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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.

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The conundrum of therapeutic intoxication

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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