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ORIGINAL INVESTIGATION

Psychiatric safety of ketamine in psychopharmacology research

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Abstract
Rationale A growing number of investigators are studying ketamine effects in healthy human subjects, but concerns remain about its safety as a research tool. Therefore, it is timely to revisit the safety of subanesthetic doses of ketamine in experimental psychopharmacology studies.
Objective To report on the safety of laboratory studies with subanesthetic doses of ketamine in healthy humans using an existing dataset.
Materials and methods Medically healthy subjects with no personal or familial Axis I psychotic spectrum disorders were administered subanesthetic doses of ketamine by intravenous infusion in a series of clinical investigations from 1989 to 2005. The safety of ketamine administration was monitored in these subjects.
Results Four hundred and fifty subjects received at least one dose of active ketamine. Eight hundred and thirty three active ketamine and 621 placebo infusions were administered. Ten adverse mental status events were documented in nine subjects/infusions that were deemed related to ketamine administration (2% of subjects, 1.45% of infusions). All but one adverse reaction resolved by the end of the test session. The side effects in the remaining individual were no longer clinically significant within 4 days of the test session. No residual sequelae were observed.
Conclusion Ketamine administration at subanesthetic doses appears to present an acceptable level of risk for carefully screened populations of healthy human subjects in the context of clinical research programs that intensively monitor subjects throughout their study participation.

Keywords NMDA receptor · Antagonist

Other members of the Yale Ketamine Study Group are listed in the Acknowledgements.

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Introduction

Ketamine is an FDA-approved anesthetic and analgesic. It is an uncompetitive antagonist at the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor (Thomson et al. 1985). Ketamine has been in clinical use since 1970 (Miller 2005) and has an excellent medical safety profile (Haas and Harper 1992; Miller 2005; Reich and Silvay 1989). As patients emerge from ketamine anesthesia, perceptual alterations such as dissociative experiences (sense of observing one's body from a distance) and illusions (misinterpretation of a real, external sensory stimulus) occur (Miller 2005). These effects are sometimes associated with excitement,

confusion, euphoria, and fear. However, the intensity of these reactions is managed by the coadministration of other medications, such as benzodiazepines (Miller 2005). Ketamine is used primarily for ambulatory surgery and for the treatment of chronic pain symptoms because of its lack of cardiovascular and respiratory depression and prominent analgesic effects (Miller 2005; Morgan et al. 2004b). It is also administered to children, who appear to have reduced propensity to exhibit emergence phenomena (Miller 2005). Recent studies suggest that ketamine may have antidepressant effects with a distinctively rapid onset (Berman et al. 2000; Zarate et al. 2006).

Subanesthetic doses of ketamine induce a range of transient dose-related psychotomimetic and cognitive effects in healthy human subjects that resemble some of the symptoms associated with schizophrenia (Krystal et al. 2003a) and also some of the subjective effects of alcohol (Krystal et al. 2003b). The schizophrenia-like symptoms include perceptual and mood changes and impairments in memory, attention, and abstract reasoning (Honey et al. 2005; Krystal et al. 1994, 1999b, 2000, 2005a; Morgan et al. 2004a; Rowland et al. 2005). Ketamine has played a significant role in investigating the contributions of glutamatergic function to the neurobiology of schizophrenia (Abi-Saab et al. 1998; Adler et al. 1999; Krystal et al. 1994, 1999a,c, 2005b; Lahti et al. 1999, 2001b; Malhotra et al. 1996; Newcomer et al. 1999) and alcoholism (Krystal et al. 1998a, 2003b). Despite the growing number of studies using ketamine, concerns remain about the safety of ketamine when used as a research tool. The concern is related to the abuse liability of ketamine and reports of persisting psychosis when self-administered in this context (Dillon et al. 2003).

Thus, it is timely to evaluate the safety of subanesthetic doses of ketamine in experimental psychopharmacology. Investigators in the Department of Psychiatry at Yale University School of Medicine have used ketamine in clinical research since 1989, and this report is drawn from a dataset on laboratory studies with subanesthetic doses of ketamine in healthy humans. As the physical side effects (e.g., nausea) of ketamine are well known (Miller 2005) and are not the focus of concern about ketamine research, this report will present data related to the emergence of mental status adverse events in these studies.

