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Ketamine for Treatment-Resistant Unipolar Depression:

Current Evidence

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Abstract

Currently available drugs for unipolar major depressive disorder (MDD), which target monoaminergic systems, have a delayed onset of action and significant limitations in efficacy. Antidepressants with primary pharmacological targets outside the monoamine system may offer the potential for more rapid activity with improved therapeutic benefit. The glutamate system has been scrutinized as a target for antidepressant drug discovery. The purpose of this article is to review emerging literature on the potential rapid-onset antidepressant properties of the glutamate NMDA receptor antagonist ketamine, an established anaesthetic agent. The pharmacology of ketamine and its enantiomer S-ketamine is reviewed, followed by examples of its clinical application in chronic, refractory pain conditions, which are commonly co-morbid with depression. The first generation of studies in patients with treatment-resistant depression (TRD) reported the safety and acute efficacy of a single subanaesthetic dose (0.5 mg/kg) of intravenous ketamine. A second generation of ketamine studies is focused on testing alternate routes of drug delivery, identifying methods to prevent relapse following resolution of depressive symptoms and understanding the neural basis for the putative antidepressant actions of ketamine. In addition to traditional depression rating endpoints, ongoing research is examining the impact of ketamine on neurocognition. Although the first clinical report in MDD was published in 2000, there is a paucity of adequately controlled double-blind trials, and limited clinical experience outside of research settings. Given the potential risks of ketamine, safety considerations will ultimately determine whether this old drug is successfully repositioned as a new therapy for TRD.

Keywords

Antidepressants; Depressive-disorders; Glutamate-receptor-agonists; Ketamine; Major-depressive-disorder; NMDA-receptor-agonists

1. Introduction

Unipolar major depressive disorder (MDD) is common, often chronic and ranks as a leading cause of disability worldwide. Antidepressant treatment resistance remains a clinically significant problem despite 50 years of research aimed at discovering effective

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treatments.[1-5] This effort culminated in the National Institutes of Health funded STAR*D study, which underscored the high prevalence, chronicity and morbidity associated with treatment-resistant depression (TRD).[3] There is thus an undeniable public health imperative to develop new therapies for TRD to address persistent mood symptoms, promote sustained remission and improve quality of life. Ketamine, a medication used in anaesthesia for more than 40 years, is reviewed in the broader context of new treatment development programmes that aim to discover rapidly acting approaches for patients with TRD. This review begins with an overview of challenges facing the development of novel therapies for MDD and the scientific rationale for this approach. The next section provides an overview of basic and clinical pharmacology of ketamine, which acts as a glutamate NMDA receptor non-competitive antagonist, among its many other properties. This section concludes with a consideration of emerging data on ketamine in chronic pain syndromes, conditions where 'off label' use is greatest and that may offer some guidance for the application of ketamine in TRD. The major section of this article reviews the published clinical trials for ketamine in TRD, and summarizes key studies through 2010. The final section reviews the impact of ketamine on neurocognition, an important outcome for ongoing clinical trials in TRD. This selective review of ketamine is derived from English-language published papers, from 1966 to 2010, identified through PubMed using the search terms 'ketamine', 'NMDA receptor' 'glutamate', 'major depression', 'mood disorder' and 'clinical trial' and the research experience of the authors.[6-11] Due to space limitations, it does not provide a comprehensive review of this rapidly growing field of investigation, but instead focuses on selected areas of importance.

1.1 Limitations of Current Treatments for Treatment-Resistant Depression

Empirically supported options for patients with an inadequate response to an antidepressant include (a) switching to an alternative antidepressant, (b) combining antidepressants from different pharmacological classes, (c) adding empirically supported psychotherapies to ongoing antidepressant treatment and (d) augmenting with an alternative medication (lithium, T3 [triiodothyronine], psychostimulant, atypical antipsychotic, etc.).[12] The olanzapine-fluoxetine combination is the only US FDA-approved pharmacotherapy for the specific indication of 'treatment-resistant depression', defined as inadequate response to two different antidepressants in the current episode.[13] Even this strategy has limited efficacy, however, and concerns about metabolic disturbances and weight gain have restricted its use. Additional atypical antipsychotic medications (aripiprazole, quetiapine) have received US regulatory approval for the adjunctive treatment of depression for patients with inadequate response to an antidepressant. Electroconvulsive therapy (ECT) is the most effective treatment for major depression, including TRD.[14] However, its use is restricted, as it requires general anaesthesia and is associated with adverse cognitive effects.[15] Other non-pharmacological treatments (vagus nerve stimulation [VNS], repetitive transcranial magnetic stimulation [rTMS]) have received regulatory approval for TRD, but either require surgical implantation (e.g. VNS), or in the case of rTMS, might be relatively less effective in more severely treatment-resistant patients than in less resistant patients.[16-18]

Despite a rapid expansion in research on neuroscientific models of depression and models relevant to mechanism of actions of antidepressants,[19,20] the antidepressant medication research 'pipeline' has essentially run dry.[21,22] All currently approved antidepressant drugs target monoaminergic mechanisms that were identified beginning 5 decades ago (with the notable exception of the melatoninergic agent agomelatine). Research into new molecular targets (e.g. corticotrophin releasing factor 1 [CRF_1] antagonists, neurokinin 1 [NK_1] antagonists, vasopressin V_{1b} antagonists, etc.) has not produced effective new treatments for depression, treatmentresistant or otherwise.[22] In response to this lack of progress, many major pharmaceutical companies have eliminated or curtailed research and development

investment.[23] Remaining programmes have generally focused on 'safe' targets (e.g. triple reuptake inhibitors, controlled-release formulations) instead of supporting research into innovative, paradigm-shifting, but potentially expensive new therapies.

