Side-effects associated with ketamine use in depression: a systematic review

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This is the first systematic review of the safety of ketamine in the treatment of depression after single and repeated doses. We searched MEDLINE, PubMed, PsycINFO, and Cochrane Databases and identified 288 articles, 60 of which met the inclusion criteria. After acute dosing, psychiatric, psychotomimetic, cardiovascular, neurological, and other side-effects were more frequently reported after ketamine treatment than after placebo in patients with depresssion. Our findings suggest a selective reporting bias with limited assessment of long-term use and safety and after repeated dosing, despite these being reported in other patient groups exposed to ketamine (eg, those with chronic pain) and in recreational users. We recommend large-scale clinical trials that include multiple doses of ketamine and long-term follow up to assess the safety of long-term regular use.

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Introduction

Major depression affects about 350 million people, making it the leading cause of disability worldwide.[1,2] Antidepressant treatments targeting the monoamine system alleviate depressive symptoms in only 50% of patients,[3] and rates become substantially lower in those whose depression has not responded adequately to two or more adequate antidepressant trials.[4] Moreover, these treatments have a long onset of action, usually 3–4 weeks.[5,6] Hence, there is an indisputable need for more efficacious and rapidly acting antidepressants, with ketamine being a key candidate. However, have investigations on ketamine in depression thus far addressed essential factors such as acute and long-term safety?

A balanced assessment of an intervention requires investigation of both benefits and harms. Usually designed to evaluate treatment efficacy or effectiveness, randomised controlled trials are often completed in a short period of time, using a limited number of doses and a relatively small number of participants. These trials are known to be poor at identifying and reporting harms,[7] which can lead to a misconception that a given intervention is safe when its safety is actually unknown. Since Berman and colleagues, in 2000,[8] reported the results of their initial pilot placebo-controlled trial investigating ketamine for the treatment of depression, a plethora of articles, including original studies, narrative reviews, and meta-analyses, have been published, endorsing the efficacy of ketamine in depression. Only a few of the original studies, however, were randomised controlled trials or systematically assessed ketamine's efficacy and safety compared to placebo or a control drug in patients with depression.[9] To date, findings from 20 randomised controlled trials have been reported, which all together include 430 participants who received ketamine. Most of these were proof of concept studies and examined the efficacy of a single dose only, and only a small number comprehensively assessed ketamine's safety, tolerability, and abuse potential. Very few examined the safety (or efficacy) of repeated treatments, relative to placebo or control treatment, although repeated treatments are increasingly being used in open label studies,[10–17] case studies,[18–33] and some clinical services.

Importantly, safety concerns have been reported in other patient groups exposed to ketamine, such as individuals with chronic pain, and recreational users. Reviews, including from WHO,[34] highlighted urinary tract symptoms as a well-documented side-effect of ketamine and listed liver toxicity, cognitive changes, and dependence as potential harms.[35] In 2012, Morgan and Curran,[36] on behalf of the Independent Scientific Committee on Drugs, concluded that frequent, daily use of ketamine is associated with ulcerative cystitis and neurocognitive deficits in working and episodic memory; they also reported that many frequent users are concerned about addiction.

Despite the 15 years that have passed since Berman and colleagues' report, there remains a large gap in knowledge regarding the long-term efficacy of ketamine in depression, potential long-term safety issues, and the absence of approved clinical guidelines for its use. With a growing interest in ketamine as a treatment for depression, as well as the increasing use of repeated dosing in both clinical and research settings,[37–40] acute and long-term safety issues must be further explored and systematically assessed. In this systematic review, we aggregate and analyse reporting of data on the safety of ketamine in depression and comment on experience from human clinical trials to date.

Methods

Search strategy and selection criteria

We followed PRISMA reporting guidelines in this systematic review. Studies were eligible for inclusion if they reported findings with adult human populations who had a validated diagnosis of unipolar or bipolar depression and had received one or more doses of ketamine (any administration route, frequency of dose, and time course were accepted). Studies also had to describe changes in depression status as a primary outcome measure. Exclusion criteria included: animal trials; studies that were non-original or mechanistic in nature; studies that described paediatric or adolescent population outcomes

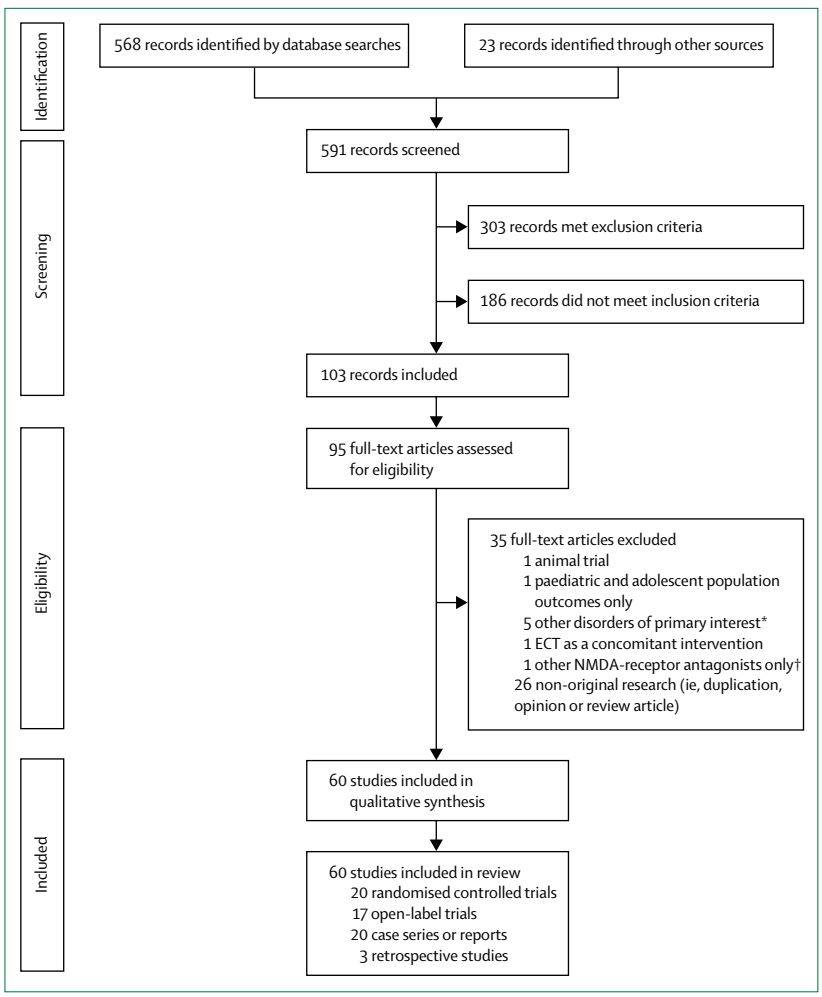

Figure 1: **Study selection**
ECT=electroconvulsive therapy. NMDA=N-methyl-D-aspartate. *Unless a patient with depression was included (ie, pain, fibromyalgia, suicidality, post-traumatic stress disorder, recreational drug use). †Nitrous oxide, MK-0657, AZD6765.

