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Ketamine: repurposing and redefining a multifaceted drug

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This short review will highlight recent clinical and basic research that supports the therapeutic utility of ketamine as a rapid-acting, life-saving antidepressant and a versatile analgesic. After 50 years of use as a dissociative anesthetic and misuse as a street drug, ketamine has re-emerged as a useful off-label agent for ameliorating various types of pain and resistant depression. In addition to its ability to inhibit N-methyl-D-aspartate (NMDA) receptors, the diverse actions of ketamine might involve epigenetic mechanisms such as microRNA regulation. Thus, ketamine is transitioning from being the pharmacologist's nightmare to one of the most interesting developments in the pharmacology of depression and pain.

Introduction

With the reorganization of the biopharmaceutical research enterprise (academia, industry, government), repurposing of existing drugs has become a desirable mechanism for getting drugs into and out of the therapeutic pipeline expeditiously at a lower overall cost [1]. Ketamine is a prime example of repurposing a multifaceted drug because it has potential for multiple, dose-dependent uses for some challenging clinical situations that involve the need for 'safe', parenteral anesthesia as well as relief of pain [2] and depression [3]. The purpose of this short review is to highlight some of the pharmacological advances that suggest ketamine has utility as a: (i) therapeutic agent in treating refractory pain and depression and (ii) pharmacological tool for discovering novel mechanisms that will lead to more-efficacious therapies for diseases involving pain and depression.

Approximately 50 years ago, D.E. Potter worked with ketamine in discovery research at Parke-Davis, Ann Arbor, MI, USA. At the time,

CI581 (ketamine) was identified as 'IT' in a report to Duncan A. McCarthy, Jr; 'IT' was the best candidate of all those phencyclidine derivatives that were tested as potential parenteral anesthetics in infrahuman primates and other species [4]. In the mid-1960s, ketamine was evaluated as an intravenous anesthetic agent in humans [5]; it was approved for clinical use in 1970. Subsequently, ketamine began its clinical life as a 'dissociative anesthetic' [6].

The parenterally administered drug was labeled clinically as a dissociative anesthetic because it induces a cataleptic state in which the eyes remain open and sensory input (perception) is suppressed at association areas (thalamic–limbic) below the level of the sensory cortex. Moreover, tone of the pharyngeal and laryngeal muscles is maintained, which lessens the possibility of aspiration should vomiting occur. Based on these properties, ketamine continues to be suitable as a parenterally administered anesthetic or sedative agent for uncooperative and/or compromised patients

including: (i) children (e.g. burn injuries, fractures); (ii) battlefield emergencies (e.g. difficult airways, reactive airway disease) and (iii) veterinary subjects. Based on its utility in adults and children, under special circumstances, the World Health Organization has listed ketamine as a core medicine (a minimum medical need for a basic health system) [7]. For example, ketamine was designated the 'preferred agent' in a relatively common emergency room procedure, such as fracture reduction that requires conscious sedation of pediatric patients [8].

However, in addition to its ability to produce a combination of analgesia, amnesia, immobility and loss of consciousness at anesthetic doses, ketamine can produce significant dose- and duration-related adverse side-effects including psychotomimetic ideation, increases in blood and intracranial pressure (relative contraindications), and excessive secretions in the airway. However, appropriate premedications can attenuate the adverse psychotomimetic effects (e.g. lorezepam) and excessive secretions

(e.g. glycopyrrolate) elicited by anesthetic doses of ketamine. The illicit use of 'street' ketamine over prolonged periods (weeks, months, years) can cause urinary tract (cystitis) symptoms [9]. In neonatal rats, repeated administration of ketamine can induce neural apoptosis, but co-administration of dexmedetomidine can provide neuroprotection [10]; thus, the combination might be preferable in pediatric patients.

More recently, at doses below those producing anesthesia, ketamine has re-emerged as an off-label rapid-acting antidepressant with the potential for treating severe depression that is resistant to other therapies [7] and an analgesic that can be administered by multiple routes (including topical), alone or in combination with other drugs [11,12]. Clinical studies suggest that ketamine is 'arguably one of the most exciting developments in antidepressant pharmacology in more than 50 years' [13]. The desired action represents an efficacious approach to amelioration of: major depressive disorder, treatment-resistant depression, bipolar affective disorder and suicidal ideation. Moreover, clinical observations indicate that ketamine can be used alone and in combination with other drugs (e.g. amitriptyline) by topical administration and other routes for relief from acute and chronic pain [12,14]. In both cases, ketamine is administered at subanesthetic doses to achieve these 'new' applications.