1.2 Rationale for Glutamate and NMDA Receptor Modulation

Glutamate is the major excitatory neurotransmitter in the brain. Similar to classic neurotransmitters, glutamate is released from nerve cells, binds to receptors and is removed by reuptake transporters. Glutamate receptor systems are very complex, and can be segregated into various distinct receptor subtypes according to their molecular and pharmacological properties (see Sanacora et al.[24] and Machado-Viera et al.[25] for comprehensive reviews). The two main classes of glutamate receptors are 'ionotropic' and 'metabotropic'. Ionotropic glutamate receptors are classified into the following three groups: NMDA, AMPA and kainate. Each group also has multiple subtypes. Similarly, metabotropic glutamate receptors are classified into three groups, with eight subtypes. Drugs can potentially bind to different glutamate receptor subtypes and therefore modulate glutamate function in varied ways (with different physiological and clinical effects). Most clinical studies across multiple CNS indications have focused on drugs that modulate glutamate function via NMDA receptors, although there is also interest in AMPA and metabotropic receptors. Glutamate and its receptor subtypes play fundamental roles in synaptic plasticity and impact basic human processes of mood, cognition and reward.[24,25] Additional roles include neurodevelopmental and neurotrophic effects (nerve cell growth, differentiation, function and maintenance), and neurodegeneration (nerve cell damage or death).

Converging evidence from *in vivo* brain imaging studies, post-mortem investigations and gene expression studies implicate abnormalities in amino acid neurotransmitter systems in the pathophysiology of MDD.[24] Studies using high-field magnetic resonance spectroscopy (MRS) have characterized regionally specific abnormalities in concentrations of glutamate, glutamine and GABA in MDD, and not unexpectedly, TRD is associated with more profound abnormalities.[24,26]

The ubiquitousness and complexity of the glutamate system had stymied drug discovery efforts until recently. Although ketamine, an open-channel nonselective NMDA receptor antagonist anaesthetic available since the 1960s, is the focus of this review, several subtype selective antagonists of the NMDA receptor (i.e. NR2B, NR2A) are under investigation in early-phase trials in TRD. In the first randomized, placebo-controlled report of a NR2B subunit-selective NMDA receptor antagonist in patients with TRD, Preskorn et al.[27] found that a single infusion of CP-101,606, administered adjunctively to paroxetine, had superior antidepressant effects compared with placebo (saline) infusion on day 5. Seventy-eight percent of CP-101,606 responders maintained their response for at least 1 week after the infusion, suggesting a durability of response beyond its elimination half-life.

2. Introduction to Ketamine

2.1 History and Clinical Indications

Ketamine, a chiral arylcyclohexylamine (RS)-2-(2-chlorophenyl)-2-methylaminocyclo-hexanone, was synthesized by Parke-Davis in 1963 and was first administered to a human subject in 1964.[28] This 'dissociative anaesthestic' was developed as a safer alternative to phencyclidine, with less propensity for hallucinations or unpleasant psychotic side effects. Ketamine was approved by the FDA in 1970 for the following three indications: (1) the sole anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation; (2) for the induction of anaesthesia prior to the administration of other general anaesthetic agents; and (3) to supplement low-potency agents, such as nitrous oxide.[29]

Other common (though not approved) indications include sedation in intensive care, analgesia and treatment of bronchospasm. The anaesthetic state produced by ketamine is characterized by normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, and cardiovascular and respiratory stimulation, with only occasional, transient and minimal respiratory depression. Surgical anaesthesia is typically produced by intravenous (IV) doses of 1–3 mg/kg.[30,31]

2.2 Pharmacology

Ketamine is classified as an NMDA receptor antagonist, although its pharmacological profile is complex and its affinity for numerous receptors has been identified. Effects on these receptors, in addition to direct effects of NMDA antagonism, may contribute to the impact of ketamine on mood and cognition. Ketamine is metabolized into two major metabolites, norketamine, the initial and predominant metabolite, and dehydronorketamine (DHNK), a minor, inactive metabolite. Norketamine is a non-competitive antagonist of the NMDA receptor and contributes to ketamine analgesia. After IV administration, the plasma norketamine level rises but remains below the plasma ketamine level for more than 2 hours. In contrast, after oral administration, plasma levels of norketamine rise much higher than the parent drugs (greater than 4-fold). See section 2.4 for a further discussion of routes of administration and table I for a summary of clinical pharmacology.