See Online for appendix

only; studies that described other disorders of primary interest, unless a patient with depression was included (ie, pain, fibromyalgia, suicidality, post-traumatic stress disorder, recreational drug use); other intervention of primary interest (eg, vagal nerve stimulation); studies that included electroconvulsive therapy as a concomitant intervention; and studies that reported on other NMDA-receptor antagonist outcomes only (eg, nitrous oxide, MK-0657, AZD6765). No restrictions were imposed on language, and articles in foreign languages were translated to English.

We searched MEDLINE, PubMed, PsycINFO, and Cochrane Database for articles published from Jan 1, 1999, to Dec 30, 2016, with the terms: "ketamine* AND (depress* OR affective* OR mood* OR bipolar*) AND (safe* OR side* OR adverse*)". The initial database search was done by three authors (BS, JF, WS) independently to ensure reproducibility.

Two authors (JF, WS) did a two-step literature search; when a title or abstract seemed to describe a study eligible for inclusion, the full article was reviewed to assess its relevance based on the inclusion criteria. Any disputes in results were settled by consensus. Any discrepancies between the two authors were resolved by consultations with a senior author.

Although randomised clinical trials provide the most reliable estimates of effect, rare serious adverse events or long-term adverse effects are unlikely to be detected. We therefore included many types of study designs.[41] Letters or comments to editors were included if they reported on a case study or series.

We collected information about study design, sample characteristics, ketamine administration details (route, dosage, number of doses), health screening before ketamine administration, pre-existing medical morbidity, concomitant medications, and timing of side-effects assessment. Using the same time definitions, we also collected information on which specific side-effects were reported to have occurred (we considered a side-effect as having occurred if the report listed its occurrence in at least one patient); and, where relevant, whether structured assessment tools or questionnaires were used to assess adverse effects or safety. Each article was quality-appraised with a relevant appraisal checklist or tool (appendix).

Analysis

Initially, we took a broad approach to assessing potential side-effects of ketamine for depression to detect a variety of adverse effects or events, whether known or previously unrecognised. We then categorised adverse effects into subgroups (psychiatric, psychotomimetic or dissociative, cardiovascular, neurological [including cognitive], and other side-effects) to include the side-effects that had been reported most frequently.

In accordance with the Cochrane Adverse Effects Methods Group approach,[42] we addressed the following issues that affect data quality: (1) selective outcome reporting; (2) withdrawal or drop-out; and (3) presence of a control group. For selective outcome reporting, we identified whether, and to what extent, side-effects were assessed and reported, which approach was used for assessing side-effects (active surveillance [ie, method described for actively enquiring about side-effects] versus passive monitoring [no method for active enquiry described, thus reports considered to represent side-effects spontaneously reported by patients]), whether structured scales or questionnaires for the assessment of side-effects were used, whether side-effects were reported systematically (ie, both presence and absence of side-effects were reported) or ad hoc (ie, only reported if they occurred), and the timeframe in which side-effects had been assessed and reported (ie, immediately after a single dose [acute], after repeated doses [cumulative], or at least 2 weeks after the last dose [long term]). To analyse

	Number of patients who received ketamine	Route; dose	Reporting period; reported measures; reporting form			
			Psychiatric or psychotomimetic side-effects*	Cardiovascular side-effects	Neurological or cognitive side-effects	Other side-effects
Randomised controlled trials						
Berman et al (2000)[8]	7	Intravenous; single	Short term†; BPRS, VAS; systematic	..	..	..
Kudoh et al (2002)[43]	60‡	Intravenous; single	..	Short term†; vital signs; ad hoc	Short term†; CAM; ad hoc	Short term; nasopharyngeal temperature, end-expiratory oxygen and carbon dioxide, VAS-pain; ad hoc (systematic for VAS-pain)
Zarate et al (2006)[44]	17	Intravenous; single	Short term, cumulative†; BPRS, YMRS, VAS, BDI; systematic	Short term; not specified; ad hoc	Short term; measures not specified; ad hoc	Short term; measures not specified; ad hoc
Diazgranados et al (2010)[45]	13	Intravenous; single	Short term, cumulative, long term†; HAM-D(17), HAM-A, BDI, BPRS, YMRS, CADSS, VAS; systematic	Short term†; vital signs, oximetry, echocardiogram; ad hoc	Reporting period not specified; measures not specified; ad hoc	Short term, long term†; blood cell counts, electrolyte panels, LFTs, ketamine and metabolites blood concentrations; systematic
Zarate et al (2012)[46]	14§	Intravenous; single	Short term, long term†; HAM-D(17), HAM-A, BDI, BPRS, YMRS, CADSS, VAS; systematic	Short term, long term†; vital signs, oximetry, echocardiogram; ad hoc	Reporting period not specified; measures not specified; ad hoc	Short term, long term†; blood cell counts, electrolyte panel, LFTs; systematic
Murrough et al (2013)[47]	47¶	Intravenous; single	Short term†; CADSS, BPRS+; systematic	Short term†; heart rate, blood pressure, oximetry, echocardiogram; systematic	Short term†; PRISE, MCCB; systematic	Short term†; PRISE; systematic
Singh et al (2013)[48]	30	Intravenous; multiple	Short term†; unspecified; ad hoc	Short term†; heart rate, blood pressure, oximetry; ad hoc	..	Short term; unspecified; ad hoc
Sos et al (2013)[49]	27	Intravenous; single	Short term†; BPRS; ad hoc	Reporting period not specified; measures not specified; ad hoc	Reporting period not specified; measures not specified; ad hoc	Short term; ketamine and metabolite concentration in blood; ad hoc
Ghasemi et al (2014)[50]	9	Intravenous; multiple	..	Short term, cumulative†; heart rate, blood pressure, oximetry; systematic	..	..
Lai et al (2014)[51]	4	Intravenous; multiple	Short term, cumulative†; BPRS, YMRS, CADSS; systematic	Short term, cumulative†; heart rate, blood pressure, oximetry; ad hoc	Short term, cumulative†; SAFTEE, orientation, simple or complex reaction time; systematic	Short term, cumulative†; SAFTEE; ad hoc
Lapidus et al (2014)[52]	18	Intranasal; single	Short term†; CADSS, BPRS+, YMRS; systematic	Short term†; heart rate, blood pressure; systematic	Short term†; SAFTEE; systematic	Short term†; SAFTEE, ketamine concentration in blood; systematic
Murrough et al (2015)[53]	12	Intravenous; single	Short term†; BPRS, CADSS, YMRS, C-SSRS; ad hoc	Short term†; heart rate, blood pressure; ad hoc	Short term, cumulative, long term†; PRISE; ad hoc	Short term, cumulative, long term†; PRISE; ad hoc
Hu et al (2015)[54]	13	Intravenous; single	Short term, long term†; BPRS, YMRS, CADSS; systematic	Short term†; heart rate, blood pressure, echocardiogram, oximetry, respiratory rate; ad hoc	Reporting period not specified; measures not specified; ad hoc	Short term†; author created checklist of so-called common somatic side-effects; systematic
Lenze et al (2016)[55]	20	Intravenous; single	Short term†; BPRS+; systematic	Short term, cumulative†; blood pressure, echocardiogram; ad hoc	Short term†; clinical and adverse events checklists; systematic	Short term†; clinical and adverse events checklist, LFTs; systematic
Li et al (2016)[56]	32	Intravenous; single	Short term†; BPRS+; mix of systematic and ad hoc	..	..	Short term; measures unclear; ad hoc
Loo et al (2016)[57]	15	Intravenous, intramuscular, subcutaneous; multiple	Short term, cumulative†; BPRS+, YMRS, CADSS; systematic	Short term, cumulative†; heart rate, blood pressure; systematic	Short term, cumulative†; SAFTEE, orientation, simple or complex reaction time; ad hoc	Short term, cumulative†; SAFTEE, ketamine concentration in blood; ad hoc
Singh et al (2016)[58]	35	Intravenous; multiple	Short term, cumulative†; BPRS+, CADSS, C-SSRS; systematic	Short term, cumulative†; vital signs, oximetry, echocardiogram; systematic	Short term, cumulative, long term; unspecified; systematic	Short term, cumulative, long term†; physical examination, lab tests (not specified),ketamine and metabolite concentration in blood; systematic
Jafarinia et al (2016)[59]	20	Oral; multiple	..	Monitoring period not specified†; physical examination, echocardiogram; ad hoc	Monitoring period not specified†; adverse events checklist; ad hoc	Monitoring period not specified†; adverse events checklist, VAS pain, open-ended question; ad hoc
Downey et al (2016)[60]	21	Intravenous; single	Short term†; CADSS; ad hoc	Monitoring period not specified; measures not specified; not available	Monitoring period not specified; measures not specified; ad hoc	Monitoring period not specified; measures not specified; not available

