Update on the pharmacological treatment of resistant depression

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Abstract

Resistance to major depressive disorder treatment causes distress to patients and their relatives, increases the number of hospital admissions, outpatient consultations, use of psychoactive drugs, and treatment costs. We review the concept and definition of treatment-resistant depression (TRD), different treatment methods, and comparative studies on treatment strategies. Despite its serious medical and psychosocial implications, the pharmacological treatment of TRD continues to be non-standardized and controversial. More research and comparative controlled studies on different treatments for resistant depression, which include neurobiological evaluations, need to be done.

Key words: Therapeutics. Depression. Review. Treatment-resistant depression. Antidepressants.

Introduction

The term "resistant" is widely employed in medical practice to point out a clinical problem with a lack of response to one or more therapeutic interventions. In the case of major depression, the most accepted definition for resistance to treatment is a lack of response to two antidepressants of different pharmacological classes¹. Despite the advances in pharmacological treatment, treatment-resistant depression (TRD) is not infrequent; the final objective of treatment, which is accomplishing a sustained recovery, is low and achieved in just 30-40% of patients after the first treatment with antidepressants². Moreover, after a proper treatment sequence, between 10 and 20% of patients continue with symptoms for 2 years or more³. TRD is a major health problem. It is linked to a prolonged period of treatment, greater suffering for patients and their

families, an increase in the number of hospitalizations, outpatient consultations, the use of psychotropic drugs, and the cost of treatment. In this article, we review literature on pharmacological treatments for TRD and their comparative studies, with the objective of offering a current outlook on its management.

TRD: Definition and stages of treatment

In 1974, different authors introduced the term TRD. However, this problem had already been described⁴. Since then, different definitions developed on what TRD is, with over 10 found in literature¹. Several groups have focused on the study and standardization of the TRD concept based on the advances of the more current treatments. The definition by Berlim and Turecki considers TRD as an episode of major depression that does not improve after two appropriate treatment tests

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Figure 1. Monoamine oxidase inhibitor; electroconvulsive therapy.

with antidepressants of different classes; this definition prevails today. Moreover, the “European Group for the Study of Resistant Depression” defines TRD when the patient is resistant to at least two appropriate consecutive treatments with antidepressants including combinations and additions of drugs⁵. Resistance to pharmacological antidepressant treatment seems to move continuously, going from complete response to complete resistance to therapeutic interventions, and is not an “all or nothing” phenomenon.

The systems that define stages of treatment could help predict the course of depression and its response to treatments in the long term. Thereby, in the GDST classification, the stages of resistance correspond to the number of failed treatments⁵. In 1997, Thase and Rush published a hierarchical model of five stages of efficacy to different therapeutic maneuvers including electroconvulsive therapy⁶ (Fig. 1). Other models have been published and studied, like the one from the Massachusetts General Hospital with five levels of resistance, and the one from the Maudsley Hospital, to name a few⁷. It is worth noting that none of the definitions of TRD or staging systems for its treatment have been researched enough in their validity and predictability⁸. These inconsistencies in definitions make real estimations of its prevalence difficult and have impeded the rigorous study of the most effective schemes for its treatment⁹.

Evaluation of a patient with resistant depression

In the evaluation of a patient with TRD, it is important to assess and reassess the case carefully. This includes the confirmation of the major depression diagnosis, making a differential diagnosis from bipolar depression and other forms of resistant depression, such as depression secondary to medical problems, or due to pharmaceuticals and drugs, among other things, and evaluates medical and psychiatric comorbidities. It is important to create a detailed record on the use of antidepressants, ideally using one of the already validated instruments, and study the severity of the depression with evaluation scales. Qualitative and quantitative evaluations of depressive symptoms ought to be a routine practice in every visit to patients with major depression, but more in those with TRD. An evaluation of psychosocial functioning, quality of life, previous adherence, current treatment, and tolerability is recommended as well. A good patient-physician relationship should be favored; this will allow professionals to be with the patient through the therapeutic process and also steer them toward not leaving the treatment and/or medical attention, even if they do not observe any changes and cheering them to fulfill their treatment. The psychological education of patients and their families is also important, along with the recognition of depressive signs

