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Review

Latin American consensus recommendations for the management and treatment of patients with treatment-resistant depression (TRD)

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ABSTRACT

Despite the abundance of literature on treatment-resistant depression (TRD), there is no universally accepted definition of TRD, and available treatment pathways for the management of TRD vary across the Latin American region, highlighting the need for a uniform definition and treatment principles to optimize the management of TRD in Latin America.

Methods: Following a thematic literature review and pre-meeting survey, a Latin America expert panel comprising 14 psychiatrists with clinical experience in managing patients with TRD convened and utilized the RAND/UCLA appropriateness method to develop consensus-based recommendations on the appropriate definition of TRD and principles for its management.

Results: The expert panel agreed that 'treatment-resistant depression' (TRD) is defined as 'failure of two drug treatments of adequate doses, for 4–8 weeks duration with adequate adherence, during a major depressive episode'. A stepwise treatment approach should be employed for the management of TRD – treatment strategies can include maximizing dose, switching to a different class, and augmenting or combining treatments. Nonpharmacological treatments, such as electroconvulsive therapy, are also appropriate options for patients with TRD.

Conclusion: These consensus recommendations on the operational definition of TRD and approved treatments for its management can be adapted to local contexts in the Latin American countries but should not replace clinical judgement. Individual circumstances and benefit–risk balance should be carefully considered while determining the most appropriate treatment option for patients with TRD.

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Introduction

Treatment resistant depression (TRD) is defined as a failure to achieve an adequate, or clinically meaningful, response to an adequate trial of antidepressant therapy. Treatment resistance is common among people diagnosed with major depressive disorder (MDD). In fact, it is estimated that approximately 50% of individuals with MDD do not respond to their first antidepressant medication.[1] The likelihood of responding to any given treatment decreases as the number of previously failed trials increases.[2]

Moreover, TRD is associated with significant impairments in psychosocial functioning.[3] Considering the large proportion of individuals with MDD who experience treatment resistance, and the substantial burden TRD places on patients, their families, and society, an understanding of treatment resistance and potential treatments is critical for clinicians and researchers in psychiatry with special focus in our region.

In this consensus paper, we will review the main approaches to defining treatment resistance, and the accompanying factors to consider when diagnosing. The different staging approaches that have been proposed to classify levels of treatment resistance were considered among our group of experts.[4] However, their use in the real-world clinical setting of our region was considered impractical. Prevalence of TRD and risk factors associated with the development of TRD will also be addressed. Finally, we will consider the different treatments for TRD: pharmacotherapy, psychotherapy, and neuromodulation. In practice, these treatment strategies are often used in combination; however, we will discuss each one individually. All approved pharmacotherapies will be discussed in terms of monotherapy and polytherapy.

Methods

A panel of Latin American experts in psychiatry specialized on diagnosis and treatment of patients with TRD worked through the internet between November 2020 and March 2021 to make consensus recommendations about management and treatment of TRD in Latin America. To achieve consensus, the RAND/UCLA methodology for reaching formal consensus was used.[5] As a consensus method, the purpose is to formalize the degree of agreement among experts by identifying and selecting, through iterative ratings with feedback, the proposals on which experts agree and those points on which they disagree or are undecided. The guideline methods are subsequently based on agreement proposals. As a practice guideline method, the purpose is to draft several recommendations that address the most relevant questions of interest in clinical practice.[6] This is a rigorous and explicit method based on involvement of user representatives and professionals in the field to which the guidelines relate, and on use of an external peer review phase, transparency, independence of development and management of conflicts of interest.

The first step in the process consisted of inclusion of working group experts. Experts were selected based on their experience in managing patients with TRD in different regions of Latin America. After the working group had been formed, the procedure consisted of the following phases:

Systematic review and synthesis of the literature: A systematic search of the literature, without language restrictions, was carried out on PUBMED for the period 1990 up to December 2020. The search terms were "TRD", together with the modifiers "treatment", "diagnosis", "depression", "unipolar", "pharmacotherapy", "approved", "neurostimulation", "psychotherapies", "response", "remission", "staging", "consensus" and "guidelines". Relevant clinical papers were circulated for review and summarization so that they could respond to the proposals and recommendations for discussion.

