Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight

Ilina Singh, Celia Morgan, Valerie Curran, David Nutt, Anne Schlag, Rupert McShane

We present a review and analysis of the ethical considerations in off-label ketamine use for severe, treatment-resistant depression. The analysis of ethical considerations is contextualised in an overview of the evidence for ketamine use in depression, and a review of the drug's safety profile. We find that, based on current evidence, ketamine use for severe, treatment-resistant depression does not violate ethical principles; however, clinicians and professional bodies must take steps to ensure that guidelines for good practice are enacted, that all experimental and trial data are made available through national registries, and that the risk potential of ketamine treatment continues to be monitored and modelled. We conclude with a set of key recommendations for oversight bodies that would support safe, effective, and ethical use of ketamine in depression.

Lancet Psychiatry 2017

Published Online
April 5, 2017
http://dx.doi.org/10.1016/S2215-0366(17)30102-5

See Online/Comment
http://dx.doi.org/10.1016/S2215-0366(17)30155-4

Department of Psychiatry and Oxford Uehiro Centre, University of Oxford, Oxford, UK (Prof I Singh EdD); **Department of Psychology, University of Exeter, Exeter, UK** (Prof C Morgan PhD); **Research Department of Clinical, Educational and Health Psychology, University College London, London, UK** (Prof V Curran PhD); **Centre for Neuropsychopharmacology, Division of Brain Sciences, Imperial College London, London, UK** (Prof D Nutt MD); **King's College London, London, UK** (A Schlag PhD); **and Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK** (R McShane PhD)

Correspondence to:
Prof Ilina Singh, Department of Psychiatry and Oxford Uehiro Centre, University of Oxford, Oxford OX3 7JX, UK
ilina.singh@psych.ox.ac.uk

Introduction

Ketamine has been hailed as the most important advance in the treatment of depression of the past 50 years.[1] Findings from several clinical trials have shown that a single, slow, intravenous dose given over about 40 min produces a rapid decrease in depressive symptoms lasting from a few hours to 14 days.[2,3] All other existing antidepressant drug treatments have a therapeutic lag of 3–4 weeks, and about a third of patients do not respond.[4]

The impressive antidepressant effects of ketamine have spurred a great deal of research interest, with growing clinical use of ketamine for the treatment of depression. At present, clinical use is off label; no pharmaceutical company yet has a marketing authorisation. Additionally, there is considerable recreational use of ketamine in some countries,[5] which has led to repeated calls for tighter regulatory controls on ketamine.[6]

Evidence for the use of ketamine in depression

The first study to draw attention to ketamine as an antidepressant was a crossover study of seven patients with major depressive disorder in 2000.[7] 6 years later, findings from a study[2] of 17 patients with treatment-resistant major depressive disorder showed that 71% of participants had a greater than 50% reduction in depressive symptoms within 24 h of ketamine administration (0·5 mg/kg intravenous infusion over 40 min), whereas the same participants showed almost no change in symptoms after placebo injection of saline. Moreover, the response was sustained for 1 week of follow-up in about a third of participants.

In a 2015 systematic review including nine ketamine trials, the drug was associated with higher levels of clinical response and remission than comparators (saline or midazolam) at 24 h, 3 days, and 7 days.[8] However, not all patients respond to ketamine and the duration of antidepressant effect is variable across individuals. Rapid reductions in suicidal ideation in patients with depression who received ketamine have been replicated.[9,10] Other research has begun to assess the potential use of ketamine in palliative care settings, where the drug's pain-reducing effects might provide an additional benefit alongside its antidepressant effects.[11,12] A study on the benefits of ketamine combined with electroconvulsive therapy treatment for major depression found no benefits in alleviating adverse cognitive effects of electroconvulsive therapy or in rate of symptomatic improvement.[13]