Similar to the NMDA antagonists 2-amino 5-phosphonovalerate (APV) and 2-amino 7-phosphonoheptanoate (APH), ketamine was shown to incompletely reduce depolarizing responses to glutamate and aspartate in slices of rat cortex.[32] These three antagonists selectively reduced responses to NMDA without affecting responses to quisqualate or kainate. The ketamine-induced reduction in NMDA responsiveness was not reversed following 3 hours of washout and ketamine acted as a non-competitive antagonist. Notably, ketamine was found to bind to a different site than APV and to be similarly potent with an equilibrium dissociation constant **(**pA_2**)** of 5.0, between that of APH and APV, which was determined to have a dissociation constant **(**K_d**)** of 6.4 μM. These results were consistent with an earlier study that found ketamine to be 0.3–2 times as potent as APV.[33] Subsequently, the inhibition constant **(**K_i**)** of ketamine was reported at 0.2 μM.[34] Ketamine has also been reported to reduce neuronal responses to acetylcholine (ACh) by inhibiting nicotinic ACh receptor activation, while also acting as an acetylcholinesterase inhibitor to raise brain ACh levels.[35-37] Another study reported that ketamine has little or no direct effects on nicotinic ACh receptors, but instead blocks ion channels.[38] In contrast, for muscarinic M_1 receptors, the log dissociation constant (pK_i**)** of 45 μM for ketamine is in a clinically relevant range though ketamine was not shown to affect stimulation-induced calcium changes.[39] The affinity of ketamine for M_2 and M_3 receptors was determined to be more than 5-fold lower, 294 and 246 μM, respectively, and unlikely to be clinically important. Interestingly, another study has suggested that ketamine upregulates muscarinic receptors.[40] Ketamine has also been shown to interact with α_1-adrenoceptors with a K_d of 3.4 mM and to interact with β_2-receptors with a K_d of 0.35 mM; though small, these interactions may relate to the haemodynamic effects of ketamine.[41]

At anaesthetic doses, ketamine has affinity for opioid μ-receptors. *In vitro* studies of the analgesic effects of ketamine suggest that ketamine may act as a low-affinity opioid agonist (concentration of drug producing 50% inhibition [IC_{50}] of 14.8 μM without sodium).[42] This affinity was reduced approximately 6-fold with the addition of sodium, suggesting that ketamine may also have opiate antagonist properties. Although the affinity of ketamine for the NMDA receptor is higher (IC_{50} 7 μM), these data suggest that effects on opioid receptors are likely relevant at anaesthetic concentrations. Of opioid receptor subtypes,

ketamine has the highest affinity for μ (K_i 26.8 μM) with decreasing affinity for σ and κ (K_i 66.0 and 85.2 μM, respectively) and the lowest affinity for δ receptors (K_i 101 μM).[43]

In terms of impact on monoamines, ketamine and its metabolites inhibit transport of serotonin, noradrenaline (norepinephrine) and dopamine.[44] In addition to its effects on transport, ketamine and its metabolites were found to inhibit deamination of monoamines. Additionally, ketamine interacts weakly with serotonin 5-HT_3 receptors.[45] Though differences in binding affinity and potency of ketamine relative to other anaesthetics have been reported, the K_i for ketamine for 5-HT_3 receptors falls outside the clinically relevant range at >90 μM.[46,47] Ketamine also stimulates dopamine D_2 receptors at high concentrations.[48] Of note, the potency of ketamine at D_2 receptors (K_i 55 nM) has been reported as higher than for NMDA receptors (K_i 3100 nM) on human receptors expressed in cultured hamster cells.[49] D_2 receptor messenger RNA expression is also induced by ketamine.[50] However, the effects of ketamine on D_2 receptors have not been uniformly replicated.[51] In high subanaesthetic concentrations in humans, ketamine was not found to affect D_2 receptor availability or dopamine release.[52] Alterations in D_1 binding have also been attributed to ketamine.[53]

Ketamine has not been reported to induce selective or consistent effects on $GABA_B$ receptors.[54] However, some preclinical data and one human SPECT study suggested that ketamine modulates $GABA_A$ activity.[55,56]

Ketamine also acts at a variety of ion channels. For example, ketamine inhibits veratridine stimulation-induced Na^+ uptake with an IC_{50} >200 μM.[57] Ketamine also affects Ca^{2+} by inhibiting influx and stimulating efflux via the Ca^{2+} ATPase. Perhaps most relevantly, ketamine inhibits hyperpolarization-activated cyclic nucleotide-gated at concentrations in the clinically relevant range, with a concentration of drug producing 50% of maximum effect (EC_{50}) of approximately 10 μM.[58]

2.3 S-Ketamine

Although most commonly administered as a 1:1 racemic mixture of (S) and (R) ketamine, S-ketamine is available for medical use outside of the US, including several EU countries (Finland, Germany, Denmark, Iceland and the Netherlands). In Europe, S-ketamine was first approved in 1998 and is indicated for induction and maintenance of general anaesthesia, for supplementation of regional anaesthesia and for analgesia in emergency medicine. S-ketamine has 3–4 times higher affinity to the phencyclidine binding site of the NMDA receptor than R-ketamine.[59] The enhanced pharmacological potency of S-ketamine suggests that use of this isomer may reduce undesirable adverse effects without altering its clinical benefit.[60] Other pharmacological differences between the isomers are that the S-isomer is 1–2 times more potent as an ACh antagonist,[36] and has a 2- to 3-fold higher potency for opiate receptors than the R-isomer.[61]

