Annals of General Psychiatry

https://doi.org/10.1186/s12991-025-00626-1

Article in Press

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Received: 18 September 2025

Accepted: 29 December 2025

Published online: 21 January 2026

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Mohammed A. Alhassan

Transforming Treatment-Resistant Depression (TRD) Care in the Gulf Cooperation Council (GCC) Countries – A Narrative Review of Emerging Therapies, Advancements, and Implementation Barriers

Mohammed A. Alhassan

Department of Medical Specialities, Psychiatry, College of Medicine, Majmaah University, Al Majmaah, 11952, Saudi Arabia

Correspondence: MAlhassan@MU.EDU.SA

ORCID - 0000-0002-3009-7187

Abstract

Background Treatment-resistant depression (TRD) remains a major clinical challenge worldwide and in the Gulf Cooperation Council (GCC) countries, where mental health disorders are on the rise. Conventional TRD therapies, including antidepressants, augmentation strategies, and electroconvulsive therapy (ECT), often result in incomplete remission or carry burdensome side effects, underscoring the need for innovative approaches.

Objective This narrative review explores the mechanisms, clinical evidence, regional adoption, and recent advances of ketamine, esketamine, and rTMS in TRD, while examining barriers to implementation and outlining future directions for care in the GCC.

Key Findings Esketamine adoption is increasing in the GCC, with the United Arab Emirates and Qatar leading implementation efforts. In both countries, esketamine and related treatments are currently administered in controlled clinical settings within leading psychiatry clinics. Region-specific governmental strategies, such as Qatar's national mental health initiatives, have further supported the structured introduction of these therapies. rTMS is also being gradually integrated into regional mental health services, with notable expansion under Hamad Medical Corporation (HMC) in Qatar. Despite these advancements, access remains limited due to regulatory challenges, high costs, and infrastructure constraints. Implementation of these therapies may serve as a foundation for future regional mental health policies, although cultural stigma, limited insurance coverage, and workforce shortages continue to pose barriers.

Conclusions Novel therapies for TRD demonstrate clinical efficacy and feasibility in the GCC. Nevertheless, their wider adoption requires addressing accessibility challenges, reducing stigma, and expanding professional training. Strategic investments, policy reforms, and awareness initiatives will be critical to embedding these treatments into mental health systems and transforming TRD care in the region.

Keywords: Treatment-resistant depression; TRD; GCC mental health; antidepressant therapies; ketamine; esketamine; repetitive transcranial magnetic stimulation; neuromodulation

1. Introduction

Major mental health disorders, specifically major depressive disorder (MDD), are increasingly prevalent in the Gulf region, posing a significant public health challenge. MDD poses a particularly challenging issue for healthcare provisions in Gulf Cooperation Council (GCC) countries, which include Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates (UAE) [1]. While these nations share similar religious, cultural, social, and political contexts, their demographics vary considerably [1, 2]. Evidence from the COVID-19 period indicates a marked temporary increase in MDD prevalence in the GCC region, with estimates reporting increases of up to 38% [1], compared with a global increase of up to 27% during the same period [3, 4] (Figure 1). However, these estimates largely reflect data collected during or immediately following the pandemic. Long-term epidemiological data preceding the pandemic indicate notable regional variation in depression burden within the GCC. For example, Balushi et al., using data collected between 1990 and 2019, reported higher depression prevalence among females compared to males (95% CI: 1.149–1.285, $p < 0.001$), with the highest prevalence observed in Kuwait and Saudi Arabia and the lowest in the UAE [5]. Approximately 30% of individuals with MDD do not respond to initial treatments, leading to the development of treatment-resistant depression (TRD) [6, 7]. In clinical research settings, TRD affects about 30% of patients with MDD [6, 7], with a global prevalence ranging between 6% and 55% [8]. TRD is linked to increased morbidity and mortality, a reduced quality of life, and disruptions in professional, social, and familial domains, including adverse impacts

on offspring [9]. In Gulf countries, historically, cultural and religious stigma has hindered the recognition of mental illness, but the growing need for effective treatment options is becoming more evident. Patients with TRD face significantly fewer effective therapeutic alternatives compared to those with non-resistant forms of depression [9]. Existing treatment approaches, such as conventional antidepressants, are often associated with high rates of non-response, relapse, and adverse effects, further complicating the management of TRD [10].

TRD imposes a significant economic burden across the GCC region, with overall expenditures, especially indirect costs, reported to be nearly three times greater than those linked to non-resistant MDD [9, 11]. The condition places significant strain on healthcare systems due to elevated treatment costs and increased resource utilization [9]. In 2020 alone, direct healthcare costs were estimated at AED 2,461 million (USD 670 million) in the UAE, KWD 304 million (USD 986 million) in Kuwait, and SAR 14,997 million (USD 4 billion) in Saudi Arabia [12] (Figure 2). Common TRD treatment strategies in the region include selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), augmentation approaches, and electroconvulsive therapy (ECT). These are the primary methods for managing TRD in the region, all of which contribute to the economic burden of the disorder [12].

Innovative interventions such as ketamine, esketamine, and repetitive transcranial magnetic stimulation (rTMS) have emerged as promising options for patients who do not respond to conventional therapies [13]. These treatments are distinguished by their rapid antidepressant effects and accumulating clinical evidence, particularly in populations with TRD.

In the GCC region, the demand for such alternatives is increasingly evident. Traditional treatment approaches often prove inadequate for a considerable proportion of patients, while factors such as stigma, limited access to specialized services, and resource constraints further contribute to unmet needs in care. In this context,

novel therapies like ketamine, esketamine, and rTMS represent potential opportunities to strengthen TRD management across the region.