Concerns about the use of ketamine for depression

Ketamine misuse has many negative long-term side-effects, which study findings suggest are confined to daily users.[14] The most serious of these side-effects is ketamine-induced ulcerative cystitis (so-called ketamine bladder).[15,16] This recently identified condition is characterised by extremely painful and frequent urination, which seems to have severe and potentially long-lasting impacts on the patient's health.[17] However, people who use drugs who take ketamine less than daily have not reported (and show no evidence of) ketamine bladder.[18] One case of ketamine-associated cystitis associated with chronic pain management has been reported.[19]

A key difference in clinical as opposed to recreational use of ketamine is the dose and frequency of use. Tolerance develops rapidly to ketamine (termed tachyphylaxis in anaesthetic practice). Frequent recreational users will compensate for this tolerance by increasing the dose used over time, such that doses of several grams per day (rather than milligrams) are consumed, generally snorted similar to cocaine.[5] By contrast, medical use in depression would generally be a single 35 mg dose (for an average-weight adult) given intravenously, which could be repeated at the same dose days or weeks later. Although an intranasal formulation is currently in development for the treatment of depression,[20] it would again be at very small doses compared with those used recreationally. Dose level and frequency are related to risk of hepatotoxicity, with increased risk for prolonged infusion (eg, hepatotoxicity has been reported at anaesthetic doses [≥1 mg/kg] and in patients receiving low-dose continuous infusions for 100 h) or frequent dosing in therapeutic contexts.[21]

In a challenge study,[22] patients with psychosis given an acute dose of ketamine in laboratory conditions experienced a resurgence of their individual psychotic symptoms that in some was protracted, lasting up to 1 week. This study clearly provoked ethical concerns and no further challenge studies have been done in patients with schizophrenia. A review[23] examining psychotomimetic phenomena across studies involving a total of 450 volunteers given similar doses of ketamine showed only six incidences of such mental states that were unpleasant enough to require the infusion to be stopped, all of which remitted completely in the hours after cessation of the infusion. Clearly, understanding of appropriate dose, infusion duration, and method of administration is still limited and requires active research attention.[24]

Ethical issues surrounding the use of ketamine in depression

Ketamine use for severe depression elicits a complex set of ethical concerns. The very limited existing literature about the ethics of ketamine use for depression has highlighted some of these, covering clinical ethics, research ethics, and health policy.[25–34] Three primary ethical concerns have emerged: the genuine need for treatment of patients with severe, treatment-resistant depression; the insufficient safety and efficacy data for off-label use of ketamine; and the misuse potential of ketamine.

Clinical experience raises further practical and ethical challenges for clinicians, which have not been well documented in the scientific literature to date. First, they should be concerned about the potential of illegal diversion or self-treatment with illegally obtained drugs. Clinicians also face uncertainty, with no proven strategy to maintain a beneficial effect of ketamine. Patients who achieve a dramatic beneficial response to ketamine might face a serious fall in morale after rapid relapse; and patients with suicidal thoughts or ideation might be harmed by the false reassurance of an abrupt, but potentially brief, reduction in suicidality. Severe and unmonitored side-effects could lead to early discontinuation of an otherwise promising treatment. Finally, ketamine can seem attractive to individuals who would rather try a drug of misuse than a conventional antidepressant, due to stigma attached to treatment with psychiatric drugs.[35]

Panel 1: **Six principles of responsible research in novel neurotechnologies[36]**

- Clearly identified need
- Securing safety and efficacy
- Generating robust evidence
- Continuous reflexive evaluation
- Coordinated interdisciplinary action
- Effective and proportionate oversight

For some commentators, these concerns are sufficiently serious to constitute reasons to avoid clinical use of ketamine in depression.[28,31,34] Others take a more moderate position, but highlight the need for judicious reporting of experimental findings and prudent professional decision making in the absence of evidence-based guidance.[26,27,32] Professional judgment and integrity are particularly relevant with regard to the need for careful and consistent monitoring of patients treated with ketamine.[26] In the USA, strict regulations, legal concerns, and stigma are among the reasons why research into ketamine for depression might be scarce.[30] However, ketamine is available therapeutically through commercial clinics in the USA.[27,29]