S-ketamine has potentially important tolerability advantages over its racemic mixture. Fifty percent of subjects experienced anterograde amnesia after a subanaesthetic dose of R-ketamine while only 8% experienced this side effect with S-ketamine.[62] Neuroimaging studies have shown rapid recovery of cerebral functions and increases in whole brain cerebral blood flow with S-ketamine.[63,64] A clinical study found that S-ketamine reduced both post-anaesthetic shivering and postoperative nausea and vomiting.[65] Finally, S-ketamine was associated with neuroprotective functions exceeding that of its racemic mixture in animal models of ischaemia and in human cognitive laboratory experiments.[66,67]

2.4 Routes of Administration

Administration routes for ketamine include IV, intramuscular (IM), intranasal (IN), epidural, subcutaneous, transdermal, intra-articular, sublingual and oral. Oral ketamine undergoes extensive first-pass liver metabolism resulting in a bioavailability of approximately 16% (table I). Oral administration is associated with higher serum levels of norketamine compared with other routes of administration. Norketamine is believed to contribute to the analgesic effect and the duration of effect.[68] A recent review of oral ketamine in chronic pain management concluded that the lack of evidence regarding efficacy does not support routine use of oral ketamine in chronic pain management. Oral ketamine may have a limited role as an add-on to other analgesics in complex chronic pain patients when other treatment options have failed.[68]

Intranasal ketamine administration has also been investigated for varied indications. Because of the frequent use of ketamine in anaesthesia, IN ketamine has also been most frequently used in this context, particularly in children. The first published use of IN ketamine in a randomized, controlled trial demonstrated efficacy in children undergoing dental procedures.[69] In addition to case studies, randomized, controlled trials have demonstrated the safety and efficacy of IN ketamine as an anaesthetic or premedication for surgical, dental and imaging procedures in paediatric populations.[70-74] An open-label trial of IN ketamine in adults with migraine headaches also suggested efficacy.[75] IN ketamine demonstrated safety and efficacy in a randomized, blinded study of 20 adults with breakthrough chronic pain,[76] although this initial report awaits replication. A trial of IN S-ketamine in 16 adults with neuropathic pain yielded similar results.[77]

As discussed in section 3.1, the IV route of administration was used in the first clinical report on major depression[78] to resemble human laboratory pharmacological models of schizophrenia. Subsequent replications have used the same IV route of administration and dosing strategy (0.5 mg/kg slow infusion over 40 minutes).

2.5 Use in Pain Conditions

Currently, the most widely accepted ‘off-label’ use for ketamine is managing severe episodes of refractory neuropathic pain, often in situations where escalating doses of opiates have contributed to the development of severe hyperalgesia. It has been known for a number of years that the analgesic efficacy of ketamine often persists beyond its anaesthetic effect.[79] Ketamine has been widely used for several acute and chronic pain conditions as monotherapy or as adjunctive therapy to opiates.[80,81] A meta-analysis revealed that ketamine was effective in reducing morphine requirements in the first 24 hours after surgery.[82] Ketamine has also been utilized in the treatment of patients with chronic refractory pain due to cancer[83] or to reduce nonresponsive pain in patients with complex regional pain syndrome (CRPS), neuropathic pain, orofacial pain or phantom pain after limb amputation.[84]

Of most relevance to TRD, repeated IV ketamine infusions have been administered for severe, treatment-resistant pain syndromes and have successfully decreased opiate requirements.[85-87] Correll et al.[85] studied 33 patients with CRPS who received open-label IV ketamine infusions. The average maximum infusion dose of ketamine was 23 mg/hour, with 70% of treatment cycles over 2–5 days. After the initial course of infusions, 25 of 33 patients (76%) reported complete pain relief, while partial relief was found in 6 patients (18%) and no benefit observed in 2 patients. Due to relapse of pain, 12/33 patients received a second course of therapy, and 2/33 patients received a third, some with higher doses (40–50 mg/hour). Regarding durability of benefit, following the first course of infusion, 54% of the 33 patients remained pain free for ≥3 months and 31% remained pain free for ≥6 months.

After the second infusion, 58% of 12 patients experienced pain relief for ≥1 year, while almost 33% remained pain free for >3 years. These findings, while encouraging, were uncontrolled. In the only published, double-blind, placebo-controlled study of outpatient IV ketamine infusions to date, a small sample of CRPS patients received infusions for 4 hours (25 ml/hour) daily for 10 days.[87] While the sample size was small, statistically significant reductions in several pain parameters were found for active ketamine. In summary, ketamine may offer short-term relief for refractory pain conditions, although the benefit of long-term use in chronic pain is uncertain. The major applicability of the pain literature to TRD is the demonstration of the feasibility of ketamine administration in the outpatient setting.

