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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.

Ghasemi et al. (2014) randomized 18 hospitalized depressed patients deemed in need of ECT to either ECT as usual for 3 treatments or to 3 serial infusions of ketamine 0.5 mg/kg over 40 min over the same time period (i.e., one week). Depression ratings (the raters were blind, but obviously not the patients) revealed slightly lower scores in the ketamine-treated group during the week of treatment and one week later. Inspection of the graphically presented serial depressive severity scores reveals that virtually all of the reduction with ketamine was associated with the first infusion — scores remained the same thereafter. Thus far, then, two of three ketamine studies have provided essentially no signal of enh]anced acute response rates with serial infusions whereas one study has.

A further very important clinical issue regarding ketamine for depression is post-response (or remission) relapse rates. If ketamine cannot induce sustainable improvement, then it is not worth much as a clinical treatment. As pointed out earlier in the single-infusion studies, return of depression scores to baseline levels within one to two weeks post-infusion was the norm. Eight out of 13 initial ketamine responders relapsed over one month in one study (Mathew et al., 2010) while 27% of ketamine responders did not relapse over one month in another trial (Ibrahim et al., 2012). In the Rasmussen et al. (2013) serial infusion study, two of the five remitters sustained the improvement over a month of follow-up. In the Murrough et al. (2013b) serial infusion study, the chances of remaining relapse-free for 83 days of post-treatment follow-up was 25%. Thus, with these two small serial infusion studies, there does seem to be a signal that this more aggressive treatment approach may be associated with more sustained improvement. To date, there are no "maintenance ketamine" studies testing the hypothesis that serial infusions at spaced intervals, say weekly (analogous to maintenance ECT), can prevent relapse. In the Lara et al. (2013) report with very low dose sublingual ketamine, it is alluded that some patients received ketamine in an ongoing manner, however, no outcome data are presented relevant to the efficacy of this strategy.

Several data sets have explicitly pointed out acute reductions in suicidality in depressed patients treated with ketamine (Diazgranados et al., 2010b; Larkin and Beautrais, 2011; Price et al., 2014; Rasmussen et al., 2013; Zarate et al., 2012). However, it is not clear whether ketamine has a specific anti-suicidal effect or if suicidal symptom reduction occurs only in tandem with other depressive symptoms.

Ketamine is generally available as a racemic mixture of s- and r-ketamine. There are some studies of differential effects of the two stereoisomers in pre-clinical models. Zeilhofer et al. (1992) showed that s-ketamine was approximately twice as potent as r-ketamine in blockade of NMDA receptors. Another group has shown that the two enantiomers have differential effects on dopamine and serotonin efflux in the rat nucleus accumbens and basal ganglia which might indicate greater psychotomimetic effects of the s-enantiomer (Hancock and Stamford, 1999; Tso et al., 2004). There are some human data available. Paul et al. (2009) found in two depressed patients that infusions of s-ketamine did not cause the dissociative side effects of racemic ketamine. Hashimoto (2014) has argued that r-ketamine may be better tolerated. Vollenweider et al. (1997), in a study in healthy volunteers given infusions of either stereoisomer, found that s-ketamine did cause more psychotomimetic effects while r-ketamine induced more relaxation, thus arguing in favor of r-ketamine as a possibly better tolerated drug. Clearly, further research is needed regarding differential therapeutic and side effects of racemic versus stereoisomeric forms of ketamine.

3. Other clinical uses of ketamine in psychiatry

The most substantial use of ketamine in psychiatry has been in depressive episodes as described. However, some literature exists for ketamine in other psychiatric situations. In an early and rather interesting data collection, Mills et al. (1998) administered serial ketamine infusions to eating disordered patients on the theory that an NMDA antagonist would impair abnormal memories that drive eating-related compulsions. Each infusion consisted of intravenous ketamine 20 mg/h for 10 h, and patients had serial infusions at intervals of 5–21 days. Nine patients were described as responders with reduced eating disordered cognitions and behaviors and improved mood while six patients were non-responders. The number of infusions ranged from 2 to 15 with a mean of 5.8.