(Table 1 continues on next page)

	Number of patients who received ketamine	Route; dose	Reporting period; reported measures; reporting form			
			Psychiatric or psychotomimetic side-effects*	Cardiovascular side-effects	Neurological or cognitive side-effects	Other side-effects
(Continued from previous page)						
George et al[61]	16	Subcutaneous; multiple	Short term, cumulative†; BPRS, YMRS CADSS; systematic	Short term, cumulative†; heart rate, blood pressure; systematic	Short term, cumulative†; orientation, reaction times, neuro-psychological tests; systematic	Short term, cumulative, long term†; SAFTEE—modified, urinary problems checklist, LFTs; systematic
Non-randomised controlled trials or open label trials						
Phelps et al (2009)[62]	26	Intravenous; single	Short term†; BPRS, CADSS; ad hoc			
aan het Rot et al (2010)[10]	10	Intravenous; multiple	Short term, cumulative†; BPRS+, CADSS; systematic	Short term, cumulative†; heart rate, blood pressure, oximetry, respiratory rate, echocardiogram; systematic	Short term, cumulative; SAFTEE-SI; systematic	Short term, cumulative, long term; SAFTEE-SI, weight; ad hoc
Mathew et al (2010)[63]	26‖	Intravenous; single	Short term†; BPRS+, CADSS, VAS, YMRS; systematic	Short term†; heart rate, blood pressure, oximetry, echocardiogram; systematic	Short term, long term†; SAFTEE, MATRICS battery (MCCB); systematic	Short term, long term†; SAFTEE, physical examination, weight, baseline blood tests, LFTs, urinanalysis; systematic
Ibrahim et al (2011)[64]	40**	Intravenous; single	Short term†; CADSS; systematic	..	..	..
Larkin et al (2011)[65]	14	Intravenous; single	Short term†; YMRS, BPRS+; systematic	Short term†; vital signs; ad hoc	..	Short term†; weight; ad hoc
Valentine et al (2011)[66]	10	Intravenous; single	Short term†; CADSS, BPRS+ HAM-A; systematic	Short term†; vital signs; systematic	..	..
Ibrahim et al (2012)[67]	42††	Intravenous; single	Short term, long term†; BPRS, CADSS, YMRS, SSI; systematic	Short term†; vital signs, oximetry, echocardiogram; systematic	..	Short term, long term†; blood cell counts, electrolyte panels, LFTs, ketamine and metabolites concentration in blood, weight; systematic
Zarate et al (2012)[68]	67**	Intravenous; single	Short term†; BPRS, BPRS+, CADSS; systematic	..	..	Ketamine and metabolite concentration in blood; systematic
Irwin et al (2013)[11]	14	Oral; multiple	Short term, cumulative†; adverse symptom checklist, SRA, KPSS; systematic	Short term, cumulative†; adverse symptom checklist; systematic	Short term, cumulative†; adverse symptom checklist, MMSE; systematic	Short term, cumulative†; adverse symptom checklist, VAS-pain, BPI-SF; systematic
Murrough et al (2013)[12]	14‡‡	Intravenous; multiple	Short term, cumulative†; BPRS+, CADSS, YMRS, VAS; systematic	Short term, cumulative†; heart rate, blood pressure, oximetry; systematic	Short term, cumulative†; SAFTEE; systematic	Short term, cumulative†; SAFTEE; systematic
Rasmussen et al (2013)[13]	10	Intravenous; multiple	Short term, cumulative†; YMRS, BPRS, CGI, SSI, SSF	Short term, cumulative†; blood pressure, oximetry, echocardiogram; systematic	Short term; measures not specified; ad hoc	Short term; measures not specified; ad hoc
Diamond et al (2014)[14]	28	Intravenous; multiple	Short term, cumulative†; BPRS, VAS; ad hoc	Monitoring period not specified; measures not specified; ad hoc	Short term, cumulative, long term†; AMI-SF, AFT, story recall, ECT-MQ; systematic	Monitoring period not specified; measures not described; ad hoc
Shiroma et al (2014)[15]	14	Intravenous; multiple	Short term, cumulative†; BPRS+, CADSS, VAS, CGI; systematic	Short term†; heart rate, blood pressure, respiratory rate, oximetry, mAldrete; systematic	Short term, cumulative†; MMSE, mAldrete; systematic	Short term; measures note specified; ad hoc
Allen et al (2015)[16]	17	Intravenous; multiple	..	Short term, cumulative; heart rate, blood pressure, oximetry; reporting form not specied; ad hoc	..	..
Ionescu et al (2015)[69]	3	Intravenous; single	Short term†; CADSS, HAM-A; ad hoc	..	..	..
Kantrowitz et al (2015)[70]	8	Intravenous; single	Monitoring period not specified; measures not specified; ad hoc	..	Monitoring period not specified; measures not specified; ad hoc	Monitoring period not specified; measures not specified; ad hoc
Cusin et al (2016)[17]	14	Intravenous; multiple	Short-term, cumulative†; BPRS, CADSS, CGI, C-SSRS; systematic	Short term, cumulative†; heart rate, blood pressure, respiratory rate, oximetry, echocardiogram; systematic	Short term, cumulative†; SAFTEE, CPFQ; ad hoc	Short term, cumulative†; SAFTEE, QLES-Q; systematic