Materials and methods

Sixteen studies involving ketamine administration were conducted from 1989 to 2005 (Table 1). All doses were administered intravenously in a bolus-plus-infusion paradigm or a continuous infusion alone, and all were subanesthetic. Bolus doses ranged from 0.081 mg/kg over 10 min to 0.26 mg/kg over 1 min, and continuous infusion doses ranged from 0.04 mg/kg to 0.75 mg/kg over 60 to 120 min, all by intravenous (i.v.) route. Additionally, in several studies, subjects also received other medications concurrently with ketamine including clozapine, haloperidol, amphetamine, glycine, lamotrigine, naltrexone, the group II metabotropic glutamate receptor agonist LY354740, nicotine, and lorazepam. With the exception of amphetamine, none of the coadministered medications produced psychosis or worsened ketamine-induced psychosis in these studies.

All studies were approved by the institutional review boards of the Yale University School of Medicine and the VA Connecticut Healthcare System, and all subjects gave written informed consent before study participation. During the informed consent process, subjects were provided with extensive information about ketamine, including the following or similar information in easily understandable language:

- There is potential for people to abuse ketamine.
- It is unclear whether exposure to ketamine in the laboratory can result in ketamine use or abuse.
- Behavioral effects of ketamine during the infusion may include feeling detached from surroundings, reduced concentration, feeling as if you are in a dream, colors or sounds seeming brighter or duller than usual, altered body sensations, blurred vision, decreased pain, increased anxiety, feeling high, confusion, hallucinations, sweating, increased blood pressure, increased heart rate, rash, nausea, and vomiting.
- Some subjects report a “hangover” on the day after ketamine administration, and some report vivid dreams for a few days afterward.

Subjects were prepared for the test day, debriefed at the end of each test session, and recontacted after the test day to monitor for adverse events. They were also informed before testing that they would be admitted to the hospital if needed. A research nurse, research assistant, and study physician attended to subjects to offer support and to help clarify the progress of the study in case ketamine caused confusion. Lorazepam was available to rapidly reduce the mental status effects of ketamine. Subjects remained at the test facility for several hours after the mental status effects of ketamine had resolved. A study physician evaluated subjects at the conclusion of testing to ensure that all clinically significant ketamine effects had resolved before leaving the testing site. Subjects who reported lingering medication effects, such as sedation, were not scheduled for additional testing until the effects resolved. Subjects were asked not to engage in demanding work after the test session and to contact the research staff if any adverse events occurred after leaving the hospital.

All Institutional Review Board (IRB) adverse event reports, and a list of ketamine infusions prematurely