In an open label trial in 10 patients with obsessive compulsive disorder (OCD), Bloch et al. (2012) administered single infusions of ketamine 0.5 mg/kg over 40 min and monitored OCD as well as depressive symptoms over 3 days. The OCD symptoms did not appreciably improve whereas depressive symptoms did. Further, these investigators in a separate report described two patients in that series who developed new onset suicidal ideations after the ketamine infusions for OCD (Niciu et al., 2013b). In a randomized crossover trial in OCD, Rodriguez et al. (2013) found substantial acute reductions in OCD severity with ketamine 0.5 mg/kg over 40 min and virtually no response with saline. Improvements with ketamine were largely sustained over 1 week of follow-up.

Feder et al. (2014), in a randomized non-crossover trial in post-traumatic stress disorder (PTSD), administered either 0.5 mg/kg ketamine or 0.045 mg/kg midazolam as "psychoactive placebo" to a total of 41 patients and followed PTSD severity ratings for seven days thereafter. Results showed greater reductions with ketamine but also impressive reductions with midazolam as well. An additional case of a young male combat veteran with PTSD was reported in two separate publications to have responded dramatically in terms of PTSD symptoms to an acute infusion of ketamine (D'Andrea and Sewell, 2013; Womble, 2013); however, the patient was also treated with midazolam and propofol, thus confounding the confidence with which the improvement can be ascribed to ketamine.

An interesting notion is that the psychedelic properties of ketamine may facilitate psychotherapeutic self-awareness in a technique called "ketamine-assisted psychotherapy" (Jansen, 2001). Krupitsky and Grinenko (1997) and Krupitsky et al. (2002, 2007) have used this method of ketamine dosing coupled with psychotherapy to aid in the treatment of addictions.

A final use of ketamine in psychiatry exploits its anesthetic properties: the use of ketamine as an anesthetic in ECT treatments. It is a logical question whether the antidepressant properties of ketamine may enhance the clinical efficacy of ECT. Three recent trials of ketamine anesthesia or ketamine augmentation of another anesthetic in ECT failed to find an added benefit of ketamine (Abdallah et al., 2012; Jarventausta et al., 2013; Rasmussen et al., 2014), though other groups have found that depression scores are improved a bit faster when ketamine is used as the ECT anesthetic or to augment another anesthetic (Loo et al., 2012; Okamoto et al., 2010; Wang et al., 2012; Yoosefi et al., 2014). Regarding the possibility that ketamine may protect against seizure-induced glutamate "excitotoxicity" related cognitive dysfunction (Olney et al., 1991), Loo et al. (2012) performed in-depth neuropsychological testing during ECT and found that addition of ketamine to another anesthetic was not associated with better cognitive performance. Given the propensity of ketamine to cause dysphoric reactions when used as an anesthetic in ECT (Rasmussen and Ritter, 2014), and the small, clinically invisible early benefits seen in some (but not all) studies, it is not recommended by this author for use in the ECT situation.

4. Safety issues with ketamine in psychiatric applications

Unquestionably, ketamine has been a highly clinically useful compound spanning five decades of use, from anesthesia to pain medicine and now to psychiatric uses for depression and possibly anxiety disorders. However, this drug has dangerous adverse effects. These include psychotic and dissociative psychiatric side effects as well as severe addictive potential. Ketamine is highly regulated in many countries, including the United States. Herein are discussed some of the basic science

findings regarding possible damage ketamine may do to the brain, followed by a consideration of the safety profile of ketamine thus far when used for depression or anxiety. Of note, there has been some evidence that long-term use of ketamine may cause urological effects, such as bladder pathology (Middela, 2011), but this issue will not be discussed further in this communication.

It has been approximately a quarter century since Olney and colleagues at Washington University in St. Louis, USA, discovered that NMDA receptor blocking drugs can cause vacuolar changes in the posterior cingulate and retrosplenial cortices of laboratory animals (Olney et al., 1989). These so-called "Olney's lesions" have caused clinical scientists to be wary of the possibility that such changes can also occur in humans and may be permanent. The idea that NMDA blockade, such as with ketamine, can cause "brain damage" has been a somewhat controversial issue in the literature, but there is no doubt that ketamine can cause psychotomimetic effects consisting of psychosis and dissociative reactions. In fact, sub-anesthetic ketamine infusions have been used in normal control subjects as well as in schizophrenics to temporarily induce such symptoms as a method of studying psychotic disorder neurobiology (Carpenter, 1999; Lahti et al., 2001; Perry et al., 2007). Olney and colleagues have even proposed an NMDA receptor hypofunction model for the neurobiology of schizophrenia (Olney et al., 1999). The crux of this hypothesis is that NMDA receptor hypofunction, through effects on GABA-ergic neurons, causes a loss of normal inhibitory tone on the glutamatergic system leading to excessive glutamatergic activity which causes a number of abnormal brain events through "excitotoxicity."