This brief review will focus on two important pharmacological actions of ketamine, those of a: (i) multipurpose analgesic and (ii) novel, rapid-acting antidepressant. It is noteworthy that the role of ketamine as a potential modulator of epigenetics, via histone deacetylase and micro-RNAs (miRNAs), might explain some of the sustained clinical effects of ketamine.

Pharmacology of ketamine
Medicinal chemistry
Commercially available ketamine is an analog of phencyclidine and is a chiral compound consisting of a racemic mixture of S- and R-ketamine: [RS]-2-(2-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. Ketamine has a molecular weight of 238 Da and a pK_a of 7.5. The trade names are: Ketanest[®], Ketanest-S[®], Ketaset[®] and Ketalar[®]. There are numerous other international trade names for ketamine. Pure S-ketamine (Ketanest-S[®]) is now available and has several advantages over the R isomer [15]. The S (+) eutomer has approximately three-to-fourfold more potency than the R (−) isomer and is twofold more potent than the racemic mixture. Interestingly, R-ketamine has greater affinity for sigma (σ_1) receptors than S-ketamine [16]. The S (+) eutomer has a shorter duration of action because it is cleared more rapidly; this latter characteristic might allow: (i) lower doses for a given indication; (ii) greater ease of titration and (iii) predictability of offset of activity (Figs 1–3).

