ACS Chemical Neuroscience

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# Classics in Chemical Neuroscience: Ketamine

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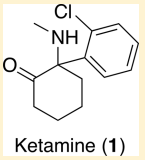
**ABSTRACT:** Ketamine, a molecule of many faces, has contributed immeasurably to numerous realms of clinical practice and scientific inquiry. From anesthesia and analgesia to depression and schizophrenia, it continues to shed light on the molecular underpinnings of pain, consciousness, and the pathophysiology of neuropsychiatric disorders. In particular, research on ketamine's mechanism of action is providing new hope in the search for therapies for treatment-resistant depression and affords insights into disorders of glutamatergic dysfunction. In this Review, we will cover aspects of ketamine's synthesis, manufacturing, metabolism, pharmacology, approved and off-label indications, and adverse effects. We will also discuss the captivating history of this molecule, its influence on neuropsychiatry, and its potential to advance the fields of chemical neuroscience and neuropharmacology.



Ketamine (**1**)

**KEYWORDS:** *Ketamine, anesthesia, schizophrenia, depression, pharmacology, history*

## INTRODUCTION

Ketamine (**1**) is a profoundly powerful molecule that acts as an analgesic, anesthetic, and antidepressant. The drug is used to perform surgeries, relieve pain, rapidly treat depression, probe the biological mechanisms underlying schizophrenia, and achieve altered states of consciousness. Before discussing in detail the synthesis, pharmacological actions, and history of this *classic* molecule, we will briefly introduce its role in these diverse fields (Figure 1).

**Anesthesia and Analgesia.** Over 200 million major surgeries are performed annually.[1] Ketamine has been used for more than 50 years to anesthetize patients undergoing such procedures. Its dissociative properties cause patients to experience a dreamlike level of detachment from their environment,[2] an especially useful quality for individuals undergoing surgery. This is a unique feature among anesthetics and is likely explained by ketamine's distinct pharmacological properties. Unlike many other anesthetics (e.g., propofol, benzodiazepines, and barbiturates), ketamine does not enhance the effects of the inhibitory neurotransmitter $\gamma$-aminobutyric acid (GABA).[3] Instead, it antagonizes the *N*-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor that functions as a membrane channel to allow calcium ($Ca^{2+}$) influx upon synaptic depolarization.[4] This is a particularly intriguing mechanism of action as it does not render the brain globally hypoexcitable, but instead produces regionally specific increases or decreases in cerebral activity.[5,6] While inhibition of NMDA receptors might be expected to decrease neuronal outputs due to increased hyperpolarization, blockade of presynaptic, tonically active channels on inhibitory interneurons in particular brain regions might prevent the release of GABA, thereby disinhibiting downstream excitatory neurons.[7] Ketamine is also a useful analgesic at subanesthetic doses. Its unique mechanism largely circumvents the respiratory depression that is common among other anesthetic and analgesic agents,[8] and psychotomimetic side effects are mostly absent at analgesic doses.[9] Ketamine has therefore been effectively implemented in the Emergency Department for the treatment of acute pain.[10] It can also be used prior to surgery to prevent postoperative pain and to decrease the use of opioids.[11,12] This is especially pertinent in light of the current opioid epidemic plaguing the United States.[13−16]

**Schizophrenia.** One of the most profound properties of ketamine is its ability to produce psychotic symptoms reminiscent of schizophrenia.[17] The linguistic origins of the word schizophrenia (Greek, "skhizein" (to split) and "phrēn" (mind)) reflect the early conception of the disorder as a splitting of psychological functions that ultimately results in a disunity of personality.[18] A more modern conceptualization of schizophrenia considers it a brain disorder affecting neural circuits that is likely caused by aberrant developmental and plasticity processes that are continually shaped by a complex interplay of personal experience and genetic susceptibilities.[19,20] Despite its prevalence, evidence for a highly heritable component and polygenic basis,[21] and its conceptualization as a circuit disorder, the underlying etiopathogenesis of schizophrenia remains poorly understood. In the 1970s, the "dopamine hypothesis" of schizophrenia was formulated based in part on the observations that antipsychotic drugs antagonize the dopamine $D_2$ receptor[22−24] and amphetamines (stimulants that increase synaptic dopamine concentrations) can induce psychosis.[25,26] However, dopamine receptor hyperactivity does not fully explain the symptoms and pathophysiology of schizophrenia. Phencyclidine (known as PCP and formerly

