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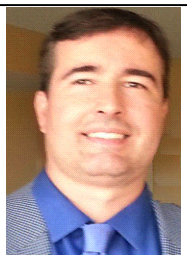
Challenging Treatment-Resistant Major Depressive Disorder: A Roadmap for Improved Therapeutics

Rafael T. de Sousa[1], Marcus V. Zanetti[1,2,3], Andre R. Brunoni[1] and Rodrigo Machado-Vieira[1,2,4,*]

[1]*Laboratory of Neuroscience, LIM-27, Institute and Department of Psychiatry, University of Sao Paulo, Brazil;* [2]*Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), University of Sao Paulo, Brazil;* [3]*Laboratory of Psychiatric Neuroimaging, LIM-21, Department and Institute of Psychiatry, University of Sao Paulo, Brazil;* [4]*Experimental Therapeutics and Pathophysiology Branch (ETPB), National Institute of Mental Health, NIH, Bethesda, MD, USA*



R. Machado-Vieira

Abstract: Major depressive disorder (MDD) is associated with a significant burden and costs to the society. As remission of depressive symptoms is achieved in only one-third of the MDD patients after the first antidepressant trial, unsuccessful treatments contribute largely to the observed suffering and social costs of MDD. The present article provides a summary of the therapeutic strategies that have been tested for treatment-resistant depression (TRD). A computerized search on MedLine/PubMed database from 1975 to September 2014 was performed, using the keywords "treatment-resistant depression", "major depressive disorder", "adjunctive", "refractory" and "augmentation". From the 581 articles retrieved, two authors selected 79 papers. A manual searching further considered relevant articles of the reference lists. The evidence found supports adding or switching to another antidepressant from a different class is an effective strategy in more severe MDD after failure to an initial antidepressant trial. Also, in subjects resistant to two or more classes of antidepressants, some augmentation strategies and antidepressant combinations should be considered, although the overall response and remission rates are relatively low, except for fast acting glutamatergic modulators. The wide range of available treatments for TRD reflects the complexity of MDD, which does not underlie diverse key features of the disorder. Larger and well-designed studies applying dimensional approaches to measure efficacy and effectiveness are warranted.

Keywords: Antidepressant, antipsychotic, diagnosis treatment, glutamate, monoamines, major depressive disorder.

INTRODUCTION

Major depressive disorder (MDD) is associated with a significant burden, affecting around 16% of the population in the US in lifetime [1]. The estimated costs of MDD are around $83 billion annually, due to many psychosocial factors including loss of workdays [2]. Estimates are that on average a depressed person loses 27.2 workdays per year [3]. A significant part of the burden corresponds to unsuccessful treatments. The results of STAR*D (Sequenced Treatment Alternatives to Relieve Depression), the most comprehensive and large clinical study on MDD, showed that remission of depressive symptoms is achieved in around only one-third of the patients after the first antidepressant trial [4]; noteworthy, the chances of achieving full remission decrease with the consecutive drug trials. This probably results from the complex and multifactorial MDD etiology, which involves biological, psychosocial, environmental, and genetic factors, which could explain why most patients fail to respond to the standard monoaminergic antidepressants, warranting new therapeutic strategies in treatment-resistant depression (TRD).

Several definitions and staging models for TRD have been proposed [5]. The considered definitions of TRD take into account number of failures to treatment, chronicity of illness, modalities of treatments used (electroconvulsive therapy (ECT), different drugs, etc), dosage of medications, as well as duration of the trials. The multiplicity of facets approached in TRD definitions reflects the complexity of MDD and the resistance to treatment.

It is commonly accepted that a patient had nonresponse when the improvement is less than 25% in a rating psychometric scale, such as Hamilton Depression Rating Scale (HAMD); a partial response to treatment would be a 25-49% improvement on rating scores; response corresponds to an improvement of at least 50% on depression scores, whereas remission is a state in which only minimal symptoms are present. TRD more commonly describes a condition in which a patient has failed to achieve response in at least one antidepressant trial, which is the working definition that will be used in this review to more widely cover the field of treatment-resistant MDD. Given the intricacy of TRD, the objectives of this article are to review the available therapeutic strategies for TRD and to provide insight into the new targets for TRD.

*Address correspondence to Prof. Rodrigo Machado-Vieira at the Laboratory of Neuroscience (LIM27), Department and Institute of Psychiatry, University of Sao Paulo, Brazil, Address: Instituto de Psiquiatria do HC-FMUSP, 3o andar, LIM-27, Rua Dr. Ovídio Pires de Campos, 785, Postal code 05403-010, São Paulo, SP, Brazil; Tel: +55 11 2661-8010; Fax: +55 11 2661-7535; E-mails: machadovieirar@gmail.com, machadovieirar@mail.nih.gov

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METHODS

We conducted a review of computerized MedLine/ PubMed database from 1975 to September 2014 searching published papers written in English. The keywords were "treatment-resistant depression", "major depressive disorder", "adjunctive", and "augmentation". Two authors reviewed 581 articles retrieved and selected 79 papers. A manual searching further considered relevant articles of the reference lists. Criteria for inclusion were clinical trials evaluating patients with the diagnosis of MDD, TRD defined as lack of response to at least one adequate pharmacological trial, and use of standardized procedures; meta-analyses synthesizing the results of clinical trials on TRD were also admitted. Proof of concept trials in MDD patients with TRD or approaching new targets in MDD were additionally included in the present review based on authors' consensus, potential of efficacy in TRD, and overall article quality.

RESULTS

Table **1** displays up to two most relevant studies per drug or modality of treatment, giving an overview of possible approaches to treatment-resistant MDD. Based on strength of evidence, the selected studies in Table **1** range from meta-analyses and double-blind studies to larger open-label trials (at least 30 patients per arm) in treatment-resistant MDD chosen among the papers included in this review.

SWITCHING OR COMBINING STANDARD ANTIDEPRESSANTS FOR TRD

Common strategies after the first antidepressant trial failure involve switching to other agent or combining another antidepressant to improve on depressive symptoms; however it is not clear whether combining or switching is the most effective strategy [6].

SWITCHING TO ANOTHER ANTIDEPRESSANT

After a first selective serotonin reuptake inhibitor (SSRI) trial, switching within or between antidepressant classes may be an effective strategy. Switching the antidepressant from one class to another is a common strategy with support in literature [7], though there is evidence suggesting that this strategy is not superior to switch within-classes [8, 9].

Venlafaxine

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI) widely used for depression and anxiety disorders. After the failure of an SSRI, switching to venlafaxine may be a more advantageous strategy when compared to switching to another SSRI. A randomized, double-blind trial enrolling 122 patients showed that switching to venlafaxine yielded a remission rate of 42% compared with 20% for paroxetine (p=0.01) [10]. Another randomized, double-blind study in a larger sample (n=406), however, found no significant difference in venlafaxine extended-release (XR) vs. citalopram to treat TRD [11]. A secondary analysis showed that in more severe MDD (HAMD-21 items [HAMD-21]>31), venlafaxine XR performed better than citalopram in improving depressive symptoms [11].

In the ARGOS unblinded study (n=3097), a relatively small but significant superiority of venlafaxine XR over other antidepressant (mostly SSRIs or mirtazapine) was demonstrated: the remission rate in the venlafaxine group was 59.3% versus 51.5% in the comparison group [12]. In STAR*D (n=727), however, remission rates (HAMD-17) with venlafaxine XR treatment (24.8%) were not significantly superior than remission rates with bupropion sustained release (21.3%) or with sertraline (18.1%) [13]. Noteworthy, evidence from several meta-analyses support the superiority of venlafaxine as antidepressant over SSRIs [14-18], especially in severe MDD [17].