Pharmacokinetics
As an analgesic or antidepressant, the favorable ratio of lipid:water solubility of ketamine renders it bioavailabile (%) by way of a multiplicity of routes of administration: intravenous (i.v.; 99%), intramuscular (i.m.; 93%), subcutaneous (s.c.), epidural or intrathecal, transnasal (25–50%), rectal and oral (16%) [9]. The relatively high lipid solubility and lower binding to plasma proteins predisposes the agent to rapid uptake by the brain as well as fairly rapid redistribution. The α-elimination phase is about 11 min, whereas the β-elimination phase is 2.5 h after
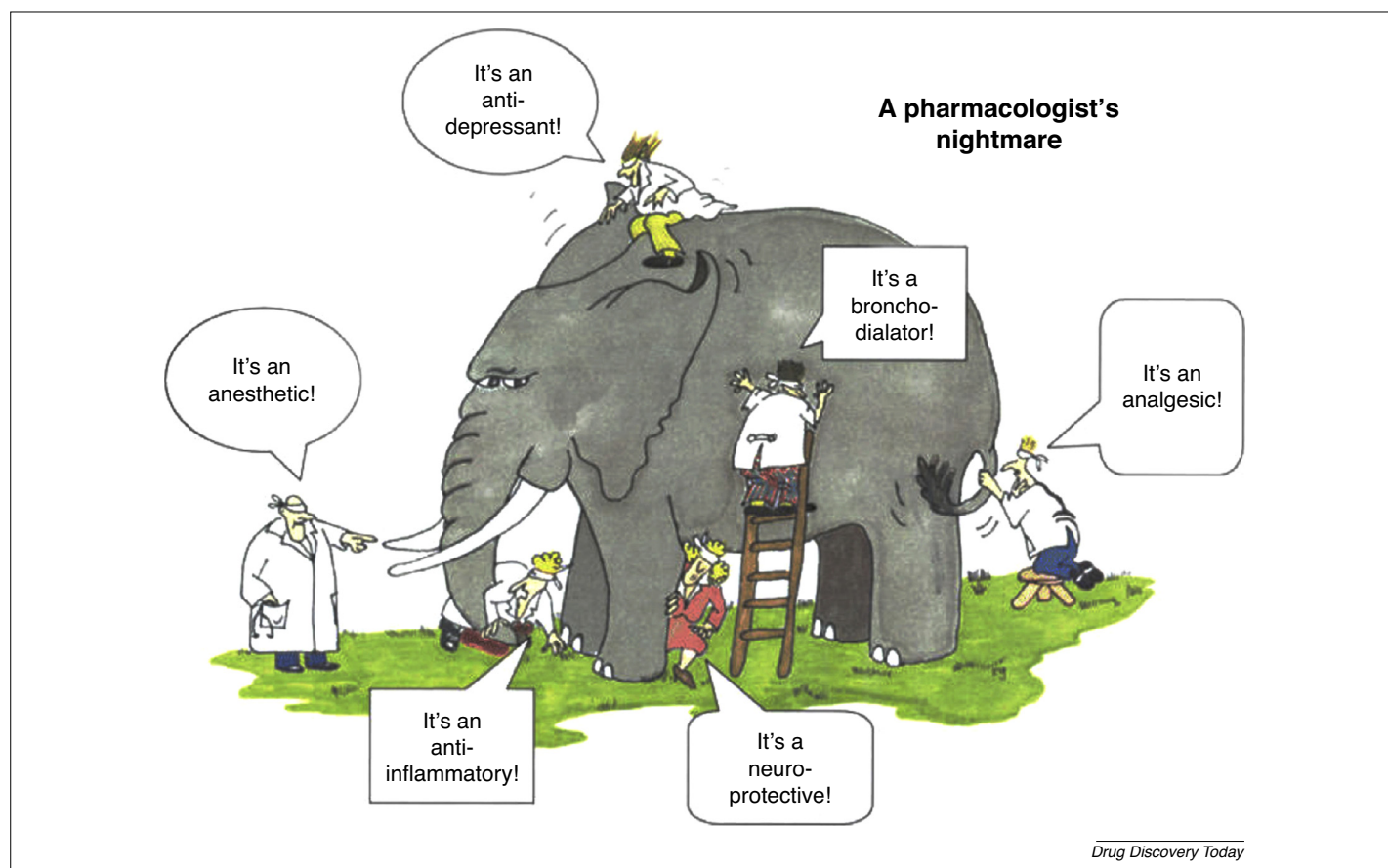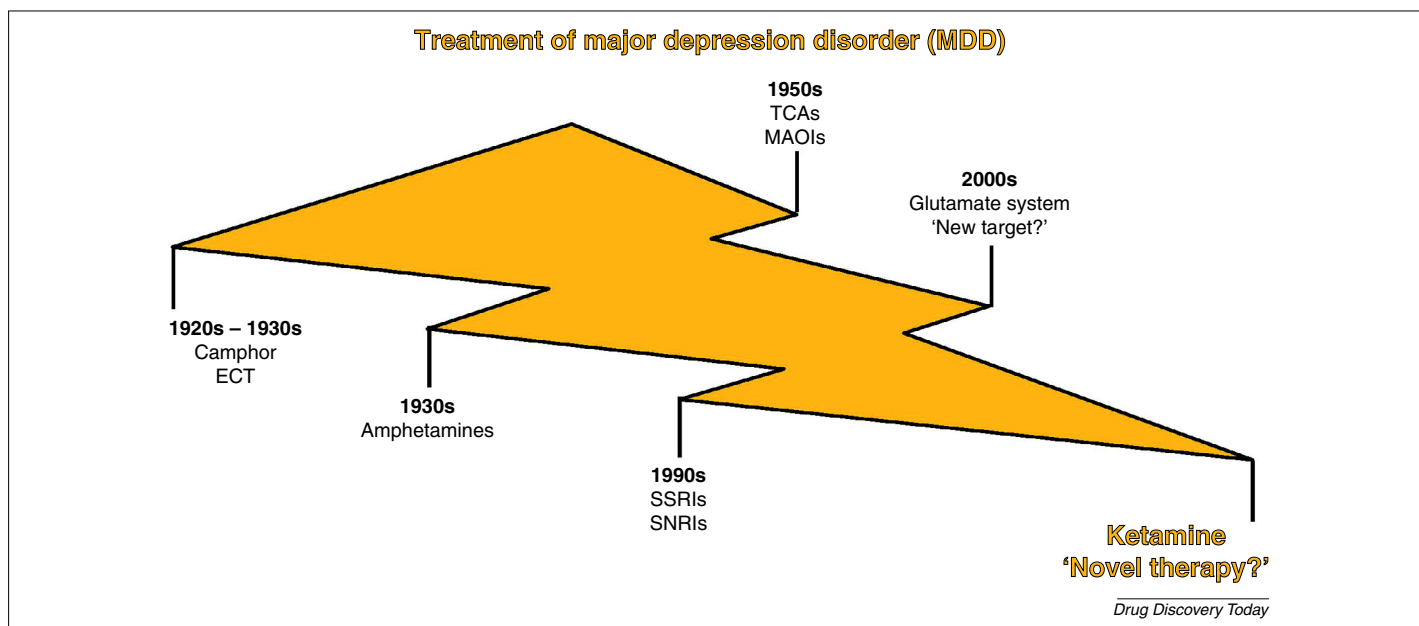

FIGURE 1

Pharmacologist's nightmare. Multifaceted activities of ketamine have suggested several potential therapeutic uses including those shown. This conundrum is reminiscent of the 'blind men and the elephant'. (Adopted from Original Artist - G. Renee Guzlas).