Table 1. Pharmacological strategies for the treatment of resistant depression

Strategy	Definition	Actions
Optimization	Improve the current treatment	Increase the dose of the antidepressant Increase the time of exposure to the drug
Change in treatment	Act to suspend the current treatment and replace it with another drug	Change of antidepressant Same pharmacological class Different class of antidepressant
Addition	Add another drug to the current treatment	A second antidepressant A second-generation antipsychotic Lithium Thyroid hormones Stimulants Drugs with activity on the NMDA receptor

NMDA: N-methyl-D-aspartate receptor; SSRI: selective serotonin reuptake inhibitor; SSNRI: selective serotonin and noradrenaline reuptake inhibitor; MOI: monoamine oxidase inhibitor; NMDA: N-methyl-D-Aspartate.

and symptoms, prognosis, suicidal risk assessment, treatment options, good sleep practices, and stimuli control, among others.

Pharmacological maneuvers for the TRD

Different pharmacological and non-pharmacological treatment maneuvers have been published and studied for the management of patients who do not respond to the initial treatment with an antidepressant. In this article, we only review the pharmacological strategies for TRD. These strategies are the optimization of treatment, and change and addition of another treatment. Independently of the selected strategy, the use of one strategy at a time is suggested to evaluate which one is more effective. Below, each of them is reviewed in detail (Table 1).

Optimization

This consists of modifying the intake of the current treatment to which the patient seems to be not responding, considering its tolerance. It is important to point out that a significant number of depressive patients sent to specialized clinics for treatment do not receive the correct dose of the antidepressant, or they have only been taking it for a short period of time¹⁰. Multiple studies show that it is important to treat a major depressive episode for 6-12 weeks¹¹. The importance of keeping patients for a proper time of antidepressant treatment before switching it has been shown in a published study with 1627 patients who had not responded to an antidepressant, where 67% of them had taken it for > 4 weeks¹². In this study, no differences were found between continuing the current treatment and changing

it for another antidepressant. On the other hand, other studies support the use of different treatments, if, after 4 weeks with an antidepressant, the patients show a reduction of depression of under 25%⁶.

Change of treatment

This maneuver consists of suspending current treatment and using a different antidepressant strategy, either pharmacological or non-pharmacological.

Change of antidepressant medication

A change in antidepressant medication should be performed gradually, reducing the dose of the current medication and beginning the new one by slowly increasing the dosage over a period of time of a week or two. Some physicians prefer to make the change of a selective serotonin reuptake inhibitor (SSRI) to another SSRI immediately, except when the patient has received fluoxetine. In that case, the waiting period should be at least 4 weeks, given its long average lifetime and the risk of serotonergic syndrome. For those patients resistant to SSRIs, a change to a noradrenaline and serotonin reuptake selective inhibitor (NSRSI) like venlafaxine is suggested, to atypical antidepressants such as bupropion or mirtazapine, tricyclic antidepressant, or monoamine oxidase inhibitors (MAOIs). A meta-analysis with four randomized studies including 1496 patients resistant to an SSRI found that remission of depression occurred in 24% of patients who were switched to another SSRI and in 28% of those switched to an antidepressant of a different class¹³. In the case of SSRI-resistant patients, different studies support that a change to venlafaxine could be more effective. A meta-analysis

