BJPsych | The British Journal of Psychiatry (2022) 221, 496–498.

Correspondence

Edited by Kiriakos Xenitidis and Colin Campbell

Contents

This editorial on the use of intramuscular clozapine[1] has the potential to mislead readers. The authors question the efficacy of intramuscular clozapine on the grounds that it is not always given when prescribed[2,3] and go on to recommend the use of intramuscular haloperidol or olanzapine as alternatives to intramuscular clozapine. Most patients who respond to clozapine are willing to continue taking it once their insight has improved but may be initially reluctant while acutely unwell. In many instances, a short period of assertive treatment is justified in order to establish the patient on an effective long-term treatment which they will ultimately accept, and this is where intramuscular clozapine is useful. All the patients in the study had declined to take clozapine prior to being prescribed intramuscular clozapine. Once prescribed intramuscular clozapine, all were again encouraged to accept oral treatment as an alternative to intramuscular. As the data show, around half then accepted oral treatment without a single administration of intramuscular clozapine but would not have done so had intramuscular clozapine not been prescribed. Intramuscular forms of haloperidol and olanzapine may have the advantage of being licensed products (although there is no UK-licensed intramuscular olanzapine at the moment), but their use in treatment-resistant patients is ethically unsupportable given the near certainty that they will be ineffective as antipsychotics in this patient group. In Kane's landmark study of clozapine,[4] 305 enrolled patients were initially treated with haloperidol at an average dose of 61 mg/day. Fewer than 2% of patients responded, and there was no mean change in symptom score for this cohort as a whole. In the study proper, 30% of these patients responded to clozapine within 6 weeks. Likewise, in a smaller study, olanzapine 25 mg/day was associated with response in only 5% of a treatment-resistant group, and 41% of the same patients subsequently responded to clozapine.[5] Some studies have shown benefit for non-clozapine antipsychotics in resistant patients, but these trials are methodologically flawed and subject to funder bias.[6] Most clinicians accept that clozapine is uniquely effective in refractory schizophrenia. We agree with the authors that intramuscular clozapine might have limited potential as an *ad hoc* intervention to prevent gaps in treatment, but not primarily because of the time this would take to arrange. The main problem with using intramuscular clozapine for those on higher maintenance doses is that the maximum oral equivalent dose to one 4 mL injection is 200 mg, and large variation in clozapine dosages can be dangerous. Rather, intramuscular clozapine is most useful as part of a pre-discussed and well-planned multidisciplinary team initiation regimen. The editorial's authors draw the reader's attention to the risks associated with inadvertently administering an overdose of intramuscular clozapine to a clozapine-naïve patient. This is equally important for oral clozapine, of course, and the two formulations have a similar duration of action. Any use of unlicensed medication carries risks and should only be done with appropriate safeguards, in appropriate settings, and following a thorough appraisal of risks versus benefits, involving the patient and their carers wherever possible. Where the benefits outweigh the risks, intramuscular clozapine can be the only route to being successfully started on this uniquely effective drug. As Casetta and colleagues showed,[2] the great majority of patients who commenced clozapine responded well and continued to take it. Without intramuscular clozapine, such patients would have remained ineffectively treated.

References

1 Bhattacherjee S, Young A, Ahuja N, Allen S. Should intramuscular clozapine be adopted into mainstream clinical practice? *Br J Psychiatry* 2021; **219**(1): 357–8.

2 Casetta C, Oloyede E, Whiskey E, Taylor DM, Gaughran F, Shergill SS, et al. A retrospective study of intramuscular clozapine prescription for treatment initiation and maintenance in treatment-resistant psychosis. *Br J Psychiatry* 2020; **217**(3): 506–13.

3 Henry R, Massey R, Morgan K, Deeks J, Macfarlane H, Holmes N, et al. Evaluation of the effectiveness and acceptability of intramuscular clozapine injection: illustrative case series. *BJPsych Bull* 2020: **44**(6): 239–43.

4 Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; **45**(9): 789–96.

5 Conley RR, Tamminga CA, Kelly DL, Richardson CM. Treatment-resistant schizophrenic patients respond to clozapine after olanzapine non-response. *Biol Psychiatry* 1999; **46**(1): 73–7.

