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Resistant Depression

Jose Alfonso Ontiveros

Abstract

The term resistant points out a clinical phenomenon in which there is a lack of response to one or more therapeutic interventions. Resistance to major depressive disorder treatment causes distress to patients and their relatives, and increases the number of hospital admissions, outpatient consultations, use of psychoactive drugs, and treatment costs. Despite its serious medical and psychosocial medical implications, the definition of treatment resistant depression continues to be ambiguous and controversial. The lack of an agreement on definition, as well as the research on the subject being difficult, limits the practical knowledge on the best treatment options for groups of treatment resistant depression (TRD) patients. We review the concept and definitions of treatment resistant depression as well as the medical literature on different treatment methods studied and comparative studies. Finally, some relevant neurobiological data are reviewed.

Keywords: treatment, major depressive disorder, resistant depression, antidepressants, review

1. Introduction

The term “resistant” is widely employed in medical practice to point out a clinical phenomenon in which there is a lack of response to one or more therapeutic interventions. The presence of treatment resistance implies a specific series of clinical interventions, typically multidisciplinary, and focuses on solving or minimizing a medical problem. Resistance to major depressive disorder treatment, but also to other depressive disorders, such as dysthymia and bipolar depression, causes distress to patients and their relatives, and increases the number of hospital admissions, outpatient consultations, the use of psychoactive drugs, and treatment costs up to six times [1]. The definition of treatment resistant depression (TRD) continues to be ambiguous and controversial despite its serious medical and psychosocial implications. In medical literature, we can find more than 10 different definitions [2]. Many authors have published staging systems with their own definitions, descriptions, and characteristics on TRD [3–7]. The most accepted definition is a lack of response to two different pharmacological classes of antidepressants [8]. However, this definition may seem simplistic today as published treatment results on TRD patients emerge. The lack of an agreed TRD definition as well as the difficulties to do research on the subject limit our practical knowledge on the best treatment options for groups of TRD patients.

We review the concept and definitions of TRD. We also review the medical literature on different treatment methods studied as well as comparative studies. Finally, we review some relevant emerging neurobiological data.

2. Treatment resistance depression (TRD)

2.1 The concept of resistant depression

Although this phenomenon had already been described, many authors have introduced the concept of TRD since 1974 [9, 10]. This concept arises at a time when there were only tricyclic, tetracyclic, and monoamine-oxidase inhibitors (MAOIs) antidepressants available. In spite of its importance, the definition of treatment resistance regarding major depression continues to be a wide and inconsistent notion. A review of the literature identifies a range of definitions for TRD that go from non-response to a single antidepressant (for 4 or more weeks) to lack of response to different classes of antidepressants and electroconvulsive therapy (ECT) [2]. Treatment should be appropriate in dose and duration [2, 11–13], and patients must have full compliance to it [13] to consider a patient as resistant to treatment. There is no consensus on the number of treatments and when these are indicators of resistance.

A dichotomic denomination has been proposed for resistant depression, viz. an absolute and a relative. Absolute resistance is an inappropriate anti-depressive response toward a treatment given for an appropriate period of time at the maximum non-toxic dose. On the other hand, relative resistance to treatment is defined when this is given at a suboptimal dose or duration [5, 10, 14]. The terms “chronic,” “refractory,” and “difficult-to-treat depression” have been employed as synonyms in the absence of a nonspecific number of clinical trials for one or more antidepressants. Treatment refractory depression refers to major depression that does not respond to multiple sequential treatments. There is no clear difference between treatment resistant depression and refractory depression [5, 8, 11]. Chronicity, however, refers to a pathological clinical phenomenon that lasts for 2 or more years. There is no consensus on depressive symptom severity to consider it as resistant. It has been suggested that a score of 16 or more on the Hamilton depression 17-item scale (HAM-D) is enough to confirm the diagnosis. However, patients with persistent mild or moderate depressive symptoms may have a worse prognosis than those in remission [15]. The definition of Berlim and Turecki [2], which considers TRD as an episode of major depression that has not improved after two proper attempts with different classes of antidepressants, prevails today. The European Medicine Agency (EMA), on a TRD definition review, considers it as a clinically relevant major depression that has not benefited from at least two appropriate attempts of treatment with at least two antidepressants with a different action mechanism [16]. The definition which considers TRD as an episode of major depression that has not improved after two proper attempts with different classes of antidepressants [2] seems to be backed up by the STAR*D study, which shows that improvement chances diminish after the second treatment failure [17, 18]. Treatment resistance to pharmacologic treatment seems to move on a continuum that ranges from total response to total resistance to therapeutic intervention and not as an all-or-nothing phenomenon [5, 19, 20]. However, no definition has been investigated regarding validity and predictability [5, 21]. Inconsistencies on the definition not only give rise to difficulties at estimating its prevalence [17, 22] but can also delay research of the most efficient treatment schemes.