(Table 1 continues on next page)

	Number of patients who received ketamine	Route; dose	Reporting period; reported measures; reporting form			
			Psychiatric or psychotomimetic side-effects*	Cardiovascular side-effects	Neurological or cognitive side-effects	Other side-effects
(Continued from previous page)						
Case studies and case series						
Correll et al (2006)[18]	2	Intravenous; multiple	Short term; measures not specified; ad hoc	Short term†; heart rate, blood pressure; ad hoc	..	Reporting period not specified†; measures not specified; ad hoc
Stefanczyk-Sapieha et al (2008)[19]	1	Intravenous; multiple	Short term; measures not specified; ad hoc	Short term†; vital signs, oximetry; ad hoc	..	Short term†; ESAS; ad hoc
Paul et al (2009)[20]	2	Intravenous; multiple	Short term, cumulative†; measures not specified; ad hoc	Short term, cumulative†; blood pressure, echocardiogram, oximetry; systematic	..	Short term, cumulative†; measures not specified; ad hoc
Paslakis et al (2010)[21]	4	Oral; multiple	Short term, cumulative; unclear measures; ad hoc	Short term, cumulative†; heart rate, respiratory rate; ad hoc	Short term, cumulative; unclear measures; ad hoc	Short term, cumulative†; routine laboratory tests; ad hoc
Irwin et al (2010)[71]	2	Oral; single	Short term†; BPRS, YMRS; systematic	..	Short term†; MMSE; systematic	Short term†; adverse symptom checklist, FIBSER, VAS-pain; systematic
Murrough et al (2011)[22]	1	Intravenous; multiple	..	..	..	..
Blier et al (2012)[23]	1	Intravenous; multiple	Short term, cumulative; measures not specified; ad hoc	..	Cumulative†; MoCA; systematic	Short term, cumulative; measures not specified; ad hoc
Cusin et al (2012)[24]	2	Intravenous, intranasal, oral, intramuscular; multiple	Short term, cumulative; measures not specified; ad hoc	..	..	..
Lara et al (2013)[25]	26	Sublingual; multiple	Reporting period not specified; unclear measures; ad hoc	..	..	Reporting period not specified; unclear measures; ad hoc
Messer et al (2013)[26]	1	Intravenous; multiple	Short term, cumulative; measures not specified; ad hoc	Short term, cumulative†; vital signs; ad hoc	Short term, cumulative; measures not specified; ad hoc	Short term, cumulative; measures not specified; ad hoc
Niciu et al (2013)[72]	2	Intravenous; single	Short term†; CADSS, Y-BOCS; ad hoc	..	..	Short term; measures not specified; ad hoc
Segmiller et al (2013)[27]	1	Intravenous; multiple	Short term; measures not specified; ad hoc	..	..	..
Segmiller et al (2013)[28]	6	Intravenous; multiple	Short term; measures not specified; ad hoc	..	..	..
Szymkowicz et al (2013)[29]	3	Intravenous; multiple	Short term, cumulative; measures not specified; ad hoc	Short term, cumulative†; vital signs; ad hoc	Short term, cumulative; measures unspecified; ad hoc	Short term, cumulative; measures unspecified; ad hoc
Womble (2013)[73]	1	Intravenous; single	..	Short term†; heart rate, blood pressure, oximetry; systematic	..	Short term; measures not specified; ad hoc
Zanicotti et al (2013)[30]	1	Intramuscular; multiple	Short term, cumulative; measures not specified; ad hoc	Short term†; heart rate, blood pressure, oximetry; systematic	Short term, cumulative; measures unspecified; systematic	..
Aligeti et al (2014)[74]	1	Intravenous; single	Short term, long term; measures not specified; ad hoc	Short term†; blood pressure, heart rate, respiratory rate, oximetry, echocardiogram; systematic	..	..
Galvez et al (2014)[31]	1	Subcutaneous; multiple	Short term, cumulative†; BPRS, CADSS; ad hoc	..	..	Reporting period not specified; measures not specified; ad hoc
Gosek et al (2014)[32]	5	Intravenous; multiple	Short term†; CADSS, CGI; ad hoc	Short term†; basic life parameters, echocardiogram; ad hoc	Short term; measures not specified; ad hoc	..
Hassamal et al (2015)[33]	1	Intravenous; multiple	Short term, cumulative; measures not specified; ad hoc	Short term†; vital signs; systematic	Short term, cumulative; measures not specified; ad hoc	Short term, cumulative; measures not specified; ad hoc

(Table 1 continues on next page)

	Number of patients who received ketamine	Route; dose	Reporting period; reported measures; reporting form			
			Psychiatric or psychotomimetic side-effects*	Cardiovascular side-effects	Neurological or cognitive side-effects	Other side-effects
(Continued from previous page)						
Retrospective studies						
Quinones et al (2012)[75]	Un-specified	Intravenous; single	..	Short term†; heart rate, blood pressure, respiratory rate, oximetry; ad hoc	..	Short term; temperature; ad hoc
Iglewicz et al (2015)[76]	31	Oral, subcutaneous; multiple	Short term, cumulative; measures not specified; ad hoc	..	..	Short term, cumulative; measures not specified; ad hoc
Nguyen et al (2015)[77]	17	Transmucosal; multiple	..	..	Reporting period not specified; measures not specified; ad hoc	..