It is emphasized that it is only through prolonged high-dose exposure to NMDA receptor blockade that damaging changes are felt to occur. What about the relatively low-dose, low-infusion rate, short-lived infusions used in modern psychiatric applications for ketamine? In a study of the use of two different dosing regimens of ketamine in post-surgery pain patients, Remerand et al. (2007) found that low-dose continuous infusions, as opposed to bolus-based administrations, of ketamine were associated with lower incidences of psychotomimetic effects. In addition, two recent reviews of the combined data on sub-anesthetic doses of ketamine in the studies of schizophrenics and normal controls found no evidence of psychotomimetic side effects lasting beyond the peri-infusion time period (Carpenter, 1999; Lahti et al., 2001; Perry et al., 2007). The Perry et al. (2007) data set involved ketamine given to 450 subjects (total number of infusions = 833). In nine cases the infusions were stopped prematurely due to psychotomimetic effects, obviously a small percentage, and in none of the patients contacted on follow up was there evidence of lingering effects. The Lahti et al. (2001) data set involved 30 schizophrenic patients who received up to four sub-anesthetic infusions of ketamine. Immediate and long-term (i.e., up to eight months) follow-up failed to reveal lasting adversity of ketamine. The Carpenter (1999) review summarized data on sub-anesthetic doses of ketamine administered to schizophrenic patients. In 56 such patient experiences, no evidence of ketamine-induced delayed onset or persisting increase in psychosis was found. Only single infusions were given. Cho et al. (2005) did report on the apparent safety of sub-anesthetic doses of ketamine in schizophrenic patients who had serial infusions, but the numbers of infusions were small (generally less than four) and spaced far apart (days to months). There was no evidence of a delayed onset, persisting psychosis. The studies of ketamine for depression and anxiety disorders have had similar results. Thus, it appears that single (or at least a few) sub-anesthetic doses of ketamine are safe. What about serial infusions over a more prolonged period of time? With the chronic, recurrent nature of mood and anxiety disorders, undoubtedly the next step in the clinical use of ketamine will be studies of "maintenance" ketamine infusions, analogous to maintenance ECT treatments. The safety profile of such use is unknown and will need to be monitored quite carefully.

Another issue with ketamine, alluded to above, is its addictive potential. With the highly controlled nature of ketamine, at least in the United States, it is unlikely any ketamine-treated patient will be able to obtain street supplies of this drug other than perhaps in rare, sporadic cases. Nonetheless, if a patient receiving let us say weekly ongoing ketamine infusions to prevent depressive or anxiety relapse develops a strong craving for this drug, then the situation may become problematic (Hillemacher et al, 2007). The patient may request an increasing dose or frequency of infusions, and clinicians may not be able to differentiate between a true relapse or exacerbation of the underlying depression or anxiety disorder and addictive-type ketamine cravings. Clinicians administering this drug are well-advised to set limits with prospective patients on dose and frequency to prevent problematic circumstances from occurring. Addictive craving is a very uncomfortable, perhaps even disabling state, even if the craved-for drug is unavailable. It is incumbent upon clinical investigators to be vigilant for the development of this phenomenon in maintenance ketamine studies.