2.2 Prevalence of resistant depression

In spite of pharmacological treatment advances in major depression, the final objective of achieving a sustained improvement continues to be insufficient [23]. It is estimated that about only 30–40% of patients achieve remission after the first attempt of treatment with antidepressants. In 3671 ambulatory patients treated

with escitalopram, only 37% achieved remission [18]. Even after an appropriate sequence of treatments, 10–20% of the patients with major depression continue with significant symptoms for 2 years or more [24, 25]. The STAR*D study (sequenced treatment alternatives to relieve depression study) showed that accumulated remission after four treatment trials with antidepressants for 14 months was 67% [26]. Patients with chronic depression seem to have less opportunity for recovery [27] and tend to be more resistant to treatment [1, 28]. TRD is also associated to longer time of treatment and increased costs [29].

2.3 Antidepressant treatment resistance assessment scales and stratification systems

2.3.1 Antidepressant treatment assessment scales

From the multiple published assessment scales, three of them stand out in literature: the Antidepressant Treatment History Form [30], the Harvard Antidepressant Treatment History [31], and the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire [6]. The clinician performs the former two; the latter is performed by the patient.

The Antidepressant Treatment History Form (ATHF; 1990; revised 1999) was originally designed to assess the efficacy of antidepressant treatment before ECT [30]. The scale has five treatment levels, which go from 0 (no treatment) to 5 (high antidepressant doses plus lithium or triiodothyronine (T3) for at least 4 weeks, including antipsychotics in patients with depression and psychotic symptoms. The scale has been modified and recently digitalized [32]. This scale has the disadvantage of not including pharmacological combination strategies or preferences on switching treatment [33]. The Antidepressant Treatment History Form has been empirically validated with the monitoring of prospective treatment [8, 33–35]. The original ATHF version has a good inter-rater reliability [3], and the digitalized version has an excellent inter-rater reliability as well, with another evaluator [32].

The Harvard Antidepressant Treatment History (HATH) allows to systematically assess the dose and duration of previous antidepressant medication trials. The patient identifies all the antidepressants taken from a list of all available once, a series of systematic questions over dose, duration, and response are asked to determine treatment response or resistance [31].

The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ) is an auto-evaluating scale that defines an appropriate antidepressant treatment as optimal dosage during 6 weeks. This questionnaire provides operational criteria for adequate dosing of each antidepressant and has been used on multiple multicentric studies in TRD. In one study, it was found that MGH and ATRQ agree with the independent evaluations of clinical researchers on remote interviews [36].

2.3.2 Treatment resistant depression stratification systems

Systems may help predict the ulterior course of depression on the long-term and its response to treatment [1]. It is important to point out that all systems based on treatment administration have limitations; they were designed when therapeutic options available at the time were more limited, and despite their clinical usefulness, they have not been properly validated.

Four stratification systems stand out in literature: the Staging Method of Thase and Rush [4], the European Staging Method [5, 37], the Massachusetts General Hospital Staging model (MGH-s) [6], and The Maudsley Staging Model (MSM) [7].

Thase and Rush proposed five levels of resistance, in which patients are categorized according to the number and antidepressant class they have failed to respond, from the most frequently used to the least usual as MAOIs or ECT [4]. Not one degree of each therapeutic trial in terms of dose and duration is recorded; it assumes that the non-response to two antidepressant agents of different classes is more difficult to treat than the non-response to agents of the same group and that the change to an antidepressant of the same group is less effective. The later may be true for tricyclic antidepressants, but it is not so at switching between different serotonin reuptake inhibitors (SSRIs) [17]. This classification considers that the most effective antidepressants on order would be MAOIs, tricyclic antidepressants, and SSRIs, which has not been validated on different meta-analyses in antidepressant trials [17, 20]. It also faces the disadvantage of not including other treatments, such as drug combinations and psychotherapy, and does not provide prognostic information [38]. The Thase and Rush scale is easy to implement and provides an accessible strategy for clinicians to treat TRD patients. However, it has been widely criticized recently, since its predictive value over the course of treatment has not been systematically evaluated [8, 33, 34].

A European Staging Method (ESM) proposes the classification between non-responders, patients with TRD, and chronic resistant depression (CRD). Non-responders are defined as patients who fail to respond to a method of treatment. Patients are considered TRD if they show poor response to two treatment options with different classes of antidepressants at a proper dose over the span of 6–8 weeks. CRD is defined as a resistant or refractory episode that lasts for more than a year despite appropriate therapeutic interventions. This scale has the advantage of including the duration of the depressive episodes and does not suggest a hierarchy of antidepressants. Non-response is clearly defined as a reduction inferior to 50% on the score of the HAMD [39] or the Montgomery Asberg Depression Rating Scale (MADRS) [40] and the TRD stages correspond to the number of failed therapeutic trials. It is assumed that patients with failure to respond to two agents of different classes would be more resistant than those who do not respond to two drugs of the same group and indirectly implies that switching to a drug from the same class is less effective [6]. It should be noted that, in this classification, the differences between TRD and CRD are arbitrary [8]. ESM does not establish that two or more attempts with failed antidepressants imply a higher level of TRD, in contrast with the publications that associate the number of changes with poor response to treatment [17, 18]. Furthermore, CRD does not consider non-pharmacological measures such as ECT or psychotherapy. To date, there are no studies that prove the predictive utility or reliability of the scale.