The review addressed four core areas: (i) mechanisms and clinical evidence of ketamine, esketamine, and rTMS in TRD, with comparisons to traditional antidepressants and global context; (ii) regional adoption and recent advances in the implementation of these therapies; (iii) cultural, societal, regulatory, and structural barriers influencing their integration into mental health care; and (iv) future directions for research, policy, and clinical practice in the GCC.

2. Methods

This study employed a narrative review design to synthesize available evidence on TRD care in the GCC countries. The review focused on summarizing current and emerging therapeutic strategies, examining recent advancements in the adoption of novel therapies, and analyzing structural, cultural, and health system barriers that influence their implementation in the region.

2.1. Literature Search Strategy

A comprehensive literature search was conducted up to May 2025 across electronic databases including PubMed, Embase, PsycINFO, and Google Scholar. Keywords and Medical Subject Headings (MeSH) terms were combined using Boolean operators and included: “treatment-resistant depression,” “TRD,” “major depressive disorder,” “emerging therapies,” “ketamine,” “esketamine,” “neuromodulation,” “digital interventions,” “Gulf Cooperation Council,” “Middle East,” “Saudi Arabia,” “United Arab Emirates,” “Qatar,” “Kuwait,” “Oman,” and “Bahrain.”

To capture regional perspectives and context-specific insights, grey literature was also reviewed, including government health reports, GCC-specific clinical practice guidelines, policy documents, and relevant materials from private clinic websites and regional media sources. In addition, reference lists of included studies were hand-searched to identify further relevant publications.

2.2. Inclusion and Exclusion Criteria

Publications were considered eligible if they:

- Reported on TRD or novel/emerging treatments for TRD.
- Addressed healthcare delivery, implementation challenges, or mental health barriers relevant to GCC countries.
- Were published in English.

Exclusion criteria included:

- Single case reports.
- Studies unrelated to TRD or mental health.
- Articles with no relevance to clinical management or healthcare implementation in the GCC.

2.3. Data Extraction and Synthesis

Eligible studies were reviewed, and data were extracted regarding treatment modalities, healthcare models, advancements, and barriers to adoption in the GCC region. Findings were synthesized narratively, structured around (i) current TRD management practices, (ii) evidence and availability of novel treatments, (iii) socio-cultural, regulatory, and systemic implementation barriers, and (iv) recent advancements.

Given the narrative scope, no formal risk of bias or quality assessment tools were applied. Instead, evidence was critically appraised for relevance, methodological rigor, and applicability to the GCC context.

3. Findings

3.1. Novel Therapeutic Approaches for TRD: Mechanisms, Clinical Outcomes, and Regional Evidence

3.1.1. Ketamine and Esketamine for TRD

3.1.1.1. Mechanism of Action

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist traditionally used as an anesthetic, is a hydrosoluble aryl-cyclo-alkylamine that exists as a 1:1 racemic mixture of its isomers, esketamine ((S)-ketamine) and erketamine ((R)-ketamine) [14]. In recent years, it has gained recognition for its rapid and robust antidepressant effects in treatment-resistant depression (TRD) [15–17]. Unlike traditional antidepressants, which primarily target monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine [18], ketamine acts through the glutamatergic system by blocking NMDA receptors. This blockade halts tonic eukaryotic elongation factor 2 (eEF2) kinase activity, leading to a reduction in eEF2 phosphorylation, the rapid release of brain-derived neurotrophic factor (BDNF) translation, and activation of TrkB receptor signaling (Figure 3). These processes rapidly restore synaptic plasticity and promote structural changes in brain regions impacted by chronic stress and depression, such as the prefrontal cortex. Additionally, ketamine reduces inhibitory GABAergic signaling by transiently suppressing NMDA receptors on inhibitory interneurons, further enhancing glutamatergic activity and activating mammalian target of rapamycin (mTOR) signaling. These combined effects result in ketamine's rapid and sustained antidepressant benefits, often observable within hours to days, compared to the weeks required for traditional treatments. These effects are related to a

transitory increase in glutamate, which helps counteract the damage caused to neurons by long-term stress, promoting neuroplasticity and increasing connectivity in mood-regulatory circuits [19, 20]. Several studies have reported significant symptom relief following intravenous administration of ketamine [21]. While research indicates that ketamine's novel mechanism of action could transform MDD treatment, further studies are needed to optimize its safety profile, predict treatment response, and evaluate long-term effects [14].

Esketamine, the S-enantiomer of ketamine, similarly blocks the NMDA receptor and modulates glutamate activity. It is considered to be three to four times more potent than the R-enantiomer and exhibits faster pharmacodynamics. The S-enantiomer has a higher binding affinity to the NMDA receptor, offering stronger anesthetic and analgesic effects while causing less lethargy and cognitive impairment [22, 23]. Administered as a nasal spray, esketamine provides a less invasive alternative to intravenous ketamine, making it more practical for use in outpatient settings [24]. Furthermore, esketamine is metabolized more quickly in the body compared to ketamine, which results in a stronger pharmacological effect with only minor side effects. Esketamine also has a potent analgesic effect and minimal impact on breathing. Additionally, the anesthesia induced by esketamine is half that of ketamine [25].

3.1.1.2. Comparative Efficacy with Traditional Antidepressants

As compared in Table 1, ketamine and traditional antidepressants (SSRIs/SNRIs) differ significantly in their onset, mechanism, administration, and long-term effects. Ketamine acts rapidly, often within hours, by enhancing glutamate release and increasing BDNF levels, promoting synaptic repair [26]. Its effects last from days to weeks, requiring periodic treatments via IV, IM, or nasal spray in clinical settings. However, it carries risks of dissociation [27]., potential addiction, and high costs due to limited insurance coverage [28, 29].