Insufficient scientific knowledge about ketamine treatment in depression means that off-label clinical use entails substantial uncertainty. This uncertainty, and the potential for misuse of ketamine, risks harms to patients, clinicians, and society. At the same time, the need for further treatments in depression is clear, and the frustrating rate at which new drugs move from bench to bedside means that off-label use of ketamine is currently increasing.[25]

A relevant ethical analysis must identify as primary challenges the recognition of patient need, balanced against the risks of harm posed by lack of scientific knowledge and the misuse potential of ketamine. However, patient need and the potential for harm can pull in opposite directions in clinical decision making. An ethical analysis must do more than describe the harms and benefits of treatment; it should provide clinicians with some guidance about how to balance these opposing ethical forces.

We draw on a recently developed framework for ethical use of novel therapeutics[36] to argue that ketamine use in depression presents an exceptional case for clinical application ahead of further trial evidence. We next consider the balance of patient need and the potential for harm in this case. We propose three key interests at stake in this balance: autonomy, innovation, and professional integrity. After outlining these interests, we make recommendations to support ethical clinical use of ketamine off label for severe, treatment-resistant depression.

As a foundation for its ethical guideline, in its report[36] on novel neurotechnologies the UK Nuffield Council on Bioethics recognised six principles of responsible research and innovation specific to these therapies (panel 1). We propose that these principles are relevant to the ethical use of ketamine for depression, in so far as the report covers novel therapeutics that are still in an experimental phase of development. Alongside these principles, the report recognises that innovation in psychiatric therapeutics is a societal good given the few effective treatments for severe, chronic mental disorders. Below we consider arguments for, and challenges to off-label ketamine use in depression through the lens of the Nuffield Council on Bioethics core principles.

 Published online April 5, 2017 http://dx.doi.org/10.1016/S2215-0366(17)30102-5

Clearly identified need

Severe depression is an illness causing substantial impairment in patients' ability to function and to lead flourishing lives. Moreover, patients' suffering has negative consequences within families, communities, and the workplace, leading to a vicious circle of stigma, shame, and guilt. These effects are amplified if a patient loses the ability to work, further diminishing dignity and patients' sense of personal and social value.[37]

The scientific literature about depression treatment suggests that 30% of patients are treatment resistant.[38] Many of these patients will respond to augmented treatments, but a quarter will respond inconsistently or not at all.[39] The need for intervention is great—severe depression is associated with increased risk of suicide[40]—but treatment-resistant depression poses a substantial clinical challenge. The treatment of most value, electroconvulsive therapy, involves induction of seizures, and many patients are unwilling to undergo it because of fears of memory loss and general stigma about electroconvulsive therapy.[41] Suicidal ideation is difficult to manage without effective treatment, and treatment resistance can contribute to a dangerous sense of hopelessness. Although ketamine can rapidly reduce suicidal ideation,[42] the problem of rapid relapse after this beneficial response needs to be carefully managed clinically.

Safety and efficacy of ketamine treatment in depression

Ketamine can be used off label for treatment of depression because it is already a licensed drug. Off-label use of medicines is common across medical specialties,[43] but it is particularly high in psychiatry, due partly to lack of licensed treatments for many disorders.[44] The precedent for off-label prescribing across affective disorders is now significant; 45% of antidepressant prescriptions are for disorders other than depression.[45] The important difference is that the treatment effects of antidepressants are much better understood than those of ketamine in patients with depressive disorders.

No matter how widespread, off-label use of medicines does not constitute a sound reason to endorse off-label ketamine use in depression. A primary challenge in off-label drug treatment is that a drug's efficacy, dosing, and side-effects are interpreted largely through clinical experience and case studies, rather than through the gold standard of evidence provided by clinical trials, increasing concerns about the potential harms of treatment for drugs lacking trial safety data for specific disorders.

