

Drugs of Potential Misuse for the Treatment of Depression and Other Psychiatric Disorders

By J E Eastham, Institute of Neuroscience, Newcastle University

Major Depressive Disorder (MDD) affects 350 million individuals world-wide. While antidepressants can be very effective for many people, as many as a third remain unwell after several adequate trials of antidepressants (Gaynes *et al.* 2009, Thase 2017, Rong *et al.* 2018). There is therefore an unmet need for patients who fail to respond to conventional therapies. It can also take 4-6 weeks of treatment with conventional antidepressants before clinically significant improvements are observed. Exploring treatments that have a rapid onset of antidepressant effects within a few days would have a great impact on patient care. There is thus a clear and urgent need for developing a rapid acting antidepressant with robust and sustained efficacy and a different mechanism of action to standard antidepressants.

Hallucinogens are psychoactive agents that can cause hallucinations, perceptual anomalies and other substantial subjective changes in thoughts, emotion and consciousness. They include (Sherwood *et al.* 2018):

- **Dissociatives** e.g., ketamine (see part 1)
- **Psychedelics** e.g., lysergic acid diethylamide (LSD), psilocybin (magic mushrooms) (see part 2)
- **Entactogens** e.g., 3,4- methylenedioxymethamphetamine (MDMA/Ecstasy) (see part 3)
- **Atypical hallucinogens** e.g., buprenorphine (see part 3)

Hallucinogens act on targets in the central nervous system temporarily rerouting electrical information that is conducted through the body along nerve cells called neurons. They have been used traditionally in medical and religious practices for centuries, however their recreational use and public concerns over abuse of these drugs has overshadowed their therapeutic potential. In the last 2 decades there has been a renewed scientific and medical interest in the treatment of several mental disorders with hallucinogens. It has been claimed that a single acute exposure to the hallucinogenic agent can elicit an immediate and lasting improvement in symptoms. This effect persists long after the drug is metabolised and gone from the body (Nichols *et al.* 2017).

Expectancy plays a large role in the qualitative effects of hallucinogens. The expectancy effect is seen in medical treatments when the patient expects a given result and therefore unconsciously affects the outcome, or reports the expected result. Some expectancy effects are unavoidable as it would be unethical not to inform patients and session monitors about the range of possible effects with hallucinogens.

The Drug Enforcement Administration in the USA schedules drugs I-V (one-five) based on whether they have currently accepted medical use in treatment in the United States, their relative abuse potential and their likelihood of causing dependence when abused. Schedule I drugs have the highest potential for abuse

and potential to create severe psychological +/- physical dependence. As the schedule changes, so does the abuse potential. Schedule V drugs represent the least potential for abuse.

In the UK the Misuse of Drugs Act classifies illegal drugs into 3 main categories. These are class A, class B and class C depending on the degree of harm attributable to each drug. Drugs most harmful are in class A, and least harmful in class C.

Part 1 - Dissociative Hallucinogenic Agents

KETAMINE

Ketamine was introduced in 1963 as an anaesthetic agent. It is a schedule three (III) compound (classified by the Drug Enforcement Administration in the United States) and a class B drug (under the Misuse of Drugs Act in the UK).

Rapid and robust antidepressant effects have been seen with ketamine. In the 1990's a pilot study in severely treatment resistant depression patients showed a single sub-anaesthetic dose of ketamine had striking and robust antidepressant effects within 4 hours of intravenous (IV – injection directly into the vein) administration (Berman *et al.* 2000). Treatment resistance is when a patient fails to respond to 2 or more adequate trials of treatment with antidepressants. An adequate trial is when a patient has been on the maximum licensed or maximum tolerated dose of medication for a period of longer than 4-6 weeks.

