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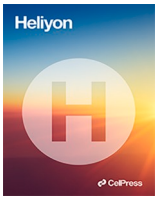

Review article

Depression, an unmet health need in Africa: Understanding the promise of ketamine

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ABSTRACT

In Africa, there is currently a paucity of data on the epidemiology of depression, its treatment and management. The prevalence of depression is severely underestimated, with unique circumstances and societal risk factors associated with depression and its public awareness. Treating and managing depression is confounded by an inaccessibility to efficient and low-cost treatments for patients with depression. The aetiology of depression is multifactorial, with various theories implicating multiple neuronal networks. Despite this, the treatment of depression is one-dimensional focussing on outdated theories of depression and mainly targeting dysfunctional neurotransmitter pathways. Hence, it is not surprising that there is a significant increase in the prevalence of patients suffering from treatment resistant depression (TRD), with a large portion of patients deriving little clinical benefit from these traditional anti-depressant therapies. This highlights the need for more effective treatment strategies for depression, especially applicable to resource limited environments such as Africa, where there is little investment in public healthcare resources towards managing mental health disorders. The clinical potential of using ketamine in managing depression has received considerable attention in the past two decades, with the FDA approving esketamine for the management of TRD in 2019. This widespread attention has significantly increased ketamine's appeal as a novel antidepressant. Consequently, many ketamine infusion clinics have been established in Africa. However, there is little regulation or guidance for ketamine infusions. Furthermore, while esketamine is expensive and hence inaccessible to a large portion of the African population, racemic ketamine is significantly cheaper and has demonstrated clinical potential. However, there is currently a limited understanding of the neurological mechanisms of action of racemic ketamine in treating and managing depression, especially in a diverse African population. Therefore, this review aims to provide an African context of depression and the therapeutic potential of ketamine by highlighting aspects of its molecular mechanism of action.

1. The current global and African context of depression

Major depressive disorder (MDD) is a debilitating mental health disorder characterized by a persistent pathological low mood state

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and lack of enjoyment in normally pleasurable activities [1]. MDD has been linked to reduced occupational and educational functionality, suicidality, a decreased quality of life, all which have a substantial global economic burden [2,3]. The Global Health Data Exchange estimates that between 251 and 310 million people worldwide currently suffer from depression and related disorders, with an 18.4% increase in the global prevalence of depression between 2005 and 2015 [4]. Hence, it is not surprising that MDD is a significant global health concern with far reaching societal impact. The contribution of depression to the worldwide disease burden is enormous, with projections estimating depression to be the leading cause of morbidity by 2030 [5]. Although, the prevalence of depression varies by region, the average estimated global prevalence is 4.4% [4]. Epidemiological data on depression in Africa is poor and reflects the prevalence of only a few higher income countries [6]. Moreover, where data is available there is high variability among different countries and the data is often inconsistent because of variances in methodological approaches, cross-sectional study designs, and sampling practices [6]. In addition, it has been suggested that most psychiatric research in sub-Saharan Africa is of poor to medium quality, possibly attributed to infectious diseases being the primary research focus [7]. Nevertheless, current data suggests that the prevalence of depression in Africa ranges between 3.9% and 9%. In South Africa the estimated prevalence of depression is 4.6%, which is only slightly below estimates in the United States (4.8%) and Europe (4.9%) [6]. However, a recent WHO Global Health report estimated that the African region comprises approximately 5.4% of the global burden of depression [4].

2. Confounding risk factors for depression on the African continent

Despite these statistics, the landscape surrounding depression in Africa looks bleak. It is suggested that the prevalence of depression is severely underestimated due to misdiagnosis and undiagnosed cases, largely due to the lack of education and awareness around mental disorders. In addition, limited professional resources particularly in rural settings, as well as stigmatization associated with mental health disorders further contributes to the inaccurate statistics [8]. In those cases that are diagnosed, it seems that the risk factors associated with depression in Africa are very different to that of high-income countries, mainly driven by a health and socioeconomic landscape that is vastly different to high-income countries [7,9]. The high burden of postpartum complications, unwanted pregnancies, the high prevalence of persons living with infectious diseases (particularly HIV and tuberculosis), drug abuse, conflict, and violence are some of the major risk factors associated with depression in sub-Saharan Africa [6]. In addition, mental healthcare often must compete with the massive infectious disease burden in sub-Saharan Africa, resulting in psychiatric disorders being severely neglected, especially in the public healthcare domain. This situation, in the face of our limited current understanding of the aetiology of depression, further confounds the effective treatment and management of depression.

