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Editors

Ketamine for Treatment-Resistant Depression

The First Decade of Progress

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Commentary

First conceptualized by Hippocrates, depression and mania are mankind's oldest known brain disorders. These illnesses are common, often disabling, and associated with a significantly elevated risk of suicide. Indeed, major depressive disorder (MDD) is the most common psychiatric disorder in developed countries, with a prevalence of approximately 17 % (Wittchen et al. 2011; Kessler et al. 2003). In 2004, the World Health Organization (WHO) ranked MDD third among the leading causes of global disease burden (Collins et al. 2011).

Today, available medications for MDD act almost exclusively on monoamine neurotransmitter systems (dopamine, norepinephrine, and/or serotonin). Unfortunately, conventional antidepressants have low rates of treatment response; one-third of patients with MDD will respond to their first antidepressant, but approximately two-thirds will achieve an initial response only after trying several classes of antidepressants and augmentation strategies (Trivedi et al. 2006). Even when these agents are effective, they are associated with a delayed onset of action of several weeks. This latency period significantly increases risk of suicide and self-harm and is a key public health issue. The situation for bipolar disorder (BD) is perhaps even bleaker. Lithium, discovered in the late 1940s, remains the only drug specifically indicated for BD; BD is otherwise managed in clinical practice with a wide array of drugs, including anticonvulsants, antidepressants, and antipsychotics. Thus, there is a strong need to identify and rapidly test novel antidepressants with different biological targets beyond the classic monoaminergic receptors and their downstream targets; these agents would also be expected to act faster and more effectively.

Into this void came the N-methyl-D-aspartate (NMDA) antagonist ketamine.

The chapters in this book chart the rapid and remarkable field of research into ketamine and other glutamatergic modulators. In the early 1990s, a seminal rodent behavioral despair model study of depression first demonstrated that the NMDA receptor complex played a major role in antidepressant action (Trullas and Skolnick 1990) (see the overview of the history of ketamine use and its clinical indications by Dr. Chang and colleagues in Chap. 1). A decade later, the first report was published of rapid antidepressant effects associated with ketamine in patients with MDD

(Berman et al. 2000). Since 2006, when ketamine began to be systematically studied (Zarate et al. 2006)—particularly in treatment-resistant depression—the number of studies investigating ketamine as well as other glutamatergic modulators in MDD has multiplied exponentially (see Chap. 3 by Dr. Blier for a summary of ketamine's clinical effectiveness in depressive disorders).

This book is the first-ever scholarly compendium of scientific information about the use of ketamine in treatment-resistant depression and related conditions, an area in which there is surging worldwide interest. It is worth noting that one author recently observed that the discovery of subanesthetic NMDA receptor antagonists as rapid and robust antidepressants revolutionized the field of mood disorders research, noting that their discovery was "arguably the most important discovery [in psychiatric research] in half a century" (Duman and Aghajanian 2012). In this book, we have brought together an international group of clinicians and researchers from a broad swath of interrelated disciplines to offer the most up-to-date information about clinical and preclinical findings in ketamine research.

The discovery of ketamine's rapid and robust antidepressant efficacy has provided hope for patients with treatment-resistant depression as well as the health professionals who work in this field. Ketamine is a paradigm-shifting agent for several reasons. First, its use as a proof-of-concept agent has led to the identification of novel glutamate-based mechanisms of disease and treatment response in depressive disorders. Second, it may hold promise as a first-in-class rapid-acting antidepressant medication. Indeed, the initial clinical studies with ketamine bolstered the view that rapid antidepressant effects are achievable in humans. These findings facilitated the development of new treatments for depression that target alternative neurobiological systems. New therapeutics could significantly lower morbidity and mortality for both MDD and BD and commensurately minimize or prevent disruption to personal, family, and occupational life and functioning as well as lower risk of suicide.

An additional area of considerable importance is—as ably reviewed by Drs. Ballard and Price in Chap. 4 of this book—that ketamine appears to have significant anti-suicidal effects. This is an area of public health where swift onset and significant response are absolutely vital and where ketamine may have an immediate impact. Notably, ketamine has also shown preliminary efficacy in other disorders such as obsessive-compulsive disorder, post-traumatic stress disorder, and alcohol/substance abuse, which may ultimately extend its utility in clinical practice; this evidence is reviewed by Drs. Rodriguez and Dakwar in Chap. 9. Synergistically, ketamine has also been used in conjunction with electroconvulsive therapy (ECT) to increase its effectiveness; Drs. Loo and Galvez review this evidence in Chap. 8.

As any reader of this book can observe by simply flipping through the evidence contained in this volume, research over the past decade—and particularly over the last five years—has made great advances toward improving our understanding of ketamine's underlying mechanisms of action (Drs. Lapidus and Wolf present an overview of the basic and clinical pharmacology of ketamine in Chap. 2) as well as compiling mounting evidence of its superior antidepressant efficacy. Importantly, this work has provided a sort of scaffolding on which our knowledge has grown

exponentially with every preclinical and clinical study (see Chaps. 6 by Drs. Hermes and Sanacora and 7 by Averill and colleagues for an overview of ketamine's mechanisms of rapid antidepressant activity gleaned from preclinical and clinical studies, respectively). This burgeoning evidence is essential for the future development of targeted therapies that are more effective, act more rapidly, and are better tolerated than currently available treatments.

Despite these promising findings, however, there has been reluctance to consider ketamine for the widespread treatment of depression because of the dissociative side effects associated with its use at even low doses and because of its abuse potential (see Chap. 5 by Drs. Rybakowski and colleagues for a thorough review of ketamine's overall safety, tolerability, and neurocognitive effects). As the chapters in this book underscore, ketamine's antidepressant mechanism has been an active topic of preclinical and clinical investigation. Significantly, as this book was going into publication, ongoing investigations building on much of the previous work outlined in these chapters unearthed another potential paradigm-shifting finding. Specifically, a team led by Todd Gould at the University of Maryland in collaboration with NIH investigators suggested that the antidepressant effects of ketamine are produced not by the drug itself, but by one of its metabolites: (2*R*,6*R*)-hydroxynorketamine (HNK) (Zanos et al. 2016); this metabolite is currently being developed as a treatment.

This discovery is an excellent example of the pace with which research in this young and exciting field is proceeding. As noted above, ketamine exerts rapid antidepressant effects in preclinical and clinical studies. However, while the field as a whole is promising, individual results with specific agents are often not, and clinical trials of other NMDA antagonists have largely failed to show the same antidepressant effects as ketamine. In this study, the investigators began by studying *(S)*- and *(R)*-ketamine; the former was found to block NMDA receptors more potently, but did not reduce depressive-like behaviors as well as the *(R)* isomer. The investigators then studied the effects of the metabolites created as *(S)*- and *(R)*-ketamine were broken down. They discovered that (2*S*,6*S*;2*R*,6*R*)-HNK were pharmacologically active and reached levels that were three times higher in female than male mice. Because female mice were also known to respond more effectively to ketamine's antidepressant effects than males, the discovery suggested that differences in these HNK metabolites might provide an explanation; when the investigators blocked formation of the metabolite, the drug's sustained antidepressant effects also disappeared. Continuing to explore the potential of one of these metabolites—(2*R*,6*R*)-HNK—the investigators further found that mice treated with a single dose of (2*R*,6*R*)-HNK showed improvements in their symptoms that lasted for three days. Intriguingly, the significant antidepressant effects of (2*R*,6*R*)-HNK were not associated with ketamine's well-known dissociative effects. Mice who received (2*R*,6*R*)-HNK had no alterations in their physical activity, coordination, or sensory perception. It is also important to note that (2*R*,6*R*)-HNK does not appear to have the same potential for abuse; when given the choice, mice chose to self-administer ketamine, but not (2*R*,6*R*)-HNK. Furthermore, (2*R*,6*R*)-HNK did not block NMDA receptors like ketamine; instead, it appeared to activate α-amino-3-hydroxy-5-

methyl-4-isoxazole propionic acid (AMPA) receptors. To confirm this, the investigators inhibited AMPA receptor activity before giving mice (2*R*,6*R*)-HNK; as expected, this blocked its antidepressant effects.

Readers of this volume will appreciate that this discovery fundamentally alters our understanding of how this particular underlying rapid antidepressant mechanism works and holds considerable promise for developing more effective, safer treatments for the millions of individuals worldwide who struggle with depression. While more work is certainly needed to elucidate whether (2*R*,6*R*)-HNK's antidepressant effect will work similarly in humans and can commensurately lead to improved therapeutics for patients, this recent study highlights the quick pace of research in the development of glutamatergic agents and underscores the role of ketamine as a proof-of-concept agent for elucidating this new class of potentially lifesaving drugs.

The diverse chapters in this book bring together data and insights from this rapidly expanding and extraordinarily promising field of study. As the information contained in this book shows, new strides are being made daily in this field. It is our hope that readers will be able to extract integrated themes and useful insights from the material contained in these diverse chapters and appreciate the paradigm-shifting contributions of ketamine to modern psychiatry and clinical neuroscience research.

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Preface

1. Historical Perspective

Ketamine is an old drug that has been reborn as a potential treatment for one of the most serious of all diseases: treatment-resistant depression. Ketamine was synthesized by Calvin Lee Stevens, Ph.D., professor of organic chemistry at Wayne State University and a chemical consultant to Parke Davis. Early preclinical pharmacological testing at Parke Davis was done by Graham Chen, M.D., Ph.D., and Duncan A. McCarthy, Ph.D. Ketamine was found to produce excellent anesthesia and was short-acting. Its safety profile in animals was evaluated by Alex Lane, M.D., head of clinical pharmacology at Parke Davis (Domino 2010).

The initial ketamine studies in humans were led by Edward F. Domino, M.D., from the University of Michigan, with the first human receiving ketamine in an intravenous subanesthetic dose on August 3, 1964. Domino recounts, with a hint of regret, that many years ago while working part-time as a clinical pharmacologist at the Lafayette Clinic in Detroit, he would be referred patients who were abusing ketamine, a number of whom were depressed. "I remember one young lady, in particular, who was a chronic phencyclidine and later ketamine abuser. She had serious bouts of mental depression. I asked her why she took these illicit drugs rather than her usual antidepressant medications. Her answer was 'Oh, doctor, my antidepressants don't work as well'. She stated that ketamine and phencyclidine worked quickly and were much better antidepressants but they didn't last as long so she took them again and again. I promptly recommended that she stop this bizarre practice because it would only harm her. I never pursued the possible antidepressant actions of ketamine". (Domino 2010)

2. Ketamine Emerges as an Antidepressant

The possibility that glutamate could be involved in depression and that N-methyl-D-aspartate (NMDA) antagonists such as ketamine could possess antidepressant-like actions can be traced to studies conducted in the early 1990s, particularly those

by Phil Skolnick and colleagues (Trullas and Skolnick 1990; Nowak et al. 1993; Paul et al. 1993; Skolnick et al.1996; Trullas 1997; Skolnick et al. 2009).

Building on the observation that inescapable stress exposure in animals disrupted hippocampal long-term potentiation, an NMDA receptor-dependent process, Skolnick and his associates found that many types of drugs that reduce NMDA receptor function had antidepressant-like effects in several animal models. Reduced NMDA receptor function emerged as a correlate of long-term antidepressant administration (Trullas and Skolnick 1990; Nowak et al. 1993; Paul et al. 1993; Skolnick et al.1996; Trullas 1997; Skolnick et al. 2009). Thus, by the mid-1990s, there was a compelling preclinical literature that supported the notion that ketamine might have antidepressant properties, but this hypothesis had not yet had an unambiguous test in humans.

In the early 1990s, John Krystal and I, when we were together at Yale, led a research group that began to focus on the role of glutamate in a number of psychiatric disorders. We were aware of the literature just cited when we initiated our first study of ketamine in depressed patients. However, we were not expecting the rapid and robust antidepressant effects of ketamine that we observed in our patients. But we thought we might be onto something important and decided to publish our findings (Berman et al. 2000).

To our surprise, the initial report had very little impact on the field. Perhaps it was just not believed that an antidepressant effect within hours was possible. Also, there was likely concern about the abuse potential and psychotomimetic effects of ketamine. For years, there was no attempt to replicate the antidepressant effects of ketamine. Consequently, when I was leading the Mood and Anxiety Disorders Program at the National Institute of Mental Health (NIMH), I suggested to Carlos Zarate and Husseini Manji that we should attempt to replicate the original findings of the study by Berman and colleagues (Berman et al. 2000).

Our NIMH research team was able to successfully replicate the findings, which were subsequently reported by Zarate and colleagues (Zarate et al. 2006). It is noteworthy that the initial paper by Berman and colleagues (Berman et al. 2000) was cited only about 20 times/year between 2000 and 2005, but after the paper by Zarate and colleagues (Zarate et al. 2006) was published, it was cited an average of 68 times/year between 2006 and 2011 and 179 times/year between 2012 and 2015. This reflects the explosion of research on the efficacy and antidepressant mechanism of action of ketamine.

Following publication of the paper by Zarate and colleagues (Zarate et al. 2006), subsequent published clinical data on ketamine has consistently indicated very strong efficacy of single doses and short-term repeated doses along with a good safety profile (Newport et al. 2015; Murrough et al. 2013; Murrough et al. 2013; Wan et al. 2015). There is also anecdotal information from practitioners using ketamine off-label that repeated doses of ketamine over longer periods of time may be effective in maintaining antidepressant response.

It is also noteworthy that ketamine may have anti-suicidal effects (Price et al. 2009; DiazGranados et al. 2010; Murrough et al. 2015) and may be effective for treating PTSD (Feder et al. 2014). Recently, provocative preclinical investigations

indicate that ketamine may have preventative effects on the ability of stress to cause depression and anxiety (Parise et al. 2013; Brachman et al. 2015; Amat et al. 2016). This needs to be tested in clinical populations.

3. The Path Forward

Much work remains to be done. The antidepressant effects of ketamine need to be evaluated in larger-scale clinical trials to determine the optimal dose, best route of administration, and durability and safety of long-term ketamine treatment.

Elucidation of ketamine's mechanism of antidepressant, putative antianxiety, and preventative actions could prove extremely valuable in helping not only guide the development of novel pharmaceutical interventions but also in advancing the basic understanding of the pathophysiology of mood disorders. Presently, most studies have focused on ketamine's action on the NMDA receptor, where it functions as a noncompetitive antagonist. A growing number of preclinical studies provide strong evidence that this action, and an ensuing cascade of effects involving increased neurotrophic factor activity and changes in synaptic plasticity, may be critical in generating an antidepressant-like response in rodent models.

It has been hypothesized that a ketamine-induced burst of glutamate release stimulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors resulting in the release of brain-derived neurotrophic factor (BDNF), the activation of tropomyosin receptor kinase B (TrkB) and Akt, and subsequent increases in mammalian target of rapamycin complex 1 (mTORC1) signaling. This leads to increased synthesis of proteins required for synapse formation and maturation. Furthermore, blockade of BDNF release or function or mTORC1 signaling eliminates the antidepressant effects of ketamine (Liu et al. 2012; Li et al. 2010; Maeng et al. 2008; for a review, see Duman et al. 2016).

Resolution of the critical elements related to the mechanism of antidepressant action of ketamine is necessary to discover "next-generation" ketamine-like antidepressant drugs.

In summary, the discovery that ketamine has rapid antidepressant qualities has been hailed, in some quarters, as the most significant advance in the treatment of depression in decades (Insel 2014). This remains to be seen, pending the results of large-scale clinical trials, including the approval process of a Food and Drug Administration review, to accurately determine the efficacy and safety of ketamine therapy for serious mood and anxiety disorders.

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Contents

Chapter 1
The History of Ketamine Use and Its Clinical Indications

Lee C. Chang, Suman Rajagopalan, and Sanjay J. Mathew

Abstract Ketamine, which has a similar chemical structure to phencyclidine, was first administered to humans in 1964 and found to produce a unique effect termed "dissociative anesthesia." In spite of the potential abuse liability, ketamine remains on the World Health Organization (WHO) Model List of Essential Medicines. It has been approved worldwide as the sole anesthetic agent for certain procedures, for the induction of anesthesia, and as an anesthetic supplement with low-potency agents like nitrous oxide. In addition, ketamine is also used for its analgesic properties in the management of cancer pain, chronic pain, and postoperative pain, among other indications. This chapter describes the history, development, clinical indications, and abuse potential of this agent.

1.1 History of the Development of Ketamine

The history and development of ketamine as an anesthetic agent are just as remarkable as the properties of the drug itself. On March 26, 1956, a new arylcyclohexylamine compound was synthesized by Dr. Harold Maddox, a chemist in Detroit, Michigan. This compound was given the chemical investigation number CI-395 (Fig. 1.1) (Maddox et al. 1964). Two years later, CI-395, now known as phencyclidine, was delivered to pharmacologist Dr. Graham Chen and his associates for

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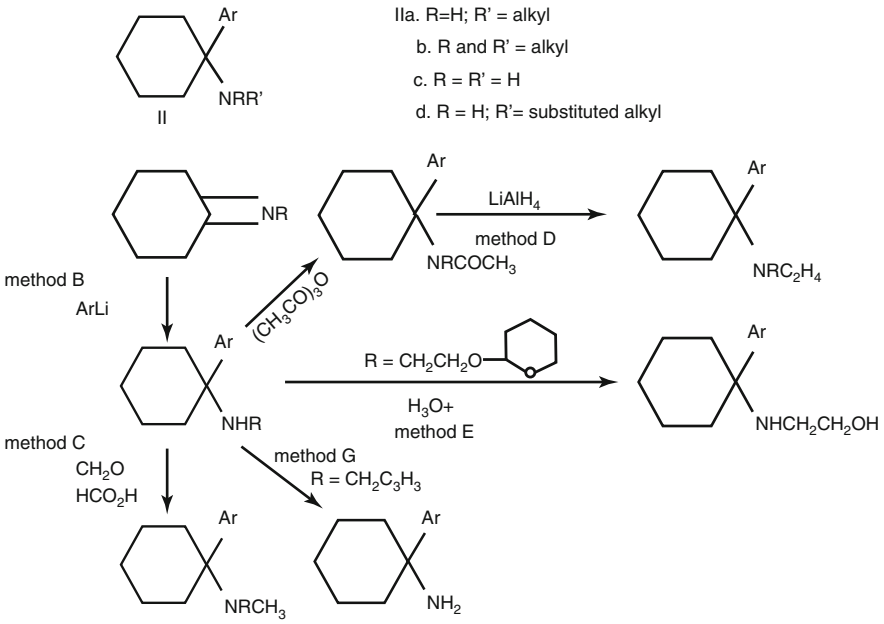

Fig. 1.1 Methods of developing phencyclidine and derivatives (Adapted with permission from *Journal of Medicinal Chemistry*. Copyright 1965 American Chemical Society)

further study. Early findings revealed that the compound produced varying effects depending on the animal species and the dosage used. In rodents, hyperactivity was often observed, whereas in dogs and monkeys, a more calming effect was noted (Chen et al. 1959). Large doses resulted in either a cataleptic response or general anesthesia in all of the animal species tested, whereas even higher dosages resulted in development of seizures. Following the publication of the work describing the unique pharmacological properties of the new compound (Chen et al. 1959), Drs. Maurice Seevers and Edward Domino at the University of Michigan, Ann Arbor, were contracted by Parke-Davis as pharmacology consultants to further study CI-395. Research studies involving the administration of phencyclidine to humans had already been initiated, and potential therapeutic uses being considered at that time included pre- and postoperative analgesia, surgical anesthesia, and treatment of mental illnesses (Domino 1964). Interestingly, this would not be the first time that Parke Davis had investigated psychoactive drugs for human use. In the 1880s, the company had marketed dried peyote cactus buttons containing the psychedelic drug mescaline as one of their products for sale (Jansen 2004).

Following studies conducted by Dr. Domino demonstrating that CI-395 was an excellent anesthetic in monkeys, Dr. Ferdinand Greifenstein, Chair of Anesthesiology at Wayne State University, Detroit, Michigan, initiated clinical development. The drug, now trademarked as Sernyl, was administered to seven human volunteers whose vital signs were monitored, as well as to 64 patients undergoing various surgical procedures. Certain dosages resulted in complete analgesia, and it was noted

that "surgical incision, and in some cases the complete operation, could be performed under Sernyl analgesia alone" (Greifenstein et al. 1958). However, administration of the drug resulted in a consistent and significant increase in blood pressure. Although initial administration of Sernyl to humans undergoing surgery indicated that it was generally a safe anesthetic, Dr. Greifenstein's studies also demonstrated that patients suffered from prolonged postsurgical emergence delirium. Ten of the 64 patients were described as "unmanageable in the postoperative period and exhibited severe degrees of manic behavior." Three of the patients experienced violent emergent reactions and one patient displayed prolonged disorientation for nearly 15 hours.

Given the prolonged duration of emergence delirium with Sernyl, Parke Davis continued developing analogues that would have the pharmacological activities but not the adverse effects of the compound. One of these compounds was discovered by Dr. Calvin Lee Stevens, a pharmacist and professor of organic chemistry at Wayne State University, Detroit, Michigan. Initially designated as CI-581, this compound was found to be short-acting and possess excellent anesthetic activity in monkeys (McCarthy et al. 1965). It would become the drug now identified as ketamine.

Dr. Domino was asked to conduct a clinical pharmacology study for this new compound. In collaboration with Dr. Guenter Corssen, an anesthesiologist at the University of Michigan in Ann Arbor, the first human dose of ketamine was administered on August 3, 1964. Starting with subanesthetic doses, the drug dose was slowly titrated up to a dose that exerted full effect as a general anesthetic. The subjects were volunteers from Jackson Prison in Michigan who described their experience as strange and associated with "having no feeling in their arms or legs." Although the chemical structure of ketamine was similar to that of phencyclidine, these initial studies suggested that it had fewer adverse effects in humans (Jansen 2004).

When describing their initial findings with ketamine, Drs. Domino and Corssen had difficulty finding the correct term to adequately describe the effects of the drug. They finally agreed on "dissociative anesthetic," a term coined by Dr. Domino's wife and one that is still in use today (Domino 2010). Although ketamine was developed in the United States, it was first patented in Belgium in 1963. This was due to the efforts of Dr. Stevens, who applied for the patent application without the consent or knowledge of Parke-Davis (Jansen 2004). Litigation quickly followed and ketamine was soon given the US patent 3254124 in 1966 for use as an anesthetic in humans and animals. Following approval by the US Food and Drug Administration (FDA) in 1970 for use in children, adults, and the elderly, ketamine became popular as a field anesthetic administered to soldiers during the Vietnam War because of its fast onset and recovery period as well as its ability to maintain or elevate blood pressure in trauma situations. During this period, ketamine hydrochloride became commercially available by prescription under the brand name of Ketalar.

Outside the United States, the first reported use of ketamine as an anesthetic was in the United Kingdom (UK) and within the British military (Barry 1971). Even as the use of ketamine for anesthesia was being studied, the potential to use the medication to treat different psychological or psychiatric problems was being explored. As early as 1974, the use of ketamine as an adjunct for antidepressive psychotherapy

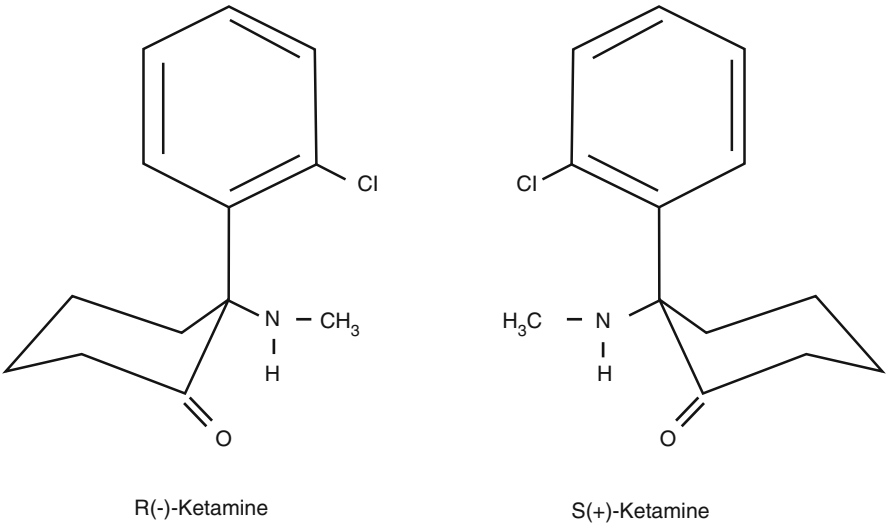

Fig. 1.2 Structural formulas of the two enantiomers of ketamine

was described in Argentina as a form of regression therapy to help treat patients (Fontana 1974). It was during this period that clinicians in Mexico began using ketamine in group settings as part of psychedelic psychotherapy sessions, which combined healing practices of Mexican Indian ceremonies with psychoanalytic techniques (Kolp et al. 2007). More recently, ketamine was used to treat patients who were at the scene of the 2005 London underground bombings. As a result of that incident, paramedics in the UK are now authorized to possess and administer ketamine for pain relief.

Ketamine and propofol are currently listed as the two injectable medicines under general anesthetics in the WHO Model List of Essential Medicines. First compiled in 1977, the Model List is updated and revised every two years; ketamine was added in 1985. Medications on the list are determined by a committee to "satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms, and at a price that individuals and the community can afford" (WHO Technical Report Series 2000). The ease of administrating and monitoring ketamine makes it an attractive alternative in developing countries where the facilities may be suboptimal; as a result, it is often the only available anesthetic for use.

1.1.1 Ketamine Enantiomers

Ketamine is available in two enantiomers: the *S*(+) and the *R*(−) configurations (Fig. 1.2). The *S*(+)-ketamine has approximately five times higher affinity for the N-methyl-D-aspartate (NMDA) receptor site than *R*(−)-ketamine (Vollenweider

et al. 1997) and is two times more potent than the racemic mixture. Thus, at equimolar doses, *S*(+)-ketamine provides similar clinical benefits with fewer undesirable side effects (Paul et al. 2009). Most pharmacological preparations include an equimolar racemic mixture of the two enantiomers. Although racemic ketamine has the broadest worldwide use, *S*(+)-ketamine is available in some European countries like Germany, Denmark, Finland, and the Netherlands (Budavari et al. 1989).

1.2 Approved Indications for Ketamine

Ketamine has been approved by appropriate regulatory bodies for use as an anesthetic and an analgesic in both human and veterinary medicine in many countries around the world. In the United States, all potent sedatives and hypnotics must be approved by the Anesthetic and Critical Care Drugs section of the FDA. Historically, the committee for this section has comprised anesthesiologists, pharmacologists, biostatisticians, pharmacotherapists, and consumer representatives. After obtaining a Notice of Claimed Investigational Exemption for a New Drug (IND), the manufacturer must first demonstrate the safety of the drug with human subjects. Significant trials are subsequently conducted to determine the efficacy of the drug and to designate it as either "approved," "approvable, provided certain conditions are fulfilled," or "nonapprovable." The FDA has approved ketamine to be used as the sole anesthetic for diagnostic and surgical procedures that do not require skeletal muscle relaxation as well as for the induction of general anesthesia. Given the sympathomimetic effects of ketamine, anesthesiologists often use the drug as the induction agent for patients who are hemodynamically compromised, such as occurs with trauma.

The specific areas of application for the use of ketamine include the following:

1. Debridement, painful dressings, and skin grafting in patients with burns, as well as other superficial surgical procedures
2. Neurodiagnostic procedures such as pneumoencephalograms, ventriculograms, myelograms, and lumbar punctures
3. Diagnostic and operative procedures of the eye, ear, nose, and mouth, including dental extractions as well as diagnostic and operative procedures of the pharynx, larynx, or bronchial tree
4. Sigmoidoscopy and minor surgery of the anus and rectum as well as circumcision
5. Extraperitoneal procedures used in gynecology such as dilation and curettage
6. Orthopedic procedures such as closed reductions, manipulations, femoral pinning, amputations, and biopsies
7. As an anesthetic for poor-risk patients with depression of vital functions
8. In procedures where the intramuscular route of administration is preferred
9. In cardiac catheterization procedures

Some properties of ketamine could be advantageous in certain clinical scenarios, making it a very useful agent in such circumstances. Given its rapid onset of action

and sympathomimetic effect, it can be used to induce anesthesia in hemodynamically compromised patients like those with trauma, cardiac tamponade, or restrictive pericarditis (Jabre et al. 2009; Morris et al. 2009). The elevation of blood pressure can be so significant that one of the current contraindications for ketamine use is in individuals where "significant elevations of blood pressure would constitute a serious hazard." Similarly, its bronchodilation properties make it an agent of choice in those with active bronchospasm or for rescue therapy for severe refractory bronchospasm in the critical care setting. Ketamine's ability to provide excellent sedation and analgesia while preserving spontaneous respiratory function in routine dosages makes it an ideal drug for patients receiving multiple daily dressing changes. Respiratory depression can occur with overdosing or when given too rapidly, and hence the FDA cautions that ketamine should be used by physicians experienced in administering general anesthetics and proficient in the management of the airway.

The approved indications in Canada, Australia, and the UK are similar to those in the United States and all focus on the anesthetic properties of the drug. Specifically, ketamine is indicated as the sole anesthetic agent for recommended procedures, for the induction of anesthesia, and to supplement low-potency agents. While the FDA has general precautionary statements for the use of ketamine in patients with elevated intracranial pressures due to the concern of potentially causing a further increase in pressure, its use in patients with a history of cerebrovascular accidents is contraindicated in Canada and Australia.

1.3 Ketamine in Pain Management

As the use of ketamine as an anesthetic agent grew among practitioners, it was soon discovered that ketamine had additional properties that could benefit patients. As it was known that phencyclidine had analgesic properties, it was therefore hypothesized that ketamine would also have such effects (Persson 2013). Research was started by healthcare providers in varying specialties to examine the use of ketamine as a potential treatment for pain management. Although the different pharmaceutical governing bodies have currently not approved the use of ketamine for pain management, the drug is used by practitioners to treat various pain conditions, including cancer pain, chronic pain, and perioperative pain.

1.3.1 Cancer Pain Management

Currently, ketamine is used in subanesthetic doses along with opioids to treat cancer pain, especially when opioids alone are ineffective in alleviating pain. Ketamine can be administered orally, intravenously, or subcutaneously for the relief of pain. A Cochrane review evaluating the use of ketamine in the management of cancer pain identified seven randomized control trials (RCTs) and 32 case reports or case series.

Only two RCTs were included in their analyses that showed an improvement in cancer-related pain when used along with morphine. Of the 32 case reports that were included in the same review, most showed an improvement in pain control when ketamine was used along with morphine. The authors concluded that more RCTs are required to assess the benefits and risks involved with the use of ketamine as an adjuvant to opioids for cancer pain (Bell et al. 2012).

1.3.2 Chronic Pain Therapy

Ketamine has been successfully used to treat different forms of chronic pain, including the treatment of chronic neuropathic pain, phantom and ischemic limb pain, postherpetic neuralgia, orofacial pain including trigeminal neuralgia, fibromyalgia, and chronic regional pain syndromes (Visser and Schug 2006). Patients with complex regional pain syndromes who were administered low-dose ketamine infusions exhibited an improvement in pain scores for weeks following the treatment (Schwartzman et al. 2009; Sigtermans et al. 2009). Following administration of ketamine through an epidural catheter, one case study describes pain relief in a patient suffering from complex regional pain syndrome that was refractory to other treatments (Takahashi et al. 1998). In patients with fibromyalgia, ketamine increased tolerance to pain, decreased pain at tender points, and reduced muscle pain and referred pain (Sorensen et al. 1997; Graven-Nielsen et al. 2000). Current data suggest that instead of acting as a traditional analgesic, ketamine may more effectively reduce symptoms of allodynia and hyperalgesia. Younger patients and those with a short duration of pain seem to be more likely to have a positive response to treatment with ketamine (Hocking and Cousins 2003). While dosage for parenteral administration in regard to chronic pain management has typically ranged from 0.125 to 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$, oral dosing for ketamine has varied widely from 30 to 1000 mg/day, suggesting a wide therapeutic window. While there is sufficient evidence to demonstrate its benefit with short-term use, more studies are needed to establish the long-term effects of ketamine and the dose required for effective treatment with minimal side effects.

1.3.3 Acute Perioperative Pain

The analgesic effects of ketamine are believed to be, at least in part, due to its effects on central sensitization and neuronal modulation of pain. Low doses of ketamine may have either synergistic or additive analgesic effects when used in combination with opioids for postoperative pain. Ketamine is an effective adjuvant, particularly for upper abdominal, thoracic, and major orthopedic surgeries. The analgesic effect of ketamine does not depend on the type of opioid administered, the dose of ketamine, or the timing of ketamine administration (Laskowski et al. 2011). Administration of ketamine prior to the surgical procedure to determine if there was

a decrease in postoperative pain scores or the amount of opioids required has been studied with variable results (Ong et al. 2005). Ketamine in small doses has also been added to patient-controlled analgesia (PCA) with morphine following thoracic surgery. This combination of morphine-ketamine PCA was found to provide superior analgesia and decrease the requirement of morphine with no increase in the incidence of hallucinations or psychological side effects (Mathews et al. 2012).

1.4 History of the Illicit Use of Ketamine

As the clinical indications for ketamine grew and interest in the drug began to spread around the world through the mid 1970s, its use for recreational purposes also grew. The first reported illicit use of ketamine was in the United States (Graeme 2000), and soon it was being combined with various other street or prescription drugs to produce different effects. The dissociative anesthetic properties of the drug were soon being discovered by those outside of the medical field.

The introduction of ketamine for nonmedical use may have been brought about by the hospital staff involved with early trials diverting the drug to the community. Two publications in the 1970s by famous authors resulted in an increased interest in the illicit use of ketamine. *Journeys into the Bright World*—written in 1978 by Marcia Moore, a Harvard graduate and astrologer, and her husband, Dr. Howard Alltounian, an anesthesiologist who was then the Deputy Chief at the Seattle Public Health Hospital—described their experiences with ketamine and supported the experience that ketamine could provide. Soon after the book was published, Mrs. Moore disappeared from her home. Two years later, her remains were found in a nearby forest close to her house and reports concluded that she had likely frozen to death following significant injections of ketamine.

Also in 1978, Dr. John Lilly published his autobiography, *The Scientist* (Fig. 1.3). Dr. Lilly was a graduate of the University of Pennsylvania Medical School, a physician, psychoanalyst, and philosopher who described in his book not only the discoveries he made but also his experiences with ketamine. Dr. Lilly was first introduced to ketamine in the late 1970s by a medical colleague as a possible method of alleviating the chronic migraines he was suffering from. Following his first injection of ketamine, Dr. Lilly described that he could actually visualize the pain move away from his body, which lasted approximately 20 minutes before it slowly returned back to his body. After receiving additional injections of ketamine, a similar experience would occur, but with the pain diminishing in intensity each time. The book also describes the effects that he observed with escalating doses and how at different thresholds he would enter into different "domains" (Lilly 1996). Dr. Timothy Leary, a psychologist and associate of Dr. Lilly, discussed the use of ketamine in his Eight-Circuit Model of Consciousness hypothesis as one of the methods of activating one of the circuits in his book *Exo-Psychology*, published in 1977.