Table 1 Ketamine studies

Study	Infused dose of ketamine		Number of subjects[a]	Number of active/placebo ketamine doses	Publication year
	Bolus	Continuous infusion			
Ketamine effects on the acoustic startle response	0.23 mg/kg over 1 min	0.58 mg/kg over 60 min	22 (20)	20/22	1994 (Karper et al. 1994)
Cognitive and behavioral effects of ketamine in subjects with family history positive (FHP) and negative (FHN) for alcoholism[b]	None	1) 0.5 mg/kg over 40 min 2) 0.1 mg/kg over 40 min	FHP 17 (17) FHN 14 (14)	33/16 26/13	2004 (Petrakis et al. 2004)
Cognitive and behavioral effects of ketamine (dose–response)[b]	None	1) 0.5 mg/kg over 40 min 2) 0.1 mg/kg over 40 min	32 (31)	61/29	1994 (Krystal et al. 1994)
Cognitive and behavioral effects of ketamine in recently detoxified alcoholic patients[b]	None	1) 0.5 mg/kg over 40 min 2) 0.1 mg/kg over 40 min	46 (45)	85/40	2003 (Krystal et al. 2003c) 1998 (Krystal et al. 1998b)
Clozapine blockade of ketamine effects	0.26 mg/kg over 1 min	0.65 mg/kg over 60 min	8 (8)	16/16	1997 (Lipschitz et al. 1997)
Lorazepam blockade of ketamine effects	0.26 mg/kg over 1 min	0.65 mg/kg over 60 min	31 (31)	57/53	1998 (Krystal et al. 1998a)
Dynamic mapping of ketamine effects on cortical activation assessed by high speed magnetic resonance imaging	0.23 mg/kg over 1 min	0.58 mg/kg over 12 min	17 (17)	19/19	Not published
Interaction of ketamine with haloperidol	0.26 mg/kg over 1 min	0.65 mg/kg over 60 min	35 (33)	54/52	1999 (Krystal et al. 1999b)
Interaction of ketamine with amphetamine	0.23 mg/kg over 1 min	0.5 mg/kg over 60 min	42 (38)	66/61	2005 (Krystal et al. 2005b)
Interaction of ketamine with naltrexone[b]	1) 0.23 mg/kg over 10 min 2) 0.081 mg/kg over 10 min	0.58 mg/kg over 60 min 0.04 mg/kg over 60 min	31 (30) 24 (22)	53/49 43/43	2006 (Krystal et al. 2006)
Interaction of ketamine with glycine	0.23 mg/kg over 1 min	0.5 mg/kg over 60 min	44 (41)	111/105	1999 (D'Souza et al. 1999)
Interaction of ketamine with lamotrigine	0.26 mg/kg over 1 min	0.65 mg/kg over 90 min	22 (22)	40/34	2000 (Anand et al. 2000)
Comparison of ketamine with thiopental in subjects with FHP and FHN for alcoholism	0.23 mg/kg over 1 min	0.58 mg/kg over 60 min	FHP 9 (8) FHN 28 (28)	14/7 49/24	(In progress)
Interaction of ketamine with LY354740	0.26 mg/kg over 1 min	0.65 mg/kg over 100 min	14 (14)	29 (no placebo)	2005 (Krystal et al. 2005a)
Interaction of ketamine with nicotine	0.26 mg/kg over 1 min	0.65 mg kg^{-1} h^{-1}× 120 min	12 (11)	19/19	(In progress)
FMRI: interaction of ketamine with lamotrigine	0.23 mg/kg over 2 min	0.68 mg/kg over 70 min	21 (20) Total: 469 (450)	38/19 Total: 833/621	(In progress)

[a] Number of subjects receiving at least one dose of active ketamine in parentheses
[b] High dose and low dose ketamine conditions

discontinued because of the mental status effects of ketamine, were reviewed. This list was recorded by nursing staff who have attended to these studies from their inception. We report only those events believed by the investigator and the IRBs to be related to ketamine administration. Charts of these subjects were reviewed. Serious adverse events were defined as (1) death, (2) a life-threatening adverse experience, (3) hospitalization or prolongation of existing hospitalization, (4) a persistent or significant disability/incapacity, or (5) a congenital anomaly or birth defect. All other adverse events were defined as non-serious.

Longer-term follow-up assessments of study participants were initiated in 2000 to determine whether there were any long-term adverse effects of ketamine exposure, including subsequent ketamine abuse. Research staff contacted subjects by telephone for follow-up interviews at varying intervals (1 week to 6 months after the final ketamine test day) depending on the study, even for subjects who dropped out prematurely. These follow-up interviews were typically conducted after subjects had been paid and were therefore more likely to report negative effects. If subjects were not available by telephone, they were contacted by mail or e-mail. In some instances, subjects returned for face-to-face interviews as part of the screening process for other studies. The interviews included an unstructured portion as well as some or all of the following questions:

- Since your last test day/interview, have you experienced any physical problems?
- Since your last test day/interview, have you experienced any emotional or psychological problems?
- Since your last test day/interview, have you had any cravings for ketamine?
- Since your last test day/interview, how many times have you used ketamine outside of a research study?

All subjects received 24-h telephone numbers to call in case of medical problems. They also received the telephone numbers of the medical center's human studies representative and research office, with instructions to report any questions or concerns.