Although preliminary trial data for ketamine treatment in mood disorders are available (with further trials underway), they are compromised by methodological and other flaws; some commentators have suggested that clinical use of ketamine for depression should wait for the outcome of more robust trials providing higher standards of evidence.[33]

Further, randomised controlled trials do not provide the observational evidence necessary to understand how patients interact with treatments outside the rigours of the trial process.[46] This knowledge is particularly important in the case of a drug with high misuse potential. Additionally, randomised controlled trials have high internal validity but low external validity; by design, trials enrol homogeneous patient populations that represent a narrow band of the diversity present in a complex, heterogeneous medical population such as patients with depressive disorders.[47]

One way to mitigate the problem of low external validity with randomised controlled trials is to do more of them, in more diverse patient populations. Several randomised controlled trials for ketamine use in depression are currently recruiting (eg, NCT01945047). However, ketamine is a generic drug, and continuous industry or public investment in a large number of expensive trials is unlikely. Such trials are required to assess the potential doses, routes, regimens, predictive factors, and drugs that could maintain the benefit of ketamine in depression. The challenge of developing a regimen for maintaining the acute benefit of ketamine is considerable. Each of the many variables that might effect safety and efficacy of such a regimen—eg, dose, routes, predictive factors—would require separate exploration. As a generic drug, a very large programme of trials would be required, which would place demands on scarce public funds and potentially delay beneficial therapies. Patients who are currently severely depressed might feel that they do not have the time to wait for the results of such studies.

Given this context, observational and single-case studies of ketamine use in depression should arguably be encouraged as part of a commitment to robust science and to patient need, as a necessary adjunct to the randomised controlled trials, and as an independently valid and valuable source of evidence for treatment safety and efficacy.[48] To achieve maximum benefit, these cases should be registered and carefully monitored, and all data should be transparently shared with professional and patient groups (subject to criteria for data privacy).

One might agree with most of the arguments above and still advocate to delay ketamine use in the clinic until better trial data are available. To address the needs of treatment-resistant patients at high risk of suicide while trials are ongoing, compassionate use access to ketamine could be an option.[49] However, the delay-advocacy position ignores the reality that ketamine is easily available commercially in independent clinics and on the black market. Such outlets will provide ketamine to patients with severe depression quickly, most likely without establishing a robust patient profile and without registering and monitoring outcomes.

Our analysis thus far suggests that there is a principled case for professional, clinical provision of ketamine treatment off label to patients with severe,

treatment-resistant depression. In the next section, we test the case against a set of key interests that apply in weighing up the balance between patient need and the potential for harm in off-label clinical use of ketamine for depression.

Balance of patient need and potential for harm

Autonomy

A general definition of autonomy in medical ethics addresses the capacity to reflect and decide on a set of choices independently, on the basis of factors that feel authentic to the individual. This account of autonomy assumes a process of self-reflection that eventually identifies a set of desires that are authentic (to the person).[50] Severe depression can undermine the exercise of autonomy, because, for example, low self-worth or a lack of volitional agency compromise identification of authentic desires.[51] These cognitive features might be causes or consequences of depression, but without effective treatment of the condition, autonomy capabilities could continue to diminish, sometimes to the point that a patient will no longer find his or her life worth living. Protection of autonomy in the treatment of severe depression is therefore both an ethical duty (to ensure that patient autonomy is not threatened by the process or outcomes of treatment) and a clinical goal (because treatment promotes or restores patient autonomy).

If there is a reasonable expectation that harmful side-effects of treatment can be managed, then a patient's expressed desire for treatment—which is an expression of autonomy interests—must carry weight in the decision-making process. Indeed, a patient with severe depression who requests ketamine treatment can be viewed as exercising autonomy interests that require protection because the diminishment of patient autonomy poses a risk to their life. Therefore, the moral duty to provide ketamine treatment when requested can be seen to have special force that might outweigh some other considerations.