Proposal list: A list of different proposals was submitted to the group in the form of a questionnaire.

Rating: The statements on which the members of the group agreed were identified. For those statements in which there was no agreement, a virtual meeting with the presence of the members of the group was organized on February 12th, 2021. Another round of votes with previous feedback and based on the published evidence was conducted. This phase concluded with selection of the proposals on which there was a consensus within the group. Existence of a consensus was defined as a situation in which 70% of the respondents agreed, and lack of consensus, in which ≥30% disagreed. The rules for rating and analysis of the scores were defined at the outset and were communicated to the group, prior to the first round. At every stage of the rating phase, members of the consensus group were able to comment about their response to each statement. All the comments made were also analyzed in a qualitative manner to include comments in the next rating phase.

Finalization: A report was drafted on a shared Google doc, drawing together all scores and comments from all the experts. The draft was circulated electronically during 14 days for further comments and suggestions. A final version of the manuscript with the consensus recommendations and treatment guidelines were approved by the group before its submission to a peer review journal.

Defining treatment-resistant depression

Achieving a widely accepted, operational definition of "treatment-resistant depression" (TRD) has been a challenge for researchers and clinicians for many years. This has created a barrier to comparing treatment studies and managing TRD. In most cases TRD is defined as the failure of an individual with MDD to achieve an adequate response to an adequate trial of antidepressant therapy during a major depressive episode (MDE). Although what constitutes both an adequate response and an adequate trial are still controversial. In fact, neither the Diagnostic and Statistical Manual of Mental Disorders (DSM-5),[7] nor the International Classification of Disease 11th Revision (ICD-11),[8] include TRD as a diagnosis. In a systematic review, 155 different definitions for TRD were identified.[9] The two most frequently applied definitions are based on the number of medication/treatment methods failed or the use of a staging model.[9]

"Adequate response" is typically defined as a 50% or greater reduction in depressive symptoms,[10] based on repeated measures using a depression rating scale such as the Hamilton Depression Rating Scale (HAM-D)[11] or Montgomery-Asberg Depression Rating Scale (MADRS).[12] TRD can be classified as having never achieved an adequate response to an adequate antidepressant trial, or as having relapsed after achieving an adequate response.[9,10] The group of experts achieved agreement on recommending the following tools in the daily practice for the management of patients suffering from major depressive episodes, ranked on decreasing order of preference: a self-rated scale of depression severity (BDI or QIDS-SR), a clinician-rated scale of depression severity (MADRS, HAM-D, or QIDS), a suicide rating scale (C-SSRS or Beck Suicide Ideation Scale) and a hypomania rating scale (Angst, MDQ, HCL-32).

There is no consensus on what constitutes an "adequate trial", particularly regarding classes of antidepressant tried, adequate dose and duration of the pharmacological trial, and even the definition of failure.[9,13,14] However, there are some agreed upon aspects. Firstly, the therapy must be one that has proven efficacy as well as being formally approved by the corresponding drug international and/or local health administration. The antidepressant medications

must also be taken at a stable and sufficient dose for a period of time deemed adequate to achieve a therapeutic effect.[14–18] There was agreement on this group of experts that the optimal minimum duration of the antidepressant treatment, once the target dose has been obtained, to judge the clinical efficacy in the treatment of unipolar depressive episode, should be four to eight weeks.

We also found some disparity in the literature about the number of different types of antidepressants that should be tried before a depressive episode is classified as treatment resistant. In clinical research, inclusion criteria typically require participants to have failed ≥2 different antidepressant therapies, sometimes stipulating different classes of antidepressants.[19] The majority of TRD definitions only consider failure to monotherapy; and do not account for psychotherapy, adjunctive pharmacotherapy, or neuromodulation techniques.[9,20,21] For our group of regional experts, and in line with the vast majority of the proposals on the literature, we consider that the failure of two pharmacological treatments of adequate duration and dose corresponds to the definition of a treatment resistant depressive episode.