**Received:** February 21, 2017
**Accepted:** April 18, 2017
**Published:** April 18, 2017





DOI: 10.1021/acschemneuro.7b00074
*ACS Chem. Neurosci.* XXXX, XXX, XXX−XXX

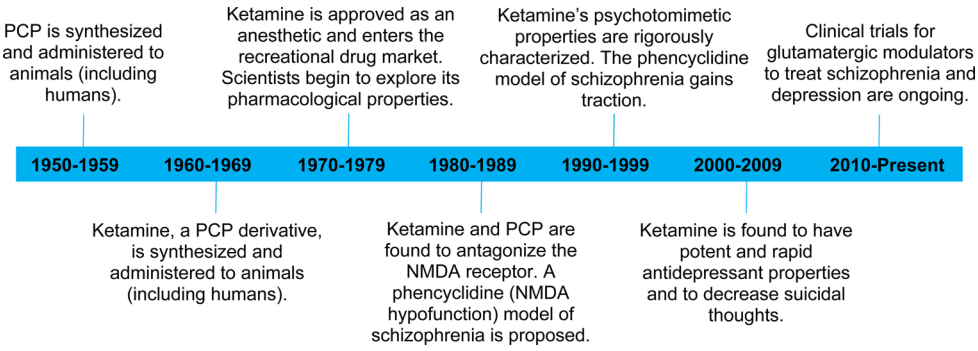



**Figure 1.** Brief timeline of ketamine.

CI-395, Sernyl, and Sernylan), like amphetamines, was found in the late 1950s to be capable of mimicking the symptoms of schizophrenia.[27] In fact, it has been argued that PCP-induced psychosis more closely resembles the disorder in its ability to recapitulate many—if not most—of the positive, negative, and cognitive symptoms.[17,28−31] When treated with PCP, healthy volunteers and patients with schizophrenia reported body-image changes ("impaired ability to distinguish between self and nonself stimuli, feelings of depersonalization, and a sense of unreality"), estrangement ("sense of being completely detached from all environmental objects and tensions"), and disorganization of thought ("the inability to maintain a set, frequent loss of goal ideas, and impairment of the "abstract attitude"").[27] In the early 1980s, PCP was discovered to bind to the NMDA receptor.[32,33] Ketamine binds to the same site on the NMDA receptor as PCP, and produces similar psychotic symptoms at high doses.[17] These observations stimulated much research and discussion, ultimately culminating in the articulation of an NMDA hypofunction model of schizophrenia near the end of the 20th century.[34−36] This model continues to provide insights into the biological mechanisms and treatment of neuropsychiatric disorders.[37−41]

Building on pharmacological evidence from studies of ketamine, recent findings from genome-wide association studies (GWAS) and studies of de novo genetic variation in the form of copy number variants (CNVs), single nucleotide polymorphisms (SNPs), and coding variants have also begun to implicate glutamatergic dysfunction in the pathogenesis of schizophrenia.[42−46] In particular, common genetic variation in loci encoding *GRIN2A*, a major subunit of the NMDA receptor, and *SRR* encoding serine racemase that controls levels of D-serine, a coagonist of the NMDA receptor, have been identified,[46] although the precise causal SNPs and risk mechanisms associated with these loci remain to be fully understood. In this context, the neuropharmacology of ketamine as an NMDA receptor antagonist may have predictive value for the directionality of these findings in terms of loss-of-function of NMDA receptor-mediated neurotransmission. Given the parallel to the identification of common genetic variation in the *DRD2* locus encoding the dopamine $D_2$ receptor that is the main target of clinically used antipsychotics,[46] these findings may prove important examples of directly linking neuropharmacology to the genetic etiology of complex neuropsychiatric disorders.

**Depression.** Depression, like schizophrenia, is complex and poorly understood with evidence for dysfunction of multiple brain circuits and alterations in neuroplasticity. Affecting over 100 million people,[47] depression is the most common psychiatric disorder among individuals who commit suicide,[48] one of the leading causes of death worldwide.[49] Treatment of depression significantly reduces the risk of suicide.[50] Unfortunately, around one-third of patients do not respond to two or more antidepressant therapies and therefore meet the criteria for treatment-resistant depression.[51] In 2000, ketamine was discovered to have rapid and potent antidepressant properties.[52] A promising study in 2006 found that a single intravenous infusion of ketamine reduces depressive symptoms in patients with treatment-resistant major depression.[53] Remarkably, a significant antidepressant effect was achieved in under 2 h and was sustained for at least 1 week in 35% of patients. In this regard, ketamine starkly contrasts commonly prescribed antidepressant drugs, for example from the class of selective serotonin reuptake inhibitors (SSRIs), which generally take weeks and continual exposure to be effective. More recently, ketamine has been shown to reduce multiple measures of suicidality in patients with treatment-resistant depression.[54−58] Scientific understanding of ketamine as an antidepressant, while still nascent, is quickly evolving and may shed light on the biological mechanisms underlying depression and suicidal ideation. Most optimistically, ketamine may contribute to the development of a novel therapy to augment or supplant current treatments for this debilitating disorder.

**Illegal Recreational Use.** Ketamine, now a Schedule III drug in the United States, became a popular street drug in the 1970s.[59] It has various names (e.g., Cat Tranquilizer, Cat Valium, Jet, Special K, Special La Coke, Super Acid, Vitamin K, Purple, etc.) and may be illegally stolen/diverted from veterinary clinics or smuggled across borders.[60] The prevalence of recreational ketamine use has not been well studied but is likely low (i.e., ∼0.1% lifetime use in the U.S.) with substantial variation between countries.[61] Nasal ingestion is a common route of administration. Changes in mood and affect occasionally coupled with dreamlike experiences and/or hallucinations were noted in the first clinical studies with ketamine.[8] Many users have reported feelings of unreality, including a sense of unity with the external environment ("melting into the surrounding"), visual hallucinations, and out-of-body sensations (sometimes referred to as the K-hole).[62] These same distortions can be accompanied by a profound fear and anxiety, and some patients report facing something akin to a near-death experience.[63]

The long-term effects of recreational and uncontrolled ketamine use are mostly unknown, although ulcerative cystitis,[64] memory problems,[65,66] and negative impacts on psychological well-being[66] have been reported in chronic users.