3. Pathogenesis of MDD

The pathogenesis of MDD is multifaceted (Fig. 1), implicating the involvement of multiple functional and molecular pathways. As such several theories underlying the development of depression, have been proposed. An in-depth discussion of the pathogenesis of MDD is beyond the scope of this review, but has been eloquently reviewed elsewhere [10]. Briefly, the monoaminergic theory is based on an imbalance in the monoamines (serotonin, noradrenaline, and dopamine), which are the most widely studied and accepted theory of depression [11]. Monoamine dysregulation explains many of the classical symptoms of depression such as lack of motivation and anhedonia [12,13]. Studies reporting increased levels of glutamate in the prefrontal cortex of individuals who have committed suicide, suggesting dysregulation in glutamate and GABA excitation/inhibition signalling. Subsequently a glutamatergic theory has been formulated to explain the development of depression [14,10,15,16]. The neuroinflammatory theory proposes chronic exposure to inflammatory mediators to trigger the development of depression, where inflammation is believed to drive many of the neurodegenerative processes observed in depression [17–19]. The neurotrophic theory posits that a decrease in neurotrophic factors, specifically brain-derived neurotrophic factor (BDNF), leads to aberrant neuroplasticity [16,20]. Failure of such adaptive processes in the

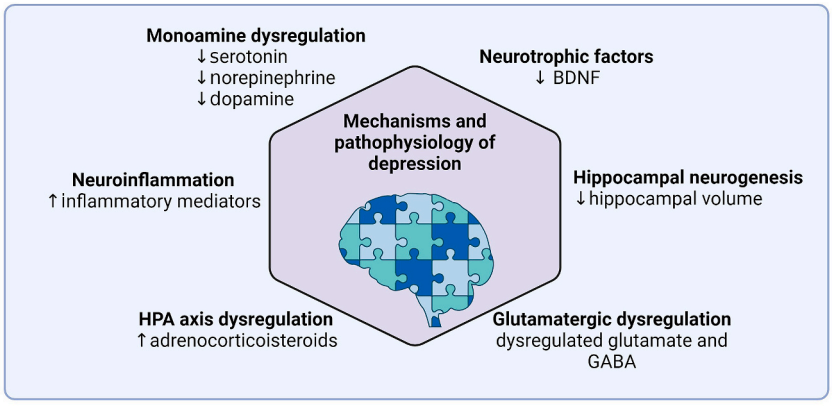

Fig. 1. A summary of the current theories believed to be associated with the development of depression, highlighting the multifaceted nature of the disorder and the need for novel therapeutics with multiple targets (adapted from [10]).

central nervous system is therefore offered as an explanation for the development of depression [21–23]. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis leading to increased circulating glucocorticoid levels has also been associated with the pathophysiology of depression [24,25]. Lastly, the pathogenesis of depression has also been linked to other specific functional brain changes including reduced hippocampal neurogenesis and impairments in fronto-cortical executive cognitive functions [26–29]. Importantly, although each of these theories have been shown to potentially contribute to the development of MDD in independent studies, it is likely that several of these mechanisms and pathways converge to establish the mental disorder. While such a hypothesis aligns well with the complexity of depression, it makes treating and managing the disorder a pharmacological conundrum. This highlights the need for more investigations into the interaction between the different proposed pathological mechanisms underlying the development of depression [30]. It is evident that the heterogenous pathophysiological mechanisms underpinning depression cannot be effectively managed by a "one-size-fits-all" solution.

4. Current treatment and management of MDD

According to the American College of Physicians guidelines monotherapy with cognitive behavioral therapy or a second-generation anti-depressant, or a combination of the two, is recommended as first line therapy for the management of mild to moderate cases of depression [31]. This approach may not be feasible in an African context, particularly in a resource constrained environment, where the access to and the cost of psychotherapy is a barrier for large sectors of the population [32]. There is a significant disparity in the African mental health workforce compared to our Western counterparts, with only 1.6 mental health workers per 100 000 population compared to 44.8 per 100 000 population in Europe, respectively in 2020. In rural communities this situation is dire with only 0.03 psychiatrists per 100 000 population in South Africa, one of the more developed countries on the continent [33]. Therefore, in Africa, the use of pharmacological agents may be a more feasible intervention in the treatment and management of depression.

Several classes of pharmacological agents have been used for the treatment and management of depression including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors (NRIs) and mood stabilizers [34,35]. Since the 1950s when the monoamine theory of depression has been proposed, the majority of antidepressant treatments focus mainly on addressing functional deficiencies in neurotransmitter pathways at the level of either neurotransmission or receptor activity [36]. Although the administration of monoamine antidepressants has proven effective, clinical outcomes have shown that the response rate is very slow and that often depressive symptoms worsen over time [37]. Considering the heterogenous aetiology of depression (Fig. 1) it is not surprising that traditional antidepressant therapies, targeting only one of these pathways, have a high failure rate [30].

