Accepted, Peer-Reviewed Author Copy
For publication in *Lancet Psychiatry*
Accepted November 16, 2016

Ketamine Treatment for Depression:
Opportunities for Clinical Innovation and Ethical Foresight

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Summary

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 ketamine's safety profile. We find that 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.

"Arguably the most important discovery in half a century: ketamine produces rapid antidepressant action in treatment resistant depressed patients." Duman & Aghajanian[1]

Ketamine has thus been hailed as the major advance in the treatment of depression of the past 50 years [1]. Numerous clinical trials have demonstrated that a single slow intravenous dose given over about 40 minutes produces a rapid decrease in depressive symptoms lasting from a few hours to 14 days [2] (see aan Het Rot [3] for a review). All other existing antidepressant drug treatments have a therapeutic lag of 3-4 weeks and around a third of patients do not respond.

The impressive antidepressant effects of ketamine have spurred a great deal of research interest, and there is also 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. In addition, there is considerable recreational use of ketamine in certain countries [4], which has led to repeated calls by some for tighter regulatory controls on ketamine [5].

What is the evidence for the use of ketamine in depression?

The first study to draw attention to ketamine as an antidepressant was a cross over study of 7 patients with major depressive disorder in 2000 [6]. Six years later a study of 17 treatment-resistant patients with Major Depressive Disorder [2] found 71% of the participants to have a greater than 50% reduction in depressive symptoms within 24 hours of ketamine administration (0.5mg/kg iv infusion over 40 mins), while the same participants showed almost no change in symptoms following the placebo saline injection. Moreover, the response was sustained for the 1-week follow-up in approximately one-third of the participants.

In a recent systematic review including 9 ketamine trials, ketamine was associated with higher rates of clinical response and remission relative to comparator (saline or midazolam) at 24h, 3 days and 7 days [7]. However not all patients respond to ketamine and the duration of antidepressant effect is very variable across individuals. Rapid reductions in suicidal ideation in depressed patients who received ketamine have been replicated [8, 9]. Other research has begun to evaluate the potential use of ketamine in palliative care settings, where the drug's pain-reducing effects may provide an additional benefit alongside its antidepressant effects [10, 11] .

Why is there concern about the use of ketamine for depression?

Ketamine abuse has been associated with a range of negative long-term side effects, which studies suggest are confined to daily users [12]. The most serious of these side effects is ketamine-induced ulcerative cystitis or 'ketamine bladder' ([13,14] . This is a recently identified condition characterised by extremely painful and frequent urination that seems to have severe and potentially long lasting impacts on the patient [15]. However, drug users who take ketamine less than daily have not reported, and show no evidence of 'ketamine bladder'. One case of ketamine-associated cystitis associated with chronic pain management has been reported [16].

A key difference in clinical as opposed to recreational use of ketamine is the dosage and frequency of use. Tolerance develops rapidly to ketamine, and in anaesthetic practice, is termed tachyphylaxis. Frequent recreational users will compensate for this by increasing the dosage used over time such that doses of several grams per day, rather than milligrams, are consumed, and these are generally 'snorted' through the nose in a similar way to cocaine[4]. [4] In contrast, medical use in depression would generally be a single 35mg dose for an

average weight adult given intravenously, which could be repeated at the same dosage days or weeks later. Although an intranasal formulation is currently in development for the treatment of depression[31] [17] this would again be at very small doses compared to those used recreationally. Dose level and frequency are related to risk of hepatotoxicity, with higher risk in prolonged infusion or frequent dosing in therapeutic contexts [18].

Patients with psychosis given an acute dose of ketamine in the lab experienced a resurgence of their individual psychotic symptoms that in some was protracted, lasting up to 1 week. [19] This work clearly provoked ethical concerns and no further challenge studies were conducted with patients with schizophrenia. Additionally, to demonstrate the safety in patients without schizophrenia, a review examining psychotomimetic phenomena across studies involving a total of 450 volunteers given similar doses of ketamine found only 6 incidences of such mental states that were unpleasant enough to require the infusion to be stopped, all of which remitted completely in the hours following the cessation of the infusion [20].