As the popularity of the drug grew, so did the number of available formulations, including powder, tablet, and liquid forms. Although the United States Department of Health and Human Services (DHHS) had filed a notice to make ketamine a

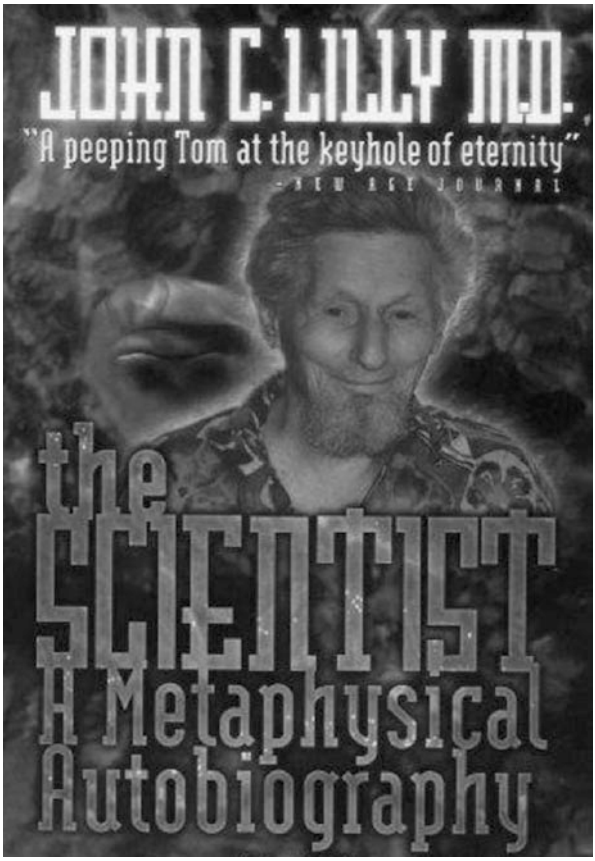

Fig. 1.3 Cover of the book *The Scientist* by Dr. John Lilly

Schedule III controlled substance in 1981, it was not until 1999 that the Drug Enforcement Agency (DEA) classified the drug as such. The DHHS described the pharmacological and behavioral effects of ketamine as similar to those of the Schedule II substance phencyclidine, but as less intense and shorter in duration. The primary source of ketamine for recreational use came from veterinary practices, with several reports of veterinary clinic burglaries occurring in an effort to obtain the drug. As a result, the American Animal Hospital Association (representing 16,000 veterinary care providers) and the American Veterinary Medical Association (with 62,000 members) both strongly supported the proposal to classify ketamine as a Schedule III agent. The findings provided by the Deputy Administrator of the DEA (Marshall 1999) found that:

1. Ketamine has less potential for abuse than the drugs or other substances in Schedules I and II
2. Ketamine has currently accepted medical use in treatment in the United States
3. Abuse of ketamine may lead to moderate or low physical dependence or high psychological dependence

As a Schedule III drug, anyone who manufactures, distributes, or dispenses ketamine must be registered to conduct such activities. In Canada, phencyclidine and all of its derivatives and analogues are classified as Schedule I according to the Controlled Drugs and Substances Act. This resulted in ketamine becoming a Schedule I drug in 2005, meaning that illegal possession of ketamine carries a much harsher penalty. In the UK, ketamine recently became a Class B drug on June 10, 2014; a report from the Advisory Council on the Misuse of Drugs (ACMD) had recommended the move after a series of deaths occurred tied to ketamine abuse and after increased reports of acute ketamine toxicity. In its statement, the ACMD reported that in 2012–2013, approximately 120,000 individuals had misused ketamine, often in the context of polydrug use. The most prevalent demographic group to abuse ketamine was males in the 20–24 age group. In the UK, ketamine had been classified as a Class C drug since January 1, 2006, and before that it was not officially a controlled substance, making it legal to possess ketamine. In the UK, phencyclidine is currently a Class A drug, and methoxetamine, another drug in the same arylcyclohexylamine group, is a Class B drug. The ACMD also indicated in their report that the doses reportedly used by those abusing the drug were typically higher than the dosage used for anesthesia. At sufficiently high doses, ketamine can result in extreme dissociation with auditory and visual hallucinations associated with temporary memory loss, an experience termed the "K-hole." Ketamine abuse is also seen as part of the dance music culture in the United States, the UK, Canada, and Australia, and it is often used in conjunction with the psychoactive drug 3,4-methylenedioxymethamphetamine (MDMA, also known as ecstasy) and other substances.

China submitted a proposal in March 2015 to the United Nations to impose international regulation on the distribution of ketamine by placing it as a Schedule I drug and restricting global access to the drug. The proposal was triggered by China's concerns about the increasing prevalence of ketamine abuse, and the proposal was supported by a number of other countries, including Russia. Soon after the proposal was announced, the WHO Expert Committee on Drug Dependence released a report stating that "…while the Committee acknowledged the concerns raised by some countries and UN organizations, ketamine abuse currently does not appear to pose a sufficient public-health risk of global scale to warrant scheduling. Consequently, the Committee recommended that ketamine not be placed under international control at this time" (Porta et al. 2015). Following statements released by several other countries that argued for the necessity and importance of ketamine, particularly in developing countries, China withdrew its motion (Blackwell 2015).

Ketamine is a widely used anesthetic, especially in developing countries, because it is easy to use and has a wide margin of safety when compared with other anesthetic agents. Countries with serious abuse problems may decide to introduce or maintain control measures but should ensure ready access to ketamine for surgery and anesthesia for human and veterinary care.

1.5 Conclusions

Even though ketamine was developed nearly half a century ago, it remains just as clinically significant today as it did on the day it was first administered to a human. Initially developed as an anesthetic drug with unique characteristics different from existing drugs, clinicians quickly realized the potential for ketamine to treat different forms of pain. The potential for ketamine abuse and misuse remains a real threat. Despite this, the WHO has recognized the importance of ketamine on a global level, and the drug remains on the Model List of Essential Medicines. As the clinical use of ketamine continues, new and exciting potential therapeutic uses for the drug are being investigated. This is the subject of much of the rest of this book.

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Chapter 2
The Basic and Clinical Pharmacology of Ketamine

Elizabeth Wolf Fourcade and Kyle A.B. Lapidus

Abstract Ketamine, an N-methyl-D-aspartic acid (NMDA) glutamate receptor antagonist developed as an anesthetic, has shown efficacy as an antidepressant in a number of studies since 2000. Multiple routes of ketamine administration, each with unique pharmacokinetics, have been investigated in the treatment of depression, including intravenous, intramuscular, intranasal, sublingual, and oral delivery.

Ketamine is most commonly administered as (*R*,*S*)-ketamine, a 1:1 racemic mixture. Ketamine's most important antidepressant activity is believed to stem from its antagonism of NMDA receptors, which are widely expressed in the brain. When NMDA receptors on gamma-aminobutyric acid (GABA)-ergic neurons are antagonized, downstream glutamatergic neurons are disinhibited. This increased glutamatergic activity impacts neural signaling, synaptic plasticity, and connectivity. Ketamine-induced synaptic potentiation and proliferation may play a key role in eliciting antidepressant effects. Ketamine also impacts other neurotransmitter systems, affecting cholinergic, opioidergic, monoaminergic, and GABAergic function.

2.1 Introduction

Ketamine, an N-methyl-D-aspartic acid (NMDA) receptor (NMDAR) antagonist developed as a surgical anesthetic in the 1960s, was introduced as a safer alternative to phencyclidine (PCP) (White et al. 1982) and is approved by the FDA for anesthetic indications. However, in what has been called "arguably the most important discovery in half a century" (Duman and Aghajanian 2012), ketamine has shown

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efficacy in managing treatment-resistant depression (TRD). Multiple clinical trials since 2000 have demonstrated ketamine's rapid (within minutes to hours) and longer term antidepressant effects in patients with major depression (Berman et al. 2000) and those with TRD (Zarate et al. 2006; Wan et al. 2015; Lapidus et al. 2014; McGirr et al. 2015; aan het Rot et al. 2010; Blier et al. 2012; Murrough et al. 2013a, b; Diamond et al. 2014; Rasmussen et al. 2013). This chapter will review the basic and clinical pharmacology that may shed light upon the antidepressant effects of ketamine and motivate future drug-discovery efforts.

2.2 Ketamine: Basic Pharmacology

Ketamine is a chiral arylcyclohexalamine with chemical name (*R*,*S*)-2-(2-Chlorophenyl)-2-methylaminocyclo-hexanone. It is formally classified as an open-channel nonselective NMDAR antagonist. However, its pharmacological profile is complex, and ketamine has affinity for multiple receptors.

Ketamine refers to (*R*,*S*)-ketamine, a 1:1 racemic mixture of (*S*+)-ketamine and (*R*-)-ketamine enantiomers. Both enantiomers interact with NMDA and other receptors (e.g., cholinergic, opioidergic, monoaminergic, and other glutamatergic receptors). However the enantiomers differ in binding affinities as defined by their inhibition or dissociation constants, K_i or K_D (see Table 2.1). For example, the NMDAR K_i of (*S*)-ketamine is 0.69 μM, whereas the NMDAR K_i of (*R*)-ketamine is 2.57 μM, indicating that the binding affinity of (*S*)-ketamine is about four times higher than the affinity of (*R*)-ketamine (Moaddel et al. 2013). Relative to (*R*)-ketamine, (*S*)-ketamine also has approximately eight times higher binding affinity for the dopamine transporter (Nishimura and Sato 1999; Nishimura et al. 1998), is approximately three times as potent at opioid receptors (Finck and Ngai 1982), and is approximately twice as potent as a cholinergic antagonist (Lodge et al. 1982). Preliminary studies have also suggested tolerability advantages for (*S*)-ketamine over racemic ketamine. Potential advantages include decreased frequency of anterograde amnesia (Pfenninger et al. 1994), more rapid recovery of cerebral function (Himmelseher and Pfenninger 1998; Paul et al. 2009), and enhanced neuroprotective properties (Proescholdt et al. 2001; Pfenninger et al. 2002). (*S*)-ketamine was approved in Europe in 1998 for indications including anesthesia and analgesia and is available in Germany, Finland, Denmark, Iceland, and the Netherlands (Mann et al. 2013).

Ketamine is metabolized in the body to products including norketamine (NK), dehydronorketamine (DHNK), six hydroxynorketamine metabolites (HNK), and hydroxyketamine (HK) (Zarate et al. 2012). An in vitro study of rat brain tissue revealed that NMDAR K_i values for most of these metabolites are many times higher than K_i values for ketamine. One exception is NK; (*S*)-NK ($K_i = 2.25$ μM) was found to have a higher binding affinity than (*R*)-ketamine ($K_i = 2.57$ μM). Accordingly, both animal studies (Leung and Baillie 1986; Holtman et al. 2008) and simulation studies in children (Herd et al. 2007) have shown some efficacy of NK in exerting anesthetic and antinociceptive effects.

Table 2.1 Known ketamine interactions

Receptor	Tissue/ substrate type	Radioligand	K_i or K_D (in μM)
NMDA	Rat brain tissue from cell lines KXα7R1 and KXα3β4R2	[^{3}H]MK-801	(*R*,*S*)-Ketamine 1.06 ± 0.14 SEM (*S*)-Ketamine 0.69 ± 0.14 SEM (*R*)-Ketamine 2.57 ± 0.28 SEM (*S*)-Norketamine 2.25 ± 0.22 SEM (*R*)-Norketamine 26.46 (*S*)-Dehydronorketamine 38.95 (*R*)-Dehydronorketamine 74.55 (2*S*,*6S*)-Hydroxynorketamine 21.19 (2*R*,*6R*)-Hydroxynorketamine >100
α7AChR	Rat brain tissue from cell line KXα7R1	[^{125}I]-α-Bungarotoxin [^{3}H]-Epibatidine	(*R*,*S*)-Ketamine = no observable effect; this is a noncompetitive inhibitor (see Sect. 2.3.2) (*R*)-Dehydronorketamine = no observable effect (*S*)-Dehydronorketamine = no observable effect
Muscarinic M1	Recombinant human M1-M3 expressed in Chinese hamster ovarian cells	[^{3}H]NMS	(*R*,*S*)-Ketamine = 45
Muscarinic M2	Recombinant human M1-M3 expressed in Chinese hamster ovarian cells	[^{3}H]NMS	(*R*,*S*)-Ketamine = 294
Muscarinic M3	Recombinant human M1-M3 expressed in Chinese hamster ovarian cells	[^{3}H]NMS	(*R*,*S*)-Ketamine = 246
Cholinesterase	Human plasma cholinesterase	Butyrylthiocholine	(*R*,*S*)-Ketamine = 494
Opiate μ receptor	Rat brain and spinal cord	[^{3}H] Dihydromorphine	(*R*,*S*)-Ketamine 26 ± 2.7 SEM
Opiate k receptor	Rat brain and spinal cord	[^{3}H] Ethylketocyclazocine	(*R*,*S*)-Ketamine 85.2 ± 26 SEM
Opiate σ receptor	Rat brain and spinal cord	[^{3}H] N-Allylnormetazocine	(*R*,*S*)-Ketamine 66.0 ± 10.0 SEM
NE transporter	Human embryonic kidney cells	[^{3}H]Norepinephrine	(*R*,*S*)-Ketamine 66.8 ± 25.9 SD No stereoselectivity
DA transporter	Human embryonic kidney cells	[^{3}H]Dopamine	(*R*,*S*)-Ketamine 62.9 ± 2.3 SD (*S*)-Ketamine 46.9 ± 15.4 SD (*R*)-Ketamine 390 ± 34.4 SD
SE transporter	Human embryonic kidney cells	[^{3}H]Serotonin	(*R*,*S*)-Ketamine 161.7 ± 28.3 SD No stereoselectivity

(continued)

Table 2.1 (continued)

Receptor	Tissue/ substrate type	Radioligand	K_i or K_D (in μM)
D_2 receptor	Cloned human D_2 receptor expressed in Chinese hamster ovarian cells	[^{3}H]Dopamine	(*R,S*)-Ketamine 0.5 ± 0.2 SEM
5-HT_2 receptor	Rat frontal cortex	[^{3}H]Ketanserin	(*R,S*)-Ketamine 15 ± 5 SEM

Moaddel et al. (2013), Arias et al. (2006), Hirota et al. (2002), Schuh (1975), Smith et al. (1987), Nishimura et al. (1998), Nishimura and Sato (1999), Kapur and Seeman (2002)
Abbreviations: K_i inhibitory constant, K_D dissociation constant, *μM* micromolar, *NMDA* N-methyl-D-aspartic acid, *α7AChR* alpha-7 acetylcholine receptor, *NE* norepinephrine, *DA* dopamine, *SE* serotonin, D_2 dopamine receptor D_2, *5-HT*$_2$ serotonin 5-hydroxytryptamine receptor 2, *[^{3}H]* hydrogen-3 isotope, *^{125}I* iodine-125 isotope, *MK-801* dizocilpine, *NMS* N-methylscopolamine (NMS)

2.3 Ketamine: Pharmacological Activity

While ketamine is formally classified as an open-channel nonselective glutamatergic NMDAR antagonist, its pharmacological profile is complex and notable for its affinity at multiple receptors and systems (Mathew et al. 2012). In this section, we discuss the activity and pharmacological effects of ketamine in the glutamatergic, cholinergic, opioidergic, monoaminergic, and GABAergic systems.

2.3.1 Glutamatergic Activity: NMDARs

Ketamine's main antidepressant activity is thought to stem from its modulation of brain glutamate transmission. A racemate of ketamine has a K_i =1.06 μM in rat brain tissue (see Table 2.1) (Moaddel et al. 2013). While ketamine is an NMDAR antagonist, ketamine's action is understood to increase glutamatergic activity in the prefrontal cortex (PFC) (Moghaddam et al. 1997). Multiple rodent studies have shown that low, subanesthetic doses of ketamine increase glutamate outflow in the PFC (Moghaddam et al. 1997; Lorrain et al. 2003; Chowdhury et al. 2012). To understand how NMDAR antagonism increases glutamate activity, it is necessary to examine the basics of glutamatergic transmission.

Glutamate has been called the "master switch" (Stahl 2013) because it can excite a majority of CNS neurons; it is the most abundant excitatory neurotransmitter in the brain (Mathew et al. 2012). Functionally, glutamate plays critical roles in learning and memory. At the cellular level, glutamate is important for synaptic plasticity, neurodevelopment, and degeneration. It also affects neurotrophins that impact neuronal survival, development, and function (Sanacora et al. 2008). Glutamate receptors are divided into two major classes: metabotropic receptors (mGluRs), which signal via G-protein cascades, and ionotropic receptors (NMDAR, kainate, and

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)), which signal via transmembrane ion channels. When glutamate binds to NMDARs, provided that the obligatory glycine-site binding cofactor is in place, a magnesium (Mg^{+}) plug is released from the NMDAR. This leads to opening of an ion channel through which Ca^{2+} and Na^{+} flow into the cell, causing depolarization (Pittenger et al. 2007; Stahl 2013).

Ketamine binds to the PCP-binding site in the NMDAR, though with tenfold lower potency than PCP (Zukin and Zukin 1979; Vincent et al. 1979). The PCP-binding site is located within the ion channel of the NMDAR; when ketamine binds to this site, the ion channel is blocked, preventing ion influx (Mealing et al. 1999; Arias et al. 2006). Ketamine binding also acts allosterically, inducing conformational changes, which further impede ion flow (Orser et al. 1997). The resulting blockade prevents depolarization and inhibits glutamate-mediated excitation of the postsynaptic cell (Kohrs and Durieux 1998; Olney et al. 1999; Adams and Moghaddam 1998).

It is somewhat counterintuitive that ketamine-mediated NMDAR antagonism would result in increased glutamatergic activity. This increase in glutamatergic activity is related to NMDAR expression on GABAergic inhibitory interneurons. These interneurons modulate activity, particularly of pyramidal cells in the PFC, which then release glutamate (Behrens et al. 2007; Grunze et al. 1996; Lorrain et al. 2003; Milak et al. 2015; Moghaddam et al. 1997). Therefore, NMDAR antagonism on the GABAergic interneurons disinhibits downstream pyramidal cells, thereby increasing glutamatergic activity (Li et al. 2002; Grunze et al. 1996; Genius et al. 2013; Milak et al. 2015). In vitro evidence from rat hippocampus indicates that GABAergic inhibitory interneurons are approximately tenfold more sensitive to NMDAR antagonism than the downstream pyramidal neurons (Grunze et al. 1996). Other evidence indicates that NMDAR blockade decreases inhibitory postsynaptic current (IPSC) frequency and amplitude, further suggesting that GABAergic interneurons are more sensitive to NMDAR blockade than the adjacent pyramidal cells (Li et al. 2002).

Ketamine-mediated increases in glutamate activity may achieve antidepressant efficacy via multiple mechanisms. Physiological changes in cell signaling, synaptic plasticity, and circuity all occur with ketamine administration. Low-dose ketamine administration activates signaling pathways, including mammalian target of rapamycin (mTOR), and increases brain-derived neurotrophic factor (BDNF), which contributes to neuroplastic changes (Iadarola et al. 2015; Autry et al. 2011; Li et al. 2010). These signaling pathways appear to be integral for ketamine's mood modulating effects. When BDNF knockout mice receive a subanesthetic-like dose of ketamine, antidepressant-like effects in the forced swim test are minimal (Autry et al. 2011). Similarly, pretreatment with an mTOR inhibitor prevents ketamine-induced synaptic growth and dendritic spine proliferation changes (Li et al. 2010).

Ketamine-induced changes in synaptic plasticity and connectivity (Abdallah et al. 2015; Li et al. 2010; Duncan et al. 2013; Cornwell et al. 2012) include increased synaptogenesis and reversal of neuronal atrophy (Duman and Aghajanian 2012; Li et al. 2010, 2011). Low-dose ketamine elicits formation of new synaptic spines in

the PFC, mediated by mTOR signaling (Li et al. 2010). Ketamine has also been shown to increase translation of neurotrophic proteins (Autry et al. 2011) and to stimulate synaptogenesis in the PFC (Liu et al. 2012).

Finally, low-dose ketamine has been found to potentiate glutamatergic signaling in specific cortical and subcortical circuits. In patients with TRD, ketamine infusion resulted in enhanced neural responses to positive emotion in the right caudate (Murrough et al. 2015). Two PET studies in TRD found ketamine-induced changes in circuit-related regional activity. In the first, ketamine decreased activity in the habenula and insula while improvements in depression severity correlated with increased metabolism in the right superior and middle temporal gyri; conversely, clinical improvement correlated with decreased metabolism in the right parahippocampal gyrus and temporoparietal cortex (Carlson et al. 2013). In the second, improvements in bipolar depression were correlated with increased metabolism in the subgenual anterior cingulate cortex (Nugent et al. 2014). An MRI study of healthy subjects revealed that ketamine infusions decreased activity in the ventromedial PFC (an area involved in the representation of pain) and increased activity of the mid-posterior cingulate, thalamus, and temporal cortical regions (Deakin et al. 2008).

2.3.2 Cholinergic Activity: Nicotinic and Muscarinic Receptors

While ketamine's most important effects are believed to involve NMDARs, ketamine also has significant effects on the cholinergic system. These include (1) competitive inhibition at muscarinic receptors (Hirota et al. 2002; Morita et al. 1995), (2) noncompetitive inhibition at nicotinic receptors (Moaddel et al. 2013; Arias et al. 2006), and (3) activity as a cholinesterase inhibitor (Cohen et al. 1974; Schuh 1975).

Racemic ketamine inhibits muscarinic receptor types M1 ($K_i = 45$ μM), M2 ($K_i = 294$ μM), and M3 ($K_i = 246$ μM) (see Table 2.1) (Hirota et al. 2002). At M1, the most prominent muscarinic subtype in the cortex and hippocampus, ketamine is strongly inhibitory (Durieux 1995). Ketamine's inhibition at M1 receptors is believed to involve synergistic effects of the *S*(+) and *R*(−) enantiomers. Recombinant expression of rat M1 receptors in *Xenopus laevis* oocytes demonstrated *S*(+) ketamine $IC_{50} = 125$ μM, *R*(−) ketamine $IC_{50} = 91$ μM, and the 1:1 racemate $IC_{50} = 48$ μM, supporting synergistic inhibition (Durieux and Nietgen 1997). Repeated ketamine administration may also differentially impact response to ketamine. In mice, repeated administration of subcutaneous ketamine increased muscarinic receptor density but decreased behavioral response to an antimuscarinic drug, scopolamine (Morita et al. 1995). Ketamine's antimuscarinic effects are of particular interest in the context of recent findings suggesting that scopolamine may have rapid-onset antidepressant effects in humans (Furey and Drevets 2006). Much like ketamine, scopolamine has also been found to enhance signaling via mTOR, increase glutamatergic activity in the PFC, and promote neurogenesis (Voleti et al. 2013).

Ketamine is also a noncompetitive inhibitor at nicotinic acetylcholine receptors (AChR), including the α7 and α4β2 nicotinic receptor subtypes. Racemic ketamine inhibits responses to 1 mM ACh in human α7 and α4β2 nicotinic AChR expressed in *Xenopus* oocytes, with IC_{50} values of 20 μM and 50 μM, respectively (Coates and Flood 2001). Ketamine is a noncompetitive inhibitor of the α7 receptor subtype, meaning that ketamine binds away from the active site, but still inhibits the activity of the receptor. Therefore, no K_i was observed in recent experiments for α7, since K_i measures activity at the active site (Moaddel et al. 2013). There are apparent mechanistic differences in ketamine's noncompetitive inhibition between α7 and α4β2. Inhibition of α7 is not voltage dependent, suggesting that ketamine may be acting at an exposed, superficial portion of the channel lumen. Conversely, inhibition of α4β2 markedly increases with membrane hyperpolarization, suggesting that ketamine acts as an open-channel blocker at this receptor (Coates and Flood 2001).

Finally, ketamine also has slight activity as a cholinesterase inhibitor in human plasma and muscle (Schuh 1975; Arora and Meltzer 1980). Ketamine's inhibition of the cholinesterase enzyme is competitive and reversible, with $K_i = 494$ μM for human plasma (Schuh 1975). However, the in vitro concentrations of ketamine required to achieve inhibition are higher than those used clinically, even for anesthesia (Davis et al. 1997). Therefore, the in vivo concentrations resulting from low-dose ketamine treatment for depression are unlikely to result in clinically significant cholinesterase inhibition.

2.3.3 Opioidergic Activity: Mu (μ), Kappa (k), and Sigma (σ) Receptors

Ketamine also has some affinity for opioid receptors, including μ, k, and σ (Hustveit et al. 1995). In vitro binding affinity of tissue from rodent brain and spinal cord is highest at the μ receptor ($K_i = 26.8$ μM), followed by the k ($K_i = 85.2$ μM) and σ receptors ($K_i = 66.0$ μM) (see Table 2.1) (Hustveit et al. 1995); these interactions may contribute to ketamine's analgesic effects. While ketamine's affinity for opioid receptors is one to two orders of magnitude lower than its affinity for NMDARs, opioid interactions may have clinical impact. Several studies have shown that intramuscular ketamine doses of 0.5–1.0 mg/kg do provide benefit for postoperative pain (Sadove et al. 1971; Hagelin and Lundberg 1980; Mathisen et al. 1995; Schmid et al. 1999). However, it is unclear whether the analgesic effects are secondary to ketamine's activity at opioid receptors or whether analgesia is mediated predominantly by ketamine's activity at NMDARs (Hustveit et al. 1995; Finck and Ngai 1982; Smith et al. 1987). One study suggested that ketamine analgesia was mediated by activity at NMDARs rather than at the opiate receptors, but a k receptor effect could not be excluded (Hustveit et al. 1995).

2.3.4 Monoaminergic Activity: Dopamine (DA), Serotonin (SE), and Norepinephrine (NE)

Ketamine has been found to modulate monoaminergic systems. This occurs via at least three mechanisms, including (1) inhibition of monoamine reuptake transporters, (2) the downstream effects of NMDAR inhibition, and (3) direct binding at the monoamine receptors (Nishimura et al. 1998). Ketamine's inhibition of monoamine reuptake transporters, including those for DA, SE, and NE, leads to increased synaptic monoamine concentrations (Azzaro and Smith 1977; Irifune et al. 1991; Smith et al. 1981). Ketamine-mediated inhibition of monoamine transporters occurs in a dose-dependent manner. Inhibition constants in human cells were found for the DA transporter ($K_i = 62.9$ μM), the SE transporter ($K_i = 161.7$ μM), and the NE transporter ($K_i = 66.8$ μM) (see Table 2.1) (Nishimura et al. 1998).

Ketamine also enhances monoaminergic activity via the downstream effects of NMDAR inhibition. As described above, NMDARs are found on multiple types of neurons, including GABAergic interneurons. Some GABAergic interneurons tonically inhibit monoaminergic activity. Therefore, ketamine-mediated disinhibition increases monoaminergic transmitter release (Irifune et al. 1992; Tao and Auerbach 1994).

A third mechanism by which ketamine enhances monoaminergic activity is via direct binding to DA and SE receptors (Seeman and Kapur 2003; Kapur and Seeman 2002). Ketamine's affinity for the DA D_2 receptor ($K_i = 0.5$ μM) rivals its affinity for NMDARs. Similarly, ketamine's affinity for the SE 5-HT_2 receptor ($K_i = 15$ μM) is also within a clinically relevant range (Kapur and Seeman 2002). Further, ketamine was able to differentiate between the high-affinity and low-affinity state of the D_2 and 5-HT_2 receptors, suggesting potential agonist-like activity. However, the experiments were performed in vitro, and the extent to which these findings meaningfully relate to ketamine's effects in humans remains to be determined (Kapur and Seeman 2002).

2.3.5 GABAergic Activity

As discussed above, ketamine's most important effect on GABAergic activity is the antagonism of the NMDARs present on GABAergic interneurons (Gunduz-Bruce 2009; Grunze et al. 1996; Behrens et al. 2007; Coyle 2006; Moghaddam et al. 1997; Lorrain et al. 2003). Antagonism of NMDARs results in loss of tonic GABAergic inhibition, which leads to increased glutamatergic transmission (Moghaddam et al. 1997; Milak et al. 2015).

Ketamine's effects on GABA levels in the brain remain unclear; some studies suggest that GABA levels are unchanged, while others suggest that GABA levels may be increased. In rodents, single and repeated ketamine doses did not change GABA levels of the medial PFC, despite increases in extracellular dopamine and serotonin metabolites (Lindefors et al. 1997). Another magnetic spectroscopy study in humans also found that subcortical GABA levels were unchanged after ketamine

administration, although glutamate levels had increased (Stone et al. 2012). However, two proton magnetic resonance spectroscopy (^{1}H-MRS) studies have suggested that ketamine may affect GABA. Ketamine increased GABA levels in both patients with major depressive disorder (MDD) (Milak et al. 2015) and those with obsessive compulsive disorder (Rodriguez et al. 2015).

2.4 Ketamine: Clinical Pharmacology in Depression

This section will review ketamine's clinical pharmacology with regard to dosing and administration. The tolerability of ketamine will also be examined, with emphasis on the effects of subanesthetic dosages.

2.4.1 Clinical Pharmacology: Dosing and Administration

Several routes of ketamine administration have been used in depression, including IV, intramuscular, intranasal, sublingual, and oral delivery. Because of differences in bioavailability between routes of administration, each method has unique advantages and challenges.

Most trials of ketamine in MDD have been small and used a single subanesthetic dose of IV racemic ketamine 0.5 mg/kg infused over a 40-minutes period (Zarate et al. 2006; Valentine et al. 2011; Murrough et al. 2014; Berman et al. 2000). Following the success of single-dose IV trials, several repeated-dose treatments have been reported ranging from four to nine infusions in small samples ranging from 10-28 subjects. Response and remission rates varied, but some subjects reported responses lasting weeks to months (aan het Rot et al. 2010; Murrough et al. 2013a, b; Rasmussen et al. 2013; Diamond et al. 2014). Also, response to a single dose of ketamine has been reported in bipolar disorder. Importantly, single-dose ketamine does not appear to induce mania at a higher rate than placebo (DiazGranados et al. 2010; Zarate et al. 2012; Diamond et al. 2014).

Intramuscular ketamine has similar bioavailability (93 %) to IV ketamine (Clements et al. 1982). Several case series and an open-label randomized study have been conducted with intramuscular ketamine doses ranging from 0.25 to 1 mg/kg. Responses observed were similar to responses to IV ketamine, and no cystitis cases were reported (Cusin et al. 2012; Harihar et al. 2013; Chilukuri et al. 2014).

Intranasal ketamine has been used in anesthesia and found to have a favorable pharmacokinetic and pharmacodynamic profile relative to oral and rectal administration (Costantino et al. 2007). Plasma ketamine concentrations in anesthetized children suggest that intranasal ketamine's bioavailability is about 50 % (Malinovsky et al. 1996). In a blinded, randomized, controlled trial of 20 MDD patients, 50 mg of intranasal ketamine was found to elicit only mild side effects and significant

antidepressant activity within 24 hours of administration (Lapidus et al. 2014). Intranasal (*S*)-ketamine is also under investigation for MDD.

Sublingual and oral ketamine have bioavailability of about 30 % and 20 %, respectively (Lara et al. 2013; Irwin and Iglewicz 2010; Paslakis et al. 2010). Of 27 patients with MDD given variable, escalating doses of sublingual ketamine, 20 experienced antidepressant efficacy (Lara et al. 2013). An open-label study of 0.5 mg/kg/day oral ketamine in hospice patients also found significant antidepressant efficacy (Irwin and Iglewicz 2010).

2.4.2 Clinical Pharmacokinetics of Ketamine

Ketamine is water and lipid soluble. It is absorbable by IV, intramuscular, intranasal, subcutaneous, epidural, oral, and rectal routes of administration (Weber et al. 2004). Ketamine's relatively low binding capacity to plasma proteins leads to rapid brain uptake and distribution (Weber et al. 2004).

The bioavailability of ketamine varies widely based on route of administration. By definition, the bioavailability of IV ketamine is 100 %. As discussed in Sect. 2.4.1, bioavailability remains high for intramuscular administration (93 %) and decreases for intranasal (50 %), sublingual (30 %), and oral (20 %) administration (Clements et al. 1982; Malinovsky et al. 1996; Lara et al. 2013; Irwin and Iglewicz 2010; Paslakis et al. 2010). These differences in bioavailability are due to gastrointestinal absorption and first-pass metabolism. The α-elimination phase half-life is only 11 minutes, while the β-elimination phase is about 2.5 hours (Wieber et al. 1975).

Ketamine undergoes extensive hepatic metabolism. It is *N*-demethylated by cytochrome P450 enzymes in liver microsomes into NK and other metabolites (Hijazi and Boulieu 2002). The principal isoform responsible for demethylation is CYP3A4, with minor contributions by CYP2B6 and CYP2C9 (Hijazi and Boulieu 2002). NK plasma levels are about three times higher after oral administration than after IV administration. The metabolites of norketamine primarily undergo renal excretion; about 91 % of ketamine is excreted in the urine as metabolites, and 1–3 % is recovered in the feces (Chang and Glazko 1974).

The volume of distribution of ketamine ranges from 1 to 3 L/kg, with a distribution half-life of seven to 11 minutes (Wieber et al. 1975; Grant et al. 1981). Parenteral ketamine (as hydrochloride) is rapidly distributed throughout the body into widely perfused tissues, including the brain. It is likely excreted into breast milk and does cross the placenta. However, it is believed to have no clinically relevant or adverse effects on neonates (Little et al. 1972).

2.4.3 Clinical Pharmacology: Tolerability

Ketamine has been used as an anesthetic for adults and children since the 1960s and has been used in neuropsychiatric research for more than two decades (Iadarola et al. 2015). Anesthetic doses from 1 to 3 mg/kg are considered to be very safe (Wan

et al. 2015). Subanesthetic doses of ketamine (from 0.1 to 1 mg/kg) have been associated with transient side effects including neurocognitive, sensory-motor, and hemodynamic changes. A pooled data study from three different clinical trials of subanesthetic IV ketamine administration in MDD patients found that adverse effects common within the first four hours of administration included dizziness, derealization, and drowsiness. One third of all patients experienced transient hemodynamic changes. However, there were no cases of persistent neuropsychiatric sequelae, medical effects, or increased substance abuse (Wan et al. 2015).

Route of administration may also affect tolerability. While there have been multiple reports of dissociative and psychotomimetic effects of ketamine with IV and intramuscular preparations, a trial of sublingual ketamine in 27 MDD patients reported no such side effects (Lara et al. 2013). A trial of intranasal ketamine also found only small increases in dissociative symptoms (Lapidus et al. 2014).

Finally, the enantiomeric forms of ketamine may differentially affect tolerability. (*S*)-ketamine, available in Europe since 1998, appears to have tolerability advantages over its racemic mixture. In one study, 16 healthy volunteers were administered intramuscular dosages of either racemic ketamine (1 mg/kg) or (*S*)-ketamine (0.5 mg/kg). While both groups experienced the same degree of analgesia, 54 % of those who received racemic ketamine experienced anterograde amnesia, while similar effects were only noted in 8 % of those receiving (*S*)-ketamine (Pfenninger et al. 1994). In a randomized crossover study, 24 healthy young adults received subanesthetic doses of IV racemic ketamine (0.5 mg/kg), (*S*)-ketamine (0.25 mg/kg), and (*R*)-ketamine (1 mg/kg); (*S*)-ketamine had less impact on concentration and memory than racemic ketamine or (*R*)-ketamine (Pfenninger et al. 2002).

2.5 Conclusion

Understanding of ketamine's basic and clinical pharmacology has grown rapidly since the first study of ketamine in depression, reported 15 years ago. The bulk of ketamine's antidepressant activity is believed to stem from its impact on brain glutamatergic activity. Increased glutamatergic activity occurs via ketamine's antagonism of NMDARs, which are heavily expressed on inhibitory neurons. When ketamine acts on these GABAergic neurons, glutamate activity increases. Changes in glutamate activity affect brain signaling, synaptic plasticity, and connectivity. Ketamine's pharmacological activity in other systems may also contribute to its efficacy; these systems include the cholinergic, opioidergic, monoaminergic, and GABAergic systems. Because ketamine is both water and lipid soluble, multiple dosing routes of ketamine administration are available; these include IV, intramuscular, intranasal, sublingual, and oral routes. Ketamine is hepatically metabolized via multiple cytochrome P450 isoforms and is renally excreted. It is generally well tolerated clinically. Ketamine's putative antidepressant effects, their rapid onset after administration, and ketamine's apparent efficacy in cases of TRD suggest this may be a paradigm-shifting therapy. While still experimental, early evidence of NMDAR antagonism, as well as ketamine's action at other receptors, suggests novel

antidepressant mechanisms and provides inspiration for further research that may offer new therapeutic possibilities.

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Chapter 3
Ketamine: Clinical Studies in Treatment-Resistant Depressive Disorders

Pierre Blier and Jean Blier

Abstract Since the first report of a robust antidepressant effect of a sub-anesthetic dose of ketamine in 2000, studies have repeatedly confirmed its therapeutic benefits in major depressive disorder (MDD) as well as in depressive episodes in patients with bipolar disorder (BD). Two features of the antidepressant response to ketamine make it striking: first, it can manifest itself within minutes or hours after the transient and generally mild dissociation has disappeared and, second, it has mostly been shown to take place in treatment-resistant patients. The response rate—which is an improvement of 50 % or more—has generally been around 50 % in placebo-controlled studies. Due to the obvious mild dissociative effects of ketamine, low doses of the benzodiazepine midazolam have been used in an attempt to preserve the blind; under such conditions the antidepressant action of ketamine has been confirmed. The main drawback of ketamine is that its antidepressant effects generally do not last more than one week. Several studies have, however, shown that repeated administration can maintain and prolong the response. Finally, clinical experience using repeated administration of ketamine has thus far revealed no significant adverse events; in addition, no tachyphylaxis to the benefits of ketamine in MDD is apparent.