Prevalence

Approximately 40–50% of individuals with MDD do not respond to their first prescribed antidepressant treatment,[1,2,22] and 20–30% do not respond to at least two treatment trials.[2,23] These findings have been replicated in different countries and continents, including our region.[3] The highest rates of TRD are reported in academic/tertiary care settings, followed by inpatient psychiatry units, outpatient units, and primary care settings.[1] The likelihood of responding to an antidepressant decreases with each additional antidepressant trial. While an individual's likelihood of responding to their first antidepressant is 50–60%, 70% of patients who fail one trial will fail a second, and 80–85% of patients will fail a third or fourth trial when they fail to respond to previous trials.[1,2,22] According with the findings from the review literature review and the consensus from our group of regional experts, we consider that the following features of the current depressive episode could be predictive of a risk of treatment resistance (ranked on descending order): illness severity/presence of psychotic symptoms, total duration of the episode, total duration untreated of the episode, onset during perimenopause period, and presence of marked anxious symptoms.

Several studies demonstrated that individuals requiring multiple stages of treatment are more likely to relapse: the relapse rate is 40% after four months if a patient responded to their first antidepressant trial, but increase to 55% if two treatments were tried.[2] Reported relapse rates among individuals requiring three to four trials are approximately 65–70%.[2]

Diagnosis and differential diagnosis

When a patient presents with resistance to an antidepressant, the recommended first treatment approach is optimization[15]: usually increasing (but occasionally decreasing) the dose of the current antidepressant for six to twelve weeks.[14,24] This may involve increasing to "supratherapeutic doses," especially if the patient has required high doses of other medications in the past, or has demonstrated good tolerability and partial response to the drug in question.[24] If drug optimization is unsuccessful, clinicians should attempt to rule out other potential causes for the persistence of an MDE despite an adequate therapeutic trial. Before confirming a diagnosis of TRD, and potentially switching or adding medication, drug adherence and pharmacokinetic factors, as well as medical and psychiatric comorbidities, should be assessed.

There are many factors that may contribute to non-adherence and an open dialogue between the clinician and patient is central to ensuring medication adherence. Reasons for medication non-adherence include the patient's negative perceptions of psychiatric medication, financial constraints, cognitive deficits, or medication side effects.[25] Our group recommends the following modalities to confirm a good adherence to medication (on decreasing order): systematic evaluation during the individual consultation, information of potential adverse reactions, evaluation of the patients with one of their relatives, research and management of adverse effects, reducing the number of everyday medications, participation in a therapeutic education and/or psychoeducation programme, treatment of psychiatric comorbidities, reducing the number of treatments and implementation of a pillbox.

The relationship between comorbid medical disorders and TRD is complex. Individuals with untreated medical comorbidities may appear to have TRD, or these medical comorbidities may worsen depressive symptoms. For example, fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome are strongly linked with depressive symptoms.[26] To treat these individuals, medications specifically targeting the underlying medical conditions, often in combination with antidepressants, may be required. The most prevalent example is hypothyroidism, which is more common in individuals with TRD compared to the general MDD population (52% versus 8–17%, respectively),[27] and treatment of hypothyroidism may lead to improvement in depressive symptoms.[28] Certain medical conditions may also prevent response to psychotropic medication, and treating these underlying conditions may improve response to standard antidepressant therapies. Diabetes, coronary artery disease, HIV infection, and cancer are all associated with a lower rate of antidepressant response.[29] Finally, commonly prescribed non-psychiatric medications, such as glucocorticosteriods and antihypertensives, are associated with depressive symptoms, and may prevent remission.[26]

Psychiatric comorbidities, such as substance abuse, obsessive–compulsive disorder, or post-traumatic stress disorder, may complicate diagnosis and treatment. Patients with these comorbidities may not achieve response with antidepressants only, and other psychiatric medications or psychotherapy may need to be added.[24] According to our group consensus recommendation, a patient with no relevant past medical history who suffers from a TRD episode, would require further examinations such as (ranked in descending order): thyroid stimulating hormone levels, free T3 and T4 plasma levels, complete blood count, blood electrolytes, liver and renal function, a full lipid profile and glucose levels, urinary and blood toxicological analysis and C-reactive protein plasmatic measurement.