Related to the possibility of sensitization to the psychotomimetic effects of ketamine is the opposite: the possibility of tolerance. Jansen (2001) reports that it is quite common to hear from ketamine addicts that the first usage of this drug brings the most substantial "high," whereas all subsequent usages bring a vastly lessened effect. Would there also be tolerance to the psychotropic effects of ketamine? A possible scenario along these lines would be the chronic refractory depressed patient who is eager to take ketamine for depression. If such a patient attains a good initial result with an acute series of infusions but tends to relapse quickly during "maintenance" infusions, then the clinician might be tempted to try higher doses or more frequent dosing intervals to re-attain the initial benefits, a plan that may exacerbate any tendency, if it exists, for delayed onset persisting psychotomimetic effects or addiction. Thus, investigators of "maintenance" ketamine usage will need to monitor for tolerance in addition to sensitization phenomena. Even if the occurrence of such a phenomenon is statistically relatively rare, with the large number of refractory depressed and anxious patients seen in mental health practice, that might translate into a significant number of patients who may be harmed by ongoing, serial ketamine administration. Indeed, the clinical pharmacologist who discovered the effects of ketamine in humans, Professor E.F. Domino, has warned in a recent editorial that ketamine is a "tiger" that needs to be "tamed"(Domino, 2010) — modern psychiatry is well advised to heed his warning and tread carefully with the next phase of ketamine clinical study (namely, maintenance administration).

5. Considerations on mechanisms of action of ketamine in psychiatric applications

Speculations about the neurobiologic mechanism of action of ketamine for depression (and perhaps for anxiety as well) have focused on the glutamatergic system. A thorough discussion of the glutamatergic system in health and disease and of ketamine's interaction with this system is beyond the scope of this communication. However, a brief overview can serve to outline the main points of current neurobiologic interest and research. Reviews can be found (Caddy et al., 2014; Catena-Dell'Osso et al., 2013; Hashimoto, 2009; Machado-Vieira et al., 2009; Skolnick et al., 2009). Herein are reviewed some aspects of the glutamatergic system, how it might be affected in depression, and how ketamine might be therapeutic.

Neurotransmitters, of course, are inhibitory or excitatory. Glutamate is the main excitatory amino acid in the human brain and is widely dispersed. Glutamate is involved in learning and memory as well as various synaptic processes. Glutamate receptors are either ionotropic or metabotropic, that is, involved with ion channels or coupled to G proteins, respectively. Glutamate has 3 ionotropic receptors: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainic acid receptors (of note, the receptors are named after known lab-synthesized selective ligands, none of which actually exists in the mammalian brain). Each of these receptors is complex and can occur in different conformations with a variety of subunits.

For example, in the NMDA receptor, a subunit which has received particular attention as a potential target for antidepressant treatment is termed NR2B, and selective blockers have been studied (Machado-Vieira et al., 2009). The glutamatergic system is quite complex and has been conceptualized as tripartite (Machado-Vieira et al., 2009) consisting of presynaptic neuron, postsynaptic neuron, and glial cell (astrocyte), the latter of which has amino acid transporter cites on its membranes to take up glutamate in the synapse and thus prevent excessive glutamate activity, which could lead to damage termed "excitotoxicity." There are multiple aspects of glutamate synthesis, storage, release, post-synaptic receptor occupancy (for both ionotropic and metabotropic receptors), and astrocytic uptake and release that may be targets for glutamatergic system modulating drugs. This system is a current focus of intense pre-clinical and clinical drug development.

Studies of the glutamatergic system in depression have taken the form of blood and CSF measurements of glutamate levels, neuroimaging studies of glutamate availability, and post-mortem analyses in depressed people and suicides of glutamate receptor densities. The results, in both humans and in rodent models of depression (which include the forced swim test and other stress-induced behavioral change paradigms) are reviewed in detail elsewhere but have been mixed in terms of whether there is glutamate excessive activity or underactivity — there is no coherent set of results (Caddy et al., 2014; Catena-Dell'Osso et al., 2013; Hashimoto, 2009; Machado-Vieira et al., 2009; Skolnick et al., 2009). Probably the most substantial evidence of a link between the glutamatergic system and depression is the robust efficacy of presumably glutamatergic modulators like ketamine and other compounds in humans and rodent models of depression.

Ketamine blocks the NMDA receptor non-competitively. Ketamine also enhances presynaptic release of glutamate through a complex effect to reduce normal GABA-ergic inhibitory tone on glutamatergic neurons, the net effect of which would increase AMPA throughput relative to NMDA throughput given the blockade of the latter; this is one theory of how ketamine's antidepressant effect may be mediated (Catena-Dell'Osso et al., 2013; Maeng and Zarate, 2007). It is also clear, however, that ketamine's neurobiologic actions span farther than the glutamatergic system, involving cholinergic receptors as well as those for mu, kappa, and sigma opioid receptors (Domino, 2010). It is not known whether these other actions may be involved in ketamine's efficacy for depression or anxiety disorders.