Therefore, after a first unsuccessful antidepressant trial, switching to venlafaxine is a strategy supported by most clinical studies, especially in more severe MDD cases.

Mirtazapine

Mirtazapine is an antagonist of receptors α-2, 5-HT_2, and 5-HT_3, and agonist of postsynaptic receptors 5-HT_{1A}, thus acting both on noradrenergic and serotonergic neuro-transmission. Although both mirtazapine and venlafaxine possess a dual action profile, mirtazapine achieved inferior remission rates than venlafaxine after an initial antidepressant failure in the ARGOS open-label study (n=3,097) [12]. In the STAR*D study, 235 patients who had 2 antidepressant failures were randomized to mirtazapine or nortryptiline [19]; mirtazapine was not significantly different from nortryptiline regarding remission rates (12.3% vs. 19.8%, respectively).

Agomelatine

Agomelatine is a drug that acts through melatonergic agonism (on MT1 and MT2 receptors) and *via* 5-HT_{2C} antagonism. Agomelatine has shown to be effective in MDD in several studies [20]. Nevertheless, there is no evidence of agomelatine efficacy specifically in treatment-resistant MDD, thus warranting future studies.

Changing to a Heterocyclic Antidepressant

In an open-label study, 92 patients with TRD received nortryptiline and had response and remission rates of nearly 40% and 12%, respectively [21]. The comparison of switching to nortryptiline or mirtazapine after treatment failure showed no difference as previously discussed [19]. After a failure with either sertraline (n=117) or imipramine (n=51), patients were assigned to a 12-week trial with the other medication and had around 50% of response on both switches [22]. Thus, switching from a SSRI to a tricyclic antidepressant (TCA) or the other way around (*i.e.* changing the antidepressant class) is likely a good strategy in TRD.

Monoamine Oxidase Inhibitor (MAOI)

The STAR*D study evaluated 109 patients who received venlafaxine plus mirtazapine or tranylcypromine after 3 consecutive trial failures [23]. The study found low remission

Table 1. The most relevant studies (up to 2) in treatment-resistant MDD for a medication or modality of treatment selected based on strength of evidence: from meta-analyses and double-blind studies to larger open-label trials (with more than 30 patients per arm) using standardized methodology.

Study	Drug and Strategy Tested	Design	Sample Size	Number of Failed Trials	Treatment	Findings
	SWITCHING TO ANOTHER ANTIDEPRESSANT					
Poirier and Boyer, 1999	**Venlafaxine**	Double-blind, randomized trial	122 patients	≥2	Venlafaxine vs. paroxetine	Switching to venlafaxine yielded a greater response rate of 51.9% for venlafaxine compared with 32.7% for paroxetine, and a greater remission rate of 42% compared with 20% for paroxetine.
Lenox-Smith and Jiang, 2008		Double-blind, randomized trial	406 patients	≥1	Venlafaxine XR vs. citalopram	No significant differences in venlafaxine extended-release (XR) vs. citalopram were observed. A secondary analysis showed that in more severe MDD (HAMD-21 items [HAMD-21]>31), venlafaxine XR performed better than citalopram in improving depressive symptoms.
Baldomero *et al*., 2005	**Venlafaxine/Mirtazapine**	Open-label trial	3,097 patients	≥1	Venlafaxine XR vs. SSRIs (or mirtazapine)	Venlafaxine XR achieved slightly significant superior remission rates (59.3%) than conventional antidepressants (51.5%), including mirtazapine (44.8%).
Fava *et al*., 2006	**Mirtazapine**	Open-label trial	235 patients	≥2	Mirtazapine vs. nortryptiline	Mirtazapine was not significantly different from nortryptiline regarding response (13.4% vs. 16.5%, respectively) or remission rates (12.3% vs. 19.8%, respectively).
Nierenberg *et al*., 2003	**Changing to a Heterocyclic Antidepressant**	Open-label trial	92 patients	≥1	Nortryptiline	Nortryptiline treatment yielded response and remission rates of nearly 40% and 12%, respectively.
Thase *et al*., 2002		Open-label trial	168 patients	≥1	Imipramine vs. sertraline	After a failure with either sertraline (n=117) or imipramine (n=51), patients were assigned to a 12-week trial with the other medication and had around 50% of response on both switches.
McGrath *et al*., 2006	**Monoamine Oxidase Inhibitor**	Open-label trial	109 patients	≥3	Tranylcypromine vs. venlafaxine plus mirtazapine	The study found low remission rates in both groups – tranylcypromine (6.9%) and venlafaxine plus mirtazapine (13.7%) – with no significant difference.
	COMBINING ANTIDEPRESSANTS					
Fang *et al*., 2011	**Buspirone/Trazodone**	Open-label trial	225 patients	≥2	Buspirone vs. trazodone (as add-on to antidepressant)	After 8 weeks of add-on treatment, remission was achieved by 32.6% of the patients with buspirone and 42.6% with trazodone; the difference between the groups was not significant.
Carpenter *et al*., 2002	**Mirtazapine**	Double-blind, randomized, placebo-controlled trial	26 patients	≥1	Mirtazapine vs. placebo (as add-on to antidepressant)	In a 4-week double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine, adjunctive mirtazapine vs. placebo produced a significantly superior response (63.6% vs. 20%, respectively) and remission rates (45.4% vs. 13.3%, respectively).

Table 1. contd…

Study	Drug and Strategy Tested	Design	Sample Size	Number of Failed Trials	Treatment	Findings
	COMBINATION WITH ATYPICAL ANTIPSYCHOTICS					
Farooq and Singh, 2014	**Olanzapine**	Meta-analysis	2,108 patients, 7 studies	≥1	Olanzapine-fluoxetine combination (OFC) vs. antidepressant or olanzapine	OFC superior to diverse drugs alone (olanzapine, fluoxetine, nortryptiline, and venlafaxine).
Thase *et al*., 2007		Pooled analysis of 2 double-blind, randomized, placebo-controlled trials*	605 patients	≥2	OFC vs. fluoxetine vs. olanzapine	Patiens using OFC were compared with patients under fluoxetine or olanzapine treatment and showed greater response (40.4% vs. 29.6% vs. 25.9%, respectively) and remission rates (27.3% vs. 16.7% vs. 14.7%).
Bauer *et al*., 2009	**Quetiapine**	Double-blind, randomized, placebo-controlled trial	493 patients	≥1	Quetiapine XR vs. placebo (as add-on to antidepressant)	Quetiapine XR (300mg/day) given adjunctive was shown to be more effective than placebo as add-on to antidepressant in eliciting response (57.8% vs. 46.3%, respectively) and remission (36.1% and 23.8%, respectively).
Bauer *et al*., 2013		Open-label, rater-blind, randomized, placebo-controlled trial	688 patients	≥1	Quetiapine XR add-on to antidepressant vs. quetiapine XR monotherapy vs. lithium add-on to a to antidepressant	Quetiapine XR (300mg/day) both as add-on or as monotherapy promoted an improvement in MADRS scores similar and non-inferior to that of add-on lithium in patients with TRD.
Mahmoud *et al*., 2007	**Risperidone**	Double-blind, randomized, placebo-controlled trial	274 patients	≥1	Risperidone vs. placebo (as add-on to antidepressant)	Risperidone (1-2 mg/day) as add-on for 6 weeks significantly improved depressive symptoms versus placebo, with response and remission rates of 46.2% vs. 29.5% and 24.5% vs. 10.7%, respectively.
Keitner *et al*., 2009 [46]		Double-blind, randomized, placebo-controlled trial	97 patients	≥1	Risperidone vs. placebo (as add-on to antidepressant)	Risperidone (0.5-3mg/day) as add-on was effective for TRD.
Berman *et al*., 2007	**Aripiprazole**	Randomized, double-blind trial	362 patients	≥2	Aripiprazole vs. placebo (as add-on to antidepressant)	Mean change in depressive symptoms was significantly greater with adjunctive aripiprazole than adjunctive placebo.
Berman *et al*., 2008		Randomized, double-blind trial	381 patients	≥2	Aripiprazole vs. placebo (as add-on to antidepressant)	Aripiprazole as add-on for 6 weeks significantly improved depressive symptoms versus placebo, with greater response (32.4% vs 17.4%, respectively) and remission rates (25.4% vs 15.2%, respectively).
Nelson *et al*., 2014	**ADJUNCTIVE LITHIUM**	Meta-analysis	237 patients, 9 studies	≥1	Lithium vs. placebo (as add-on to antidepressant)	There was an odds ratio of 2.89 favoring response to lithium against placebo. (Most of the trials studied lithium added to TCAs).
		Open-label trial	142 patients	≥2	Lithium vs. triiodothyronine (as add-on to antidepressant)	Patients showed a remission rate of 15.9% with adjunctive lithium versus 24.7% with triiodothyronine augmentation, even though this difference was not significant. A possible explanation for the low remission rates with lithium augmentation is the use of low lithium doses in the study.