However, a patient can be viewed as exercising autonomy only if they receive sufficient information to make an informed decision about off-label ketamine treatment.[52] The value of consent is diminished if sufficient information is not available, and it is null if the patient lacks capacity or is coerced.[53] The criteria for consent to experimental treatment with ketamine must be carefully considered, because insufficient evidence from randomised controlled trials is available to analyse the harm–benefit ratio, and (relatedly) patients' inability to evaluate the harms of potential side-effects. However, the combination of clinical experience and available trial data arguably provides sufficient information for valid patient consent.

The capacity of patients with severe depression who are desperate for treatment has also been questioned,[33] but distress should not be conflated with lack of capacity. The distressed drive of a desperate patient with depression to seek relief for their psychic pain is not, of itself, indicative of loss of capacity. The distress might or might not interfere with the ability to take in and properly weigh up information about the risks and benefits of a new treatment. Depression creates a negative cognitive bias that can undermine balanced judgment.[54] Patients with severe depression are more usually indecisive and cautious than recklessly risk taking.[55] It is this indecisiveness—rather than the patient's desperation—that more frequently creates a dilemma for a clinician caring for a patient with severe depression. The levels of agency in the relationship are, by definition, highly asymmetric. A balanced presentation of the evidence, and of medical ignorance, can support patient decision making, but clinicians must guard against the harms of excessive paternalism that are an inevitable risk in the doctor–patient relationship.[56]

These challenges to information and consent in depression treatment and, by extension, to patient autonomy interests are not unique to ketamine; they also exist in relation to deep brain stimulation, another experimental psychiatric treatment for patients with severe depression.[57] The particular challenges around consent can be addressed initially through acknowledgement of these risks, institutional review of consent processes (in the case of research), and a commitment to ongoing monitoring and evaluation of patients.[36] In practice, signed confirmation that detailed, up-to-date, written information has been received would meet this need. The information provided to patients should be explicit about the absence of information about strategies to maintain any acute benefit and the paucity of data about long-term risks.

When patients with capacity want to pay for a trial of ketamine, which they understand has an undefined and possibly small chance of benefit, the distinction between acute and chronic treatment is a crucial consideration in the avoidance of harm. The acute risks of medical ketamine are well known; many patients experience dose-dependent acute effects. Very few patients, if any, have long-term sequelae of treatment. What evidence there is about longer-term oral or intravenous[58] use in medical contexts is relatively reassuring.[59]

Further strategies to ensure best practice in relation to consent should be considered: an interval between the consultation and first treatment allows a period for reflection and discussion with family and carers. The presence of a friend or relative in the consultation to act as an advocate can be helpful. As ever, the clinician must ensure that the decision-making process enables the patient to make an informed, autonomous decision.

Such processes cannot remove the risks inherent in this experimental treatment. However, in respect of patients' autonomy interests, it is important to recognise that paternalism cuts both ways. We should not err on the side of paternalistic precaution when weighing up the balance of need and potential for harm in ketamine treatment.

 Published online April 5, 2017 http://dx.doi.org/10.1016/S2215-0366(17)30102-5

Innovation

Innovation that leads to better tolerated, more effective therapies for chronic mental illness benefits patients, families, and clinicians, has important public health benefits, and reduces the societal impacts of mental illness.[36] For these reasons, innovation is a key interest in the balance of patient need and the potential for harm, and the precautionary principle should not operate a priori in a way that stifles innovation. The potential harms of ketamine must be managed in such a way that allows the innovative potential of its use in severe depression to be tested. Indeed, the innovative potential of ketamine-related compounds has been recognized by the US Food and Drug Administration for both treatment-resistant depression and for major depression with imminent risk of suicide.[60]

Innovation to address the problem of treatment-resistance necessarily includes innovation in the pathways to clinical use of a particular intervention. We have already outlined some of the limitations of the conventional pathway through randomised controlled trials. It is also worth noting that, if access to ketamine were restricted to those involved in clinical trials, very few patients would receive it, creating unequal conditions (particularly for patients in low-resource settings and those with little access to clinical trials).[61] Therefore, off-label use of ketamine for treatment-resistant depression in single cases can contribute to innovation and to justice, if the harms of ketamine use can be minimised and the benefits maximised in the form of systematic and transparent data recording and sharing.