What are the ethical issues surrounding the use of ketamine in depression?

Ketamine use for severe depression motivates a complex set of ethical concerns. The very limited existing literature on the ethics of ketamine use for depression has highlighted some of these, covering clinical ethics, research ethics and health policy[35-40]. [21-30] The authors of these papers agree on three primary ethical concerns: genuine need for treatment of patients with severe, treatment-resistant depression; lack of safety and efficacy data in off-label use of ketamine; and the abuse potential of ketamine.

Clinical experience raises further issues that pose practical and ethical challenges for clinicians; these challenges have not been well documented in the literature to date.

Clinicians must be concerned about the potential of illegal diversion or self-treatment with illegally obtained drugs; and they face uncertainty given the lack of a proven strategy to maintain a beneficial effect of ketamine. Patients who experience a dramatic beneficial response to ketamine may face a serious fall in morale following rapid relapse; and suicidal patients may 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 those who would rather try a drug of abuse than a 'conventional' antidepressant, due to stigma attached to psychiatric drug treatments [31].

For the more cautious authors, these concerns are sufficiently serious to constitute reasons to avoid clinical use of ketamine in depression. [24, 27, 30]. Other authors 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 [22, 23, 28]. Professional judgment and integrity are particularly relevant with regard to the need for careful and consistent monitoring of patients treated with ketamine [22]. Authors writing from a US perspective have, on the one hand, criticised the restrictions on research on controlled substances for clinical use [26] and, on the other, expressed strong concerns about the availability of ketamine in commercial clinics [23, 25].

As the available literature elaborates, lack of scientific knowledge about ketamine treatment in depression means that off-label clinical use entails significant uncertainty. This uncertainty, and the potential for misuse of ketamine, pose risks of harm to patients and clinicians, and to 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 [21].

A relevant ethical analysis must identify as primary challenges the recognition of patient need on the one hand, and the risks of harm posed by lack of scientific knowledge and the abuse potential of ketamine, on the other. However, there should be a further recognition that 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.

In what follows, we draw on a recent framework for ethical use of novel therapeutics[41] [32] to argue that ketamine use in depression presents an exceptional case for clinical application ahead of further trial evidence. Drawing on the ethical framework and the literature, 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.

Nuffield Council on Bioethics: Report on Novel Neurotechnologies

As a foundation for its ethical guideline, the UK Nuffield Council on Bioethics (NCOB) recognized six principles of responsible research and innovation specific to novel neurotechnologies.

Box 1: Six Principles of Responsible Research in Novel Neurotechnologies

- Clearly identified need

- Securing safety and efficacy
- Generating robust evidence
- Continuous reflexive evaluation
- Coordinated interdisciplinary action
- Effective and Proportionate Oversight

We propose that these principles are relevant to the ethical use of ketamine for depression, in so far as the Report covers novel therapeutics for mind and brain that are still in an experimental phase of development. Alongside these principles, the NCOB Report recognizes that innovation in psychiatric therapeutics is a societal good given the lack of 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 NCOB core principles.

Clearly Identified Need

Severe depression is an illness causing significant impairment in patients' ability to function and to lead flourishing lives. Moreover, patients' suffering has negative consequences within families, communities and the workplace representing a vicious circle that can involve stigma, shame and guilt. The impacts of this vicious circle are amplified if a patient loses the ability to work, which further diminishes dignity and a sense of personal and social value in patients [33].

The literature on depression treatment suggests that 30% of patients are treatment-resistant [34]. Many of these patients will respond to augmented treatments, but a quarter of these patients will respond inconsistently or not at all [35] Treatment-resistant depression poses a

significant clinical challenge. The treatment of most value in treatment-resistant depression, electro-convulsive therapy (ECT), involves inducing seizures. Many patients are unwilling to undergo this treatment because of fears of memory loss, as well as general stigma about ECT. [36]. The need for intervention is great: Severe depression is associated with higher risk of suicide [37]. Suicidal ideation is difficult to manage without effective treatment, and the struggle to find effective treatments may itself exacerbate suicidal thinking. Ketamine may rapidly reduce suicidal ideation [38]. The problem of rapid relapse following this beneficial response needs to be carefully clinically managed.