6 Taylor DM. Clozapine for treatment-resistant schizophrenia: still the gold standard? *CNS Drugs* 2017; **31**(3): 177–80.

Cecilia Casetta, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **Fiona Gaughran**, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **James MacCabe**, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **Ebenezer Oloyede**, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **Sukhi Shergill**, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **David Taylor**, Institute of Psychiatry, Psychology and Neuroscience, London, UK; Director of Pharmacy, South London and Maudsley NHS Foundation Trust, UK. Email: david.taylor@slam.nhs.uk

doi:10.1192/bjp.2021.201

The conundrum of therapeutic intoxication

14 December 2021

In 'Esketamine: uncertain safety and efficacy data in depression', Horowitz and Moncrieff maintain their concerns about the uncertain effects associated with esketamine.[1] We agree with the authors that several clinical questions deserve ongoing exploration. However, we challenge their criticism of the pleasurable 'highs' associated with esketamine intoxication.

The clinical relevance of acute subjective effects has been central to healthcare's growing fascination with medical hallucinogens[2] – drugs that puzzlingly carry both potential for abuse and therapeutic benefit. Here, we use the term 'medical hallucinogen' to represent substances such as ketamine, psilocybin and MDMA, which differ meaningfully in chemical structure and activity but induce qualitatively similar and dose-dependent alterations in perception, mood and cognition. When considering these agents, it is worth recognising (a) the potential for a 'therapeutic intoxication', in which a short-term, positively experienced drug state mediates clinical effect; and (b) that the associated risks of the acute 'high', particularly the risk of misuse or abuse, might be safely contained within an adequately supportive treatment setting.

The possibility of a therapeutic intoxication is consistent with current research into medical hallucinogens. Subjective 'happiness' during ketamine infusions, for example, appears to predict antidepressant response over time.[3] Crucially, this acute effect predicts responses at follow-up assessment points beyond the mere 'hours' mentioned by Horowitz and Moncrieff, and rather extends to 2 weeks post-administration. These and other data suggest that

https://doi.org/10.1192/bjp.2022.58 Published online by Cambridge University Press

positively experienced drug intoxication in carefully screened, well-controlled and psychologically informed treatment contexts can occur safely[4] and mediate subsequent benefits that persist well beyond the day of administration.

These treatment 'highs' can then be examined through a lens that considers addiction but not exclusively so. We propose that there is value to a broader perspective on the emotional and subjective qualities associated with intoxication – one which acknowledges risk and the prospect of a conceptually novel approach to the varieties of suffering that compel individuals to seek psychiatric care. Psilocybin and MDMA, but not cocaine, seem to support enduring and complex possibilities for self-learning that can be harnessed with psychological interventions.[5] Such data indicate granularity and suggest that positively experienced intoxication is not alone sufficient for therapeutic growth. Similarly, ketamine and its derivatives are not routinely administered in contexts that include psychotherapy, but the combination may facilitate new insights and ways of being for people.[6] Although biological psychiatry has not always concerned itself with these aims, the field is uniquely positioned to help.

The ongoing study of medical hallucinogens may at times overestimate their benefits and underestimate their risks, and, for this, scientific integrity is essential. Moreover, not every 'high' is therapeutic, and models for hallucinogen use that contribute to experiential avoidance, medication dependence and a diminished sense of agency for patients should be scrutinised. However, a nuanced evaluation of risk and appropriate mitigation strategies can support the development of a new kind of psychiatry. Emerging psychiatric interventions, in our view, should not be condemned merely on the basis that some patients report enjoying the associated subjective effects – an intervention is not 'bad' just because it feels 'good'.

Declaration of interest

D.S.M. and D.B.Y. receive support from the Johns Hopkins Center for Psychedelic and Consciousness Research provided by Tim Ferriss, Matt Mullenweg, Blake Mycoskie, Craig Nerenberg, and the Steven and Alexandra Cohen Foundation. K.C.O. practices ketamine-assisted psychotherapy in her private psychiatry practice.

References

1 Horowitz M, Moncrieff J. Esketamine: uncertain safety and efficacy data in depression. *Br J Psychiatry* 2021; **219**: 621–2.