In contrast, SSRIs/SNRIs take weeks to months for noticeable effects by gradually increasing serotonin (and norepinephrine for SNRIs) through presynaptic reuptake inhibition [30]. They require daily oral dosing, are widely accessible, and generally covered by insurance. While side effects include fatigue, weight gain, and sexual dysfunction, long-term risks are better understood compared to ketamine [31].

3.1.1.3. Clinical Evidence and Outcomes

Table 2 summarizes the key clinical trials assessing the efficacy of ketamine for TRD. The first clinical study on arketamine for TRD patients was carried out in 2020 by Leal at al., followed by numerous global studies consistently demonstrating the effectiveness of ketamine for TRD [32]. In this initial open-label pilot trial for TRD, seven patients received a single intravenous infusion of arketamine (0.5 mg/kg), resulting in a significant reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) scores from a mean of 30.7 to 10.4 after 24 hours, with a mean difference of 20.3 points (95% CI: 13.6–27.0; $p < 0.001$) [32]. Additionally, a study conducted by Chen et al found that 40-minute intravenous ketamine infusions (0.5 mg/kg) administered on days 1 and 4 produced a response rate of 63.3% [33]. Similarly, Phillips et al. reported that after six repeated infusions, 59% of participants achieved a response, defined as a ≥50% reduction in the total MADRS score, while 23% reached remission, indicated by a MADRS score of ≤10 [34]. A study involved 403 patients with TRD across five clinical sites in the United States. Results showed that 55.4% of patients treated with ketamine achieved a clinical response, compared to 41.2% of those treated with ECT, a significant difference of 14.2% (95% CI: 3.9–24.2; $p < 0.001$) [35]. Previous studies recommend a dose of 0.5 mg/kg for optimal efficiency [36, 37], lower doses have been found to be less effective [38]. In recent years, there has been a growing interest in the use of ketamine for treating suicidal ideation. Multiple studies have shown that multiple infusions of ketamine were rapidly effective in reduction of suicidal ideation [39, 40]. Additionally, a Meta-analysis found that a single intravenous infusion of ketamine produced a rapid reduction in suicidal ideation, with its anti-

suicidal effect becoming apparent within 24 hours [40]. However, in the Gulf region, there is a significant shortage of clinical trials. The limited evidence available, primarily from small-scale studies conducted in the UAE and Saudi Arabia, shows promise but requires further validation through larger, region-specific trials.

Esketamine has been the subject of more large-scale and late-phase trials for TRD than arketamine [23]. Table 3 tabulates the key clinical trials assessing the efficacy of esketamine for TRD. A large study involving 297 patients with TRD found that ongoing treatment with esketamine nasal spray delayed the time to relapse when compared to a placebo after 16 weeks of treatment [41]. In another randomized, multicenter, double-blind, placebo-controlled study conducted by Singh et al. 30 patients with TRD were enrolled. Participants received either 0.2 or 0.4 mg/kg intravenous (IV) infusion of esketamine or a placebo over 40 minutes. Those treated with esketamine (both dosing regimens) exhibited clinical improvements, as measured by MADRS scores, compared to the placebo group by the second day after treatment [42]. Furthermore, Correia-Melo et al. found that 29.4% of patients treated with esketamine achieved remission within 24 hours, as measured by MADRS scores, in a trial involving 63 patients with TRD who received a single 0.25 mg/kg dose [43].

Clinical data reinforce esketamine's efficacy, with studies indicating rapid symptom improvement and generally positive patient responses. However, challenges such as side effects and financial inaccessibility continue to limit its broader adoption in Gulf region [21].

3.1.1.4. Side Effects, Monitoring, and Safety

Esketamine shows significant promise in treating TRD, but it comes with several side effects that require close monitoring. Commonly reported side effects include headache, dissociation, dizziness, rewarding effects, abuse liability, and cognitive dysfunction [41]. More concerning issues include transient blood pressure elevation and the potential for abuse. As a result, patients usually undergo monitoring in a clinical setting for

at least two hours after treatment to ensure safety observe for any emergent side effects [40]. Moreover, healthcare providers should regularly assess patients' mental status and vital signs to effectively manage these risks and optimize the treatment outcomes of esketamine.

3.1.2. Repetitive Transcranial Magnetic Stimulation (rTMS) for TRD

3.1.2.1. Mechanism of Action

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that has gained recognition as a promising treatment for depression. By targeting the left dorsolateral prefrontal cortex (L-DLPFC), rTMS uses electromagnetic impulses to modulate neural activity in brain regions associated with mood regulation. This modulation promotes neuroplasticity (Figure 4), preserves residual neural functions, and facilitates skill acquisition, thereby alleviating depressive symptoms [44]. Unlike pharmacological treatments, rTMS does not involve medication, offering an alternative therapeutic approach for individuals with depression [45].

3.1.2.2. Global and Regional Efficacy Evidence

Table 4 shows the key differences in rTMS adoption between global regions (Western countries) and GCC countries. Globally, rTMS has become an established treatment for TRD, with high response and remission rates reported in numerous studies [46, 47]. The therapy has been adopted by many of the Western health care systems, with the National Institute for Health and Care Excellence (NICE) of the UK, for example, recommending rTMS in the treatment of depression following failure of other treatments. There is widespread availability of rTMS in both public and private healthcare settings in western countries.

Most modern rTMS trials have enrolled patients who did not respond to first-line antidepressant therapies [48, 49], highlighting its critical role in managing TRD. In these regions, adoption is influenced by a stable regulatory environment and insurance coverage that makes it relatively accessible and accepted within mental health practices [50, 51]. According to Thompson et al., the response and remission rates among TRD patients treated with rTMS exhibit considerable variability, ranging from 39.5% to 70% for response rates and from 16.6% to 76.9% for remission rates [52].

Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) is a novel approach to TMS, recently been approved by the FDA for treating TRD [53]. It utilizes MRI-guided precision to identify the specific brain region for stimulation and employs an accelerated schedule of multiple brief TMS sessions daily over a five-day period [54]. However, the requirement for structural and/or functional MRI substantially increases treatment complexity and overall cost [55], which may limit its scalability and routine clinical implementation, particularly in resource-constrained healthcare settings such as those in the GCC.

Intermittent Theta-Burst Stimulation (iTBS) is an advanced form of rTMS approved by Health Canada for treating TRD. This non-invasive brain stimulation technique involves repetitive stimulation of a targeted brain region to strengthen neural connections and modulate communication between brain areas. A typical iTBS regimen consists of daily sessions delivering approximately 600 pulses over six weeks. Personalized Accelerated iTBS (PaiTBS), a novel therapeutic approach for TRD, demonstrates robust remission rates while maintaining safety, efficacy, and feasibility [56–58]. This protocol leverages functional connectivity Magnetic Resonance Imaging (fcMRI) to guide stimulation targeting the L-DLPFC region most functionally anticorrelated with the subgenual cingulate cortex (sgACC) in each individual. PaiTBS has shown significant promise, with enhanced response rates of 71% and remission rates of 57%, outperforming non-personalized aiTBS and

traditional iTBS [59]. However, the reliance on fcMRI adds considerable financial and infrastructural demands [55], limiting its affordability for both institutions and patients.

rTMS has gradually gained acceptance in GCC countries, through its adoption rate remains lower than in Western countries. Challenges to its broader implementation include regulatory and cultural barriers, as well as the high costs associated with advanced neuroimaging-guided protocols and limited funding for advanced mental health treatments. For instance, while some medical centers in Saudi Arabia and UAE now provide rTMS, its availability remains limited to a few centers, and many insurance providers do not cover the treatment, further restricting access to the patients. Gulf countries are still trying out regulation and public acceptance of rTMS as a standard therapeutic option [60].

The adoption of rTMS in the Gulf states requires regional-based research to assess its long-term treatment efficacy and suitability for the local population. This effort should be complemented by training programs for mental health professionals and the development of regulatory frameworks to integrate rTMS into Gulf health systems. The steps, so far, in GCC toward rTMS shows a general trend in using mental health treatments; this is bound to integrate within the foreseeable future.

3.1.2.3. Efficacy of rTMS in Treating TRD

Clinical trials worldwide have demonstrated that rTMS is indeed an effective treatment for TRD. A study conducted in China by Wang et al., involving 119 TRD patients treated with 15 Hz stimulation over the L-DLPFC, reported a response rate of 57.98% immediately after 5 days of treatment [61]. A scoping review of randomized controlled trials (RCTs) conducted across multiple regions, North America (9 studies), Europe (5 studies), Asia (2 studies), and Australia (1 study), revealed that 16 out of 17 studies confirmed the efficacy of rTMS treatment

for TRD [62]. Real world outcomes of rTMS within the Japanese demonstrate its efficacy in treating TRD. Among 102 patients with TRD who received rTMS over the L-DLPFC, 43.1% achieved remission [63].

Promising results have emerged from initial studies in the Gulf region, showing significant symptomatic improvements in patients with depression. One study conducted at the American Center for Psychiatry and Neurology in Abu Dhabi, UAE, reported high response and remission rates with rTMS treatment for MDD. Specifically, the study found a 58% response rate and a 30% remission rate. However, the study's small sample size and lack of long-term follow-up limit the ability to generalize these findings [64].

3.2. Adoption and Regional Advances in the GCC

3.2.1. Integrating New Treatments into Public Health Systems

Recent advancements in mental health care across GCC countries demonstrate a growing but uneven adoption of advanced treatments for TRD, including rTMS and esketamine. Following regulatory approvals of esketamine by the U.S. Food and Drug Administration and the European Medicines Agency in 2019 [14], several GCC countries have introduced these modalities into clinical practice. Based on our targeted survey of publicly identifiable clinical services, the UAE currently has the highest concentration of active rTMS and esketamine providers, predominantly within private psychiatric and hospital settings. Furthermore, the UAE became one of the first countries worldwide to adopt esketamine [65], offering it in private mental health settings [29].[66][67][68] Qatar and Saudi Arabia show emerging but more limited availability, with rTMS and/or esketamine offered primarily through major tertiary hospitals and specialized mental health centers. In contrast, Oman, Bahrain, and Kuwait currently have only a small number of identified centers providing these interventions. The clinics and institutions actively delivering rTMS and esketamine across GCC countries are summarized in Table 5.

3.2.2. Regional and Global Research Collaborations

Global collaborations have played a crucial role in advancing the adoption of ketamine, esketamine, and rTMS throughout the Gulf. For instance, workshops in the United States, held in cooperation with the FDA to address the wider ranges of ketamine, such as off-label uses in depression and pain. These efforts have highlighted the need for further research and established avenues for future international collaboration [69].

Such institutional collaborations between institutions of the Gulf and global health organizations could help expedite research into optimal dosing strategies, long-term safety, and effectiveness in various populations. Moreover, this integration of research would address specific cultural and environmental factors that shape mental health issues in the region.