The Massachusetts General Hospital Staging model (MGH-s) was published for the first time by Fava [6] based on the scale by Thase and Rush. The MGH-s considers dosage optimization and separately prolonging the duration of treatment, as well as an operational criterion for minimal dose and duration of treatment. It includes measures for titration and combinations and does not rank antidepressant classes [41] or an implied preference between them or a change to the same group of drugs. The MGH-s considers the number of failed treatments and the intensity and optimization of each attempt and generates a continuous variable that reflects the degree of resistance to antidepressants. MGH-s generates a continuous score that reflects the level of resistance. However, this score is randomly given [8]. Dosage optimization and duration are considered equal to increase or combination, which does not seem to be backed up on literature [42–44]. Finally, the higher score given to ECT is not sufficiently explained [7, 45].

A study published a comparison between the MGH-s and the Thase and Rush Staging Method on a sample of 115 ambulatory patients with major depression. All

results showed that both models have a high correlation, but the multivariable analysis demonstrated that the MGH-s had a better prediction for non-remission [45].

Fedaku et al. [7] published The Maudsley Staging Model (MSM) method of stratification, in which the TDR score varies from 3 to 15. TRD stages are shown in three categories: mild (scores 3–6), moderate (scores 7–10), and severe (scores 11–15). It incorporates the duration and severity of the depressive episode. MSM considers class switching between different antidepressant groups, and between the same group has the same score. The scale is easy to use and may be employed as a tridimensional model regarding duration, severity, and treatment. It has been criticized, however, that disease duration is arbitrary and does not include the number of titrating attempts. Empiric value and inter-rater reliability was proven with prospective data obtained from the notes of 88 patients on a TRD specialized unit and follow-up of 62 patients in this group for a medium of 29.5 months [7].

2.4 Resistant depression treatment general principles

Qualitative and quantitative assessment of depressive symptoms with evaluation scales on each visit, assessment tool employment, and watching over adverse effects should be a routine practice in the approach to the patient with major depressive disorder, and even more so with the TRD patient. Furthermore, it is recommended to evaluate psychosocial performance, quality of life, treatment compliance and tolerance, and provide 24-h assistance [46]. It is important to encourage patients not to abandon treatment or medical attention despite of not perceiving any results. A good relationship between the clinician and the patient is also important to guarantee treatment compliance [15]. Finally, the role of psycho-education for the patients and their relatives should not be forgotten, as this includes sign and symptom identification, prognosis, suicide risk assessment, treatment options, sleep hygiene, impulse control, and sleep restriction among others. Behind restriction the initial management of depressive patients is usually done by primary care physicians or internists, but they should be referred to a mental health specialist if there is not an appropriate response to two or more treatments, as well when suicidal or homicidal ideation, psychotic or catatonic behavior are detected.

2.4.1 Treatment strategies

For patients with major depressive disorder who do not respond to initial treatment with an antidepressant, there are diverse management strategies [5, 14, 30, 47–50] which have been classified and arranged in three groups as follows: (1) optimization; (2) treatment switching (to a different antidepressant, psychotherapy, or ECT); (3) augmentation or adding other treatment to the one already in use, such as a different drug, psychotherapy, or ECT (**Table 1**). Regardless of the strategy, it is recommended always to use one strategy at a time to assess which is the most effective. We will review each one of them.

2.4.1.1 Optimization

Optimization consists of improving the current treatment, while supervising good tolerance. It should be noted that, in some studies with patients diagnosed as resistant and sent to specialized clinics, it has been reported that an important number of them did not receive an appropriate dose of the medication or had been taking it behind for a brief period of time [51]. This would represent a case of pseudo-resistance. Several studies show that it is important to treat a major depressive episode for 6–12 weeks before concluding non-remittance [6, 26, 52]. A study in

Strategy	Definition	Action
Optimization	Consists in improving the current treatment	Increase antidepressant's dosage Increase time exposure on treatment
Treatment switching	It is the act of suspending the current treatment and replacing it with other	Change of antidepressant Same classe of antidepressant Different classe of antidepressant Switching to psychotherapy ECT
Augmentation	Consists of adding other treatments	A second antidepressant A second-generation antipsychotic Lithium Thyroid hormones Stimulants NMDA receptor acting drugs rTMS Psychotherapy

Table 1.
Treatment strategies for resistant depression.

1627 patients, where 67% of them received less than 4 weeks of treatment and did not show response to an antidepressant [53], did not find any difference between continuing the current treatment or changing to another antidepressant. This supports the importance of keeping the patients on an antidepressant treatment for an appropriate amount of time before changing it. On the other hand, multiple studies show that if patients have less than 25% reduction of symptoms after 4 weeks treatment, it could be indicated to switch to a different treatment strategy [54].

2.4.1.2 Treatment switching

Treatment switching is the act of suspending the current treatment and replacing it with a different pharmacologic or non-pharmacologic anti-depressive strategy. This includes using a different antidepressant, switching to psychotherapy, or ECT.

2.4.1.3 Changing antidepressants

It has been suggested that, in order to switch antidepressant medications, the current medication should be gradually discontinued while the new one is slowly introduced throughout 1–2 weeks and the dosage of the new antidepressant agent should be given at a corresponding amount to the one being discontinued. The clinician should be aware of increases of adverse effects and, in relation to SSRIs, the risk of serotonin syndrome. Some clinicians prefer to switch from an SSRI to another instantly, except when the patient has received fluoxetine, where the waiting time should be no less than 4 weeks before using another SSRI due to its long half-life.