DOI: 10.1021/acschemneuro.7b00074
ACS Chem. Neurosci. XXXX, XXX, XXX−XXX

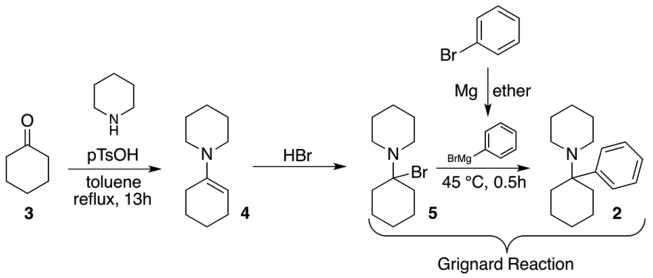
Habitual administration of high doses may also promote localized changes in white matter,[67,68] gray matter,[69] and dopaminergic neurotransmission.[70] Death from acute ketamine toxicity, while extremely rare, may be a concern especially among populations in which the drug is highly abused.[71]

## CHEMICAL SYNTHESIS

Ketamine is an arylcyclohexylamine with one chiral center and thus two enantiomers ((*R*)-ketamine and (*S*)-ketamine). It has a molecular weight of 237.73 and a cLogP of 2.46. The molecule has two hydrogen bond acceptors (the amino group and the ketone) and one hydrogen bond donor (the amino group). These properties satisfy Lipinski's rules (criteria intended to evaluate the oral activity of a drug) and are therefore consistent with ketamine's high biological activity in humans.

Ketamine's chemistry reflects the evolution of arylcyclohexylamines as anesthetics. The Grignard reaction was used to synthesize phencyclidine (PCP, **2**, Scheme 1),[72] a novel

**Scheme 1. Synthesis of PCP Reported by Parke-Davis in the Primary Literature**




anesthetic agent with peculiar properties. In this scheme, cyclohexanone (**3**) was reacted with piperidine and *p*-toluenesulfonic acid to form 1-(cyclohex-1-en-1-yl)piperidine (**4**). Hydrobromic acid was added to **4**, and the resulting 1-(1-bromocyclohexyl)piperidine (**5**) was converted to **2** with the Grignard reagent phenylmagnesium bromide. Initial clinical studies with **2** revealed promising, potent anesthetic action with a low risk of respiratory depression.[73] However, patients often emerged from PCP-induced anesthesia in a state of prolonged delirium,[27,74,75] prompting the search for a comparably potent drug with more acceptable side effects. These efforts led to the eventual synthesis of ketamine (CI-581, **1**) an effective analgesic that harbors the beneficial anesthetic properties of PCP, but with less psychiatric and epileptogenic side effects.[8]

The first synthesis of ketamine was carried out in the early 1960s by Dr. Calvin Lee Stevens, an Organic Chemistry professor at Wayne State University and chemical consultant at Parke-Davis and Company in Detroit, Michigan.[2] Parke-Davis, now a subsidiary of Pfizer, reported on the synthesis of a series of arylcyclohexylamines related to PCP in 1964.[72] In 1962, Dr. Stevens and Parke-Davis filed a patent application that was granted in 1966 detailing the synthesis of ketamine and related compounds (Scheme 2).[76] Grignard reagent **6** was added to 2-chlorobenzonitrile (**7**) then hydrolyzed to form (2-chlorophenyl) (cyclopentyl)methanone (**8**). Bromination of **8** formed the unstable bromoketone **9** which was then treated with methylamine to produce (*Z*)-1-((2-chlorophenyl) (methylimino)methyl)cyclopentan-1-ol (**10**). Finally, thermal rearrangement of **10** resulted in 2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one (**1**), now known as ketamine.

## MANUFACTURING INFORMATION

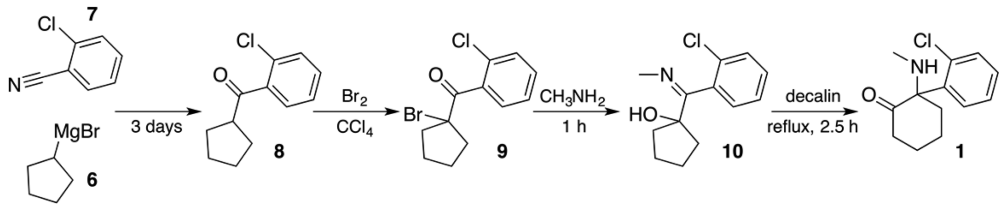
Ketamine (brand name Ketalar) is manufactured by various pharmaceutical companies for use in humans and nonhuman animals. After its synthesis in the early 1960s and preclinical/clinical testing, it was approved by the Food and Drug Administration (FDA) in the United States in 1970. Ketamine is sold as an injectable solution in the following doses: 10 mg/mL (20 mL), 50 mg/mL (10 mL), and 100 mg/mL (5 mL, 10 mL).[77] Prices range from approximately $0.01 to 0.10 per milligram.[77] Thus, a dose of 0.5 mg/kg for a 70 kg individual would cost $0.35−3.50. Johnson & Johnson manufactures a nasal spray containing an enantiopure solution of (*S*)-ketamine, which earned a breakthrough therapy designation from the FDA in 2013.[78] More formulations are likely to emerge as many other clinical trials for ketamine and related molecules are ongoing.