Short-term side-effect assessments were completed within 4 h. Cumulative side-effect assessments were completed after multiple doses. Long-term side-effect assessments were completed at least 2 weeks after last dose. BDI=Beck depression inventory. BPI-sf=brief pain inventory short form. BPRS=brief psychiatric rating scale. BPRS+=brief psychiatric rating scale positive symptom subscale. CADSS=clinician administered dissociative states scale. CAM=confusion assessment method. CGI=clinical global impression. CPFQ=cognitive and physical functioning questionnaire. C-SSRS=Columbia suicide severity rating scale. ESAS=Edmonton system assessment system. FIBSER=frequency, intensity and burden of side-effects rating. HAM-A=Hamilton anxiety rating scale. HAM-D(17)=Hamilton rating scale for depression (17-item). KPS=Karnofsky performance status scale. MATRICS=Measurement and treatment research to improve cognition in schizophrenia. MCCB=MATRICS consensus cognitive battery. MMSE=mini-mental state exam. MoCA=Montreal cognitive assessment. mAldrete=modified Aldrete scoring system. PRISE=patient-related inventory of side-effects. QLES-Q=quality of life enjoyment and satisfaction questionnaire. SAFTEE=systematic assessment for treatment emergent effects. SAFTEE-SI=systematic assessment for treatment emergent effects specific inquiry. SRA=suicide risk assessment. SSI=scale for suicidal ideation. SSF=suicide status form. VAS=visual analogue scale. YMRS=Young mania rating scale. *Other than primary outcome measures. †Active assessment. ‡25 of these patients were administered ketamine over a reduced infusion time period. §Replicated study design of Diazgranados et al (2010).[45] ¶Neurocognitive outcomes published in separate publication using same study design and sample as in Murrough et al (2015).[78] ||Neurocognitive outcomes published in separate publication using same study design and sample as in Murrough et al (2014).[79] **Possible sample overlap with other studies published by this group (Zarate et al [2006];[44] Diazgranados et al [2010];[45] Zarate et al [2012];[46] and Phelps et al [2009][62]).††Some patient results also included in the report by Ionescu et al (2014).[80] ‡‡Some patient results were also reported by aan het Rot et al (2010).[10]

***Table 1*: Study design, patient and dosing information, side-effect assessment, and reporting**

withdrawal or drop-out, we gathered as much information as possible to avoid directly interpreting such data as surrogate markers for safety or tolerability because of potential bias. We assessed the presence of a control group in order to distinguish between adverse events (ie, those which appear after intervention onset) and adverse effects (ie, adverse events for which causality is likely).

A meta-analysis was initially planned, but after data extraction it was deemed that quantitative analysis via meta-analytical methods was not appropriate for the side-effects reported because the articles reviewed were clinically diverse, including a variety of different administrative routes and doses with different control comparators, differences in reporting methods (including non-specific qualitative statements about side-effects), and bias for some of the individual studies (including reporting bias). Thus, a qualitative review of data was undertaken.

Results

We included 60 studies in our analysis (figure 1, table 1), which included 899 patients who had received at least one dose of ketamine (table 2). Most study reports did not include a placebo or control group (figure 2). Acute side-effects were assessed in 55 (92%) studies, whereas cumulative side-effects were analysed in 24 (40%) studies, and long-term side-effects were assessed in 12 (20%) studies (figure 3). In studies that did include a placebo or comparator intervention, side-effects across all categories were more commonly reported in patients who received ketamine.

Acute psychiatric side-effects from ketamine were described in 23 (38%) studies, whereas psychotomimetic or dissociative side-effects were described in 43 (72%) studies, some of which used structured scales (figure 4). Overall, the timepoints used for measurements differed between studies; however, any changes in score were generally self-limiting.

The most common acute psychiatric side-effect was anxiety, followed by agitation or irritability, euphoria or mood elevation, delusions or unusual thoughts, panic, and apathy. Less common side-effects were detachment, emotional blunting, psychosis, emotional lability, craving attention, and formal-thought disorder. When symptoms were delayed, such as with anxiety, worsening depression or suicidality, or both, and hypomania, it was unclear if they were explicitly linked to the ketamine treatment. An isolated case of a suicide attempt was reported in one study.[58] Across all the studies analysed, the most common psychiatric reason for withdrawal from a trial was worsening mood (12 participants), followed by anxiety (six participants) and suicidal ideation (five participants). Less common psychiatric reasons for withdrawal included panic attack (two participants) and irritability (one participant). An

absence of psychosis or mania as a potential side-effect was reported in five (8%) studies.

The most common psychotomimetic side-effect reported was dissociation, followed by perceptual disturbance, odd or abnormal sensation, derealisation, hallucinations, feeling strange, weird, bizarre, or unreal, and depersonalisation. No long-term psychotomimetic side-effects were reported; however, most studies assessed for psychotomimetic side-effects only over the short term (usually within 4 h post-ketamine dose). Dissociation was the only psychotomimetic cause cited for withdrawal from studies (two participants in total). The absence of psychotomimetic or dissociative effects was reported in five (8%) studies.

In general, studies using the intravenous route of administration tended to report more psychotomimetic or dissociative side-effects than those that used other routes of administration (eg, oral, subcutaneous, intramuscular). 36% of non-intravenous studies reported psychotomimetic side-effects, compared with 72% of intravenous studies.

Of the 60 studies included in this analysis, 23 (38%) reported acute changes in the cardiovascular status of patients. The most common cardiovascular changes were increased blood pressure and increased heart rate.Other reported cardiovascular side-effects included palpitations or arrhythmia, chest pain, tightness, or pressure, dizziness on standing, decreased blood pressure, and decreased heart rate. Five patients were withdrawn because of cardiovascular side-effects. Most cardiovascular effects were reported as occurring during or immediately after intravenous ketamine administration. In general, these effects resolved within 90 min of the administered dose.

The most common neurological side-effects cited were headache and dizziness. Less common neurological side-effects included sedation or drowsiness, faintness or light-headedness, poor coordination or unsteadiness, and tremor or involuntary movements. Most studies reported only short-term neurological effects.

Cognitive side-effects included poor memory or memory loss, poor concentration, confusion, and cognitive impairment or diminished mental capacity. Similarly, if cognitive side-effects were described, these were reported over the short term only. Potential cognitive side-effects were not assessed in most studies.

Numerous other side-effects were reported in 32 (53%) studies, with the greatest variety reported in patients receiving intravenous ketamine. These side-effects mainly related to the gastrointestinal, ocular, respiratory, and urological systems.

The most frequently reported other side-effects were blurred vision and nausea. Less common side-effects included insomnia or sleep disturbance, decreased energy, general malaise, or fatigue, restlessness, dry mouth, vomiting, and crying or tearfulness.

Urinary side-effects were assessed in only five studies. Liver function tests were specifically reported to have been completed in seven studies, with two study outcomes including abnormalities post-ketamine dose.[55,61] Only two studies enquired about the development of ketamine dependence or abuse.[23,26]

Scales (eg, SAFTEE, PRISE) to systematically assess other side-effects were used in 15 (25%) studies. Most study groups relied on passive monitoring of treatment-emergent adverse events, and only a few groups followed

	Number of published articles*	Number of patients who received ketamine†	Number of patients who received multiple doses†
Intravenous	49	737‡	214
Per oral	6	72	66
Intramuscular	3	7	7
Subcutaneous	4	25	25
Intranasal	2	18	1
Sublingual	1	26	26
Transmucosal	1	17	17
Total	..	902§	356

*Some studies used multiple administrative routes. †Values are approximations, as number of doses per route for some patients was unclear in some of the studies. ‡One study,[75] in which ketamine was administered intravenously, had an unspecified number of patients. § Three patients received more than one ketamine administration route.

