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Depression and anxiety disorders CHAPTER 3 Ketamine Background Over the past two decades, ketamine, an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and dissociative anaesthetic, has emerged as a novel and effective rapid-acting antidepressant. In 2000, Berman and colleagues reported findings from a landmark RCT, administering a single subanaesthetic dose of IV ketamine (0.5mg/kg over 40 minutes) to individuals with MDD.1 Ketamine produced a significant antidepressant effect within hours after the infusion that increased progressively up to 3 days after administration. This finding has since been replicated in several trials in both unipolar and bipolar depression (including treatment-resistant individuals).2–6 In addition, perinatal or prenatal ketamine and esketamine reduce the risk of postnatal depression by about 50–75%.7–9 The use of ketamine as anaesthesia may enhance the effect of ECT.10 Ketamine appears to be broadly as effective as ECT.11,12 Ketamine is a racemic mixture composed of equal amounts of the two enantiomers (S)-ketamine and (R)-ketamine (esketamine and arketamine), with esketamine binding more potently to the NMDA receptor. Although racemic ketamine remains an off-label treatment for treatment-resistant depression (TRD), an esketamine nasal spray (Spravato®) is approved for use in TRD (in conjunction with an oral antidepressant) in Europe and the USA. A 2023 trial has shown greater benefit in TRD for augmentation of antidepressants with nasal esketamine than with quetiapine.13 Interestingly, although benefits were evident for both esketamine and quetiapine immediately, the effects continued to build over 32 weeks. The use of the term ‘rapid-acting antidepressant’ might be reconsidered in light of these results. Mechanism At present, the precise mechanisms of action for the antidepressant effects of ketamine and esketamine are not clear, but it has been proposed these effects are mediated via blockade of NMDA receptors on gamma-aminobutyric acid (GABA)ergic interneurons that normally act to suppress glutamate release from glutamatergic neurons.14 This disinhibition results in an acute cortical glutamate surge, activation of post-synaptic alpha-amino-3-hydroxy-5-methyl-4--isoxazolepropionic acid (AMPA) receptors, with downstream effects on synaptogenesis and neuroplastic pathways.14 Route of administration The optimal method for administering ketamine for TRD is not fully established. IV ketamine (0.5mg/kg over 40 minutes) is the gold standard for off-label ketamine administration, with the best supporting evidence for efficacy, and may be more effective than intranasal administration.15,16 Other routes of administration have also been proposed including subcutaneous, intramuscular, oral and sublingual, although further research is needed to qualify the relative efficacy and safety of these routes, as well as the optimal dosing regimen in each case. Each route has its own advantages and challenges in terms of bioavailability, duration of effect, practicality and patient comfort. While no definitive dosing strategy for ketamine has been established across the different routes and

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