Misuse potential

Innovation in treatment includes innovation in treatment delivery technologies. Most trials have used a low dose (typically 0·5 mg/kg) of intravenous ketamine, but a wide variety of other routes (oral, sublingual or transmucosal, subcutaneous, and intranasal) have been reported. These alternatives have the potential benefit that they are less invasive and can be self-administered by the patient outside of the clinic, thereby promoting patient autonomy and, possibly, compliance in treatment. However, this development is potentially at the price of increased misuse potential. As with analgesia and breakthrough pain, the use of progressively higher and more frequent doses to avert relapse is inevitable, if the patient has access to large supplies. Such addiction and misuse would not only undermine good treatment outcomes; it could potentially add fuel to the global black market in ketamine[5] either through illegal diversion or, more likely, by patients pursuing illegal routes to access the drug if their physicians refuse to prescribe it.

At the same time, it is important not to confuse the desire to continue taking a drug that treats chronic symptoms which re-emerge when the drug is stopped, with the craving of addiction: paracetamol can be used repeatedly to treat a chronic pain; the dialysis patient feels better after each exchange.

There is already wide experience of successful use of long-term oral ketamine without such tolerance or tachyphylaxis.[62,63] For example, daily dosing with oral ketamine (eg, 150 mg) has been used successfully in the context of pain. However, as the interval between ketamine doses declines, so the potential for addiction increases. So far, there are just two case reports of ketamine use.[27,64] In one, intranasal ketamine was prescribed for depression at a dose of 75–150 mg intranasally every 4 h as needed,[27] but was poorly monitored and was being used 10–12 times daily with clear evidence of intoxication. In the other study,[64] intravenous ketamine (0·5 mg/kg) was administered on alternate days for 2 weeks with evidence of emergent craving.

The experience of using oral ketamine, benzodiazepines, oral opiate analgesia, and methadone for pain all offer potential models for successful management of addiction potential: short courses, prescriptions for small quantities, regular review, dosing intervals of at least 3 days, and directly observed therapy. Nevertheless, innovation in the development of ketamine and metabolite-related compounds should prioritise lowering of the misuse potential of ketamine.[65]

Dependence is unlikely to occur in the context of clinical trials. Thus, careful prospective monitoring of real-world experience is essential to identify the incidence of misuse and dependence. Professional guidelines detailing harm minimisation strategies should not reject use of ketamine out of hand on the basis of risk; instead, they should achieve a balance between the benefits of innovation and patient autonomy on the one hand, and the potential for harm on the other. In the next section, we outline a set of harm minimisation strategies and recommendations pertinent to the case of off-label use of ketamine for depression.

Harm minimisation: strategies and recommendations

Professional virtue and integrity

Health professionals carry responsibility for assessment of patient need, and for the decision to experiment with ketamine treatment. In the absence of evidence and guidelines, and in light of the potential for individual and societal harm associated with ketamine treatment, a great deal of ethical weight rests on the virtue qualities of the clinician.[36] The Nuffield Council on Bioethics Novel Neurotechnologies Report identified three virtues of particular importance in the context of novel neurotechnologies: inventiveness, humility, and responsibility (panel 2).