Table 1. contd…

Study	Drug and Strategy Tested	Design	Sample Size	Number of Failed Trials	Treatment	Findings
	COMBINATION WITH ATYPICAL ANTIPSYCHOTICS					
Aronson *et al*., 1996	**AUGMENTATION WITH THYROID HORMONES**	Meta-analysis	292 patients, 8 studies	≥1	Triiodothyronine as add-on	Patients treated with triiodothyronine augmentation were twice as likely to respond as controls, but when only double-blind studies were analyzed, there was no significant difference between placebo and triiodothyronine.
	TARGETING OTHER BRAIN SYSTEMS					
Ravindran *et al*., 2008	**Adjunctive Psychostimulant Therapy**	Double-blind, randomized, placebo-controlled trial	145 patients	1 to 3	Methylphenidate vs. placebo (as add-on to antidepressant)	Methylphenidate did not significantly improve depression in depression scores when compared to placebo. However, methylphenidate significantly improved fatigue and apathy.
Appelberg *et al*., 2001	**Combination with buspirone**	Double-blind, randomized, placebo-controlled trial	102 patients	≥1	Buspirone vs. placebo (as add-on to antidepressant)	No significant benefits of adding buspirone to SSRI in the treatment of MDD, when compared to placebo.
Landén *et al*., 1998		Double-blind, randomized, placebo-controlled trial	119 patients	≥1	Buspirone vs. placebo (as add-on to antidepressant)	No significant benefits of adding buspirone to SSRI in the treatment of MDD, when compared to placebo.
	TARGETING GLUTAMATE					
Zarate *et al*., 2006	**Ketamine**	Double-blind, randomized, placebo-controlled, cross-over trial	18 patients	≥2	Ketamine vs. placebo	Significant improvement of patients receiving ketamine vs. placebo, with very large effect size after 24h.
Lapidus *et al*., 2014		Double-blind, randomized, placebo-controlled, cross-over trial	20 patients	≥1	Ketamine vs. placebo	Intranasal ketamine yielded a fast antidepressant effect, with a response rate of 44% vs. 6% in the placebo group after 24 hours.
Heresco-Levy *et al*., 2013	**D-cycloserine**	Double-blind, randomized, placebo-controlled trial	26 patients	≥2	D-cycloserine vs. placebo	D-cycloserine was effective against depressive symptoms in patients with treatment-resistant MDD; 54% of the patients usind D-cycloserine responded vs. 15% of the patients randomized to placebo.
Ellis *et al*., 2014	**Scopolamine**	Double-blind, randomized, placebo-controlled, cross-over trial	31 patients	≥2	Intravenous scopolamine vs. placebo	Intravenous scopolamine yielded 32% rate of response and 19% of remission against 0% of response and remission with placebo.
	NUTRACEUTICALS & PHYSICAL EXERCISE					
Papakostas *et al*., 2010	**S-adenosyl methionine (SAMe)**	Double-blind, randomized, placebo-controlled trial	73 patients	≥1	SAMe vs. placebo (add-on to antidepressant)	Patients on SAMe add-on to antidepressant had greater response and remission rates (36.1% and 25.8%, respectively) than patients receiving adjunctive placebo (17.6% versus 11.7%, respectively).

Table 1. contd…

Study	Drug and Strategy Tested	Design	Sample Size	Number of Failed Trials	Treatment	Findings
	NUTRACEUTICALS & PHYSICAL EXERCISE					
Papakostas *et al*., 2012	**L-methylfolate**	Double-blind, randomized, placebo-controlled trial	75 patients	≥1	L-methylfolate vs. placebo (add-on to antidepressant)	Patients treated for 60 days with L-methylfolate add-on to SSRI had greater response rate and symptom decrease than patients receiving placebo.
De la Cerda *et al*., 2011	**Physical exercise**	Open-label trial	82 patients	≥1	Fluoxetine plus physical exercise vs. fluoxetine	Physical exercise (plus fluoxetine) was more effective than fluoxetine to decrease depressive symptoms.
	SOMATIC TREATMENTS					
O'Reardon *et al*., 2007	**Repetitive transcranial magnetic stimulation (rTMS)**	Double-blind, randomized, sham-controlled trial	301 patients	1 to 4	rTMS vs. sham	rTMS was superior to sham intervention for the improvement of depressive symptoms.
Lam *et al*., 2008		Double-blind, randomized, sham-controlled trial	1,092 patients, 24 studies	≥1	rTMS vs. sham	Response and remission rates with rTMS treatment were 25% and 17%, significantly greater than sham condition, 9% and 6%, respectively.
	PSYCHOTHERAPY APROACHES					
Wiles *et al*., 2013	**Cognitive-behavior therapy (CBT)**	Open-label, randomized trial	469 patients	≥1	Antidepressant plus CBT vs. antidepressant alone	Associating CBT to treatment as usual more than doubled the response rate (46% versus 22% in the usual care group) after 6 months of follow-up.
	Cognitive therapy (CT)	Open-label, equipoise-stratified randomized trial	304 patients	≥1	Citalopram plus CT vs. citalopram plus other medication vs. switch to CT vs. switch to other medication	Cognitive therapy switch or as augmentation to citalopram had similar response and remission rates as other medication strategies as a second level approach for MDD patients with inadequate response to an initial trial of citalopram.

MDD - major depressive disorder, SSRI - selective serotonin receptor inhibitor, TCA - trycyclic antidepressant , TRD - treatment-resistant depression. *This study was included in the meta-analysis of Farooq & Singh (2014).
2.5h arranging references.

rates in both groups – tranylcypromine (6.9%) and venlafaxine plus mirtazapine (13.7%) – with no significant difference. Noteworthy, mean dose in the tranylcypromine group was relatively low (36.9 mg/day) and almost half of the patients on tranylcypromine had less than 6 weeks of treatment, which significantly limits the interpretation of the findings.

In two controlled, partial crossover studies involving MDD subjects who had undergone at least 2 unsuccessful TCAs trials, 47 patients were assigned to tranylcypromine, which was effective in around 50% of them [24]. However, the small sample size and the design of the studies limit the interpretation of this finding.