3.2.3. Training and International Collaborations

GCC countries are experiencing a growing demand for digital health professionals with multidisciplinary expertise in healthcare, informatics, and information technology to support advanced mental health services, including telepsychiatry, outcome monitoring, and data-driven implementation of novel TRD treatments such as rTMS and esketamine. These professionals are essential for enabling remote assessments, continuity of care, and integration of digital tools within national mental health systems. However, despite increasing investments in training programs and regional initiatives, a persistent gap remains between academic preparation and practical workforce needs, with professional roles and career pathways still poorly defined [70]. Recent international initiatives emphasize the importance of advancing training in emerging therapies. For instance, in June 2024, a collaborative training program was held involving the US FDA and the Reagan-Udall Foundation for the FDA. This hybrid public workshop, titled "Understanding Current Use of Ketamine for Emerging Areas of Therapeutic Interest," brought together clinicians, researchers, and federal partners to discuss the potential applications of ketamine in emerging therapeutic areas. The event covered various topics such as the scope

of ketamine use, including approved and compounded products, safety concerns, and the promotion through online and accessibility of ketamine [69]. Psychiatry professionals from GCC countries have shown increasing interest in participating in such workshops to enhance their knowledge and practices. Partnerships with international countries that have established professional expertise in advanced treatments can serve as a valuable platform for collaboration to enhance the professional development of GCC countries. For instance, Emirates Hospital Group in Dubai offers advanced rTMS treatment at the Emirates Psychiatry Clinic in collaboration with The London Psychiatry Centre [71].

3.3. Societal and Structural Barriers to Adoption

3.3.1. Safety Challenges

Despite its therapeutic effectiveness, the use of ketamine in the Gulf has several challenges. One of the most significant issues is regulatory: ketamine is classified as a controlled substance in many GCC countries, complicating its availability and raising concerns about misuse and addiction [72, 73]. There are significant concerns regarding addiction, as chronic ketamine use has been linked to dependency and an increased risk of drug abuse, making long-term use a major issue for patients [74].

3.3.2. Sociocultural factors

Sociocultural factors GCC countries can influence the acceptance and utilization of advanced treatments for TRD, such as rTMS and ketamine/esketamine therapies. Cultural and religious interpretations of mental illness, stigma surrounding psychiatric care, and preferences for gender-concordant providers may reduce help-seeking behavior and delay referral to specialized TRD services [75]. In addition, language and communication barriers, particularly in healthcare systems staffed predominantly by non-Arabic-speaking clinicians [76], may further complicate patient engagement and adherence to complex, repeated interventions required for TRD

management. Together, these barriers highlight the need for culturally sensitive, patient-centered approaches when implementing advanced TRD treatments in the GCC region.

3.3.3. Regulatory and Policy Hurdles in the GCC

Western countries have strong regulatory frameworks that ease the approval and implementation of advanced treatments like rTMS [83, 84]. However, the pattern of adoption across the GCC appears fragmented, reflecting broader systemic challenges in mental health infrastructure and regulatory harmonization across the region. Despite recent advancements, regulatory barriers and infrastructure limitations continue to hinder the widespread implementation of esketamine and ketamine-based treatments across the region [85]. Most GCC nations have outdated or inadequate mental health legislations, which provides limited patient rights protection, lack of anti-discrimination policies, and offers little clarity regarding involuntary treatment. This regulatory gap affects ethical and patient-centered care, posing challenges to the standardized and effective implementation of mental health service [75, 86].

Although some progress has been made in the Saudi Arabia and Kuwait with the introduction of specific mental health laws, the standards still fall short of international benchmarks. As a result, existing regulations do not fully protect patient rights or ensure comprehensive care within the mental health sector. Additionally, regulatory challenges hinder the approval and use of innovative treatments, such as ketamine. Due to its classification as a controlled substance in many of the region’s countries, the use of ketamine as an antidepressant is tightly regulated. For instance, in Saudi Arabia, ketamine is included in the Narcotics and Psychotropic Substances Law [87], restricting its access to specialized authorized centers, which complicates its application in mental health treatment. These regulatory challenges highlight the need for broader mental health policies in the Gulf, particularly regarding the ethics, accessibility, and effectiveness of mental health treatments.

3.3.4. Cost and Healthcare Infrastructure

The medical costs associated with TRD include outpatient physician visits, medications, hospitalizations, monitoring, adverse events, and other treatments. The direct financial burden of TRD in 2020 was estimated at 3,994 million USD for Saudi Arabia, 982 million USD for Kuwait, and 670 million USD for the UAE over a one-year period. Additionally, productivity loss due to TRD ranged from 32% to 43%.

Access to healthcare and the associated costs in the GCC countries present significant challenges. While mental health services are generally free for citizens, expatriates and migrant workers, who represent a large portion of the population, have limited access. Moreover, high out-of-pocket costs and inadequate insurance coverage for mental health care create a significant barrier, particularly for non-citizens.

The cost of esketamine is a key factor limiting its accessibility. Initial treatment can cost between $4,700 and $6,700 in the first month, with ongoing monthly expenses ranging from $2,300 to $3,500. These expenses are driven by both the price of the drug and additional clinic fees. Esketamine must be administered under medical supervision due to potential adverse side effects, such as dizziness, nausea, and dissociation. Patients are required to stay in the clinic for at least two hours after each dose for monitoring before returning home [28].

While esketamine represents a significant breakthrough in the treatment of TRD in the Gulf region, its high costs and limited insurance coverage often restrict access, particularly to private clinics and select governmental hospitals where it is available. To exploit the full therapeutic potential of esketamine, the Gulf countries must overcome economic and regulatory barriers, making the treatment more accessible and affordable for individuals with urgent mental health needs [28, 29].

In the UAE, rTMS treatments are available in high-end clinics such as Emirates Hospital in Dubai. These facilities, often in collaboration with centers like The London Psychiatry Centre, offer rTMS for a range of conditions,

including depression, OCD, and anxiety. However, these treatments are typically not covered by insurance, requiring patients to bear the full cost [71]. Similarly, rTMS is becoming available in special centers in Saudi Arabia and some other Gulf countries. However, its integration into public healthcare systems remains limited. Without insurance coverage, the treatment remains unaffordable for much of the population.