Individuals high in self-criticism might suffer from a more severe depression. Also, severe life events experienced during or prior to antidepressant therapy predict a poor response to treatment.

Treatment strategies

For TRD, monotherapy or polytherapy treatment options may be considered. Monotherapy, specifically switching to a different antidepressant, is usually the starting point as this eliminates the risk of adverse drug interactions and places a lower financial burden on patients which is usually a crucial factor in our countries.[3]

We have agreed on screening for particular clinical features to prescribe a specific class of antidepressant medication due to its potential higher efficacy: SNRIs or TCAs if physical pain, SSRIs or SNRIs if high suicidal risk, mirtazapine or mianserin if marked weight loss or insomnia and SSRIs or SNRIs if marked anxious features.

However, when psychiatric medications are combined, they may have complementary pharmacodynamics that enhance antidepressant outcome. Moreover, if a drug shows partial effi-

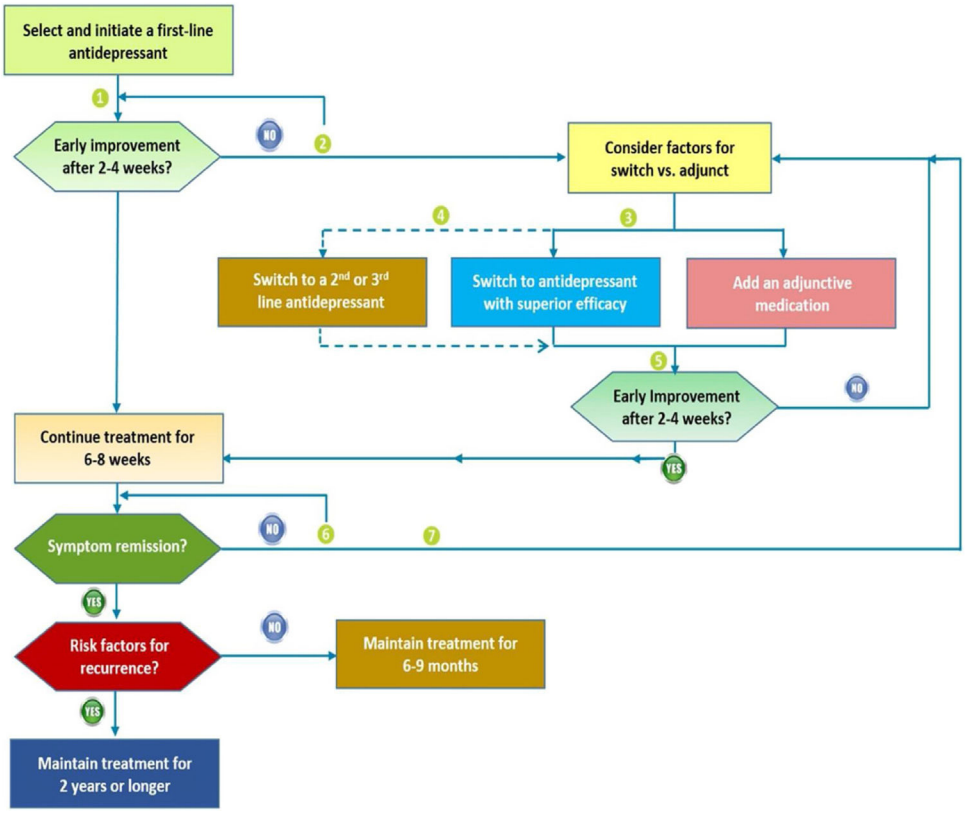

Fig. 1. Proposed algorithm useful for the management of an inadequate response of the treatment of a depressive episode of an adult patient. 1. Monitor outcomes using measurement-based care. 2. Depending on tolerability, first optimize antidepressant by increasing dose. 3. For early treatment resistance, consider adjunctive use of psychological and neurostimulation treatments. 4. After failure of 1 or more antidepressants, consider switch to a second-line or third-line antidepressant. 5. For more resistant depressions, consider longer evaluation periods for improvement. 6 and 7. Depending on tolerability, increase dose if not at maximal doses. For more chronic and resistant depressions, consider a chronic disease management approach, with less emphasis on symptom remission and more emphasis on improvement in functioning and quality of life.