3. Clinical Studies in Mood Disorders

3.1 Single-Dose Intravenous Ketamine

The first report in patients with mood disorders, conducted in the inpatient research unit setting at Yale University School of Medicine, New Haven, CT, USA, described a rapid antidepressant effect following a single IV dose of ketamine.[78] Eight patients were administered ketamine hydrochloride (0.5 mg/kg infusion over 40 minutes) or saline under randomized double-blind conditions, in a crossover design, with the primary aim of testing ketamine as a pharmacological probe of NMDA receptor function. Ketamine significantly reduced Hamilton Rating Scale for Depression-25 item ($HRSD_{25}$) scores within 4 hours. Further reductions in $HRSD_{25}$ scores were found at 24, 48 and 72 hours post-infusion, and persisted in some patients beyond 72 hours. $HRSD_{25}$ scores were significantly reduced from baseline in the ketamine arm compared with the saline arm, with four of eight patients demonstrating a 50% or greater reduction in $HRSD_{25}$ scores at 72 hours post-infusion. Ketamine administration was associated with significant but transient increases in psychotomimetic symptoms, as reflected in the Brief Psychiatric Rating Scale (BPRS), particularly the positive symptoms subscale. Depression severity returned to baseline levels several days to 1 week following ketamine infusion.

The findings were unanticipated, especially the robustness and rapidity of benefit, and the durability beyond the elimination half-life of the drug. Ketamine appeared to directly target core depressive symptoms such as sad mood, suicidality, helplessness and worthlessness, rather than inducing a nonspecific mood-elevating effect. The acute mood improvement associated with ketamine was temporally dissociated from ketamine-induced neuropsychiatric effects, including psychotomimetic and dissociative, and feelings of ‘high’. Visual Analog Scale (VAS)-high scores returned to baseline by 110 minutes after infusion, while improvement in core depressive symptoms persisted following the cessation of infusion. Neither the transient elevations in BPRS nor the VAS high scores correlated with decreases observed in $HRSD_{25}$ scores.

A larger replication study in patients with TRD was subsequently conducted at the Intramural Research Program of the National Institute of Mental Health (NIMH).[88] This study used a similar randomized, placebo-controlled, double-blind, crossover design, and found highly similar effects as the initial Yale study. Patients receiving ketamine showed significant improvement in depressive symptoms compared with placebo within 110 minutes. The effect size for the ketamine-placebo difference was very large (d = 1.46 [95% CI, 0.91, 2.01] after 24 hours and moderate-to-large (d = 0.68 [95% CI 0.13, 1.23]) after 1 week. Of the 17 subjects receiving ketamine, 12 (71%) met response criteria and 5 (29%) met remission criteria 24 hours post-ketamine. The response was durable in a sizeable proportion of patients: approximately 50% of patients maintained the antidepressant response at 72 hours, defined as a 50% reduction in baseline $HRSD_{21}$ scores. Six subjects (35%) maintained response for at least 1 week; two patients remained depression free for at least 2 weeks.

Taken together, these two proof-of-concept inpatient studies suggested that a single subanaesthetic dose infusion of IV ketamine could generate a rapid and relatively sustained antidepressant response, even in patients with previous medication resistance. However, the acute neuropsychiatric side effects of ketamine and uncertainties regarding continuation therapy remain significant unanswered issues. To address these questions, investigators at the Mount Sinai School of Medicine, New York NY, USA conducted a pilot study aimed at optimizing the safe delivery of IV ketamine with lamotrigine pretreatment, and enhancing time to relapse following ketamine with the glutamate-release inhibitor riluzole.[7] Based on a report in healthy volunteers,[89] it was hypothesized that a single oral dose of lamotrigine, an anticonvulsant mood stabilizer that decreases pre-synaptic glutamate release, would blunt the acute neuropsychiatric effects of ketamine in TRD patients. The psychotomimetic side effects of ketamine were hypothesized to be associated with increased pre-synaptic glutamate release. In addition, based on pilot data for the efficacy of riluzole in mood disorders,[90-92] and potential mechanistic synergy between riluzole and ketamine, riluzole would increase relapse-free survival time in patients who had shown an initial antidepressant response to ketamine.

In this pilot study, 26 patients were randomized to a single dose of lamotrigine (300 mg) or placebo 2 hours prior to receiving open-label IV ketamine (0.5 mg/kg over 40 minutes). Study participants with TRD were medically healthy (exclusion criteria included uncontrolled hypertension, cardiopulmonary disease, obstructive sleep apnoea and a history of a difficult airway following previous exposure to anaesthetics). The infusion procedure was conducted by an anaesthesiogist, with telemetry and vital signs monitoring for 4 hours post-infusion. Patients received infusions in a quiet private room with muted lighting. Seventeen patients (65%) met response criteria (≥50% reduction from baseline on the Montgomery-Åsberg Depression Rating Scale [MADRS]) 24 hours following ketamine administration. Fourteen patients (54%) met response criteria 72 hours following ketamine administration. These patients were then eligible to participate in a 4-week, randomized, double-blind, placebo-controlled, flexible-dose, continuation trial of riluzole (100–200 mg/day). No significant differences were found in time to relapse between riluzole and placebo groups. Lamotrigine did not significantly impact the mild, transient, psychotomimetic side effects associated with ketamine. Although the two primary hypotheses of the study were not supported, the response rate confirmed the two previous reports.[78,88] Overall, ketamine administration was associated with relatively few acute neuropsychiatric effects, potentially contributing to the negative result for lamotrigine pretreatment. With a small sample size, the failure of riluzole to separate from placebo for relapse prevention post-ketamine could have been attributed to a type II error. Larger placebo-controlled studies testing riluzole and other strategies for relapse prevention following ketamine (including additional doses of ketamine) are in progress at several centres worldwide (NCT00088699; NCT01441505).