COMBINING ANTIDEPRESSANTS

An open-label study enrolled 225 patients with TRD treated with paroxetine augmented with other drugs. After 8 weeks of add-on treatment to paroxetine, remission was achieved by 32.6% of the patients with buspirone and 42.6% with trazodone [25]; the difference between the groups was not significant. Reboxetine add-on to duloxetine in MDD patients who did not respond to an 8-week duloxetine trial was evaluated in an open-label study; 76% of the patients on reboxetine augmentation for 12 weeks responded and 69.3% remitted [26].

In a 4-week double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine, adjunctive mirtazapine produced a significantly superior response rate of 63.6% versus 20% of the placebo [27]. In MDD patients with and without TRD, other two double-blind trials found that mirtazapine combination with SSRI, bupropion, or venlafaxine was superior to either agent alone [28, 29]. Consistently, a meta-analysis in MDD including not only TRD showed that mirtazapine combination to SSRI was superior to a SSRI alone (RR=1.88, 95% CI, 1.06-3.33) [30].

However, as reported above, in the STAR*D study MDD patients receiving a combination of mirtazapine plus venlafaxine after 3 treatment failures had a remission rate of only 13.7% [23]. Moreover, Rush *et al*. [31], in a single-blind, 12-week study with 665 patients with severe or recurrent MDD, found similar remission (37.7%-38.9%) and response (57.4%-59.4%) rates among the three study groups: mirtazapine (up to 45mg/day) plus venlafaxine XR (up to 300mg/day), escitalopram (up to 20mg/day) plus placebo, and bupropion sustained-release (SR) (up to 400mg/day) plus escitalopram. Also, at the long-term follow-up of 7 months, remission rates (41.8%-46.6%), response rates (57.4%-59.4%), and most secondary outcomes were not significantly different [31].

One meta-analysis assessing the efficacy of antidepressant combinations in MDD found that a TCA plus SSRI was superior to the SSRI alone in achieving both remission (RR=8.58, 95% CI=1.70-43.32) and response (RR=1.78, 95% CI=1.07-2.93) [30]. More studies are needed to establish the best combinations for TRD.

COMBINATION WITH ATYPICAL ANTIPSYCHOTICS (AAP)

Atypical antipsychotics (AAP) are drugs able to modulate dopaminergic system and monoamine reuptake, with some agents also showing 5-HT_2 receptors antagonism and blockade of α_2-adrenergic receptors. Two meta-analyses of placebo-controlled trials have demonstrated that adjunctive AAP is an effective approach in the treatment of TRD, with a NNT of nearly 9 [32, 33]. The evidence for specific AAP agents is reviewed below.

Olanzapine

The efficacy of olanzapine-fluoxetine combination (OFC) for TRD was tested in 5 double-blind, controlled trials with mean modal dosages 8-13 mg/day of olanzapine and 37-52 mg/day of fluoxetine. Two of these studies have shown that OFC was more effective than olanzapine or fluoxetine monotherapy [34, 35] and the other 3 trials did not find significant superiority of OFC for treating TRD [35-37]. However, a meta-analysis found OFC superior to diverse drugs alone (olanzapine, fluoxetine, nortryptiline, and venlafaxine) [38].

An integrated analysis evaluated the outcomes of the 5 abovementioned studies [39], which were very similar in design, enrolling MDD patients resistant to two antidepressant trials at adequate doses and duration. Subsequently, in a second phase the patients were randomized double-blindly to treatment with OFC (n = 462), fluoxetine (n = 342), or olanzapine (n = 342) for 8 to 12 weeks. Treatment with OFC was associated with a greater improvement in depressive symptoms than treatment with either fluoxetine or olanzapine alone, as measured by the change from baseline to endpoint in the Montgomery-Asberg Depression Rating Scale (MADRS), and response and remission rates. A follow-up of 444 TRD patients who responded to a 12-week OFC trial assigned the patients double-blindly to maintenance treatment with OFC or fluoxetine for more 27 weeks; patients who responded to OFC relapsed less than patients treated with fluoxetine alone in the follow-up (10.9% vs. 28.3%, respectively) [40].

Quetiapine

The efficacy of quetiapine was tested in TRD by a number of double-blind, placebo-controlled, clinical trials. Quetiapine XR (300mg/day) given adjunctive to continuing antidepressant was shown to be effective in a trial enrolling 493 MDD patients with inadequate response; the antidepressant action of quetiapine was significantly different from placebo already at week 1 [41]. A post-hoc analysis showed the efficacy of 6-week trials of quetiapine as adjunct treatment to both SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) for treating TRD [42]. In another trial from the same group, quetiapine XR (300mg/day) both as add-on (n=231) or as monotherapy (n=228) promoted an improvement in MADRS scores similar to that of add-on lithium (n=229) in patients with TRD [43]. Importantly, a pooled analysis from four different studies on the efficacy of quetiapine XR monotherapy (50-300 mg/day) in MDD (not only treatment-resistant cases) found a consistent antidepressant effect across different levels of clinical severity [44].

Risperidone

One open-label 4-6 weeks trial on risperidone (0.25-2 mg/day) augmentation in MDD patients with insufficient response to citalopram (n= 386) found a remission rate of 63% at endpoint [45]. In a multicenter, double-blind, placebo-controlled investigation involving 274 MDD patients with suboptimal response to antidepressant treatment, risperidone (1-2 mg/day) as add-on for 6 weeks significantly improved depressive symptoms versus placebo, with response and remission rates of 46.2% vs. 29.5% and 24.5% vs. 10.7%, respectively [46]. Another double-blind, placebo-controlled study confirmed the efficacy of add-on risperidone (0.5-3mg/day) for TRD [47]. In addition, risperidone augmentation to antidepressant treatment was effective against suicidal ideation in a pilot study [48].

Aripiprazole

Aripiprazole augmentation to antidepressants has also been shown to be an effective strategy for TRD. Three 6-week, double-blind, placebo-controlled trials testing add-on aripiprazole (2-20 mg/day) for non-responders to antidepressant treatment showed improvement in depressive symptoms [49-51]. These studies enrolled each one around 180 patients in the aripiprazole augmentation arm; the improvement in depressive symptoms occurred regardless of MDD severity at baseline [52] and of patients having or not

minimal response (<25% reduction in MADRS) after initial antidepressant therapy [53]. Nevertheless, one large double-blind, placebo-controlled trial of adjunctive low-dose aripiprazole (2 mg/day) in MDD patients with inadequate response to prior antidepressant therapy (n=225) reported good tolerability, but only marginal efficacy over placebo [54].

Ziprasidone

Up to date, only one small, open-label trial investigated the potential of ziprasidone augmentation in TRD. A total of 64 TRD patients not responding to SSRI monotherapy were randomized to sertraline 100 to 200 mg/day, sertraline 100 to 200 mg/day plus ziprasidone 80 mg/day, or sertraline 100 to 200 mg/day plus ziprasidone 160 mg/day, and no significant differences in response rates were observed after 6 weeks [55]. In the same line, another study found no efficacy in ziprasidone against placebo for MDD [56].

The abovementioned findings in AAP have been corroborated and synthesized by a recent meta-analysis, reporting odds ratios (ORs) for remission of 1.42 (1.01–2.0) for OFC, 1.79 (1.33–2.42) for quetiapine, 2.37 (1.31-4.30) for risperidone, and 2.01 (1.48-2.73) for aripiprazole; ORs for response were also significant for quetiapine (1.53 [1.17-2.0]), risperidone (1.83 [1.16–2.88]), and aripiprazole [2.07 [1.58–2.72]), but were not for OFC [1.30 [0.87-1.93]) [33]. Also, asenapine is a new antipsychotic that showed to be effective in treating bipolar depression [57] and animal models [58]; studies in treatment-resistant MDD are warranted.