For patients resistant to SSRIs, it has been suggested to switch to a selective nor-adrenaline and serotonin reuptake inhibitor (SNRI), atypical antidepressants, such as bupropion or mirtazapine, tricyclic antidepressants, or MAOIs. There are, however, few studies that compare switching to each one of these groups of drugs. In one meta-analysis that included four randomized studies with 1496 patients resistant to an SSRI, remission was evident in 24% of the patients who received another SSRI, and in 28% who were introduced to a different class of antidepressant such as bupropion, mirtazapine, or venlafaxine [55]. Regarding patients resistant to SSRI, many studies, including some meta-analyses, support changing to venlafaxine [17, 55]. A meta-analysis with 3375 patients with depression resistant to an SSRI showed that changing to another SSRI led to remission on 45% of the subjects, but 54% remitted when changing to venlafaxine [17]. Concerning atypical antidepressants, the few comparative studies available on TRD patients have not found differences respecting efficacy [18, 42]. In a group of patients resistant to paroxetine, a study that compared extended

release venlafaxine (225 mg/day) and mirtazapine (45 mg/day) found remissions of 41 and 36% respectively [56]. In another study, 477 patients resistant to an SSRI treated for 14 weeks with bupropion SR (average dose 238 mg/day) or sertraline (average dose 136 mg/day) remission was achieved on 21 and 18% of the subjects, respectively [57]. An 8-week study that compared mirtazapine (45 mg/day) with paroxetine (20 mg/day) in 100 patients with TRD, remission was achieved in 36 and 47% with similar tolerance. Finally, a comparative study with mirtazapine (average dose 30 mg/day) and sertraline (average dose 120 mg/day) in 250 TRD patients, remission was similar (38 versus 28%, respectively) without statistical difference [58–60]. Nevertheless, there were more adverse effects with mirtazapine such as sedation, fatigue, weight gain, and xerostomia. In TRD patients, efficacy and tolerability of tricyclic antidepressants is comparable to that of atypical antidepressants and SSRIs [61]. Currently, tricyclic antidepressants have become the fourth or fifth line of treatment in TRD patients due to undesired adverse effects such as anticholinergic effects, cardiotoxicity, and lethal potential with overdose. The STAR*D study reported the fourth or fifth line of treatment in major depressive patients due to undesired adverse effects such as anticholinergic effects, cardiotoxicity, and lethal potential with overdose. In TRD patients, efficacy and tolerability of tricyclic antidepressants is comparable to that of atypical antidepressants and SSRIs. In the STAR*D study, an open 14-week trial in 235 patients compared nortriptyline (average dose 97 mg/day) with mirtazapine (average dose 42 mg/day) showing a comparable remission of 20 versus 12% and equal tolerance [62]. In a double-blind randomized study, 168 imipramine- or sertraline-resistant patients treated for 12 weeks were randomly assigned to the other treatment [63]. Remission was comparable (23% versus 32%) with more discontinuation with imipramine switching due to adverse effects (9 versus 0%). MAOIs are rarely used today, since they carry lethal potential by interacting with other drugs and food containing tyramine [64]. Nevertheless, changing to a MAOI may still be helpful for some TRD patients [17, 64]. A randomized trial with 46 imipramine-resistant patients who received phenelzine (45–90 mg/day) for 6 weeks and 22 phenelzine-resistant patients who were switched to imipramine (150–300 mg/day) reported a higher response on patients who received phenelzine rather than imipramine (67 versus 41%) [64]. For severely depressed patients with TRD, there is not enough evidence that indicates which kind of antidepressant is superior [65]. Tricyclic antidepressants may be preferred [66]. However, a meta-analysis of 25 randomized trials on 1377 hospitalized depressed patients who received tricyclic antidepressants or SSRIs showed that tricyclic antidepressant superiority over SSRIs was low with a higher rate of adverse effects [67].

2.4.1.4 Switching to psychotherapy

Changing from a pharmacologic approach to psychotherapy may be rejected by many TRD patients [68], but still is a reasonable approach. A 12-week trial with 122 patients who did not respond to citalopram and were randomized to cognitive behavioral therapy (CBT) or different antidepressants (bupropion, sertraline, or venlafaxine) [68] reported similar remission (25 and 28%). Another study with 140 patients who did not respond to a trial with nefazodone or CBT and then were switched to the other treatment [69] reported a comparable remission of 36 and 27%, respectively.

2.4.1.5 Electroconvulsive therapy

For patients with TRD with severe depression, ECT continues to be the therapy of choice [28, 66, 70–72]. The most important indications for ECT are persistence of suicidal ideation, suicide attempt, severe weight loss with malnutrition, dehydration, food or fluids rejection, and malignant catatonia. ECT is also indicated in cases

of depression with psychotic symptoms and if there is previous history of response to this treatment. ECT has been shown superior to pharmacotherapy as shown by multiple meta-analyses and randomized studies [65]. A meta-analysis of 18 studies with 1144 patients that compared ECT with pharmacotherapy found that ECT was more effective [71]. ECT approach is recommended by many guidelines [66, 70, 72, 73]. ECT is not exempt of anesthetic risks, adverse effects, logistic problems, treatment rejection, and relapse.