A recent report from the NIMH group using a single IV ketamine infusion at the same dosing parameters (0.5 mg/kg over 40 minutes) supported an antidepressant benefit in patients previously non-responsive to ECT.[93] In this open-label study of 42 TRD patients, 17 had previously failed to respond to ECT and 23 had not previously received ECT. Both groups of patients showed significant improvement in depressive symptoms at 230 minutes post-infusion.

3.2 Repeated-Dose Ketamine in Treatment-Resistant Depression

Repeated-dose ketamine is a potential antidepressant continuation strategy for patients who show initial response to ketamine infusion, similar to the strategy described previously for chronic refractory pain conditions. To pilot this strategy, Mount Sinai School of Medicine investigators administered open-label, repeated-dose IV ketamine over 2 weeks in ten patients with TRD who had failed to respond to a mean of eight antidepressants in their

lifetime.[8] On day 1, patients received a 40-minute IV infusion of ketamine (0.5 mg/kg) in an inpatient setting with continuous vital-sign monitoring. The primary efficacy measure was a change from baseline in the total MADRS score. If patients showed at least a 50% reduction in MADRS scores on day 2, they received five additional infusions on an outpatient basis on Monday-Wednesday-Friday, a schedule modelled after ECT. Following the sixth infusion, follow-up visits were conducted twice weekly for 4 weeks or until relapse. Relapse was defined as a MADRS score >50% of the pre-ketamine baseline and >20 for two consecutive visits or a Clinical Global Impression-Improvement scale (CGI-I) score of 6 ('much worse') at any visit.

A repeated subanaesthetic dose of ketamine elicited minimal psychotic symptoms, as detected by the BPRS positive subscale. Three patients experienced noteworthy but transient dissociative symptoms. Side effects during and following each ketamine infusion were generally mild. Nine of ten patients met the response criterion after the first infusion, and all nine continued their response throughout the 2-week period. The mean reduction in the MADRS score after the sixth infusion was 85%. Relapse occurred, on average, 19 days after the final infusion while patients remained off antidepressant medication. There was a very wide range in the time until relapse between individual patients, from 6 days to greater than 3 months, while patients remained antidepressant medication free.[11] Overall, the safety of repeated-dose IV ketamine for TRD was demonstrated, at least for six infusions over 2 weeks. No patient engaged in drug-seeking behaviour during the trial (per urine toxicology) or in the study follow-up period (per self-report). No patient reported cognitive deficits in excess of what was reported at baseline; however, the lack of formal neuropsychological testing and the small sample size limit interpretation.

A small case series recently described administration of three ascending doses of open-label IM ketamine in two patients with treatment-refractory bipolar II depression.[94] An initial dose of 0.5 mg/kg produced only a small decrease in depressive symptoms at 24 hours post-injection, while higher doses (0.7 and 1.0 mg/kg) produced greater reductions in symptoms. In one case, the reduction in symptoms following 0.7 mg/kg was consistent with remission, although the duration of benefit was not indicated in the report. All doses were tolerated and side effects included light-headedness, sedation and dissociative symptoms, similar to those reported after IV administration. The authors propose that an IM route of ketamine administration may facilitate rapid antidepressant response in depression based on a pharmacokinetic model suggesting higher peak ketamine exposures (i.e. higher maximum plasma drug concentration values) following IM administration compared with IV administration. Although this pharmacokinetic model and associated case series is very preliminary,[95] it encourages the conduct of future studies to better evaluate pharmacokinetic parameters and different routes of administration of ketamine in depressed patients.

3.3 Impact on Suicidal Ideation

A promising new lead following these initial single- and repeated-dose investigations was the impact of ketamine on suicidal ideation. A *post hoc* analysis of the Mount Sinai School of Medicine's two trials in TRD found that IV ketamine (0.5 mg/kg over 40 minutes) was associated with rapid reductions in explicit and implicit suicidal cognitions within the first 24 hours after infusion, which persisted for patients who received additional infusions.[9] To measure implicit cognitions, a computerized test (the Implicit Association Test [IAT]) was used to track implicit cognitions related to suicide over the course of treatment. The IAT is a performance-based measure of association between concepts, and has shown some promise for suicide assessment in varied clinical samples.[96] To measure explicit suicidal ideation, the suicide item on the MADRS and the Scale for Suicidal Ideation (SSI) was used. As a caveat to these reports, it is important to note that the TRD patient samples were not

markedly suicidal. The acute, rapid-onset, anti-suicidal properties of open-label IV ketamine (0.5 mg/kg over 40 minutes) were recently confirmed in a report by the NIMH group in a sample of 33 patients with TRD.[97] In this study suicidal ideation scores decreased on the SSI within 40 minutes of infusion, and remained low throughout the first 4 hours post-infusion. Ten subjects had a SSI score of ≥4 at baseline, which dropped to below 4 in all patients within 80 minutes of the start of infusion. A recent preliminary report in the emergency room setting found that a single IV bolus of ketamine (0.2 mg/kg over 1–2 minutes) rapidly improved suicidal ideation in 14 depressed patients, suggesting a novel strategy in this setting [NCT01209845].[98] An open-label report in the palliative care setting also observed improvements in suicidal ideation in patients with terminal illnesses.[99]