Although AAP have a smaller risk of producing extrapiramidal symptoms than their first generation counterparts, it is important to notice that augmentation treatment with AAPs is potentially associated with other adverse events, as shown by two recent meta-analyses [33,59]. The most frequent side effects were sedation (OFC, quetiapine, and aripiprazole), metabolic abnormalities such as dyslipidemia and hyperglicemia (especially OFC, but also quetiapine), weight gain (especially OFC, but also quetiapine, risperidone, and aripiprazole), and akathisia (aripiprazole). Nevertheless, overall the use of AAP adjunctive to antidepressant therapy is an effective strategy for TRD.

ADJUNCTIVE LITHIUM

Lithium is an ion with action on intracellular signaling systems, such as the inositol pathway, the enzyme glycogen synthase kinase 3-β, and mitochondrial function/oxidative stress [60,61]. The ion is commercially available in the form of the salt lithium carbonate.

Initial studies have shown lithium efficacy as add-on treatment in treatment-resistant MDD [62]. A recent meta-analysis evaluated the efficacy of lithium augmentation to antidepressants in 9 double-blind trials including mostly MDD patients (n=237) [63]. There was an odds ratio (OR) of 2.89 favoring response to lithium against placebo. Most of the included trials studied lithium added to TCAs; 3 investigations evaluated lithium adjunctive to SSRIs (or other newer antidepressants) and found an OR of 3.06 (95% CI, 1.19-7.88) for response, with an NNT of 5. Moreover, open-label studies have shown that lithium add-on to venlafaxine and desipramine is an effective strategy in TRD, with response rates of 35-65% [64, 65].

However, in the STAR*D study, MDD patients who failed to respond to two antidepressant trials showed a remission rate of 15.9% with adjunctive lithium versus 24.7% with triiodothyronine (T3) augmentation, even though this difference was not significant [66]. A possible explanation for the low remission rates with lithium augmentation is the use of low lithium doses in STAR*D study.

Lithium showed a good tolerability when compared to other adjunctive medications for TRD. In the large study of quetiapine versus lithium as add-on strategies (n=460) discussed above, discontinuation rates because of adjunctive lithium were 7.9% against 10.0% with add-on quetiapine [43]. Common side effects of lithium treatment include polyuria, polydipsia, tremor, and thyroid dysfunction [67].

Potential advantages of augmentation with lithium include its efficacy on relapse prevention in MDD [68, 69], although there are no long-term studies of lithium use in patients with TRD. Also, a recent meta-analysis found reduced suicide risk (0.36; 95% CI, 0.13-0.98) in MDD patients under lithium treatment [70].

AUGMENTATION WITH THYROID HORMONES

The use of thyroid hormones, especially T3, adjunctive to antidepressants for the management of TRD has received some support in the literature, as discussed in more detail here.

One meta-analysis carried out almost 20 years ago and encompassing 8 studies (n=292) showed that T3 augmentation was effective in euthyroid patients with TRD [71]. In this meta-analysis, patients receiving T3 augmentation were twice as likely to respond as placebo-treated patients, corresponding to a 23.2% increase in response rates. Another meta-analysis on T3 augmentation to TCA found it to be significantly more effective than placebo in accelerating clinical response [72].

While the evidence of efficacy for T3 augmentation to TCAs is well established, data on T3 adjunctive to SSRIs are more scarce. A systematic review on T3 augmentation to SSRIs conducted in 2008 found only a few open-label and controlled trials with highly variable design/ methodology and concluded that the available evidence was inconclusive [73]. Since then, only one 8-week, double-blind, randomized placebo-controlled study has been published, comparing flexible dose sertraline plus T3 (n=54 completers) versus sertraline plus placebo (n=54 completers) in MDD outpatients with variable clinical courses (resistance to previous SSRI trials was not an inclusion or exclusion criteria) [74]. At endpoint, no significant difference on response and remission rates (65% of placebo versus 61.8% of T3 treated subjects achieved response; 50.6% of placebo versus 40.8% of T3 treated patients achieved remission) was observed. As mentioned above, in the STAR*D trial T3 augmentation to ongoing antidepressant treatment (citalopram,

sertraline, bupropion SR or venlafaxine XR) resulted in a modest remission rate of 24.7% in MDD patients who had experienced unsatisfactory results with two prior medication treatments [66].

Only three open-label, uncontrolled trials on the efficacy of adjunctive thyroxine (T4) in TRD have been published so far. All these investigations have enrolled small samples (n=17-28) of patients with both unipolar and bipolar depression, and found remission rates of 21.5% - 64.7% [75-77]. Thus, due to the poor design and small sample sizes of these investigations, the currently available evidence is insufficient to indicate the use of T4 in TRD.

Adverse effects of thyroid hormones include bone demineralization in the long-term and cardiac arrythmias, especially when thyroid hormones are given in high doses [76, 78].

In conclusion, the results of early studies suggest that T3 augmentation to TCA is a potentially useful strategy in TRD. However, more recent trials evaluating the efficacy of adding T3 to SSRI or other newer antidepressants in MDD patients with an insufficient response have found less exciting results.

TARGETING OTHER BRAIN SYSTEMS

Adjunctive Psychostimulant Therapy

Psychostimulants are agents that promote wakefulness and cognitive enhancement, acting primarily on the dopaminergic system. They are commonly prescribed for treating mood disorders in clinical practice, but the data supporting this practice is still limited.

Two double-blind clinical trials (n=60 and n=145) evaluating the efficacy of methylphenidate in TRD have found no significant improvement in depression scores when compared to placebo [79,80]. However, in one of these studies methylphenidate significantly improved fatigue and apathy [80]. Results from both randomized controlled trials and a meta-analysis suggest that adjunctive treatment with modafinil or armodafinil are effective in improving depression in patients with incomplete response to standard treatment, with significant positive effects also on fatigue symptoms and wakefulness [81,82]. One proof-of-concept trial showed lisdexamfetamine dimesylate add-on to escitalopram to be more effective than placebo in treating depressive residual symptoms [83].

Overall, most studies available to date on psychostimulant efficacy as add-on treatment to antidepressants have comprised relatively small sample sizes and had short-term duration, which limit the interpretation of the results [84]. Thus, while there have been some favorable findings to support modafinil augmentation in MDD patients with insufficient response to an antidepressant trial, larger well designed placebo-controlled studies with longer follow-up are still warranted before psychostimulants use in TRD can be formally recommended.

Other Dopaminergic Agents

Pramipexole is a D2-D3 receptor agonist used primarily for Parkinson's disease. An 8-week double-blind trial enrolling 174 MDD subjects showed that monotherapy with pramipexole 1.0mg/day was as effective as fluoxetine 20mg/day and more effective than placebo in reducing HAMD, MADRS and global clinical scores [85]. In this study, a high drop-out rate due to adverse effects was observed with 5.0mg/day dosage [85]. Only two small studies have assessed the efficacy of pramipexol monotherapy or in combination with escitalopram specifically in TRD cases [86,87]. Although suggesting that pramipexol monotherapy at doses of nearly 1.0mg/day might be an effective option for TRD — a response rate of 66.7% on MADRS scores was observed after 16 weeks by Lattanzi *et al*. [86], the small samples, and uncontrolled or flawed design of these investigations limit the interpretation of these findings [86, 87]. Importantly, a high dropout rate (69%) mostly due to severe side effects was observed by Franco-Chaves *et al*. [87] in the arm of pramipexole plus escitalopram 10mg/day.