Constitution of Robust Evidence for 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 ([39] but it is particularly high in psychiatry, due in part to lack of licensed treatments for many DSM-5 conditions [40]. The precedent for off label prescribing across affective disorders is now significant - 45% of antidepressant prescriptions are for conditions other than depression [41]. 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 study reports, rather than through the 'gold standard' evidence provided

by clinical trials. Lack of trial data on a drug for a specific condition increases concerns about the potential harms of treatment.

In the case of ketamine treatment for depression, preliminary trial data is available, as outlined above, and further trials are underway. However, some have argued that existing trial data on ketamine use in mood disorders should not be regarded as meeting a high standard of evidence due to methodological and other flaws and that clinical use of ketamine for depression should wait for the outcome of more robust trials [29].

However, RCTs do not provide the observational evidence necessary to understand how patients interact with treatments outside the rigours of the RCT process [42]. This knowledge is particularly important in the case of a drug with high misuse potential. In addition, RCTs have high internal validity but low external validity: by design, trials enroll homogeneous patient populations that represent a narrow band of the diversity present in a complex, heterogeneous medical population, such as patients with depressive disorders. [43].
One way to improve the low external validity problem of RCTs is to do more RCTs, with diverse patient populations. Several RCTs for ketamine use in depression are currently recruiting [44]. However, ketamine is a generic drug, and continuous industry or public investment in a significant number of expensive trials is unlikely. Such trials are required to assess the potential doses, routes, regimes, predictive factors and drugs that may maintain the benefit of ketamine in depression. RCTs also take a long time, which patients with severe treatment-resistant depression might not have.

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 RCTs, and as an independently valid and valuable source of evidence for treatment safety and efficacy [45]. In order 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 the most of the arguments above and still advocate for a delay on ketamine use in the clinic until better trial data is available. To address the needs of treatment-resistant patients at high risk of suicide while trials are ongoing, one might propose compassionate use access to ketamine as an option [46]. However, the delay-advocacy position ignores the reality that ketamine is quite easily available commercially in independent clinics and on the black market. Such outlets will provide ketamine to severely depressed patients 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 in ketamine treatment for depression: Key interests

Autonomy

A general definition of autonomy in medical ethics addresses the capacity to independently reflect and decide upon a set of choices, 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 authentic (to the person) desires [47]. As described above, 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 [48] . These cognitive features may be cause or consequence 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/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 (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 severely depressed patient who requests ketamine treatment can be viewed as exercising autonomy interests that require protection *because* the diminishment of patient autonomy poses a risk to the life of the depressed patient. Therefore the moral duty to provide ketamine treatment when a depressed patient requests treatment can be seen to have special force that might outweigh some other considerations.

However, a patient can only be viewed as exercising autonomy if the patient receives sufficient information to make an informed decision about off-label ketamine treatment. [49]. The value of consent is diminished if sufficient information is not available, and it is null if the patient lacks capacity or is coerced [50]. The criteria for consent to experimental treatment with ketamine must be carefully considered, due to lack of RCT evidence to inform

an analysis of the harm/benefit ratio, and, relatedly, patients' inability to evaluate the harms of potential side effects. However, as we note above, the combination of clinical experience and available trial data arguably provides sufficient information for valid patient consent.

The capacity of severely depressed patients 'desperate for treatment' has also been questioned [29], but this conflates two different issues: distress and capacity. The distressed drive of a desperate, depressed patient to seek relief for their psychic pain is not, of itself, indicative of loss of capacity. The distress may or may 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 than can undermine balanced judgment [51]. Severely depressed patients are more usually indecisive and cautious than recklessly risk-taking. [52]. It is this indecisiveness, rather than the patient's desperation, that more frequently creates a dilemma for clinician caring for a severely depressed patient. 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 evitable risk in the doctor-patient relationship [53].