One of the methodological issues that have plagued psychopharmacology research is the minimal separation of apparent efficacy of putative antidepressant medications from placebo pills (Rutherford and Roose, 2013). Ketamine seems to separate quite nicely from placebo conditions, as discussed above. However, further scrutiny of the clinical literature on ketamine casts some doubt on the confidence with which an inherent neurobiologic mechanism can be reflexively invoked as "the" mechanism of ketamine-related improvement in rating scales. In all the ketamine-versus-saline studies, the results are quite dramatic: at one to three days post-infusion, rating scale scores for the condition in question are much reduced after ketamine, whereas those after saline infusions are virtually unchanged. In the two studies of ketamine versus midazolam, the rating scales are not only highly reduced for ketamine but also for midazolam, albeit not as much as for ketamine (Feder et al., 2014; Murrough et al., 2013a). In fact, in the Murrough et al. (2013a) study in chronic, treatment-refractory depressives, there was a 28% day 1 response rate with midazolam, which is an ultra-short-acting benzodiazepine. Why would patients with longstanding depressions, treated with numerous modalities, have such a high rate of responding with just one small midazolam infusion? In those two midazolam-controlled studies, that compound is referred to as "psychoactive placebo," and indeed it is quite likely that expectational mechanisms are at play. However, why would it be assumed that ketamine's effect is mediated through its inherent neurobiologic activity while midazolam is a placebo? Might not ketamine simply be a better placebo than midazolam? After all, both compounds have very short half lives (about 2–3 h), and a challenge for an inherent biologic explanation of either medication's efficacy would be to explain why 24 h after an infusion, long after it has been excreted from the body, there is still a benefit. On the other hand, expectation-related efficacy mechanisms would be more likely to explain apparent efficacy at such a time point assuming that an initial chain of expectations begins at the time of infusion-related effects.

The reader is referred to Benedetti (2009) for an excellent and thorough explanation of placebo- and other expectation-related phenomena in clinical medicine. Briefly, the chain of expectation-related psychological phenomena begins with information the patients receive prior to the infusions, based on things they have researched themselves (which is robust in today's cyber-space availability) and have been told during the informed consent process. Next, the infusions occur and cause side effects or no effect at all, which further leads to a chain of expectation-related reactions (for example, "I had a visual illusion during the infusion, so it must have been this new drug ketamine, so I'm going to get better now"). The fact that certain neurobiologic indices may reliably correlate with ketamine-related improvement does not prove that it is the inherent biologic actions of ketamine that caused improvement. This may reflect the neurobiology of the placebo phenomenon. An analysis of pooled data from several of the controlled studies on ketamine revealed that degree of dissociative symptoms experienced during ketamine infusions robustly correlated with degree of reported rating scale improvement (Luckenbaugh et al., 2014). Interestingly, the authors speculated that the reason for this is because the biologic mechanisms underlying the dissociation may be the same as those mediating the antidepressant effect. However, it is equally plausible that dissociative side effects caused a chain of expectations within the patients leading to reported improvement, whether real (placebo) or false (spurious improvement). The ultra-rapid nature of the reported improvements in psychiatric applications of ketamine would likely enhance expectation-related effects. A recent analysis of placebo-controlled studies with fluoxetine (Rutherford et al., 2014) revealed that expectation-related phenomena likely contributed significantly to the results. The same is probably true with ketamine.