Results

Fifteen studies included only healthy research subjects, and one study included alcohol-abusing subjects postdetoxification. Together, these studies amount to 469 subjects (450 received at least one dose of active ketamine), 833 active ketamine infusions, and 621 placebo infusions. Forty six subjects had histories of alcohol abuse or dependence, and the remaining were healthy subjects. The subjects were between the ages of 21 and 65 years (the majority in their 20s), in good physical health, taking no medications, and without a current or past psychiatric diagnosis other than alcohol abuse or dependence in selected protocols (determined by the Structured Clinical Interview for DSM-III-R-Non-Patient Edition; Spitzer et al. 1990). Although occasional substance use (including ketamine) that did not meet the DSM criteria for abuse or dependence was not an exclusion criterion, subjects were required to abstain from alcohol and illicit drugs during study participation, and this was confirmed with urine drug screens on each study day. Further, subjects who had a first degree relative with an Axis I psychotic disorder were excluded. In many of the studies, research staff administered the Wisconsin Scale of Psychosis Proneness (Chapman et al. 1982) to detect individuals who might have a history of subtle psychotic or near-psychotic experiences and confirmed the history provided by subjects by contacting an informant identified by the subject at the time of screening.

There were no serious adverse events, as defined above, in any of the studies. Ten significant mental status adverse events were documented in nine subjects receiving nine active ketamine infusions that were deemed related to ketamine (2% of subjects, 1.45% of infusions; Table 2). The subjects who reported these adverse events included healthy subjects and one recently detoxified alcoholic. Five were men, and the majority were in their 20s to early 30s.

The mental status adverse events included three medically stable subjects who became unresponsive to verbal stimuli. All became responsive again within minutes of discontinuation of ketamine infusion and were back to their baselines by the end of the study day:

- A subject who received oral LY354740 100 mg in addition to ketamine was nonverbal after receiving the ketamine bolus (0.26 mg/kg over 1 min) and 2 min of the ketamine infusion (0.65 mg kg^{-1} h^{-1} over 100 min). She was able to squeeze the nurse's hand on command and became verbal again within 1–2 min after the infusion was discontinued. She stated that she felt as if she were "in a movie" and did not think verbal communication was necessary because the staff could read her mind.
- A subject who received oral LY354740 400 mg in addition to ketamine was nonverbal after receiving the ketamine bolus (0.26 mg/kg over 1 min) and 5 min of the ketamine infusion (0.65 mg kg^{-1} h^{-1} over 100 min). He was able to open his eyes when his name was called but did not respond verbally. He became verbal again within 30 min after the ketamine infusion was discontinued. The same subject also reported nightmares, insomnia, and decreased ability to concentrate for 3–4 days after the test day. The symptoms did not prevent him from returning to work and resolved completely within 2 weeks.

Table 2 Ketamine mental status adverse events (active ketamine administrations only)[a]

Event	Scheduled ketamine dose	Other study drug received	Response
Medically stable but not responsive to verbal and painful stimuli	0.1 mg/kg over 401 min	None	Infusion terminated
Subject described sensation as "no control, not a good feeling."	0.23 mg/kg over 1 min followed by 0.5 mg/kg over 60 min	Amphetamine 0.25 mg/kg	Infusion terminated
Subject became tearful×30 min	0.23 mg/kg over 10 min followed by 0.58 mg/kg over 60 min	Naltrexone 2 mg	Infusion terminated
Subject described sensation as "very unpleasant."	0.26 mg/kg over 1 min followed by 0.65 mg/kg over 100 min	None	Infusion terminated
Medically stable but not responsive to verbal stimuli	0.26 mg/kg over 1 min followed by 0.65 mg/kg over 100 min	LY354740 100 mg	Infusion terminated
Medically stable but not responsive to verbal stimuli[b]	0.26 mg/kg over 1 min followed by 0.65 mg/kg over 100 min	LY354740 400 mg	Infusion terminated
Subject reported nightmares, insomnia, and decreased ability to concentrate for 3–4 days following test day[b]	0.26 mg/kg over 1 min followed by 0.65 mg/kg over 100 min	LY354740 400 mg	Improved after 4 days and resolved after 2 weeks
Subject described sensation as "weird" and requested infusion termination	0.23 mg/kg over 1 min followed by 0.58 mg/kg over 60 min	None	Infusion terminated
Subject became tearful, described sensation as "panicky" and requested infusion termination.	0.26 mg/kg over 1 min followed by 0.65 mg kg^{-1} h^{-1}×120 min	None	Infusion terminated
Subject described sensation as "too high, walls closing in" after bolus and requested infusion cancellation.	0.26 mg/kg over 1 min followed by 0.65 mg kg^{-1} h^{-1}×120 min	None	Infusion cancelled[c]