FIGURE 2

History of treatment of major depression. A schematic representation of the history of treatment of major depression is given. During 1920–1930, herbs and electricity [electroconvulsive therapy (ECT)] were used to treat depression. Later, in the 1930s, amphetamines were used as antidepressants. As a result of serendipitous discoveries in the 1950s, tricyclic antidepressants (TCAs) and monoamine oxidase A inhibitors (MAOIs) were prescribed to treat depression. Subsequently, in the 1990s, selective serotonin reuptake inhibitors (SSRIs) and/or selective noradrenaline reuptake inhibitors (SNRIs) became the most widely prescribed antidepressant drugs. In the 2000s, scientists initiated vigorous research into the glutamate (NMDA) system as a means to obtain a more rapid elevation of mood. Once dubbed a 'pharmacologist's nightmare', ketamine has been heralded as the most exciting development in antidepressant pharmacology in more than half a century.

i.v. administration. Hepatic cytochrome P-450 (CYP) enzymes (CYP3A4 > CYP2C9 > CYP2B6) metabolize ketamine extensively by demethylation to the principal metabolite, norketamine (NK). Although NK is biologically active, it has only one-third to one-fifth the activity of racemic ketamine and is eliminated by renal excretion. Owing to its relatively high lipophilicity, ketamine can be only partially removed by dialysis.

One of the most interesting facts about the pharmacokinetic profile of ketamine is that several ketamine metabolites [dehydronorketamine (DHNK), hydroxynorketamine (HNK)4a and HNK4c] were consistently higher in patients with bipolar depression (BPD) than in patients with major depressive disorder (MDD) [17]. Thus, N-demethylation of ketamine to NK is reduced in patients with MDD relative to BPD. This latter observation could be because the phenotypic expression of the CYPs. In addition, an inverse relationship was noted between ketamine metabolites and psychotomimetic or dissociative side-effects.

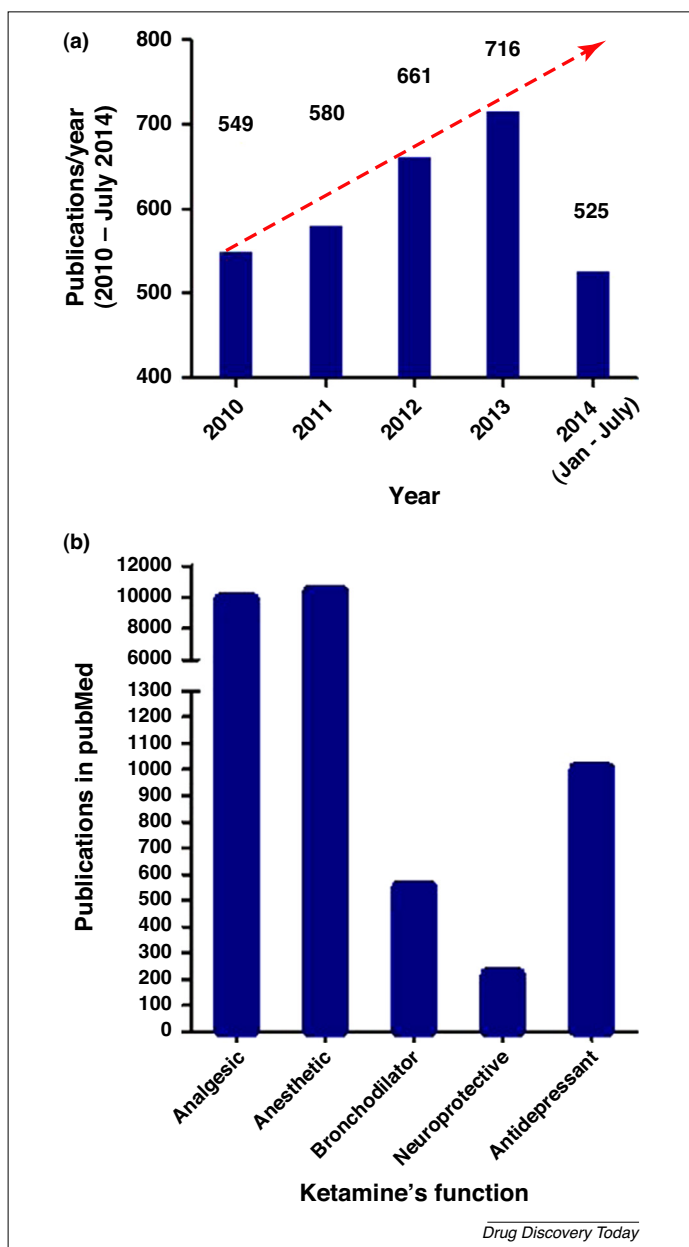### Pharmacodynamics
Receptor effects
Ketamine interacts with an array of receptors, directly and/or indirectly (See Table 1) [9]. The most studied receptor interaction is the ionotropic glutamate receptor N-methyl-D-aspartate