including 3375 SSRI-resistant depressive patients found that with the change to another SSRI, there was 45% incidence of remissions and 54% incidence of remissions with a change to venlafaxine¹⁴. There are still few published studies where atypical antidepressants with SSRI or NSRI are compared in patients with TRD. In a group of patients resistant to paroxetine SSRI, a study that compared venlafaxine and mirtazapine found remissions of 41% and 36%, respectively¹⁵. In a different 8-week study which compared mirtazapine and paroxetine in 100 patients with TRD, remission was at 36% and 47%, respectively, with similar tolerance¹⁶. The use of tricyclic antidepressants has gone to being the fourth or fifth option of treatment for patients with major depression due to their adverse and undesirable effects, which are anticholinergic and cardiotoxic and include potential mortality by overdose. However, in other studies in patients with TRD, the efficacy and tolerability of tricyclics seem comparable to those of atypical antidepressants and SSRI. In a study with 168 patients resistant to imipramine a tricyclic or sertraline an SSRI treated for 12 weeks, patients were double-blind crossed to one or the other treatment¹⁷. The authors reported a remission rate of 23% and 32%, respectively. Tricyclic antidepressants have been a preference for many physicians for severely sick depressed patients¹⁸. Nevertheless, a meta-analysis of 25 randomized studies with 1377 hospitalized depressive patients who received tricyclics or SSRIs found that the superiority of tricyclics over SSRIs was low, with a higher number of collateral side effects¹⁹. Today, MAOIs are rarely used since they cause a hypertensive crisis if combined with other medications including antidepressants or foods rich in tyramine. However, change to an MAOI remains helpful for some patients with TRD. A randomized study where 46 patients resistant to the tricyclic imipramine received the MAOI phenelzine and 22 patients resistant to phenelzine received imipramine for 6 weeks reported a response of 67% in those patients who received phenelzine and 41% in those who received imipramine²⁰.

Maneuvers of addition

These consist of adding another treatment to the treatment in course, either pharmacological or not (Table 2). The previous response, safety, medical comorbidity, ease of use, preferences of the patient, and costs are factors to consider when adding another treatment to the current one.

Table 2. Pharmacological strategies in addition to the treatment of depression resistant

Type of drug	Drug
Antidepressants	Buspirone Mirtazapine Bupropion
Stabilizers	Lithium Lamotrigine
Antipsychotics	Aripiprazole Quetiapine Brexpiprazole Risperidone Olanzapine Ziprasidone
Drugs with activity on the NMDA receptor	Ketamine Esketamine
Stimulants	Modafinil Methylphenidate
Other	Thyroid hormone Scopolamine Mecamylamine L-methylfolate S-Adenosylmethionine

NMDA: N-methyl-D-Aspartate; SAME: S-adenosylmethionine.

Addition of a second antidepressant

For those depressions that partially respond to monotherapy with antidepressants, the second antidepressant is usually added. Moreover, a meta-analysis of eight studies with 808 patients who did not respond to an antidepressant and that compared a combination of antidepressants with a change to monotherapy found a similar improvement with both treatments²¹. The medications which have been studied the most combined are mirtazapine and bupropion. The use of mirtazapine as an additional drug in patients with TRD is supported in the results of open and controlled placebo studies. In the Sequenced Treatment Alternatives to Relieve Depression study, mirtazapine was added to the treatment of patients resistant to venlafaxine and was compared to the change to tranylcypromine an MAOI, where it was found that both treatments did not make a difference regarding efficacy²². Despite its popularity, the use of bupropion, a noradrenergic/dopaminergic antidepressant as an addition maneuver requires more studies to justify its use in patients with TRD²³. Buspirone, a partial agonist of the serotonergic receptor 1A, was compared in bupropion as an addition maneuver, finding a similar efficacy²⁴. Other addition maneuvers studied in patients with TRD include the combination with