[a] All events resolved and were deemed related to ketamine
[b] Occurred in same subject/infusion
[c] Received only ketamine bolus and not continuous infusion

– A recently detoxified alcoholic subject who received only ketamine was responsive only to deep pain stimuli after receiving 18 min of the ketamine infusion (0.5 mg/kg over 40 min). He was responsive to verbal stimuli within 5 min after the infusion was discontinued.

Six subjects reported distress related to the mental status effects of ketamine resulting in discontinuation of ketamine infusion. In addition to ketamine, one subject also received amphetamine; one subject received naltrexone; and the other four subjects received only ketamine. The distress, which resolved within minutes after termination of ketamine infusion, was described variously as "no control," "not a good feeling," "feeling panicky," "very unpleasant," "weird," "too high," "walls were closing in," "felt out of my element," "distorted," and "too intense." Two subjects became tearful. The effects reported by these subjects were experienced by other subjects without the same degree of distress or the need for intervention.

Most adverse events resolved within minutes after discontinuation of ketamine; all adverse events improved within 4 days of ketamine administration and were not present after 2 weeks. No residual sequelae were observed. Mental status adverse events in response to ketamine infusions were generally mild and transient, and there were no serious ketamine-related adverse events as defined above. Typical expected, nondistressing effects of acute ketamine administration (e.g., transient perceptual alterations and mild sedation) are not reported here.

Two significant mental status adverse events were documented in two healthy subjects (one male, both in their 20s) receiving placebo ketamine infusions (0.32% of placebo ketamine infusions). One subject reported anxiety and mild dyspnea that resolved immediately after termination of the active glycine infusion. Another subject who received no other study medication became tearful immediately after the scheduled termination of the placebo ketamine infusion and remained tearful for about 40 min. On discussion, he attributed this to recent social stressors and did not feel that it was related to the study participation. Neither subject had residual sequelae.

One hundred subjects were contacted for follow-up assessments at 1 week after study participation, 39 at 1 month, 50 at 3 months, and 34 at 6 months. Although these subjects comprised a relatively small subsample of ketamine study subjects, the data collected to date have yielded no reports of emotional or psychological problems, cognitive deficits, medical or neurological problems, cravings for ketamine, use of ketamine outside the research setting, unusual perceptions, sluggishness, flashbacks, or paranoid thoughts (Tables 3 and 4). Moreover, none of the subjects who were not formally followed have reported any instances of ketamine abuse precipitated by their participa-

Table 3 Follow-up data summary

Time point	No	Yes
Since your last test day/interview, have you experienced any physical problems?		
1 week	87	3 (fatigue and nausea; increased headaches; lightheadedness, nausea, nightmares, vivid dreams)
1 month	29	0
3 months	50	0
6 months	24	0
Since your last test day/interview, have you experienced any emotional or psychological problems?		
1 week	90	0
1 month	29	0
3 months	50	0
6 months	24	0
Since your last test day/interview, have you had any cravings for ketamine?		
1 week	90	0
1 month	29	0
3 months	50	0
6 months	24	0
Since your last test day/interview, have you experienced any adverse events?		
1 week	9	1 (fatigue)
1 month	9	1 (hospitalization unrelated to ketamine administration)
6 months	10	0

tion in our ketamine study protocols. No subject reported mental status sequelae after follow-up.