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3.1 Introduction

The treatment of major depressive episodes is an arduous task for clinicians for several reasons. First, although patients may have been ill for weeks or months, it is often a professional or social crisis that prompts the consultation. In this context, all antidepressant medications are plagued by a delayed onset of action of at least two weeks, making rapid relief an unachievable necessity. Second, upon an initial trial, a mere third of patients will typically achieve remission, thus leaving the majority to go through additional treatment options (i.e., switches and combinations) without the benefit of having predictors of response (Rush et al. 2006). Although steps can be taken to accelerate the implementation of such subsequent strategies (Blier 2013), many patients have to go through numerous time-consuming trials before a successful combination is achieved. As time passes, chances of achieving remission diminish (Keller et al. 1992). Although several factors may account for this, depression is known to exert deleterious effects on the brain and other organ systems, for instance, through increased inflammatory mediators (Anisman 2009). Hopelessness grows over time, putting patients at greater risk of engaging in suicidal behaviors. When suicide becomes imminent, a common approach is hospitalization and electroconvulsive therapy (ECT), which still encompasses delays. Even if remission is achieved after a few trials, relapses are frequent and subsequent episodes may become more difficult to treat.

The availability of a therapeutic agent that has the potential to overcome the abovementioned drawbacks has been long awaited. In 2000, a first report of the antidepressant action of a sub-anesthetic dose of ketamine occurring within a few hours, albeit in a small sample of patients, was a landmark paper in the field of mood disorders research (Berman et al. 2000). This chapter provides a broad overview of the clinical studies published until early 2016 that used racemic ketamine and its *S*-enantiomer (Table 3.1). Both controlled trials and some open-label studies of ketamine will be reviewed to support the strategy and highlight both benefits and drawbacks. Additionally, some practical aspects for the use of ketamine will be considered.

3.2 Placebo-Controlled Studies of Ketamine

The first study by Berman and colleagues (2000) used a dose of 0.5 mg/kg infused intravenously over 40 minutes in a randomized, crossover, double-blind design in eight patients with major depressive disorder (MDD) and one patient with bipolar disorder. It is important to mention here that it is almost impossible to maintain the blind as ketamine under such conditions produces mild but clear dissociation symptoms that generally peak within 15 minutes in the vast majority of individuals. They also fade away in most cases within the same time frame following the end of the infusion. To date, there is no placebo-type medication that can mimic the same effects as ketamine. In the report by Berman and colleagues, six patients

Table 3.1 Summary of placebo-controlled studies that assessed the antidepressant effect of ketamine or esketamine administered intravenously or intranasally, respectively, in 345 treatment-resistant patients

Study	Sample size	Design	Ketamine regimen	Response: 50 % decrease
Berman et al. (2000)	8 MDD 1 bipolar	Crossover	0.5 mg/kg, iv, 40 minutes	50 % vs 17 % 4 hours to 3 days
Zarate et al. (2006)	18 MDD	Crossover	0.5 mg/kg, iv, 40 minutes	56 % vs 10 % 24 hours
Diazgranados et al. (2010)	18 bipolar	Crossover	0.5 mg/kg, iv, 40 minutes	56 % vs 0 % 40 minutes 44 % vs 0 % 24 hours
Zarate et al. (2012)	15 bipolar	Crossover	0.5 mg/kg, iv, 40 minutes	64 % vs 5 % 40 minutes 43 % vs 1 % 24 hours
Murrough et al. (2013a, b)	72 MDD	Parallel midazolam: 0.045 mg/kg 40 minutes	0.5 mg/kg, iv, 40 minutes	64 % vs 28 % 24 hours
Sos et al. (2013)	30 MDD	Crossover	0.27 mg/kg in 10 minutes 0.27 mg/kg next 20 minutes	37 % vs 4 % 24 hours
Lapidus et al. (2014)	20 MDD	Crossover	50 mg intranasal	44 % vs 6 % 24 hours
Singh et al. (2015)	30 MDD	Parallel	0.2 or 0.4 mg/kg, iv, 40 minutes	67, 64 % vs 0 %, 24 hours
Daly et al. (2015)	67 MDD	Parallel	28, 56, 84 mg esketamine intranasal 2/week × 2 weeks	38, 36, 50 % vs 10 %, day 15
Li et al. (2016)	48 MDD	Parallel	0.2 and 0.5 mg/kg, iv, 40 minutes	38, 25 % vs 0 % 40 minutes 38, 25% vs 19% 4 hours
Lenze et al. (2016)	20 MDD	Parallel	0.6 mg/kg/hours iv × 96 hours or 0.5 mg/kg, iv × last 40 minutes	70 % on CGI 24 hours

MDD major depressive disorder, *CGI* Clinical Global Impression scale

had a 50 % decrease in their Hamilton Depression Rating Scale (HAM-D; from a severe intensity range) three days after ketamine, with an overall significant effect documented four hours after the infusion that increased over the following 72 hours. The mean decrease in baseline HAM-D scores was 13 points, and core symptoms of depression were significantly attenuated. The crossover was done one week apart with some residual but nonsignificant effects when ketamine was administered first. Obviously, the clinician-administered HAM-D is not an ideal

scale to detect short-term changes in MDD and may misrepresent improvement as, for instance, the three sleep items have to be prospectively carried forward for assessments on the day of the infusion. The self-rated Beck Depression Inventory (BDI) yielded similar results as the HAM-D between baselines until day three postinfusion. Despite the abovementioned limitations of this study, these observations made by an established research team were truly groundbreaking.

A first replication was published by a different group six years later using an identical design in a sample of 18 patients with MDD (HAM-D 21 ≥ 18) who were treatment-resistant but medication-free for the study period (Zarate et al. 2006). Similar results as in the first report were observed: ketamine produced mild transient side effects, had an onset of antidepressant action after 80 minutes, the beneficial effect peaked after one day (12 patients had a 50 % decrease in symptoms; five patients met remission criterion), and the beneficial action faded within seven days. The same investigators carried out two similar studies in patients with bipolar I or II disorders ($n = 18$ and $n = 15$, respectively) who were maintained on lithium or valproate, using a week crossover period (Diazgranados et al. 2010; Zarate et al. 2012). In the first study, seven out of 16 patients had responded after 24 hours, and five had remitted. In the second study, six out of 14 patients responded, and four remitted. The antidepressant effect faded within seven days in nearly all patients.

In an attempt to maintain the blind when using ketamine, a third group of investigators from two sites used the benzodiazepine midazolam (0.045 mg/kg also over a 40-minutes iv infusion) in a parallel design with medication-free, treatment-resistant patients randomized in a 2:1 ratio (Murrough et al. 2013a). The onset of action of ketamine was rapid, as reported in previous studies. After 24 hours, 30 of 47 patients had responded to ketamine, whereas seven of 25 had responded (≥50 %) to midazolam, as assessed via the Montgomery-Asberg Depression Rating Scale (MADRS). In addition, 25 of 47 and of 25 had a Clinical Global Impression (CGI) rating scale score of 1 or 2 out of 7 (CGI; 1 = not ill at all and 2 = minimally ill). Although midazolam produced more benefit than the saline infusion that had been used previously, ketamine still produced a rapid and robust antidepressant effect in treatment-resistant MDD patients.

The three controlled studies thus far reviewed in MDD patients were carried out without antidepressants. Sos and colleagues (2013) studied 30 hospitalized patients with moderate levels of depression (mean MADRS score 20–25) who maintained their medication regimen. The mode of administration of ketamine was slightly different than in the other studies: there was a loading dose of 0.27 mg/kg for the first 10 minutes and another 0.27 mg/kg over the next 20 minutes. Ten of 27 patients responded to ketamine, and one of 19 to placebo based on a 50 % decrease on the MADRS.

A recent brain imaging study used two doses of intravenous ketamine (0.2 and 0.5 mg/kg over 40 minutes) and placebo in a sample of 48 randomized individuals with treatment-resistant depression, with some patients having comorbidities such as panic disorder and social phobia (Li et al. 2016). Although there was a significantly greater number of responders 40 and 80 minutes postinfusion in the low and higher ketamine groups, the difference was no longer significant compared to placebo at the four hour time point: four out of 16, six out of 16, and three out of 16, respectively.

Another randomized, controlled, blinded study in 20 patients used the standard 0.5 mg/kg intravenous dose of ketamine over 40 minutes (Lenze et al. 2016). All patients received an infusion for 96 hours: half received a saline solution for 95 hours and 20 minutes and ketamine for the last 40 minutes, and 10 received a 96-hours ketamine infusion of 0.6 mg/kg/h. This prolonged infusion was used to reproduce the conditions under which ketamine is sometimes used to treat chronic pain. The patients had MDD that was highly treatment-resistant (between seven and 31 failed trials), and they were nearly all markedly ill with a mean MADRS score above 30. Clonidine was administered to minimize increases in blood pressure and the psychotomimetic effects of ketamine. Positive symptom scores on the Brief Psychiatric Rating Scale (BPRS) peaked at day three in the group that received the constant infusion of ketamine but were of the same magnitude as in the 40-minutes infusion group. The therapeutic benefit was similar in both groups on postinfusion day 1, with seven of 10 patients have a CGI score in the much or very much improved range.

Two studies have now investigated the effects of ketamine administered intranasally: one with a dose of 50 mg of racemic ketamine and one with the *S*-enantiomer, which has a higher affinity than the *R*-enantiomer for the phencyclidine binding site of the N-methyl-D-aspartate (NMDA) receptor (Vollenweider et al. 1999). In the first study, the 18 patients had failed, on average, four medication trials and had a mean MADRS score of 30 (Lapidus et al. 2014). The onset of action was detectable 40 minutes after the administration of ketamine; after 24 hours, eight of 18 patients responded to ketamine, and one of 18 to placebo. Minimal dissociative or psychotomimetic symptoms were noted without a significant difference between the saline and ketamine sprays. These results are interesting as they were obtained with lower plasma levels of ketamine than in the prior studies using the intravenous route (at 40 minutes: 84 intranasally vs. 200 ng/ml intravenously), likely with a better preservation of the blinding procedure.

The study with intranasal *S*-ketamine enrolled 67 patients with treatment-resistant depression while maintaining their antidepressant regimen in a 3:1:1:1 ratio in four groups (placebo, 28, 56, and 84 mg) and were treated twice in one week (Daly et al. 2015). The two higher doses were selected in order to match the plasma levels achieved with the standard 0.5 mg/kg intravenous dose of ketamine. After one week, 28 placebo patients who were still ill were re-randomized to placebo or to one of the three doses of *S*-ketamine. At day eight, the response and remission rates were: (1) placebo: 10 % response and 10 % remission, (2) 28 mg dose: 38 % response and 13 % remission, (3) 56 mg dose: 36 % response and 27 % remission, and (4) 84 mg dose: 50 % response and 40 % remission. There was an extension period in this study that will be discussed later.

In summary, there are now 11 controlled studies involving 345 patients that have examined the antidepressant action of intravenous or intranasal (with determination of plasma levels) ketamine in patients with treatment-resistant depression under fairly similar conditions. While the blind is nearly impossible to maintain when using ketamine, it is important to emphasize that its therapeutic effect has consistently been documented in treatment-resistant patients. Indeed, this group of patients typically presents low placebo responses, especially in academic centers where most of the abovementioned trials were carried out (Dunlop et al. 2012).

3.3 Open-Label Reports on the Efficacy of Ketamine

Since the initial report in 2000 investigating the antidepressant effect of ketamine in depression, there have been numerous case reports and case series supporting the benefits of ketamine in treatment-resistant depression. It is not possible, however, to rely on such reports to further determine response or remission rates as there may be a publication bias in favor of positive data. It is beyond the scope of this chapter to review these publications exhaustively, but such papers have been included in recent literature reviews (Newport et al. 2015; Kishimoto et al. 2016; Xu et al. 2015). Two of these reviews also summarize the effects of non-NMDA receptor antagonists and provide odds ratios of response to ketamine. Nevertheless, it is important to mention that ketamine infusions can be efficacious even in patients who did not respond to ECT (Ibrahim et al. 2011).

3.3.1 Repeated Administration of Ketamine

The evidence supporting the acute antidepressant effect of ketamine is overall compelling. In addition, several reports show a robust decrease in suicidal ideation, thus rendering this strategy all the more clinically relevant. This issue is covered in detail in Chapter 4 of this book. Nevertheless, it is also clear that the antidepressant effect of a single administration of ketamine is limited to about seven days in the vast majority of patients. Several groups have examined whether the benefits of ketamine could be extended with repeated administration. These reports are discussed in order of appearance in the literature (Table 3.2).

Murrough and colleagues (2013b) used a thrice-weekly infusion regimen of ketamine (0.5 mg/kg, iv) for two weeks in 24 treatment-resistant patients after a washout of their medication (10 of these patients had been reported in a prior publication; aan het Rot et al. 2010). Responders ($n = 17$) presented a sustained response throughout the weeks, finishing the infusion period with a mean MADRS score below 10 (mean baseline MADRS = 32), whereas nonresponders showed no improvement with repeated administration. Response after two hours of the first infusion, or lack thereof, was a strong predictor of the two-week outcome. The median time to relapse was 18 days, and four patients did not relapse up to the end of study (day 83). Only three participants received psychotropic medications during follow-up.

Serial infusions of up to four infusions of the standard dose of ketamine—but over a 100-minutes period—produced remission (MADRS ≤ 10) in five of 10 patients who maintained their medication regimen (Rasmussen et al. 2013). Two patients sustained their remission over a four-week period. In that study, ketamine infusions were not repeated if patients achieved remission; one to four infusions were used, indicating that there was an incremental effect in some patients.

In another study of six patients with bipolar disorder and 22 with MDD taking an average of 3.2 psychotropic medications, three or six infusions were carried out over

Table 3.2 Summary of open-label studies assessing the antidepressant effect of repeated ketamine administration in 124 patients with treatment-resistant MDD

Study	Sample size	Ketamine regimen	Response	Duration of response
Murrough et al. (2013b)	24	0.5 mg/kg, iv, 40 minutes	71 %	Median time to relapse: 18 days; probability of no relapse: 0.25 at day 83
Rasmussen et al. (2013)	10	0.5 mg/kg, iv 100 minutes	50 %[a] 40 % remission	Two patients: no relapse after four weeks
Diamond et al. (2014)	28[b]	0.5 mg/kg, iv 40 minutes	29 % 11 % remission	4 patients > 25 days 2 patients > 84 days 2 patients > 165 days
Shiroma et al. (2014)	14	0.5 mg/kg, iv 40 minutes	92 % 67 % remission	Mean time to relapse: 16 days; No relapse after four weeks in five patients
Cusin et al. (2016)	14[c]	0.5 mg/kg, iv 40 minutes	42 % 17 % remission	4 of 5 patients relapsed after two weeks
Daly et al. (2015)	34	56 or 84 mg esketamine intranasal 1/week × 2 weeks 1/2 weeks × 4 weeks	65 % 32 % remission	56 % after eight weeks

[a]Responders had a lower daily dose of benzodiazepines than nonresponders
[b]Six patients were taking benzodiazepines
[c]Eight patients were taking benzodiazepines

17 days (Diamond et al. 2014). Of the eight responders, only three responded within six hours after the first infusion, and the remaining individuals' response developed by the third infusion. The duration of the response from the final infusion lasted between 25 and 168 days (median: 70). The buildup of the therapeutic response after the initial infusion of ketamine was observed in another study of 14 patients that used the thrice-weekly regimen for two weeks (Shiroma et al. 2014). Three patients responded and one remitted after one infusion, while 11 responded and eight remitted at the end of the two-week treatment period. The mean time to relapse was 16 days, and five of 11 responders maintained their status for four weeks. Another 14 patients were included in a two-step repeated dose ketamine augmentation over three weeks, whereby the first three doses were administered over 45 minutes at a 0.5 mg/kg intravenous dose and the next three at 0.75 mg/kg (Cusin et al. 2016). Only one of 14 patients responded after three infusions, and five of 12 completers responded after six infusions with one patient remitting. One patient maintained response after 14 days.

Finally, the study described above using intranasal *S*-ketamine had an open-label prolongation phase (Daly et al. 2015). Treatment session frequency was reduced from twice weekly in the acute phase to once weekly for three weeks and then every other week for the next four weeks. From the data available at day 74, 22 of 34 patients were responders and 11 were remitters. Following cessation of the five-ketamine

inhalations, a two-month follow-up showed that 23 of 41 patients were still responders, while 17 were remitters.

Taken together, these results indicate that some patients may benefit from serial ketamine infusions even if they did not have a marked response to a first treatment. This is consistent with observations from an ongoing study that uses the thrice-weekly regimen for two weeks (Phillips et al. 2016). In addition, these patients go on to receive an additional four weekly infusions over one month if they responded to the prior six infusions.

An important feature of the ketamine response is that there is presently no evidence that tachyphylaxis develops over time. In the six abovementioned studies, patients either sustained or increased their response to ketamine. Similarly, over the last four years in the Mood Disorders Research Unit at The Royal's Institute of Mental Health Research, there have been patients who have had numerous ketamine infusions while attempting to find a pharmacological strategy to sustain response, without evidence of a loss of response. For instance, in an early report (Blier et al. 2012), a patient presented the same favorable response to over 50 infusions before she was referred for deep-brain stimulation. This invasive procedure was ineffective. She responded again to serial ketamine infusions for another 50 infusions at various intervals, and the effectiveness has recently been able to be prolonged with the addition of 80 mg/day of levomilnacipran.

3.4 Clinical Response and Psychotomimetic and Dissociative Side Effects

Given that ketamine exerts significant side effects, it is possible that the clinical improvement is somewhat mechanistically related. Indeed, in an analysis of 108 patients who received ketamine (Luckenbaugh et al. 2014), there was a significant correlation between the Clinician-Administered Dissociative States Scale (CADSS) score immediately after the infusion and percent change in HAM-D scores at 230 minutes and day seven postinfusion ($r=0.35$ and 0.41, respectively), but not at day one ($r=0.21$). Sos and colleagues (Sos et al. 2013) also reported a 0.40 correlation between these variables. Since the optimal dose of ketamine has not been established, it is difficult to directly link the issue of dissociative side effects and clinical benefits. In addition, the correlation coefficients are not very high, and looking at the scattering of the data points, there are clearly several outliers, thus shedding doubt on this interpretation. Since ketamine is given on a mg/kg basis and not on ideal body weight, patients with higher BMIs received a greater absolute amount of ketamine and, therefore, may have had more dissociative side effects. In order to fully understand this correlation, it will be important in the future to report the BMI of patients if ketamine is given on a mg/kg basis.

3.5 Unanswered Questions Regarding the Clinical Use of Ketamine

Given the state of the literature on ketamine use in MDD, there are obviously several areas that need further investigation. These include optimal doses and regimens, routes of administration, eventual toxicity with long-term administration, and ideal medications most likely to sustain the benefits. With regard to toxicity, the field should be prudent and diligent but not alarmist, as ketamine has been used for decades as an anesthetic agent worldwide because it does not depress cardiovascular and respiratory parameters. Furthermore, it is still in routine use in pediatric emergency rooms and in ECT suites. Importantly, sub-anesthetic doses are currently being used at intervals that allow complete elimination between infusions. Ketamine has had bad press in the media because it is a drug with abuse potential and has led to medical complications such as interstitial cystitis. It is important to mention that studies using ketamine for depression have largely excluded patients with a significant history of drug abuse. In addition, the urinary complication often requiring surgery has been reported in individuals taking massive repeated doses of oral ketamine (16 g/week; Yee et al. 2015), which can lead to accumulation of metabolites. Finally, the purity of abused drugs from illicit sources should be questioned.

On a more positive note, one can wonder if ketamine could accelerate the therapeutic response of standard antidepressant medications. A recent study explored this possibility by using a single intravenous infusion of ketamine vs. placebo in 30 patients with MDD receiving open-label, minimal effective dose escitalopram for four weeks (Hu et al. 2016). There was evidence for an accelerated onset in the first two weeks but not after four weeks. While this difference may not be worth the investment-benefit ratio, it may be valuable to examine rapidly titrated antidepressant combinations in patients presenting with significant suicidal ideation. Indeed, a low dose of ketamine (0.2 mg/kg, iv) given in a bolus was reported to markedly attenuate suicidal ideation in an emergency room setting (Larkin and Beauclair 2011).

Thus far, there is no evidence for any antidepressant medication producing adverse events during ketamine infusion. However, there is clinical experience indicating that benzodiazepines can dampen or even prevent the antidepressant action of ketamine (Frye et al. 2015; Ford et al. 2015; see Table 3.2). This clinical observation supports the theory that ketamine may act by blocking NMDA receptors on gamma-aminobutyric acid (GABA) neurons (Zarate and Niciu 2015). A current trial requests that patients abstain from using benzodiazepines at least 12 hours prior to ketamine infusion (Blier 2013). This precaution should be considered when devising clinical trials, and clinicians must be aware of this peculiarity when using ketamine for depression.

3.6 Closing Remarks

It is obvious in 2016 that the therapeutic activity of ketamine in mood disorders is groundbreaking, as supported by clinical studies in the last 10 years. Unfortunately, there was a time lag of several years before attempts to verify the first claim of efficacy were initiated. The specter of its abuse potential, the necessity of using the intravenous route to administer the medication, and the fact that ketamine belonged to another specialty field all likely prevented the field of psychiatry from moving ahead promptly. These hurdles in fact are still deterrents even for some of our colleagues to initiate their research using ketamine in academic centers. The involvement of the pharmaceutical industry is now accelerating the development of this new therapeutic avenue. Furthermore, it will be interesting to determine whether ketamine nonresponders could respond to agents targeting other elements of the NMDA receptor, such as the glycine site (i.e., rapastinel; Burch et al. 2016).

Considering the risk-benefit ratio for the use of ketamine in depressive disorders, there is now sufficient clinical evidence in favor of its use in severely ill patients who have been assessed by an experienced clinician as a bridge strategy to other antidepressant treatments and when carried out in a medically supervised environment. Nevertheless, with the advent of such rapid-acting medications, whether it is some form of ketamine or other agents acting through similar mechanisms, clinicians will have to be vigilant and educate patients so that punctual use of a rescue strategy does not impair the assiduous maintenance treatment of mood disorders.

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Chapter 4
Ketamine and Suicide Risk

Elizabeth D. Ballard and Rebecca B. Price

Abstract Suicide is a psychiatric emergency, and there are limited pharmacological options to treat acute risk. Recent findings that intravenous ketamine is associated with reductions in suicidal thoughts have fueled interest in ketamine as an antisuicidal agent. The initial data on ketamine and suicide are promising but have not reached the level and rigor of the ketamine and depression literature (which itself is not conclusive). Existing evidence suggests ketamine has a beneficial effect on suicidal thoughts, but additional randomized trials are needed to substantiate this pattern, particularly among samples selected for high suicide risk. Future directions for the field include potential mechanisms or biomarkers of response, clinical correlates, and the relationship of ketamine to suicidal behaviors such as suicide attempts and death by suicide.

4.1 Suicide as a Psychiatric Emergency

Over 40,000 Americans killed themselves in 2014 (Centers for Disease Control and Prevention 2016). Worldwide, it is estimated that one million individuals kill themselves each year (World Health Organization 2014). Even more prevalent is suicidal behavior that does not end in death; there are an estimated 400,000 emergency

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department (ED) visits for suicide-related reasons each year (US Consumer Product Safety Commission). In the United States, the suicide rate has not declined for the last five decades (National Action Alliance for Suicide Prevention 2014), underscoring the importance of better understanding and treating suicide risk.

One possible reason for the relatively stable rates of death by suicide is the dearth of effective treatments specifically targeting suicide risk. As of the writing of this chapter, only one medication is FDA-approved for suicide risk: clozapine, which is specifically indicated for reducing suicide risk in individuals with schizophrenia (Griffiths et al. 2014). The evidence around the ability of selective serotonin reuptake inhibitors (SSRIs) to decrease suicidal thoughts and behaviors is mixed (Leon et al. 2014), and controversies surrounding SSRIs and increased suicide risk, particularly in children and adolescents, may have led to decreased rates of antidepressant prescriptions (Libby et al. 2007; Valuck et al. 2007). Paradoxically, these reductions in antidepressant prescriptions may have led to increased rates of suicide (Lu et al. 2014) due to an increase in untreated depression—a pattern that further highlights the need for additional treatment options with unambiguous effects on suicide risk. There are some indications that other interventions such as electroconvulsive therapy (ECT) and lithium may have antisuicidal properties, but randomized clinical trials (RCTs) of the specific impact of these interventions on suicide risk have not yet been published (Griffiths et al. 2014), leaving uncertainty regarding their clinical efficacy in suicide prevention. In the psychotherapy literature, both dialectical behavior therapy (DBT) and cognitive behavioral therapy (CBT) for suicide prevention have been associated with robust reductions in the rate of suicide attempts (Linehan et al. 2006; Brown et al. 2005). However, these treatments are difficult to disseminate, necessitating intensive training on the part of clinicians, and are generally expected to take from three to 12 months for benefits to emerge.

In their Prioritized Agenda for Suicide Prevention, the National Action Alliance for Suicide Prevention highlighted the importance of developing more effective biological treatments for suicidal individuals. Specifically, their agenda includes two aspirational goals related to this topic: (1) *Ensure that people who are thinking about suicide but have not yet made a suicide attempt receive interventions to prevent suicidal behavior* and (2) *Find new biological treatments and better ways to use existing treatments to prevent suicidal behavior* (National Action Alliance for Suicide Prevention 2014). An ideal way to meet each of these aspirational goals may be to identify biological agents exhibiting both specific antisuicidal properties and a rapid time course of therapeutic onset, thus capable of providing immediate relief that rapidly removes the impetus to engage in suicidal acts.

Ketamine, an N-methyl-D-aspartate (NMDA)-receptor antagonist, may be a potential intervention that meets each of these criteria. While the bulk of the research to date has focused on ketamine's rapid antidepressant effects (Zarate et al. 2006, 2012; Berman et al. 2000; Murrough et al. 2013), there has been increasing attention to the potential impact of ketamine on suicidal thoughts. A distinctive characteristic of interventions such as ketamine is the speed with which the antidepressant (or antisuicidal) effects are detected. Most of the currently used treatments for suicide risk, both pharmacologic and psychotherapeutic, require weeks to months to take

full effect. In contrast, ketamine's effects are observed within minutes to hours. The burgeoning literature around ketamine and suicide, while not conclusive, suggests new directions for understanding the rapid treatment of suicide risk. Over the course of this chapter, the research literature on ketamine and suicidal thoughts will be reviewed, including clinical trials and potential biomarkers/mechanisms of action. Future directions for the field will be suggested in the interest of advancing research into this area as well as providing more effective treatments to vulnerable patients.

4.2 Research Evidence for Ketamine and Suicidal Ideation

The research evidence for ketamine and suicidal ideation currently includes case reports, open-label trials, and RCTs with saline or midazolam placebo. Most of these trials were conducted in individuals with major depressive disorder (MDD) or bipolar disorder (BD), although Murrough and colleagues' recent RCT using patients selected for suicidal thoughts may represent the next stage of this research (Murrough et al. 2015). At the time of writing, a search on clinicaltrials.gov with the search terms "suicide" and "ketamine" yielded 16 trials, which suggests that the research literature in this area will only grow. Table 4.1 depicts the published research evidence of ketamine and suicidal thoughts. All ketamine infusions were intravenous at 0.5 mg/kg over 40 minutes unless otherwise stated.

Price and colleagues published the first analysis of suicidal thoughts in a study of 26 patients with treatment-resistant depression who received open-label ketamine (Price et al. 2009). Using the suicide item from the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979), a single subanesthetic dose of ketamine was associated with a significant reduction in suicidal thoughts at 24 hours. A subsample of these patients ($n=9$) received repeated doses of ketamine over 12 days, with maintained effects of reduced ideation. In another open-label trial of ketamine in 33 patients with treatment-resistant MDD (DiazGranados et al. 2010), suicidal ideation on the suicide item from the MADRS, Hamilton Depression Rating Scale (HAMD) (Hamilton 1960), and Beck Depression Inventory (BDI) (Beck and Beamesderfer 1974), as well as the full-item Scale for Suicide Ideation (SSI) (Beck et al. 1979) were all significantly decreased at 230 minutes postketamine infusion. Assessments of anxiety and hopelessness also decreased over this time frame. Similar results were found in another sample of patients with treatment-resistant depression in India, with reductions in suicidal ideation at the 230-minutes time point as measured by the SSI and HAMD; unlike previous studies, however, results were not maintained at Day 1 (Thakurta et al. 2012).

In a naturalistic, open-label study in an emergency department setting, 14 depressed patients with suicidal ideation received intravenous push low-dose ketamine (0.2 mg/kg) (Larkin and Beautrais 2011). Suicidal ideation as measured by the MADRS suicide item was reduced at 230 minutes, and results were maintained for up to 10 days of daily follow-up. Additionally, there has been a case report of ketamine infusion in a suicidal patient with intent and plan to kill herself

Table 4.1 Clinical trials of ketamine and suicidal ideation

Author	Patient sample	Design	Findings
Randomized controlled trials			
Zarate et al. (2012)	15 patients with BD I or II	Crossover, randomized trial of ketamine compared to saline placebo	Significant difference at 230 minutes, which was sustained up to Day 3, as assessed via MADRS suicide item
Price et al. (2014)	51 patients with treatment-resistant MDD	Parallel randomized control trial of ketamine compared to midazolam	Significant difference at 24 hours, compared to midazolam, on a composite score of suicidal ideation
Murrough et al. (2015)	24 patients with mood or anxiety disorders and suicidal ideation	Parallel, randomized trial of ketamine compared to midazolam	No significant difference between groups at 24 hours, but difference emerged at 48 hours using the BSS. Significant difference at 24 hours on the MADRS suicide item
Open label			
Price et al. (2009)	26 patients with treatment-resistant MDD	Open label, a subset of responders to ketamine received repeated doses	Significant reduction from baseline at 24 hours on the MADRS suicide item; reductions sustained for 12 days in those receiving repeated doses
DiazGranados et al. (2010)	33 patients with treatment-resistant MDD	Open label	Significant reduction from baseline at 230 minutes on the SSI, the HAMD suicide item, the MADRS suicide item, and the BDI suicide item
Larkin and Beautrais (2011)	14 patients with MDD and suicidal ideation	Open label of intravenous push low-dose ketamine (0.2 mg/kg)	Significant reduction from baseline at 240 minutes, which was sustained up to 10 days, using the MADRS suicide item
Thakurta et al. (2012)	27 patients with MDD	Open label	Significant reduction from baseline at 230 minutes using the SSI and the HAMD suicide item. Change was not maintained at 24 hours
Case reports			
Zigman and Blier (2013)	One patient with MDD and suicidal ideation		Mood benefits lasted eight days and intense suicidal thoughts did not return for a month
De Gioannis and De Leo (2014)	Two patients with MDD/BD and suicidal ideation	Oral solution of ketamine 100/mg/ml, starting at 0.5 mg/kg	Reduction in suicidal ideation at 24 hours, maintained with repeated doses over months

Abbreviations: BD bipolar disorder, *MDD* major depressive disorder, *SSI* Scale for Suicide Ideation, *HAMD* Hamilton Depression Rating Scale, *MADRS* Montgomery-Asberg Depression Rating Scale, *BDI* Beck Depression Inventory, *BSS* Beck Scale for Suicide Ideation.

(Zigman and Blier 2013); her suicidal thoughts were reduced within 40 minutes of the infusion, and this mood effect was maintained for eight days. The patient reported that her intense suicidal thoughts did not return for a month after the ketamine infusion. Another case report described the use of an oral ketamine solution (100 mg/ml) administered in two patients with depression and suicidal thoughts. These doses started at 0.5 mg/kg and were gradually increased to 3 mg/kg in one patient and 1.4 mg/kg in the other. Suicidal ideation, as measured by the MADRS suicide item, was reduced within 24 hours, and effects were maintained by repeated administrations over the next few weeks (De Gioannis and De Leo 2014).

In a double-blind, randomized, crossover, placebo-controlled trial of 15 patients with BD I or II currently in a depressive phase, Zarate and colleagues found a reduction in suicidal ideation after ketamine infusion (Zarate et al. 2012). There was a two-week lag between placebo infusions of saline and ketamine infusions. Ketamine was associated with reductions in suicidal ideation from 40 minutes to three days after the infusion on the MADRS suicide item. Using the HAMD suicide item, there were lower suicidal ideation scores from 40 to 80 minutes and at Day 2. Using the BDI suicide item, there was a significant difference from 40 minutes through Day 2. In another randomized, parallel trial of ketamine as compared to a midazolam placebo, reductions in suicidal ideation were found in a sample of 57 patients with treatment-resistant depression (Price et al. 2014). Suicidal ideation was measured by a composite of the self-reported Beck Scale for Suicide Ideation (BSS) (Beck and Steer 1991), the MADRS suicide item, and the Quick Inventory of Depressive Symptomatology (QIDS) suicide item (Rush et al. 2003). Significant reduction on the suicide ideation composite was found with ketamine compared to midazolam at 24 hours after the infusion.

Finally, Murrough and colleagues published an RCT of ketamine in patients selected for suicide risk (Murrough et al. 2015). Specifically, inclusion was limited to patients with suicidal ideation (defined as a score of four or more on the MADRS suicide item) and mood/anxiety spectrum disorders. Patients were randomized to ketamine or midazolam placebo, and the first assessment occurred at 24 hours (Day 1). Using the BSS as the primary outcome measure, there was no significant difference between the two groups at Day 1, but an effect for ketamine emerged at Day 2; it is not known whether there was a rapid effect at 230 minutes postinfusion. However, using the MADRS suicide item, an effect for ketamine was found on Day 1, which was reduced to trend level on Day 2. Ketamine was also associated with reduced irritability and panic but not reduced anxiety, mania, or insomnia.

In sum, the research evidence for the efficacy of ketamine on suicidal thoughts is growing but not conclusive. Studies to date have methodological limitations including small sample sizes and the possibility of bias due to the lack of control group in most studies, as well as the potential for inadequate blinding among RCTs (see Murrough et al. 2013). Although existing findings are fairly consistent in suggesting a rapid reduction in suicidal ideation following ketamine, some minor discrepancies are seen across trials. Apparent discrepancies may be related to low power given the small sample sizes routinely obtained or could reflect differences in the time frame examined and/or mode of assessment (Ballard et al. 2015), with assessments such

as the MADRS suicide item sometimes diverging from longer assessments, such as the SSI. Inclusion criteria for entry into the study may also reduce the generalizability of results to high-risk suicidal samples, as initial studies were almost exclusively post hoc analyses from antidepressant treatment trials. Trials with suicidal individuals often present ethical difficulties for researchers, as individuals with an acute plan to harm themselves may not be appropriate to participate in research, particularly in the case of a placebo-controlled trial. Therefore, while the trials include suicidal individuals, they may not represent the clinical severity that would be seen in relevant clinical settings such as psychiatric emergency departments.

4.2.1 Relationship of Antisuicidal Response to Antidepressant Response

The reduction in suicidal thoughts as related to the reduction in depressive thoughts warrants particular mention. Because ketamine was first investigated in patients with MDD and other depressive disorders, there is a larger evidence base supporting ketamine's antidepressant effects. One possible mechanism for ketamine's impact on suicidal thoughts is through reductions in depressive symptoms. Indeed, analyses of patients across RCTs of fluoxetine and venlafaxine have demonstrated that depression mediated reductions in suicidal thoughts (Gibbons et al. 2012). At the same time, while depression is an important risk factor for suicide, not all individuals who kill themselves are depressed (Conwell et al. 1996). Therefore, interventions are needed that can affect suicide risk, regardless of the particular diagnosis. It is thus important to know whether ketamine affects suicidal thoughts independently from reductions in depression. Such results have implications for understanding the neurobiology of suicide risk as well as for defining the scope of patients for whom ketamine is recommended.

Investigations of the relationship between ketamine's antisuicidal and antidepressant effects appear to be limited to three analyses. Ballard and colleagues, in a reanalysis of ketamine trials in 133 patients with treatment-resistant depression, found that changes in depression only accounted for up to 19 % of the variance in changes in suicidal ideation at 230 minutes postinfusion (Ballard et al. 2014a). Additionally, when controlling for the effects of ketamine on depression, ketamine was still independently associated with reductions in suicidal thoughts. Similar results were found for anxiety. In contrast, Price and colleagues found in their initial, uncontrolled study (Price et al. 2009) that after controlling for change in depression from baseline to 24 hours, the observed reduction in suicidal ideation following ketamine was no longer significant, suggesting that ketamine's antisuicidal effects were mediated by depression reduction. Similarly, Price and colleagues used formal mediational models to evaluate the relationship between change in suicidal ideation composite scores (at 24 hours) and change in depression, assessed both prior to suicidal ideation change (4 hours postinfusion) and concurrent with suicidal ideation (24 hours postinfusion) (Price et al. 2014). Changes in suicidal ideation at

24 hours were fully mediated by depression change at both time points. The divergence in findings may be related to differences in statistical approach, research design, sample size, or study population (for instance, the analysis by Ballard and colleagues included depressed patients with both MDD and BD ($n = 133$)). However, it is important to note that both analyses were conducted in patients selected for depressive disorders, creating samples with uniformly high levels of depressive symptom severity at baseline. Further investigation of the relationship between changes in suicidal thoughts and depressive thoughts is indicated in samples with varying levels of depressive symptoms at baseline.

