antagonism of glutamatergic *N*-methyl-D-aspartate (NMDA) receptors; disinhibition of pyramidal cells producing an extracellular glutamate surge; amplification of glutamate non-NMDA receptor and downstream mammalian target of rapamycin (mTOR) signalling pathways; and increase in neurotrophins (brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF)).[3] All of these are assumed to contribute to the generation of ketamine's rapid but short-term antidepressant response.[2]

When ethanol vapour is repeatedly applied to rodents, their prefrontal pyramidal neurons develop an increase in dendritic spine density in the first abstinence days,[4] which may resemble the synaptic remodelling observed after a single sub-anaesthetic ketamine pulse.[2] While the first is interpreted as reflecting plasticity changes on the way to addiction,[4] the second has been shown to reverse chronic-stress-mediated decreases in spine density and is assumed to morphologically represent the antidepressant response.[2] Do a few ethanol pulses work similarly, 'refreshing' on stressed spines of a non-addicted brain? Intriguingly, low ethanol doses are followed by antidepressant-like effects in Porsolt's swim test on mice.[3]

Against this background, there remain in my mind a few primarily depressed alcohol-dependent individuals, who reported an improvement of their depressed state after a few glasses of beer or wine. This improvement lasted for some abstinent days (ethanol's antidepressant response); however, this was only in the beginning of their drinking career. To cope with depression more sustainably, these patients gradually increased the frequency and amount of alcohol intake, which resulted in hangover and tolerance to ethanol's putative antidepressant response. Ethanol's antidepressant response might have been weaker than that of ketamine, considering ethanol's weaker antagonism of NMDA receptors and stronger stimulation of γ-aminobutyric acid (GABA) type A receptors.[3] Once these patients were addicted, aversive withdrawal symptoms, craving and alcohol-seeking behaviour occurred, which worsened their depression and fuelled more frequent or continuous drinking.

Abstaining alcohol-dependent individuals have lower limbic brain glutamate concentrations than normal controls,[5] suggesting a long-term adaptation to too many glutamate surges alongside harmful drinking. Can this also happen to the brain when ketamine is frequently applied, thus giving birth to an aberrant learning process, such as addiction? Moreover, prolonged intake of either ethanol or ketamine is associated with gene expression of specific NMDA receptor subunits, sustained inhibition of synaptic long-term potentiation and decreasing levels of neurotrophins[3] – themselves all related to an addicted brain and precursors to neurotoxicity.

Ketamine and ethanol are good examples of psychoactive drugs, whose wanted – even therapeutic – effects (e.g. the antidepressant response) can silently turn to adverse effects (e.g. addiction or neurotoxicity) after exceeding an individual critical amount and duration of intake. This is based on their ability to use the same pathway to trigger cortico-limbic plasticity involved in the generation of antidepressant response, tolerance and addiction. If at all possible, finding the optimal route of administration and dosing of ketamine to produce a preferably long-term antidepressant response without burgeoning tolerance (even to ketamine's antidepressant response) remains a big challenge.[3]

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doi: 10.1192/bjp.209.5.434b

Authors' reply: We thank Professor Bonnet for his comments regarding our review on ketamine's potential for the management of pain and treatment-resistant depression. In his letter, Professor Bonnet focuses on ketamine's liability for misuse if it is broadly accepted in the clinic. He purports the idea that ketamine may have a similar liability for misuse as ethanol and backs his idea with preclinical and clinical studies showing functional changes in spine synapse remodelling and glutamatergic systems. He argues that ketamine might share some pharmacological effects with ethanol, and that such effects may eventually lead to addiction by triggering similar brain circuitry.

It is indeed true that ketamine and ethanol both relieve pain at moderate concentrations, and that both may lead to loss of consciousness at high concentrations. However, we believe that here the parallel ends, for the following reasons. First, pharmacologically, ketamine and ethanol are quite different substances; whereas ketamine isomers and their metabolites specifically bind to NMDA and aminomethylphosphonic acid (AMPA) receptors, this is very unlikely for simple molecules such as ethanol and its metabolites. Second, ethanol is a lipophilic molecule, and at higher doses it will influence GABA neurotransmission through its direct action on the chlorine channel. It might even influence cell membrane integrity at very high doses, thus indirectly influencing central neurotransmission. Third, benzodiazepines also indirectly increase GABA neurotransmission and are effective anxiolytics, but they are devoid of antidepressant effects. It can also be argued that current animal models of depression have limited value and are more likely to be measuring anxiety than depression. Fourth, in a recent *Nature* article,[1] compelling evidence was presented that it is not ketamine itself but its OH-norketamine metabolite that is responsible for the antidepressant effect through its action on AMPA receptors. This is also in line with earlier studies showing that ketamine has antagonistic properties at both NMDA and AMPA receptors. It was also noted that the metabolite displayed very few side-effects, which is consistent with a very specific action.[1]

Thus, however intriguing the suggestion of our esteemed colleague might be, we believe that any pharmacological resemblance between ketamine and ethanol is merely superficial. Still, ketamine may be responsible for addiction through its action on the reward system through dopamine D_2 and serotonin 5-HT_{2C} receptors in the ventral tegmental area.[2,3] We also agree that finding the optimal route of administration and dosing of ketamine to produce a preferably long-term antidepressant response without burgeoning tolerance remains a big challenge. Hopefully, the OH-norketamine metabolite will open the door to a new generation of rapidly acting antidepressants

https://doi.org/10.1192/bjp.209.5.435 Published online by Cambridge University Press

with minimal adverse effects and less liability for misuse and addiction.

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doi: 10.1192/bjp.209.5.435

Corrections

Population prevalence of depression and mean Beck Depression Inventory score. *BJPsych*, **195**, 516–519. The beta distribution formula for parameter β (p. 517, column 2) should read

$$\beta = 7.8680 - 0.1949 \times \text{mean BDI (scaled to range 0–63)}.$$

Seneca on anger, mercy and sadistic homicide – in 100 words. *BJPsych*, **209,** 250. Visionary as Seneca was, he cannot be credited for influencing the fictional psychiatrist Hannibal Lecter. It is in Aristotle's *Nicomachean Ethics* that an account of a mentally deranged slave who ate the liver of his fellow can be found.

doi: 10.1192/bjp.209.5.436