## METABOLISM

Ketamine displays high CNS permeability,[79,80] with estimates of binding to plasma proteins ranging from ∼10−50%.[81−83] Its bioavailability varies dramatically depending on the route of administration. Orally administered ketamine at 0.5 mg/kg has a bioavailability of 17% and peak concentration of 45 ng/mL at 30 min while intramuscular (IM) ketamine at the same dose has a bioavailability of 93% and peak concentration of 240 ng/mL at 22 min.[84] The bioavailabilities of intranasal and intrarectal formulations in children are 25% and 50% respectively.[85] The half-life of ketamine ranges from 2 to 3 h[84,86] and does not differ substantially between the (*R*) and (*S*) enantiomers.[87]

Metabolic transformation of ketamine (Figure 2) is thought to be vitally important to its therapeutic efficacy. Less than 4% of the parent drug (**1**) is detected in urine following intravenous administration.[88] The most common metabolic transformation is *N*-demethylation to norketamine (**11**), a reaction that occurs at a faster rate for (*S*)-ketamine.[89,90] Hydroxylation of both ketamine and norketamine has also been observed. Ketamine can be hydroxylated at carbon 6 to hydroxyketamine (**12**) which undergoes subsequent *N*-demethylation to 6-hydroxynorketamine (**13**), the major

**Scheme 2. Synthesis of Ketamine Reported by Parke-Davis in the Patent Literature**






DOI: 10.1021/acschemneuro.7b00074
ACS Chem. Neurosci. XXXX, XXX, XXX−XXX

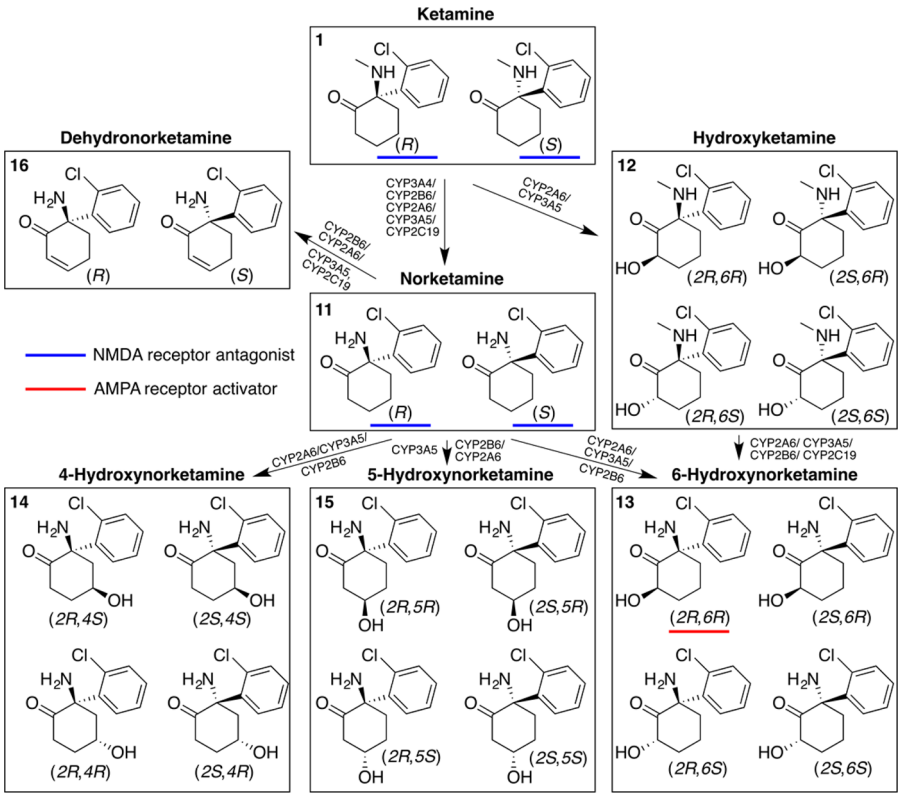



**Figure 2.** Structures of ketamine and its known metabolites.

hydroxylated ketamine metabolite.[91] Norketamine is hydroxylated at carbons 4 (**14**), 5 (**15**), and 6 (**13**).[92] Norketamine can also be transformed to dehydronorketamine (**16**).[93] Phenolic and glucuronic metabolites of ketamine have been identified,[94] but they have not been extensively studied.

The conversion of ketamine to norketamine is fairly rapid due to high first-pass metabolism. Peak concentrations of norketamine are achieved at around 60 min with considerable variation between individuals.[84,86] The cytochrome $P_{450}$ (CYP) enzymes CYP3A4 and CYP2B6 are likely responsible for this conversion.[95,96] On the other hand, the conversion of ketamine to hydroxyketamine is probably catalyzed by CYP2A6 and CYP3A5.[97] The parent drug along with these two metabolites (norketamine and hydroxyketamine) are modified in a regioselective and stereoselective manner by at least five different CYPs,[97] presenting a level of metabolic complexity that may account for part of the heterogeneity in clinical response to ketamine.