4.3 Future Directions for Ketamine and Suicide Research

4.3.1 Neurobiological Mechanisms of Antisuicidal Response to Ketamine

As the clinical trial literature on ketamine and suicide risk continues to grow, a key question will be to uncover the mechanisms of action responsible for ketamine's effects on suicidal thoughts. Reduction in depressive symptoms after ketamine infusion is likely related to a number of neurobiological factors, both cellular and molecular, and has been hypothesized to be related to α-Amino-3-hydroxy-5--methyl-4-isoxazolepropionic acid (AMPA) to NMDA-receptor throughput (Maeng et al. 2008). It has also been hypothesized that antidepressant response could be related to increased synaptogenesis secondary to release of brain-derived neurotrophic factor (BDNF) (Autry et al. 2011). Further work is needed to evaluate whether reductions in suicidal thoughts after ketamine infusion are related to similar processes or to distinct neurobiological pathways.

One method of investigating suicide-specific mechanisms is to identify specific biomarkers associated with antisuicidal response. In one such analysis, positron emission tomography (PET) imaging was conducted before and 230 minutes after ketamine infusion in 19 medication-free patients with treatment-resistant depression (Ballard et al. 2014b). Regional cerebral glucose metabolism was evaluated in three areas of interest with regard to suicidal thoughts: the amygdala, the infralimbic cortex (Brodmann area 25), and the subgenual anterior cingulate. Baseline suicidal thoughts were associated with regional cerebral glucose metabolism in the infralimbic cortex, while baseline mood was not associated with metabolism in this area. Additionally, reductions in suicidal thoughts, but not depression, were associated with reduced metabolism in the infralimbic cortex. Therefore, it is possible that brain regions such as the infralimbic cortex are associated with the presence of and changes in suicidal thoughts, but not mood, which would provide further evidence of ketamine's specific antisuicidal effects.

Another promising line of inquiry involves investigations of BDNF in the context of antisuicidal response to ketamine. Antidepressant response to ketamine is associated with increases in plasma BDNF (Haile et al. 2014), and antidepressant effects

may be more robust in individuals with the Val/Val allele of BDNF single nucleotide polymorphism (SNP) rs6265 (Val66Met) (Laje et al. 2012). BDNF has also been implicated in suicide risk; specifically, reduced BDNF levels were found in MDD patients who attempted suicide compared to MDD patients without suicidal behavior and to healthy controls (Kim et al. 2007). Additionally, a meta-analysis of the BDNF SNP rs6265 (Val66Met) found that the Met-carrying genotypes and the Met allele were associated with history of suicide attempt (Zai et al. 2012). As a next step, it would be beneficial to know whether plasma BDNF and the Val/Val allele are associated with antisuicidal response to ketamine, which could provide further evidence of the role of BDNF in the neurobiology of suicide risk.

Furthermore, because changes in BDNF have also been associated with changes in sleep after ketamine administration (Duncan et al. 2013), the association of sleep-related variables to antisuicidal response is another potential area of study. Sleep difficulty is a commonly studied risk factor for suicide and has been associated with suicidal thoughts, attempts, and death over the long term (Pigeon et al. 2012; Bernert et al. 2014; Gunnell et al. 2013). A recent meta-analysis demonstrated that sleep difficulties, including insomnia, are associated with suicide risk independent of the effects of depression (Pigeon et al. 2012). More recent research demonstrated that nighttime-EEG-defined nocturnal wakefulness, particularly later in the night, was associated with next-day suicidal thoughts in a sample of patients with treatment-resistant depression (Ballard et al. 2016). This association was significant when controlling for age, gender, and severity of depressive symptoms. Further investigations examining the role of changes in sleep in relation to ketamine and suicide risk are therefore warranted.

Finally, elevated inflammatory and pro-inflammatory cytokines have been reported in individuals at risk for suicide (Janelidze et al. 2011) and are a posited neurobiological mechanism of suicide. Specific inflammatory markers that are implicated in suicide risk are also known modulators of NMDA-receptor function, suggesting a link to ketamine's neurobiological action as an NMDA antagonist. Specifically, the ratio of quinolinic acid, an NMDA-receptor agonist, to kynurenic acid, an NMDA-receptor antagonist, was reported to be elevated among recent suicide attempters, suggesting a tip in the balance in favor of NMDA stimulation (Erhardt et al. 2012). This finding suggests that ketamine, an NMDA antagonist, might resolve the imbalance, thereby reducing suicide risk. Future studies could test this hypothesis by measuring neuroinflammatory markers before and after ketamine administration.

4.3.2 Clinical Correlates of Antisuicidal Response to Ketamine

In addition to biomarkers of treatment response, clinical correlates of reductions in suicidal thoughts may also provide insight into ketamine's impact on suicidal thoughts. For example, anxiety symptoms are associated with suicide risk,

particularly the transition from suicidal thoughts to suicide attempts (Nock et al. 2010b). While most of the ketamine literature has focused on depression, ketamine also has a demonstrated impact on anxiety, and an RCT has also been conducted in individuals with posttraumatic stress disorder (PTSD) (Feder et al. 2014). Further work, particularly in patients with significant anxiety symptoms, may be able to explore whether the effect of ketamine on suicidal thoughts is in part mediated by anxiety. Anhedonia is also associated with suicide risk (Fawcett et al. 1990), and reductions in anhedonia may be associated with reductions in suicidal thoughts independent of the cognitive/affective symptoms of depression (Winer et al. 2014). Because reductions in anhedonia have been shown to be independent of antidepressant response after ketamine (Lally et al. 2014, 2015), it is also possible that antisuicidal response to ketamine may be mediated by reductions in anhedonia. In short, further exploration of the relationship of suicidal thoughts to depression, anxiety, and anhedonia, both before and after ketamine administration, may help to understand how these symptoms interrelate and can help focus the development of targeted treatments for this vulnerable population.

4.3.3 Ketamine and Suicidal Behavior

Lastly, future research will need to address the relationship between ketamine and suicidal behavior, specifically suicide attempts and deaths. Because of the rapidity of ketamine's effects, the primary outcome used in existing studies of ketamine and suicide is suicidal thoughts rather than behaviors. Suicidal thoughts can fluctuate over time and can be tracked using repeated measurement over the course of minutes to hours (Ballard et al. 2015). Because most studies have involved administration of a single ketamine infusion, which has a limited duration of effects (days to weeks), detecting the impact of ketamine on suicidal behavior is difficult without very large sample sizes. Additionally, for safety reasons, many ketamine trials are conducted in inpatient settings or intensive outpatient settings with follow-up contacts, which may themselves be protective for suicidal behavior. In contrast, interventions with a later onset and longer-acting effects, which are conducted on a long-term outpatient basis over months to a year, often use suicidal behavior or attempts as primary outcomes. The distinction between suicidal thoughts and suicidal behavior is not insignificant, as suicidal ideators and attempters have different clinical characteristics, including different diagnostic profiles (Klonsky and May 2014). Many ideators will never go on to attempt or die by suicide; therefore it is critical to understand whether the subset of individuals at highest risk of *acting* on suicidal thoughts can obtain sufficient relief through ketamine in order to prevent these acts.

To address this critical question, further work is needed to evaluate whether reductions in suicidal thoughts following ketamine lead to reductions in suicidal behavior. As ketamine begins to be evaluated in outpatient or emergency settings—

that is, outside of the relative safety of an inpatient unit—this issue will be particularly important for researchers to address. Given the challenges inherent in measuring low-base-rate behaviors that emerge over a longer time course (e.g., suicide attempts, completed suicide), one possible alternative would be to identify appropriate proxies for suicidal behavior or variables that can be acutely assessed after ketamine that have the potential to prospectively predict future suicidal behavior with high accuracy. An example of this approach exists in the open-label and randomized trials performed by Price and colleagues, who included a performance-based measure of implicit suicidal cognition (the Implicit Association Test) as an outcome measure. Performance on this measure was previously used to prospectively predict future suicide attempts, conferring a sixfold increase in risk of reattempt among a high-risk sample of recent attempters (Nock et al. 2010a). Changes in task performance, which were observed by Price and colleagues following ketamine, could therefore represent a proxy for reduced risk of actual suicide attempts, although the exact stimulus set that showed an effect following ketamine (words related to "escape") differed from that used to predict prospective suicide attempts (words related to "suicide"). As a second example, impulsive aggression is a proposed endophenotype for suicide risk (Mann et al. 2009) that may promote the agitated states associated with suicidal behavior. Future work may benefit from investigating ketamine's effects on markers of impulsive aggression, such as emotional reactivity and impulsivity to stressful situations, as proxies for real-world suicide risk.

4.4 A Next-Generation Treatment Model for Suicide Risk

This chapter has reviewed the existing evidence regarding ketamine's effects on suicidality and has suggested several avenues for further inquiry. While many questions remain to be resolved, the potential impact of ketamine on suicidal thoughts suggests the promise of a new treatment model for suicide risk. Currently, it is known that the highest suicide risk occurs around transitions in care, specifically the first week of a psychiatric inpatient hospitalization and the first week after discharge from a psychiatric inpatient stay (Qin and Nordentoft 2005). Since current therapeutics have a delayed onset lasting more than a week, little can currently be offered to reduce suicide risk during these acute periods. A suggested new paradigm (see Fig. 4.1) proposes that initiating a rapid-acting intervention, such as ketamine, may reduce suicidal thoughts in the short term, in order to stabilize the patient during the acute crisis. At the same time, longer-acting interventions can be established, including pharmacotherapies and psychotherapies, which could start to take effect just as the effects of the short-acting interventions are dissipating. Such a model would "bridge the gap" across different health-care settings, with the hope of treating current suicidal thoughts and thereby preventing suicidal behavior.

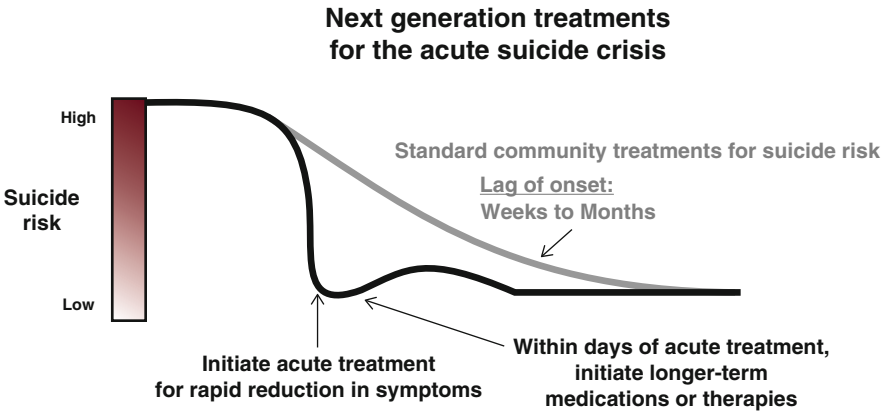

Fig. 4.1 A proposed model for the next-generation treatment of an acute suicide crisis. In the proposed model, treatments are initiated to rapidly reduce suicide risk within minutes to hours. After acute suicide risk has been reduced, patients can be connected with longer-term medications and therapies to maintain the treatment effect over time

4.5 Conclusions

There is a burgeoning literature on the relationship between ketamine and suicidal thoughts. While initial results are promising, they are not yet conclusive. Results from many clinical trials are forthcoming, which should help to clarify whether ketamine's initial promise is upheld in samples specifically selected for elevated suicide risk. Further evaluation of potential biomarkers and clinical correlates of treatment response may help clarify potential neurobiological mechanisms for the reduction of suicidal thoughts, ideally leading to novel treatment innovations.

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Chapter 5
Ketamine: Its Safety, Tolerability, and Impact on Neurocognition

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Abstract Ketamine, a high-affinity, noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, has long been used in anesthesiology and also as a drug of recreational abuse. In the last decade, the evidence has shown that a subanesthetic dose of ketamine has rapid and robust antidepressant effects in patients with treatment-resistant major depressive disorder (MDD) and bipolar depression. For the treatment of depression, the most widely used paradigm is a single 0.5 mg/kg intravenous infusion of ketamine. However, serial infusions, as well as oral and intranasal routes, have also been investigated. This chapter will discuss issues related to ketamine's safety, tolerability, and effects on neurocognition. In patients with mood disorders, the safety and high tolerability of ketamine used intravenously at subanesthetic doses, and in low doses by other routes, has been demonstrated in many clinical studies. As a result of studies on healthy volunteers and of a ketamine model of schizophrenia (with ketamine-induced positive and negative symptoms and impaired cognition), ketamine has been perceived as a drug that exerts deleterious effects on neurocognition. However, giving ketamine in low doses to depressed patients has not been connected with a negative effect on cognition, and some studies have even shown an improvement in this respect. Possible mechanisms for this phenomenon—for example, ketamine's ability to modify cognitive-emotional interactions in the brain—have been suggested. This chapter also discusses the issues of ketamine's safety, tolerability, and effects on neurocognition when used as anesthesia for electroconvulsive therapy.

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5.1 Introduction

The introduction of ketamine—a high-affinity, noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist—for the treatment of depression has, in recent years, been one of the most important events in psychopharmacology. Ketamine, a phencyclidine derivative and an antagonist of the glutamatergic NMDA receptor, also affects the glutamatergic α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors, sigma-1 receptors, and μ-opioid receptors, as well as noradrenaline and serotonin transporters and many others. Ketamine exists as a mixture of two enantiomers (*S*(+) and *R*(−)) that have different affinity to the receptors, with *S*(+)-ketamine having a three- to fourfold higher potency (Mion and Villevieille 2013).

Ketamine has been used in anesthesiology for more than 50 years. The drug has been described as a "dissociative anesthetic" due to its psychological potency to produce a feeling of separation of the mind from the body (Domino et al 1966). In dissociative anesthesia, there is a functional dissociation between the limbic system and the cerebral cortex.

Ketamine has also been a drug of recreational abuse. The 2006 National Survey on Drug Use and Health in the USA reported a rate of 0.1 % for ketamine abuse for persons ages 12 or older; the highest rate (0.2 %) was found in those aged 18–25 (Use of Specific Hallucinogens: 2006). Because of the easy availability of the drug among healthcare staff, a significant percentage of addicts belong to this group. The most frequent unusual experiences with ketamine are distorted perception, visual disturbances, and euphoric and floating sensations, frequently accompanied by anxiety and agitation. Prolonged use often leads to ketamine dependence as well as to severely impaired self-control with a higher risk of injury to self and others (Moore and Bostwick 1999).

However, the main psychopharmacological breakthrough in the last decade is the accumulation of evidence showing that a sub-anesthetic dose of ketamine produces a rapid and robust antidepressant effect in patients with major depressive disorder (MDD) and bipolar depression, including treatment-resistant patients. This antidepressant effect may be related to the activation of the connections between the anterior cingulate cortex and amygdala and, at the cellular level, the activation of brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR), as well as the inhibition of glycogen synthase kinase-3 (GSK-3). This may lead to an acute enhancement of synaptic signaling and a concomitant increase in the number and function of new synapses in the prefrontal cortex (Zarate and Niciu 2015).

For the treatment of depression, the most widely used paradigm is a single intravenous infusion of a racemic mixture of ketamine (0.5 mg/kg). Some clinical data have also been obtained for multiple intravenous ketamine infusions as well as for oral or intranasal ketamine administration. This chapter will discuss ketamine's safety and tolerability, as well as its effects on neurocognition, mostly in the context of ketamine use in patients with mood disorders.

5.2 Safety and Tolerability of Ketamine

Ketamine acts both on the central nervous system (CNS) and on different peripheral organs in the body. The dopaminergic effects in the CNS are partially responsible for ketamine's effects, including euphoria, hallucinations, and addiction. Moreover, modulation of opioids in the brain and spinal cord is attributed to its analgesic effect, and some other sympathomimetic effects are potentiated by its agonistic effect on α- and β-adrenergic receptors. It also has antagonistic effect on monoaminergic, muscarinic, and nicotinic receptors in the CNS (Bergman 1999).

Ketamine causes a moderate sympathomimetic action via increased dopamine release and reuptake inhibition, resulting in cardiovascular hyperactivity reflected by tachycardia and hypertension, increased cerebral blood flow, higher cerebral metabolic rates for oxygen and glucose, and elevated intracranial (ICP) and intraocular pressure (IOP) (Takeshita et al. 1972). Usually, these symptoms are classified as mild to moderate, except for patients with a history of hypertension, cardiac failure, or cerebrovascular accidents (Haas and Harper 1992). Therefore, one should consider the following conditions as relative contraindications to ketamine administration, either for anesthesia or at subanesthetic doses: history of myocardial infarction within the last three months, unstable angina or uncontrolled cardiac failure, severe vascular disease, cerebral vascular disorders, raised intracranial pressure, pheochromocytoma, or penetrating eye injury (Kranaster et al. 2011).

In contrast to hemodynamic changes, respiratory depression seems to be clinically insignificant in everyday medical practice, and it may occur only rarely and at high doses of ketamine that stimulate the opioid receptors (Reich and Silvay 1989). Lack of respiratory depression after ketamine makes it a fairly safe drug when used by infusion and/or as an anesthetic. However, some cases of respiratory depression have been documented after rapid intravenous bolus in adults and intramuscular injection in children (Moore et al. 1997).

With the exception of the smooth muscles of the bronchial tree, ketamine strengthens muscle tone and maintains laryngeal and pharyngeal reflexes (Reich and Silvay 1989). The drug has not been shown to significantly affect the kidney or liver, although urinary bladder infections have been reported in chronic users (Chu et al. 2008). In vitro studies suggest that its immunosuppressive action occurs via decreased production of proinflammatory cytokines (Kawasaki et al. 1999).

In sum, although ketamine is not devoid of side effects, it is considered an anesthetic with a good safety profile. Its major disadvantage is the occurrence of emergence reactions including psychotomimetic symptoms such as hallucinations, nightmares, dizziness, delirium, and vestibular-type symptoms manifested by nausea, vomiting, and vertigo, which limits its medical but not psychiatric or recreational use (Rasmussen et al. 2014).

In recreational ketamine users, most of the psychotomimetic effects are associated with hemodynamic (mostly tachycardia), locomotor (altered body perception, dizziness), and gastric (nausea, vomiting) side effects. Very rarely, polyneuropathy, hyperthermia, or fatal liver failure are observed, but these are generally due to

ketamine levels in serum that are generally several-fold higher than those associated with anesthesia (Weiner et al. 2000). Interestingly, Jansen (2000) stated that repeated users of ketamine may become as quickly addicted as nonaddicted, with withdrawal syndrome ceasing completely within seven to 10 days of the final ketamine episode. In contrast, Chen and colleagues (2004) reported dependence after one year of abuse in almost 80 % of subjects, with withdrawal syndrome in 50 %. Tolerance to ketamine is high and appears to develop quickly. Kamaya and Krishna (1987) described one subject who developed tolerance from an occasional 50 mg oral dose to 500 mg four to five times a day, switching to intramuscular injection with a dose of 300–750 mg five to six times a day within a month.

An initial randomized, placebo-controlled trial of a subanesthetic dose of ketamine in seven patients with depression was performed by Berman and colleagues (2000). A reduction in depressive symptoms was observed after intravenous administration of 0.5 mg/kg ketamine, as measured by the Hamilton Depression Rating Scale (HAM-D). In this pilot study, the authors described transient cognitive impairment and euphoria that subsided over several hours after the injection.

A larger randomized controlled trial comparing ketamine and a placebo in patients with treatment-resistant MDD was performed by Zarate and colleagues (2006). Adverse reactions such as perception disturbances, confusion, euphoria, increased blood pressure, dizziness, and increased libido were reported more frequently in subjects who received ketamine than in the placebo group. Disorders of the digestive system, increased thirst, headache, a metallic taste, and constipation also occurred more frequently among the patients than in the placebo group. Ten percent or more of the patients reported dry mouth, dizziness or faintness, difficulty falling asleep, and flatulence only during the drug infusion; ketamine was not associated with any hemodynamic, respiratory, or laboratory changes. Most of these side effects subsided within 80 minutes of discontinuing intravenous ketamine administration. Euphoria, derealisation, or depersonalization did not persist for more than 110 minutes.

Similar results were obtained in patients with treatment-resistant bipolar depression who were also receiving lithium or valproate (Diazgranados et al. 2010). Adverse events were reported in approximately 10 % of the patients receiving either ketamine or a placebo. The reactions included dizziness, fatigue, drowsiness, cognitive effects, anxiety, restlessness, nausea, blurred vision, and headaches. Adverse events such as psychotic experiences, dry mouth, tachycardia, and increased blood pressure were reported in less than 10 % of patients receiving ketamine. High blood pressure and tachycardia occurred in two patients but returned to normal within a few minutes after infusion.

In a study by Mathew and colleagues (2010), no serious side effects were observed with intravenous ketamine. There was a transient increase in mean blood pressure and heart rate, which generally returned to baseline levels after 40–80 minutes. The most frequently reported adverse reactions during ketamine infusion and for up to 240 minutes afterward were blurred vision, fatigue, dizziness, fainting, drowsiness, lethargy, a sense of otherness and unreality, headaches, numbness, tingling, ringing in the ears, and speech disorders.

In a study comparing intravenous ketamine and midazolam in depressed patients, the reactions occurring with significant frequency with both drugs subsided within the first day and included blurred vision, dizziness, and malaise. Nausea and vomiting were significantly more frequent in patients receiving ketamine. Among all the side effects in the ketamine group were nausea/vomiting (34 %), dry mouth (26 %), constipation (4 %), diarrhea (4 %), dizziness on standing (21 %), palpitations (11 %), chest pain (4 %), increased perspiration (11 %), itching (4 %), dry skin (2 %), rash (2 %), dizziness (45 %), headache (32 %), poor coordination (26 %), tremors (13 %), blurred vision (43 %), ringing in the ears (4 %), poor concentration (26 %), restlessness (21 %), anxiety (15 %), decreased energy (15 %), fatigue (15 %), and general malaise (6 %) (Murrough et al. 2013a).

Naughton and colleagues (2014) reviewed these findings and reiterated that most adverse effects related to ketamine intravenous infusion usually disappeared within 80 minutes after cessation of the infusion.

Ketamine infusion has also been used in patients suffering from obsessive-compulsive disorder. Rodriguez and colleagues (2013) reported that all subjects (15 patients) experienced mild increases in blood pressure and heart rate during ketamine infusion. There were also dissociative and psychotic symptoms (in 14 and 12 individuals, respectively) as well as symptoms of mania (in one case). After infusion of the drug, three patients complained of dizziness and two of nausea and headaches. One patient vomited. These symptoms subsided after a few minutes. One person reported constipation on the second and third day after ketamine administration. No serious adverse reactions occurred during the infusion.

Current treatment options for severe mood disorders may be extended to include repeated ketamine infusions. Messe and colleagues (2010) performed various regimens of serial ketamine and saline infusions in two treatment-resistant depressive patients. The authors observed a mild increase in talkativeness and decreased inhibition during intravenous ketamine infusion that ceased within two h postinfusion and a 10 mmHg elevation in both systolic and diastolic blood pressures that returned to preinfusion values within three h postinfusion.

Murrough and colleagues (2013b) reported the safety and efficacy of six infusions of ketamine over a period of 12 days. While 67 % of the patients did not experience any clinically significant change in vital signs, 33 % did experience elevated blood pressure and/or heart rate; one participant did not respond satisfactorily to antihypertensive treatment but stabilized after the infusion was discontinued.

Diamond and colleagues (2014) reported on 28 patients with treatment-resistant MDD or bipolar depression who were treated over three weeks with either three or six ketamine infusions (0.5 mg/kg over 40 minutes). Most patients experienced transient side effects, including perceptual distortions, detachment, anxiety, nausea, and confusion during the infusion. The procedure was discontinued in two patients because of an acute adverse reaction during the infusion and in five patients due to increased anxiety and no therapeutic benefit.

The largest study to date on the safety, tolerability, and acceptability of ketamine in treatment-resistant depression involved 205 intravenous ketamine infusions (0.5 mg/kg over 40 minutes) in 97 participants (Wan et al. 2015). The study found

that almost 30 % of the patients had higher blood pressure during continuous infusion, including more than 14 % of those subjects treated concomitantly with antihypertensive agents. In the first four h after the infusion, the most common general adverse effects were drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal. Ketamine resulted in small but significant increases in psychotomimetic and dissociative symptoms. There were no cases of persistent psychotomimetic effects, adverse medical effects, or increased substance use in a subgroup of patients with available long-term follow-up information.

Ketamine can be administered by any available approach: intravenous, intramuscular, oral, sublingual, nasal, rectal, and even subcutaneous and epidural, in doses depending on the route of administration and the therapeutic effect desired (Pai and Heining 2007).

The effects of orally administered ketamine were assessed in a paper of Irwin and colleagues (2013) where 14 subjects in hospice care with symptoms of depression received a daily oral dose of ketamine hydrochloride (0.5 mg/kg) over a 28-day period. No vital sign changes and no serious adverse events due to ketamine occurred during the study. Diarrhea occurred in one patient, trouble sleeping occurred in one patient, and trouble sitting still occurred in one patient.

Lapidus and colleagues (2014) found that intranasal administration of 50 mg ketamine was safe, well-tolerated, and highly effective in 20 patients with MDD who had not responded to at least one antidepressant. In the first few minutes after administration they observed a slight increase in psychotic and dissociative symptoms and a small increase in arterial blood pressure that tended to be prolonged up to four h. Budavari and colleagues (1989) regarded this route as one that was well-tolerated by patients (no stinging irritation) if the neutral (pH 7.5) water-soluble formulation was used.

Lara and colleagues (2013) administered ketamine to their patients sublingually. Only two of 26 patients reported overstimulation, with very good antidepressant reaction. Subcutaneous administration of ketamine also provided an antidepressant effect with good tolerability. The side effects experienced included light-headedness and blurred vision, which disappeared 60 minutes after administration (Galvez et al. 2014).

In our center, a single infusion of ketamine has been administered by an anesthesiologist maintaining anesthesia standards of monitoring. Exclusion criteria include severe hypertension, aneurysm, and/or vascular malformation in the CNS; unstable angina; uncontrolled hyperthyroidism; severe respiratory disease; glaucoma; history of seizures; allergy and/or a history of allergic reaction during anesthesia; coexisting psychotic illness; pregnancy; young age (<18); and general conditions classified as four or more by the American Society of Anesthesiologists (ASA) (Permoda-Osip et al. 2015).

Our studies administered a single ketamine injection to patients with bipolar depression who were maintained on mood-stabilizing drugs of the first (lithium, valproate, carbamazepine) and/or second generation (clozapine, olanzapine, quetiapine, aripiprazole) (Rybakowski 2007) and for whom antidepressant drugs were not effective. In our first report of 25 patients, ketamine infusion was generally

well-tolerated, and the side effects observed included sleepiness in two patients, transient visual hallucinations in one patient, and transient symptoms of depersonalization and derealisation in almost all cases. All these side effects only lasted for the duration of the drug infusion. In most patients, small, short-term, increases in blood pressure were noted. In one case, the patient's blood pressure increased significantly. During the 14-day observation period following ketamine infusion, none of the patients reported side effects associated with the procedure (Permoda-Osip et al. 2012).

Good tolerance was confirmed in our second report, which included 42 patients. No serious side effects were observed. Most patients experienced slight increases in blood pressure during infusion, as well as transient symptoms of depersonalization and derealisation that, in one of the patients, amounted to a psychotic episode that subsided on cessation of drug administration (Permoda-Osip et al. 2014).

Ketamine has also been considered as an anesthetic drug for electroconvulsive therapy (ECT) that works to augment the antidepressant effect of ECT in patients suffering from MDD. Patients qualified for this method of treatment receive anesthetic doses of ketamine ranging from 1 to 1.5 mg/kg administered in a slow intravenous bolus. It has been suggested that such patients will need fewer ECT sessions, achieving faster and better recovery compared to those who use propofol or thiopental as an anesthetic (Okamoto and Tetsuji 2010; Kranaster et al. 2011). However, the clinically significant increase in blood pressure after ketamine administration may be undesirable, especially during an ECT session that, in itself, generates hyperactivity of the cardiovascular system (Rasmussen et al. 2014).

In our hospital, to avoid hemodynamic and cardiovascular adverse effects after the administration of ketamine, as well as to prevent developing tolerance during repeated ECTs, a special protocol has been developed. After excluding contraindications to the first procedure, patients undergo anesthesia with thiopental (2.0–2.5 mg/kg) and succinylcholine (0.5–1.0 mg/kg) in order to test any unexpected elevation of blood pressure or unwanted tachycardia during an ECT. When cardiovascular stability during seizures was satisfactory, the second ECT was performed using ketamine as an anesthetic agent with synergistic antidepressant properties in doses of 1.0–1.5 mg/kg and then for the next fourth, sixth, eighth, and tenth ECT sessions. If not, the anesthesia in the next sessions was continued without ketamine.

We also studied levels of NT-proBNP (N-terminal pro B-type natriuretic peptide), a sensitive biomarker of heart stress and damage, before ECT and then after the second, sixth, and tenth sessions. Patients for whom thiopental was used in all ECT sessions were compared to those for whom ketamine was used for the second, fourth, sixth, eighth, and tenth sessions. No significant differences were found in BNP levels between the groups or during the course of ECT within each group. These results show that BNP levels reflecting the load on the circulatory system are similar for patients who are alternatively anesthetized with thiopental and ketamine and those patients who are anesthetized with thiopental alone (Wisniewski et al. 2015).

5.3 Ketamine and Neurocognition

Ketamine has mostly been perceived as a drug that exerts deleterious effects on neurocognition. This perception was mainly due to the results of studies conducted in healthy volunteers as well as to a ketamine model of schizophrenia, both of which showed ketamine-induced positive and negative symptoms of schizophrenia, along with impaired cognition.

More than 20 years ago, Krystal and colleagues (1994) performed a pivotal randomized, double-blind, placebo-controlled trial in 19 healthy subjects recruited by advertisements from the community. The subjects completed three test days involving the 40-minutes intravenous administration of a placebo, ketamine hydrochloride (0.1 mg/kg), or ketamine hydrochloride (0.5 mg/kg). Behaviors associated with the positive and negative symptoms of schizophrenia were assessed using the Brief Psychiatric Rating Scale. Changes in perception and behaviors associated with dissociative states were assessed by the perceptual aberration subscale of the Wisconsin Psychosis Proneness Scale and the Clinician-Administered Dissociative States Scale. Cognitive function was assessed via the mini-mental state examination and by tests sensitive to frontal cortical dysfunction including a continuous performance vigilance task, a verbal fluency task, the Wisconsin Card Sorting Test, and tests of immediate and delayed recall. They concluded that ketamine produced behaviors similar to the positive and negative symptoms of schizophrenia, eliciting alterations in perception and impaired performance on tests of vigilance and verbal fluency as well as on the Wisconsin Card Sorting Test. The drug evoked symptoms similar to dissociative states and preferentially disrupted delayed word recall, sparing immediate recall, and postdistraction recall. On the other hand, ketamine had no significant effect on the mini-mental state examination at the doses studied.

Ten years later, in a double-blind, placebo-controlled study of 54 healthy volunteers, Morgan and colleagues (2004) examined the effects of infusions of two doses (0.4, 0.8 mg/kg) of ketamine upon the five human memory systems, aspects of executive functioning, and schizophrenia-like and dissociative symptoms. Ketamine produced a dose-dependent impairment to episodic and working memory, a slowing of semantic processing, and impairment in recognition memory and procedural learning. Attention, perceptual priming, and executive functioning were not affected. In addition, ketamine induced schizophrenia-like and dissociative symptoms that did not correlate with cognitive measures.

For nearly two decades, the administration of ketamine in healthy subjects and in experimental models has served as a procedure for producing symptoms of schizophrenia as well as those of impaired cognition. This was interpreted within the framework of the NMDA receptor hypofunction hypothesis of this illness, because ketamine is an antagonist of this receptor (Gilmour et al. 2012). For example, Blackman and colleagues (2013) demonstrated that, in monkeys, the administration of ketamine caused a dose-dependent failure in context processing replicating, with the same specific pattern of errors committed by patients with schizophrenia when performing the same task. D'Souza and colleagues (2012) found that ketamine

induced transient cognitive deficits as well as behavioral effects in 37 healthy subjects that resembled negative and positive symptoms seen in schizophrenia; these were not alleviated by the cholinergic agonist nicotine. On the other hand, in a rat model of schizophrenia, Zugno and colleagues (2013) demonstrated that an acetylcholinesterase inhibitor, rivastigmine, effectively improved the cognitive deficits associated with different memory tasks induced by ketamine. Monte and colleagues (2013) found that ketamine-induced schizophrenia-like behaviors in mice, including cognitive deficits, were reversed by minocycline.

Cognitive disturbances were also found in subjects taking ketamine as a drug of abuse. Several years ago, Curran and Monaghan (2001) demonstrated that the frequent use of ketamine produces long-lasting impairment in episodic memory and in aspects of retrieval from semantic memory. In a large-scale longitudinal study, Morgan and colleagues (2010) found that cognitive deficits were mainly observed in frequent users where increasing ketamine use over the year was correlated with decreasing performance on spatial working memory and pattern recognition memory tasks. Recently, Morgan and colleagues (2014) demonstrated that heavy ketamine users displayed spatial memory deficits accompanied by changes in medial temporal lobe activation.

On the other hand, ketamine, as a noncompetitive NMDA receptor antagonist, can block the damaging action of excitotoxic amino acids on the central nervous system. Since the turn of the century, evidence has been accumulating of ketamine's possible neuroprotective effects. Proeschold and colleagues (2001) demonstrated that the *S*(+) ketamine isomer significantly reduced neuronal cell loss in the cerebral cortex after global forebrain ischemia. A review of the experimental and clinical evidence for ketamine's neuroprotective effects shows that this drug may provide beneficial effects in neurologically impaired patients after brain injury. Ketamine may also exert beneficial short-term effects on postoperative delirium and cognitive dysfunction in patients after cardiac surgery (Hudetz and Pagel 2010).

In mood disorders, cognitive disturbances form an important element of the diagnostic criteria of depression. Usually, they are intensified during a depressive episode and reduced after antidepressant treatment. Cognitive dysfunctions form an intrinsic part of both MDD (Trivedi and Greer 2014) and bipolar depression (Raust and Bellivier 2011). We demonstrated that during a depressive episode, bipolar patients are more neuropsychologically impaired than patients with MDD (Borkowska and Rybakowski 2001). In depressed patients, cognitive dysfunctions may persist even after they achieve clinical remission. Currently, cognitive deficits emerge as a potential target because, to a great extent, they compromise the functional outcome of patients with mood disorders (Solé et al. 2015).

Few studies have investigated the effect of subanesthetic doses of ketamine on cognitive function in depressed patients. The first results appeared several years ago, when Murrough and colleagues (2013c) assessed neurocognitive functioning in 25 patients with treatment-resistant depression treated with a single 0.5 mg/kg infusion of ketamine. Patients who responded to ketamine 24 hours following treatment had a poorer baseline neurocognitive performance than nonresponders. In turn, cognitive impairments immediately after the infusion predicted a lower

response rate at 24 hours. In the same year, Lara and colleagues (2013) evaluated very low-dose ketamine, used sublingually, as an add-on to antidepressant or mood-stabilizing drugs in 26 outpatients with treatment-resistant MDD or bipolar depression and found that some patients reported a procognitive effect of this procedure.

In a study by Shiroma and colleagues (2014), 15 patients with treatment-resistant depression had their neurocognitive performance measured before and over the course of six ketamine infusions performed within two weeks, followed by a four-week observational period. The antidepressant response through six infusions was greater among those depressed subjects with lower attention at baseline. After the sixth infusion, a significant improvement was found in visual memory, simple working memory, and complex working memory scores, which correlated with an improvement in the severity of depressive symptoms; these were not associated with likelihood of subsequent relapse during follow-up. The authors concluded that worse baseline neurocognitive results may predict response to ketamine and that six ketamine infusions in individuals with treatment-resistant depression may improve some aspects of their neurocognitive performance.

Recently, Murrough and colleagues (2015a) studied 62 patients with treatment-resistant depression free of concomitant antidepressant medication using the neurocognitive assessments of the MATRICS Consensus Cognitive Battery (MCCB) before and, seven days after, a single intravenous infusion of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg). Neurocognitive performance improved following the treatment regardless of which treatment was used. There was no differential effect of treatment on neurocognitive performance and no association with antidepressant response. Slower processing speed at baseline predicted greater improvement in depressive symptoms 24 hours following ketamine infusion. The authors concluded that a single infusion of ketamine had no adverse neurocognitive effects at seven days posttreatment, and that baseline neurocognitive impairment was associated with a greater antidepressant response.