Early clinical trials used 0.5mg/kg of ketamine IV infused over 40 mins. Antidepressant effects are evident within 2-4 hrs of treatment and are sustained for 3-7 days (Abdallah *et al.* 2015). Repeated IV doses prolonged the treatment response (Murrough *et al.* 2013). Up to 6 infusions of repeated ketamine - administered once, twice or three times a week were found to be efficacious in maintaining treatment response (Abdallah *et al.* 2015). Murrough (Murrough *et al.* 2013) studied 24 subjects with treatment resistant depression. They had a wash out of antidepressant medication then up to 6 IV infusions of ketamine at a dose of 0.5mg/kg over a period of 40 mins three times a week over 12 days. The response rate was 71%. Clinical response is defined as a 50% or greater reduction in depression scores on a depression rating scale. Among responders, the average time to relapse after the last ketamine infusion was 18 days. 4 of the responders were relapse free at the end of the study (83 days). This suggests there are a subset of patients able to sustain response for several weeks/months after the last ketamine dose.

In a study by Thase (2017), 40-60% of patients showed an antidepressant effect with ketamine and this persisted for up to 7 days. Most individuals who respond do so with the 1st 1-4 infusions. It is possible that some non-responders convert to responders if given repeated treatments 1-2 times per week (Andrade 2017). Some ketamine responders require an indefinite course of maintenance infusions. The optimum dose may differ between individuals, therefore individual dose titration is best - although this is not routinely carried out in clinical practice (Loo 2018). There is no dosing interval that can be universally recommended (Andrade 2017).

The long-term use of ketamine treatment (>2weeks) is not well studied (Loo 2018). The limitation of ketamine trials that have so far been conducted and reported in the scientific literature include:

- Short term efficacy of a single infusion
- Short duration of follow up
- Lack of blinding to treatment (patients who take ketamine get acute adverse effects resulting in them being aware that they have had ketamine rather than the dummy treatment)

An additional finding with ketamine is that it may have an effect of reducing suicidality. When patients present to the emergency department in acute suicidal crises - the emergency room dosing of ketamine may help to shorten or avoid hospitalisation. The effects of ketamine infusions on suicidal ideations are as rapid and of comparable magnitude to the effects on mood and core depressive symptoms (Wilkinson *et al.* 2018). Rapid resolution of suicidal ideation was seen after a single infusion of ketamine in patients with treatment resistant depression (Price *et al.* 2009, DiazGranados *et al.* 2010) and does not seem to simply be due to an improvement in mood. Some patients have decreased suicidal ideas without significant changes in their mood (Grunebaum *et al.* 2018).

Side effects

Mild-moderate transient side effects are seen within the 1st 2hrs of treatment. Adverse effects settle within a few minutes of stopping the infusion and generally are gone within 2hrs (Abdallah *et al.* 2015).

- Transient Euphoria
- Dissociative effects- a distortion of perception of sight and sounds
- Psychotomimetic effects-mimics symptoms of psychosis including delusions +/-or delirium
- Cognitive impairment- this is a decline in cognitive abilities, including memory and thinking skills
- Sedation
- High Blood Pressure
- Increase in heart rate
- Lowered mood
- Over elevated mood
- Drowsiness
- Anxiety
- Dizziness
- Nausea

Patients can develop a progressive tolerance to the antidepressant effects of ketamine over months of ketamine therapy. Individuals who abuse ketamine, develop tolerance fairly rapidly and typically escalate the dose taken over a period of sustained use. Risks of such misuse include (Thase 2017):

- Persistent cognitive impairment in short and long- term memory

- Potential damage to the brain
- Aseptic/ulcerative cystitis – damage to the bladder.

These effects are hopefully avoided through the careful and controlled use of ketamine under medical supervision. There is no evidence of these effects in longer term studies conducted to date.

The optimum route of administration of ketamine is unknown (Loo 2018). The route of administration determines the peak blood levels and how much gets into the body. Ketamine gets into the body best when administered directly into a vein or inhaled through the nose. Much less gets into the body if the drug is swallowed (17-20%) (Serafini *et al.* 2014).

Most recently, the drug company Johnson and Johnson have been developing a version of ketamine (esketamine) for inhalation through the nose. They are hoping that this will be granted a license and be able to be used around the world. Canuso (Canuso *et al.* 2018) and Daly (Daly *et al.* 2018) demonstrated that intranasal esketamine had a clinically meaningful effect compared to a dummy treatment. There was a rapid improvement in depressive symptoms, including some measures of suicidal ideation among depressed patients at imminent risk of suicide. Canuso looked at 68 patients randomly assigned to receive intranasal esketamine or a placebo twice a week for 4 weeks. These patients received comprehensive standard of care treatment. Esketamine use resulted in a rapid improvement of depressive symptoms - including some measure of suicidal ideation among depressed patients at imminent risk of suicide. Daly studied 67 patients receiving intranasal esketamine twice a week for a period of time. After 1 week there was a significant improvement in depressive symptoms. This improvement appeared to be sustained with a reduced dosing frequency for up to 9 weeks. Patients continued with their existing antidepressant treatment during this study. Intranasal ketamine has benefits for comfort, cost, safety and efficacy compared with other routes of administration.

