Safety systems in other industries are not evaluated based on the number of accidents, but on the reliability of processes and the avoidance of accident-producing contexts. The only intervention shown repeatedly to reduce errors in controlled studies is the use of bar code readers that, when a label is scanned, display the drug name, concentration, and expiration date/time, and speak the drug name aloud.\textsuperscript{13,14} Unfortunately, these technologies are expensive, and requests for them are often denied by the hospital finance team. Over time, we expect that these systems will become more widespread, and will reduce some, but not all, medication errors. Bar code scanners combined with colour coding and a range of other design, process, technology, training, and organisational approaches will be more effective.\textsuperscript{15} Safety science, systems engineering, human factors, and emerging disciplines in complex adaptive systems will demonstrate that debating colour labelling alone is moot, because a single safety intervention will not be as effective as carefully designed systems approaches.

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Ketamine and depression

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Since Domino and colleagues\textsuperscript{1} reported the first clinical use of ketamine more than half a century ago, there have been many clinical and laboratory studies to determine both mechanism(s) of action and the most appropriate clinically useful properties of this enigmatic drug. These include analgesia, favourable cardiorespiratory profile, anti-
inflammatory effects, and anticancer actions. In addition, antidepressant actions of ketamine have been recognised that are of clinical applicability. In psychiatry, many clinical studies demonstrate that existing antidepressant medications show limited effectiveness and slow onset of clinical response. Indeed, development of new therapeutic strategies for major depression represents a major clinical need and represents an area where there is much pharmaceutical interest. Does ketamine fit the bill? In this editorial, this new facet is explored in terms of utility and mechanisms of actions.

Clinical evidence and relevance of the antidepressant actions of ketamine

Several systematic reviews and meta-analyses of the clinical utility of ketamine for patients with major depressive disorder have been reported. Han and colleagues reported on nine studies and found that ketamine could produce rapid amelioration of major depressive disorder. Alberich and colleagues reported that bipolar depression may also be treatable with ketamine although its effective duration was short. These data were obtained from one clinical trial, five cohort studies, and four case reports. Moreover, Wilkinson and colleagues reported on 10 identified comparative intervention studies in which either saline or midazolam was included as a control treatment. It was concluded that ketamine rapidly (within 1 day) and significantly reduced suicidal ideation and this effect continued for up to 1 week. Although mood depression is often reported in postoperative patients, small doses of ketamine (0.5 mg kg⁻¹) at induction of anaesthesia may reduce mood depression with an increase in serum brain-derived neurotropic factor (BDNF). This is correlated significantly with the Patient Health Questionnaire-9 depression rating scale. However, two Cochrane Database Systematic Reviews showed limited evidence for ketamine’s efficacy over placebo in both unipolar and bipolar depression. Grunebaum and colleagues reported that ketamine could cause clinically significant reduction in suicidal ideation in depressed patients within 24 h compared with midazolam. Gamble and colleagues also reported that ketamine anaesthesia provided faster response and remission after electroconvulsive therapy (ECT) compared with propofol anaesthesia. However, a number of clinical trials suggest ketamine anaesthesia may not significantly improve depression after ECT. It should be noted that depression is not a simple unitary phenomenon, and what is true for one condition might not be true for all. High-quality RCTs (with adequate blinding) are required to determine the differential efficacy of ketamine for unipolar and bipolar depression and how to sustain any antidepressant response.

Potential mechanisms of antidepressant actions of ketamine

N-Methyl-D-aspartate receptor mechanism

Ketamine is recognised as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, and this mode of action
contributes to its anaesthetic properties. Trullas and Skolnick reported that MK-801, a non-competitive NMDA receptor antagonist, produced antidepressant-like actions in a mouse model of depression. Using a chronic unpredictable stress model, Jiang and colleagues found that a sub-anesthetic dose of ketamine (10 mg kg\(^{-1}\) i.p.) induced rapid antidepressant effects in adult male rats. This was based on (1) an increase in body weight, (2) increased spontaneous locomotor activity to anxiety-eliciting situations in the open field of the elevated plus maze, (3) more entries into the open arm of the elevated plus maze, (4) increased activity in the forced swimming test, and (5) higher sensitivity to sucrose after ketamine treatment.