lamotrigine, stimulants such as methylphenidate and atomoxetine, analeptics such as modafinil, and pindolol, among others. Published studies with lamotrigine, atomoxetine, and pindolol have failed to prove their efficacy in patients with TRD^{25,26}. In the case of stimulants, despite the popularity of their use, placebo-controlled studies against methylphenidate have negative results²⁷. Modafinil, an analeptic drug with an inhibiting effect on the reuptake of noradrenaline and dopamine, has not shown a sustained antidepressant effect in two controlled studies. However, a subsequent retrospective analysis suggests that it may help patients with TRD with sleepiness and fatigue²⁸. Among the cholinergic agents, scopolamine, an intravenous muscarinic antagonist, has shown promising results in patients with TRD. Furthermore, mecamlamine, a nicotinic receptor antagonist, added to citalopram, was superior to placebo²⁹. From the medications which act over the N-methyl-D-aspartate receptor (NMDA), memantine has been studied, showing negative results, and riluzole, an inhibitor of the liberation of glutamate, employed in the treatment of amyotrophic lateral sclerosis, did not show efficacy in a controlled study to prevent relapse after the use of ketamine³⁰. Ketamine, the analgesic antagonist of the NMDA receptor is being used more and more in patients with TRD. In a controlled study against placebo, this medication showed not only positive antidepressant results in patients with TRD but also a quick action mechanism³¹. However, the application of ketamine is complicated since it is administered intravenously, and it requires an anesthesiologist and very frequent hospitalization. Today, the intranasal administration of ketamine is being examined, and an S-enantiomer of racemic ketamine in patients with TRD has shown positive results³². Recently, esketamine has been added to the list of accepted addition maneuvers for patients with TRD.

Atypical antipsychotics

The addition of atypical antipsychotics in patients with TRD is becoming more accepted thanks to recent studies. An analysis of 16 studies compared the addition of aripiprazole, olanzapine, quetiapine, or risperidone against placebo in 3480 non-psychotic depressive patients who failed to respond to at least one essay with antidepressant monotherapy, found that with this maneuver of addition, 31% of patients improved, compared to only 17% with placebo³³. However, the suspension of the medication due to adverse effects was greater with antipsychotics (9% vs. 2%, respectively). There is an interesting report of a meta-analysis which included

11 randomized studies with over 3000 patients with TRD³⁴. This study found that the efficacy of the addition of atypical antipsychotics could increase in patients in relation to the degree of their resistance to antidepressants. Thereby, the addition of atypical antipsychotics was of major benefit in patients who did not respond to three or four essays compared to patients who did not respond to one treatment. The following order of the use of atypical antipsychotics has been suggested, based on their benefit and lack of adverse events; aripiprazole, quetiapine, risperidone, and more rarely, ziprasidone or olanzapine, and the use of brexpiprazole if aripiprazole produces akathisia¹⁶. These results concur with the results of a meta-analysis including eight studies with 2260 patients, in which aripiprazole was added against placebo, showing a high rate of response and remissions³⁵.

Lithium

The addition of lithium was reported for the 1st time by De Montigny in patients resistant to tricyclic antidepressants. A meta-analysis with 10 placebo-controlled studies showed that the addition of lithium at a 600-900 mg/day dose (plasma levels above 0.4 mEq/L) was superior to placebo³⁶. Lithium is equally effective when added to the first- and second-generation antidepressants combined with a possible benefit in the reduction of suicidal risk. A meta-analysis including nine double-blind controlled lithium and placebo studies with 234 patients with TRD found a robust efficacy of treatment with lithium, which ought to be administered for no < 7 days at a dosage of 600-800 mg a day to observe results³⁷.

Thyroid hormone

The thyroid hormone, specifically triiodothyronine, has been used as an addition maneuver since the 60s. The usual initial dose of triiodothyronine (T3) in the shape of liothyronine is between 25 pg. to 50 pg. and with thyroxine (T4), 150 pg. An initial meta-analysis with T3 proved to be more effective than placebo³⁸. However, subsequent studies have proven a low effectiveness. Thus, a meta-analysis was run with four randomized studies which included 95 patients who did not respond to tricyclic antidepressants, and where the addition of T3 or T4s against placebo was studied³⁸, showing a response in 53% of patients who received T3s without a statistical difference with the placebo.

L-methylfolate (5-methyltetrahydrofolate) and S-adenosylmethionine (SAME) have been evaluated as addition agents in TRD. L-methylfolate, an active intermediate of folate added at doses of 15 mg/day, has shown results superior to placebos in 75 patients with TRD³⁹. A study against a placebo with SAME in 73 patients with TRD at a dose of 800 mg twice a day showed superiority over the placebo in remission and response to treatment⁴⁰.