Unanswered questions

- What is the optimal dose?
- Preferred route of administration?
- Frequency of administration to maintain treatment response?
- Effects on cognitive function- positive or negative effects?
- How sustainable are the anti-suicidal properties?

Mechanisms of Action (Salvadore *et al.* 2013)

The exact mechanism of action of ketamine, or how it treats depression, is not known. However, ketamine has effects on the chemical messenger glutamate within the brain. Glutamate has been directly or indirectly implicated to play a role in mood and anxiety disorders. Like other “neurotransmitters”, glutamate is released from nerve cells and binds to “receptors”. Glutamate receptor systems are complex. One type of glutamate receptors are called N-Methyl-D-Aspartate (NMDA) receptors. Ketamine blocks NMDA receptors - it is an “NMDA antagonist”. NMDA receptors may play a fundamental role in depression, particularly in patients who have not

responded to conventional antidepressants (Krystal *et al.* 2013). Through its effect on NMDA receptors, ketamine can have multiple effects including:

- Restores decreases in connections between different parts of the brain
- Increases the number of connections between nerve cells
- Increases the chemical messenger dopamine which may help decrease symptoms such as tiredness and increase the ability to experience pleasure
- Increases chemicals which promote brain growth and repair

Predictors of response to ketamine (Rong *et al.* 2018)

While still very preliminary and requiring confirmation in further larger studies, a number of factors may predict a good response to ketamine:

- Greater probability of response if there is a family history of alcohol use disorder
- A higher Body Mass Index (BMI) predicts a greater improvement in depressive symptoms
- Improved response if there is no history of suicide attempts

Ethical concerns

There are a number of potential ethical issues around using ketamine clinically to treat depression. Not least of these is concerns regarding drug misuse. This is in part addressed by the use of ketamine in carefully controlled situations.

However, the enthusiasm for the use of ketamine as an antidepressant has clearly travelled far ahead of the evidence. There is a genuine need for treatment of patients with treatment resistant depression. However to date there is insufficient safety and efficacy data to guide the use of ketamine. The use and dosing is largely based on small scale clinical experience and case studies rather than large clinical trials. Long term use of ketamine for treatment resistant depression needs evidence from randomised control trials to critically evaluate its efficacy and tolerability. These issues may be in part resolved with the large scale studies being conducted by Johnson and Johnson with esketamine.

Ketamine should currently be considered as an augmentation therapy to be used alongside other antidepressants. In patients in whom ketamine is required for continuation and maintenance therapy, sessions are best scheduled at an individualised frequency (typically once in 3-5 days) where each dose is administered a little before the effect of the previous dose wears off (Andrade 2017). Careful and consistent monitoring is necessary. Rapid relapse needs careful management clinically.

The excitement that accompanies the antidepressant action of ketamine must be tempered by the need to systematically evaluate the potential benefits and limitations of this treatment. The challenge remains to find the best way to sustained antidepressant response to ketamine, taking into account the development of tolerance (even in its antidepressant response) and dependence. Novel NMDA receptor modulators are being tested to mimic the rapid antidepressant effects of

ketamine while minimising adverse effects (Krystal *et al.* 2013). It seems likely that additional effective therapies may soon be available for patients with the more advanced stages of treatment resistant depression.