## PHARMACOLOGY

Both ketamine and norketamine act as noncompetitive antagonists at the NMDA receptor via binding to an allosteric site distinct from the glutamate-binding site.[98] This receptor is a critical modulator of CNS neurotransmission, and excitability changes produced by ketamine antagonism may explain the drug's anesthetic and analgesic properties.[32,99−101] Observable analgesia is achieved at doses of 0.1−0.5 mg/kg,[8,101] while anesthesia requires doses of >1 mg/kg.[8] In regards to effects on neurocircuitry, somatosensory and auditory regions including the sensory motor cortex and the inferior colliculus show significantly reduced glucose metabolism when exposed to anesthetic doses of ketamine (10 mg/kg), whereas limbic structures tend in the opposite direction.[5] In addition, recent evidence points to a ketamine-induced disruption in information transfer between the primary motor cortex and the somatosensory cortex,[102] an effect that is common among diverse classes of anesthetics.[103] The (*S*) enantiomers of both ketamine and norketamine appear to bind to the NMDA receptor with ∼5−8 times the affinity of their (*R*) counterparts: (*R*)-ketamine → $K_i$ = 1.4 μM, (*S*)-ketamine → $K_i$ = 0.3 μM, (*R*)-norketamine → $K_i$ = 13 μM, (*S*)-norketamine → $K_i$ = 1.7 μM.[98] Expectedly, the (*S*) enantiomer of ketamine also behaves as a more potent anesthetic[87] and analgesic.[104] However, based on one preclinical examination of ketamine's antidepressant effects, (*R*)-ketamine seems to be a more potent antidepressant, suggesting that the antidepressant effects of the drug may be distinct from—or not fully explained by—its action at NMDA receptors.[105] Supporting this theory, sustained activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors by (2*R*,6*R*)-hydroxynorketamine, a ketamine metabolite that does not antagonize NMDA receptors, appears to be a necessary component of the antidepressant response.[105] This metabolite is primarily derived from (*R*)-ketamine, potentially explaining the enantiomeric discrepancy in antidepressant properties.[105]

The downstream mechanism responsible for the antidepressant properties of ketamine-induced NMDA receptor antagonism and/or AMPA receptor activation has been the subject of a plethora of recent and exciting research. Commonly prescribed SSRIs tend to have a delayed onset of antidepressant response. For example, fluoxetine (Prozac), a classic example of an SSRI, generally takes at least 2 weeks and sometimes more than 1 month to achieve a therapeutic effect.[106] Conversely, a single intravenous injection of ketamine results in rapid onset (<72 h) of antidepressant effects[52,53,107,108] that may be sustained for 1−2 weeks.[109] Previous studies suggested that


DOI: 10.1021/acschemneuro.7b00074
ACS Chem. Neurosci. XXXX, XXX, XXX−XXX

ketamine's ability to induce mammalian target of rapamycin (mTOR) signaling to increase the number of synapses in the prefrontal cortex (PFC) distinguished it from SSRIs.[110] Supporting this hypothesis, glucose metabolism in this region is augmented at subanesthetic doses.[111] However, more recent experiments have revealed that mTOR signaling can also be regulated by chronic treatment with the SSRI fluoxetine,[112] indicating that such regulation is not, in fact, a property unique to ketamine. Induction of this pathway is dependent on AMPA receptor activation[113] and is observed after treatment with subanesthetic doses of (*R*,*S*)-ketamine, (*R*,*S*)-norketamine, and (2*S*,6*S*)-hydroxynorketamine.[114] As mentioned above, a more recent study in preclinical rodent models suggests that the bulk of the antidepressant effects produced by ketamine result from AMPA receptor activation by (2*R*,6*R*)-hydroxynorketamine.[105] Whether this holds true in humans remains to be understood. Notably, inhibitory GABAergic interneurons are especially sensitive to NMDA receptor inhibition,[115] rendering them likely targets of ketamine action. Exposed to a low dose of ketamine, these neurons are presumably inhibited, thereby disinhibiting downstream glutamatergic neurons and enhancing the release of glutamate.[116,117] It is possible, then, that indirect AMPA receptor activation by ketamine-mediated NMDA receptor inhibition coupled with either direct or indirect AMPA receptor activation by one or more ketamine's metabolites synergistically oppose the symptoms of depression. Downstream of NMDA receptor inhibition, antidepressant effects likely necessitate blockade of eukaryotic elongation factor (eEF2) kinase, resulting in derepression of brain-derived neurotrophic factor (BDNF) synthesis.[7,118,119] Indeed, ketamine-induced synaptogenesis in the PFC of mice is impaired by a BDNF Val66Met mutation.[120] Taken together, the available studies on ketamine's antidepressant activity suggest that a pathway involving direct and/or indirect AMPA receptor activation, BDNF synthesis, and mTOR signaling ultimately culminates in PFC synaptogenesis that in turn may restore inhibition of limbic structures to improve depressive symptoms.[121] Activation of the ventral hippocampus-medial prefrontal cortex pathway may also be an essential component of this antidepressant response.[122] However, the specific neurocircuitry and complete spectrum of molecular targets involved in the antidepressant actions of ketamine have yet to be elucidated.

Subanesthetic doses (i.e., 0.1−0.5 mg/kg) of ketamine hold tremendous promise for the treatment of depression. Doses on the higher end of this spectrum, however, can produce schizophrenia-like symptoms in healthy volunteers[17] and can exacerbate psychosis when administered to individuals with schizophrenia.[31,123−125] Increased global brain connectivity following ketamine administration appears to correlate with positive and negative symptoms characteristic of schizophrenia.[126] The fact that ketamine, an NMDA receptor antagonist, can produce and worsen schizophrenia-like symptoms suggests that glutamatergic dysfunction may underlie the pathophysiology of schizophrenia. Further supporting this theory, the atypical antipsychotic clozapine can antagonize the psychotomimetic effects of ketamine,[127] while the typical antipsychotic haloperidol, which is much more selective for dopamine $D_2$ receptors, blocks neither ketamine-induced psychosis[123] nor cerebral metabolic activation.[128] The previous paragraph discusses PFC activation via GABAergic-mediated disinhibition of glutamatergic neurons as a possible mechanism underlying the antidepressant effects of ketamine. Surprisingly, this mechanism may also explain the schizophrenia-like symptoms produced by the drug.[129] Thus, ketamine may correct PFC hypoactivation in depression while exacerbating PFC hyperactivation in schizophrenia. Intriguingly, recent clinical data suggests that ketamine's antidepressant response is correlated with psychotomimetic symptoms (e.g., delusions, suspiciousness, disordered thoughts, and hallucinations),[130] lending further support to the notion of a shared pathway among these two complex psychiatric disorders. A larger, more recent study, however, did not find such an association, and instead noted a positive correlation between the dissociative side effects (e.g., amnesia, out-of-body experiences, distorted visual perceptions, and identity disturbances) and antidepressant response.[131]