Such challenges to information and consent in depression treatment and, by extension, to patient autonomy interests are not unique to ketamine; they exist in relation to another experimental psychiatric treatment for severely depressed patients: deep brain stimulation (DBS) [54]. In the case of ketamine, as with DBS, 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. [32]. 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 lack of current information on the strategies for maintaining any acute benefit and the paucity of data on 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, experience long term sequelae of treatment. What evidence there is of longer term medical oral or intravenous [55] use is relatively reassuring [56].

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 recognize 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.

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 [32]. 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. This is to say that the potential harms of ketamine must be managed in such a way that allows the innovative potential of ketamine use in severe depression to be tested. Indeed, the innovative potential of ketamine-related compounds has been recognized by the FDA for both treatment resistant depression and for major depression with imminent risk of suicide [57].

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 RCT pathway. 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 limited access to clinical trials [58]. 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 minimized, and the benefits maximized, in the form of systematic and transparent data recording and sharing.

Misuse Potential

Innovation in treatments includes innovation in treatment delivery technologies. Most trials have used a low dose (typically 0.5mg/ml) of intravenous ketamine, but a wide variety of other routes (oral, sublingual/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 the clinic, thereby promoting patient autonomy and, possibly, compliance in treatment. However, this is potentially at the price of greater abuse

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 abuse would not only undermine good treatment outcomes. It would also potentially add fuel to the global black market in ketamine [4] 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 which treats chronic symptoms which reemerge 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 tachyphalaxis [59, 60]. For example, daily dosing with oral ketamine (eg 150mg) 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. In one, intranasal ketamine was prescribed for depression at a dose of 75-150mg intranasally 4 hourly as needed [23] was poorly monitored and was being used 10-12 times daily with clear evidence of intoxication. In the other [61], intravenous ketamine (0.5mg/kg) was administered on alternate days for two weeks with evidence of emergent craving.

The experience of using oral ketamine, benzodiazepines, oral opiate analgesia and methadone all offer potential models for successfully managing the addiction potential: short courses, prescriptions for small quantities, regular review, dosing intervals of at least 3 days, directly

observed therapy. Nevertheless, innovation in the development of ketamine and metabolite-related compounds should prioritize lowering the abuse potential of ketamine [62].

Dependence is unlikely to occur in the context of clinical trials. Thus, careful prospective monitoring of a real world experience is essential to identifying the incidence of misuse and dependence. Professional guidelines detailing harm minimization strategies should not reject use of ketamine out of hand on the basis of risk; instead, they must 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 minimization 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 [32] The NCOB Novel Neurotechnologies Report identified three virtues of particular importance in the context of novel neurotechnologies: inventiveness, humility and responsibility:

Box 2: Three Virtues

- **Inventiveness** – expressed through technological innovation and by identifying ways of providing wider access to therapies.
- **Humility** – acknowledging the limits of current knowledge and of our 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.

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 based in the best interests of the patient, without intrusion of personal interest or ambition. Responsibility 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 also reinforce the ethical principle of continuous reflexive evaluation. 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 United States, Sisti et al. [23] point out that private clinics use potentially coercive financial incentives to attract and maintain ketamine patients as active users, such as offering the patient a $500 rebate after the first six ketamine infusions. Such behaviours diminish public trust in treatment innovation, and thereby hurt patients in extreme need, as well as the health professionals who manage their care.

Recommendations for monitoring and regulation

As we have outlined above, 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 developing recommendations of monitoring and regulation of ketamine use in depression, we embed the principle of proportionate oversight, and we aim to structurally integrate 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 bodies 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, say, 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 and professional virtue and integrity. On the other hand, if this were 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 literature and the analysis above, we propose a set of key action points for oversight bodies in Box 3 below.