In our preliminary study, we assessed neurocognitive performance using the Trail Making Test (TMT) and the Stroop Color-Word Interference test before and on the third day after a single infusion of ketamine. The study was performed on 18 patients with bipolar depression receiving mood-stabilizing drugs of the first and/or second generation (Rybakowski 2007). Performance on all tests significantly improved on the third day after ketamine infusion, which correlated positively with baseline intensity of neuropsychological impairment and was not associated with either baseline intensity of depression or reduction of depressive symptoms after three or seven days. These results suggest that in patients with bipolar depression receiving mood-stabilizing drugs, a single ketamine infusion may improve neuropsychological performance independently of any antidepressant effect (Permoda-Osip et al. 2015).

A question thus arises. Why is ketamine, which is generally regarded as a cognition-impairing agent when used in subanesthetic doses in depressed patients, devoid of adverse neurocognitive effects and may even exert a beneficial influence on cognition? It can be speculated that this is due to the specificity of cognitive abnormalities in depression and to a modulation by ketamine of the mechanism of

interaction between cognition and emotions in the brain. Cognitive abnormalities in depression are, to a great extent, caused by an impairment of so-called "hot" (emotion-laden) cognition. Alterations in "hot" processing are shown in tasks using emotionally valenced stimuli (Roiser and Sahakian 2013). Such a concept was confirmed in two recent studies. Scheidegger and colleagues (2015) studied neuroimaging, working memory tasks, and mood assessment in 23 healthy subjects. Based on the results obtained, they proposed that ketamine modulates cognition-emotion interaction in the brain by inducing lateralized and valence-specific effects in emotion-related cortical midline regions, working-memory-related lateral prefrontal regions, and the insula. In emotion-related cortical midline regions, ketamine abolishes enhancement of the deactivation normally observed during cognitive effort, while in the right dorsolateral prefrontal cortex and the left insula, the previously described pattern of increased activation due to emotional content is abrogated exclusively for negative stimuli. This specific effect of ketamine on cognition-emotion interaction in the brain indicates that its effect on amelioration of negative biases in depressed patients might be related to less interference of cognitive processing by negative emotional content.

In the study by Murrough and colleagues (2015b), 20 patients with treatment-resistant depression who were free of antidepressant medication underwent functional magnetic resonance imaging at baseline and 24 hours following administration of a single intravenous dose of ketamine (0.5 mg/kg). Patients were compared with 20 age- and sex-matched healthy volunteers scanned at one time point. Compared with the healthy volunteers, patients with treatment-resistant depression showed reduced neural responses to positive faces within the right caudate nucleus. Following ketamine, neural responses to positive faces were selectively increased within a similar region of the right caudate. Greater connectivity of the right caudate during positive emotion perception was associated with improvement in depression severity following ketamine.

It is also possible that ketamine-induced improvement in cognitive function can be related to acutely increased synaptogenesis, which is also an underlying antidepressant effect of ketamine (Zunszain et al. 2013). However, as the relationship between improvement in cognition and in depression after ketamine is not clear, these studies show that worse baseline neurocognitive results may predict antidepressant response to ketamine (Shiroma et al. 2014; Murrough et al. 2015a) as well as stronger neurocognitive improvement (Permoda-Osip et al. 2015).

Recently, a question has also been raised as to whether ketamine can also exert beneficial effects on cognition when used as an anesthetic drug for ECT, in addition to augmenting antidepressant activity. An initial paper by McDaniel and colleagues (2006) obtained encouraging results, but the subsequent findings have been mixed. In a Finnish study, a subanesthetic dose of *S*-ketamine (0.4 mg/kg) before ECT treatment (using propofol anesthesia) did not augment the efficacy of ECT in patients with treatment-resistant depression and was associated with increased post-treatment disorientation and restlessness (Jarventausta et al. 2013). Rasmussen and colleagues (2014) demonstrated that ketamine anesthesia, compared with methohexital, did not accelerate the antidepressant effect of ECT and did not diminish

cognitive side effects. Two recent meta-analyses investigated randomized controlled trials of ketamine augmentation. Fond and colleagues (2014) found that ketamine had some advantages over propofol or thiopental anesthesia, while McGirr and colleagues (2015) concluded that, overall, this procedure is not associated with better clinical efficacy and increases the likelihood of confusion.

Our study looked at 11 male and 34 female patients with drug-resistant depression, aged 21–75 years. Fifteen patients received only thiopental anesthesia, 15 had their second and third ECT sessions with ketamine, and 15 had ketamine for the second, fourth, sixth, eighth, and tenth sessions. Ketamine was used in anesthetic doses of 1–1.5 mg/kg. Cognitive functions were measured before and after ECT, assessing visual-spatial abilities, verbal auditory memory, working memory, and executive functions. After the last ECT session, patients with added ketamine anesthesia for every second session had better clinical improvement but more marked worsening of verbal memory (Rybakowski et al. 2016).

5.4 Conclusions

In patients with mood disorders participating in clinical studies, ketamine used intravenously in subanesthetic doses and in low doses by other routes was safe and well-tolerated, and no serious side effects have been reported. Furthermore, giving ketamine in low doses to depressive patients has no negative effects on cognition, and some studies have even shown an improvement in this respect. This is important because cognitive deficits have in recent years been considered as a potential target in the treatment of depression. One caveat to these research trial results is that we have little information on these issues in clinical practice settings.

In discussing issues of safety, tolerability, and neurocognition concerning the use of ketamine as the anesthetic agent for ECT in treatment-resistant depression, we conclude that such an application may be useful for augmenting the antidepressant effect of ECT, assuming a prudent evaluation for and adequate protocol of ECT sessions. On the other hand, studies performed so far have not proven that the use of ketamine as anesthesia for ECT exerts a beneficial effect on cognition.

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Chapter 6
Ketamine's Mechanisms of Rapid Antidepressant Activity: Evidence from Preclinical Studies

Gretchen Hermes and Gerard Sanacora

Abstract Enthusiasm over the growing series of reports describing ketamine's rapid onset of robust antidepressant activity in clinical trials has ignited a large number of back-translational efforts attempting to employ rodent models to better characterize the antidepressant properties of the drug and to improve our understanding of its underlying mechanisms of antidepressant action. On balance, these preclinical studies have yielded fairly consistent findings demonstrating that ketamine has a broad range of behavioral effects consistent with antidepressant activity in a variety of rodent models. Many of these studies further suggest that ketamine's effects are unique from other classic antidepressant drugs in producing more durable effects in some models and more rapidly reversing the behavioral effects of chronic stressor exposure in other models. The preclinical studies are also beginning to elucidate the drug's mechanisms of antidepressant activity, with the majority of recent studies suggesting that increased levels of regional alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) receptor activation and brain-derived neurotrophic factor (BDNF) expression, as well as enhanced synaptic plasticity, are critical components of the response. However, there remain several points of disagreement and inconsistency in the preclinical literature that require additional investigation, including the effectiveness of other NMDA receptor-targeting drugs and the specific targets of ketamine's proximal effects. This chapter provides an overview and critical review of this preclinical literature. It is anticipated that a more complete understanding of ketamine's mechanisms of antidepressant action will allow for a safer and more efficient use of ketamine in the clinical setting and afford us new opportunities for novel drug development.

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6.1 Background

Reports that ketamine and several other agents are capable of producing rapid antidepressant effects in previously treatment-resistant depressed patients have stimulated a highly productive period of reverse translation. The results of those clinical studies combined with the recent preclinical research findings have shed new light on mechanisms underlying vulnerability to depression, providing us with a better understanding of mood disorder pathogenesis and pathophysiology and providing novel targets for antidepressant treatment development.

Although reports describing the rapid (within hours) and sustained (lasting several days to weeks) antidepressant effects of a single infusion of sub-anesthetic dose ketamine in depressed patients (Berman et al. 2000; Zarate et al. 2006) are responsible for igniting widespread interest in ketamine and N-methyl-D-aspartate (NMDA) receptor antagonists as potentially rapidly acting antidepressant agents, the groundwork for these studies was laid decades ago. In 1990, Trullas and Skolnick proposed that NMDA receptor antagonists represented a potentially new class of antidepressants (Trullas and Skolnick 1990). Their hypothesis was based on two sets of preclinical findings. The first was a series of studies demonstrating that stress-induced behavioral deficits and disruptions in hippocampal long-term potentiation (LTP) could be reversed by NMDA receptor antagonists like dizocilpine (MK-801) (Trullas and Skolnick 1990). The second was based on findings that chronic, but not acute, administration of classic antidepressants altered NMDA receptor binding (Paul et al. 1994). The convergence of these findings was interpreted as an indication that the glutamatergic neurotransmitter system—and specifically modulation of the NMDA receptor—could provide a novel target for future antidepressant drug development (Skolnick 1999). These studies have been complimented by decades-long work in rodent models of depression that have supported the development of novel drugs that target multiple foci of the glutamatergic synapse as antidepressant agents (Pilc et al. 2013). The objective of this chapter is to provide an overview and critical review of the preclinical work attempting to evaluate the antidepressant properties of these agents and to characterize the mechanisms of action that underlie ketamine's rapid antidepressant actions.

6.2 Preclinical Evidence

6.2.1 Preclinical Behavioral Response to Ketamine

In order to better evaluate the validity and meaningfulness of these preclinical findings, we begin with a brief review of rodent behavioral models that have broadened our understanding of the antidepressant-like properties of ketamine and other NMDA receptor-modulating agents. Major depressive disorder (MDD), like other psychiatric disorders, has a phenomenological description based on a cluster of

symptoms likely related to complex pathophysiologic processes. Recent efforts have shifted the research focus to endophenotypes, less complex, more stable phenotypes that lie on the pathway between genotype and disease (Gottesman and Gould 2003). These explicit functional domains include (1) altered regulation of positive affective behaviors such as reflected in motivation and reward processing (despair, reduced motivation, or anhedonia (the inability to experience pleasure)), (2) altered regulation of negative affective states and behaviors (anxiety, anger, guilt, fear), (3) cognitive impairment (inability to shift attention, ruminations, poor concentration), and (4) dysregulation of visceral motor and arousal systems (autonomic dysregulation, changes in appetite, sleep, and physical sensations of discomfort and pain). The predictive validity of rodent models has always been based, more or less, on the replication of these altered functional domains and their normalization with antidepressant treatment.

6.2.2 Ketamine and Rodent Measures of Behavioral Despair

Reflecting proposed abnormalities in positive affective regulation, the forced swim test (FST) is perhaps the most well-validated assay of behavioral despair. When placed in cylinders containing water, rodents become rapidly immobile, floating passively or making only limited movements in order to remain afloat. The measure of immobility is correlated with behavioral despair. Time spent immobile has been reduced by short-term administration of antidepressants from a variety of classes including tricyclic antidepressants (TCAs), selective-serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs) (Cryan et al. 2005). Numerous studies have shown that a single administration of a sub-anesthetic dose of ketamine produces acute reductions of immobility in the FST shortly after injection. However, as discussed below, the interpretation of studies examining more immediate effects of ketamine are confounded by other nonspecific actions of the drug such as its effects on locomotor behavior. Perhaps more importantly, in the FST and nearly every other behavioral assessment in rodents, there are conflicting findings that fail to detect acute effects of ketamine in mice (Bechtholt-Gompf et al. 2011) and in rats (Popik et al. 2008).

A particularly striking aspect of ketamine's behavioral pharmacology profile, distinct from conventional antidepressants, is the protracted behavioral effects that can persist for days or even weeks after a single drug administration. The majority of studies indicate that the FST remains sensitive to the prolonged effects of ketamine for at least one week post a single injection (Ma et al. 2013; Yilmaz et al. 2002; Garcia et al. 2008; Maeng et al. 2008). This suggests that a single dose of ketamine may induce more sustained effects in the neural circuitry of despair than a single administration of a monoaminergic drug. Interestingly, these differences in the duration of drug effects challenge an earlier theory that classic antidepressants worked by modifying NMDA receptor expression and function (Paul et al. 1994).

The ability of other NMDA receptor antagonists to produce longer-lasting effects in the FST is less well established. In a direct comparison of the effects of memantine and ketamine on the FST, memantine showed no proximal behavioral effects in the hours after administration or at seven days postinjection (Gideons et al. 2014). Other studies showed that the NMDA receptor antagonist MK-801 failed to show the prolonged effects on the FST that were seen with ketamine, despite showing similar acute effects (within hours) on the FST (Autry et al. 2011; Zanos et al. 2016). However, others have shown that NMDA receptor antagonists such as RO 25-6981 and CPP do have enduring antidepressant effects lasting at least 24 hours in the FST (Li et al. 2011; Chowdhury et al. 2016; Autry et al. 2011).

The tail-suspension test (TST) is thought to be a less aversive assay of behavioral despair than the FST. Mice are suspended by their tails without the possibility of escape or support from nearby surfaces. During the test, usually lasting six minutes, escape-oriented behaviors are quantified; more escape-related activity is correlated with less behavioral despair. The TST has well-established predictive validity because it too can be used to assess antidepressant-like responses from various drug classes (Cryan et al. 2005). Here again the preclinical literature demonstrates that ketamine reduces behavioral despair—levels of immobility—in mice acutely, with studies reporting reductions in immobility time at 30 minutes (Mantovani et al. 2003; Rosa et al. 2003) and 24 hours (Koike et al. 2011a) following a single injection of ketamine. In another recently published study on chronic social defeat, RO25-6981 (an NR2B-selective NMDA receptor antagonist) and AP5 (a competitive NMDA receptor glutamate antagonist) had long-lasting antidepressant effects measured in the TST and splash test 24 hours postinjection of these NMDA receptor antagonists (Workman et al. 2015).

6.2.3 Ketamine and Anhedonia: The Sucrose Preference Test

Anhedonia, the loss of pleasure or reduced reactivity to rewarding stimuli, is a core symptom of MDD and is believed to reflect abnormalities in the circuitry and physiology regulating positive affect behavior and represents an important problem across a spectrum of mental illnesses. Isolating the neural circuitry and biochemistry underlying anhedonia opens the door to targeted drug development and new modalities of behavioral treatment that may also stimulate or normalize reward circuitry.

In the sucrose preference test, researchers assess the animal's interest in seeking out a sweet drink relative to plain drinking water. A bias toward the sweetened drink is typical, and failure to do so is considered indicative of anhedonia/depression. The test has validity based on its sensitivity to chronic stress and antidepressant treatment. Repeated administration of ketamine (seven days) reversed the decrease in sucrose consumption in rats exposed to chronic stress (Garcia et al. 2009). Furthermore, administration of a low dose of ketamine (0.5 mg/kg) for 10 days significantly increased sucrose consumption in Wistar-Kyoto rats (Akinfiresoye and

Tizabi 2013). Marked increases in sucrose consumption in rats persisted at one week after a single treatment with ketamine (10 mg/kg) (Li et al. 2011), indicating, again, significant protracted effects of ketamine on an important behavioral assay.

6.2.4 Ketamine and Anxiety: Elevated Plus Maze and Hyponeophagia

Effective treatment of anxiety and other negative affective states and behaviors is an important clinical concern in management of MDD, as patients with treatment-refractory depression exhibit increased comorbid anxiety compared to treatment-responsive MDD patients (Fava et al. 2000). Rodent models of anxiety, based largely on fear of open unprotected spaces, have had a long-standing equivocal response to classic antidepressant treatment (Paslawski et al. 1996). Several studies now suggest that the elevated plus maze (EPM) can be used to assess the anxiolytic effects of ketamine. A single ketamine injection was shown to induce an anxiolytic response in rats during exposure to the EPM 30 minutes after the injection (Engin et al. 2009). A similar effect was observed in mice one and two h following treatment (Hayase et al. 2006). These studies showed that the EPM was not sensitive to very low doses of ketamine and that only higher—but still sub-anesthetic—doses (30 mg/kg) induced a significant anxiolytic effect. Moreover, lower doses of ketamine did not induce an anxiolytic response in the EPM in stress-naïve mice (Autry et al. 2011). Again, potentially demonstrating the unique duration of behavioral effects associated with ketamine, Parise and colleagues described significant anxiolytic effects in the EPM in rats two months after the completion of a 15-day dosing regimen of 20 mg/kg per day during adolescence (Parise et al. 2013).

Other ethologically relevant tests of anxiety make use of a rodent's reluctance to consume even highly palatable foods (bait shyness) when placed in novel environments. Highly emotional rodents demonstrate a longer latency to approach food with lower food consumption within a fixed test time (Ramos and Mormede 1998). In the novelty-suppressed feeding (NSF) test and novelty-induced hypophagia (NIH) tests, the latency to feed is increased, and the amount of food consumed is reduced in a novel environment. These tests have considerable face validity, although interpreting results with the NSF may be limited by the use of food deprivation.

Hyponeophagia is one of the few anxiety-related tests that is reliably attenuated following chronic, but not acute, administration of classic antidepressant drugs (Bodnoff et al. 1988; Dulawa and Hen 2005). Ketamine, in contrast, reduced the latency to eat within hours of treatment. The effective dose range for ketamine in this task varied across studies: 30 minutes and 24 hours following 5–10 mg/kg (Li et al. 2010; Carrier and Kabbaj 2013) and 30 mg/kg (Iijima et al. 2012), but all tests resulted in a significant reduction in the latency to feed in the novel environment. Moreover, ketamine (10 mg/kg) successfully reduced the latency to eat in the NIH one h postinjection (Burgdorf et al. 2013). More sustained effects of acute ketamine

treatment (3 mg/kg) were observed 48 hours following treatment in mice exposed to chronic stress, although ketamine did not reduce feeding latency in stress-naïve mice in this study (Autry et al. 2011).

6.2.5 *Ketamine and Complex Behavioral Models, Sex, and Strain Differences*

There is general consensus that the chronic mild stress (CMS) paradigm, which challenges rodents with a series of unpredictable mild stressors over a prolonged period, produces behavioral changes consistent with features of depression (Krishnan and Nestler 2011). These behavioral changes include changes in appetite, diurnal rhythm, grooming, anhedonia, behavioral despair, and impaired cognition. Numerous studies using the CMS model have demonstrated that standard antidepressant treatment reverses the behavioral outcomes of CMS when given over a period of weeks (Browne and Lucki 2013). Because the CMS model is a widely accepted rodent model of depression, it is frequently used to screen novel therapeutics like ketamine. Studies have shown that ketamine reverses CMS-related behavioral despair and anhedonia (Ma et al. 2013; Li et al. 2011) as well as learned helplessness (Autry et al. 2011). Protracted effects of acute ketamine treatment were evident in CMS-exposed mice tested at four, six, and eight days after a single ketamine treatment (Ma et al. 2013). At least two studies have suggested that mice exposed to CMS have an increased sensitivity to ketamine (Ma et al. 2013; Li et al. 2011).

Because stress exposure is one of the most important risk factors for psychiatric illnesses—including MDD and post-traumatic stress disorder (PTSD)—ketamine's potential role in both preventing and reversing the pathogenic effects of stress is critically important. A recent study showed that in stress-inducing behavioral paradigms—chronic social defeat (SD), learned helplessness (LH), and chronic corticosterone (CORT) treatment models—rodents responded to prophylactic treatment with ketamine with reduced stress-induced behavior in the FST, NSF, and the sucrose splash test (Brachman et al. 2016).

Other rodent models of depression with important links to human histories of trauma and neglect have also been responsive to ketamine. In a normally gregarious rodent species, social isolation produces disruptions in grooming and diurnal rhythm, hyperactivity, neophobia, and perseverative behaviors, as well as deficits in sensorimotor gating and anhedonia (Fone and Porkess 2008). In numerous studies, pathological behaviors produced by social isolation have been responsive to antipsychotics and SSRIs. Recent reports have shown that a single sub-anesthetic dose of an NMDA receptor antagonist can reduce behavioral despair and restore grooming in chronically isolated rodents (Haj-Mirzaian et al. 2015).

Maternal deprivation during the preweaning period has also been a paradigmatic rodent model for depression. Reports have shown that a single dose of ketamine rescued immobility in the FST in adult animals that experienced preweaning

maternal deprivation (Reus et al. 2015). Exposure to trauma and neglect early in development are well-established precursors to treatment-refractory depression. Successful use of ketamine in these complex developmental models of stress and adversity shows promise for future use of novel treatments as possible preventive agents.

6.2.6 *Sex Differences in the Antidepressant Effects of Ketamine in Rodent Models*

Women represent an important demographic in MDD and are twice as likely to have depression and depressive symptoms as men of the same age. Preclinical researchers have been slow to respond to this disparity in the clinical population. Typically, male rodents are used in preclinical behavioral pharmacology studies, and therefore, preclinical work has not addressed the salient and mood-related role of shifting reproductive hormone levels in women. In a study examining ketamine's effect on ovarectomized Wistar rats, researchers found that ketamine was effective in reducing immobility in the FST (da Silva Moreira et al. 2016). In another recent report, researchers demonstrated that in mice exposed to CMS, female mice had antidepressant responses on the FST at lower doses of ketamine than their male counterparts. However, the protracted benefits of ketamine accrued for males not females (Franceschelli et al. 2015). A recent study suggests that some of the differences in male and female response may be secondary to differences in the metabolic degradation of ketamine between the sexes and to an increased amount of hydroxynorketamine (HNK) generated in female mice (Zanos et al. 2016). The translational value of these studies on sex-dependent effects of ketamine's antidepressant properties remain unclear as there have not been consistent reports of sex-related effects in clinical trials with ketamine to date.

6.2.7 *Summary of Preclinical Behavioral Responses to Ketamine*

Consistency in preclinical studies is often as rare as is agreement in human research. Differences across animal laboratories can emerge from varying conditions in the vivarium, differences in animal handling and housing conditions, the developmental stage of the animals being tested, and paradigms for inducing stress. However, in sum, the emerging evidence suggests that ketamine does produce wide-ranging effects on despair, anhedonia, and anxiety following a single administration in a number of different rodent models. Moreover, ketamine appears to be unique and different from classic antidepressant drugs in producing sustained effects in these assays and reversing the behavioral effects of chronic stress after a single infusion. The evidence showing similar durable effects for other NMDA receptor antagonist

drugs is less consistent, with some studies showing both rapid and sustained effects of these drugs and others showing only rapid-onset short-duration effects.

Several important caveats are worth mentioning with regard to rodent research in this area of novel rapidly acting antidepressant drug development. First, ketamine at sub-anesthetic doses, as well as several of the other NMDA receptor antagonists, can induce locomotor activation in rodents. This could be a major confound in attempts to interpret studies examining the effects of ketamine (or other NMDA receptor-targeting drugs) over the hours immediately following dosing as the behavioral tests used in these assays rely on motor activity (Browne and Lucki 2013); thus, drugs that activate rodents can produce false positives. In the case of ketamine, low-dose intraperitoneal injections (5–15 mg/kg) have been shown to induce hyperactivity (da Silva et al. 2010). In addition, repeated administration of ketamine (50 mg/kg) can sensitize rats to its activating effects (Popik et al. 2008). This serves as a caution to researchers that the activating effects of ketamine should be thoroughly established for animal strains and testing environments prior to making specific conclusions related to the drugs' effects on tests of anxiety, despair, or anhedonia that require locomotion to perform and evaluate. Furthermore, as expanded on below, studies suggest that NMDA receptor-targeting drugs exhibit very complex dose- and time-dependent response relationships. Considering these facts, it is important to compare results from similarly designed studies when attempting to make conclusions about the drugs' effects.

6.3 Ketamine's Mechanism of Antidepressant Action

6.3.1 From the Monoamine Hypothesis to Changes in Synaptic Plasticity

The monoamine hypothesis reigned as the dominant model in depression research for over 40 years. This hypothesis was based largely on findings that drugs acting through various mechanisms to increase synaptic concentrations of monoamines could ameliorate the symptoms of depression. The central argument was that the underlying physiological basis for depression was a deficit in central noradrenergic and/or serotonergic neurotransmission and that, by targeting these neuronal/synaptic deficits with SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs), normal function could be restored in depressed patients. This hypothesis was critically important in the development of multiple effective antidepressant medications over the past five decades. However, the hypothesis could not account for why many patients did not benefit from these drugs and was insufficient to explain the slow onset and gradual clinical response to monoaminergic antidepressant treatments when the increase in availability of monoamines is rapid (Hirschfeld 2000).

These and several other inconsistencies in the monoaminergic hypothesis have led to the development of other hypothesized mechanisms of drug action. The recogni-

tion of amino acid neurotransmitter abnormalities in the brains of depressed patients, the mounting evidence that altered regional levels of neuroplasticity may play a central role in the pathogenesis of mood disorders and possible mechanism of action, and the discovery of ketamine's rapid antidepressant effects have stimulated great interest in the glutamatergic system as a primary mediator of antidepressant drug effects (Sanacora et al. 2008). However, ketamine (a known glutamatergic NMDA receptor antagonist) is known to affect several other neurotransmitter systems and physiological pathways that could be critical in generating the observed antidepressant response. The remaining sections will provide an overview of the role of glutamatergic neurotransmitters in the pathophysiology of mood disorders and attempt to review the information in order to help us better understand ketamine's mechanism of antidepressant action.

6.3.2 The Importance of Glutamate Neurotransmission in Preclinical Pathophysiological Studies

Although it was not readily recognized as a neurotransmitter until the early 1980s, the amino acid glutamate is now accepted as the major excitatory neurotransmitter in the central nervous system. Glutamate mediates the vast majority of fast excitatory transmission in the brain, while γ-aminobutyric acid (GABA) mediates the majority of fast inhibitory transmission. In humans, 80 % of neurons in the neocortex are excitatory and form 85 % of all synapses, while roughly 20 % of the neurons are inhibitory, forming 15 % of the synapses (Douglas and Martin 2007). Glutamate is now also recognized as the major neurotransmitter regulating local protein synthesis and synaptic plasticity (Whalley 2014). Through these regulatory effects on brain physiology and structure, glutamate is believed to have dramatic effects on normal and pathological behavior. Commensurate with the critical role played by glutamate in mediating a wide array of brain functions, there are complex and redundant mechanisms regulating glutamate neurotransmission.

In brief, there is tight physiological regulation of glutamate metabolism, synaptic release, clearance, and postsynaptic receptor expression and function. Glutamate is primarily derived from the carbon backbone of glucose and is part of a much larger metabolic pathway (Pellerin and Magistretti 2004). In this regard, it is important to note that in addition to glutamate's role as a neurotransmitter, it also serves as a metabolic precursor to GABA and as a component of various other physiologically important amino acid-based derivatives, e.g., the antioxidant glutathione.

Within the neuron, cytosolic glutamate crosses the vesicular membrane via the activity of vesicular glutamate transporters (VGLUTs) (Takamori 2006). Targeted reductions of VGLUT expression have been shown to reduce glutamate packaging into synaptic vesicles and are associated with deleterious effects and neuropsychiatric sequelae (Wallen-Mackenzie et al. 2010). Glutamate is released into the synaptic cleft via a Ca2+ and soluble N-ethylmaleimide-sensitive factor attachment protein

receptor (SNARE)-dependent manner (Sudhof and Rothman 2009). Studies demonstrating that the packaging and release of vesicular glutamate are modulated by stress and psychotropic drugs (Musazzi et al. 2010) suggest that altered levels of glutamate release could be a primary factor mediating stress-related pathophysiology and possibly serve as a target for drug development (Popoli et al. 2012).

Elevated concentrations of extracellular glutamate—and especially increased levels of extrasynaptic glutamate—are believed to be the primary mechanism underlying excitotoxic cellular damage (Hardingham and Bading 2010). Thus, rapid removal of extracellular glutamate is critical to avoiding cellular damage. Glutamate is actively cleared from the extracellular space by excitatory amino acid transporters (EAATs), primarily found on synaptically associated astrocytic processes (O'Shea 2002; Jensen et al. 2015). The location of the EAATs relative to the geometry of the synapse places them in a critical position for preventing glutamate spillover and activating extrasynaptic glutamate transporters (Tzingounis and Wadiche 2007). Interestingly, EAAT dysfunction has specifically been implicated in the pathology of several neurodegenerative disorders (Beart and O'Shea 2007) as well as disorders reflecting altered regulation of positive affect (McCullumsmith and Sanacora 2015).

Once returned to the cytosol, glutamine synthetase, an astrocyte - and oligodendrocyte-specific enzyme, converts glutamate into glutamine. A net exchange of glutamine from astrocytes to neurons is then achieved with energetic support. Back in the neuron, glutaminase reconverts glutamine to glutamate to complete the glutamate/glutamine cycle. The glutamate is then available for subsequent repackaging into synaptic vesicles. Several studies have identified reduced expression levels of EAATs and glutamine synthetase in the brains of patients with mood and psychotic spectrum disorders (Sequeira et al. 2009; Bernard et al. 2010; Choudary et al. 2005; McCullumsmith and Meador-Woodruff 2002). Other studies have demonstrated that chronic unpredictable stress decreases the rate of glutamate/glutamine cycling in rodents (Banasr et al. 2010) and further suggest that impaired glutamate clearance and cycling could lead to elevated levels of extrasynaptic glutamate that produce an inhibitory feedback on presynaptic glutamate release. Thus, it has been proposed that exposure to chronic stress could lead to dysregulated glutamate neurotransmission in which point-to-point transmission is decreased, but spillover to extrasynaptic spaces is increased in several brain regions.

6.3.3 The Importance of Glutamate Receptor Pharmacology and Relevance to Psychopathology

Glutamate receptors can be divided into two broad categories: ionotropic and metabotropic (see Fig. 6.1). Three classes of ionotropic glutamate receptors have been identified and named based on agonist selectivity: NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA), and kainate (KA). The

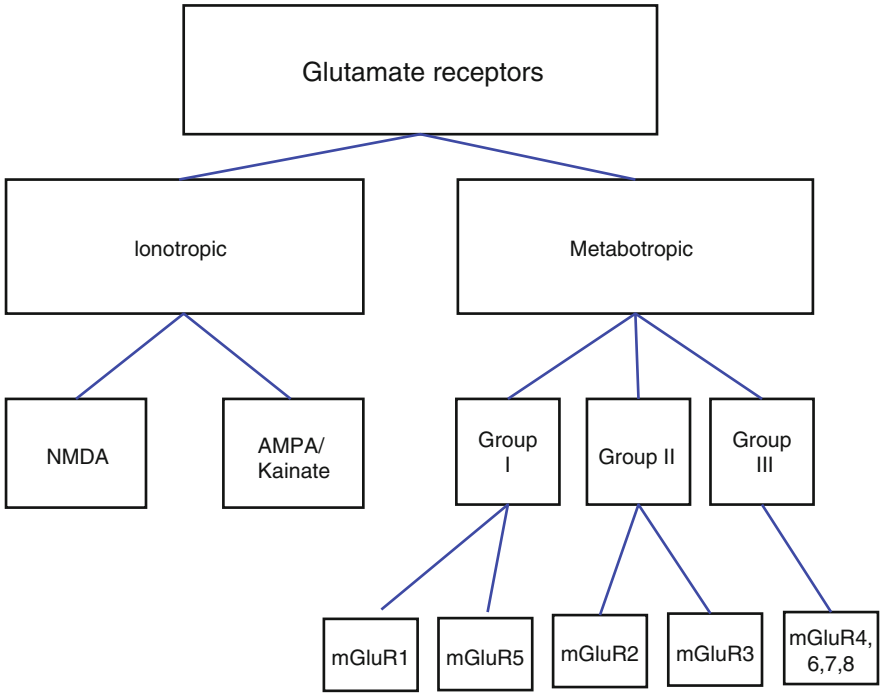

Fig. 6.1 Glutamate receptor classification. *NMDA* N-methyl-D-aspartate, *AMPA* alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid, *mGluR* metabotropic glutamate receptor

ionotropic glutamate receptors have diverse functions based on differing channel properties based on subunit composition, expression profile, and cellular location, which allows them to serve unique purposes within the brain. NMDA receptors are among the most tightly regulated in the mammalian brain with multiple binding sites that modulate the probability of ion channel opening, viz., sites for two obligatory co-ligands (glutamate and glycine or D-serine), polyamines, and cations (Mg2+, Zn2+, and H+). There are three families of NMDA receptor subunits: (1) NR1, (2) NR2A-D, and (3) NR3A-B. Glutamate binds to the NR2 subunit, while glycine and D-serine bind to a site on the NR1 subunit. Several NMDA receptor antagonists act through voltage-dependent blockade of the channel pore, e.g., phencyclidine (PCP), ketamine, and MK-801. As mentioned above, glutamatergic neurotoxicity is believed to be mediated through the NMDA receptor, especially the differential activation of extrasynaptic relative to synaptic NMDA receptors (Hardingham et al. 2002; Vanhoutte and Bading 2003; Ivanov et al. 2006; Leveille et al. 2008; Xu et al. 2009; Hardingham and Bading 2010).

AMPA receptors are also widely expressed in the mammalian CNS and mediate fast excitatory neurotransmission in response to glutamate binding. They can be blocked by specific quinoxalinediones including 6-nitro-7-sulphamobezo(f) quinoxaline-2,3-dione (NBQX), a potent and selective AMPA receptor antagonist.

Kainate receptors are also ionotropic receptors that mediate fast excitatory neurotransmission in some brain regions (Alt et al. 2004). AMPA receptor trafficking has been widely studied, especially as it relates to learning and memory. Stress hormones have recently been recognized to play a role in AMPA receptor trafficking (Groc et al. 2008; Krugers et al. 2010; Yuen et al. 2011) and may provide a mechanism for the dose-dependent ("inverted U") facilitative and suppressive effects of corticosteroid hormones on synaptic plasticity and cognition (Martin et al. 2009).

In contrast to the ionotropic glutamate receptors that depend on cation flux, metabotropic glutamate receptors exert their effects via the recruitment and activation of intracellular G-proteins and downstream signal transduction pathways. Most metabotropic receptors localize primarily to perisynaptic and extrasynaptic locations on neurons and glial cells and modulate synaptic activity and plasticity. Eight unique metabotropic glutamate receptors have been identified (mGluR1-8); these have been subdivided into three functional groups on the basis of amino acid homology, agonist binding, and activated downstream signal transduction cascades (Kim et al. 2008). Group I metabotropic glutamate receptors comprising mGluR1 and mGluR5 elicit their downstream effects by two mechanisms: (1) phospholipase C via inositol-1,4,5-triphosphate (IP3) to release Ca2+ from intracellular stores and (2) diacylglycerol (DAG) to stimulate protein kinase C (PKC). Group II metabotropic glutamate receptors (mGluR2 and mGluR3) and group III metabotropic glutamate receptors (mGluR4-8) are coupled to inhibitory G-proteins (Gi) that decrease intracellular cyclic adenosine monophosphate (cAMP) by inhibiting the adenylyl cyclase/protein kinase A pathway.

Postsynaptic activation of metabotropic glutamate receptors modulates ion channel activity and can potentiate or inhibit channel activity depending on its unique downstream signal transduction cascades. Presynaptic metabotropic glutamate receptors can decrease both excitatory glutamatergic and inhibitory GABAergic neurotransmission. Both positive and negative modulators of presynaptic group II and III metabotropic glutamate receptors are being developed and tested for clinical efficacy in clinical trials.

6.3.4 Intracellular Signal Transduction from the Postsynaptic Density to the Nucleus

Ionotropic and metabotropic glutamate receptors interact with a number of postsynaptic proteins such as postsynaptic density protein (PSD) of 95 kDA (PSD-95). PSD-95 mechanically stabilizes the synapse and bridges glutamate receptors to the cytoskeleton. PSD-95 also binds to postsynaptic signal transduction effectors that mediate the phosphorylation of various protein kinases and leads to the translocation of AMPA receptors from more intracellular compartments to the PSD. A similar cycling process also occurs with KA receptors through PSD-95 and other scaffolding proteins, e.g., glutamate receptor-activating protein (GRIP) and SAP-97 (synapse-activating protein of 97 kDa). Metabotropic glutamate

receptors, found more commonly at perisynaptic and extrasynaptic sites, interact with different "scaffolding" proteins (e.g., Shank and Homer), but also affect downstream signaling cascades that modulate gene expression, local protein synthesis, and cytoskeletal transformations associated with neuroplasticity. Several studies have identified altered expression of postsynaptic proteins and changes in synaptic plasticity as contributing to stress-induced pathologies in rodent models. Similar changes have been identified in individuals suffering from a variety of neuropsychiatric diseases (de Bartolomeis et al. 2014; Feyissa et al. 2009; Karolewicz et al. 2009).