Despite substantial healthcare improvements, GCC countries' health care spending remains below the international average, which may hinder the development of comprehensive mental health care programs [86, 88].

3.4. Future Directions for TRD Management in the GCC

3.4.1. Expanding Adoption and Clinical Integration

Given the positive preliminary outcomes associated with novel TRD therapies, their adoption in the Gulf region is likely to grow as mental health infrastructure continues to develop. Esketamine and rTMS are currently administered in controlled clinical settings, but future innovations may make these therapies more accessible, cost-effective, and viable for use in primary care. Standardized protocols for administration, monitoring, and follow-up are essential to ensure safe and effective integration into national healthcare systems. Consistent provider training, the establishment of clear clinical protocols, and the revision of current TRD treatment guidelines are essential to ensure safe and equitable integration into national healthcare systems [1, 89].

3.4.2. Research and Regional Collaboration

Given the novelty and rapidly evolving nature of this field, there is an immediate need for systematic reviews and other forms of rigorous evidence synthesis to evaluate the safety, efficacy, and real-world feasibility of these treatments within the GCC context. Generating high-quality, context-specific evidence will be essential to inform clinical guidelines, support policymaking, and ensure the responsible and equitable implementation

of these innovative therapies. In addition, greater cross-country collaboration and investment in public-sector adoption pathways are likely needed if these novel therapies are to make a meaningful impact on the region's burden of TRD. Gulf countries could engage with universities and international research centers to establish clinical trials and data-sharing agreements, enabling the localized implementation of these treatments. In addition, such collaborations could provide training for mental health professionals, enhancing their capacity to administer these therapies safely and effectively, ultimately leading to improved patient outcomes across the region.

3.4.3. Policy and Healthcare System Initiatives

The significant clinical and economic burden of TRD in GCC countries requires policy interventions to improve access to innovative treatments. Research has shown that TRD-related healthcare costs, including indirect societal costs, are approximately three times higher than those associated with MDD [12]. Given this substantial burden, policy measures should focus on improving screening, enhancing healthcare integration, reducing stigma, leveraging genetic testing, and adopting digital health solutions.

3.4.4. Education, Public Awareness, and Community Engagement

Education and public awareness are essential for successfully integrating rTMS into mainstream healthcare practices [93, 94]. Public awareness campaigns and mental health literacy programs would need to accompany the rollout of these therapies to overcome the existing stigma and educate the population about their benefits and risks. Cultural perceptions of mental illness often hinder patients from seeking help, making community engagement essential. Initiatives like #NoShame public awareness campaign in Kuwait are making progress by challenging this stigma and promoting open discussion about mental health [75]. As well as involving patients' families and social circles in treatment planning can further enhance adherence, reduce isolation, and enhance overall treatment outcomes [92].

4. Conclusions

Treatment-resistant depression remains a critical public health challenge in the GCC, where cultural, economic, and systemic barriers continue to limit access to effective care. Novel therapies such as ketamine, esketamine, and rTMS have demonstrated promising mechanisms of action and clinical effectiveness, with esketamine now administered in controlled clinical settings in leading psychiatry clinics in Dubai and Qatar, and rTMS expanding across mental health facilities, particularly through initiatives led by Hamad Medical Corporation. Region-specific strategies, including Qatar's national mental health plans, are facilitating the structured adoption of these therapies.

Despite these advances, widespread integration of innovative treatments remains limited by cost, accessibility, and societal stigma. Addressing these challenges requires coordinated efforts among governments, healthcare providers, and researchers to strengthen infrastructure, expand professional training, and raise public awareness. Embedding these treatments into national health policies, supported by region-specific research, will be essential to ensure equitable access and optimizing patient outcomes.

By building on early successes and addressing persistent barriers, the GCC has the opportunity to lead a paradigm shift in TRD management, improving quality of life for individuals and advancing the regional mental health agenda.

Declarations

Ethics approval and consent to participate

This study did not require ethical approval, because this review was based on publicly available scientific literature.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

Mohammed A. Alhassan was responsible for conceptualizing the study, conducting the literature review, analyzing the findings, and writing the manuscript.

Acknowledgments

Author extends the appreciation to the Deanship of Postgraduate Studies and Scientific Research at Majmaah University for funding this research work.

Authors' information (optional)

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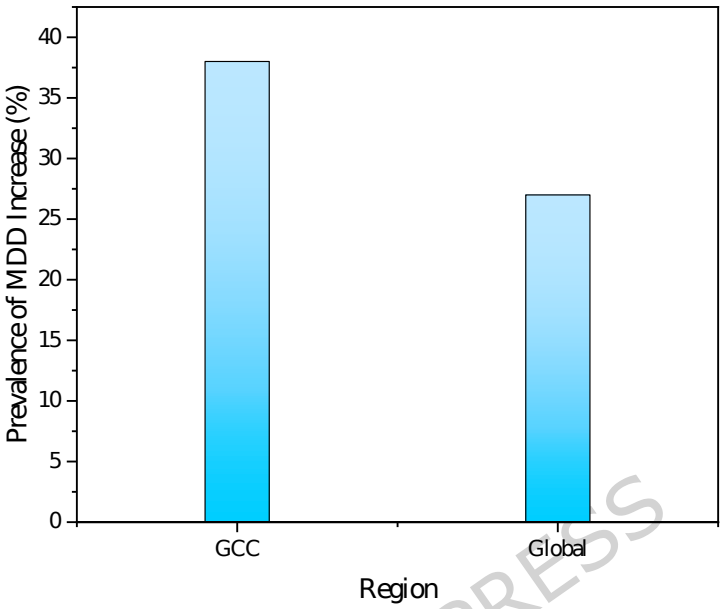

Figure 1. Prevalence of MDD in GCC post-COVID in comparison to the global average.