Table 1
Augmentation strategies for TRD, recommendations and level of evidence.

Level of evidence	Adjunctive agent (dosage)	Recommendation
1	Lithium (600–1200 mg/d) Aripiprazole (2–15 mg/d) Brexpiprazole (1–3 mg/d) Quetiapine (150–300 mg/d) Risperidone (1–3 mg/d) IN Esketamine (56–84 mg) Olanzapine + fluoxetine (3 + 25–12 + 50 mg/d)	1
2	Mirtazapine (30–60 mg/d) Bupropion (150–450 mg/d) Mianserin (30–60 mg/d) T3 (25–50 mcg/d) Modafinil (100–400 mg/d)	2

cacy it may be preferable to combine this drug with an adjunctive agent, rather than switch medications entirely. There was agreement in our group to consider the algorithm displayed in Fig. 1 as being useful for the management of an inadequate response of the treatment of a depressive episode.[15] We have also reached full agreement on applying the criteria for level of evidence and expert recommendations for approved medications as outlined in Table 1.[15]

There was also agreement among the members of our group on recommending the following therapeutic strategy for a patient with no significant medical or psychiatric history who has a depressive unipolar episode with no response to a first line antidepressant (e.g., SSRI) in monotherapy of adequate dose and duration (ranked on descending order): switch to SNRI in monotherapy and structured psychotherapy in combination.

Switching antidepressants

The switching strategy is typically the next step after poor tolerability or complete non-response to an initial antidepressant.[24] Clinicians may choose to switch to a different class of antidepressant (ex. SSRI to an SNRI) or switch within the same class (ex. citalopram to fluoxetine).

While the vast majority of studies look at switching to a different SSRI, as this is typically the first class of antidepressant prescribed, data show efficacy is comparable when switching between any antidepressant classes.[2,30] Aside from switching between SSRI and SNRI antidepressants, switching to mirtazapine, bupropion or vortioxetine, or tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs), should also be considered. Decisions about which agent to select are usually based on specific symptom targets: for example, insomnia might favour mirtazapine[31] while anergia would suggest bupropion.[32] Overall, individuals switched from an SSRI to mirtazapine show remission rates comparable to those who switched to another SSRI,[33] although participants in one trial experienced faster response and remission when switched to mirtazapine compared to an SSRI.[34] Elsewhere, significantly fewer participants achieved remission when switched to mirtazapine compared to venlafaxine,[35] and experienced similar levels of remission when switched to mirtazapine or nortriptyline.[36] TRD individuals switched to bupropion experience comparable remission rates to those switched to an SSRI or SNRI,[2] and bupropion may be a good option for patients experiencing antidepressant-related sexual dysfunction.[37,38]

When comparing remission rates across studies, switching to vortioxetine led to numerically higher remission rates than

switching to sertraline, venlafaxine, bupropion, or citalopram.[39,40] Like bupropion, vortioxetine may be a good switching option for patients experiencing treatment-emergent sexual dysfunction, as vortioxetine switching led to significantly greater improvements in sexual functioning compared to escitalopram.[41]

In most developed nations as well as in Latin America, TCAs have been largely replaced by newer antidepressants with better safety and tolerability profiles, but not superior efficacy.[42] Interestingly, melancholic patients in particular may benefit from switching to a TCA.[43] Due to the increased toxicity in overdose and higher burden of adverse events associated with TCAs, it is recommended that they should only be prescribed when patients have failed different previous trials with newer antidepressants.[24]

There is limited evidence on the efficacy of switching to an MAOI for TRD, as the majority of these studies assess switching from a TCA. MAOIs were historically recommended for individuals with atypical features, but evidence to support this is also limited: MAOIs are more effective than TCAs, but not SSRIs, for the treatment of atypical depression.[44] MAOIs are typically recommended only after other drug classes have been ineffective because of the need for careful attention to food and drug interactions associated with MAOIs.[15,45] Unfortunately, MAOIs are currently not available in many countries of our region.

