most dramatic reduction in scores occurred after the first infusion, and scores stayed relatively constant after that point. Thus, there did not seem to be much further improvement beyond the first infusion.

In another study of serial-infusion ketamine, Rasmussen et al. (2013) administered up to 4 twice-weekly infusions of ketamine, 0.5 mg/kg over 100 min, to depressed patients. In this study, patients were treated until either pre-defined remission occurred or four infusions without a remission. Five of the 10 patients met criteria for remission: one after one infusion, three after two infusions, and one after four infusions. Thus, there was a signal that serial infusions may enhance efficacy rates. Lara et al. (2013) used very low dose ketamine sublingually (10 mg doses) serially at intervals of every 2 to 7 days and found that 20 of 26 patients seemed to achieve remission or response. However, there was no systematic assessment of depression severity and no standardized depression rating scale scores were used, thus rendering this an impressionistic data collection. It is noteworthy, though, that such low doses seemed effective in a large proportion of their depressed patients.

Table 1
Randomized, controlled, single-infusion trials of ketamine for depression.

Study	Sample size	Diagnosis[a]	Design	Ketamine dosing[b]	Control group[b]	Results[c]
Berman et al. (2000)	8	MDD	Randomized Crossover	0.5 mg/kg 40 min	Saline	50% ketamine response rate[d]
Zarate et al. (2006a)	18	MDD	Randomized Crossover	0.5 mg/kg 40 min	Saline	71% ketamine response rate
Diazgranados et al. (2010a)	18	BPD	Randomized Crossover	0.5 mg/kg 40 min	Saline	44% ketamine response rate
Zarate et al. (2012)	11	BPD	Randomized Crossover	0.5 mg/kg 40 min	Saline	43% ketamine response rate
Sos et al. (2013)	27	MDD	Randomized Crossover	0.54 mg/kg 30 min	Saline	37% ketamine response rate
Murrough et al. (2013a, 2013b)	72	MDD	Randomized Non-crossover	0.5 mg/kg 40 min	Midazolam 0.045 mg/kg 40 min	64% ketamine, 28% midazolam response rates
Lapidus et al. (2014)	18	MDD	Randomized Non-crossover	50 mg Intranasal	Saline Intranasal	44% ketamine response rate

[a] MDD = major depressive disorder (unipolar); BPD = bipolar disorder, depressed.
[b] All are intravenous except Lapidus et al. (2014).
[c] Refers to ketamine group only except for Murrough et al. (2013a, 2013b). All saline control groups were associated with essentially no responding.
[d] "Response" refers to an at least 50% reduction in depression ratings. For Berman et al. (2000), response rate is within 72 h post-infusion. For all other studies, response rates are at 24 h post-infusion.