A growing body of evidence points to other pharmacological approaches showing promise in the treatment of depression. For instance, antidepressants that target the glutamatergic system have shown rapid clinical responses. However, results have been mixed with many of these drugs still undergoing clinical investigation [38,39]. Targeting HPA axis dysfunction by treatment with the glucocorticoid receptor antagonist mifepristone, has been shown to be effective in reducing depressive symptoms [40]. Similarly, drugs that modulate microglial-mediated neuroinflammation, such as minocycline, also show efficacy in alleviating depressive symptoms [41]. Further studies into these antidepressants are warranted, especially in view of the limited research available on the usefulness of these agents in an African context [6].

Nevertheless, it is estimated that at least 33% of people who have depression are either partly responsive or resistant to conventional antidepressant therapies, a condition referred to as treatment resistant depression (TRD) [42,43]. The most widely, accepted definition states that TRD is diagnosed when the patient shows resistance to at least two different courses of antidepressant treatments of adequate dose and duration [44,45]. Since there is a strong association between TRD and suicide and suicidal ideation [42], the urgent need for effective treatment strategies for this condition is evident. This need is exemplified by unconventional approaches, such as creatine [46] and psychedelics [47] being considered for the treatment of depression.

5. Ketamine as a potential 'silver arrow' for depression management in Africa

Ketamine, a decades-old anaesthetic drug, has recently emerged as a treatment for managing depression. Ketamine was first discovered in the 1960s and was used for its rapid-onset anaesthesia with profound analgesic effects. The commonly used form of ketamine (*RS*-ketamine) is a racemic mixture of isomers *(S)*-ketamine (esketamine) and *(R)*-ketamine (arketamine) and is an affordable and widely used but also abused drug [48]. In recent years, ketamine has been shown to remarkably improve clinical depressive symptoms in patients with TRD [49]. The clinical antidepressant effects of esketamine have been observed hours after administration, peaking within 24–72 h and lasting for as long as two weeks [50]. Studies show a significant reduction in depressive symptoms after acute ketamine administration, with a response rate of more than 60% within 24 h, and over 40% at 7 days post-administration. More importantly, this effect is sustained over several weeks following repeated doses of ketamine [49]. Unlike most antidepressants that require chronic administration, acute ketamine administration (0.5 mg/kg, infused over 40 min i. v.) produced rapid relief of depressive symptoms [50]. The resulting antidepressant effects following infusion support the hypothesis that these clinical effects are as a result of exposure to ketamine and not due to its potential narcotic and/or intoxicant properties [50]. These acute hallucinogenic and euphoriant effects of esketamine subside shortly after administration and are followed by the beneficial longer-lasting antidepressant effects [51]. Remarkably, these effects are observed only in patients with depression, thereby casting doubt on ketamine's long-standing reputation as an intoxicant [51].

Based on its demonstrated clinical efficacy, in 2019, the US Food and Drug Administration (FDA) approved the use of esketamine (the *(S)*-enantiomer of ketamine) as an antidepressant nasal spray (Spravato™) [52]. Despite this, a recent meta-analysis has suggested

that intravenous racemic ketamine is more effective at managing depression than intranasal esketamine [53]. Moreover, it has been shown that 0.5 mg of racemic ketamine is able to reach the same bioavailability as that of 56 mg of esketamine [54]. The lower cost and higher bioavailability of racemic ketamine make it the obvious choice for managing depression in resource limited environments. In addition, the UK National Institute for Health and Care Excellence (NICE) did not support the use of an esketamine nasal spray for TRD, based on the uncertainties over its clinical efficacy and cost effectiveness [55].

Considering the limited bioavailability and the costs associated with the chiral separation of its enantiomers, the promising use of racemic ketamine as the preferred formulation to treat and manage MDD requires further investigation. The low cost of racemic ketamine will allow its use in resource limited environments, such as Africa, where access to current approaches to managing MDD is limited for a large portion of the population. Therefore, comprehensive empirical studies investigating the physiological and pharmacodynamic mechanisms of action and the differences in effects between the enantiomers of ketamine are warranted.