(NMDA), where ketamine behaves as a non-competitive antagonist. The NMDA–glutamate receptor is associated with Ca^{2+} channels of dorsal root neurons that transmit pain signals and are also involved in central sensitization [2]. As a result of being a ligand- and voltage-dependent antagonist, ketamine inhibits the channel-related flux of cations (Ca^{2+} and Na^+) in the presence of glutamate and glycine. Ketamine [S-(+)-ketamine > racemic ketamine] has also been reported to inhibit hyperpolarization-activated, cyclic-nucleotide-modulated (HCN1) channels [18]. In addition to actions on the ionotropic glutamate receptor, ketamine interacts with certain cholinergic, sigmaergic and opioidergic receptors as well as mono-aminergic uptake systems (Table 1); these interactions might contribute to its analgesic effects [19]. Interestingly, R-ketamine has greater affinity for sigma (σ_1) receptors than S-ketamine [15]. S-(−)-ketamine has more affinity for the PCP binding site of the NMDA receptor and, as a result, tends to have greater capacity to produce hallucinations. Because ketamine can interfere with the neuronal reuptake of catecholamines and serotonin, the functions of the cardiovascular–respiratory system, as well as the descending inhibitory, neural pathways that participate in the analgesic effect, can be influenced.

Epigenetic effects
Interestingly, noncoding RNA molecules such as miRNAs have emerged as crucial regulators of neuronal functions. The ability to influence gene expression via epigenetic mechanisms might be an interesting approach to novel therapies for psychiatric and mood disorders. For example, miRNAs are gene regulators that might represent therapeutic targets for developing novel treatments for psychiatric diseases. In this regard, miRNA expression might be part of the mechanism by which the antidepressant action of ketamine regulates various brain regions [20]. Moreover, the ability of ketamine and other antidepressants (e.g. imipramine) to alter histone deacetylase (HDAC) in the nucleus accumbens, simultaneously with alleviation of stress-induced depression, suggests a role for epigenetics in this condition [21]. These data indicate that epigenetic molecular events are necessary to reverse specific stress-induced behavior [22]. These epigenetic mechanisms might also account for the sustained therapeutic effects of ketamine.

A recent study shows that pharmacological (dizocilpine) or genetic (NR1 hypomorphism) disruption of NMDA receptor signaling reduces levels of a brain-specific miRNA, miR-219, in the prefrontal cortex of mice. In vivo inhibition of miR-219 in the murine brain significantly modulated behavioral responses associated

FIGURE 3

(a) Increase in ketamine-related publications. PubMed search covering the past five years shows a significant increase in ketamine-related research. **(b)** Publications showing multifaceted roles of ketamine. An intensive PubMed search shows significantly higher publications for the role of ketamine as an analgesic (9874) and/or anesthetic (10 393) as compared with a role as a bronchodilator (553) or neuroprotector (220). Recently, numerous ketamine-related articles (1003) were published regarding its utility in a variety of mood disorders.

with disrupted NMDA receptor transmission. Furthermore, pretreatment with the antipsychotic drugs haloperidol and clozapine prevented dizocilpine (MK801)-induced effects on miR-219 [23]. By contrast, another recent study showed that ketamine regulates the expression of miR-219 in hippocampus [19]. This finding supports the possibility that ketamine might reverse stress-induced depression, in part, via miRNA-regulated pathways. It is of interest

that miR-206 is a crucial novel gene for the expression of brain-derived neurotrophic factor (BDNF) induced by ketamine [24].