Amantadine is an uncompetitive antagonist of NMDA glutamatergic receptor that enhances dopaminergic neurotransmission by counteracting glutamatergic inhibitory inputs on presynaptic dopaminergic neurons. There is only one small (n=50), open-label and uncontrolled study that compared imipramine 100mg/day monotherapy versus imipramine plus amantadine 150mg/day for TRD, reporting a significant reduction in HAMD scores after 6 weeks [88], and an even smaller open-label study (n=8) with positive results [89].

Combination with Buspirone

Buspirone is an anxiolytic drug that acts on 5-HT_{1A} receptor as a partial agonist. Although buspirone has shown efficacy for treating MDD in open-label studies, the two double-blind, placebo-controlled trials available to date found no significant benefits of adding buspirone to SSRI in the treatment of MDD [90, 91].

Targeting Glutamate

Several evidences point to role of glutamate and NMDA receptors in the pathophysiology of MDD. The imbalance in glutamate neurotransmission may result in increased NMDA agonism consequently activating brain circuits involved in MDD [92]. Clinical evidences for a glutamatergic hypothesis of depression include interventions that modulate glutamate function improving depressive symptoms in patients with MDD [93]. The modulation of glutamatergic system has been shown to be direct (*e.g*., ketamine and riluzole) or indirect (*e.g*., scopolamine).

The antidepressant action of ketamine is probably mediated by increasing glutamatergic throughput at the a-amino-3-hydroxy-5-methyl- 4-isoxazolepropionic acid (AMPA) receptor relative to N-methyl d-aspartate (NMDA) receptor [94]. Due to its glutamatergic properties, ketamine has demonstrated a very fast onset of antidepressant action, one to four hours after a single intravenous (IV) infusion (0.5mg/kg) [95]. In open-label clinical trials, riluzole, another glutamatergic agent, have significantly decreased depressive symptoms after 1-2 weeks of treatment in TRD patients [96, 97]. A recently tested herb, Radix Polygalae, that acts on glutamate has shown a very fast onset of action

in mice models; 30 minutes after extract infusion the antidepressant-like behavior changed in mice [98].

Although the studies evaluating ketamine are robust in showing the rapid improving of symptoms including suicidal ideation in TRD [99], the antidepressant effect of ketamine IV infusions is reported to last for around 2 weeks only [100,101]. In order to maintain the antidepressant effect, repeated IV ketamine infusions would be needed. In order to overcome the need for support services when using ketamine IV, ketamine intranasal was developed. A recent double-blind, placebo-controlled trial on the efficacy of intranasal ketamine in MDD observed a fast antidepressant effect and good tolerability, with a response rate of 44% in the ketamine group and 6% in the placebo group after 24 hours [102]. It is important to notice, however, ketamine is a drug with psychomimetic effects and potential for abuse; also, the therapeutic use of ketamine may trigger dissociative symptoms [103].

Studies with scopolamine IV infusion have shown antidepressant efficacy. In a double-blind, placebo-controlled, crossover clinical trial, scopolamine has been shown to be effective in MDD [104] Moreover, augmentation with oral scopolamine yielded a significantly greater improvement in depression symptoms in MDD patients than placebo in a double-blind 6-week trial, with a remission rate of 65% in the active group against 20% in the placebo group [105]. In BD and MDD patients resistant to 2 antidepressant trials, oral scopolamine decreased depressive symptoms when compared to placebo [106].

A double-blind RCT showed the antagonist of glutamatergic NMDA receptor D-cycloserine effective against depressive symptoms in patients with treatment-resistant MDD, reinforcing a role of the glutamatergic system as an important target for depression treatment [107].

In sum, the use of glutamatergic agents has shown promising results in the short-term treatment of TRD. However, there is a lack of larger, well-designed trials aiming to assess the role of these agents in the long-term, *i.e.*, maintenance treatment of MDD.

Nutraceuticals and Hormone Supplementation

Evidence shows a relationship between low folate levels and depression; low folate levels were associated with a worse response to antidepressant treatment [108]. In addition, a polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene, which encodes an enzyme crucial for folate metabolism, has been associated with a more severe course of MDD [109].

The evidence prompted investigation on S-adenosylmethionine (SAMe) and L-methylfolate as adjunctive agents for TRD. In a preliminary study, patients with SAMe add-on (up to 800 b.i.d.) to SSRI or SNRI showed higher response and remission rates than patients receiving placebo [110]. In double-blind trials, patients treated for 60 days with L-methylfolate add-on to SSRI had greater response rate and degree of change in depression symptom score than patients receiving placebo [111]; the NNT was around 6. Studies with larger samples are warranted to confirm these promising findings.

A preliminary open study showed low-dose testosterone effective as augmentation to treatment as usual in treatment-resistant MDD women [112], though evidence does not support use of testosterone in eugonadal men with TRD.

Targeting Inflammation

A possible pathophysiological mechanism associated with TRD is inflammation [113]. Understanding the inflammatory molecular mechanisms of treatment response may provide new strategies for treatment-resistant patients in order to reduce negative outcomes such as suicidal behavior. Targeting specific cytokines that are associated with suicidal behavior such as IL-2, IL-6, IL-8, and tumor necrosis factor (TNF) [114] could help prevent suicidality in TRD patients.

Importantly, MDD patients with baseline increased IL-6, low HDL cholesterol, hypertriglyceridemia, and hyperglycemia were less likely to achieve remission after 2 years of treatment than patients without these inflammatory and metabolic dysregulations [115].

The evidence of inflammatory processes in MDD has been the rationale for studying the anti-inflammatory celecoxib as an adjunctive to antidepressant treatment. A recent meta-analysis evaluated four double-blind, placebo-controlled trials (totaling 150 patients) on adjunctive celecoxib for MDD [116]. Patients receiving adjunctive celecoxib showed a better improvement on depressive symptoms (mean difference=3.26; 95% CI, 1.81-4.71) as well as higher response (OR=6.49; 95% CI, 2.89-14.55) and remission (OR=6.58; 95% CI, 2.55-17.00) rates than patients receiving placebo. Overall, celecoxib was well tolerated.

A proof-of-concept double-blind, RCT, studied tumor necrosis factor (TNF) antagonist infliximab treatment for 60 TRD patients (mostly MDD) [117]; although the patients on infliximab did not have a greater improvement in depressive symptoms than patients on placebo, patients with increased TNF at baseline responded more than patients without baseline TNF increase. Also, infliximab-treated responders showed a greater decrease in reactive C protein from baseline to endpoint than placebo-treated responders.

Physical Exercise

Adjunctive aerobic exercise of 16 kcal per kg per week (KKW) expenditure had a trend for higher efficacy than 4 KKW of exercise expenditure with a NNT of 7.8 in a trial enrolling 126 patients [118]; noteworthy, in this study increased TNF-α at baseline was associated with a better response to physical exercise [119], suggesting a possible role of aerobic exercise on targeting specifically the inflammatory dimension of MDD. Three meta-analyses with some overlapping studies also support an antidepressant effect of physical activity, especially aerobic exercise, although this effect seems to have a short-term duration and modest effect-size only [120-122].

SOMATIC TREATMENTS

Electroconvulsive Therapy (ECT)

Electroconvulsive therapy (ECT) is one of the most investigated treatments for mental disorders, being introduced by Ugo Cerletti and Lucino Bini in the 1930s. ECT uses potent electric stimuli for inducing therapeutic seizures.