***Table 2*: Total number of published articles and patients in the reviewed studies, by ketamine administration route**

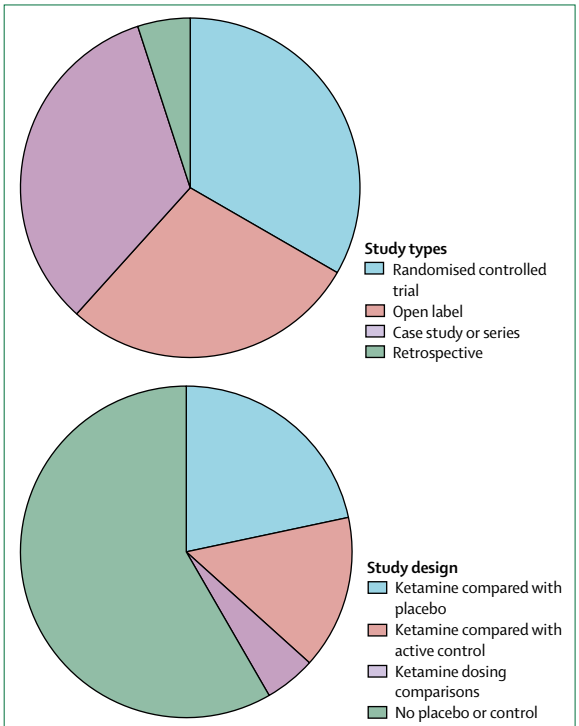

***Figure 2*: Study types and design**

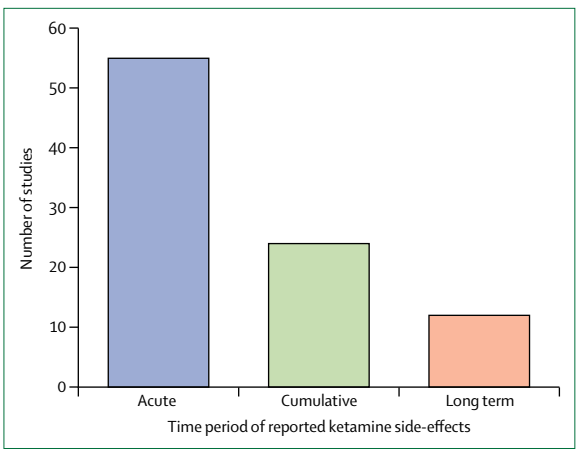

***Figure 3*: Time period of reported ketamine side-effects**

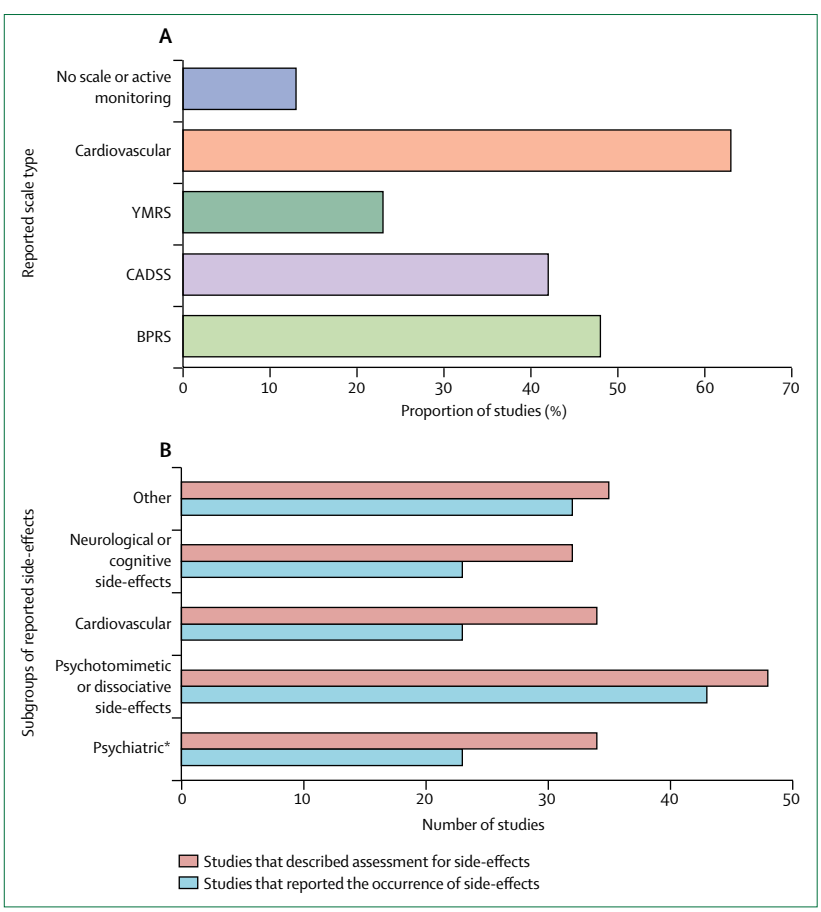

***Figure 4*: Use of structured side-effect enquiry and subgroups**
(A) Proportion of studies that used structured side-effect scales. (B) Number of studies that reported side-effects (shown per subgroup). BPRS=brief psychiatric rating scale. CADSS=clinician-administered dissociative states scale. YMRS=Young mania rating scale. *Other than primary outcomes.

up on these other adverse events beyond the acute treatment period. Thus, the long-term trajectory and consequences of these reported other side-effects are largely unknown.

If side-effects were assessed for, they were predominantly reported in an ad-hoc fashion. Psychiatric or psychotomimetic side-effects were systematically reported in only 25 (42%) studies; cardiovascular side-effects were systematically reported in 19 (32%) studies; neurological or cognitive effects were systematically reported in 14 (23%) studies; and all other side-effects were systematically reported in 14 (23%) studies. When considering the side-effect reporting from randomised controlled trials only, the most common acute side-effects were reported at similar rates as for other study designs. However, long-term side-effect risks or other potential side-effects, including cognition, urinary tract symptoms, or dependency risk, were rarely assessed or commented on in randomised controlled trials (figure 5).

Discussion

We systematically reviewed 288 published reports of studies in which ketamine was administered to people who had depression. Our objective was to identify the main side-effects related to this intervention and to discern whether differences were apparent between single (acute) versus repeated dosing (cumulative and long-term). Side-effects were categorised to facilitate collation and analysis of results; notably, most people receiving ketamine had acute side-effects. In summary, our main findings were: (1) acute side-effects are common after a treatment of ketamine; (2) active assessment, surveillance, and reporting of side-effects during trials of ketamine for patients with depression are inadequate; (3) most of the side-effects reported were associated with ketamine given intravenously; (4) most of the assessed side-effects were reported to occur immediately after single-dose administration (acute); (5) the most common side-effects to be reported were headache, dizziness, dissociation, elevated blood pressure, and blurred vision (figure 5); (6) most side-effects were reported to have resolved shortly after dose administration; (7) psychiatric side-effects were also apparent, the most common being anxiety; (8) many side-effects were assessed through passive monitoring only; (9) if side-effect assessment was completed, it was predominantly reported in ad-hoc form; and (10) from the analysis, we could only draw conclusions regarding single dosing and acute side-effects because insufficient data were available regarding the side-effects of repeated dosing and possible cumulative and long-term risks.