6.4 Ketamine's Mechanism of Action

Acute ketamine exposure has repeatedly been shown to induce rapid dendritic spine morphogenesis (Duman et al. 2016; Autry et al. 2011), although recent studies suggest that the extent of this effect may also be somewhat sex-dependent (Sarkar and Kabbaj 2016). Most of the currently available data suggest that spine morphogenesis and enhanced AMPA receptor activity are associated with, and possibly mediate, the rapidly induced, sustained antidepressant response of ketamine. However, the more proximal mechanisms driving the changes in synaptic plasticity and remodeling remain less well established. An early study by Maeng and colleagues (Maeng et al. 2008) demonstrated that the antidepressant effects of ketamine and other NMDA receptor antagonists could be blocked by coadministration of drugs that inhibit AMPA activation. This finding has been widely replicated in rodent models (Koike et al. 2011a) and has been used as the strongest evidence to suggest AMPA activation is critical to ketamine's mechanism of antidepressant action. In fact, direct stimulation of AMPA receptors has been shown to produce antidepressant effects independent of NMDA receptor antagonism, suggesting that AMPA activation alone may be necessary and sufficient to generate an antidepressant-like response in rodent models (Alt et al. 2006). However, other studies suggest that a combination of AMPA potentiation with other ketamine-induced effects produces a synergistic antidepressant-like effect (Du et al. 2006). This may be achieved by altering the relative ratio of AMPA to NMDA activation.

There is less agreement regarding the mechanisms via which ketamine—and possibly other rapidly acting antidepressants—leads to increased AMPA activation and the mechanisms through which increased AMPA activation produces changes in synaptic plasticity and synaptogenesis. Early work suggested that increases in glutamate neurotransmission following NMDA receptor antagonist administration were mediated by a burst of pyramidal cell glutamate release secondary to a decrease in GABAergic inhibitory feedback on the pyramidal neurons in layer V of the prefrontal cortex (PFC) (Homayoun and Moghaddam 2007). This hypothesis holds that tonic firing of these GABA interneurons is driven by NMDA receptors and that the active, open-channel state of these receptors allows ketamine to enter and block channel activity. Consistent with the hypothesis that a burst of glutamate release is

associated with antidepressant action, recent studies examining the effects of ketamine and other putative rapidly acting antidepressants on glutamate neurotransmission suggest that the drugs do increase glutamate release and cycling (Chowdhury et al. 2016). The fact that similar dose-response curves were established for both the effects on 13C-enrichment and on antidepressant-like behaviors suggests that increased rates of cycling are associated with behavioral response. Further evidence showing that mGlu2 receptor antagonist drugs—which block presynaptic inhibition of glutamate release—produce similar cellular and antidepressant-like effects in rodent models provides additional support for this hypothesis (Dwyer et al. 2012; Koike et al. 2011b).

It is further postulated that the resulting glutamate burst stimulates AMPA receptors, leading to an increased release of brain-derived neurotrophic factor (BDNF) and stimulation of TrkB in several brain regions. The required increase in BDNF and TrkB signaling has also been one of the most commonly replicated findings, with most, but not all (Lindholm et al. 2012), studies suggesting this is a critical component of the antidepressant response. An interesting study demonstrated that the synaptogenic actions of ketamine are blocked in mice with a knock-in of the BDNF Val-66-Met allele (Liu et al. 2012) that impairs BDNF mRNA transport to dendrites and activity-dependent release (Chen et al. 2006) as well as in conditional BDNF mutant mice (Autry et al. 2011), thus providing strong support for the role of BDNF in generating the cellular and behavioral changes associated with ketamine. Interestingly, a preliminary clinical study found a significantly lower rate of response to a single ketamine treatment in depressed val66met BDNF allele carriers (Laje et al. 2012). These data suggest that BDNF is critical to antidepressant response and also that the polymorphisms of the gene may provide a useful biomarker to guide treatment planning in clinical settings.

Other studies suggest that activation of TrkB increases mTORC1 signaling, leading to the increased synthesis of proteins that are required for synapse maturation and formation (i.e., GluA1 and PSD-95) (Duman et al. 2016; Li et al. 2010). These studies demonstrate that under conditions in which mTORC1 signaling is blocked (such as with concomitant rapamycin infusions), the synaptic and behavioral actions of ketamine are blocked. However, other investigators have failed to demonstrate that ketamine induces significant changes in mTORC1 signaling and have not found the increase in the signaling pathway to be critical in inducing antidepressant-like response to ketamine (Autry et al. 2011).

A second hypothesis holds that a burst of glutamate release is not necessary to induce the activity of postsynaptic AMPA receptors but instead that ketamine blocks NMDA receptor-mediated spontaneous miniature excitatory postsynaptic currents at rest (Autry et al. 2011; Kavalali and Monteggia 2012; Nosyreva et al. 2013). This has the effect of deactivating eukaryotic elongation factor 2 (eEF2) kinase and results in reduced eEF2 phosphorylation and de-suppression of BDNF translation. The increase in BDNF activity then leads to further increases in AMPA receptor insertion into PSD regions and increases in spine density and is thus consistent with the previous model indicating that the regulation of protein synthesis by spontaneous

neurotransmission may serve as a viable therapeutic target for the development of rapidly acting antidepressants.

A very recent manuscript suggests that NMDA receptor antagonism may not be at all necessary in order for ketamine to produce its unique rapid onset of antidepressant-like effects (Zanos et al. 2016). These investigators performed a series of studies that seemed to demonstrate that a metabolite of ketamine—HNK—may be both necessary and sufficient to generate the more durable behavioral effects on the mouse FST. This was supported by evidence that HNK had very low affinity for the NMDA receptor. Further, chemical manipulation of the parent drug (ketamine) in a way that preserved binding to the NMDA receptor but prevented metabolism to HNK completely attenuated the sustained antidepressant-like effects of the drug. Results from the study also suggest that the metabolite of the *R*-ketamine enantiomer could be producing the majority of the antidepressant effect. These results parallel another recent study also suggesting that *R*-ketamine has greater potency and longer-lasting antidepressant effects than *S*-ketamine (Yang et al. 2015). While the mechanism by which HNK generates its proximal effects is unclear, findings thus far are consistent with previous models showing that AMPA activation and BDNF expression are required to produce behavioral effects.

Interestingly, previous studies have shown that HNK has antagonistic activity at the α7-nicotinic acetylcholine receptor (Paul et al. 2014). Acting through this receptor, HNK modified the expression of serine racemase (Moaddel et al. 2015), the enzyme responsible for the production of D-serine. As mentioned above, D-serine is an endogenous coactivator of the NMDA receptor at the glycine site. In addition, the α7-nicotinic acetylcholine receptor has been shown to mediate glutamate release (Konradsson-Geuken et al. 2009), postsynaptic ionic glutamate receptors, and even the regulation of glutamate transporters (Morioka et al. 2015). All of these effects could modulate glutamatergic synaptic neurotransmission and serve as critical steps in generating antidepressant-like response.

In summary, there is strong and convincing data suggesting that ketamine and possibly other NMDA receptor antagonists can alter glutamatergic neurotransmission, at least in the region of the prefrontal cortex, where most of the studies have been focused to date. It appears that an increased activation of AMPA receptors in this brain region is necessary to achieve antidepressant response. It is less clear whether AMPA activation is sufficient to generate the response. The majority of the evidence suggests that increased activation of TrkB receptors by BDNF is also a required step in generating antidepressant behavioral response. However, there remains some disagreement on the exact mechanisms through which ketamine causes the increased activation of AMPA receptors in the brain regions of interest. This could either be through (1) induction of increased presynaptic glutamate release, (2) blockade of NMDA receptor-mediated spontaneous miniature excitatory postsynaptic resting currents resulting in reduced eEF2 phosphorylation and de-suppression of BDNF expression, or (3) a completely non-NMDA-dependent mechanism possibly involving the regulation of D-serine or the α7-nicotinic acetylcholine receptor (Fig. 6.2).

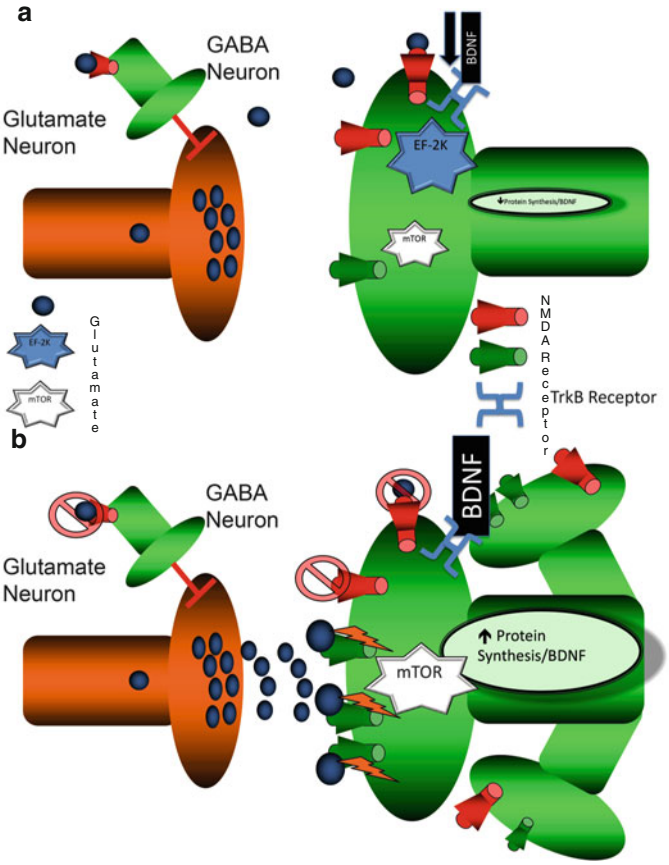

Fig. 6.2 Putative glutamate-mediated mechanisms of ketamine's antidepressant action. (**a**) The glutamate burst hypothesis holds that under baseline or depressed states, glutamate release is dampened, possibly by the inhibition of pyramidal neurons in the prefrontal cortex (*PFC*) by gamma-aminobutyric acid (*GABA*) interneurons or possibly by increased levels of extracellular glutamate that inhibit glutamate release through presynaptic metabotropic glutamate receptors (mGluR)2 receptors (not shown in figure). The decreased stimulated glutamate release is believed to result in reduced stimulation of postsynaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (*AMPA*) receptors resulting in reduced brain-derived neurotrophic factor (*BDNF*) activation of TrkB receptors, reduced levels of local protein synthesis, and lower levels of synaptic plasticity. An alternative hypothesis posits that resting N-methyl-D-aspartate (NMDA) receptor-mediated spontaneous miniature excitatory postsynaptic currents activate eukaryotic elongation factor 2 (eEF2) kinase, increasing eEF2 phosphorylation and suppressing BDNF translation and local protein synthesis. Both of these hypotheses propose that decreased levels of regional BDNF expression, protein synthesis, and synaptic plasticity contribute to the pathophysiology of the baseline depressed state. (**b**) The glutamate burst hypothesis proposes that ketamine (and other NMDA receptor antagonist drugs) increases levels of glutamate release from presynaptic cells, possibly by preferential blockade of inhibitory GABAergic interneurons. The increased levels of synaptic glutamate activate AMPA receptors and initiate a cascade of events leading to local protein and neurotrophic synthesis (mediated in part through mTORC1 activation) that results in increased levels of synaptic plasticity and the associated antidepressant-like behavioral changes. (**c**) The inhibition of resting NMDA receptor activation hypothesis suggests that some NMDA receptor antagonists such as ketamine are capable of blocking the spontaneous activation of NMDA receptors (in the absence of action potentials), thereby attenuating eEF2 phosphorylation and allowing the translation of BDNF and other target transcripts. This ultimately leads to increased levels of AMPA insertion to the postsynaptic membrane and increased levels of synaptic plasticity

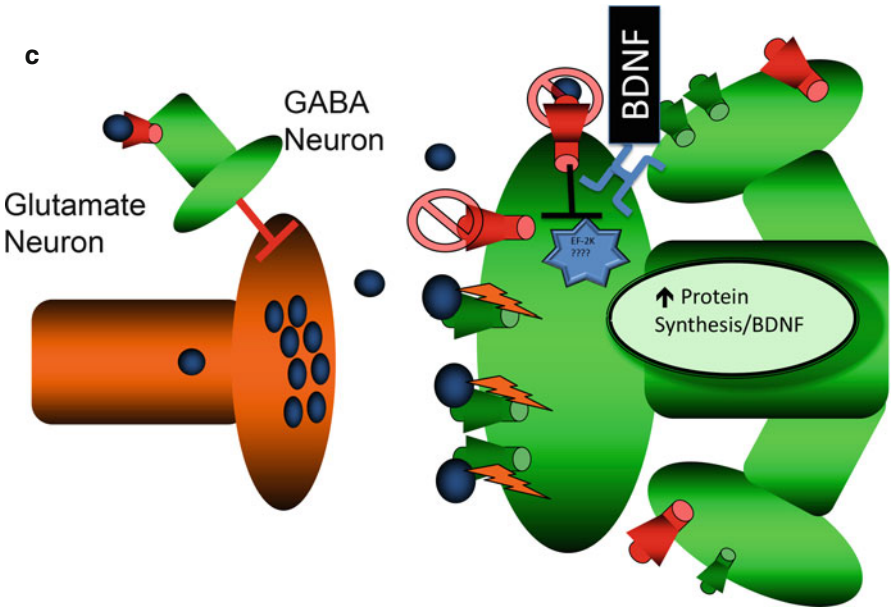

Fig. 6.2 (continued)

6.4.1 Additional Mechanisms of Action: Dopamine and Opiate Receptors

Recent preclinical work on the role of monoamines suggests that ketamine may have potentially important systems-level effects. In a rat model of learned helplessness (LH; inescapable stress), researchers looked at ketamine's effect on dopaminergic function in the ventral tegmental area (VTA). Impairments in the VTA have been hypothesized to correlate with anhedonia, one of the most severe and refractory behavioral domains of MDD (Belujon and Grace 2014). In this report, ketamine restored synaptic function in stress-induced synaptic dysfunction; ketamine also reestablished the depleted dopamine neuron population in the VTA. The same group found that ketamine restored depleted dopaminergic function in rodent models of substance abuse (Belujon et al. 2016). These results suggest, at least in a preclinical model, a potential role for ketamine in treating the anhedonia associated with mental illness.

Ketamine's effects on opioid receptors have been acknowledged for several decades (Finck and Ngai 1982). Preclinical studies indicate that ketamine increases mu-opioid receptor density in hippocampal tissue (Kekesi et al. 2011) and enhances mu-opioid-induced ERK1/2 phosphorylation in cell lines, as well as speeds wait time for resensitizing ERK1/2 signaling (Gupta et al. 2011). Moreover, in antinociception studies of ketamine in mice, analgesic effects were blocked by mu and lambda antagonists, but not by kappa antagonists (Pacheco Dda et al. 2014). An earlier study also reported that ketamine produced kappa-mediated disruption of cognition in rodents, suggestive of its dissociative properties in humans (Nemeth et al. 2010). However, NMDA receptors may play a role in opioid-induced analgesia

(Mion and Villevieille 2013), with studies pointing to ketamine's analgesic properties involving both opioid and NMDA receptors (Mehta et al. 2012). Taken together, data from a variety of sources indicate that ketamine does have some agonistic-like effects on the mu-opioid receptor, which may suggest a potential risk of abuse. However, rodent studies on reinforcing properties have been mixed. Intracranial self-stimulation appears not to be increased by the drug (Hillhouse et al. 2014); however, as others have pointed out, this does not eliminate the risk of abuse (Yang and Hashimoto 2014) as choice preference-based use can be increased with ketamine (Suzuki et al. 1999).

Nevertheless, recent data that the drug produces behavioral effects through mu receptor binding provide a rather different framework for assessing its positive and negative pharmacological properties. Indeed, studies combining ketamine with the mu-antagonist naloxone in rodents and man could be informative. Perhaps related to mu-opioid effects are the observations that a positive family history of alcohol abuse is a predictor of antidepressant response to ketamine (Luckenbaugh et al. 2012).

6.4.2 Potential Anti-inflammatory Effects of Ketamine

The relationship between excessive activation of inflammatory pathways and the pathophysiology and treatment of depression has recently gained increased attention (Haroon et al. 2016). We know that psychological and social stressors can increase levels of inflammatory cytokines in humans, and that cytokine infusions (e.g., interferon) can produce sickness behavior with characteristics of depression (Miller and Raison 2016). Serum levels of the pro-inflammatory cytokines interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) are increased in depressed patients, and levels are normalized by antidepressant treatment. Inflammatory cytokines derived from microglia (the brain's resident innate immune cells) influence synaptic plasticity and spine synapse formation under physiological conditions (Brites and Fernandes 2015). Together, these studies demonstrate that normal brain function requires low levels of inflammatory cytokines but that elevated levels can contribute to damage, atrophy, and loss of spine synapses.

In a series of clinical and preclinical studies, ketamine was shown to have several effects on inflammatory processes, including the regulation of IL-6-mediated inflammation, the ratio of IL-6 to IL-10 following immune challenges, and levels of TNF-α (De Kock et al. 2013; Zunszain et al. 2013). A recent study in depressed patients also provided evidence to suggest that ketamine's effects on adipokines—cytokines secreted by adipose tissue that modulate both metabolism and inflammation—may also contribute to the mechanism of rapid onset of antidepressant action. Baseline levels as well as post-treatment changes in adipokine levels appear to correlate with ketamine treatment response (Machado-Vieira et al. 2016).

There is also evidence to suggest that ketamine may modulate the kynurenine pathway. Administration of lipopolysaccharide (LPS) to rodents is one of the most commonly used animal models of inflammation-induced depression. LPS has been

shown to activate the kynurenine pathway, increasing levels of 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid (which can activate NMDA receptors) release from activated microglia. Interestingly, pretreatment with ketamine was shown to block LPS induction of depressive-like behavior through a mechanism that was hypothesized to involve ketamine's ability to block quinolinic acid activation of NMDA receptors (Walker et al. 2013).

6.5 Conclusion

The discovery and development of ketamine as a rapid-acting antidepressant may be one of the most exciting breakthroughs in the treatment of mental illness in the last 50 years. Studies of ketamine's antidepressant properties in humans and rodents have both been promising on balance. Development of drugs that modulate the glutamatergic system and downstream cell signaling pathways represent a significant opportunity for ongoing preclinical and clinical research.

However, several research priorities remain:

1. Future research will need to clearly establish the enduring effects (both beneficial and deleterious) of single and repeated ketamine dosing as clinical populations will ultimately require ongoing care until remitted status is achieved. Presently, there is a dearth of rodent studies investigating the long-lasting effects of ketamine and especially those of other NMDA-receptor-targeting drugs.
2. Our survey of ketamine's mechanism of action indicates that researchers consistently find increased glutamatergic activation in the prefrontal cortex to be a critical component of the mechanism of action. Most studies also suggest that regional increases in BDNF expression are a necessary component of the response. However, there is inconsistency and disparity in findings related to the mechanisms driving these downstream effects of ketamine and whether similar responses can be achieved with other NMDA receptor-targeting agents.
3. There is also increasing evidence to suggest that other, non-NMDA-mediated mechanisms also contribute to ketamine's mechanism of antidepressant action. Ongoing work exploring its mechanism of action will pave the way for better second- and third-generation drugs acting through the glutamatergic system.
4. Concerns for the safety of ketamine as a long-term treatment for depression are ongoing and founded on both clinical and preclinical data, requiring more investigation.

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Chapter 7
Ketamine's Mechanism of Rapid Antidepressant Activity: Evidence Gleaned from Clinical Studies

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Abstract The discovery of antidepressant medications more than 50 years ago was one of the major breakthroughs in medical science. Today, the field of antidepressant drug development is experiencing a paradigm shift. Changing perceptions regarding the neurobiology of depression and the serendipitous discovery of ketamine's rapid antidepressant effects have ushered in a new era of innovative research and novel drug development. This chapter provides a selective review of the suspected mechanisms of ketamine's rapid antidepressant action in human subjects gleaned from multiple controlled and open-label trials. We also briefly review the underlying neurobiology of depression, potential biomarkers of ketamine response, the efficacy and safety profile of ketamine, current limitations to its widespread use, and considerations for novel drug development that hold promise for improved psychotherapeutic treatments for depressive and trauma-related disorders.

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7.1 Ketamine: A New Era in Antidepressant Drug Development

The field of antidepressant drug development is experiencing a paradigm shift. Changing perceptions regarding the neurobiology of depression and the serendipitous discovery of ketamine's rapid antidepressant effects have ushered in a new era of innovative research and novel drug development. This chapter provides a selective review of the evidence for ketamine's mechanisms of rapid antidepressant action as gleaned from clinical studies. We begin with a brief historical perspective on traditional antidepressants and review the limitations of currently available pharmacologic interventions for depression. Next, we present the glutamatergic and neuroplasticity hypotheses of depression and describe clinical evidence supporting ketamine's efficacy and safety profile as a novel agent for treatment-resistant depression (TRD). Potential limitations to ketamine's widespread clinical use and evidence gaps in the literature are also reviewed. We then describe potential clinical biomarkers as well as the neurobiological underpinnings and mechanisms of action currently believed to underlie ketamine's antidepressant effects; these include neurocircuitry and neurobiology that are key to affect regulation and molecular pathways involved in synaptogenesis as related to cognition and emotion. Associated evidence gleaned from preclinical studies is detailed in Chap. 6 of this book. We conclude by summarizing the evidence and providing some areas for continued investigation and consideration for novel drug development.

7.2 A Brief Historical Perspective of Mainstream Antidepressants

The discovery of antidepressant medications more than 50 years ago was one of the major breakthroughs in medical science. Over the last several decades, however, antidepressant research has generated only marginal advancement in the development of mechanistically novel psychopharmacologic interventions for depression. Consequently, very few improvements in clinical efficacy have been achieved. Depression is the leading cause of distress and disability worldwide and a major contributor to the overall global burden of disease (World Health Organization 2015; Vos et al. 2012; Collins et al. 2011), causing chronic, recurrent symptoms, heightened risk of suicide, poor functional outcomes, increased morbidity, and a profound socioeconomic burden (Kessler et al. 2003; Rush et al. 2006).

The urgent need for innovative drug development is underscored by shortcomings in the clinical effectiveness of standard antidepressant treatments. The psychotropic medications we use today have not undergone major evolution since the time of their inception. The 1950s and 1960s saw the creation of the first monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (Lopez-Munoz and Alamo 2009). The 1980s brought with them the development of the first selective serotonin

reuptake inhibitors (SSRIs) (Lopez-Munoz and Alamo 2009). These three classes of antidepressants were developed under the monoaminergic hypothesis of depression, which asserts that depressive symptoms are due to a functional deficiency of monoamine levels in the central nervous system (CNS) (Heninger et al. 1996). Traditional antidepressants are believed to ameliorate depressive symptoms by increasing the synaptic availability of these monoamine neurotransmitters (i.e., serotonin, dopamine, and norepinephrine) (Heninger et al. 1996; Hirschfeld 2000; Bunney and Davis 1965; Schildkraut 1995).

7.3 The Limitations of Traditional Antidepressants

A large clinical trial conducted by the National Institute of Mental Health found that traditional antidepressants have significant limitations for many patients. Only one-third of patients achieve symptom remission after their first medication trial (Gaynes et al. 2009), and many of those who do improve are unable to achieve sustained remission (Rush et al. 2006). Despite aggressive efforts to identify a tolerable and effective psychopharmacologic intervention, only two-thirds of patients achieve significant symptom remission even after adequate trials of four unique antidepressant medications over a one-year period (Gaynes et al. 2009). Further, these medications fall short of treating the full spectrum of symptoms for many patients; thus, even when some improvement is noted, many patients continue to exhibit refractory symptoms (Gaynes et al. 2009). This state of affairs is discouraging, but more importantly, it is a considerable liability for individuals already at heightened risk of suicide or self-harm (Murrough et al. 2015c; Zunszain et al. 2013). There is a clear and urgent need to develop novel, rapid-acting antidepressants with robust efficacy for patients who do not benefit from existing medications. Mounting evidence suggests that low doses of ketamine, a drug that targets the glutamatergic system, may possess both of these properties, acting rapidly and robustly to treat patients with severe TRD.

7.4 Shifting Perspectives in the Neurobiology of Depression

Although the monoaminergic hypothesis of depression has dominated the field of antidepressant drug development for nearly half a century, interest in a glutamatergic hypothesis and related glutamate-based antidepressant drug development is not entirely new. Its scientific history really begins in the late 1950s, when it was noted that D-cycloserine, an antibiotic used to treat tuberculosis and later found to be an *N*-methyl-D-aspartate (NMDA) glutamate receptor modulator, possessed mood-enhancing properties (Crane 1959). Across the next four decades, preclinical studies investigated the mood-altering effects of several NMDA receptor modulators (for a review, see Skolnick et al. 2009; Krystal et al. 2013). In the early 1990s,

preclinical studies reported evidence of antidepressant-like activity with NMDA receptor antagonists in rodent models (Trullas and Skolnick 1990). This line of research began an avalanche of work in this arena, providing accumulating evidence for a glutamate hypothesis of depression that integrates data from multidisciplinary fields including neurotrophic mechanisms, neurogenesis, gene expression, synaptic function and plasticity, and remodeling of neural circuitry (for a comprehensive overview, see Sanacora et al. (2012)).

7.5 The Glutamatergic Hypothesis of Depression

It is not surprising to find that the glutamatergic system is involved in affective disruptions and mood disorders. Empirical evidence indicates that (1) glutamate is the major CNS excitatory neurotransmitter, and the overwhelming majority of synapses and neurons in the CNS are glutamatergic (Orrego and Villanueva 1993), and (2) synaptic glutamate neurotransmission largely mediates both emotion and cognition, two phenomena inextricably linked to depression (Pessoa 2008). Further, data from clinical studies suggest that dysregulated glutamate transmission exists in a number of limbic/cortical areas (Sanacora et al. 2012) in the brains of depressed individuals relative to non-depressed comparison subjects, as does altered glutamate content (Kucukibrahimoglu et al. 2009; Mitani et al. 2006; Yuksel and Ongur 2010).

7.6 Exploring Novel Pharmacology for Improved Antidepressant Effects

Ketamine, an FDA-approved anesthetic medication and noncompetitive, high-affinity NMDA receptor antagonist, first synthesized by Parke-Davis in 1963, has been investigated within the frameworks of neuropsychopharmacology and biological psychiatry since the late 1980s. Initially, the effects of ketamine were examined in healthy subjects as a neuropsychopharmacologic model of addiction and psychosis (Anand et al. 2000; Krystal et al. 1994, 1998, 1999, 2003c, 2005a, b; Petrakis et al. 2004) and then among patients with schizophrenia (Krystal et al. 2003a) and alcoholism (Krystal et al. 2003b) as a way to explore the association between dysfunction in synaptic glutamate and NMDA receptor function. Through serendipitous discovery, ketamine was found to produce rapid and profound antidepressant effects in depressed adults following the administration of a single low-dose intravenous infusion (Berman et al. 2000), a finding that was later confirmed in larger randomized controlled studies of patients with treatment-resistant depression (Zarate et al. 2006; Murrough et al. 2013a). Given the significant dearth of effective psychopharmacologic interventions for treatment-refractory depression, this finding was particularly exciting and laid the foundation for a new generation of novel antidepressant research and development targeting the glutamatergic system.

A critical step in optimizing the clinical use and benefit of ketamine and similar, novel, rapid-acting NMDA receptor antagonists is to determine the mechanisms underlying their demonstrated antidepressant effects as well as their psychotomimetic and dissociative side effects. Preclinical and clinical investigations are currently underway that seek to advance the field's understanding of the neurobiological mechanisms, including neurochemical, neurocircuitry, genetic, molecular, cellular, and pharmacological markers of the clinical effects of ketamine (for reviews, see Caddy et al. (2014); Fond et al. (2014); McGirr et al. (2014); Abdallah et al. (2015a, c); Krystal et al. (2013); Mathew et al. (2012); Murrough (2012); Zarate et al. (2013)).

7.7 Stress, Depression, and the Neuroplasticity Hypothesis

Evidence suggests that neuroplasticity and synaptic homeostasis—foundational mechanisms in neuronal adaptation—are disturbed in mood disorders (Duman and Aghajanian 2012; Pittenger and Duman 2008; Popoli et al. 2012). Specific focus has been placed on synaptic plasticity and neural remodeling as related to the glutamatergic system and glutamate hypothesis of depression, and converging evidence gleaned from these investigations has led to a neuroplasticity or synaptogenic hypothesis of depression (Abdallah et al. 2015c; Pittenger and Duman 2008). Depression and prolonged stress have been associated with synaptic depression and neuronal atrophy in the hippocampus and prefrontal cortex (PFC) (Kang et al. 2012; Bessa et al. 2009; Yuen et al. 2012), while other brain regions such as the nucleus accumbens and amygdala have demonstrated alterations consistent with neuronal hypertrophy and synaptic potentiation (Bessa et al. 2013; Vyas et al. 2004). In the hippocampus and PFC, these synaptic alterations are thought to result from stress-induced changes in glutamate release and reuptake and astroglial loss leading to sustained increases in extracellular glutamate; this, in turn, precipitates excitotoxicity, altered synaptic strength, and reduced dendritic retraction, spine density, and branching in the PFC (Popoli et al. 2012; Krystal et al. 2013; for a review see Sanacora and Banasr 2013).

Stress and depression appear to strip the brain of fine connections between nerve cells (dendritic spines) within brain circuits that regulate mood. It is suspected that achievement and maintenance of homeostatic control of mood networks is vital to antidepressant treatment and response. Interestingly, long-term (but not acute) neuropsychopharmacologic intervention with traditional antidepressants has been demonstrated to block and reverse these neural deficits and promote synaptogenesis (Duman and Aghajanian 2012). Preclinical evidence suggests this blockage, reversal, and synaptogenesis is significantly accelerated following ketamine administration (Duman and Aghajanian 2012; Li et al. 2010). The time course appears to be comparable to the antidepressant effects of a single ketamine injection in humans (Duman and Aghajanian 2012).

7.8 Pharmacokinetics of Ketamine

Since the early 1960s, ketamine has been used primarily for the induction and maintenance of anesthesia in adult patients. More recently—and in addition to its use as a neuropsychopharmacologic probe of NMDA receptor function in animal and human experimental investigations of psychiatric disorders including schizophrenia, alcohol use disorders, and mood disorders—ketamine has been widely used for a variety of off-label and investigational purposes including pain management, status epilepticus, traumatic brain injury, peripheral inflammation, pediatric procedural sedation, and as a sedative for veterinary procedures (Abdallah and Krystal 2014). Most commercial and investigational preparations of ketamine in the United States contain equal (1:1) concentrations of its two enantiomers: *R*(−) ketamine and *S*(+) ketamine (Reich and Silvay 1989). Most clinical ketamine trials have used the racemic mixture, although case reports suggest reduced psychotomimetic effects and improved tolerability with the *R*- or *S*-enantiomers (Paul et al. 2009; Denk et al. 2011; Yang et al. 2015a). Ketamine is sufficiently lipophilic to be metabolized and redistributed into fatty tissues quite quickly, with a plasma half-life of four minutes and a plasma terminal half-life of 2.5 hours (Abdallah and Krystal 2014). It can be administered intravenously, intramuscularly (93 % BA – bioavailability), intranasally (50 % BA), intrarectally (25 % BA), or orally (20 % BA) (Mion and Villevieille 2013). Intravenous infusion has been the most widely studied administration paradigm, both because of the high bioavailability and because this route allows for enhanced control of drug exposure (Krystal et al. 2013).

7.9 Support for Ketamine's Rapid and Robust Antidepressant Effects

The rapid-acting and profound antidepressant effects of ketamine have been well replicated in numerous clinical studies (Berman et al. 2000; Murrough et al. 2013a; Zarate et al. 2006), underscoring the rationale for targeting the glutamatergic system and the feasibility of developing truly novel rapid-acting antidepressant agents (Niciu et al. 2014; Abdallah et al. 2015a, c; Machado-Vieira et al. 2009a; Zarate et al. 2006; aan Het Rot et al. 2012). To date, several studies have investigated the efficacy of intravenous subanesthetic (0.5 mg/kg) ketamine infusion in individuals with major depressive disorder (MDD) or bipolar depression (Abdallah et al. 2012; Berman et al. 2000; Valentine et al. 2011; Diazgranados et al. 2010a; Zarate et al. 2006, 2012; aan het Rot et al. 2010; DiazGranados et al. 2010b; Ibrahim et al. 2011, 2012; Machado-Vieira et al. 2009b; Mathew et al. 2010; Phelps et al. 2009; Price et al. 2009; Salvadore et al. 2009, 2010, 2011; aan Het Rot et al. 2012; Preskorn et al. 2008; Sanacora et al. 2013; Murrough et al. 2013a). Results from these trials have consistently reported rapid antidepressant effects within four hours of ketamine's administration (Abdallah et al. 2015a, c; Berman et al. 2000; Bessa et al. 2009, 2013; Caddy et al. 2014; Duman and Aghajanian 2012; Fond et al. 2014; Kang et al. 2012;

Krystal et al. 2005b; Mathew et al. 2012; McGirr et al. 2014; Murrough 2012; Murrough et al. 2013a; Pittenger and Duman 2008; Popoli et al. 2012; Sanacora and Banasr 2013; Vyas et al. 2004; Yuen et al. 2012; Zarate et al. 2006, 2013). Short-term response rates ranged from 43 to 90% (Phelps et al. 2009; aan het Rot et al. 2008), with sustained antidepressant effects observed for seven to 28 days after a single infusion (Ibrahim et al. 2012; Zarate et al. 2006). Notably, repeated intravenous doses prolonged treatment response (Murrough et al. 2013b), and intranasal administration exerted rapid antidepressant effects comparable to intravenous administration but with minimal psychotomimetic and dissociative effects (Lapidus et al. 2014). These rapid antidepressant effects have also been demonstrated in patient groups known to respond poorly to traditional pharmacologic antidepressant interventions, including TRD patients and those with anxious depression who achieved minimal to no response to electroconvulsive therapy (ECT) (Diazgranados et al. 2010a; Ibrahim et al. 2011; Ionescu et al. 2014a, b). Two trials found increased response to ketamine in patients with a family history of alcoholism (Luckenbaugh et al. 2012; Phelps et al. 2009), a finding that could be related to the enhanced NMDA function previously observed in this population (Petrakis et al. 2004). In addition, ketamine rapidly and effectively reduced suicidal ideation within hours of administration (Price et al. 2009, 2014; DiazGranados et al. 2010b; Ballard et al. 2014; Murrough et al. 2015c).

Three meta-analyses of clinical ketamine trials in depressed individuals have supported the short-term efficacy of ketamine's antidepressant effects (Caddy et al. 2014; Fond et al. 2014; McGirr et al. 2014). Each found that ketamine was associated with increased clinical response and remission relative to comparators (e.g., saline/placebo, midazolam) in individuals with either MDD or bipolar depression, regardless of treatment-resistant status and of whether or not study participants were medicated (Caddy et al. 2014; Fond et al. 2014; McGirr et al. 2014). In addition, the suspected neurobiological effects of ketamine were further supported by the relatively consistent time course of response across studies – i.e., improvement within four hours, peak response around 24 hours, and efficacy for approximately one week, as well as the maintenance of efficacy through repeated treatment (Mathew et al. 2012). Notably, these studies were primarily open-label or crossover single-site trials. Additional randomized controlled trials (RCTs) are required to further substantiate these promising findings.

Preliminary data suggest that the antidepressant effects of ketamine may be effectively extended for up to several months via repeated ketamine infusions (Blier et al. 2012; Szymkowicz et al. 2013). Maintenance of antidepressant treatment response was found to be safe and efficacious with up to six infusions of repeated ketamine administered once, twice, or three times per week (Murrough et al. 2013b; Diamond et al. 2014; Rasmussen et al. 2013; Shiroma et al. 2014; Segmiller et al. 2013). Other investigations reported safety and efficacy using a single administration of variable dosages and routes of ketamine, including 0.2 mg/kg intravenous bolus (Larkin and Beautrais 2011), 50 mg intranasal (Lapidus et al. 2014), and 0.5 mg/kg or 0.25 mg/kg intramuscular injection (Chilukuri et al. 2014). While encouraging, more data will be required in order to establish a precise estimate of ketamine's efficacy and safety in patient populations.

7.10 Safety and Tolerability of Ketamine

A single ketamine treatment has a strong history of safety when administered as an anesthetic medication at doses much higher than the low, subanesthetic doses given in depression trials (Krystal et al. 2013). However, the long-term effects and optimal dosing of repeated ketamine administration are not fully known. Across depression studies thus far, single administrations of ketamine have been generally well tolerated, although drug-induced mild to moderate acute, yet transient, adverse effects were observed including dissociation, perceptual disturbances, cognitive alterations, dysphoria, euphoria, and anxiety during infusion (Abdallah et al. 2015c). Physical side effects have also been noted including nausea, vomiting, dizziness, mild sedation, and elevations in blood pressure and heart rate. These adverse effects abate within a few minutes of stopping ketamine infusion and generally fully recover within one to two hours of treatment (Abdallah et al. 2015a).