Discussion

In psychiatric research, the concern about ketamine as a psychopharmacological probe is related to acute and persistent psychotropic side effects and abuse liability. This report is drawn from an existing dataset on laboratory studies with subanesthetic doses of ketamine in healthy humans.

The findings from this review show that subanesthetic doses of ketamine can be associated with mild, transient mental status adverse events. These adverse events occurred very infrequently in our studies (in fewer than 2% of subjects receiving active ketamine infusions) and resolved spontaneously. In our longer-term follow-up data, we found no evidence of ketamine abuse by subjects following study participation and no evidence of subsequent psychiatric problems related to ketamine exposure (alone or in combination with other study drugs). A recent analysis of this data failed to find evidence of sensitization to the effects of ketamine in those subjects who had more than one exposure to this drug (Cho et al. 2005). These findings are consistent with the lack of long-term effects reported with anesthetic doses of ketamine (Corssen et al. 1971; Moretti et al. 1984) and further document the safety of subanesthetic doses of ketamine as a psychopharmacologic probe in healthy subjects. Careful selection of subjects, preparation of subjects for the effects of ketamine, and debriefing of subjects after each test session likely contributed to the low occurrence of significant adverse mental status events.

Similarly, previous studies showed that subanesthetic doses of ketamine administered to schizophrenic patients induced events that were mild and of brief duration (Carpenter 1999). Combined data from several centers revealed that psychosis and anxiety measured by the Brief Psychiatric Rating Scale were transiently elevated 20–30 min after ketamine administration but returned to baseline within 30–60 min. There was no evidence of a prolonged or residual effect. Other researchers (Lahti et al. 1995, 2001a) reported similar safety findings.

Table 4 Ketamine usage outside of a research study

Time point	Not at all	One time	Two to three times	Four to six times	Seven to ten times	Regularly
Since your last test day/interview, how many times have you used ketamine outside of a research study?						
1 week	72	0	0	0	0	0
1 month	39	0	0	0	0	0
3 months	50	0	0	0	0	0
6 months	34	0	0	0	0	0

Ketamine studies, along with postmortem findings in schizophrenia patients and in vivo measurements of altered glutamate metabolism (Olney and Farber 1995), support the NMDA receptor hypofunction hypothesis of schizophrenia. Of the available options for probing the glutamatergic system in human subjects, ketamine has received the most attention. Ketamine has several desirable qualities as a laboratory agent. It has a short half-life and transient effects; it has been well-studied in the clinical setting; it is relatively easy to administer; and it does not usually cause cardiovascular and respiratory depression (Miller 2005). Although its effects are not isomorphic to schizophrenia, subanesthetic doses of ketamine produce transient positive symptoms, negative symptoms, learning impairments, perceptual alterations, and poorer performance on tests sensitive to frontal cortical dysfunction in healthy human subjects (Krystal et al. 1994, 2005a; Malhotra et al. 1996). In addition to its use as a psychopharmacological probe, the ketamine model of psychosis presents an opportunity to test potential new treatments for schizophrenia (Krystal et al. 2005a). The ketamine paradigm has also advanced a glutamate hypothesis of alcoholism (Krystal et al. 1998b, 2003b) that may be relevant for medication development for this disorder.

The limitations of this review include the largely retrospective nature of the data, changing standards of IRB reporting since the initiation of these studies, reliance on spontaneous self-report from subjects, and the availability of longer-term follow-up data in only a subset of the subjects. In conclusion, ketamine administration at subanesthetic doses appears to present an acceptable level of risk for carefully screened populations of healthy human subjects in the context of clinical research programs that intensively monitor subjects throughout their study participation.