ECT is indicated for several psychiatric disorders; however, one of the most frequent indications of ECT is TRD. The UK ECT review group, in a recent meta-analysis [123], showed that active ECT is more effective than sham ECT (mean difference in endpoint Hamilton scores of 9.7 points) and antidepressant drug treatment (mean difference of 5.2 points). Bilateral ECT is significantly more effective than unilateral ECT (mean difference of 3.6 points). In another meta-analysis, Ren *et al*. [124] showed that ECT is significantly more effective than rTMS in terms of response and remission (RRs of 1.41 and 1.38, respectively). Subgroup analyses revealed that ECT is more effective than rTMS only for psychotic depression. It should be noted, however, that only 9 trials (n=425 patients) were enrolled and the "doses" of rTMS varied among studies. In fact, another meta-analysis [125] found that rTMS was as effective as ECT when higher "doses" were used, *i.e.*, 20Hz stimulation, ≥ 1200 pulses per day or longer period of treatment.

ECT is associated with short- and long-term cognitive side effects. *Delirium* and memory disturbances are often observed immediately after ECT and are usually time-limited. However, retrograde amnesia can be persistent and long lasting. Some groups of patients (older age, lower education level, lower IQ, concomitant use of lithium) are especially prone to develop such effects. In such patients, ECT is usually applied with specific parameters to minimize the risk of side effects – *e.g*., right unilateral (RUL) and bifrontal (BF) electrode positioning and dose titration to use the lowest possible and effective dose [126]. Also, due to the use of anesthetic and muscle relaxing agents, ECT should not be combined with a variety of pharmacological drugs and severe and life-threatening conditions.

ECT is highly recommended for MDD that did not respond to pharmacological treatment [127], although many physicians do not indicate ECT for this condition considering the resistance of patients and ECT cognitive side effects.

Magnetic seizure therapy is a technique involving brain stimulation to produce therapeutic seizures through a high-frequency rTMS without inducing cognitive impairment. A pilot open-label study enrolling 13 patients with treatment-resistant MDD showed efficacy in reducing depressive symptoms [128]. Further studies are needed to confirm the preliminary findings.

Repetitive Transcranial Magnetic Stimulation

TMS is a neuromodulatory technique introduced in the 1980s by Barker *et al*., who showed that single electro-magnetic pulses over the motor cortex elicited painless muscular contractions in the contralateral hand. Later on, other studies showed that repetitive pulses of TMS (rTMS) induce neuroplastic effects according to the parameters of polarization: high-frequency rTMS (usually ≥10Hz) induced an increase in cortical excitability, while slow or low-frequency rTMS – (usually ≤1Hz) induced opposite effects [129].

The first rTMS studies for the treatment of depression were conducted in the 1990s. Pascual-Leone *et al*. [130] showed depression improvement when high-frequency rTMS was applied over the left DLPFC, but not over the right DLPFC or the occipital cortex. After an important double-blind RCT suggesting efficacy of rTMS in treatment-resistant MDD [131], two multicenter rTMS trials were pivotal and consolidated rTMS use as a clinical (non-experimental) treatment. In one of them, O'Reardon *et al*. [132] evaluated 301 patients with treatment-resistant MDD without current antidepressant therapy. RTMS was applied over the left DLPFC at a 10Hz (120% motor threshold), 3000 pulses/day for 4-6 weeks. Active rTMS was statistically superior to sham intervention for the improvement of depressive symptoms at endpoint as assessed with the Montgomery-Asberg Depression Rating Scale (MADRS). In a FDA-sponsored study, George and colleagues [133], evaluated the effect of daily, 10-Hz rTMS (3000 pulses/day) over the left DLPFC in 199 treatment-resistant MDD without concomitant antidepressant use. Primary outcome revealed a significant (p=0.02) superior remission rate of active (14.1%) vs. sham (5.1%) rTMS. Importantly, Lisanby and colleagues [134], in a secondary analysis of the study of O'Reardon *et al*., demonstrated that patients with unipolar depression who had failed only a single adequate medication trial for the index episode were more likely to have a therapeutic response to the rTMS protocol than those who have failed 2–4 antidepressant trials.

Lam *et al*. [135] performed a meta-analysis to evaluate the efficacy of rTMS for TRD. The authors reviewed 24 studies (n=1092 patients), finding that pooled response and remission rates were 25% and 17%, and 9% and 6% for active rTMS and sham conditions, respectively. The authors also underscored that dropouts and adverse event rates were low. In another recent meta-analysis presenting studies overlapping with the former meta-analysis, Gaynes *et al*. [136] investigated randomized clinical trials that recruited patients presenting a previous failure to two antidepressant drug treatments. The authors observed that active vs. sham rTMS was significantly more effective for the treatment of depression considering depressive (symptom's) improvement, response rate and remission rate. In terms of improvement of symptoms, active rTMS decreased symptoms > 4 points compared to sham rTMS, which is a clinically meaningful effect according to NICE guidelines. Response rates in the active rTMS were 29%, with a corresponding NNT between 5 and 9 when considering response rates in the sham arm of 10% and 5%, respectively. With lower evidence, this meta-analysis also observed remission rates around 30% and a NTT between 5 and 7 when comparing active vs. sham rTMS.

Currently, rTMS is a FDA-approved treatment for patients who did not show improvement with pharmacotherapy – *i.e.*, indicated to patients with at least some degree of treatment

resistance. Nevertheless, optimal parameters for rTMS in this subgroup remain an open question. Although usually rTMS is applied over 12-15 days, treatment lengths can vary between 5 and 30 week-days, and it seems that longer periods might be associated with greater improvement [133,137]. Also, although high-frequency rTMS over the left DLPFC is commonly used for treatment, low-frequency rTMS seems to be equally effective, at least when considering non-TRD trials as well [138]. It is still unclear whether and how rTMS should be combined to pharmacotherapy to provide optimal results in patients with TRD, who are usually using two or three different drug classes. In fact, rTMS is a well-tolerated technique with few, mild adverse effects. The most serious adverse effect is seizure, with an incidence of <0.01% [139]. Other potential adverse effects are rare and include syncope episodes due to vasodepressor-related mechanisms, headaches and acute psychiatric changes, such as treatment-emergent affective switches. However, a meta-analysis indicates that the rate of treatment-emergent affective switches did not significantly differ between rTMS and the sham procedure [140]. Finally, there are only a few contra-indications of rTMS, which basically involves not using rTMS near implantable, electronic devices (as they can be resetted due to magnetic pulse) or metallic objects implanted or located in the head.

After the treatment of the acute depressive episode, it is still unclear how rTMS should be used in the maintenance phase. One proposal is to perform rTMS sessions two times a week. In this context, a 6-month follow-up reported 62% of MDD TRD patients (n=42) maintaining response [141]. Also, a recent clinical trial enrolled 59 consecutive patients with TRD who have responded to rTMS treatment, randomizing them into a 20 week maintenance period for receiving active or sham rTMS two times a week. At final follow up maintenance rTMS was associated with a significantly lower relapse rate (37.8%) compared to participants on the sham procedure (81.8%) [142]. Although promising, this finding deserves replication.

A recent TMS coil enables the stimulation of deeper brain regions in a method called deep rTMS, which has been shown effective and safe in an open-label trial in TRD [143]. More studies, however, are warranted to establish the efficacy of the new method.

Other Neuromodulatory Therapies

Vagus Nerve Stimulation (VNS) is an invasive neuromodulatory technique that consists in stimulating the left vagus nerve by using an electrode and implantable pacemaker. VNS probably acts by a "bottom-up" phenomenon, through stimulation of the vagus nerve and subsequent stimulation of subcortical and cortical structures associated with depression. Although its efficacy for epilepsy is well established, the evidence in depression is limited, considering that most of the data are originated from open-label studies and series of cases [144-147], with only one double-blind RCT, which showed inconclusive results [148]. Nevertheless, VNS is approved in the US for treating patients who failed to at least four antidepressant drug treatments [149].