Guidelines for the treatment of patients with resistant depression

Multiple guidelines suggest how to employ an increase in treatment (The American Psychiatric Association, United Kingdom National Institute of Health, and Clinical Excellence Guidelines)^{41,42}. Nevertheless, few controlled studies have been conducted comparing the efficiency of the different pharmacological maneuvers suggested for patients with TRD, and most studies published so far do not make a distinction between patients with little to no benefit from those who improve unsatisfactorily.

Reviews of randomized studies against placebo show that the benefits of maneuvers or changes in treatment are equally effective. The average rate of remission with an additional maneuver was 27%, while the rate of a change in treatment was 22%, with response rates (defined as a reduction of depressive symptoms of 50% or more) of 38% and 40%, respectively⁴³. A randomized study of 375 patients with TRD where different treatments were assigned, including five options of addition and two of change, showed similar results, with 37% and 41% for each strategy⁴⁴. Some studies suggest that the addition maneuvers are somewhat superior regarding effectiveness compared to a change in antidepressant treatment. In an open, randomized, 12-week study, including 1522 patients who remained severely depressed despite treatment with some antidepressants⁴⁵, the patients received three treatments: addition of aripiprazole (target dose 5-15 mg/day), addition of bupropion (target dose 300-400 mg/day), or change to bupropion as monotherapy. Antidepressant response, defined as a reduction in symptoms equal to or greater than 50%, was higher with aripiprazole (74%) than with the addition of bupropion (66%) or a change to bupropion as monotherapy (62%). In a review of 12 randomized studies, results show that the addition of lithium, SSRIs, or an atypical antipsychotic was not statistically different in antidepressant efficacy in patients with TRD⁴⁶. Regarding cost benefit, the addition

of lithium is less expensive than atypical antipsychotics. Change in medication, which should always be discussed with the patient, has the advantage of accomplishing a greater adherence than when several drugs are administered, in addition to a lower risk of collateral effects, pharmacological interactions, and lower cost of treatment. In recent article, 48 randomized controlled studies were analyzed with 11 pharmacological agents used as additional maneuvers in patients with TRD, in which 6654 patients were included⁴⁷. This meta-analysis included studies with the following atypical antipsychotics: aripiprazole, olanzapine, quetiapine, and risperidone, along with the antidepressants bupropion and buspirone, lithium, thyroid hormones, methylphenidate, pindolol, and lamotrigine. The analyzed studies were compared against themselves or a placebo; the number of patients who responded to treatment was defined as primary efficacy. The analysis proved a higher efficacy of quetiapine, aripiprazole, thyroid hormones, and lithium in comparison to placebo. No differences were found in abandonment rates and adverse effects for these treatments. However, compared to placebo, quetiapine, olanzapine, aripiprazole, and lithium were less well-tolerated.

Conclusions

This review of literature shows that different pharmacological maneuvers are effective in the management of depressive patients who are resistant to conventional antidepressants. There is not enough scientific information that can guide the physician in the selection of the best treatment for a specific patient with TRD. We also lack enough studies, which validate which treatment maneuvers could be more effective, and which ought to be employed consecutively. In those patients who show an inadequate response to the first treatment, the physician can rely on different options to change or add to the treatment, but if this second option fails, other maneuvers seem to be equally effective according to the data published in literature⁴⁸. We frequently find ourselves at this crossroad in patients with TRD in a trial and error situation, which can be prolonged and discouraging until we are able to find a treatment which can sufficiently help the patient. Future research in patients with TRD ought to focus not only on the comparative effectiveness and efficacy of pharmacological treatments but also on the possible neurobiological factors involved, including genetic and pharmacogenetic studies⁴⁹, thus establishing the bases

necessary for the selection of the best scheme for the management of these patients.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments on humans or animals were done for this article.

Data confidentiality. The authors declare that there are no patient data in this article.

Right to privacy and informed consent. The authors declare that there are no patient data in this article.

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