Anti-inflammatory or immunomodulatory effects

Immunoinhibitory (anti-inflammatory) effects of ketamine have been described *in vitro* in laboratory [25] and clinical [26] settings; the use of ketamine is recommended in patients

with sepsis undergoing surgery owing to its anti-inflammatory effects. Again, several studies demonstrated the involvement of epigenetics regulating inflammation specifically in sepsis [27]. However, a paucity of data exists with regard to the detailed mechanisms of the anti-inflammatory effects of ketamine. These latter effects have been attributed to inhibition of transcription activator protein-1 and nuclear factor (NF)-κB, as well as lowering of serum levels of interleukin (IL)-6, tumor necrosis factor (TNF)α, inducible nitric oxide synthase (iNOS) and C-reactive protein. In summary, ketamine is a unique homeostatic regulator of the acute inflammatory reaction and stress-induced immune disturbances [28]. Therefore, ketamine acts as an immunomodulator rather than an immunosuppressive agent. It is noteworthy that the anti-inflammatory actions of ketamine also could contribute to analgesic effects in certain inflammatory conditions characterized by pain.

Other effects
There are claims that ketamine is also useful in treatment of drug withdrawal syndromes: alcohol [29] and opioids [30]. The drug has been used with and without psychotherapy as part of the regimen. Because of the recent increase in use and abuse of opioids, difficulties involved in opioid withdrawal are becoming a health problem of significant magnitude. In a six-month study of a small cohort, ketamine was deemed useful in managing opioid withdrawal [31]. The rationale for ketamine use in withdrawal scenarios is presumed to be based on demonstrations that: (i) NMDA antagonists (ketamine) suppress opioid dose requirements and opioid-induced withdrawal in humans and (ii) S-(+)-ketamine can reduce withdrawal-evoked hyperexcitation as determined by encephalography.

Recently proposed clinical uses
Ketamine: a multipurpose analgesic
Ketamine is a parenteral (i.v., i.m., s.c.) anesthetic but also provides substantial analgesia at sub-anesthetic doses. It is classified as a Schedule III substance primarily because it can produce psychotomimetic effects at higher doses that are generally those required for anesthesia. The first published effect of ketamine-induced analgesia was for pediatric ophthalmologic procedures [32]. However, its analgesic efficacy in nociceptive and neuropathic pain is evident, alone or in combination, when administered by the oral, intranasal, transdermal, rectal, topical or s.c. routes [11]. The most common mixtures that are compounded for topical use are: ketamine

TABLE 1

Ketamine: multiple modes of action

Receptors	Channels and ions	Reuptake systems	Enzymes	Epigenetics
Glutamate (ionotropic)		Serotonin (↓) (5HT)	NO synthesis (↑) (neuronal)	miRNA (↓ or ↑)
NMDA (NC ⋀⋀⋀) AMPA	Na$^+$, K$^+$, Ca^{2+} (↓)			HDAC (↓)
Opioid (↓) μ K σ	Cl$^+$ (↑)	Norepinephrine (↓) (NE) Dopamine (↑) (DA)		
GABA GABA$_A$ (↑)		GABA (↑)		
Cholinergic Muscarinic (↓) Nicotinic (↓)				
Dopamine D$_2$ (↑)				
Toll-like TLR4 (↓ expression)				

Abbreviations: NC, noncompetitive; GABA, gamma amino butyric acid; NO, nitric oxide; HDAC, histone deacetylase.

Activity: ↑, stimulates; ↓, inhibits.

(10%), ketoprofen (10%), lidocaine (5%); however, it is also compounded with other agents as well (amitriptyline, clonidine, gabapentin, pregabalin, baclofen) [12]. Intranasally administered ketamine is particularly useful for its opioid-sparing effect; especially when there is breakthrough pain [31], as occurs during opioid therapy of chronic and acute postoperative pain [33,34]. Intranasal *S*-ketamine is also useful in a pre-hospital setting wherever delivery of analgesia proves challenging such as difficulty establishing i.v. access or in treating acute injuries in a harsh winter environment [35]. Significant reductions in pain scores occur within 5–10 min of administration by the intranasal route. Likewise, patients undergoing cesarean section had lower pain intensity and less analgesic consumption when given ketamine (0.5 mg/kg) s.c. before or after surgery [36].