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References

Abi-Saab WM, D'Souza DC, Moghaddam B, Krystal JH (1998) The NMDA antagonist model for schizophrenia: promise and pitfalls. Pharmacopsychiatry 31(Suppl 2):104–109

Adler CM, Malhotra AK, Elman I, Goldberg T, Egan M, Pickar D, Breier A (1999) Comparison of ketamine-induced thought disorder in healthy volunteers and thought disorder in schizophrenia. Am J Psychiatry 156:1646–1649

Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A, Krystal JH (2000) Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of *N*-methyl-D-aspartate receptor antagonists. Arch Gen Psychiatry 57:270–276

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47:351–354

Carpenter WT Jr (1999) The schizophrenia ketamine challenge study debate. Biol Psychiatry 46:1081–1091

Chapman LJ, Chapman JP, Miller EN (1982) Reliabilities and intercorrelations of eight measures of proneness to psychosis. J Consult Clin Psychol 50:187–195

Cho HS, D'Souza DC, Gueorguieva R, Perry EB, Madonick S, Karper LP, Abi-Dargham A, Belger A, Abi-Saab W, Lipschitz D, Bennet A, Seibyl JP, Krystal JH (2005) Absence of behavioral sensitization in healthy human subjects following repeated exposure to ketamine. Psychopharmacology (Berl) 179:136–143

Corssen G, Oget S, Reed PC (1971) Computerized evaluation of psychic effects of ketamine. Anesth Analg 50:397–401

D'Souza DC, Gil R, Zuzarte E, Zimmerman L, Abi-Saab D, Damon D, White J, Krystal J (1999) Glycine-ketamine interactions in healthy humans. 6th international congress on schizophrenia research (Schizophr Res), Santa Fe, NM, pp 213

Dillon P, Copeland J, Jansen K (2003) Patterns of use and harms associated with non-medical ketamine use. Drug Alcohol Depend 69:23–28

Haas DA, Harper DG (1992) Ketamine: a review of its pharmacologic properties and use in ambulatory anesthesia. Anesth Prog 39:61–68

Honey GD, Honey RA, O'Loughlin C, Sharar SR, Kumaran D, Suckling J, Menon DK, Sleator C, Bullmore ET, Fletcher PC (2005) Ketamine disrupts frontal and hippocampal contribution to encoding and retrieval of episodic memory: an fMRI study. Cereb Cortex 15:749–759

Karper LP, Grillon C, Charney DS, Krystal J (1994) The effect of ketamine on prepulse inhibition and attention. 33rd annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214

Krystal JH, Karper LP, Bennett A, D'Souza DC, Abi-Dargham A, Morrissey K, Abi-Saab D, Bremner JD, Bowers MB Jr, Suckow RF, Stetson P, Heninger GR, Charney DS (1998a) Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans. Psychopharmacology (Berl) 135:213–229

Krystal JH, Petrakis IL, Webb E, Cooney NL, Karper LP, Namanworth S, Stetson P, Trevisan LA, Charney DS (1998b) Dose-related

ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. Arch Gen Psychiatry 55:354–360

Krystal JH, Belger A, D'Souza DC, Anand A, Charney DS, Aghajanian GK, Moghaddam B (1999a) Therapeutic implications of the hyperglutamatergic effects of NMDA antagonists. Neuropsychopharmacology 21:S143–S157

Krystal JH, D'Souza DC, Karper LP, Bennett A, Abi-Dargham A, Abi-Saab D, Cassello K, Bowers MB Jr, Vegso S, Heninger GR, Charney DS (1999b) Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology (Berl) 145:193–204

Krystal JH, D'Souza DC, Petrakis IL, Belger A, Berman RM, Charney DS, Abi-Saab W, Madonick S (1999c) NMDA agonists and antagonists as probes of glutamatergic dysfunction and pharmacotherapies in neuropsychiatric disorders. Harv Rev Psychiatry 7:125–143

Krystal JH, Bennett A, Abi-Saab D, Belger A, Karper LP, D'Souza DC, Lipschitz D, Abi-Dargham A, Charney DS (2000) Dissociation of ketamine effects on rule acquisition and rule implementation: possible relevance to NMDA receptor contributions to executive cognitive functions. Biol Psychiatry 47:137–143

Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R (2003a) NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology (Berl) 169:215–233