2.4.1.6 Augmentation

Augmentation consists of adding other treatment (pharmacologic or non-pharmacologic) to the current one [74]. A new drug, psychotherapy, or transcranial magnetic stimulation (TME) might be added. This approach has been widely used and studied; combination therapy with antipsychotics, lithium, or triiodothyronine (T3) are generally well tolerated [52, 58, 75–79], while combination therapy of MAOI with other antidepressants may cause serotonin syndrome or hypertensive crisis [80]. Previous response, safety, comorbidities, ease of use, patient's preference, and costs are factors to consider while adding other drugs to the current treatment. TRD patients, who have had additions and do not respond in 6–12 weeks at the desired dose or do not tolerate the combination, should be switched to a second combination [58]. Some authors suggest discontinuation of the supplementary drug and addition of a new one progressively over 1–2 weeks [58].

2.4.1.7 Adding a second antidepressant

Concerning depression with partial response to monotherapy with antidepressants, a second drug is usually added. However, a meta-analysis of eight studies with 808 patients that did not respond to monotherapy and that compared antidepressant combination with monotherapy, found a similar improvement on both groups [81]. The most studied antidepressants are mirtazapine and bupropion.

Mirtazapine use as an augmentation drug on TRD patients is supported by the results of open and placebo-controlled studies [81, 82]. On the STAR*D study, mirtazapine was added to patients resistant to venlafaxine and was compared with switching to tranylcypromine (a MAOI). Both approaches had no different effects [83]. However, addition of mirtazapine to resistant patients requires additional studies to establish its efficacy.

Bupropion, a noradrenergic/dopaminergic reuptake inhibitor, was studied in TRD patients [84]. Bupropion has a good tolerability and low side effect profile, including few sexual side effects.

Buspirone, a serotonin (5-HT_{1A}) receptor partial agonist, was studied in randomized, double-blind, placebo-controlled trials combined with an SSRI in patients with TRD [85]. Buspirone, at a dosage of 41 mg/day, was compared on the STAR*D study with Bupropion SR at 267 mg/day, with similar effectiveness [44]. As with mirtazapine, bupropion addition is a popular practice as an enhancing maneuver, but additional studies are needed to justify its use on TRD patients.

2.4.1.8 Second-generation antipsychotics

For second-generation antipsychotics in patients with TRD, the following order was suggested based on benefit and a lower rate of adverse effects: aripiprazole, quetiapine, risperidone, and less frequently ziprasidone or olanzapine [58, 77, 86, 87]. Also, the use of brexpiprazole has been suggested if aripiprazole generates akathisia [88, 89]. The analysis of 16 studies comparing the addition of aripiprazole,

olanzapine, quetiapine, or risperidone with placebo on 3480 patients with non-psychotic depression who failed to at least one attempt with antidepressant monotherapy [90] showed improvement in 31% of the patients who received the additional drug (31%) versus placebo (17%). Discontinue due to adverse effects was higher with antipsychotics (9 versus 2%), 4% for aripiprazole, 12% for quetiapine, and 7% for risperidone [90]. In an open, randomized 12-week trial with 1522 patients who stayed severely depressed after treatment with an antidepressant [75], the subjects received three types of treatments: aripiprazole increase (target dose 5–15 mg/day), bupropion increase (target dose 300–400 mg/day), or switching to bupropion. Response (reduction equal or higher than 50% of depression) was greater with aripiprazole (74%) than increasing bupropion (66%) or switching to bupropion (62%). There were more adverse effects with aripiprazole, such as akathisia, somnolence, weight gain, and laboratory abnormalities, but patients experienced more anxiety with bupropion. A meta-analysis of 11 randomized trials on TRD patients ($n > 3000$) found that effectiveness of the augmentation of atypical antipsychotics might rise with the increase of the resistance [90]. For example, the augmentation may carry more benefit for patients that do not respond to three or four failed attempts compared with those who do not respond to one.

2.4.1.9 Lithium

Augmentation of treatment with lithium was reported for the first time by De Montigny by combining it with tricyclic antidepressants [91]. Thereafter, multiple studies have demonstrated its efficacy. A meta-analysis of 10 placebo, controlled studies showed that the addition of lithium at a dose to 600–900 mg/day (plasma levels higher than 0.4 mEq/L) was superior to placebo [78, 92]. A meta-analysis of nine trials with 237 patients comparing lithium versus placebo found a higher response with lithium [84]. Lithium was effective in the augmentation with first- and second-generation antidepressants attached to a possible benefit in reducing suicide risk. A meta-analysis of nine studies with 234 patients, where double-blind trials with lithium and placebo on TRD patients were included, showed a broad effectiveness with this approach [93]. The authors concluded that it should be given for no less than 7 days at dose of 600–800 mg/day [93]. An analysis of the literature reviewing 12 randomized studies on lithium augmentation of SSRIs or atypical antipsychotic drug therapy found no statistical difference that favors the use of one approach or the other [94].