Combination therapies

When an antidepressant shows good tolerability and partial efficacy, combining antidepressants may be preferable to switching. Combination strategies avoid drug discontinuation symptoms and cross tapering,[46] and combining two antidepressants may lead to complementary neuropharmacological mechanisms that enhance efficacy further than when taking either antidepressant alone.[46] Of course, clinicians must check for any contraindications or potential adverse interactions that may result from combining two different drugs. Another option for polytherapy treatment involves the combination with another psychoactive medication that is not an antidepressant. This strategy is generally used when the patient has tolerated the current antidepressant well and obtained partial response.

Two of the most frequently prescribed add on antidepressants are bupropion and mirtazapine. However, the evidence to support bupropion, in combination with an SSRI, is weak.[47] Mirtazapine is often combined with SSRIs and SNRIs, based on the suggestion that this combination enhances monoaminergic neurotransmission, improves symptoms of insomnia, and counteracts gastrointestinal side effects of SSRIs/SNRIs.[48]

Another adjunctive antidepressant that is approved in Latin America is mianserin.

Unfortunately, this antidepressant showed limited efficacy for patients with TRD.[49,50]

Atypical antipsychotics

Atypical antipsychotics are the most-studied class of non-antidepressant adjunctive agents for SSRIs and SNRIs.[15,19] In addition, because many of these agents have undergone global trials to obtain an indication as adjunctive agents when one or more traditional antidepressant(s) were not effective, both the size and quality of these databases are substantially greater than for other adjunctive agents.

In placebo controlled trials involving atypical antipsychotics, rates of remission are achieved at about twice the rate with adjunct atypical antipsychotics compared to placebo.[51–53] However, several atypical agents are associated with significant adverse events including weight gain, insulin resistance, dyslipidemia, and metabolic syndrome.[54]

Extrapyramidal symptoms are also prevalent with certain atypicals.[55]

As of the end of 2020, only the specific combination of olanzapine and fluoxetine has FDA approval for TRD, and analyses support greater remission rates with this combination than fluoxetine alone.[56,57] Adjunctive aripiprazole performed better than placebo in improving depressive symptoms among major depressive disorder patients with unsatisfactory response to an antidepressant medication.[56,58,59] Brexpiprazole is a relatively new atypical antipsychotic that, like aripiprazole, acts as a dopamine multifunctional agent with a low potential for inducing extrapyramidal symptoms.[60] Both aripiprazole and brexpiprazole have been approved by FDA, EMA and several Latin American regulatory agencies as add on medications to antidepressants for MDD with partial response.

Other atypical antipsychotics that have been investigated in MDD as add on to antidepressant monotherapy include quetiapine, risperidone, and ziprasidone. Among these, quetiapine extended release currently demonstrates the most evidence for its efficacy in MDD.[53,58] Therefore, it has received formal regulatory approval by the main regulatory agencies to treat major depressive disorder as add-on therapy to an antidepressant medication.

Lithium

Lithium, in addition to its role as an antimanic and prophylactic agent in bipolar disorder, has been recognized as an adjunctive agent for TRD since the 1980s.[61] Currently, adjunct lithium is not prescribed as often as it once was, though older evidence suggests it is may be effective in TRD.[62] In a 2015 meta-analysis, adjunct lithium led to significantly higher response rates than placebo in TRD, but was poorly tolerated compared to other common augmentation strategies.[58] The majority of adjunct lithium trials have looked at augmentation to a TCA, making it is difficult to determine the efficacy of lithium added to newer antidepressants.

Our group achieved agreement on recommending the following therapeutic strategies to potentiate an antidepressant treatment in a patient, with no significant organic or psychiatric history, suffering from a major depressive episode: lithium and quetiapine, aripiprazole, intranasal (IN) Esketamine, T3 and olanzapine.