Passive monitoring of side-effects relies on spontaneous reports and is very helpful to detect new, rare, and serious side-effects.[81] Active surveillance includes a preorganised process to discover more information on side-effects, including additional detail, which usually cannot be achieved via passive monitoring methods.[82] An important factor that has emerged from our literature analysis is the inadequacy of active and structured inquiry of known or potential side-effects. Although the brief psychiatric rating scale, the clinician-administered dissociative states

scale, and basic cardiovascular measures are used in many studies, methods for assessing other categories of side-effects, including neurological, cognitive, gastrointestinal, and urological side-effects, were not specifically reported. This is particularly important in view of our findings that neurological and other side-effects, when considered categorically, were reported to occur just as often as or more often than cardiovascular or psychiatric side-effects. Although ketamine is considered a safe drug for its principal approved application regarding anaesthesia (which usually involves a single one-off dose),[83] the prospect of ketamine use in depression will likely entail multiple and repeated doses during a long period of time.

Repeated use of ketamine in other adult populations, including patients undergoing anaesthesia, patients with chronic pain, and recreational users, has been linked with urological toxicity, hepatotoxicity, cognitive deficits, and dependency risks. For example, in 2007, Shahani and colleagues[84] first described chronic users of ketamine who developed severe genitourinary symptoms. Since then, a large volume of additional reports associating ketamine with bladder toxicity have described cystitis and bladder dysfunction, an increase in urinary frequency, urgency, dysuria, urge incontinence, and occasionally painful haematuria.[85–87] Secondary renal damage has also been described in severe cases,[36] and Chen and colleagues[88] have published the first case of renal infarction after nasal insufflation of ketamine. Ketamine use has also been linked with urological toxicity in patients receiving treatment for chronic pain, with some patients developing genitourinary symptoms after only 9 days of treatment.[89–91]

More than 20% of people who use ketamine for recreational purposes are estimated to have urinary tract symptoms,[92] although investigators from Spain and Hong Kong report a much higher prevalence (46% and 90%, respectively).[93] The mechanism by which ketamine causes urological toxicity is not understood, but findings from in-vitro studies have shown a direct interaction between ketamine and the bladder urothelium,[94,95] and in one study, ketamine exposure was associated with apoptosis of urothelial cells.[93] The damage appears to be dose related, and although initially thought to improve or resolve entirely after cessation of ketamine use, this might not be the case.[96]

Ketamine has been reported to negatively affect the liver and biliary tract. Noppers and colleagues[97] showed that liver injury might occur after prolonged or repeated infusion of ketamine, or both. Six patients were scheduled to receive two continuous, intravenous, 100 h ketamine infusions (infusion rate 10–20 mg/h) separated by 16 days. Three patients developed hepatotoxicity after the start of the second infusion. Other reports of liver toxicity in users of recreational ketamine exist,[98] and Bell[99] and Sear[100] have expressed serious concerns. The mechanism by which ketamine causes liver injury is not understood but might be related to metabolic events causing increased lipid peroxidation and free radical formation.[100] In a preclinical study, ketamine was found to increase flow resistance across the sphincter of Oddi,[101] but in a more recent study in human beings, ketamine use in a single dose of 20 mg did not affect sphincter of Oddi parameters.[102] Other authors have proposed that the N-methyl-D-aspartate receptor antagonistic effect of ketamine might cause smooth muscle relaxation and subsequent dilatation of the biliary tree and gallbladder dyskinesia via a central pathway.[103]

Compared with healthy controls without a history of drug abuse, people who use ketamine frequently can also have severe impairments in both short-term and long-term memory.[104] In a double-blind randomised

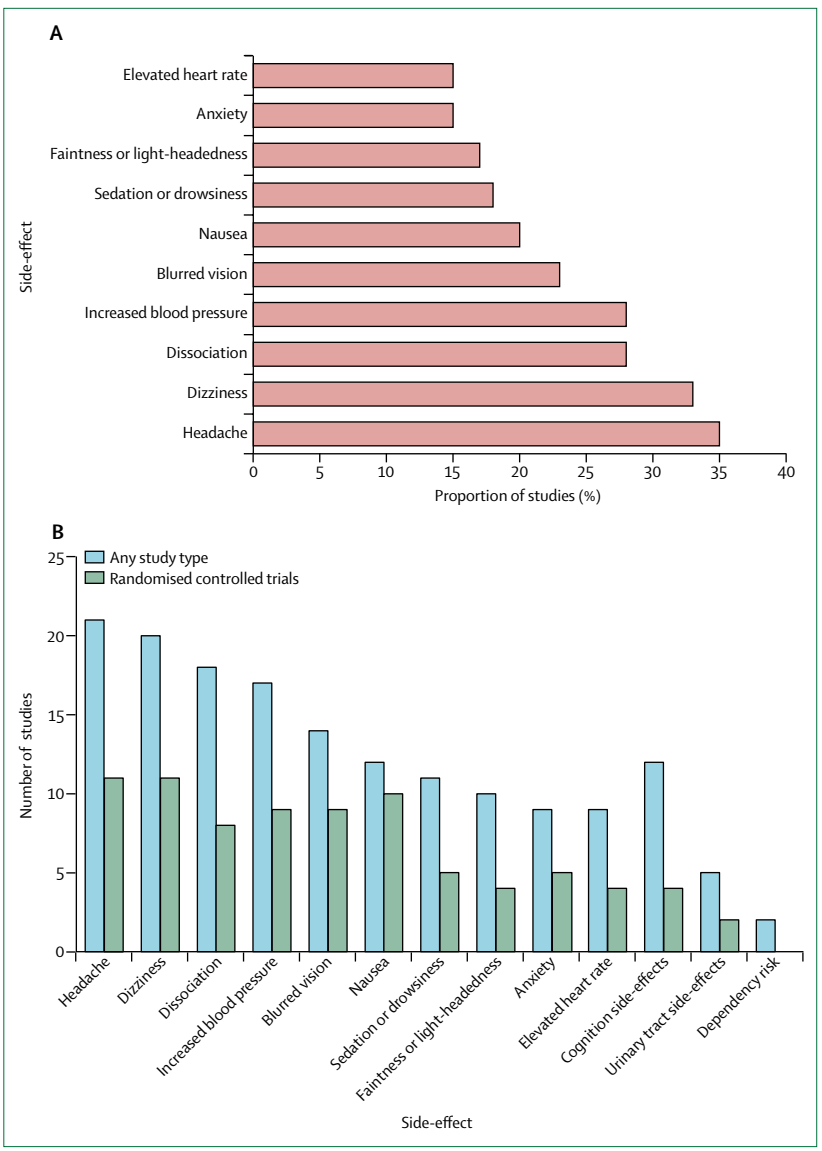

Figure 5: **Most common side-effects reported by studies and reporting of side-effect occurrence in randomised controlled trials**

crossover study, Hartvig and colleagues[105] found that short-term memory could be acutely impaired dose-dependently by intravenous administration of 0·1 mg/kg and 0·2 mg/kg, as assessed by a word recall test. Krystal and colleagues[106] and Malhotra and colleagues[107] have replicated these results. People who have become chronic recreational ketamine users have a regionally selective up-regulation of D1 receptor availability in the dorsolateral prefrontal cortex, an effect also seen after chronic dopamine depletion in animals.[108] These data suggest that repeated use of ketamine affects prefrontal dopaminergic transmission, a system involved in working memory and executive function.