2.4.1.10 Thyroid hormone

Thyroid hormone, in particular T3, has been used as an augmenting agent since the 1960s [95]. The usual dose of T3 in the form of liothyronine is 25–50 pg and with thyroxine (T4) is 150 pg. An initial meta-analysis with T3 showed effectiveness against placebo [79]. Subsequent studies, however, have shown limited evidence of its effectiveness. A meta-analysis with four randomized studies with 95 patients who did not respond to tricyclic antidepressants compared augmentation with T3 versus placebo or T4 showed response in 53% patients who received T3 but had not statistical difference with placebo [79]. However, T3 augmentation is not very popular in the UK nor in the USA [96].

2.4.1.11 Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique in which a sequence of high-intensity magnetic pulses is used to stimulate cortical neurons to treat neuropsychiatric disorders including major depressive disorder

[97]. This technique may be ambulatory, can be added to the current antidepressant treatment, and has good tolerability. Initial systematic reviews on mixed populations of depressed patients that included non-resistant patients supported their use on TRD patients [98–103]. A meta-analysis of 24 trials that included 1092 patients who underwent rTMS and sham conditions showed rTMS was superior in clinical improvement of patients with TRD. The response and remissions were 25 and 17% and 9 and 6% for the rTMS and sham conditions, respectively [104]. Short duration rTMS (1–4 weeks) has an evident antidepressant effect on TRD patients and is well tolerated. Nevertheless, remission rates and responses with rTMS are low and it is unknown if there is a sustained effect. Not known is whether effects of TMS are sustained over time and its speed of onset [104].

2.4.1.12 Psychotherapy

Addition of CBT usually helps TRD patients, as demonstrated by multiple randomized studies [105–107]. In a randomized 1-year study with CBT (12–18 sessions), it was observed that remission occurred more on CBT group of patients (28%) than in patients who did not receive it (15%). In another study, depressive symptoms were minor on a self-report 40 months after patients received CBT [108]. A 12-week study compared citalopram plus 16-session CBT with citalopram plus additional pharmacological approaches such as bupropion or buspirone in 182 ambulatory patients resistant to citalopram [109]. The number of patients who achieved remission was similar (23 and 33%). A 12-week study that compared nefazodone treatment with 16- to 20-session CBT versus nefazodone alone on 446 ambulatory patients with chronic depression (medium of 8 years) showed remission in more patients undergoing the combination (48 versus 29%) [110]. In hospitalized patients with severe depression, combination therapy is a common practice and its effectiveness is clear. A 12-week study that compares CBT and pharmacotherapy with pharmacotherapy alone in 20 hospitalized patients with chronic depression found a similar improvement [111]. An observational 12-week study with CBT added to pharmacotherapy in 24 hospitalized patients with chronic depression [112] found a 46% reduction in depressive symptoms. In TRD patients, other types of psychotherapy such as group, family, or interpersonal therapy have not been well studied.

2.4.1.13 Other addition maneuvers

Several addition maneuvers have been employed in TRD patients, such as lamotrigine combination, stimulants like methylphenidate, modafinil, and pindolol among others. A meta-analysis which included 10 studies with 289 patients undergoing lamotrigine treatment concluded that this drug had little effect on non-bipolar TRD patients [113]. Controlled studies evaluating placebo versus methylphenidate have been negative despite its regular use [114]. Modafinil did not show a sustained effect in two controlled studies. However, a subsequent retrospective analysis suggests that modafinil may help TRD patients with fatigue and somnolence [115]. Pindolol, a non-selective beta-adrenergic antagonistic with effect in the 5-HT_{1A} auto-receptor has shown negative results against placebo on TRD patients [116]. N-methyl-D-aspartate (NMDA) receptor acting drugs like memantine, ketamine, and riluzole have been studied. Controlled studies with memantine, an NMDA-receptor antagonist, have been negative [117]. Ketamine, an NMDA-receptor antagonist anesthetic, has shown positive antidepressant results in a controlled study against placebo in patients with TRD [118]. Riluzole, a putative glutamate release inhibitor used in the treatment of amyotrophic lateral sclerosis, did not show effectiveness on a controlled study to prevent relapse after ketamine use [119].

2.4.2 Studies comparing switching versus augmentation maneuvers

Multiple guidelines suggest how to use augmentation or switching maneuvers (The American Psychiatric Association, United Kingdom National Institute of Health and Clinical Excellence guidelines among others) [28, 66, 120, 121]. However, few randomized studies comparing the effectiveness of these maneuvers on TRD patients have been performed and most of them do not differ between those patients with little or no benefit from those who improve partially.

Various studies show that augmentation or switching maneuvers are equally efficient. Thus, multiple evaluations reviewing placebo-controlled randomized studies regarding augmentation and switching approaches show similar results [76]. The medium rate of remission with augmentation was 27% and switching was 22%, with response rates (reduction of 50% or more of the symptoms) of 38 and 40%, respectively [122]. A prospective study with citalopram on two groups of 269 patients who preferred augmentation with bupropion or buspirone to switching citalopram to bupropion, sertraline, or venlafaxine had a similar remission. A randomized study with 375 TRD patients, where several treatments were assigned, including five augmentations and two switching options [123, 124] showed similar results with 37 and 41% for each strategy. On the other hand, in a group with 1522 patients (85% men), almost 50% of them undergoing post-traumatic disorder, and who continued severely depressed after the first course of treatment with an antidepressant, almost all of them on psychotherapy, the augmentation approach with aripiprazole (5–15 mg/day) or bupropion (300–400 mg/day) was slightly superior to switching antidepressants to bupropion as monotherapy [75]. Remission was achieved in 29% of the patients with aripiprazole augmentation, 27% with bupropion augmentation, and 22% with switching to bupropion. Surveillance over 24 months of the remitted patients ($n = 396$) showed that approximately 25% of the patients in each group relapsed. There were more adverse effects in the aripiprazole group [75]. Other studies show that augmentation approach with aripiprazole may be more effective in women than in men [125].