Ketamine is also known to increase hippocampal BDNF levels, which may be important for producing a rapid onset of antidepressant action. The NMDA receptor hypothesis is as follows (Fig. 1). Although anaesthetic doses of ketamine reduce prefrontal glutamatergic transmission, subanaesthetic doses increase glutamate cycling and as a result, extracellular glutamate increases in the prefrontal cortex (PFC). NMDA receptor blockade of \(\alpha\)-aminobutyric acidergic (GABAergic) interneurons inhibits their activity. In addition, ketamine inhibits presynaptic NMDA receptors followed by reduction in presynaptic hyperpolarisation-activated cyclic nucleotide-gated channel 1 (iHCN1) channel activity, which would lead to increased glutamate release and thereby subsequent postsynaptic glutamate receptor activity. Postsynaptic \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are activated andextrasynaptic NMDA receptors are inhibited. A combination of AMPA receptor activation and extrasynaptic NMDA receptor inhibition facilitates the post-synaptic activation of neuroplasticity-related signalling pathways involving BDNF and the mammalian target of rapamycin (mTOR). Synthetic NMDA receptor blockade by ketamine leads to suppression of eukaryotic elongation factor-2 (eEF2) kinase. Phosphorylation of eEF2 gradually decreases and BDNF translation increases. Upregulation of BDNF translation evokes tyrosine-related kinase-B (TrkB) signalling leading to trans-phosphorylation and downstream activation of extracellular signalling related kinases (ERks) and protein kinase-B (Akt/ PKB), and suppression of glycogen synthase kinase-3 (GSK-3). As a result, mTOR is activated to induce synaptogenesis. Y and colleagues suggest that the rapid antidepressant effects of ketamine may be attributable to blocking of NMDA receptor-dependent bursting activity in lateral habenula neurons, an ‘anti-reward centre’, to activate a downstream reward centre. These biochemical responses may mediate the rapid and long-term antidepressant effects of ketamine. Interestingly, Williams and colleagues recently reported that naltrexone markedly diminished ketamine-induced antidepressant effects in patients with treatment-resistant depression. They concluded that opioid system activation, particularly \(\mu\)-opioid receptors, is required to produce the acute antidepressant effect of ketamine. It is likely that the NMDA receptor antagonism potentiates endogenous \(\mu\)-opioid receptor activity to produce the antidepressant actions as clinically relevant concentrations of ketamine induce \(\beta\)-endorphin expression.

Non-NMDA receptor mechanism

Catecholamine turnover

Current antidepressants are selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), and norepinephrine and dopamine reuptake inhibitors (NDRIs). Ketamine can increase monoamine release, including of norepinephrine, dopamine, and serotonin, and inhibits their reuptake. Ketamine may therefore have more conventional antidepressant actions related to those of SNRIs, NaSSAs, and NDRIs. However, SSRIs may stimulate serotonin type 3 receptors (5HT3Rs), which are expressed with insulin-like growth factor-1 (IGF-1) in the same neurons in the hippocampal dentate gyrus. IGF-1 has antidepressant effects. Kondo and colleagues found that 5HT3R regulates the hippocampal extracellular levels of IGF-1 levels, which mediates 5HT3R-dependent hippocampal neurogenesis. As we found expression of IGF-1 was upregulated in response to ketamine in C6 glia cells, an increase in IGF-1 by ketamine may contribute to its antidepressant effects.

Anti-inflammatory actions

Recent studies strongly indicate a relationship between inflammation and major depression. Indeed, inflammatory mediators may be potential markers of depression and treatment responsiveness. Several transcription factors such as NF-E2-related factor 2 (Nrf2) and nuclear factor-\(\kappa\)B (NF-\(\kappa\)B) have been reported to contribute to depressive disorders. In addition, integrative brain analysis of rat and human PFC transcriptomes demonstrates that a number of convergent genes may be involved in the pathogenesis of depressive disorders as 80% of these genes relate functionally to the stress response signalling cascade involving NF-\(\kappa\)B, activator protein 1 (AP1), and ERK/MAPK (mitogen-activated protein kinase), which are associated with depressive disorder, neuropasticity, and neurogenesis. In fact, anti-inflammatory agents such as NSAIDs, statins, and cytokine inhibitors have potential antidepressant properties, whereas pro-inflammatory treatment often induces psychiatric side-effects such as depressive symptoms. In this regard, ketamine has anti-inflammatory effects, which have been confirmed in clinical settings. Dale and colleagues performed a systematic review and meta-analysis and found that intraoperative ketamine attenuates inflammatory reactivity after surgery as postoperative plasma interleukin (IL)-6 was significantly lower with ketamine. Ketamine can decrease the binding affinity of lipopolysaccharide (LPS) for LPS-binding protein and suppress phosphorylation of several protein kinases and transcription factors including NF-\(\kappa\)B and AP-1 via Toll-like receptor (TLR)-mediated signal transduction in the sepsis model. Thus, it is likely that ketamine exerts anti-inflammatory actions not only in systemic inflammation but also in neuroinflammation including depressive disorders. However, recent clinical trial data do not support the anti-inflammatory effects of ketamine as a single sub-anesthetic dose (0.5 mg kg\(^{-1}\)) did not prevent postoperative delirium, which may be attributable to neuroinflammation, in elderly patients undergoing major surgery. Further studies will be necessary to determine the effects of ketamine on neuroinflammation.