5.1. *Proposed antidepressant mechanism of action of ketamine*

There has been some theories and hypotheses proposing the potential mechanisms whereby ketamine exerts its antidepressant action (Fig. 2). The results of several of these theories suggest that the activation of local protein synthesis that promotes dendritic spine growth and synaptogenesis is instrumental in mediating the beneficial effects of ketamine [56]. Ketamine has therefore been suggested to improve cortical structural connectivity in animals and reverse impairments in cortical functional connectivity in depressed patients [57,58]. These hypotheses lend itself to several putative biomarkers that can be assessed as potential screening tools as an indicator for the initiation of treatment and for the measurement of drug efficacy in patients with depression. Moreover, recent evidence from preliminary studies in our laboratory suggests that the level of glucocorticoids, which are regulated via the HPA axis, may mediate ketamine's effect on neurotrophic factors, a finding that warrants further investigation.

While *N*-methyl-D-aspartate receptor (NMDAR) antagonism is the known mechanism of action of ketamine in its anaesthetic use,

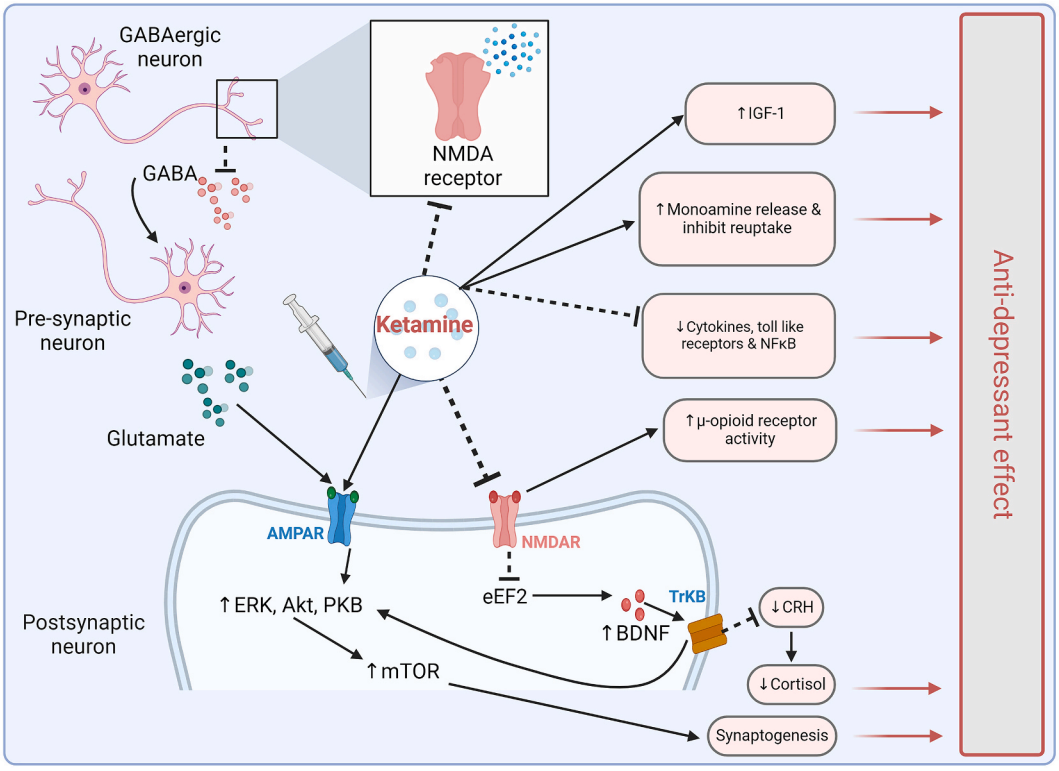

Fig. 2. Ketamine's proposed anti-depressant mechanism of action. The most widely accepted hypothesis of ketamine's mechanism of action is that the drug antagonizes the *N*-methyl-D-aspartate receptors (NMDARs) and excites the α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs). Increased AMPAR excitation increases the local expression of brain-derived neurotrophic factor (BDNF). BDNF binds to tyrosine receptor kinase B (TrkB) receptors, triggering signalling cascades that upregulate and enhance the activity of other transcription factors, such as cAMP response element binding protein (CREB), involved in the synthesis of neurotrophins. These changes have been shown to improve cortical structural connectivity in animals and reverse impairments in cortical functional connectivity in depressed patients. Other proposed effects of ketamine include potentiation of endogenous μ-opioid receptor activity, increasing neurotransmitter release or inhibiting re-uptake thereby increasing overall neurotransmitter synaptic concentrations, reduction in pro-inflammatory cytokines and increased insulin-like growth factor-1 (IGF-1). CRH, corticotrophin releasing hormone; eEF2, eurokaryotic elongation factor 2; Akt, protein kinase; PKB, protein kinase B; mTOR, mammalian target of rapamycin; NFκB, nuclear factor kappa B; GABA, gamma-aminobutyric acid.

other NMDAR antagonists have failed to produce rapid and effective relief from symptoms in depressed patients [59,60]. This demonstrates that despite ketamine-mediated NMDAR antagonism increasing the downstream expression of BDNF, this is not the only mechanism by which ketamine induces its anti-depressant effect. Evidence regarding the inhibition of the antidepressant effect of (*R,S*) ketamine in rodents with the use of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antagonists demonstrate that AMPAR activation significantly contributes to the therapeutic benefits of racemic ketamine [61].