Neuromodulation

Neuromodulation techniques have been employed for a variety of disorders such as chronic pain, movement disorders, epilepsy, and psychiatric disorders.[63] For TRD, neuromodulation techniques may be invasive or non-invasive. Among all current neuromodulation therapies, electroconvulsive therapy (ECT) still constitutes the most accessible biological no pharmacological resource in our region.

Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) serves as the prototypic method of neurostimulation in depression. While the exact mechanism of action for ECT is unknown, the dominant hypothesis is that induction of a seizure cause changes in neurotransmitters, neuroplasticity, and functional connectivity in the brain.[64–68] Between six and fifteen treatments, given two to three times per week, are typically required to achieve response and/or remission; treatment more than three times per week is associated with greater cognitive side effects.[64]

ECT is one of the most effective treatments for MDD with partial or unsatisfactory response to pharmacotherapies.[64,69,70] Approxi-

mately 50% of patients with TRD respond to ECT,[71] although in a meta-analysis more than half of individuals relapsed within the first year.[72] It is unclear whether adjunct antidepressant medication is beneficial during a course of ECT: it does not appear to improve immediate response rates, but may reduce likelihood of relapse.[72,73] After a successful course of ECT, maintenance strategies include subsequent prescription of antidepressant medication, psychotherapy, or maintenance ECT (M-ECT).[64,73] Despite the commonly reported cognitive impairments post-treatment, both patients and health care workers' stigma towards ECT have become a major challenge for its application in our reagion.[74,75]

Psychotherapy

Psychotherapy is recommended for TRD in addition to pharmacological treatment and/or neurostimulation.[76] In a recent systematic review of TRD, the most common forms of psychotherapy were CBT, cognitive behavioural-analysis system of psychotherapy (CBASP), mindfulness-based cognitive therapy (MCBT), and interpersonal psychotherapy (IPT).[76] When individual or group psychotherapy and medications are given in conjunction, the antidepressant effect is greater than either alone.[76,77]

NMDA receptor antagonist: Esketamine

The EMA and the FDA first approved IN Esketamine for TRD in 2019, followed by other countries of our region in 2020. IN Esketamine is typically prescribed as an adjuvant to standard oral antidepressant medications, administered twice weekly at 56 or 84 mg. In two recent systematic reviews, IN Esketamine displayed rapid and significant reductions in depressive symptoms lasting at least 28 days when given at recommended doses.[78,79] As with other pharmacological and biological treatments, there are side effects associated with tolerability issues such as dizziness, dysgeusia, somnolence, dissociation, and increased heart rate and blood pressure which should be supervised during its administration by health care provider.[78] Besides the approval for adults with TRD in both acute and maintenance phases, Esketamine IN is also the first medication approved for depressive symptoms in adults with major depressive disorder (MDD) with suicidal ideation or behaviour.[80,81]

Conclusion

Treatment-resistant depression is a complex psychiatric diagnosis with varying degrees of severity. TRD may be difficult to diagnose, as many confounding factors, such as poor treatment adherence and comorbid medical or psychiatric conditions, may lead to misdiagnosis. Consideration of comorbidities, life stressors, personality traits, as well as genetic and biological factors can help in determining the risk of developing TRD. It is also important to mention the role of estrogens and the HPA axis in the pathogenesis or treatment of TRD. Until the diagnostic sensitivity can identify subtypes within MDD with distinct therapeutic targets, current strategies should be followed sequentially. Currently, standard of care for a patient who presents as treatment resistant starts with optimization strategies, followed by switching or combination of standard antidepressant medications. Adjunctive strategies are the logical next step. In some severe cases of TRD, neuromodulation may be effective. ECT still constitutes the most effective no pharmacological therapeutic option for TRD. Finally, the approval of Esketamine IN as add on to a first line antidepressant medication represent a promising path for newer innovative treatments.

Conflicts of interest

No author or immediate family member has financial relationships with commercial entities that might appear to represent potential conflicts of interest with the information presented.

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