External trigeminal nerve stimulation is a therapeutic strategy that implies in the application of electric current on the region of a trigeminal nerve branch, which propagates the stimuli to brain. A small open-label study (n= 11) found 8-week external trigeminal nerve stimulation effective for treating TRD in MDD patients [150]. These preliminary results merit replication in larger trials.

Deep Brain Stimulation (DBS) is a technique in which electrodes connected to pulse generators are implanted in specific brain areas. DBS has achieved remarkable results for Parkinson disease, although the evidence of efficacy for depression is limited, as studies have enrolled small samples and investigated several different brain areas for electrode placement, notably the subgenual cingulate cortex. Nevertheless, some studies have shown good response rates in highly refractory samples [151] and a recent meta-analysis found an effect size of 1.71 (95% CI: 1.47-1.96) for DBS versus sham in TRD [152].

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique that changes cortical excitability through two electrodes placed over the scalp. A recent meta-analysis enrolling 259 patients showed that active vs. sham tDCS was effective for depression, considering change in scores and response and remission rates [153]. However, trials enrolling patients with treatment-resistant depression showed non-significant results for tDCS. Future studies are necessary to determine in which samples tDCS should be applied.

PSYCHOTHERAPY APROACHES

A number of studies and two meta-analyses [154, 155] demonstrate that the presence of a comorbid diagnosis of personality disorder to MDD more than double the risk of a poor outcome, including response to pharmacological treatment. One European multicenter investigation studied 346 patients with nonresistant MDD and 356 subjects with TRD and found that the presence of personality disorder was significantly related to TRD [156]. Factors potentially involved in this relationship are: 1) TRD subjects with a comorbid personality disorder present higher discrepancy between self-rated and observer-rated scores in depression symptoms – and higher discrepancy also predicts slower response to treatment independent of objective illness severity [157]; 2) Comorbidity with personality disorders was found to be a predictor of nonadherence among patients with mood disorders [158].

So far, however, few investigations have assessed which specific personality disorders or traits are associated to treatment resistance. One small case-control investigation found that, relative to MDD patients in remission (n=31) and healthy controls (n=174), TRD subjects (n=35) showed higher scores for harm avoidance, and lower scores for reward dependence, self-directedness, and cooperativeness in Cloninger's Temperament and Character Inventory [159]. A 3-year naturalistic follow-up study found that the presence of avoidant personality disorder was a risk factor for a severe relapse in MDD patients who had been discharged from hospitalization (n=458) [160]. Interestingly, a TMS trial in

TRD found that improvement in depression symptoms was significantly associated with higher baseline levels of agreeableness, conscientiousness and extraversion [161].

These results highlight the relevance of dysfunctional personality traits in TRD and reiterate the needs to move beyond attempts to modify symptoms without taking into consideration the patient's personality, coping skills, and social system [162]. Thus, associating psychotherapeutic approaches to other biological treatments is an important strategy in the management of TRD.

Interestingly to this regard, in the STAR*D study cognitive therapy (either alone or as augmentation) was demonstrated to be as effective (*i.e.*, similar response and remission rates) as other medication strategies as a second level approach for MDD patients with inadequate response to an initial trial of citalopram [163]. Also, one large randomized controlled trial on the effectiveness of cognitive behavioural therapy (CBT) adjunctive to usual care (n=234) versus usual care (including pharmacotherapy) alone (n=235) [164] showed that associating CBT more than doubled the response rate (46% versus 22% in the usual care group) after 6 months of follow-up. Overall, while there is a large body of evidence suggesting that most psychotherapy approaches – cognitive, behavioral and short-term psychodynamic, among others – are equally effective in the treatment of non-resistant MDD [165,166], there is a paucity of controlled trials with adequate follow-up periods in TRD [5].

Nevertheless, considering the impact of a comorbid personality disorder in the treatment outcome of MDD, it is important to mention the result of a well-conducted meta-analysis that demonstrated a superior efficacy of long-term psychodynamic psychotherapy (LTPP) over less intensive forms of psychotherapy in patients with complex mental disorders (defined as personality disorders, chronic mental disorders, or multiple mental disorders) [167]. Therefore, for TRD patients with severe personality disorders and who don't benefit also from structured and/ or short-term psychotherapy interventions, LTPP might be considered.

CONCLUSION

The present review summarizes the current pharmacological and non-pharmacological strategies available for managing TRD. The diversity of treatments reflects the complexity of MDD, in which a single strategy cannot account for the diverse facets of the disorder [168]. Due to this complexity, the management of TRD should ideally target the variants relevant to each patient [169]. The paucity of strong evidence to guide clinical decision reflects the need of larger and well-designed studies in TRD.

Switching from an SSRI to venlafaxine is a strategy supported by the literature, although the advantage of switching to venlafaxine over other SSRIs is not clear. However, in more severe cases of TRD, venlafaxine showed to be especially useful. The combination of antidepressants, especially mirtazapine, may be beneficial for some patients with TRD, although further studies are needed to establish the superiority of mirtazapine combined with other antidepressants over antidepressants alone. Augmentation of antidepressants with lithium or T3 has received wide support in the literature, although in most of the studies they have been evaluated as adjunctive drugs to TCAs and the effect-sizes were usually small. AAPs have shown good efficacy as augmentation agents in several well-designed studies and meta-analyses, but metabolic side effects may limit their use. Moreover, the lack of independent trials (not sponsored by pharmaceutical industries) is a limitation of the studies on AAP. Although there are some promising results on the use of modafinil as an augmentation strategy, the role of psychostimulants in TRD is not yet established.

The first drugs used in the treatment of MDD, MAOIs and TCAs, share the same essential mechanism of action with the newer antidepressant classes SSRIs and SNRI, among others: modulation of monoaminergic neurotransmission. Although after the first trial this conventional strategy has shown 70% of response, only 28% of the patients achieve full remission [4]. Results from STAR*D study show that remission rates decrease in the following medication trials. The findings suggest that the drugs modulating monoaminergic neurotransmission have an important but insufficient role in the treatment of MDD, especially TRD.

The discover of new treatments with other targets may greatly improve the strategies for TRD. Also, studies focusing on TRD patients could provide insight into clinical and neurobiological specificities of MDD that resisted to conventional treatment. In this context, the use of non-steroidal anti-inflammatory celecoxib, L-methylfolate, and SAMe is promising. Similarly, the studies of drugs targeting glutamatergic system (*e.g.*, ketamine, scopolamine, and riluzole) may provide new strategies for TRD. Physical exercise seems an interesting strategy for TRD at least in the short-term, though further studies are needed to clarify which patients would benefit the most. ECT has a strong evidence of efficacy in TRD, whereas the evidence for other neuromodulation strategies is limited. Finally, considering that dysfunctional personality traits are associated with poorer outcomes in MDD and that the few available controlled trials on the efficacy of psychotherapy in TRD have shown positive results, psychotherapy should be considered to TRD subjects, especially in cases with comorbid personality disorder.

Overall, the risk/benefit assessment and evidence-based decision making are essential to define the best therapeutic approaches for TRD.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

AAP	=	Atypical antipsychotics
BD	=	Bipolar Disorder
HAM-D	=	Hamilton Depression Scale

MAOI	=	monoamine oxidase inhibitors
MDD	=	major depressive disorder
rTMS	=	repetitive transcranial magnetic stimulation
SNRI	=	serotonin and norepinephrine reuptake inhibitor
SSRI	=	selective serotonin reuptake inhibitor
STAR*D	=	Sequenced Treatment Alternatives to Relieve Depression
TCA	=	tricyclic antidepressant
tDCS	=	transcranial direct current stimulation
TRD	=	treatment-resistant depression

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