2 Yaden DB, Griffiths RR. The subjective effects of psychedelics are necessary for their enduring therapeutic effects. *ACS Pharmacol Transl Sci* 2021; **4**: 568–72.

3 Chen M-H, Lin W-C, Wu H-J, Bai Y-M, Li C-T, Tsai S-J, et al. Happiness during low-dose ketamine infusion predicts treatment response: reexploring the adjunctive ketamine study of Taiwanese patients with treatment-resistant depression. *J Clin Psychiatry* 2020; **81**: 20m13232.

4 Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. *J Psychopharmacol* 2008; **22**: 603–20.

5 Lepow L, Morishita H, Yehuda R. Critical period plasticity as a framework for psychedelic-assisted psychotherapy. *Front Neurosci* 2021; **15**: 710004.

6 Dore J, Turnipseed B, Dwyer S, Turnipseed A, Andries J, Ascani G, et al. Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *J Psychoactive Drugs* 2019; **51**: 189–98.

David S. Mathai, The Johns Hopkins University School of Medicine, Baltimore, USA; **David B. Yaden**, The Johns Hopkins University School of Medicine, Baltimore, USA; **Kelley C. O'Donnell**, New York University Grossman School of Medicine, New York, USA. Email: pmathai1@jhu.edu

doi:10.1192/bjp.2022.58

Author reply

31 January 2022

We agree that a drug is not necessarily bad just because it feels good – drugs that produce generally pleasant effects (e.g. benzodiazepines) are useful in some situations.

The trouble is that when a drug makes you feel euphoric, 'high' or just pleasantly 'merry', it is difficult to distinguish these drug-induced alterations from long-lasting and clinically relevant effects on mood. Depression scores will be lower than they would otherwise be, but this does not indicate that anything has happened to the individual's underlying mood, and evidence for long-term benefits is weak and confounded by the problems we described in our original article. The same effects would occur with alcohol or cocaine. But even unpleasurable or neutral drug-induced experiences may reduce feelings of depression by virtue of distracting people from their underlying feelings.

A further problem is the difficulty – if not impossibility – of doing double-blind studies with drugs that induce psychoactive effects, especially those that produce as unique effects as psychedelics. Many of the people coming forward for research are young men who have used psychedelics before, so know what to expect,[1] and we know that expectations exert a strong influence on outcome across numerous conditions.[2]

Some of the esketamine studies show how profound the placebo effects associated with the administration of psychedelics can be. In the only positive trial of esketamine, people allocated to placebo improved by a huge 17.0 points on the Montgomery–Åsberg Depression Rating Scale over 4 weeks.[3] Having said this, we accept that people may occasionally gain insights through the use of psychoactive substances, though this is not necessarily restricted to psychedelics, and there are safer routes to personal development – such as exercise, art, exposure to nature and psychotherapy.

Furthermore, the opioid crisis has shown just how short-sighted it is to think that the risks of misuse and dependence can be safely contained by 'an adequately supportive treatment setting', with a recent report on esketamine finding evidence of intoxication, tolerance, dependence and abuse from pharmacovigilance data and patient reports,[4] also present in clinical practice.[5] This is only one subset of the harms produced by esketamine, which include bladder damage,[6] cerebrovascular and cardiovascular consequences,[5,7] and concerns over connection to increased suicides.[8] 'Bad trips' are also an issue.[4]

We are particularly concerned by the commercialisation of psychedelic 'treatments'. Ketamine clinics have become an industry in the USA, and venture capitalists are also funding psychedelic research centres, waiting for the go ahead for medical use.[9] Like any business, there is an imperative to expand the market and to keep people coming back; hence, treatment indications are often elastic and include feeling 'blocked', 'lacking purpose' or experiencing stress.[9] Similarly, despite being presented and evaluated as a one-off or short-term intervention, there is a tendency toward long-term use as witnessed in the US ketamine clinic industry.[10] It is likely that these people include many who have become physically or psychologically dependent, as well as those who are desperate for a cure, all of whom make profitable customers.

People have used psychoactive drugs to change and expand their consciousness for centuries, including to block out painful emotions and thoughts; this may have short-term benefits but is rarely an effective strategy in the long run. How these substances are regulated is an important debate and should not be replaced by a process of medicalisation that may end up harming and exploiting vulnerable people.