Ketamine not only produces analgesia [37] it also reduces capsaicin-evoked mechanical hyperalgesia at a gel concentration of 50 mg/ml. It was proposed that the mechanism of action might be reduction of central sensitization caused by absorption of ketamine into circulation. However, it most probably involves a peripheral effect on nociceptors [3]. There were no substantial side-effects evoked by ketamine

concentrations when administered in the gel vehicle used in this study [38].

Topical amitriptyline–ketamine was shown to be effective for treatment of rectal, genital and perineal pain and discomfort [14]. The type of cream vehicle can influence the efficacy of some analgesic agents in combination medications administered via the percutaneous route [39]. Topical gel treatment with baclofen (10 mg), amitriptiline (40 mg) and ketamine (20 mg) decreased chemotherapy-induced peripheral neuropathy (CIPN) symptoms in selected patients [40]. Overall, there was no appreciable systematic absorption of ketamine in these studies; the hint of potential benefits warrants further study. Evidence suggests that further clinical studies are required to determine if ketamine suppresses the effectiveness in cancer-related pain such as that produced by chemotherapy [40]. Ketamine has been tested as an adjuvant to opioids in the treatment of cancer-related neuropathic pain. Neuropathic pain in cancer patients is the product of nervous tissue damage owing to tumor growth or infiltration and/or neuropathic chemotherapy.

Ketamine has also been touted as a treatment for complex regional pain syndrome [41].

In this condition, patients experience severe chronic pain which is accompanied by a constellation of signs and symptoms related to complex sensory, autonomic, motor and dystrophic events [42,43]. NMDA antagonists, such as ketamine, continue to hold significant interest because of their potential ability to alter the central sensitization noted in chronic pain states. In this condition, the hypothesis is that manipulation of NMDA receptor activity by ketamine 'reboots' aberrant activity of the brain [43]. As a clinically proven NMDA antagonist, ketamine has the potential to: (i) aid in unraveling mechanisms mediating chronic pain and other pain states and (ii) provide new evidence of the role for NMDA receptors in neuronal plasticity and central sensitization in humans.

Ketamine: a novel, rapid-acting antidepressant

Clinical studies in patients suffering treatment-resistant depression suggest that the antidepressant effect of ketamine: (i) occurs very early in the course of treatment by i.v. infusion; (ii) exerts a broad-spectrum antidepressant effect and (iii) is sustained to subsequent infusions if there was a rapid response to the first infusion [44].

In a laboratory setting, acute administration of ketamine can produce effects in behavioral screens and other rodent models for depression (e.g. forced swim test) [45]. Because mood disorders have been linked to abnormalities in circadian rhythms, the antidepressant actions of ketamine have been associated with changes in the function of the circadian molecular machinery [46]. Ketamine can dampen phase-shifting responses to light as well as alter the circadian rhythm of glutamate receptors. A behavioral and molecular analysis in zebrafish showed that Sirtuin1 (Sirt1) was regulated by ketamine [47]. This is an interesting observation related to epigenetic mechanisms because Sirt1, NAD$^+$-dependent HDAC plays a significant part in circadian rhythm [48].

It is of interest that major depression affects twice as many women as men. Evidence in rodents suggests that there might be gender differences (hormonal influences in response to ketamine). In rodents, the antidepressant effects of ketamine are more prominent in female rats; the response was abolished by ovariectomy and restored by replacement of estrogen and progesterone [49].

Additional scientific evidence, in a clinical setting, suggests an important role for NMDA receptor signaling via ketamine (0.5 mg/kg i.v.) as rapid treatment for major depression [50] and bipolar depression [51] as well as those resistant to electroconvulsive therapy (ECT) or with suicidal ideation. It has been demonstrated that ketamine and electroconvulsive therapy possess activity on common pathways suggesting convergence. Moreover, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor involvement is suggested to be crucial for the antidepressant effects of ketamine [52]. Nevertheless, it is noteworthy that ketamine also interacts with a multiplicity of receptor systems (opioidergic, monoaminergic, cholinergic), ion channels, enzymes and epigenetic systems.