6. Future directions

There are several avenues and recommendations for further study of clinical applications of ketamine in psychiatry. First, there probably should be no more ketamine-versus-saline studies. It is too easy for patients to distinguish between inert saline and the classic effects of even sub-anesthetic ketamine infusions; thus, any so-called double-blind comparison between ketamine and saline is in reality a two-group open-label study. Regarding the subject of using an "active placebo" as comparator, the efficacy differences between ketamine and midazolam have not been as dramatic as those between ketamine and saline; this either reflects that ketamine has a combination of expectation-related as well as inherent neurobiologically-based mechanisms or perhaps all expectation-related efficacy, as it is quite unlikely that midazolam's efficacy is anything but expectation-related. Midazolam, at the time of its infusion, is likely to be associated with strong anti-anxiety effects that "set the patient up" cognitively to expect longer-lasting improvement, thus accounting for its remarkable apparent efficacy in the two studies of depression and PTSD (Feder et al., 2014; Murrough et al., 2013a). Perhaps a better placebo comparator than midazolam is dexmedetomidine, a selective alpha-2 adrenergic agonist used as an adjunct in anesthetic procedures and for sedation in mechanically ventilated intensive care patients (Anger, 2013). It is not a "psychotropic" drug, so no immediate anxiolytic or euphoriant properties would likely occur that might beset a series of expectations of ultimate efficacy as might occur with midazolam. Further, the pharmacokinetics and pharmacodynamics of dexmedetomidine probably more closely mimic those of ketamine than does midazolam.

Further studies should attempt to enhance the acute remission/response rates with ketamine. Manipulation of such variables as total ketamine dose, infusion rate, and frequency of treatments might shed more light on whether acute efficacy may be enhanced. The use of intranasal or intramuscular preparations obviously would be more convenient, and further study of those is indicated. The differential efficacy/tolerability of s- versus r- versus racemic ketamine should be further studied. Prevention of post-ketamine relapse rates is probably the predominant issue in the clinical use of ketamine in psychiatry at this time. It has become clear from the acute phase study follow ups that relapse rates are high and occur quickly. The obvious next step is the use of maintenance ketamine infusions, perhaps weekly or thereabouts much like maintenance ECT treatments. Investigators of this technique will need to be vigilant for signs of delayed onset, persisting psychosis or precipitation of ketamine cravings and addiction.

It is probably also worth recommending that in future publications of ketamine in psychiatry, ketamine should not be referred to simply as an "NMDA blocker," as has been the case in some of the currently existing publications (Diazgranados et al., 2010b; Zarate et al., 2006a). The use of this phrase presupposes that the mechanism of ketamine is known and seems to rule out other biologic and psychologic mechanisms. Indeed, there are multiple other compounds with known NMDA receptor antagonistic properties which are not effective antidepressants, such as riluzole (Mathew et al., 2010), memantine (Zarate et al., 2006b), dextromethorphan, amantadine, and ethanol. Clearly, more is at play in this field than mere "NMDA blockade."

The study of ketamine affords an opportunity to distinguish between a "drug high" and what is in some sense a "true" antidepressant effect. Ketamine, like other abused drugs (alcohol, benzodiazepines, opiates, and stimulants) can cause an immediate euphoriant effect — is this a "false drug high" or merely a short-lived "true" antidepressant effect? The current enthusiasm for ketamine must be tempered by its known addictive potential and probable tolerance effects.

Another avenue worth exploring with ketamine is to elaborate on its full psychopathologic symptom profile. In other words, which symptoms of depression or anxiety disorders does ketamine improve? So far, the types of patients enrolled in ketamine studies have been chronic, treatment refractory, non-psychotic patients. Does ketamine have efficacy in fulminantly melancholically or psychotically depressed patients? If not, then this is an opportunity to explore the pathophysiologic differences between these two types of depressions. Furthermore, it is apparent that induction of mania does not occur with ketamine (Niciu et al., 2013a) — might this drug actually be effective for mania?

In the anesthesiology field, it was noted long ago that agitated emergence reactions with ketamine could be muted with benzodiazepine pre-treatment (Domino, 2010). Interestingly, Olney et al. (1991) found in their laboratory studies that NMDA-blockade-induced vacuolar lesions could be prevented by pre-treatment with GABA-ergic or anti-muscarinic drugs. One wonders whether such use clinically in depression and anxiety studies with ketamine might improve the tolerability of this drug.

In summary, ketamine has generated enormous interest both as a potential treatment that might be useful clinically in its own right and as a neuropharmacologic probe into glutamatergic mechanisms in psychiatric disorders. While short-term studies do show promise, more data are needed on long-term ketamine use before this drug can be recommended for routine use. Indeed, several prominent psychiatrists have recommended against promiscuous use of ketamine before more data are published (aan het Rot et al., 2012; Kellner, 2014; Rush, 2013; Schatzberg, 2014). The clinician would be wise to heed these recommendations. It is premature to declare that psychiatry has "tamed the ketamine tiger."

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