Beyond the aforementioned glutamate receptors (NMDA and AMPA), a handful of diverse proteins are subject to modulation by ketamine. It has affinities of <100 $\mu$M for opioid, $\sigma$, and muscarinic receptors with substantial differences between enantiomers.[132] Ketamine inhibits a subset of nicotinic acetylcholine receptors,[133−135] as do the ketamine metabolites (*R*,*S*)-norketamine, (*R*,*S*)-dehydronorketamine, (2*S*,6*S*)-hydroxynorketamine, and (2*R*,6*R*)-hydroxynorketamine.[133] Ketamine may act as a partial agonist at $D_2$ receptors and has also been shown to bind to the 5-$HT_2$ receptor.[136] Both enantiomers may also influence reuptake of norepinephrine, dopamine, and serotonin.[101] This polypharmacology could underlie certain therapeutic benefits and/or side effects of ketamine. The drug's rather promiscuous nature has led some researchers to urge caution when making oversimplified inferences pertaining to models of schizophrenia.[136] Still, ketamine's actions on glutamate receptors are its most well-studied and likely most relevant to its clinical effects. The relevance of glutamatergic neurotransmission is supported by the fact that the neither the $D_2$ antagonist haloperidol[123] nor the opiate receptor antagonist naltrexone[137] can prevent ketamine-induced psychosis, although patients who are dependent on ketamine may benefit from the latter.[138] Moreover, ketamine and its metabolites have recently been shown to have no substantial in vivo affinity for various monoaminergic transporters and receptors (dopamine, noradrenaline, and serotonin transporters and dopamine receptors $D_1$−$D_5$), implicating an indirect basis for altered dopaminergic neurotransmission.[139]

## APPROVED AND OFF-LABEL INDICATIONS

Ketamine is approved by the FDA as a general anesthetic in humans[77] and is widely used in veterinary medicine.[140] It is used off-label for analgesia,[141] complex regional pain syndrome,[142] rapid endotracheal intubation,[143] and refractory status epilepticus.[144] More recently, ketamine has seen increasing off-label use for treatment-resistant depression.[145] Ketamine clinics for treating depression have opened around the U.S. Many clinicians have urged caution against using ketamine off-label for depression due to limited data, pointing to a dearth of studies evaluating long-term risk and a lack of phase III clinical trial data.[146−149]

## ADVERSE EFFECTS

Ketamine's side-effect profile is quite unique among anesthetic agents. Emergence from ketamine-induced anesthesia is often accompanied by psychotomimetic and dissociative symptoms including dreamlike states, hallucinations, changes in mood and


DOI: 10.1021/acschemneuro.7b00074
ACS Chem. Neurosci. XXXX, XXX, XXX−XXX

affect, delirium, and confusion. Benzodiazepines such as midazolam can be effective in minimizing many of these emergence phenomena.[150−153] Ketamine has absolute contraindications for individuals with diagnosed or suspected schizophrenia (as it can exacerbate the symptoms of this disorder) and infants under 3 months of age.[77] It can produce mild respiratory depression and hypercapnia[8,154] and may rarely induce laryngospasm.[155] Oral secretions have also been observed. Significant increases in blood pressure and heart rate are among ketamine's most concerning side effects in the context of anesthesia.[8] Side effects of chronic subanesthetic ketamine administration are less well understood. Neuronal vacuolization has been seen in rats administered a single, high-dose (40 mg/kg) ketamine infusion.[156] Dissociative and psychotomimetic side effects have been observed at doses of 0.5 mg/kg but are much less prevalent at doses of 0.1 mg/kg.[17] Current evidence suggests that ketamine is a remarkably safe drug when administered appropriately by trained medical professionals.

## HISTORY AND IMPORTANCE IN NEUROSCIENCE

The molecular, cellular, and circuit-level processes underlying the manifestation of many neuropsychiatric disorders have yet to be fully elucidated. Still, advances within the last century justify a sense of cautious optimism. Chemical treatments for depression and schizophrenia emerged in the 1950s. This decade represented a tremendously hopeful advance for patients with neuropsychiatric disorders and a terrific success for neuropsychopharmacology. The monoamine oxidase inhibitor (MAOI) iproniazid and the tricyclic antidepressant (TCA) imipramine revolutionized care for patients with depression.[157] Likewise, the antipsychotics chlorpromazine and haloperidol revolutionized care for patients with schizophrenia.[158] Shortly after the introduction of these drugs, widespread deinstitutionalization swept across various countries. Pharmacological advancements allowed many psychiatric patients to control symptoms that had made it difficult if not impossible to hold an occupation and carry out daily activities. Moreover, research into the mechanism of action underlying the therapeutic efficacy of these treatments provided a deeper understanding of the molecular underpinnings of depression and schizophrenia.