In the context of ketamine treatment for depression, inventiveness requires a degree of clinical experience and expertise that enables sound and reasoned decision making under conditions of risk and uncertainty. Humility means the ability to make clinical decisions on the basis of the best interests of the patient, without intrusion of personal interest or ambition. Responsibility

***Panel 2:* Three virtues of importance in the context of novel neurotechnologies[36]**

- Inventiveness: expressed through technological innovation and by identifying ways to provide widened access to therapies
- Humility: acknowledging the limits of current knowledge and ability to use technologies to alleviate the harms of brain disorders
- Responsibility: shown by robust research and clinical practices, and by avoiding hype in communication about their potential uses

***Panel 3:* Key actions for oversight bodies**

- Professional bodies should provide guidance to ensure that ketamine treatment for depression and other affective disorders conforms to high ethical standards. Such guidance should include:
  - Publication of dynamic good practice guidelines for ethical use of ketamine for depression, which are continually updated based on reviews of new data
  - Guidance on the maximum quantity of intranasal, oral, or sublingual ketamine that can be supplied to patients to take at home, and the maximum interval between reviews by the prescriber
  - A statement that, before initiating a trial of ketamine, patients should be informed about (and encouraged to consider) all viable, licensed options for treatment
  - Recommendations on whether written consent should be required
  - An example of content of a patient information sheet
  - Requirement of contribution to national registries of structured data about the safety and efficacy of repeated doses of ketamine
- Professional bodies, together with national institutions (eg, the US Food and Drug Administration, the European Medicines Agency, and the UK Medicines and Healthcare Products Regulatory Agency) should evaluate the need for risk evaluation and mitigation strategies to minimise risk of off-label ketamine in depression and to maximize benefits[66,67]
- These national institutions should support development of the international evidence base for the safety and efficacy in ketamine treatment for depression, including:
  - Development and maintenance of national registries to share trial information and safety and efficacy data, and to report data from single case studies
  - Linking up of national registries through an international network (possibly hosted by existing structures such as the US Prescription Drug Monitoring Program)[68]
  - Publication of recommendations about any governance procedures, including suggestions for oversight procedures in institutions supporting ketamine clinics
  - Support for research to investigate the therapeutic and misuse potential of ketamine in depression, and to model the effects of diverse risk management pathways for patient need, medical use, and societal harms

The Prescription Drug Monitoring Program provides a mechanism by which health-care providers and pharmacists can check to see if a patient has obtained a prescription for the same drug from another source or multiple controlled drugs. This way, so-called doctor shopping can be reduced. Moreover, surveillance approaches are increasingly used to provide assurance that if unintended consequences do happen, they will be detected and dealt with in a timely manner.

denotes a clinician who will contribute to improving the research knowledge base about ketamine use for depression, and who will not make undue claims for ketamine treatment. These three virtues reinforce the ethical principle of continuous reflective equilibrium.

It is in the interest of professional bodies to support the education and development of these essential virtuous qualities of clinicians who administer ketamine treatment for depression, and to promote the principle of reflexive evaluation of clinical practice in this context. For example, in their discussion of the availability of ketamine use for depression in the USA, Sisti and colleagues[27] point out that some private clinics use potentially coercive financial incentives to attract and maintain patients as active ketamine users, such as offering a financial rebate after the first six ketamine infusions. Such behaviours diminish public trust in treatment innovation, and thereby hurt both patients in extreme need and the health professionals who manage their care.

Recommendations for monitoring and regulation

The increasing off-label use of ketamine for depression in the absence of long-term safety data raises complex ethical challenges that urgently require a reasoned response. In our recommendations for the monitoring and regulation of ketamine use in depression, we embed the principle of proportionate oversight, and aim to incorporate the principles of continuous reflexive evaluation and interdisciplinary action. We emphasise the need for an approach that views clinical guidance in this case as a dynamic process, in which guidance is systematically reviewed and updated as clinical evidence accumulates through transparent reporting of cases. We also underline the need for professional and oversight bodies to work together to ensure high ethical standards in off-label ketamine use in depression.