Effects of the ketamine metabolite (2R,6R)-hydroxynorketamine

Yao and colleagues found that not only ketamine but also its metabolite (2R,6R)-hydroxynorketamine induce lasting alterations in AMPA receptor function and synaptic plasticity at glutamatergic synapses in the brain reward circuit including...
the nucleus accumbens and the ventral tegmental area. These antidepressant actions are independent of NMDA receptor inhibition.

Enantiomeric differences in the antidepressant actions of ketamine

Clinically available ketamine used in many countries exists as a racemic mixture containing equal amounts of two enantiomers, \(S\)-ketamine and \(R\)-ketamine. \(S\)-ketamine has greater potency and higher clearance for anaesthesia and analgesia than \(R\)-ketamine. \(^{35}\) \(S\)-ketamine has about four- and three-fold greater antagonist potency for NMDA\(^{21}\) and \(\mu\)-opioid receptors,\(^{33}\) respectively. In addition, \(S\)-ketamine produces better intraoperative amnesia and fewer psychotic emergence reactions and less agitation.\(^{21}\)

There are many case reports of antidepressant effects of \(S\)-ketamine.\(^{34}\) Repeated administration of \(S\)-ketamine has been reported to be effective in both bipolar and unipolar depressed patients with pharmacotherapy, psychotherapy, and ECT resistance, suicidal crisis, or both.\(^{25}\) However, several animal studies have shown that \(R\)-ketamine produces more potent, safer, and longer-lasting antidepressant actions.\(^{25}\)

How can \(R\)-ketamine induce more beneficial antidepressant effects than \(S\)-ketamine? The mechanism remains elusive, but one possible explanation might be as follows. \(R\)-ketamine significantly attenuates the reduction in dendritic spine density, BDNF/TrkB signalling, and synaptogenesis in the PFC, hippocampal cornu ammonis-3 (CA3) region and dentate gyrus.\(^{36}\) In addition, a positron emission tomography study suggests that the psychotomimetic and hyperfrontal metabolic actions of ketamine are probably induced by \(S\)-ketamine as psychotomimetic doses increase the cerebral metabolic rates of glucose (CMRglu) in the frontal cortex and thalamus; equimolar doses of \(R\)-ketamine decreased CMRglu with no psychotic symptoms.\(^{36}\)

Side-effects of ketamine

The first systematic review of the safety of ketamine in the treatment of depression after single and repeated doses has been published recently.\(^{37}\) The most common acute psychiatric side-effect was anxiety followed by agitation or irritability, euphoria or mood elevation, delusions or unusual thoughts, panic, and apathy. The most common psychotomimetic side-effect reported was dissociation, followed by perceptual disturbance, odd or abnormal sensation, derealisation, hallucinations, feeling strange, weird, bizarre, or unreal, and depersonalisation. No long-term psychotomimetic side-effects were reported. The most common cardiovascular changes were increased blood pressure and increased heart rate. The most common neurological side-effects were headache and dizziness. The most frequently reported other side-effects were blurred vision and nausea. In general, these side-effects resolve shortly after dose administration.

Although there are no reports regarding chronic adverse reactions of ketamine in this population, several studies have been performed on the efficacy of ketamine for treatment of chronic pain.\(^{34,37}\) Occurrence of ketamine-induced adverse reactions is limited and often well tolerated.\(^{38-41}\) However, Niesters and colleagues\(^{39}\) reported that repetitive or continuous administration of ketamine caused liver enzyme elevations in about 10% of patients, which returned to normal within 3 months of cessation. In contrast, recreational ketamine users often develop urological toxicity, hepatotoxicity, cognitive deficits, and dependency risks. Regarding urological toxicity, cystitis, and bladder dysfunction, an increase in urinary frequency, urgency, dysuria, urge incontinence, occasionally painful haematuria, and secondary renal damage have been reported. More than 20% of recreational ketamine users are estimated to have urinary tract symptoms, although much higher rates have been reported (46% and 90%).\(^{37}\) These data indicate severe adverse reactions often occur when used under uncontrolled circumstances. In addition, recreational ketamine users use high doses and simultaneously several illicit drugs of abuse. Contamination of ketamine with other substances may also contribute to the adverse reactions.\(^{29}\) It is difficult to be sure if these adverse reactions are directly caused by ketamine per se. Any long-term clinical use will require careful monitoring of patients to detail this profile.

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