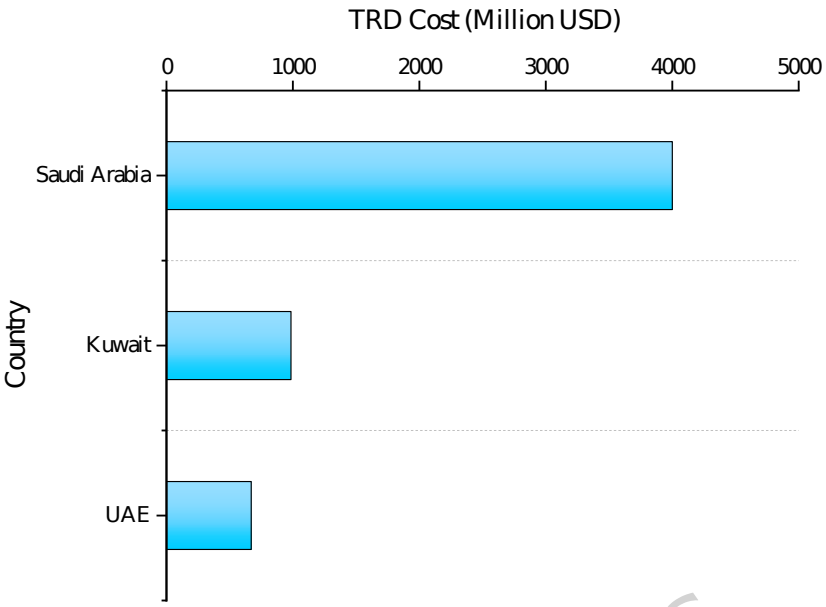

Figure 2. Comparison of the economic burden of TRD in GCC.

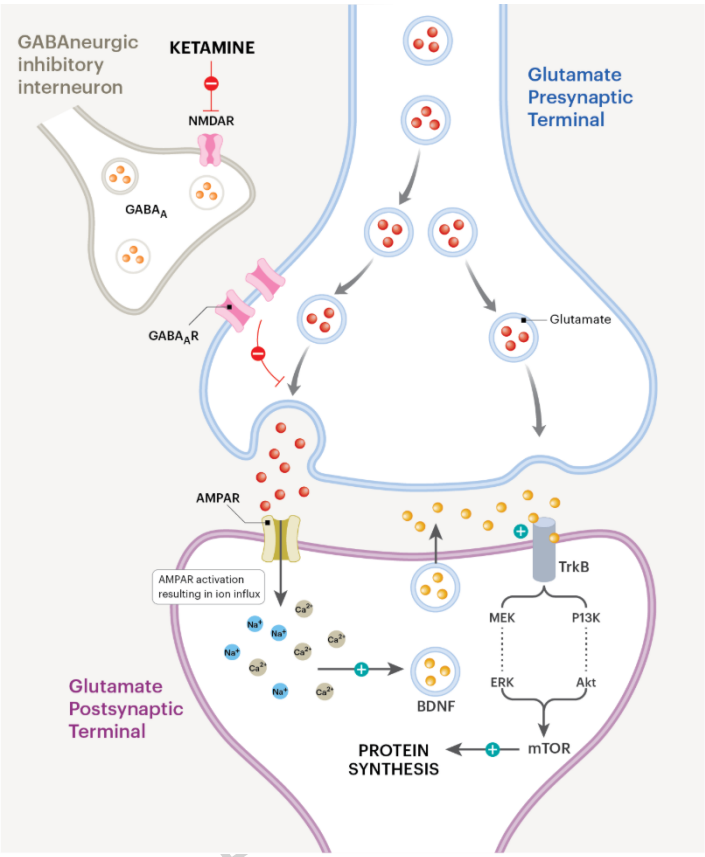

Figure 3. Proposed mechanism of ketamine as an antidepressant.

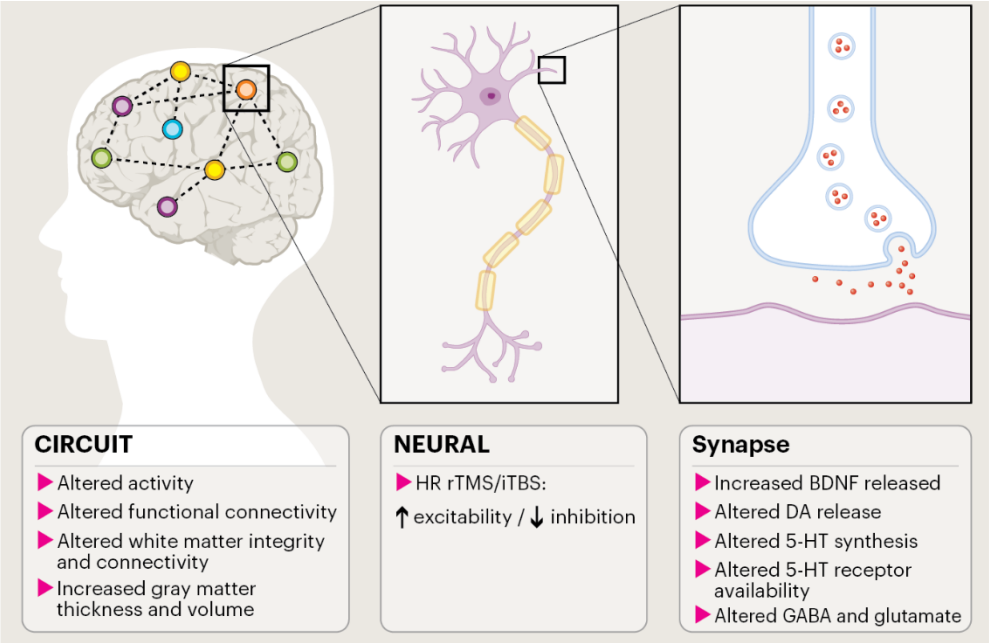

Figure 4. Neuroplasticity effects of rTMS.