Despite this sudden burst in progress, a decades-long stagnation in developing therapeutics with novel mechanisms of action has plagued the field of psychiatry. Dozens of new psychopharmaceuticals have entered the market, an increase in quantity that has been met with a proportionate increase in neither mechanistic diversity nor effectiveness as 20−30% of patients with schizophrenia do not respond to antipsychotic treatments.[159−161] As a result, hundreds of thousands of individuals derive limited benefit from these molecules, a fact that has profound implications for mental health and costs the United States alone over $34 billion per year.[162] Moreover, most of these drugs only treat the positive symptoms of schizophrenia (hallucinations, delusions, disorganized thoughts, and disordered movement) with little impact on the negative (blunting of affect, reduced pleasure, and social withdrawal)[163] and cognitive (deficits in working memory, verbal learning and memory, visual learning and memory, verbal comprehension, attention, processing speed, problem solving, and social cognition) symptoms.[164−166] The facts are similarly staggering for depression: around one-third of patients do not respond to two or more first line antidepressant therapies,[51] and nearly 20% of individuals with treatment-resistant depression have attempted suicide.[167] These sobering statistics implore the fields of chemical neuroscience and pharmacology to address the enormous burden of neuropsychiatric disorders.

In this context, beyond its role as an anesthetic and analgesic, ketamine holds the potential to transform our current models of neuropsychiatric disorders and spark the next revolution in drug development beyond monoamine-based mechanisms. Studies on ketamine emerged out of an investigation of the intriguing psychiatric properties of PCP where its administration to rodents was noted to cause hyperactive and psychotomimetic effects.[168] By the mid 1960s, many PCP derivatives had been synthesized of which ketamine possessed qualities that made it a promising anesthetic agent in monkeys: (1) it was highly potent and produced no significant respiratory depression; (2) it was safe at a wide range of doses (3−48 mg/kg); (3) it did not produce convulsions; and (4) it was short acting.[169] Not only were these effects reproducible in human studies, but the prolonged emergence delirium seen with PCP was either nonexistent or dramatically shortened in people treated with ketamine.[8] Still, many of the treated volunteers felt floating sensations, experienced numbness in their limbs, and underwent changes in mood and affect. Some had hallucinations or dreamlike experiences and even believed themselves to be dead. These psychological alterations generally lasted for less than half an hour and were perceived to be pleasant by most of the subjects.[8] Ketamine was henceforth referred to as a dissociative anesthetic. The first clinical study of ketamine used on patients undergoing surgical procedures was a great success.[170] These and other studies led ketamine to be placed on the list of FDA-approved anesthetics in 1970.

During the 1970s, while the research community continued to characterize its pharmacokinetics and pharmacodynamics,[88,171−177] ketamine use spread with a handful of prominent physicians and other individuals outside of the medical establishment consuming the drug recreationally and as a means to explore human consciousness.[2] Despite this increase in scientific and public interest, the mechanistic basis of ketamine's unique effects remained elusive until the early 1980s. Some pharmacological properties were indeed known: (1) ketamine was capable of reducing the activity of neurons within the spinal cord;[178] (2) unlike many other anesthetic agents, ketamine did not enhance inhibitory neurotransmission;[179] and (3) ketamine-induced neuronal depression was not consistent throughout the nervous system, and regionally specific excitation had also been observed.[180] However, ketamine's cellular target(s) had not been identified. In 1983, the response of excitatory spinal neurons to stimulation with NMDA were shown to be diminished in the presence of ketamine or PCP.[32] NMDA receptor antagonism thus provided a potential mechanistic explanation for ketamine's analgesic and anesthetic properties.

Beyond providing a deeper understanding of analgesia and anesthesia, this monumental discovery was intriguing in light of the psychiatric symptoms induced by ketamine and PCP. It was thought that NMDA receptor disruption might contribute to the pathophysiology of schizophrenia.[28,29] Following the introduction of this hypothesis, the psychiatric effects of ketamine were more rigorously characterized with many impactful papers published in the mid-1990s detailing ketamine's psychotomimetic properties.[17,123−125] At the time, a dopamine hypothesis of schizophrenia prevailed.[22,181] At face value, ketamine presented a challenge to this hypothesis; its


DOI: 10.1021/acschemneuro.7b00074
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mechanism did not involve binding to dopamine receptors, yet, compared to dopaminergic modulators such as amphetamines, it more faithfully mimicked the symptoms of schizophrenia. This conundrum was at least partially resolved in 1997 when evidence emerged linking ketamine's glutamatergic modulation and dopaminergic dysregulation.[116] Antagonism of NMDA receptors by ketamine was shown to have the effect of increasing glutamate release in the PFC. Enhanced glutamate release led to an increase in dopamine release that could be prevented by administration of an AMPA receptor antagonist. Thus, it was hypothesized that the ketamine-induced increase in glutamate release resulted in stimulation of non-NMDA glutamate receptors in the PFC, culminating in enhanced dopamine neurotransmission and potentially explaining the psychotomimetic effects of the drug. In agreement with this hypothesis, a study in 1999 found that mice with reduced expression of NMDA receptors behave in a manner consistent with models of schizophrenia.[35] Moreover, these behaviors are readily ameliorated following treatment with antipsychotic drugs that antagonize the dopamine $D_2$ receptor. These findings added credibility to the PCP model of schizophrenia that has become widely known as the "NMDA receptor hypofunction" model.[34,36]