With patients not tolerating the antidepressant dose, it is preferable to switch antidepressants. While there is evidence that suggests that augmentation is somehow superior to switching antidepressants, the decision should be discussed with the patient. Clinical criteria would be that patients who have had partial benefit from the initial antidepressant and have few adverse effects may prefer an augmentation approach and those with less improvement and more adverse effects might prefer switching medication. However, in patients resistant to a second treatment, there is no evidence that shows how many approaches should be done before considering change of treatment. Authors suggest 1–3 trials before switching [58, 74]. Changing medications has the advantage of achieving a better compliance to treatment than when more than one medication is used [126] adding a lower risk of adverse effects, pharmacologic interactions, and costs. A study evaluated 48 trials that included 6654 patients. A comparison was made between randomized studies, which compared 11 agents used on augmentation approaches: atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone), antidepressants (bupropion, buspirone), lithium, thyroid hormone, methylphenidate, pindolol, and lamotrigine [87]. The studies analyzed were compared between them or placebo in patients with TRD and the proportion of patients who responded to treatment was defined as primary effectiveness. The analysis showed that primary effectiveness was higher with quetiapine, aripiprazole, thyroid hormone, and lithium in relation to placebo, but even higher for the former two in the sensitivity analysis. There were no differences regarding discontinuation rate and adverse effects (acceptability) for these treatments [87]. Quetiapine, olanzapine, aripiprazole, and lithium were less well tolerated than placebo [87].

A randomized 8-week study on 140 TRD patients with paroxetine plus risperidone, paroxetine plus trazodone, and paroxetine plus thyroid hormone showed similar remission rates of 27, 43, and 38%, respectively [123]. A 6-week randomized open study that compared adding quetiapine (target dose 300 mg/day) with adding lithium (target plasma concentration from 0.6 to 1.2 mmol/L) in 450 resistant patients got a similar remission rate of 32 and 27%, respectively [127].

A meta-analysis with 48 randomized trials ($n > 6000$ depressed patients) in which efficiency of augmentation agents was evaluated using results from comparisons between drugs (on head to head trials), as well as indirect comparisons of the drugs through their relative effects with a common comparator (typically a placebo) [123]. The response (reduction equal or higher than 50%) or remission was more frequent when aripiprazole, lithium, olanzapine, quetiapine, risperidone, or thyroid hormone (T3 or T4) was added, compared to placebo; results from each one were comparable. Discontinuation due to adverse effects was higher with aripiprazole, lithium, olanzapine, and quetiapine than with placebo.

2.4.3 Promising new treatments

2.4.3.1 Acetylcholine receptor acting drugs

Medications that act on the cholinergic system seem promising in the treatment of TRD patients. Controlled studies versus placebo with intravenous scopolamine (a muscarinic antagonist) in TRD patients showed promising results [128]. Mecamylamine, a nAChR antagonist added to citalopram, was also superior to placebo [129]. Other drugs like mecamylamine, S-mecamylamine, and varenicline are currently in a preliminary stage of study in depressive patients [129, 130].

2.4.3.2 N-methyl-D-aspartate (NMDA) acting drugs

Ketamine, an NMDA-receptor antagonist, has shown antidepressant effects in TRD patients in a controlled study versus placebo [118]. However, ketamine, a dissociative anesthetic administration which complicates TRD patient treatment due to its route of administration (intravenous), requires hospitalization and consultation with an anesthesiologist. The rapid effects of ketamine usually disappear in 4–6 days. Also, it is possible that patients who improve on ketamine require a long-term course of maintenance. Ketamine has been given intranasal, or by sublingual delivery. Lapidus et al. [131] compared intranasal administration of ketamine 50 mg and placebo in 20 TRD patients. Patients improved at 24 h, but not at 72 h after administration. Recent studies are currently researching intranasal administration of esketamine, the S-enantiomer of racemic ketamine on TRD patients. Initial results are very promising [132]. If accepted, esketamine would enter the list of enhancement approaches for TRD patients.

Deep brain stimulation, vagus nerve stimulation, and neurosurgical lesions have also been evaluated in different studies as therapeutic options in highly resistant TRD patients [133].