Chronic ketamine abuse is known to impair cognitive functioning and cause deleterious brain changes as measured by in vivo neuroimaging. Little evidence is available regarding the effects of repeated doses of ketamine in a therapeutic and monitored context as these types of studies are relatively new. Evidence gleaned from studies of individuals who use ketamine recreationally provides cause for concern. Of note, many of these are relatively small studies of polydrug users. One of the largest investigations to date examined the neuropsychiatric and cognitive effects of chronic ketamine use in 150 participants including frequent, infrequent, and ex-ketamine users, as well as polydrug users, at baseline and at one-year follow-up (Morgan et al. 2009, 2010). These reported frequent ketamine users demonstrated impaired working and episodic memory and deficits in executive functioning in addition to increased schizotypal, dissociative, delusional, and depressive symptoms (Morgan et al. 2009, 2010). Interestingly, fewer cognitive deficits were noted in the ex-ketamine users group, suggesting it is possible that those impairments seen in the frequent users group are somewhat reversible upon cessation of ketamine, likely depending in part on frequency and amount of use. It should be noted that delusional symptoms persisted in ex-users as well as current frequent users, and that all ketamine users showed increased depressive symptoms (Morgan et al. 2009, 2010).

7.11 Limitations and Evidence Gaps in Clinical Research

Recently published meta-analyses highlight the current limitations in ketamine/depression research and areas for future investigations. Notably, these draw attention to the need for additional research to carefully evaluate the optimal route(s) of administration, dosing, and treatment schedules; to further characterize the durability of effects and the long-term safety, tolerability, and efficacy of ketamine; and to explore the potential effects of other novel glutamatergic agents that may possess fewer or less severe side effects, decreased excitotoxicity potential, and lowered

abuse liability (Caddy et al. 2014; Fond et al. 2014; McGirr et al. 2014). Although not noted in ketamine trials to date, an additional concern requiring further careful examination is whether or not there are any suicidal ideation/intent/behavior bounce-back or rebound effects (Krystal et al. 2013).

Additionally, the lack of complete investigator and patient blinding to treatment status, due to the functional unblinding secondary to the acute psychotomimetic, dissociative, cognitive, and physical side effects of ketamine remains a limitation in the empirical evidence supporting its mainstream use as an antidepressant. To optimize blinding to treatment status, a recent controlled trial compared ketamine's demonstrated rapid antidepressant effects to midazolam, an anesthetic benzodiazepine and active comparator (Murrough et al. 2013a). Individuals in the ketamine group demonstrated enhanced symptom improvement compared to those in the midazolam group, providing further support to NMDA receptor modulation as a novel mechanism for antidepressant drug development (Murrough et al. 2013a). Finally, while these supporting data are quite promising and have considerable implications for innovative drug development and improved psychopharmacologic interventions for patients with TRD, they come from primarily well-controlled clinical trials with strict eligibility criteria, leaving the generalizability to "real-world" patients in question (Mathews and Zarate 2013).

7.12 Molecular Biomarkers Underlying Ketamine's Effects

Molecular studies have started to identify signaling pathways implicated in the observed stress-related synaptic dysfunction. Evidence suggests that synaptic deficits are precipitated by inhibition of the mammalian target of rapamycin (mTOR) signaling pathway (Ota et al. 2014) as well as a decrease in neurotrophins such as brain-derived neurotrophic factor (BDNF) and its high-affinity receptor TrkB (Duman and Monteggia 2006; Autry et al. 2011; Sen et al. 2008). Enhancing mTOR signaling or elevating BDNF concentrations produces antidepressant effects, whereas the inhibition of mTOR signaling or reduction of BDNF leads to depressive-like behavior and blocks the effects of antidepressants in animal models of depression (Ota et al. 2014; Duman and Monteggia 2006). Synaptic scaling refers to a major form of homeostatic plasticity that regulates the overall strength of neuronal synaptic connectivity (Abdallah et al. 2015c). For example, a prolonged increase in neuronal activities produces a downscaling in overall synaptic strength (Turrigiano 2011). Synaptic scaling is regulated by inflammatory cytokines (e.g., tumor necrosis factor (TNF)) (Beattie et al. 2002) and by neurotrophins (e.g., BDNF) (Rutherford et al. 1998). Alterations in both factors have been associated with depression (Duman and Monteggia 2006; Dantzer et al. 2008). In humans, reduced central and peripheral BDNF levels were found in depressed patients (Duman and Monteggia 2006; Sen et al. 2008), and a functional variant of BDNF polymorphism (Val66Met) has been related to depression (Egan et al. 2003; Laje et al. 2012), especially in males (Verhagen et al. 2010). Interestingly, in a controlled trial of ketamine and

midazolam in patients with TRD, ketamine significantly increased plasma BDNF levels in responders but not nonresponders, and depressive symptoms were negatively correlated with BDNF (Haile et al. 2014). No associations between midazolam and BDNF were noted, providing support for plasma BDNF as a potential peripheral biomarker relevant to ketamine treatment response (Haile et al. 2014). Taken together, these data provide evidence that enhancing mTOR and BDNF signaling—leading to reversal of depression or stress-induced neuronal atrophy (e.g., in the prefrontal cortex and hippocampus (Zunszain et al. 2013)), prefrontal synaptogenesis, and normalized synaptic connectivity—is a required step for efficacious antidepressant treatment (Abdallah et al. 2015c). However, other investigators have failed to demonstrate that ketamine significantly alters mTORC1 signaling, nor have they found increases in the signaling pathway critical to inducing antidepressant-like response to ketamine (Autry et al. 2011).

7.13 Sleep Architecture and Circadian-Based Biomarkers

It is well known that sleep problems are cardinal to depressive disorders. Disturbed sleep associated with abnormalities in circadian rhythms has been associated with the pathophysiology of depression (Zunszain et al. 2013). It has been suggested that there may be circadian-based biomarkers, as ketamine's influence on these processes play a significant role in the drug's mechanism of action (Zunszain et al. 2013; Colwell et al. 1990). Additionally, slow sleep wave activity (SWA) can serve as a potential marker of cortical synaptic strength and thus synaptic plasticity (Zarate et al. 2013; Esser et al. 2007). A recent study explored ketamine's acute effects on depressive symptoms relative to SWA and found that both BDNF levels and early sleep SWA were elevated posttreatment (Duncan et al. 2013). Further, those patients who experienced ketamine-induced symptom reductions demonstrated altered BDNF levels proportional to changes in electroencephalography (EEG) parameters (Duncan et al. 2013).

7.14 Central Biomarkers Supported by Neuroimaging Findings

Various neurobiological measures have been used in clinical studies to advance the field's understanding of the neural underpinnings of ketamine's antidepressant effects and to further characterize treatment response. A recent magnetic resonance imaging (MRI) study investigated the association of smaller hippocampal volume – a suspected biomarker of antidepressant treatment response (e.g., Frodl et al. 2008; MacQueen and Frodl 2011) – and ketamine's rapid antidepressant effects (Abdallah et al. 2015b). They found a significant association between rapid symptom improvement and left hippocampal volume; specifically, those patients with a relatively smaller left hippocampus demonstrated a larger antidepressant

effect 24 hours post-ketamine (Abdallah et al. 2015b). No associations were found between right hippocampal volume and ketamine-induced symptom changes (Abdallah et al. 2015b). A separate functional MRI (fMRI) study examined brain responses to positive and negative emotional stimuli in the form of human facial expressions in patients with TRD compared to healthy volunteers prior to ketamine treatment (Murrough et al. 2015b). Patients subsequently underwent fMRI 24 hours following treatment with ketamine. Prior to treatment, patients showed reduced response to positive stimuli within the striatum – a component of the brain reward circuitry. Following treatment, patients demonstrated a rapid normalization in brain responses to positive stimuli within the striatum; functional connectivity of the striatum was related to the magnitude of antidepressant response (Murrough et al. 2015b).

In a magnetoencephalography (MEG) study, poor response to ketamine was predicted by high pregenual anterior cingulate activity during a working memory task (Salvadore et al. 2010). Conversely, another MEG study found elevated antidepressant response among depressed patients with high pretreatment rostral anterior cingulate activity in response to exposure to fearful faces (Salvadore et al. 2009). Interestingly, patients with poor pretreatment connectivity between the left amygdala and the pregenual anterior cingulate demonstrated improved ketamine treatment response (Salvadore et al. 2010). Further, ketamine treatment responders, but not nonresponders, showed elevated stimulus-evoked somatosensory cortical excitability approximately six hours posttreatment (Salvadore et al. 2010). This finding was interpreted as evidence of a positive relationship between synaptic potentiation and response to ketamine treatment (Cornwell et al. 2012). An EEG study provides additional evidence of the relationship between ketamine's antidepressant effects and synaptic potentiation. This study provides support for increased synaptic strength the night following ketamine treatment by examining sleep waves as putative markers of synaptic plasticity (Duncan et al. 2013).

When administered at low (subanesthetic) doses, ketamine's antagonism of the glutamatergic NMDA receptor appears to be the first step in a cascade of events that includes (1) rapid increases in presynaptic glutamate release and (2) enhanced regional activity in excitatory networks and significant alterations in synaptic plasticity and connectivity (Abdallah and Krystal 2014). These neural alterations appear within 24 hours of ketamine administration, the peak time of antidepressant response. Consistent with this cascading effect, preclinical studies have repeatedly shown an extracellular glutamate surge following the administration of low-dose ketamine (Moghaddam et al. 1997). Recently, pilot magnetic resonance spectroscopy (MRS) evidence in eight depressed patients found rapid increases in the total level of Glx (an MRS signal comprising glutamate + glutamine) in the medial prefrontal cortex (Milak et al. 2016). Moreover, an association between the psychotomimetic effects of ketamine and synaptic glutamate alterations in humans has been suggested by studies demonstrating that glutamate release inhibitors, such as lamotrigine or group II metabotropic agonists, mitigate these behavioral symptoms (Anand et al. 2000; Deakin et al. 2008; Krystal et al. 2005a, 2010). Interestingly, some, but not all, depression trials have found a positive correlation between the acute perceptual side effects of ketamine and its antidepressant effects (Sos et al. 2013; Luckenbaugh et al. 2014).

7.15 Immunomodulatory Biomarkers of Ketamine Response

Inflammation plays a critical role in maintaining homeostasis (Loix et al. 2011). Elevated levels of inflammation have been shown to be significantly associated with the development and maintenance of depression as well as poorer initial treatment response (Zunszain et al. 2011; Loix et al. 2011; Miller et al. 2009). Further, many pharmacologic agents are known to influence inflammation, and ketamine has demonstrated positive, regulating effects via interactions with inflammatory cell recruitment, cytokine production, and regulation of inflammatory mediators, thereby limiting overall exacerbation of systemic inflammation (Loix et al. 2011). Compared to non-depressed individuals, both medically healthy and medically ill individuals with depression and suicidal ideation demonstrated elevated concentrations of pro-inflammatory cytokines and acute-reactive protein levels including TNF-α, interleukin (IL)-1β, and IL-6 (Miller et al. 2009; Serafini et al. 2013; Erhardt et al. 2013; Steiner et al. 2008; Lindqvist et al. 2009) as well as C-reactive protein (CRP) (Walker et al. 2015). Evidence suggests that inhibition of these cytokines improves depressive symptoms and enhances antidepressant treatment response (Maes et al. 2014; Miller et al. 2009; Yang et al. 2015b). This would suggest that TNF-α, IL-1β, IL-6, and CRP are potential predictive biomarkers of treatment response to antidepressants (Yang et al. 2015b), including ketamine.

A review of ketamine's antidepressant action noted the important role of the drug's direct impact on pro-inflammatory cytokines and involvement in the tryptophan (TRY)-kynurenine (KYN) pathway (Zunszain et al. 2013). Another recent study examined the relationship between ketamine treatment response and inflammatory cytokines in patients with TRD to see if these predicted treatment response (Yang et al. 2015b). At baseline, plasma and serum levels of TNF-α and IL-1β were significantly higher in patients with TRD compared to non-depressed comparison subjects, and IL-1β and IL-6 were significantly elevated in the responder group relative to the nonresponder and control groups. At 230 minutes and one day post-ketamine administration, serum levels of IL-1β were significantly decreased in the treatment responder group; levels of TNF-α and TRY/KYN remained stable post-infusion (Yang et al. 2015b). These results suggest that pretreatment serum IL-1β may be a useful predictive biomarker of ketamine treatment response. Additional studies replicating this result are required to substantiate this.

Two recent meta-analyses have reported positive associations between both plasma and serum concentrations of each of these immunomodulatory molecules and depression (Howren et al. 2009; Dowlati et al. 2010). Interestingly, cerebral spinal fluid IL-6 was found to be significantly higher in individuals who attempted suicide compared to healthy control subjects, and those individuals who attempted suicide via violent means/methods demonstrated the highest concentrations (Lindqvist et al. 2009). Another study exploring the modulating role of inflammatory metabolites of glutamate NMDA receptors found that long-term dysregulation of the kynurenine pathway, including excess production of quinolinic acid (QUIN, an NMDA receptor agonist), was related to increased vulnerability for developing depressive symptoms (Bay-Richter et al. 2015).

7.16 Ketamine's Effects on Cognitive Function

Cognitive dysfunction cardinal to depressive disorders contributes significantly to disability and disease burden, suicide risk, treatment non-compliance, and refractory treatment response (Herrera-Guzman et al. 2010; Baune et al. 2010; Simon et al. 2000; Zajecka 2003; Bora et al. 2013; Hasselbalch et al. 2011, 2012). As noted above, ketamine's antagonism produces enhanced activity in excitatory networks and marked changes in synaptic strength plasticity in animal models (Li et al. 2010; Moghaddam et al. 1997; Duman and Voleti 2012; Anand et al. 2000; Deakin et al. 2008; Homayoun and Moghaddam 2007; Krystal et al. 2005a). This enhanced synaptic plasticity occurs approximately 24 hours after ketamine administration, the peak time of antidepressant response. Considering the critical role of synaptic plasticity in cognitive function, the question is raised whether the demonstrated ketamine-induced synaptogenesis would translate into enhanced cognition 24 hours posttreatment.

Although ketamine studies have consistently demonstrated acute, transient cognitive deficits during infusion, the hypothesized pro-cognitive effects of ketamine 24 hours posttreatment—and the relationship between cognitive function and treatment response—are not fully studied. In a controlled trial in which 25 participants with TRD were randomized to ketamine or midazolam, there were no differential effects of treatment on cognitive performance and no correlation with antidepressant response (Murrough et al. 2013c). Interestingly, poorer baseline cognitive performance, specifically low processing speed, uniquely predicted symptom improvement at 24 hours post-ketamine. This group replicated their findings in a larger controlled trial of 62 patients that included a seven-day follow-up (Murrough et al. 2015a). Again, no differential response was observed between those randomized to ketamine or midazolam, and slower processing speed uniquely predicted greater symptom improvement 24 hours post-ketamine administration. The authors further found that cognitive performance improved posttreatment regardless of the treatment condition; there were no adverse cognitive effects present in the ketamine group seven days post-administration (Murrough et al. 2015a).

Another recent study of ketamine's effect on the neurocognitive performance of patients with bipolar depression revealed pro-cognitive effects approximately 72 hours post-infusion (Permoda-Osip et al. 2014). These results appeared to be independent of depression severity or improvement, suggesting ketamine may possess pro-cognitive effects in addition to its influence on mood symptoms (Permoda-Osip et al. 2014). These investigations provide promising preliminary evidence. Future studies with larger sample sizes and longer-term follow-up are required to further characterize the cognitive effects of ketamine. It is also important that future studies of ketamine-induced neurocognitive changes implement a standardized method of assessment to remedy the problem of "approximate replication" (Murrough et al. 2015a; Kapur et al. 2012), so that we are better able to confidently report any demonstrated changes as treatment-related rather than potentially a simple artifact of variable measurement methods. Additionally, it is important to consider that the antidepressant effects of ketamine may ameliorate some of the cognitive

deficits seen in depression regardless of any potential synaptic alterations, thus obscuring any drug-induced neuropsychological changes (aan Het Rot et al. 2012).

7.17 Conclusions and Future Directions

For approximately 50 years, antidepressant research has been dominated by the monoaminergic hypothesis of depression, and there was little evolution in psychopharmacologic interventions, leaving depression as a leading cause of disease and disability across the world. The past two decades have seen a slow, but sure, paradigm shift concerning the neurobiology of depression and a related shift in approaches to formulating novel antidepressant agents. Ketamine trials have helped found a new generation of glutamate-based antidepressant research, and ketamine has proven to be a useful prototype in drug development. In addition to its replicated rapid and robust antidepressant effects, emerging evidence provides early support for ketamine's use with often hard-to-treat populations including posttraumatic stress disorder and obsessive-compulsive disorder (see Chap. 9 of this volume) and in severe suicidal ideation (see Chap. 4). In addition, mounting evidence demonstrates increased neuronal plasticity post-ketamine treatment. Thus, the question is raised whether ketamine-enhanced plasticity translates into improved cognition. Given the limitations to ketamine's widespread use noted above (e.g., psychotomimetic effects, relatively short duration of effect, abuse liability, unknown effects of long-term, low-dose use) and the current evidence gaps, it is critical that research continue in this arena, not only to further investigate ketamine but also to investigate other NMDA receptor modulators. Novel NMDA receptor modulators are currently being tested to mimic ketamine's rapid antidepressant effects while minimizing its adverse effects (e.g., perceptual disturbances) and addiction potential (for a review, see Krystal et al. 2013). This field of research has promising implications for improved psychotherapeutic interventions for individuals suffering from depressive and trauma-related disorders.

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Chapter 8
Ketamine and Electroconvulsive Therapy

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Abstract There is interest in giving ketamine during anaesthesia for electroconvulsive therapy (ECT) to enhance efficacy and block cognitive side effects associated with ECT. A number of randomised controlled trials and other studies have compared ECT outcomes when ketamine (as sole or adjunctive anaesthetic) or other anaesthetic agents are used. The body of evidence to date suggests that adding ketamine to ECT results in a faster onset of antidepressant response (similar to results seen with ketamine alone, without ECT) but does not result in greater efficacy by the end of the ECT course. Results are inconclusive regarding whether ketamine reduces the cognitive side effects of ECT. Adverse effects associated with the use of ketamine include raised blood pressure, psychotomimetic side effects (though these appear less problematic in the context of ECT treatment) and—when ketamine is given at higher doses—a longer time to post-procedure recovery. At present, the evidence does not support the routine use of ketamine for ECT, but ketamine may be useful for patients who require a rapid antidepressant response. The potential of combined ECT-ketamine treatment to increase efficacy in patients refractory to treatment with ECT alone (or ketamine alone) remains to be investigated.

8.1 Introduction and Overview

Ketamine has been used as a general anaesthetic agent for decades but is now less commonly used due to associated psychotomimetic side effects, which are dose-related. Ketamine can be used as a main anaesthetic agent or as an adjunct given in

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combination with other anaesthetic agents. Psychotomimetic effects may be less of an issue when ketamine is used as the anaesthetic for the ECT procedure for two reasons. First, when used with ECT, the risk of psychotomimetic effects is considered to be lower compared with other procedures (Rasmussen et al. 1996). Second, ECT studies have often used ketamine as an adjunct rather than as a sole anaesthetic, thus incurring lower risk of psychotomimetic effects.

There are three main reasons for the interest in using ketamine in ECT anaesthesia:

1. Compared to commonly used general anaesthetic agents (e.g. methohexital, thiopentone, propofol), ketamine is considered less likely to raise the seizure threshold. Raising the seizure threshold makes it more difficult to elicit generalised seizures with ECT.
2. With recent studies showing that ketamine itself has strong antidepressant effects, there has been interest in synergistic antidepressant effects when ketamine is given with ECT.
3. Preclinical data and preliminary reports suggest the possibility that ketamine, when used within ECT anaesthesia, may reduce the cognitive side effects associated with ECT.

Studies of the use of ketamine during ECT anaesthesia are heterogeneous in several respects. In some studies, ketamine was used as the sole anaesthetic, whereas in others it was used at reduced dosage as an adjunct combined with other general anaesthetic agents. Accordingly, the doses of ketamine used in the studies differed (see Table 8.1). In some studies, ketamine was used at similar doses (0.5 mg/kg) to studies in which ketamine alone (without ECT) was used to treat depression. In other studies, ketamine was given at the full anaesthetic dose (usual range 1–4.5 mg/kg). The studies also differed greatly in the type of ECT used. This refers to electrode placement (e.g. bitemporal, bifrontal or right unilateral ECT), ECT dose used, method for determining dose (based on the individual's seizure threshold or fixed or estimated dose) and stimulus parameters (e.g. variations in pulse-width). It is likely that all of these factors influenced outcomes, i.e. the effect of ketamine on both efficacy and cognitive outcomes of ECT when given as part of ECT anaesthesia. The studies discussed below are also heterogeneous in terms of patient populations treated. It is possible that the interaction of ketamine and ECT and effects on clinical outcomes will differ depending on patient age, level of treatment resistance, concurrent medications, subtype of depression, etc.

Studies discussed in this chapter include meta-analyses, randomised controlled trials (RCTs) in which patients were randomised to receive ketamine or not during ECT anaesthesia, parallel design studies in which patients were assigned to one or the other treatment but not by a randomised method, open label studies, and retrospective reports.

Table 8.1 Studies on the use of ketamine during ECT anaesthesia

Study	*N*	Sample	Design	Outcome measures	Findings
Meta-analyses					
Fond et al (2014)	118 (58 ketamine, 60 controls – propofol or thiopentone) – four studies included	103 MDD; 15 bipolar	Meta-analysis: ketamine as sole or adjunctive anaesthetic for ECT vs thiopentone/ propofol anaesthesia	Efficacy, safety	Greater antidepressant improvement with ketamine early in treatment course, but not at end of course. Ketamine side effects appear dose related. However, studies were heterogeneous
McGirr et al. (2015)	182 from five RCTs	165 MDD; 17 bipolar	Meta-analysis of efficacy of ketamine as an adjunctive agent to ECT	Efficacy, safety	ECT with ketamine augmentation was not associated with higher response or remission rates at treatment end than ECT alone. ECT with ketamine augmentation was related to higher rates of confusion (disorientation and prolonged delirium)
RCT studies					
Loo et al. (2012)	51	MDD, bipolar	Parallel RCT comparing ketamine (0.5 mg/kg) or saline added to thiopentone (3–5 mg/kg) for RUL UB ECT	*Primary*: neuropsychological (MCGC figure, HVLT, COWAT, SDMT, WJCOT, AMI-SF at baseline, after six ECTs at the end of ECT course, one month later). *Primary*: mood (MADRS) at baseline and weekly	Addition of ketamine did not reduce cognitive impairment compared to saline. Modest enhancement of efficacy was found in the ketamine group over the first week, but no overall increase in efficacy across the whole ECT course

(continued)

Table 8.1 (continued)

Study	*N*	Sample	Design	Outcome measures	Findings
Wang et al. (2012)	48	MDD	Parallel RCT comparing ketamine (0.8 mg/kg), propofol (1.5 mg/kg) and ketamine (0.8 g/kg) plus propofol (1.5 mg/kg); one single ECT treatment, BT brief ECT	*Primary*: efficacy (HDRS scores pre and at day 1, 2, 3 and 7 post-ECT); *Secondary*: side effects	Improvement in depression was greater in the ketamine and propofol + ketamine groups compared to the propofol group. Adverse effects were lower in the propofol + ketamine group than in the ketamine group
Abdallah et al. (2012)	18	MDD, bipolar	Parallel RCT comparing thiopental (3.5 mg/kg) alone or thiopental (3.5 mg/kg) plus ketamine (0.5 mg/kg) for RUL or BL ECT (PW or type of BL electro-placement not specified)	*Primary*: efficacy (HDRS-25) at baseline and after first and sixth ECT sessions	No differences in depression outcomes between groups at any time point
Yoosefi et al. (2014)	31	MDD	Parallel RCT comparing ketamine (1–2 mg/kg) and thiopentone (2–3 mg/kg) for ECT anaesthesia; BL ECT (type of BL placement and PW not specified)	*Primary*: efficacy (HDRS), cognition (MMSE) at baseline, at 48 hours, within seven days post-ECT, one month after. *Secondary*: seizure duration, hemodynamic parameters	Depression scores improved in both groups; significant improvement in mood in ketamine group at 48 hours compared to thiopentone; improvement in cognition in the ketamine group that persisted at one-month follow-up
Jarventausta et al. (2013)	32	MDD, severe or psychotic	Parallel RCT comparing *S*-ketamine (0.4 mg/kg) or saline added to propofol (0.5 mg/kg initial bolus, then titration method) for RUL and BL ECT (type of BL ECT and PW not specified)	*Primary*: efficacy (MADRS). *Secondary*: seizure threshold, seizure duration, charge	No difference between add-on ketamine or placebo in the magnitude or speed of response. No difference in mean seizure threshold, mean duration or mean charge between groups

Rasmussen et al. (2014)	38	MDD	Parallel RCT comparing ketamine (starting dose 1 mg/kg) with methohexital (starting dose 1 mg/kg) for brief BT ECT and RUL UB	*Primary*: self-rated mood (PHQ-9; HADS), cognition (MMSE) at baseline; after ECT 2, 4, and 6. *Secondary*: haemodynamics, post-anaesthesia side effects (after each ECT session)	No differences in self-rated mood, cognition, or side effects between groups at any time point
Yen et al. (2015)	20	MDD, bipolar	Crossover RCT, alternate methohexital (1 mg/kg) and ketamine (1 mg/kg) for six ECT sessions; RUL ultrabrief ECT	*Primary*: reorientation time, anaesthetic recovery time. *Secondary*: seizure duration, adverse effects	Ketamine induction resulted in longer reorientation times and higher number of adverse effects than methohexital. No differences in post-anaesthesia recovery times
Alizadeh et al. (2015)	42	MDD	Parallel RCT comparing ketamine (0.3 mg/kg) or saline added to propofol (1 mg/kg) for BT ECT (PW not specified)	*Primary*: efficacy (HDRS) at baseline, post-ECT 3, end of ECT and two weeks after the course; "Cognitive Performance Recovery Time" after each ECT. *Secondary*: motor seizure duration, haemodynamics	No differences in efficacy outcomes between groups. Ketamine group had a shorter cognitive performance recovery time. No differences in seizure duration or hemodynamic outcomes
Salehi et al. (2015)	160	MDD	Parallel RCT comparing ketamine (0.8 mg/kg) with thiopentone (1.5 mg/kg) for eight ECT sessions (electrode placement and pulse-width not specified)	*Primary*: efficacy (HDRS-17). *Secondary*: side effects, seizure duration	Improvement in depression was greater in the ketamine group after eight ECT sessions; side effects were more frequent in the ketamine group (blood pressure increase, headache, nausea and fear). No differences in seizure duration between groups

(continued)

Table 8.1 (continued)

Study	*N*	Sample	Design	Outcome measures	Findings
Open label studies					
McDaniel et al. (2006)	10	MDD, bipolar	Pilot naturalistic study; ketamine (1 mg/kg) or etomidate (0.3 mg/kg) for RUL ECT (PW not specified)	*Primary*: short-term memory (modification of the short-term memory item of the MMSE) at baseline and after ECT 6	Ketamine patients showed significantly less impairment in short-term memory function than patients with etomidate
Okamoto et al. (2010)	31	MDD	Open label comparing ketamine (mean dose 0.86 mg/kg) or propofol (mean dose 0.94 mg/kg) for brief pulse ECT (electrode placement not specified)	*Primary*: efficacy (HDRS-17, baseline, after 2, 4, 6 and 8 ECT). *Secondary*: safety, charge and seizure duration	Ketamine produced greater decreases in depression scores than propofol after the second and fourth ECT sessions, but not at other time points. Hallucinations and hypertension significantly higher in the ketamine group
Retrospective studies					
Krystal et al. (2003)	36	MDD, bipolar, schizoaffective depressed	Retrospective analysis on patients who switched from methohexital (1 mg/kg) to ketamine (0.7–2.8 mg/kg) because of short seizures; RUL or BL ECT (type of BL placement or PW not specified)	*Primary*: seizure duration, seizure intensity (slow wave activity). *Secondary*: safety and cognitive side effects (post-ECT reorientation time)	Seizures were longer and had greater intensity with a switch from methohexital to ketamine; faster reorientation times following the switch to ketamine. No differences in cardiovascular side effects

Kranaster et al. (2011)	42	MDD	Retrospective chart review from patients receiving *S*-ketamine (mean dose, 46.7 mg) or thiopentone (mean dose, 236.0 mg) for RUL or BL ECT (PW or type of BL placement not specified)	*Primary*: efficacy (HDRS-21), cognition (MMSE). *Secondary*: safety, seizure parameters	Patients in the ketamine group needed fewer ECT sessions until completion and presented significantly superior efficacy outcomes at the end of the ECT course; patients in the ketamine group did not present a decline in MMSE scores, compared with patients in the thiopentone group. Use of urapidil was higher in the ketamine group. EEG concordance was higher in the ketamine group

RCT randomised controlled trial, *ECT* electroconvulsive therapy, *PW* pulse-width, *BL* bilateral, *BT* bitemporal, *RUL* right unilateral, *UB* ultrabrief, *MDD* major depressive disorder, *HDRS* Hamilton Depression Rating Scale, *MADRS* Montgomery-Asberg Depression Rating Scale, *MMSE* Mini-Mental State Examination, *MCGC* Medical College of Georgia Complex Figure, *HVLT* Hopkins Verbal Learning Test, *COWAT* Controlled Oral Word Association Test, *SDMT* Symbol Digit Modalities Test, *WJCOT* Woodcock-Johnson Cross-Out Test, *AMI-SF* Autobiographical Memory Interview – Short Form, *PHQ* Patient Health Questionnaire, *HADS* Hospital Anxiety and Depression Scale

8.2 Use of Ketamine During ECT Anaesthesia: Antidepressant Efficacy

Several parallel group design studies have examined the addition of ketamine during ECT anaesthesia. Most of these were RCTs. Studies either gave ketamine alone as the anaesthetic agent or used a sub-anaesthetic dose as an adjunct given together with other general anaesthetic agents. Generally, the studies found that patients who received ketamine during ECT anaesthesia had a faster onset of antidepressant response, but there was no difference in efficacy outcomes by the end of the ECT course. The meta-analysis by Fond and colleagues (2014) examined both efficacy outcomes during the ECT course and at the end of the course. They found faster response, reflected in greater change in mood scores during the ECT course, but no difference in outcomes at the end of the ECT course. This was confirmed in a subsequent meta-analysis by McGirr and colleagues (2015) that examined response and remission rates and change in depression scores over the whole ECT course, finding no difference between the groups that did and did not receive ketamine during ECT anaesthesia.

Interestingly, approximately half of the parallel group studies found an efficacy difference, whereas the other half did not. It is likely that methodological differences between the studies may account for these apparent discrepancies. The study by Abdallah and colleagues (2012) was the smallest of all the studies ($N = 18$) and was probably underpowered to find any between-group differences. Jarventausta and colleagues (2013) found that co-adjuvant ketamine did not increase the efficacy of ECT; this study is interesting because it was the only one to use *S*-ketamine, and this was given at a dose of 0.4 mg/kg, which is approximately equipotent to a dose of 0.8 mg/kg racemic ketamine (the form of ketamine used in the other studies). The study by Jarventausta and colleagues is also the only study to specifically include patients with psychotic depression (10 of 32 patients), which is a very strong predictor of response to ECT. One interpretation is that in this highly ECT-responsive patient sample, given the likely high response to ECT alone, the potential of additional benefit with ketamine was reduced, i.e. a ceiling effect. Rasmussen and colleagues (2014) used similar methods to RCTs that found greater efficacy with ECT midcourse; however, the findings of this study may have been negative due to the mood assessments used. The patients self-rated their mood using two relatively simple rating scales, in contrast to other studies that typically used the observer-rated Hamilton Depression Rating Scale (HDRS) and Montgomery-Asberg Depression Rating Scale (MADRS). Lastly, a study by Alizadeh and colleagues (2015) also found no difference in efficacy. This study used ketamine at a relatively low dose of 0.3 mg/kg. Recent dose-finding studies suggest that the antidepressant efficacy of ketamine is lower at doses ≤ 0.5 mg/kg (Lai et al. 2014; Xu et al. 2016).

It is interesting to note that although one reason for using ketamine in ECT anaesthesia is that it is considered to be less likely to increase seizure threshold, none of the above studies reported a clear difference in seizure threshold when ketamine was used as the sole anaesthetic or as an adjunct, compared to typical drugs

used for anaesthetic induction in ECT. It is quite likely that much larger samples, combined with careful seizure threshold titration, will be required to elucidate this matter.

A number of the above studies also reported on the duration of the ictal EEG in patients treated with and without ketamine. Studies reported that the seizure was of similar or slightly longer duration with ketamine, though the significance of this for determining clinical outcomes is uncertain, as there is no clear linear relationship between seizure duration and clinical outcome. Only two studies commented on seizure quality (Krystal et al. 2003; Kranaster et al. 2011). Results suggested improved seizure quality (more intense or generalised seizures) when ketamine was used instead of methohexital, but the significance of this finding for ECT clinical outcomes (efficacy, side effects) is uncertain, as the relationship between EEG quality and these outcomes has not been systematically studied for ketamine anaesthesia in ECT. It cannot be assumed that research findings on ictal EEG quality and efficacy outcomes demonstrated with other anaesthetic agents also apply to ketamine.

Overall, the available studies suggest that the use of ketamine may speed the onset of antidepressant response to ECT but does not result in greater efficacy at the end of the ECT course. It is also unclear whether there are any persistent efficacy differences weeks to months after the end of the ECT course. The longest follow-up period was in the RCT by Loo and colleagues (2012). In that study, the ketamine group appeared to have higher depression scores at one month follow-up, but due to the small numbers available at follow-up ($N = 16$), results were not formally analysed or interpreted. Thus, the long-term implications of using ketamine in ECT anaesthesia remain unknown.

An important aspect that has not been hitherto studied is whether the addition of ketamine for patients who do not respond to ECT alone may be beneficial in increasing antidepressant response.

8.3 Use of Ketamine During ECT Anaesthesia: Cognitive Outcomes

Another reason for the use of ketamine during ECT anaesthesia is for potential neuroprotective effects, i.e. reducing the cognitive side effects of ECT. There are some data from preliminary clinical studies and animal studies suggesting that use of ketamine or another *N*-methyl-D-aspartate (NMDA) antagonist may reduce cognitive side effects associated with ECT (for a review, see MacPherson and Loo (2008)). A small preliminary pilot study by McDaniel and colleagues (2006) reported that patients asked to recall four words learned before ECT performed better when they received ECT with ketamine rather than etomidate anaesthesia. Recently, Alizadeh and colleagues (2015) reported that patients administered memantine (an NMDA antagonist) had fewer cognitive side effects than patients administered placebo during ECT. Zhu and colleagues (2015) reported that

administration of ketamine reduced cognitive side effects during electroconvulsive shock in rats, with protective effects possibly acting via neuroinflammatory mechanisms.

Results from small RCTs have been mixed. Only a few studies have examined cognitive outcomes before and after a treatment course of ECT. Most of these only used the Mini-Mental State Examination (MMSE) and achieved inconsistent results (Yoosefi et al. 2014; Kranaster et al. 2011; Rasmussen et al. 2014). The only study to examine this issue comprehensively using a relatively detailed neuropsychological battery was the one by Loo and colleagues (2012), which is also the largest RCT in this field. The study found no advantage in cognitive outcomes in the ketamine group. However, the authors noted that the type of ECT used was ultrabrief right unilateral, and thus the negative result might be explained by floor effects (because ultrabrief right unilateral ECT causes relatively fewer cognitive side effects). Furthermore, a significant decline in cognitive outcomes was noted in both treatment groups (i.e. there was some potential for the demonstration of neuroprotective effects with ketamine).