BOX 3: KEY ACTIONS FOR OVERSIGHT BODIES (e.g. US Food and Drug Administration; European Medicines Agency; Professional Societies) [63]

1. *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:*

i. Publication of dynamic good practice guidelines for ethical use of ketamine for depression, which are continually updated based on reviews of new data:

   a. Provide guidance on the maximum quantity of intranasal, oral, or sublingual ketamine that can be supplied to patients to take at home, and/or the maximum interval between reviews by the prescriber.
   b. A statement that, before initiating a trial of ketamine, patients should be informed about, and encouraged to consider all viable, licensed options for treatment
   c. Recommendations on whether written consent should be required
   d. An example of content of a patient information sheet
   e. Require contribution to national registries of structured data on the safety and efficacy of repeated doses of ketamine

2. *Professional bodies, together with national institutions, e.g. US Food and Drug Administration (FDA); European Medicines Agency (EMA); UK Medicines and Healthcare Products Regulatory Agency (MHRA) should evaluate the need for Risk Evaluation and Mitigation Strategies (REMS,) to minimize risk of off-label ketamine in depression and to maximize benefits* [64, 65].
3. *National institutions, e.g. FDA, EMA ,MHRA should support development of the international evidence-base on safety and efficacy in ketamine treatment for depression:*

i. Develop and maintain national registries to share trial information and safety and efficacy data; and to report data from single case studies:

   a. National registries should be linked up through an international network. They may be hosted by existing structures such as the US Prescription Drug Monitoring Program (PDMP) [66, 67]
   b. Publish recommendations on any governance procedures, including suggestions for oversight procedures in institutions supporting ketamine clinics
   c. Support research to investigate the use and abuse potential of ketamine in depression; and to model the impacts of diverse risk management policy pathways on patient need, medical use, and societal harms

Conclusions

The balance of risk and benefit is such that new restrictions around the use of ketamine for depression are not needed. However, those prescribing it should have a heightened degree of humility and responsibility. This will help to prevent the current promising development from being stopped or delayed by clinical mistakes which may increase policymakers' concerns about the drug and decrease public trust [23, 31]. While 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 limited. 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, and incidence of abuse of repeated dosing. This 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.

Acknowledgments

The authors would like to 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 benefitted from comprehensive feedback provided by anonymous reviewers.

Author Contributions

Ilina Singh developed the literature review and led the first draft and revision of the ethics section

Celia Morgan developed the literature review and led the first draft and revision of the science/clinical section

Valerie Curran contributed to the literature review and read and contributed to all drafts of the paper

David Nutt contributed to the literature review and read and contributed to drafts of the paper

Anne Schlag developed the recommendations section for the initial draft and revised version

Rupert McShane read and contributed to all drafts of the paper

Declaration of interests

Since January 2009, David Nutt has served on advisory Boards for BMS, Lilly, Shire, Lundbeck, Servier, Pfizer, Reckitt Benkiser, and D&A pharma. He has received speaking honoraria from these companies and also from Janssen, BMS, GSK, and Schering-Plough.

Since 2015, Ilina Singh 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.

Rupert McShane has had NIHR grant funding to study ketamine, is participating in trials of esketamine, runs a clinic which provides ketamine treatment and has consulted for Johnson and Johnson, and Eleusis.

Dr. Schlag reports personal fees from Drugscience Charity

Professor Curran holds a research grant from Johnston & Johnston through UCL Business

Dr. Morgan reports grants from Medical Research Counci MR L/023032/1) for ketamine research; and consultancy for Janssen Pharmaceuticals outside the submitted work.

Search strategy and selection criteria

References for the ethics papers in this review were identified through searches of PubMed and Google Scholar for articles published from January, 2005 to August, 2016, by use of the terms "ethics", "ketamine", "depression", "abuse", “misuse”, and “safety”. Relevant medical and clinical articles were identified through the authors’ professional networks; searches through the authors’ personal databases; in Google Scholar and PubMed; and by anonymous reviewers. Articles resulting from these searches and relevant references cited in those articles were reviewed. Only articles published in English were included.

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