2.5 Neurobiological aspects of resistant depression

Most antidepressants act by modulating serotonin, noradrenaline, and dopamine neurotransmission, but other neurotransmission routes seem to be involved such as cholinergic, glutamatergic, neuropeptides, and neuromodulators among others. The complex neurotransmission systems are prone to failure in the short- or long-term, blocking antidepressant action. Besides, different antidepressant

treatments seem to exert action by different mechanisms modulating different cerebral regions [134]. Genetic variants may explain up to 42% of antidepressant response [135]. Genetic polymorphisms for cytochrome P-450 (CYP) enzymes may lead to a reduction on enzyme activity of the CYP2D6 or CYP3A4 variants, leading to intolerance to antidepressants on high plasmatic levels [136, 137]. Some patients are rapid metabolizers, resulting in low plasmatic levels at standard doses of antidepressants, leading to resistance. Evaluation of these genetic variants is accessible with pharmacogenetic studies of antidepressants. Other resistance genetic variants may be related to p-glycoprotein (p-gp), also known as the ABCB₁ drug multiresistance gene [138]. Besides this, other polymorphic variants have been associated with response to antidepressants. In the case of serotonin 2A gene (HTR2A), both coding and noncoding polymorphisms have been associated to low SSRIs response [139–141]. Furthermore, single nucleotide polymorphisms (SNPs) of the genes for brain-derived neurotrophic factor (BDNF) [142, 143], the norepinephrine transporter [144], tryptophan hydroxylase 2 [145, 146], corticotrophin releasing hormone receptor 1 [147], the glucocorticoid receptor [148, 149], and the common promoter polymorphism of the serotonin transporter gene [150–155] have been associated with low SSRI response.

It has been published that the activation of the immune system and neuroinflammation represent a primary event in the pathophysiology of TRD [156–158] and that the effect of NSAID may increase the effect of antidepressants [159].

Finally, the catecholaminergic hypothesis of depression [160, 161], which associates depression with low levels of neurotransmitters, was accepted to explain not only the neurobiochemistry of depression, but also the effect of antidepressant drugs. This hypothesis postulates that, in depression, the function of the dopamine, noradrenaline, and indolamine serotonin monoamines is decreased. In support of this, different studies have shown changes in plasma, urine, and cerebrospinal fluid concentrations of these neurotransmitters and their metabolites, changes in the density of neuroreceptors in platelets and neurons, flattened curves in neuroendocrine challenges and also early relapses with the blockade of restriction enzymes for neurotransmitter synthesis in patients who had achieved depression remission with antidepressant treatment [162]. The existence of subtypes of depression, where noradrenergic, serotonergic, or dopaminergic negative balance is predominant, has been also postulated. Patients with these subtypes of depression hypothetically would respond better to antidepressant drugs with noradrenergic, serotonergic and dopaminergic effects. Unfortunately, clinical studies on the effect of antidepressants with different mechanisms of action show contradicting results, and today there are not clear clinical or biological parameters to predict the results of different antidepressant treatments [163]. It should be noted that any theory about the cause of TRD would be simplistic including that the deficit of a single neurotransmitter, genetic, or immune system and neuroinflammation responses would be present in most TRD patients. However, knowing if there are groups of patients that may respond better to drugs with different mechanisms of action continues to be important for the treatment of patients with TRD [164].

It has been suggested that, in the selection of an antidepressant drug, the clinician must observe the overall response of the patient with major depression [165]. Also, in the selection of an antidepressant drug, the clinician must observe the possible relationship between the drug's biochemical effect and its effects on specific symptoms but also on adverse events. This became more relevant when a drug or group of drugs have failed to improve the patient and a new one has to be supplied, when adverse events force treatment change or when augmentation or change of antidepressant treatment is considered.

3. Conclusions

Once resistance to treatment with two drugs with different action mechanisms has been established, the next best therapeutic decision is *terra ignota* because there is not enough scientific information available to validate which steps are to follow: whether change treatment, adding an antidepressant, “buster therapies” like addition of lithium, thyroid hormone or stimulants, add atypical antipsychotics, rTMS or employment of newly treatments such as ketamine, or ECT. In the evaluation stages for the treatment of a patient with TRD it is important to make an evaluation and reassessment of the case. This includes confirming the diagnosis of major depressive disorder, making the differential diagnoses of bipolar depression or other forms of resistant depression such as secondary to other medical issues, drugs, etc. Medical and psychiatric comorbidities, as well as depression severity should be assessed. Also, a detailed clinical history on antidepressant use should be performed. The application of diagnostic tools or evaluation scales is relevant.

Despite of its importance and frequency, there is no consensus over what TRD is. Advances have been made over assessment tools to evaluate resistance to treatment. However, there is no consensus over which is the best stratification system for TRD. There is a lack of research that validates which treatment approaches may be more effective and which ones should be used in the different stages in the management of a resistant patient. Unfortunately, advances over neurobiology of depression cannot be transferred yet to a clinical level to help the physician choose the best treatment for a patient with major depression and even less so for a TRD patient [163, 164]. In patients who have an inadequate response to the first line of treatment, the clinician has many options to change the treatment, but if the second approach fails, other approaches seem to be equally effective in according to what is published on the literature and there are no clear guidelines that support one or the other. This outlook is discouraging for patients and physicians who are on trial and error until they find something that helps the patient. Future research on TRD patients should be centered on neurobiological factors involved in the development of the resistance including pharmacogenetics. Without the development of techniques that help us predict which factors are related to this phenomenon, treatment of TRD patients will continue to be insufficient.

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