4. The Impact of Ketamine on Cognitive Function

4.1 Acute Ketamine Use and Cognition

Experimental laboratory studies in clinical and non-clinical samples over the last 3 decades have investigated the acute cognitive effects of ketamine. A bolus injection followed by a maintenance dose infusion or a constant slow infusion of a subanaesthetic dose of IV ketamine induces acute impairments of working, episodic and semantic memory.[100] These impairments were found to be consistent across healthy volunteers, individuals with recreational use of ketamine and individuals with concomitant use of varied illicit drugs.[101] Studies in healthy volunteers reported acute impairments of their ability to encode new information and perform delayed recall tasks.[102,103] Although ketamine appears to impact information encoding, it did not impact retrieval of previously learned information.[102-105] Furthermore, in healthy volunteers, acute impairments resolved and no residual deficits were found 3 days following drug administration.[106]

4.2 Chronic Ketamine Use and Cognition

Unfortunately, little information exists regarding the impact on cognition of chronically administered ketamine as reports have generally been limited to small-scale studies of poly-drug abusers. Cognitive impairment amongst recreational users may be dose and use-frequency dependent. The largest published study to date investigated the effects of chronic ketamine use on neurocognitive function in 150 participants.[101] Cognitive performance of polydrug users and healthy controls were compared with the following three groups: ex-ketamine users, infrequent ketamine users and frequent ketamine users. Cognitive impairments were significant among frequent users who self-administered greater than 1g of ketamine at a minimum frequency of 4 times per week. Frequent users also showed impairments in recognition and working memory. No significant differences in performance were observed between controls, poly-drug users, and infrequent or ex-ketamine users.

This report also suggested that cognitive impairment associated with chronic and frequent ketamine use are reversible with abstinence.[101] The reversibility of cognitive deficits associated with ketamine use in humans was analogous to the reversible neurotoxicity in animals following repeated doses of NMDA receptor antagonists.[107] While it appears that the effects of ketamine are reversible following cessation of chronic ketamine use,[108] other effects seem to persist after decrease/discontinuation.[109] It has been suggested that persistent cognitive impairment may be a byproduct of the irreversible cell death observed in preclinical experiments following repeated high-dose ketamine.[110] Numerous limitations of the available cognitive data, (i.e. small sample sizes, heterogeneous study designs, varied ascertainment of ketamine use, and differences in ketamine dose and method of administration) suggest the critical importance of testing the impact of chronic ketamine on neurocognitive outcomes in longer-term, prospective, controlled studies.

5. Neural Mechanisms Underlying the Antidepressant Activity of Ketamine

An emerging body of research implicates specific alternation in a network of prefrontal, subcortical and limbic brain regions in MDD.[111-113] Major depression appears to be characterized by enhanced activity or sensitivity to negative stimuli in subcortical and limbic emotion-processing regions coupled with deficient activity or inefficient functioning in prefrontal cortical regions implicated in cognitive control processes and emotion regulation.[112,114,115] Monoamine, amino acid, neuropeptide and neuroendocrine transmitter systems are believed to influence behavioural symptoms through their impact on neuronal functioning within these critical neurocircuits.[113] Within this framework, ketamine is hypothesized to exert its antidepressant effects via its impact on the balance of functioning within these mood processing and regulation systems through direct effects on the glutamate system and through indirect effects on other neurochemical systems. Specifically, ketamine is hypothesized to shift the balance of neural activity from limbic and subcortical emotion-processing structures to cortical regulatory structures, including medial and lateral regions of the prefrontal cortex (PFC).

Ketamine appears to facilitate neural activation in regions of the PFC in humans as measured by positron emission tomography (PET) and [18F]fluorodeoxyglucose,[116,117] consistent with the observation that ketamine results in a net increase in excitatory glutamatergic transmission in cortical regions in animals (see Vollenweider and Kometer[118] for a recent review). Increased activity within the PFC is also observed following successful treatment with an antidepressant,[119] supporting enhancement of PFC activity as a potential antidepressant mechanism of ketamine. Ketamine has also been shown to increase striatal dopamine signalling in healthy volunteers using PET and [11C]raclopride.[120] Interestingly, a series of two functional MRI studies of ketamine in healthy volunteers did not find evidence for global increases in neural activity associated with ketamine, but instead documented reduced activity specifically within limbic emotion-processing regions in response to fearful versus neutral facial expressions during the ketamine compared with placebo condition.[121,122] The authors hypothesized that the observed attenuation of limbic responses to emotional stimuli may underlie the behavioural blunting that is sometimes seen acutely with ketamine administration. These findings also suggest that the ability of ketamine to attenuate limbic responses to negative emotional stimuli may be related to its mechanism of antidepressant action, similar to what has been reported for conventional antidepressants.[123] While it is likely that ketamine acts through emotion processing and regulation systems in the brain to exert its antidepressant effects, the specific nature of these changes is unclear and represents an active area of investigation.