References

- Abdallah, C. G., L. A. Averill and J. H. Krystal (2015). "Ketamine as a promising prototype for a new generation of rapid-acting antidepressants." *Ann N Y Acad Sci* **1344**: 66-77.
- Andrade, C. (2017). "Ketamine for Depression, 4: In What Dose, at What Rate, by What Route, for How Long, and at What Frequency?" *J Clin Psychiatry* **78**(7): e852-e857.
- Berman, R. M., A. Cappiello, A. Anand, D. A. Oren, G. R. Heninger, D. S. Charney and J. H. Krystal (2000). "Antidepressant effects of ketamine in depressed patients." *Biol Psychiatry* **47**(4): 351-354.
- Canuso, C. M., J. B. Singh, M. Fedgchin, L. Alphs, R. Lane, P. Lim, C. Pinter, D. Hough, G. Sanacora, H. Manji and W. C. Drevets (2018). "Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study." *Am J Psychiatry*: appiajp201817060720.
- Daly, E. J., J. B. Singh, M. Fedgchin, K. Cooper, P. Lim, R. C. Shelton, M. E. Thase, A. Winokur, L. Van Nueten, H. Manji and W. C. Drevets (2018). "Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment Resistant Depression: A Randomized Clinical Trial." *JAMA Psychiatry* **75**(2): 139-148.
- DiazGranados, N., L. A. Ibrahim, N. E. Brutsche, R. Ameli, I. D. Henter, D. A. Luckenbaugh, R. Machado-Vieira and C. A. Zarate, Jr. (2010). "Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder." *J Clin Psychiatry* **71**(12): 1605-1611.
- Gaynes, B. N., D. Warden, M. H. Trivedi, S. R. Wisniewski, M. Fava and A. J. Rush (2009). "What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression." *Psychiatr Serv* **60**(11): 1439-1445.
- Grunebaum, M. F., H. C. Galfalvy, T. H. Choo, J. G. Keilp, V. K. Moitra, M. S. Parris, J. E. Marver, A. K. Burke, M. S. Milak, M. E. Sublette, M. A. Oquendo and J. J. Mann (2018). "Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial." *Am J Psychiatry* **175**(4): 327-335.
- Krystal, J. H., G. Sanacora and R. S. Duman (2013). "Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond." *Biol Psychiatry* **73**(12): 1133-1141.

Loo, C. (2018). "Can we confidently use ketamine as a clinical treatment for depression?" *Lancet Psychiatry* **5**(1): 11-12.

Murrough, J. W., A. M. Perez, S. Pillemer, J. Stern, M. K. Parides, M. van der Rot, K. A. Collins, S. J. Mathew, D. S. Charney and D. V. Iosifescu (2013). "Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression." *Biol Psychiatry* **74**(4): 250-256.

Nichols, D. E., M. W. Johnson and C. D. Nichols (2017). "Psychedelics as Medicines: An Emerging New Paradigm." *Clin Pharmacol Ther* **101**(2): 209-219.

Price, R. B., M. K. Nock, D. S. Charney and S. J. Mathew (2009). "Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression." *Biol Psychiatry* **66**(5): 522-526.

Rong, C., C. Park, J. D. Rosenblat, M. Subramaniapillai, H. Zuckerman, D. Fus, Y. L. Lee, Z. Pan, E. Brietzke, R. B. Mansur, D. S. Cha, L. M. W. Lui and R. S. McIntyre (2018). "Predictors of Response to Ketamine in Treatment Resistant Major Depressive Disorder and Bipolar Disorder." *Int J Environ Res Public Health* **15**(4).

Salvadore, G. and J. B. Singh (2013). "Ketamine as a fast acting antidepressant: current knowledge and open questions." *CNS Neurosci Ther* **19**(6): 428-436.

Serafini, G., R. H. Howland, F. Rovedi, P. Girardi and M. Amore (2014). "The role of ketamine in treatment-resistant depression: a systematic review." *Curr Neuropharmacol* **12**(5): 444-461.

Sherwood, A. M. and T. E. Prisinzano (2018). "Novel psychotherapeutics - a cautiously optimistic focus on Hallucinogens." *Expert Rev Clin Pharmacol* **11**(1): 1-3.

Thase, M. E. (2017). "New medications for treatment-resistant depression: a brief review of recent developments." *CNS Spectr* **22**(S1): 39-48.

Wilkinson, S. T., E. D. Ballard, M. H. Bloch, S. J. Mathew, J. W. Murrough, A. Feder, P. Sos, G. Wang, C. A. Zarate, Jr. and G. Sanacora (2018). "The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis." *Am J Psychiatry* **175**(2): 150-158.