At the molecular level, ketamine-mediated suppression of resting NMDA receptor activity leads to inhibition of elongation factor 2 (eF2) kinase and dephosphorylation of eF2; subsequently, de-repression of BDNF messenger RNA results in augmentation of BDNF synthesis [53]. Thus, one of the other actions of ketamine that has been implicated as being crucial in the antidepressant action of ketamine experimentally is an increase in BDNF [54]. Recent evidence showed a role of miR-21 and miR-206 in BDNF regulation. By contrast, ketamine has been shown to inhibit the upregulation of miR-21 expression and matrix metalloproteinase (MMP)9 protein level after cerebral ischemia [55].

There are several other miRNAs that might be involved with ketamine action and BDNF regulation. One of the common targets is miR-598-5p which might have a role in antidepressant activity. Thus, ketamine and ECT treatment possess the ability to reverse stress-induced changes in multiple miRNAs [20].

Early-life stress is a major contributory factor to the onset of depression later in life. miRNAs and HDACs are novel regulators of eukaryotic gene expression. In this regard, histone acetylation is considered a promising therapeutic target in mood disorders because histone acetylation reduces histone affinity for DNA. Thus, HDAC is considered a major epigenetic regulator of gene expression for several key proteins. In the nucleus accumbens of rats deprived of maternal care administration of ketamine and imipramine decrease HDAC activity indicating that this mechanism might account, in part, for relief of stress-induced depression [22]. Likewise, ketamine and ECT treatment can reverse several stress-induced changes to miRNA in the hippocampus in early-life stress-induced pathologies [20]. Temporally, ketamine activates a series of complex intracellular and extracellular events in neuronal tissue that eventually induce increased synaptic plasticity (e.g. long-term potentiation and learning processes); whether the activity is regionally specific needs further study. Therefore, the evidence alluded to above strengthens the assumption that ketamine could act, in part, by epigenetic mechanisms via miRNA- and HDAC-regulated pathways. This eventuality might offer a novel avenue for the therapeutic approach to prevent or treat depression in the future.

Additionally, there are experimental data available that implicate a role for mammalian target of rapamycin (mTOR) and glycogen synthase kinase (GSK)-3 in the rapid antidepressant action of ketamine [56,57]. Likewise, as stated previously, dysregulation of circadian rhythms has been implicated in the generation of depression. Altered clock gene machinery could represent an essential pathophysiological defect in mood disorders. Presumably, ketamine might act at the level of NMDA and/or AMPA receptors in the suprachiasmatic nucleus to influence CLOCK:BMAL1 function leading to altered gene expression [46].

Three criteria that have been proposed for antidepressants are that they should: (i) act rapidly, delivering symptomatic relief within hours to days; (ii) produce positive outcomes in a predictable manner and in a large fraction of the patient population and (iii) provide sustained relief over the long-term to help patients

reintegrate into society. In this regard, clinical studies have shown consistently that the antidepressant effect of ketamine is: (i) manifested within hours to one day (rather than weeks); (ii) relatively consistent (two-thirds of patients respond in a meaningful way) and (iii) longer than expected (from several days up to two weeks in some patients) as based on its half-life. Over the past ten years, ketamine has become the prototype glutaminergic antidepressant [58]. Thus, 50 plus years after its initial discovery, ketamine portends to offer new and promising roles as a therapeutic entity [37,59] and a tool for research in conditions characterized by pain [12,19] and/or depression [17,60]. As of July 2014, Phase II clinical trials of intranasal esketamine [S-(+)-ketamine] for treatment-resistant depression are underway (http://clinicaltrials.gov/show/NCT01998958).

Concluding remarks

Ketamine is an example of how an existing drug can be readapted for multiple licit uses including treatment of pain and depression. The unexpected, but welcome, revival of interest in ketamine represents a prime example of how existing, multifaceted drugs can be repurposed and find 'new' life as therapeutic agents and pharmacological tools to investigate new avenues of research in mechanisms mediating pain and nociception and depression. The mechanisms of ketamine effects are continuing to be delineated; moreover, novel mechanisms involving epigenetics could be responsible for some of its clinical activity. Ketamine is a valuable pharmacological tool in translational research and has the potential to revolutionize therapy of several complex conditions that include pain and depression as prominent symptoms.

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