Krystal JH, Petrakis IL, Krupitsky E, Schutz C, Trevisan L, D'Souza DC (2003b) NMDA receptor antagonism and the ethanol intoxication signal: from alcoholism risk to pharmacotherapy. Ann N Y Acad Sci 1003:176–184

Krystal JH, Petrakis IL, Limoncelli D, Webb E, Gueorgueva R, D'Souza DC, Boutros NN, Trevisan L, Charney DS (2003c) Altered NMDA glutamate receptor antagonist response in recovering ethanol-dependent patients. Neuropsychopharmacology 28:2020–2028

Krystal JH, Abi-Saab W, Perry E, D'Souza DC, Liu N, Gueorguieva R, McDougall L, Hunsberger T, Belger A, Levine L, Breier A (2005a) Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. Psychopharmacology (Berl) 179:303–309

Krystal JH, Perry EB Jr, Gueorguieva R, Belger A, Madonick SH, Abi-Dargham A, Cooper TB, Macdougall L, Abi-Saab W, D'Souza DC (2005b) Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. Arch Gen Psychiatry 62:985–994

Krystal JH, Madonick S, Perry E, Gueorguieva R, Brush L, Wray Y, Belger A, D'Souza DC (2006) Potentiation of low dose ketamine effects by naltrexone: potential implications for the pharmacotherapy of alcoholism. Neuropsychopharmacology 31:1793–1800

Lahti AC, Koffel B, LaPorte D, Tamminga CA (1995) Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 13:9–19

Lahti AC, Holcomb HH, Gao X, Tamminga CA (1999) NMDA-sensitive glutamate antagonism: a human model for psychosis. Neuropsychopharmacology 21:S158–S169

Lahti AC, Warfel D, Michaelidis T, Weiler MA, Frey K, Tamminga CA (2001a) Long-term outcome of patients who receive ketamine during research. Biol Psychiatry 49:869–875

Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA (2001b) Effects of ketamine in normal and schizophrenic volunteers. Neuropsychopharmacology 25:455–467

Lipschitz DS, D'Souza DC, White JA, Charney DS, Krystal JH (1997) Clozapine blockade of ketamine effects in healthy subjects. Biol Psychiatry 41 S:23S (abstract #76)

Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier A (1996) NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. Neuropsychopharmacology 14:301–307

Miller RD (2005) Miller's Anesthesia, 6th edn. Elsevier, Amsterdam, The Netherlands

Moretti RJ, Hassan SZ, Goodman LI, Meltzer HY (1984) Comparison of ketamine and thiopental in healthy volunteers: effects on mental status, mood, and personality. Anesth Analg 63:1087–1096

Morgan CJ, Mofeez A, Brandner B, Bromley L, Curran HV (2004a) Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology 29:208–218

Morgan CJ, Mofeez A, Brandner B, Bromley L, Curran HV (2004b) Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose–response study. Psychopharmacology (Berl) 172:298–308

Newcomer JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, Craft S, Olney JW (1999) Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology 20:106–118

Olney JW, Farber NB (1995) Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 52:998–1007

Petrakis IL, Limoncelli D, Gueorguieva R, Jatlow P, Boutros NN, Trevisan L, Gelernter J, Krystal JH (2004) Altered NMDA glutamate receptor antagonist response in individuals with a family vulnerability to alcoholism. Am J Psychiatry 161:1776–1782

Reich DL, Silvay G (1989) Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth 36:186–197

Rowland LM, Astur RS, Jung RE, Bustillo JR, Lauriello J, Yeo RA (2005) Selective cognitive impairments associated with NMDA receptor blockade in humans. Neuropsychopharmacology 30:633–639

Spitzer RL, Williams JBW, Gibbon M, First MB (1990) Structured Clinical Interview for DSM-III-R-Non-Patient Edition (SCID-NP, Version 1.0 with supplement for DSM-IV). American Psychiatric, Washington, DC

Thomson AM, West DC, Lodge D (1985) An *N*-methylaspartate receptor-mediated synapse in rat cerebral cortex: a site of action of ketamine? Nature 313:479–481

Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK (2006) A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63:856–864