A few studies have also examined recovery of orientation and cognitive functioning immediately after a single ECT treatment. This is clinically significant because the length of time required for recovery after ECT determines the period of post-procedural observation required, and the length of time to reorientation after a single ECT has been found to predict retrograde amnesia over a course of ECT (Sobin et al. 1995; Martin et al. 2015). Again, results have been mixed. Alizadeh and colleagues (2015) found a shorter time to "cognitive performance recovery" (not defined), and Krystal and colleagues (2003) found a faster reorientation time in the ketamine group. In contrast, Yen and colleagues (2015) found that the ketamine group had a longer reorientation time. The comparison of reorientation time between anaesthetic agents reflects not only possible cognitive sparing effects but also the time required for emergence from anaesthesia. Ketamine has a longer half-life (two to four hours) than most other anaesthetic agents used in ECT; thus, particularly when given at higher doses, it is likely to result in a longer time before emergence from anaesthesia than other anaesthetic agents. This likely accounts for the discrepancy in the above results. Yen and colleagues (2015) gave ketamine at a dose of 1 mg/kg, whereas Alizadeh and colleagues only used 0.3 mg/kg (Alizadeh et al. 2015).

Overall, the question of whether ketamine has neuroprotective (i.e. cognitive sparing) effects when given with ECT anaesthesia remains unresolved. A large multicentre trial in the UK in which ketamine or placebo will be added during anaesthesia for bitemporal ECT will provide more definitive data (Trevithick et al. 2015).

8.4 Adverse Effects

It has been consistently reported across the above studies that the addition of ketamine during ECT anaesthesia is associated with a higher rate of side effects. The main side effects are an increase in blood pressure (which may be problematic for

some patients as both ECT and ketamine raise blood pressure and heart rate), longer time to recovery after the procedure and specific effects associated with ketamine: psychotomimetic effects, disorientation, restlessness, headaches, and a feeling of fear on awakening from anaesthesia. The meta-analysis by McGirr and colleagues (2015) found a significant increase in confusion, disorientation, and prolonged delirium after ketamine compared to placebo, but no increase in agitation, blood pressure, or affective switch. Another important consideration is that the subjective experience of awakening from ketamine anaesthesia is less pleasant than that associated with typically used induction agents and as such is disliked by some patients (Rasmussen and Ritter 2014).

Another consideration is whether the addition of ketamine may increase risk of a switch into mania or hypomania. A few patients with bipolar disorder in the RCT by Loo and colleagues (2012) experienced a manic switch when ketamine was used. However, given the small numbers, it is unclear if the use of ketamine in ECT is associated with an increased risk of a manic switch; ECT alone may increase the risk of a manic switch (Loo et al. 2011).

8.5 Conclusions and Future Directions

Overall, the data to date do not suggest that the addition of ketamine increases the efficacy of a treatment course of ECT overall in terms of end of treatment outcomes. However, the weight of the studies suggests that the speed of onset of antidepressant effects is more rapid when ketamine is added to ECT. This might be useful in cases of acute suicidality or high clinical severity, when a rapid response is required. In these studies, the antidepressant effect of ECT plus ketamine appeared similar to that of studies in which ketamine was used alone (at sub-anaesthetic doses) to treat depression. Further, the possibility that the addition of ketamine may reduce the cognitive side effects of ECT is an important topic for further research but remains at present an open question.

It is important to note that there are substantial differences between studies that likely account for the discrepancy in results. These include the dose of ketamine used, ECT treatment technique, comparator anaesthetic agent, study methods, and patient population group. At present, the optimal approach for using ketamine with ECT is unclear—i.e. what combination of the above factors is most likely to produce a beneficial outcome, either for efficacy or cognition. Thus, there is the potential that ketamine may yet be a beneficial adjunct to ECT therapy, but for specific patient populations or ECT treatment approaches. There is no literature to guide investigators with regard to in which contexts it may be particularly useful to combine ketamine with ECT. For example, if a patient is not responsive to ECT alone, it would be important to note whether the addition of ketamine results in greater efficacy and if the combination of ketamine and ECT is then more beneficial than ketamine alone. Further, in patients in whom seizures cannot be elicited with ECT due to an exceptionally high seizure threshold, it would be interesting to observe whether

the use of ketamine anaesthesia would be beneficial in reducing the seizure threshold, permitting seizure elicitation and resulting in useful efficacy.

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Chapter 9
Emerging Data for Ketamine in Obsessive-Compulsive, Stress-Related, and Substance Use Disorders

Carolyn Ines Rodriguez and Elias Dakwar

Abstract As described in previous chapters, a growing body of evidence supports the clinical utility of ketamine in major depression. A smaller body of evidence suggests utility in other disorders, including obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and alcohol/substance use disorders. This chapter reviews the available data and suggests new avenues for research.

9.1 Ketamine in Obsessive-Compulsive Disorder (OCD)

9.1.1 Obsessive-Compulsive Disorder (OCD): Diagnosis, Pathophysiology, and Current Treatments

Obsessive-compulsive disorder (OCD) is a debilitating mental illness characterized by intrusive thoughts (obsessions) and compelling repetitive behaviors (compulsions) (American Psychiatric Association et al. 2013; Murray and Lopez 1996). OCD has a point prevalence of 1 in 100 adults, with a lifetime prevalence rate of about 2 % (i.e., approximately two times more common than schizophrenia) (Kessler et al. 2005; Ruscio et al. 2010). Onset usually occurs in adolescence or early adulthood (Ruscio et al. 2010). Some individuals have mild to moderate symptoms and spend a few hours a day obsessing and performing compulsions, with only modest

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impact on their daily activities, while others experience constant intrusive thoughts and incapacitating interference (American Psychiatric Association et al. 2013).

Studies in humans and animals implicate abnormalities in cortico-striato thalamo-cortical (CSTC) (Ahmari and Dougherty 2015) and other circuits in OCD pathophysiology (Milad and Rauch 2012). Multiple neurotransmitter systems are likely involved, including serotonin, dopamine, glutamate, and gamma-aminobutyric acid (GABA) (see Sect. 9.1.3). One hypothesis posits that dysregulation of these circuits leads to dysfunction in core neural processes (e.g., response inhibition, sensory processing, reward habits, fear extinction, and reward processing) (Gillan et al. 2011; Milad et al. 2013; Ahmari et al. 2012; van Velzen et al. 2014; Marsh et al. 2015; Figee et al. 2011). The dysfunction then produces the hallmarks of OCD: intrusive thoughts and repetitive behaviors.

There are two evidence-based monotherapies for patients with OCD: pharmacotherapy with serotonin reuptake inhibitors (SRIs, i.e., clomipramine and the selective serotonin reuptake inhibitors (SSRIs)) and cognitive-behavioral therapy (CBT) in the form of exposure and response prevention (typically referred to as ERP or EX/RP). The American Psychiatric Association (APA) practice guidelines for the treatment of adults with OCD (Koran et al. 2007) recommends as first-line treatments the pharmacotherapy with SRIs, EX/RP, or their combination. SRI pharmacotherapy and EX/RP therapy share several limitations. First, symptom relief is incomplete. Most SRI responders achieve on average only a 20–40 % reduction in symptoms (Pigott and Seay 1999; Greist et al. 1995). Similarly, after about 35 h of expert EX/RP treatment delivered once or twice per week, about 33–43 % achieve minimal symptoms (Simpson et al. 2013). Second, treatment response lags treatment initiation by about two to three months. The long duration of EX/RP treatment—once or twice weekly for up to 25 sessions (and anxiety-provoking exposures) (Kozack and Foa 1997)—helps explain why up to 25 % of patients who start drop out. Expert consensus guidelines define an adequate SRI trial for OCD patients as a minimum of eight to 12 weeks, with at least six weeks at the maximum dose comfortably tolerated (Koran et al. 2007). Why the SRI response time for OCD takes longer than for depression is unclear, but may implicate a slower rate of autoreceptor desensitization, which is crucial for SRI efficacy, in brain regions (e.g., orbitofrontal cortex) involved in OCD (El Mansari and Blier 2006). Third, treatment-unique limitations include unwanted side effects (e.g., sexual) for SRIs, and lack of accessibility and/or affordability for EX/RP. In view of these limitations, research is needed to develop novel classes of medications. In addition, uncovering methods for speeding response to EX/RP and increasing the proportion of responders would be quite helpful.

9.1.2 Clinical Applications of Ketamine for OCD

Human genetic studies, imaging studies, and animal models of OCD have led to the "glutamate hypothesis of OCD," originally proposed by Rosenberg and colleagues in 2000 (Rosenberg et al. 2000). This hypothesis states that glutamatergic

abnormalities in cortico-striatal circuits contribute to OCD symptoms (Rosenberg et al. 2000; Graybiel and Rauch 2000; Pittenger 2011). Glutamate is the most common excitatory neurotransmitter in the nervous system and functions via *N*-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate subtypes, and G-protein-coupled receptors. Several medications that modulate glutamate reduce OCD symptoms. These agents, each thought to modulate glutamate in different ways, have shown promise in case reports, open-label studies, or small controlled trials as augmentation to SRIs, not as monotherapy. Agents include lamotrigine, topiramate (Van Ameringen et al. 2006), minocycline (Rodriguez et al. 2010), *N*-acetylcysteine, and riluzole (Coric et al. 2005; Lafleur et al. 2006; Pittenger et al. 2008). More recent placebo-controlled, randomized studies of both *N*-acetylcysteine (Costa et al. 2015) and riluzole (Pittenger et al. 2015), however, did not find statistically significant differences between treatment groups.

NMDA receptor (NMDAR) antagonism represents a promising mechanism for better targeting OCD. Knockout of a gene encoding a postsynaptic scaffolding protein at glutamate synapses leads to altered fronto-striatal activity, OCD-like behavior, and elevated expression of NMDAR subunits (Welch et al. 2007). Further, animal studies indicate that these changes in NMDAR expression and fronto-striatal activity are a critical driver of OCD-like repetitive behaviors (Ahmari et al. 2013; Burguiere et al. 2013; Welch et al. 2007). In humans, memantine, an NMDAR antagonist, has shown promising results in OCD (Pasquini and Biondi 2006; Poyurovsky et al. 2005; Aboujaoude et al. 2009; Feusner et al. 2009; Stewart et al. 2010; Ghaleiha et al. 2013; Bakhla et al. 2013; Haghighi et al. 2013). In a case report, treatment of an unmedicated OCD individual with ketamine (0.5 mg/kg IV over 40 minutes) produced rapid anti-obsessional effects, but the patient returned to baseline severity by one week post-infusion (Rodriguez et al. 2011). Taken together, animal and human data support the NMDAR as a novel target.

Given these promising findings, three clinical studies further examined ketamine in patients with OCD. First, in an open-label study in 10 OCD subjects, Bloch and colleagues found modest reductions in OCD symptoms one to three days following ketamine infusion (Bloch et al. 2012). Second, in a small, proof-of-concept, randomized, controlled, double-blind, crossover study, a single dose of IV ketamine (also 0.5 mg/kg IV over 40 minutes) produced rapid resolution of obsessions in unmedicated adults with OCD (Rodriguez et al. 2013). Furthermore, a single dose of IV ketamine led to complete resolution of OCD symptoms during infusion and sustained effects in 50 % of subjects one week post-infusion in the absence of an SRI (Rodriguez et al. 2013). Sampling and methodological differences may explain the discrepancy in the findings of Rodriguez and colleagues (2013) and those of Bloch and colleagues (2012). Rodriguez and colleagues (2013) included only subjects with nearly constant intrusive obsessions (more than 8 hours a day), whereas Bloch and colleagues (2012) did not require that their subjects have constant obsessions. Individuals with constant intrusive obsessions may represent an OCD subtype more sensitive to ketamine's effects. Alternatively, measuring the anti-obsessional effects of ketamine may be difficult in individuals whose obsessions are not reliably constant. An important differ-

ence is that the latter study (Rodriguez et al. 2013) required subjects to be medication free, whereas Bloch and colleagues (2012) allowed concomitant medications. Concomitant medications may influence ketamine's effects on OCD symptoms.

A third study in unmedicated OCD adults tested whether a brief course of EX/RP could extend ketamine's effects (Rodriguez et al. 2016). The rationale was (1) ketamine is reported to enhance plasticity and extinction learning in rodents (Duman 2014; Liu et al. 2012; Gideons et al. 2014) and (2) enhanced extinction learning may facilitate CBT gains, as described in the trials above that combined CBT with medication thought to facilitate extinction learning (e.g., D-cycloserine) (Craske et al. 2014; Hofmann 2014). Mimicking those trials, EX/RP was abbreviated (i.e., 10 1-hours exposure sessions) but delivered during the putative time interval when ketamine facilitates extinction learning (within 14 days) (Duman 2014). At the end of EX/RP (week 2), 63 % of patients demonstrated treatment response (≥35 % Y-BOCS reduction). Importantly, individuals varied in their response, with one subject having no benefit, the majority benefitting for up to two weeks, and one no longer meeting criteria for OCD (i.e., achieving minimal symptoms post-infusion that persisted throughout the CBT and for up to six months in a naturalistic follow-up). These results corroborate prior findings (Rodriguez et al. 2011, 2013) that IV ketamine can rapidly reduce obsessions in unmedicated OCD patients and advance the growing literature on enhancing CBT with agents that facilitate extinction learning (Craske et al. 2014; Hofmann 2014). Study limitations were typical of an open-label trial, including lack of randomization to a comparison group, thereby possibly creating allocation and ascertainment (response) bias. The trial data suggest that a brief course of EX/RP may help some individuals maintain the improvement experienced with ketamine; however, a randomized controlled trial is needed to determine whether the improvement seen after two weeks of EX/RP is due to the addition of EX/RP or whether the effects of ketamine persist longer in some patients than was previously described. These studies introduce the exciting possibility that medications that rapidly reduce OCD symptoms may be found.

9.1.3 Exploration of the Mechanism of Ketamine in OCD

Whether ketamine's mechanism underlying rapid anti-obsessional activity is similar to that described in major depressive disorder (MDD; see Chaps. 6 and 7) or directly targets dysfunctional OCD circuits (e.g., hyperactivity, connectivity of the CSTC circuits) (Ahmari and Dougherty 2015) remains unknown. The first report to examine the time course of neurochemical effects of a single intravenous ketamine infusion in OCD compared ketamine versus saline using proton magnetic resonance spectroscopy (^{1}H MRS) (Rodriguez et al. 2015). Consonant with current OCD models of glutamatergic abnormalities (for a review, see Pittenger et al. 2011) and MRS studies reporting that ketamine increased glutamatergic compounds (Stone et al. 2012; Rowland et al. 2005), the authors hypothesized that compared to saline, ketamine would increase the excitatory neurochemicals glutamate + glutamine (Glx) in

the medial prefrontal cortex (mPFC), a region implicated in OCD pathology. Given recent evidence of GABA abnormalities in OCD (Simpson et al. 2012), exploratory analyses also examined whether ketamine increased mPFC GABA levels. Contrary to the hypothesis, in this proof-of-concept study ketamine did not significantly increase mPFC Glx/W levels in unmedicated adult OCD participants over time. However, ketamine did significantly increase mPFC GABA/W levels over time. Post hoc analyses showed that a single time point—approximately 1 hours post-ketamine infusion—was driving this effect. That GABA/W increased is interesting given recent findings indicating GABA abnormalities in OCD (Greenberg et al. 2000; Zai et al. 2005; Richter et al. 2012). In addition, unmedicated patients with OCD exhibit baseline GABA deficits in the mPFC compared to matched healthy controls (Simpson et al. 2012). Low baseline mPFC GABA levels may be part of the brain's attempt to regulate or compensate for OCD symptoms. Together with evidence of low cortical GABA levels in OCD, the study's findings suggest that models of OCD pathology should consider the role of GABAergic abnormalities in OCD symptomatology. The results also suggest that future research is needed regarding on which level(s) (or unit of analysis) ketamine acts (e.g., molecules [Glx/GABA], circuits, or neural synchrony).

9.1.4 Summary of Ketamine in OCD

In OCD, as in MDD, ketamine has rapid and robust effects. For patients who want to use ketamine clinically, excitement must be tempered with the reality that ketamine has psychotomimetic and other side effects, and its efficacy is transient. Further research is needed to (1) understand the mechanism of ketamine's effects in OCD, (2) explore how to prolong ketamine's clinical effects with either EX/RP therapy or medications, and (3) minimize ketamine's side effects. These efforts may enhance the utility of ketamine and open new avenues for novel medications that target the NMDAR.

9.2 Ketamine for Stress-Related and Substance Use Disorders

Unlike OCD, which does not require an inciting event or environmental stressor for its emergence, stress-related disorders such as post-traumatic stress disorder (PTSD) and substance use disorders (SUDs) can be conceptualized as disorders of learning and involve traumatic events or repeated substance use progressing into psychopathology and behavioral impairment. It is now recognized that the pathogenesis for both groups of disorders involves similar glutamate-mediated neural adaptations and that correcting these alterations via the promotion of neuroplasticity may serve to provide benefit. Before we discuss the applications of ketamine for PTSD and SUDs, we summarize what is known about the adaptations involved in both

disorders and review how the pro-neuroplasticity mechanisms of ketamine may serve to address them.

9.2.1 Ketamine and Neuroplastic Adaptations

Glutamate neurotransmission plays a critical role in fear, neural plasticity, memory, and learning (Galvan 2010; Walker and Davis 2002; Del Arco and Mora 2009; Popoli et al. 2012; Almeida et al. 2010; Skolnick et al. 2009; Nair and Singh Ajit 2008). Numerous animal studies have demonstrated that disruptions in glutamate neurotransmission are implicated in the development of stress-related and affective disorders as well as, SUDs, including the promotion of fear sensitization, cue conditioning and reactivity, and problematic depression-like adaptations to repeated trauma ("learned helplessness") (Galvan 2010; Goldstein et al. 2007; Walker and Davis 2002; Del Arco and Mora 2009; Popoli et al. 2012; Almeida et al. 2010; Skolnick et al. 2009). The neurocircuitry associated with these disorders has been identified as well and involves regions where the afferent and efferent projections are primarily glutamatergic. As mentioned earlier, glutamate is the most abundant excitatory neurotransmitter in the mammalian brain and constitutes the primary synaptic network for prefrontal communication (Kalivas 2009). Impaired prefrontal regulation of midbrain structures such as the nucleus accumbens and amygdala is a well-described correlate of not only affective and anxiety disorders but also SUDs (McFarland and Kalivas 2001; Amat et al. 2005; Luu and Posner 2003; Goldstein and Volkow 2002). Anterior cingulate cortex (ACC) alterations, in particular, have been associated with stress sensitivity (Amat et al. 2005; Luu and Posner 2003), as well as with high reactivity to cues and an increased risk of relapse (Goldstein and Volkow 2002; Stuber et al. 2010; Garavan et al. 2000; Kosten et al. 2006; Goldstein et al. 2007).

In light of these findings, glutamate modulators have long been proposed as treatments for psychiatric disorders characterized by pathological neural adaptations, including depression, PTSD, and SUDs. Though various receptors are engaged in glutamate-mediated learning, the NMDAR may be particularly important, as NMDAR-dependent learning is thought to be central to neuroplasticity and sensitization to drug cues and stressors (Nicoll and Malenka 1999; Tang et al. 1999). Data collected with laboratory animals indicate that NMDAR and other glutamate modulators, such as direct current stimulation (DCS) and memantine, exert promising effects on stress- and dependence-related adaptations and functional deficits, but ketamine has been the most consistently effective glutamate modulator to demonstrate antidepressant effects (Newport et al. 2015).

It has been widely proposed that ketamine may lead to therapeutic effects because, alongside acute modulatory effects on glutamate neurotransmission, it exerts unique downstream effects on neural plasticity and connectivity (Maeng et al. 2008; Li et al. 2010). The antidepressant effect of ketamine has been attributed primarily to the promotion of prefrontal synaptic remodeling through AMPA

activation (Maeng et al. 2008), increased mammalian target of rapamycin (mTOR) signaling (Li et al. 2010), and mechanisms involving brain-derived neurotrophic factor (BDNF) (Li et al. 2010). Normalization of glutamate homeostasis at the ACC may also play a role (Salvadore et al. 2009). Additionally, the unique co-occurrence of AMPA activation and NMDAR antagonism in the case of ketamine leads to a net increase in presynaptic glutamate release (Maeng et al. 2008), but without the risk of excitotoxicity produced by unopposed AMPA activity (Jayakar and Dikshit 2004). This balance of AMPA and NMDAR effects represents a novel avenue for modulating glutamate neurotransmission and may be crucial to ketamine-induced neural plasticity (Maeng et al. 2008; Jayakar and Dikshit 2004; Jourdi et al. 2009). Ketamine-induced neurogenesis may also extend to the hippocampus (Peng et al. 2011). Further, ketamine has sustained effects on modulating connectivity in the default-mode network (Scheidegger et al. 2012); abnormal resting-state connectivity and excitability has been implicated in various disorders, including depression, PTSD, and SUDs (De Luca et al. 2006; Lanius et al. 2010; Bluhm et al. 2009; Greicius et al. 2007). These unique effects on prefrontal neuroplasticity and glutamate neurotransmission may address PTSD and SUDs, as they do depression (Jayakar and Dikshit 2004), by counteracting the synaptic deficits discussed above and restoring healthy prefrontal functioning through neural remodeling (Li et al. 2010; Jayakar and Dikshit 2004; Jourdi et al. 2009).

9.2.2 Post-traumatic Stress Disorder (PTSD): Diagnosis, Pathophysiology, and Current Treatments

PTSD is a highly prevalent and disabling disorder. According to a recent epidemiological study, the lifetime prevalence of PTSD is 6.8 %, and it is associated with substantial impairments in functioning (Kessler et al. 2005). PTSD emerges in response to traumatic experience and typically involves persistent difficulties with reexperiencing the trauma, hypervigilance, and avoidance. Depressive symptoms also constitute a common feature of PTSD. Current standard treatments involve antidepressants, including SRIs, atypical antipsychotics, and behavioral treatments, such as prolonged exposure (PE) therapy. Unfortunately, these treatments typically take weeks to work and may be ineffective for a large proportion of patients. Other related limitations of available treatments include high attrition rates, inadequate improvement, and SRI side effects. As with OCD and depression, efforts are needed to expedite the response to either pharmacotherapy or PE and to improve remission rates to treatment.

Impaired fear extinction is thought to be a central behavioral deficit in PTSD and may account for the persistence of trauma-related distress in the disorder. Fear extinction consists of two basic processes: (1) *learning*, or the gradual decrements of a conditioned fear response (CR) by repeated exposure to a conditioned stimulus (CS) in the absence of the unconditioned stimulus, and (2) *recall*, or the retrieval and expression of the learned extinction memory (no CR to the CS) after a delay.

In both human and animal studies, the amygdala is primarily involved in extinction learning, whereas the ventromedial prefrontal cortex (vmPFC) (corresponding to the infralimbic cortex in rodents) and hippocampus are involved in extinction recall (Quirk and Mueller 2008; Likhtik et al. 2008; Herry et al. 2008; Sotres-Bayon et al. 2006; Myers and Davis 2007).

The dorsal anterior cingulate cortex (dACC) may also be involved in fear expression. Impaired extinction recall, in particular, has been found to correlate with dysregulation of this neurocircuitry by functional magnetic resonance imaging (fMRI). During extinction recall, individuals with PTSD, as compared to trauma-exposed controls, predictably demonstrate greater dACC activation, as well as lesser vmPFC and hippocampus activation, during an extinction recall task. Extinction-related dysfunction in the fear circuitry is also implicated in other disorders, such as generalized anxiety disorder and OCD, and represents an important target of pharmacotherapy (Graham and Milad 2011).

NMDAR-dependent learning is thought to be crucial to the process of extinction (Nicoll and Malenka 1999). Researchers have therefore endeavored to address PTSD by facilitating extinction via NMDAR agonism, with one aim being the enhancement of extinction-oriented therapy such as PE (Ressler et al. 2004). For example, D-cycloserine (DCS), an NMDAR partial agonist with preclinical effects on extinction, was hypothesized to be helpful for PTSD by promoting trauma-related memory extinction through the facilitation of learning (acquisition) and memory formation (consolidation) (Heresco-Levy et al. 2002). DCS did not separate from placebo, however, in a recent randomized, controlled trial when outcomes were analyzed as originally intended (by intent-to-treat analysis), suggesting the lack of a robust response (de Kleine et al. 2012). Anticonvulsants with downstream effects on the glutamatergic system, such as lamotrigine and carbamazepine, have also been investigated (Lipper et al. 1986; Hertzberg et al. 1999); according to a single preliminary study, lamotrigine appeared to be possibly effective at dampening PTSD symptoms (Hertzberg et al. 1999).

9.2.3 Clinical Applications of Ketamine for PTSD

NMDAR modulation, as well as the promotion of neuroplasticity to facilitate extinction learning, may therefore work to improve PTSD, as well as potentially optimize the response to PE. Before we discuss a recent proof-of-concept trial investigating the efficacy of ketamine for PTSD, we summarize prior research evaluating the neuroprotective effects of ketamine pertaining to stress-related disorders. Specifically, prior research in humans aimed to elucidate the effects of peri-traumatic administration on the development of PTSD (Schonenberg et al. 2005; McGhee et al. 2008). Results are inconsistent; one group found that ketamine *increased* the likelihood of developing PTSD (Schonenberg et al. 2005), while other researchers found the opposite effect, with ketamine exhibiting a greater protective effect against PTSD in the case of burn victims than other anesthetics administered at the

time of surgery (McGhee et al. 2008). The propensity for sub-anesthetic ketamine to generate dissociative and anxiogenic experiences have further led some researchers to propose that ketamine might enhance the salience and neural imprinting of traumatic experience (Chambers et al. 1999), but the safety with which sub-anesthetic ketamine has been administered to sometimes acutely troubled patients in clinical research settings without adverse consequences or persistent distress has cast doubt on this hypothesis. A recent study suggests that ketamine protects rodents from developing depression-like responses to chronic stress (Brachman et al. 2016), suggesting that ketamine may disrupt the development of problematic neuroplastic adaptations.

A recent trial evaluated the efficacy of a sub-anesthetic ketamine infusion equivalent to the antidepressant dose (0.5 mg/kg over 40 minutes) on PTSD severity ascertained using the Clinician Administered PTSD Scale (CAPS) (Feder et al. 2014). The authors hypothesized that the trajectory of response would be similar to that characterizing the antidepressant effect: rapid and relatively sustained. As compared to the active control (midazolam), ketamine led to significant reductions in CAPS scores, which in some cases extended for greater than two weeks. This rapid and robust improvement in CAPS is unprecedented in the treatment of PTSD and suggests new directions in pharmacotherapy development. As with OCD and depression, more research is needed to replicate these effects to develop methods by which to sustain the response (e.g., pairing ketamine with PE) and to develop comparable compounds associated with less toxicity.

9.2.4 Substance Use Disorders (SUDs): Diagnosis, Pathophysiology, and Current Treatments

SUDs remain a significant public health problem (United Nations Office on Drugs and Crime (UNOCD), World Drug Report, 2013). A hallmark of SUDs is the progressively uncontrollable pursuit of drug use in the midst of mounting adverse consequences. Various deficits are recognized to contribute to this trajectory, including the development of physiological dependence, drug cravings, heightened reactivity to stress and drug cues, impulsivity, and diminished sensitivity to natural rewards. Behavioral treatments for SUDs are aimed at promoting abstinence through improving motivation for change and accelerating the pursuit of healthy goals, as in motivational enhancement therapy, modifying behavior by rewarding cessation of drug use (contingency management), and inculcating cognitive-behavioral skills that may help to prevent relapse. Pharmacotherapy may also have a role in promoting abstinence. Available options include maintenance strategies (such as methadone for opioid dependence or nicotine replacement therapy), antagonist strategies (e.g., naltrexone for opioid dependence), and strategies aimed at addressing the deficits that serve to maintain drug use (e.g., topiramate to address the glutamate-mediated neuroadaptations in alcohol and cocaine use disorders). Despite decades of research, the treatment of SUDs remains beset by many challenges, including a lack of

effective medications for certain disorders (e.g., cocaine use disorder), modest or inconsistent efficacy (e.g., topiramate, naltrexone), and poor response to efforts at behavioral modification, with high rates of dropout from behavioral treatment representing a common problem.

As the field continues to elucidate the neurobiological correlates of SUD-related problems, we have gained a greater understanding of neurobiological vulnerabilities that perpetuate problematic use (Karila et al. 2008; Kalivas and O'Brien 2008) and that may be targeted by the development of innovative medications. As mentioned earlier, alterations in glutamate neurotransmission represent one such target (Uys and LaLumiere 2008; Schmidt and Pierce 2010; McFarland and Kalivas 2001; Kalivas 2009).

While it is widely recognized that there is substantial overlap in the pathophysiology of stress-related and affective disorders, it is only recently that we have come to identify comparable neuroplastic adaptations in the development of SUDs. As with PTSD and depression, SUD-related disturbances in glutamate neurotransmission can have both neuronal and regional ramifications, ranging from receptor-specific changes to broad prefrontal alterations in activity and neurotransmission (McFarland and Kalivas 2001; Kalivas 2009). Of receptor-specific changes, perhaps best characterized are alterations in NMDARs (Kalivas 2009). NMDARs have been found to be upregulated with chronic drug and alcohol exposure (Uys and LaLumiere 2008; Schmidt and Pierce 2010; McFarland and Kalivas 2001; Kalivas 2009), and changes in NMDAR structure and functioning are thought to account for dependence-related cue responsivity, disruptions in reward circuitry, neurotoxicity, and stress sensitivity (Uys and LaLumiere 2008; Schmidt and Pierce 2010; McFarland and Kalivas 2001; Kalivas 2009; Kalivas and O'Brien 2008; Goeders 2002; Sinha et al. 1999, 2003, 2006; Skolnick et al. 2009; Almeida et al. 2010). Alterations in glutamate neurotransmission have also been implicated in disruptions in mesolimbic dopamine signaling and reduced reward sensitivity (Kalivas 2009; Kalivas and O'Brien 2008).

Reactivity to stress and triggers is a common deficit in both SUDs and stress-related disorders, even as the behavioral manifestations may be dissimilar. Stress, especially when uncontrollable (Goeders and Guerin 1994), increases drug self-administration in rodents (Piazza et al. 1990; de Wit and Stewart 1981; Kosten et al. 2000), and stressors, including drug cues (de Wit and Stewart 1981), promote reinstatement of drug use, likely through glutamate and NMDAR signaling (Uys and LaLumiere 2008; Schmidt and Pierce 2010; McFarland and Kalivas 2001; Kalivas 2009; Erb et al. 1996; Shaham et al. 2000). In humans, heightened reactivity to cues and stress demonstrably leads to cravings, relapse, and progressively uncontrollable drug use (Sinha et al. 1999, 2003, 2006). Moreover, the heightened stress sensitivity brought on by compulsive use implicates prefrontal pathology resembling "learned helplessness"—a disturbance in prefrontal glutamate neurotransmission that is typically associated with depressive symptoms and neural deficits (Skolnick et al. 2009; Almeida et al. 2010) and that in substance users might correlate with demoralization and impaired self-efficacy, in addition to heightened craving and stress sensitivity (Sinha et al. 2003, 2006; Goldstein and Volkow 2002).

Data collected with laboratory animals indicate that NMDAR antagonists and other glutamate modulators reduce self-administration, reinstatement, and cue responsivity (Uys and LaLumiere 2008; Schmidt and Pierce 2010; McFarland and Kalivas 2001; Kalivas 2009; Bespalov et al. 2000; Popik et al. 2003; Uzbay et al. 2000; Myers and Carlezon 2010). Preclinical animal research with agents directly promoting neuroplasticity has also been promising, with mechanisms involving mTOR found to be central to the anti-alcohol effects of ketamine (Sabino et al. 2013) and a prefrontal infusion of BDNF found to disrupt cocaine use in rodents (Berglind et al. 2007). Research in humans with glutamate modulators other than ketamine, however, has failed to show comparable effects. For example, memantine, an NMDAR antagonist, increased cocaine's subjective effects in humans and failed to reduce self-administration (Collins et al. 1998, 2006); a subsequent clinical trial also failed to show an effect (Bisaga et al. 2010). Similarly, DCS, an NMDAR partial agonist, has not demonstrated robust effects in humans (Price et al. 2009). Other interventions having downstream effects on glutamate, such as tricyclic antidepressants and anticonvulsants, have produced mixed results, particularly in cocaine use disorders (Schmidt and Pierce 2010; Karila et al. 2008; Oliveto et al. 1999; Gawin et al. 1989; McDowell et al. 2005).

9.2.5 Clinical Applications of Ketamine for SUDs

Ketamine may benefit SUDs by addressing the neuroplastic adaptations driving problematic use, as well as facilitating behavioral modification through comparable mechanisms. Research in this area is quite preliminary at present, though numerous clinical trials are ongoing to better understand the efficacy of sub-anesthetic ketamine for alcohol and cocaine use disorder.

Ketamine was first tested for SUDs using a psychedelic psychotherapy framework. In a series of trials evaluating the utility of ketamine in addiction treatment, it was found that intramuscular sub-anesthetic doses of ketamine, in conjunction with an existential psychotherapy platform the authors termed "ketamine psychedelic therapy," led to sustained abstinence from heroin and alcohol (Krupitsky et al. 2002; Krupitsky and Grinenko 1997). The treatment framework was "psychedelic" insofar as it aimed to utilize the psychoactive effects of ketamine therapeutically. This involved providing psychotherapy so as to facilitate a reappraisal of values; other components of the psychotherapy were aimed at precipitating conversion-type phenomena, such as a near-death experience, with the intention of cultivating a new set of priorities and goals more consistent with sobriety. The effects on abstinence seemed to be dose dependent, with the high dose of sub-anesthetic ketamine leading to significantly greater abstinence rates two years after administration than the lower dose (Krupitsky et al. 2002). Other reported effects include greater reduction in heroin craving and greater positive changes in emotional attitudes in the high-dose group (Krupitsky et al. 2002).

Recent research has further investigated the efficacy of sub-anesthetic ketamine infusions in deficits related to cocaine use disorders, focusing on neurobiological mechanisms. The premise is that addictive disorders may be associated with neuro-adaptations comparable to those characterizing depressive and anxiety disorders and that ketamine may be able to target these addiction-related deficits in a similarly rapid and robust way (Dakwar et al. 2014b). Indeed, a recent rodent study suggests that ketamine ameliorates the distress associated with withdrawal from amphetamines (Belujon et al. 2016).

Reactivity to cues, low motivation for non-drug rewards, and reduced self-efficacy are adaptations that may be particularly responsive to agents promoting neuroplasticity (Volkow and Morales 2015), such as ketamine. In a controlled cross-over study (Dakwar et al. 2014b), it was found that a single sub-anesthetic infusion of ketamine at a dose lower than the antidepressant dose (0.41 mg/kg over 50 minutes) increased motivation to quit drug use, as well as reduced cue-induced craving, in cocaine-dependent research volunteers, relative to the active control lorazepam. A subsequent ketamine infusion (0.71 mg/kg over 50 minutes) led to further reductions in cue-induced craving. Nearly half the participants maintained abstinence after completion of this inpatient study during the four-week follow-up period, confirmed by urine toxicology, despite not being interested in treatment at study entry. Infusions were well tolerated, with no participants reporting robust drug-liking, persistent psychoactive effects, or ketamine misuse during follow-up.

Interestingly, as with the research with opioids and alcohol mentioned above, there may be psychological mechanisms to these effects. Ketamine in the sub-anesthetic dose range leads to an array of infusion-dependent psychoactive effects, ranging from psychotomimetic to dissociative and mystical-type effects (Dakwar et al. 2014a). A secondary analysis of the above trial found that a subset of psychoactive effects similar to those characterizing conversion experiences appears to mediate the effect of ketamine on motivation enhancement in particular (Dakwar et al. 2014a). This is congruent with the hypothesis, first formulated by William James nearly a century ago, that non-ordinary experiences may have therapeutic effects.

In the absence of behavioral data, it is not possible to conclude whether these effects on motivation and craving represent new evidence that ketamine exerts specific benefits for drug dependence or whether they constitute an extension of its recognized impact on comparable subjective states, such as anxiety or dysphoria. Further research is needed to better understand the effect of ketamine on behavioral outcomes related to SUDs, such as drug self-administration and abstinence. Research is also needed to understand how to leverage the apparently robust effects of ketamine into persistent behavioral changes.

9.3 Future Directions

Understanding and further defining the common targets of ketamine in OCD, PTSD, and SUDs will allow for the identification of new classes of rapid-acting treatments. It will also assist with elucidating genetic and neurobiological correlates of

psychopathology. Although we are starting to understand the neurobiological hyperactivation of brain circuits in various disorders, the pathophysiology of these circuits and the etiology of this malfunction require more study. New horizons for research include more clearly identifying the neural correlates of psychiatric symptoms in order to understand the underlying mechanism of disease. Research with ketamine may help this process by allowing for better understanding of how its rapid effects on neurotransmitter levels and neural circuits leads to symptom improvements. This may also help with devising optimal combinations of different treatment modalities (e.g., frequency of ketamine dosing, integration with behavioral treatment) so as to comprehensively address the variety of deficits underlying these disorders.

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