To date, very few studies have examined the effect of ketamine on neurocircuitry in patients with MDD. Two recent studies utilizing magnetoencephalography (MEG) reported correlations between baseline neuro-magnetic signals localized to the anterior cingulate cortex (ACC) in patients with MDD and rapid antidepressant response to open-label ketamine.[124,125] The ACC has been implicated in a number of studies investigating the neural correlates of treatment response in depression,[126,127] and the subgenual ACC is a target of deep brain stimulation for TRD studies in the US and elsewhere.[128] In one study, patients with MDD showed an abnormal increase in ACC activity to rapidly presented fearful faces over the course of an experimental session, which was correlated with subsequent antidepressant response to a single dose of IV ketamine (0.5 mg/kg).[124] In a second study utilizing MEG and a non-emotional working memory paradigm, the authors found an inverse correlation between ACC response to increasing memory load and symptom improvement following ketamine.[125] In this study, functional connectivity between the ACC and the left amygdala was also inversely correlated with symptom change. While these studies provide preliminary evidence for ACC activity as a potential biomarker

to predict response to ketamine, they do not directly inform neurocircuitry models related to the specific action of ketamine since measures of neural activity were collected only prior to ketamine treatment. Further study utilizing pre-post imaging designs, as well as placebo control conditions, are necessary.

A recent MRS study examined the impact of ketamine on measures of amino acid neurotransmitters (e.g. glutamine, glutamate, GABA) in a voxel located in the occipital cortex in patients with MDD, and found no change in MRS measures over time compared with placebo.[129] In this study, ten patients with TRD underwent MRS imaging at baseline, 3 hours and 48 hours post-infusion with ketamine or saline in a 1-week crossover design. Although this study replicated the rapid antidepressant effects of ketamine, changes in occipital amino acid transmitters were not associated with therapeutic response.

Molecular changes associated with the antidepressant effect of ketamine have only recently begun to be investigated in preclinical models. Ketamine was found to rapidly activate the mammalian target of rapamycin (mTOR) pathway, leading to increased synaptic signalling proteins as well as an increased number and function of new spine synapses in the PFC of rats.[130] Further, blockade of mTOR signalling prevented ketamine-induced synaptogenesis and depressive behavioural responses. These data are consistent with hypotheses linking the antidepressant effects of NMDA receptor antagonists to enhancement of neurotrophic and neuroplasticity-related factors and fit more broadly within neurotrophic theories of depression.[131,132] The study by Li et al.[130] also reported that the molecular and behavioural effects of ketamine were blocked by an AMPA receptor antagonist (NBQX), extending a previous report.[133] In summary, neuroimaging and molecular studies have identified new targets for understanding the neural basis for the antidepressant properties of ketamine that extend beyond the NMDA receptor and glutamate.

6. Conclusions

The purpose of this review was to place early reports of ketamine for treatment-resistant unipolar major depression in a broader context. While much is known about the pharmacological profile of ketamine from its long history as an anaesthetic and analgesic agent, mechanisms associated with therapeutic benefit in depression are unknown. While ketamine attenuates NMDA receptor function, it is uncertain which specific pathways (i.e. modulation of glutamate release, effects on glutamate receptor activation, extracellular glutamate clearance, glutamate metabolism, etc.) are salient to the early and sustained improvements observed in some patients in clinical trials.

It is important to recognize that clinical trials for ketamine in MDD are in their infancy, and the broader effectiveness of ketamine in clinical settings has not been systematically examined. Enthusiasm generated from early ketamine studies is tempered by concerns about the validity of these studies' saline-controlled, within-in subjects crossover design, concerns that the antidepressant activity of ketamine is short lived and uncertainty regarding its safety in this population. As of 2011, no randomized, adequately controlled trials of repeated-dose ketamine for MDD have been published. Evidence in support of repeated ketamine adminstration has been limited to open-label case reports[134,135] and an open-label case series.[8] Accordingly, ketamine therapy remains a highly experimental treatment approach for MDD and adoption in psychiatric practice settings at this time is premature.

A second generation of ketamine studies is focused on many unanswered issues, including dose optimization, alternative drug delivery routes, methods to prevent relapse following resolution of depressive symptoms and understanding the neural basis for the putative antidepressant actions of ketamine. In addition to traditional depression rating endpoints,

clinical trials are examining the impact of ketamine on neurocognition. Testing the safety and tolerability of repeated-dose ketamine remains a high priority of future investigations. Given the potential risks of ketamine, safety considerations will ultimately determine whether this old drug is successfully repositioned as a new therapy for treatment-resistant mood disorders.

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Dr Mathew and Dr Charney (Dean of Mount Sinai School of Medicine) and the Mount Sinai School of Medicine have been named on a use patent application of ketamine for the treatment of depression. If ketamine were shown to be effective in the treatment of depression and received approval from the FDA for this indication, Dr Charney and the Mount Sinai School of Medicine could benefit financially. Dr Mathew has relinquished his claim to any royalties and will not benefit financially if ketamine is approved for this use.

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Table I

Pharmacology of racemic ketamine

Characteristic	Ketamine hydrochloride
Elimination half-life	2–2.5 hr
Metabolism	Hepatic
Cytochrome system	CYP2B6, CYP3A4, CYP2C9 (minor)
Metabolites	Norketamine, dehydronorketamine (minor)
Distribution half-life	10–15 min
High-affinity site	PCP site of NMDA receptor
Bioavailability	Intramuscular: 93%
	Intranasal: 25–50%
	Oral: 16–20%

CYP = cytochrome P450 enzyme; **PCP** = phencyclidine.