At this point in history, ketamine had treated countless patients and made important contributions to multiple fields of study. The drug had been used to gain insights into the molecular mechanisms underlying analgesia, anesthesia, and schizophrenia. Evidence for NMDA receptor involvement in affective disorders, such as depression, emerged around the same time as the NMDA receptor hypothesis of schizophrenia. In 1990, the NMDA receptor antagonists 2-amino-7-phosphonoheptanoic acid (AP-7) and dizocilpine (MK-801) were shown to closely mimic the effects of antidepressants in animal models of depression-like behavior.[182] Specifically, mice treated with these compounds exhibited less immobilization when confronted with inescapable stressors. Then, in the mid-1990s, radioligand binding to NMDA receptors was shown to be altered in the cerebral cortices of mice treated with antidepressants (TCAs, MAOIs, SSRIs, atypical antidepressants, and electroconvulsive therapy)[183] and in the frontal cortices of suicide victims.[184] Near the end of the decade, regionally specific alterations in mRNA expression of a subset of NMDA receptor subunits were observed in mice treated with antidepressants.[185] This conglomeration of evidence begged a critical question: Does ketamine, a known NMDA receptor antagonist, have any effect on patients with depression?

In 2000, a low dose (0.5 mg/kg) of ketamine was injected intravenously into seven patients with depression.[52] A marked reduction in depressive symptoms was achieved in under 72 h and sustained for up to 2 weeks. It was postulated that ketamine's rapid onset of action compared to existing antidepressant therapies reflected engagement with cellular entities directly implicated in depression (NMDA receptors) rather than upstream targets (serotonin transporters).[186] This direct interaction might result in a rapid and sustained enhancement of neuroplasticity, effectively combating the hypoplastic state associated with depression.[187] A study in 2002 showed that a single dose of ketamine ameliorated behavioral despair in rats for up to 10 days, further supporting the role of glutamatergic signaling in depression.[188] In 2006, a randomized, placebo-controlled, double blind crossover study was conducted in 18 patients with treatment-resistant major depression.[53] Subjects' symptoms improved within 2 h of ketamine injection and were sustained for about 1 week on average. These results have now been replicated in a number of patients with major depressive disorder[130] and bipolar disorder,[189,190] rendering the antidepressant effects of ketamine beyond dispute.[191] Ketamine has also been shown to decrease suicidal thoughts.[54,55,58,190,192] After starting a new antidepressant regimen, the risk of suicidal behavior is highest in the first 9 days,[193] which is undoubtedly concerning given the delayed onset (2−3 weeks or more) of symptom relief that is a core feature of most antidepressant medications. Taken together, these data suggest that ketamine not only behaves as a potent antidepressant, but its rapid onset may also prevent countless patients from attempting suicide.

Multiple models have been proposed to explain the molecular underpinnings of ketamine's antidepressant effects. One emphasized in the Pharmacology section of this Review that is perhaps most strongly supported involves presynaptic NMDA receptor blockade on GABAergic interneurons leading to disinhibition of PFC glutamatergic neurons and culminating in synaptogenesis and restored neuroplasticity.[121,194,195] AMPA receptors may also be involved in these effects. The ketamine metabolite (2*R*,6*R*)-hydroxynorketamine activates AMPA receptors through either direct or indirect mechanisms and has potent antidepressant properties in mouse models of depression.[105] Additionally, AMPA receptor antagonists are capable of blocking the antidepressant effects of ketamine in rats.[196] Such a finding could be attributed to the obstruction of AMPA receptor stimulation dependent on glutamate release following NMDA receptor blockade or NMDA-independent AMPA receptor activation.

In summary, efforts to understand ketamine's unique, albeit complex, mechanism has shed light on the pathology of psychosis and affective disorders and has led to the synthesis of numerous small molecule modulators of glutamatergic neurotransmission that are currently under development.[195] Many antidepressant and antipsychotic therapies based on glutamatergic models of depression and schizophrenia are being explored in preclinical studies and clinical trials.[197] Ketamine, and the neuropharmacological insights derived from it, continues to change perceptions and is undoubtedly a *classic* in chemical neuroscience.

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M.W.T. and H.B.Y. wrote the paper. D.F.I. and S.J.H. contributed passages to various sections, provided input to M.W.T. and H.B.Y. throughout the writing process, and edited the final manuscript.

### Notes

The authors declare the following competing financial interest(s): The authors declare no competing financial interests. D.F.I., upon writing this manuscript, was a faculty member at MGH and Harvard Medical School but as of March 13, 2017 will be an employee of Janssen Pharmaceuticals, which is conducting clinical trials on esketamine. D.F.I. receives research funding from the NIH/NIMH (K23-107776), Brain and Behavior Research Foundation (NARSAD Young Inves-



DOI: 10.1021/acschemneuro.7b00074
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tigator Award), and MGH Executive Committee on Research. S.J.H. serves on the scientific advisory board of Rodin Therapeutics, Frequency Therapeutics, and Psy Therapeutics.

## ■ ACKNOWLEDGMENTS

We are grateful for the comments of anonymous reviewers who helped to ensure a balanced and up-to-date perspective on the evolving field surrounding ketamine research.

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DOI: 10.1021/acschemneuro.7b00074
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