Data from studies of people with chronic pain and depression have been less conclusive. In a study by Koffler and colleagues,[109] cognitive effects of ketamine in patients treated for chronic pain were extensively assessed with several neuropsychological tests before infusion and at 6 weeks post-infusion; they concluded that ketamine had no residual cognitive effects at 6 weeks. Murrough and colleagues (2014[79] and 2015[78]) reported that low-dose ketamine was associated with minimal acute neurocognitive effects in patients with treatment-resistant depression 40 min after ketamine infusion. They also reported that any changes in cognition appeared to be transient in nature, with no adverse neurocognitive effects 7 days after treatment. In both Koffler's and Murrough's studies, however, the follow-up periods were short, making it difficult to comment on long-term risks associated with repeated use.

Another question raised from this literature review relates to the safety of using ketamine in patients with depression who might have other comorbid medical disorders. It is unclear in many studies whether comprehensive health screens were completed before ketamine initiation. For instance, given that acute blood pressure changes are commonly reported after a ketamine dose, particularly if given intravenously, should practitioners be more cautious in administering ketamine to patients with a history of cardiovascular disease? According to WHO, ketamine is contraindicated in patients with moderate-to-severe hypertension, congestive cardiac failure, or a history of cerebrovascular accident.[110] Despite low doses of ketamine being used in depression studies, caution should be taken if repeatedly used. This concern is also reflected in the scientific literature about chronic pain, in which investigators conclude that ketamine use should be restricted because of side-effects,[111] that rapid acting routes of administration of ketamine such as injection or intranasal route should be avoided, and doses should be kept as low as possible for other administration routes.[112]

Ketamine is a drug of recreational misuse. The incidence of dependency is unknown, but findings from both preclinical and clinical studies in the anaesthesia setting have shown that repeated doses of ketamine are associated with rapid development of tachyphylaxis,[36] and in the scientific literature describing recreational misuse, craving for ketamine, compulsive behaviour, and rapid development of tolerance are common in people who use ketamine frequently.[113] This phenomenon has also been described in pigeons and monkeys, who repeatedly self-administered freely available ketamine and at increasing amounts with time.[114,115] Only a very few cases (fewer than 15) of human ketamine dependence have been described in the past 20 years,[116–121] including a recent report of tolerance leading to escalating use of ketamine in an individual with depression.[122] Repeated ketamine administration in depression might be associated with the risk of dependency in susceptible individuals. Despite low ketamine doses being used in depression studies, urological toxicity, liver function abnormalities, negative cognitive effects, and risk of dependence might limit the safe use of ketamine as a long-term antidepressant treatment. These aspects require further careful examination before ketamine is adopted as a clinical treatment for depression.

Systematic reviews of side-effects can provide valuable information to describe adverse events (frequency, nature, seriousness), but they are hampered by a lack of standardised methods to report these events and the fact that side-effects are not usually the primary outcome of included studies.[123–126] An important limiting factor in our analysis was our inability to conduct a formal meta-analysis because of the heterogeneity in the assessment and reporting of side-effects between studies as well as many differences in study designs and methods and because of the difficulty of analysing the actual incidence of side-effects versus the reporting of side-effects. Most reports of the occurrence of a side-effect were qualitative, using inconsistent terminology and varying timepoints, and sometimes the reports did not specify the number of patients who had the side-effect, but stated in generic terms that the side-effect was observed to have occurred. A major implication of our review findings is that data for side-effects should be collected though active surveillance in future ketamine-related depression studies and side-effects potentially related to ketamine should be reported systematically (panel). Structured rating scales should be used to enquire about specific potential side-effects that appear just after a treatment

***Panel*: Future research priorities**

- Systematic assessment of ketamine's efficacy and safety in patients with depression compared with placebo or a control drug, particularly in repeated dose or long-term use
- Assessment of repeated dosing regimes, consideration of comorbid physical health factors, and full reporting of potential side-effects
- A Ketamine Side Effect Tool and a Ketamine Safety Screening Tool are being developed and validated to assist investigators in this area of research

dose, between doses, and during the long term. The frequency of reported side-effects or adverse drug reactions is greater when patients are directly questioned than when unstructured methods are used.[127] Similarly, screening before treatment begins would help identify those patients who might be at high risk of particular side-effects. This screening could include the collection of information around comorbid physical health and concomitant medications. We are developing and validating the Ketamine Side Effect Tool and Ketamine Safety Screening Tool for these purposes.

Most of the studies we identified used racemic ketamine. Large depression trials using the S-isomer of ketamine are now underway. The incidence and severity of acute and long-term side-effects with R-isomers and S-isomers of ketamine versus the racemic mixture, and metabolites of these primary compounds, are questions that remain to be answered.

Conclusion

Ketamine's pharmacological profile makes it an interesting and possibly useful drug for the treatment of refractory depression. Acute side-effects associated with single-dose use in depression are common, although generally transient and resolve spontaneously. High doses and repeated administration have been associated with potentially serious and possibly persistent toxic effects both in patients treated for chronic pain and in people who use recreational ketamine. These side-effects include urological, hepatic, craving or dependence, and cognitive changes. To date, these side-effects have not been adequately assessed in studies investigating ketamine use in depression. Almost all randomised controlled trials assessed the safety of single sessions of ketamine, but with only short-term follow up. The safety of long-term, repeated ketamine dosing, as is increasingly used in clinical practice, is therefore uncertain. Data on the safety of this practice, including long-term outcomes, are essential before ketamine can be used for clinical treatment of depression. Further large-scale clinical trials including patients with depression, which include multiple doses of ketamine, long-term follow up, careful monitoring, and reporting of all potential side-effects are recommended.

Contributors

BS, JF, and WS completed the literature search. BS and JF collected data. BS, FJ, VG, and WS extracted data. BS, VG, and CKL interpreted the data. BS, VG, and CL wrote this paper. BS and JF compiled the tables. BS, VG, and CKL developed the Ketamine Side Effect Tool, and JF revised the references.

Declaration of interests

CKL declares fees for attending a Janssen Advisory Board Meeting. All other authors declare no competing interests.

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