We consider it unlikely that the dangers of ketamine use would justify a different regulatory response to that of, for example, short-acting benzodiazepines such as lorazepam. Our analysis suggests that such off-label use can be ethical and it is important that any monitoring and regulation strategies are proportionate, and should not stifle innovation in treatment development or threaten the interests of patient autonomy, professional virtue, and professional integrity. However, if ketamine was a new drug, the manufacturer would usually collect safety data from open-label extensions of the licensing clinical trials. Therefore, we underline the importance of reporting on clinical practice and monitoring of outcomes. There is a risk that, if unmonitored, the risks of dependence and of cognitive, urological, and other damage will go unquantified.

Drawing on the scientific literature and this analysis, we propose a set of key action points for oversight bodies in panel 3. In spirit, these recommendations overlap considerably with the recommendations made in a consensus statement by the American Psychiatric Association.[69] We are optimistic about the emergent broad agreement on the importance of robust clinical ethics procedures and systematic reporting of cases of off-label ketamine treatment.

Search strategy and selection criteria

We searched PubMed and Google Scholar for articles published from Jan 1, 2005, to March 9, 2017, with the terms "ethics", "ketamine", "depression", "abuse", "misuse", and "safety". We identified relevant medical and clinical articles through our professional networks, searches through our personal databases, through Google Scholar and PubMed, and by suggestions from anonymous reviewers. We reviewed articles resulting from these searches and relevant references cited in those articles. Only articles published in English were included.

Conclusions

The balance of risk and benefit is such that new restrictions around the use of ketamine for depression are not needed. However, clinicians prescribing it should have a heightened degree of humility and responsibility. This will help to prevent the development of ketamine as a promising depression therapy from being stopped or delayed by clinical mistakes that increase policy makers' concerns about the drug and decrease public trust.[27,35] Although our focus has been to provide ethical analysis and guidance for off-label clinical use of ketamine for depression, many of the ethical concerns we identify are broadly relevant to ketamine treatment in the context of research.

At present, clinicians should advise patients that knowledge about ketamine treatment is poor. The key information that is needed to enhance the ethical use of ketamine for affective disorders is structured, long-term, naturalistic data on the safety of repeated dosing, including incidence of misuse. Gathering of these data should be managed by national registries. Routine submission of data to such registries should be expected of all clinics. Efficacy trials of strategies for maintaining initial benefit are also required.

In the meantime, we hope that the recommendations proposed here go some way to enabling innovative use of ketamine for treatment-resistant depression to continue, with appropriate care, precaution, and foresight.

Contributors

IS developed the literature review and led the first draft and revision of the ethics section. CM developed the literature review and led the first draft and revision of the science and clinical section. VC contributed to the literature review and read and contributed to all drafts of the paper. DN contributed to the literature review and read and contributed to drafts of the paper. AS developed the recommendations section for the initial draft and revised version. RM read and contributed to all drafts of the paper.

Declaration of interests

Since January 2009, DN has served on advisory boards for Bristol-Myers Squibb, Lilly, Shire, Lundbeck, Servier, Pfizer, Reckitt Benkiser, and D&A Pharma. He has received speaking honoraria from these companies and also from Janssen, Bristol-Myers Squibb, GlaxoSmithKline, and Schering-Plough. Since 2015, IS has served on an independent ethics advisory group supported in part by Johnson & Johnson Pharmaceutical Companies. She receives no compensation for her participation in this group. RM has had UK National Institute for Health Research grant funding to study ketamine, is participating in trials of esketamine, runs a clinic that provides ketamine treatment, and has consulted for Johnson & Johnson and Eleusis. AS reports personal fees from DrugScience. VC holds a research grant from Johnson & Johnson through UCL Business. CM reports grants from the Medical Research Council (MR L/023032/1) for ketamine research, and consultancy for Janssen Pharmaceuticals outside the submitted work.

Acknowledgments

We thank the Lived Experience Group at the University of Exeter Mood Disorders Centre for their helpful comments on an earlier version of the paper. We also benefited from comprehensive feedback provided by anonymous reviewers.

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