The mechanistic hypotheses surrounding our current understanding of ketamine's mechanism of action includes the downstream antagonism of the GluN2B subunit of NMDARs. The antagonism of these receptors leads to an increase in BNDF levels and the shuttling of AMPA glutamate receptors (AMPAGRs) to the synapse, via the inhibition of eukaryotic elongation factor-2 (eEF2), leading to an increase in synaptic elasticity. Ketamine may also directly block NMDARs on GABA interneurons, reducing glutamate inhibition and increasing the stimulation of AMPAGRs, resulting in a local increase in BDNF levels. Local BDNF release activates cellular protein synthesis via the stimulation of TrkB receptors and is necessary for increasing dendritic spine growth and synaptic plasticity [50]. Molecular target of rapamycin complex 1 (mTORC1) is an essential target in this pathway as it has been shown that inhibition of this step prevents the antidepressant effects of ketamine [56].

While strong empirical evidence exists for these hypotheses, the majority of investigations focused on individual molecular and intracellular pathways. However, the complexity of the aetiology of depression and the significant observed effectiveness of ketamine in its treatment, suggest that this drug may have a multifaceted mechanism of action (Fig. 2) [62]. It is therefore more likely that ketamine acts on several pathways believed to be involved in the pathophysiology of depression. Studies geared at investigating these pathways simultaneously, should provide a more comprehensive understanding of ketamine's mode of action. Such information has the potential to revolutionise the clinical management of MDD and TRD at a personal and population level, an approach that will be of significant benefit on a continent where the social and economic impact of depression is severely underestimated.

Despite the promising findings following ketamine administration in patients with TRD, a few unanswered questions remain. For instance, in practice, there is a major concern regarding an effective protocol to be followed to maintain the clinical antidepressant effect of ketamine seen with acute administration. Furthermore, the safety of ketamine during long term administration has not been established. Moreover, the uncertainty of ketamine's dose-related abuse potential and resultant dissociative effects are further barriers to the optimal use of ketamine in antidepressant therapy.

6. Conclusion

Taken together, there is a paucity of data surrounding the epidemiology of depression, and its treatment and management in Africa. The prevalence of depression in Africa is potentially severly underestimated. This coupled with the unique circumstances and risk factors associated with depression on the African continent, highlights the need for high-quality research on depression and its treatment in Africa. Recent evidence shows the clinical potential for using ketamine in managing MDD and TRD. However, the risk for abuse of ketamine, the lack of research in Africa, and poor understandig of the mechanisms of action of ketamine warrant a comprehensive investigation in preclinical and clinical models of depression. A greater understanding of ketamine's mechanism of action may improve its clinical applications. Furthemore, identifying the associated indicators for treatment initiation and treatment maintenance to impact treatment efficacy. This has the potential to inform public health policy surrounding the treatment and management of MDD and TRD using ketamine.

The greater awareness of the potential benefits of ketamine in managing depression, especially TRD, is likely to accelerate ketamine research in an African population. This will provide important clinical data on potential biomarkers for the onset of ketamine therapy and knowledge on its mechanism of action in a diverse genetic population. In addition, an improved understanding of ketmaine's effects may drive research into the delivery and administration of ketamine leading to innovative devices and delivery mechanisms to make drug administration easy and possibly removing the need for the dosing to be done by healthcare professionals. High quality research on ketmaine has the potential to shape public healthcare policy for its use in low-resource governmental institutions, providing affordable, easily accessible treatments for the management of depression. In addition, optimal use of ketamine in the management of TRD may decrease side-effects and lead to optimised dosing regimens which will also likely improve patient compliance. It is envisaged that increasing our understanding of ketamine and its neurobiology, will improve the treatment outcomes and well-being of patients with depression.

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Data availability

All data used to support this article are included in the article.

CRediT authorship contribution statement

Aletta ME. Millen: Writing – review & editing, Writing – original draft, Conceptualization. **William MU. Daniels:** Writing – review & editing. **Sooraj Baijnath:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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