Table 1. Comparison of ketamine and traditional antidepressants (SSRIs/SNRIs in terms of onset of action and side effects.

Aspect	Ketamine	Traditional Antidepressants (SSRIs/SNRIs)
Onset of Action	Often works within hours after administration [26].	Takes weeks to months for noticeable effects [30].
Mechanism	Enhances glutamate release and increases BDNF levels, promoting rapid synaptic repair [19, 20].	Increases serotonin (and norepinephrine for SNRIs) by inhibiting presynaptic reuptake, leading to gradual changes in brain chemistry [94].
Duration of Effects	Effects can last from days to weeks, requiring periodic treatments [95].	Requires daily dosing for long-term effectiveness [96].
Administration	Given via intravenous (IV) infusion, intramuscular (IM) injection, or nasal spray in a clinical setting [97].	Taken orally as daily pills [96].
Common Side Effects	Dissociation, dizziness, nausea, dysgeusia, and vertigo [27].	Flatulence, somnolence, memory impairment, decreased concentration, yawning, fatigue, dry mouth, weight gain, light headedness, and sweating [31].
Long-Term Use Risks	Potential for addiction and cognitive impairments with repeated use; long-term effects are not fully understood [27].	The most reported long-term side effects are constitutional symptoms, sexual dysfunction, neuropsychiatric symptoms, and gastrointestinal symptoms [31].

Cost & Accessibility	Expensive; not covered by most insurance plans; requires specialized medical facilities [28, 29].	More affordable and widely prescribed; covered by most insurance plans [98].

Table 2. Summary of key clinical trials assessing the efficacy of ketamine for TRD.

Reference	Country	Sample Size	Ketamine Dose and Administration	Outcome
[32]	Brazil	7	Single IV infusion (0.5 mg/kg)	Mean MADRS score reduced from 30.7 to 10.4 after 24 hours ($p < 0.001$)
[33]	Taiwan	49	40-min IV infusions (0.5 mg/kg) on Days 1 & 4	63.3% response rate
[99]	Canada	41	Six repeated IV infusions (0.5 mg/kg)	59% response rate, 23% remission (MADRS ≤10)
[35]	United States	403	IV ketamine vs. ECT	55.4% response with ketamine vs. 41.2% with ECT ($p < 0.001$)
[39]	United States	80	Single IV infusion (0.5 mg/kg) vs. midazolam	Greater SSI score reduction, higher response rate (55% vs. 30%), short-lived side effects,

				sustained improvement for up to 6 weeks.

Table 3. Summary of key clinical trials assessing the efficacy of esketamine for TRD.

Reference	Country	Sample Size	Esketamine Dose and Administration	Outcome
[100]	United States, Europe, Brazil	297	Esketamine nasal spray, ongoing treatment for 16 weeks	Delayed time to relapse compared to placebo.
[42]	United States	30	0.2 or 0.4 mg/kg IV infusion over 40 min	Clinical improvement in MADRS scores by day 2.
[43]	Brazil	63	Single 0.25 mg/kg IV infusion	29.4% achieved remission within 24 hours (MADRS scores).

Table 4. Key differences in rTMS adoption between global regions (Western countries) and GCC countries.

Factor	Global (Western Countries)	GCC Countries
Adoption Level	Widely adopted in healthcare systems	Limited adoption, available in few centers
Regulatory Status	Approved by NICE (UK), FDA (USA), Health Canada	Still under regulatory evaluation
Insurance Coverage	Often covered by insurance	Mostly not covered, limiting access
Treatment Availability	Available in both public and private healthcare	Available in select medical centers
Patient Acceptance	Well-accepted as a non-invasive alternative	Lower acceptance, preference for traditional treatments (e.g., ECT, medication)

Advanced rTMS Approaches	SAINT, iTBS, PaiTBS widely researched and applied	Limited regional research and application
Challenges	Variability in response rates, cost concerns	Regulatory barriers, cultural hesitancy, lack of infrastructure

Table 5. Publicly identifiable TMS/rTMS and ketamine-based treatment centers in GCC.

Country	Clinic / Institution	Treatment type	References
UAE	American Wellness Center (Dubai)	rTMS	[1]
	Novomed (Dubai, Abu Dhabi, Al Ain)	TMS	[2]
	Mediclinic Deira (Dubai)	TMS	[3]
	German Neuroscience Center (Dubai)	TMS	[4]
	Journey Wellness Centre (Dubai)	TMS	[5]
	Emirates Hospital (Dubai)	rTMS	[6]
	Camali Clinic (Dubai)	Esketamine	[7]
	Reem Hospital (Abu Dhabi)	Esketamine	[8]
	The Valens Clinic (Dubai)	Esketamine	[9]
Qatar	The View Hospital (Doha)	rTMS	[10]
	Hamad Medical Corporation – Mesaieed General Hospital	TMS	[11]
	Hamad Medical Corporation – Mesaieed General Hospital	Esketamine	[11]
Saudi Arabia	Eradah Mental Health Complex	Esketamine	[12], [13]
	King Khalid University Hospital	Esketamine	[14]
	Dr. Erfan & Bagedo General Hospital	rTMS	[15]
	Medicare Clinics (Riyadh)	rTMS	[16]
Kuwait	MindWell	rTMS	[17]
Bahrain	Sulwan Psychiatric Hospital	Esketamine	[18]
Oman	Medical Care Complex	TMS	[19]

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