

Pharmacologic approaches to treatment resistant depression: Evidences and personal experience

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Abstract

AIM: To review evidence supporting pharmacological

treatments for treatment-resistant depression (TRD) and to discuss them according to personal clinical experience.

METHODS: Original studies, clinical trials, systematic reviews, and meta-analyses addressing pharmacological treatment for TRD in adult patients published from 1990 to 2013 were identified by data base queries (PubMed, Google Scholar e Quertle Searches) using terms: "treatment resistant depression", "treatment refractory depression", "partial response depression", "non responder depression", "optimization strategy", "switching strategy", "combination strategy", "augmentation strategy", selective serotonin reuptake inhibitors antidepressants (SSRI), tricyclic antidepressants (TCA), serotonin norepinephrine reuptake inhibitors antidepressants, mirtazapine, mianserine, bupropione, monoamine oxidase inhibitor antidepressant (MAOI), lithium, thyroid hormones, second generation antipsychotics (SGA), dopamine agonists, lamotrigine, psychostimulants, dextromethorphan, dextropropranolol, ketamine, omega-3 fatty acids, S-adenosyl-L-methionine, methylfolate, pindolol, sex steroids, glucocorticoid agents. Other citations of interest were further identified from references reported in the accessed articles. Selected publications were grouped by treatment strategy: (1) switching from an ineffective antidepressant (AD) to a new AD from a similar or different class; (2) combining the current AD regimen with a second AD from a different class; and (3) augmenting the current AD regimen with a second agent not thought to be an antidepressant itself.

RESULTS: Switching from a TCA to another TCA provides only a modest advantage (response rate 9%-27%), while switching from a SSRI to another SSRI is more advantageous (response rate up to 75%). Evidence supports the usefulness of switching from SSRI to venlafaxine (5 positive trials out of 6), TCA (2 positive trials out of 3), and MAOI (2 positive trials out of 2) but not from SSRI to bupropione, duloxetine and mirtazapine. Three reviews demonstrated that the benefits of intra- and cross-class switch do not significantly differ. Data on combination strategy are controversial regarding

TCA-SSRI combination (positive results in old studies, negative in more recent study) and bupropion-SSRI combination (three open series studies but not three controlled trials support the usefulness of this combination) and positive regard mirtazapine (or its analogue mianserine) combination with ADs of different classes. As regards the augmentation strategy, available evidences supported the efficacy of TCA augmentation with lithium salts and thyroid hormone (T3), but are conflicting regard the SSRI augmentation with these two drugs (1 positive trial out of 4 for lithium and 3 out of 5 for thyroid hormone). Double-blind controlled studies showed the efficacy of AD augmentation with aripiprazole (5 positive trials out of 5), quetiapine (3 positive trials out of 3) and, at less extent, of fluoxetine augmentation with olanzapine (3 positive trials out of 6), so these drugs received the FDA indication for the acute treatment of TRD. Results on AD augmentation with risperidone are conflicting (2 short term positive trials, 1 short-term and 1 long-term negative trials). Case series and open-label trials showed that AD augmentation with pramipexole or ropinirole, two dopamine agonists, could be an effective treatment for TRD (response rate to pramipexole 48%-74%, to ropinirole 40%-44%) although one recent double-blind placebo-controlled study does not support the superiority of pramipexole over placebo. Evidences do not justify the use of psychostimulants, omega-3 fatty acids, S-adenosyl-L-methionine, methylfolate, pindolol, lamotrigine, and sex hormone as AD augmentation for TRD. Combining the available evidences with our experience we suggest treating non-responders to one SSRI bupropion or mirtazapine trial by switching to venlafaxine, and non-responders to one venlafaxine trial by switching to a TCA or, if TCA are not tolerated, combining mirtazapine with SSRI or venlafaxine. In non-responders to two or more ADs (including at least one TCA if tolerated) current AD regimen could be augmented with lithium salts (mainly in patients with bipolar depression or suicidality), SGAs (mostly aripiprazole) or DA-agonists (mostly pramipexole). In patients with severe TRD, *i.e.*, non-responders to combination and augmentation strategies as well as to electroconvulsive therapy if workable, we suggest to try a combination plus augmentation strategy.

CONCLUSION: Our study identifies alternative effective treatment strategies for TRD. Further studies are needed to compare the efficacy of different strategies in more homogeneous subpopulations.

Key words: Treatment resistant depression; Combination; Augmentation; Switching; Non responder depression; Partial response depression; Major depressive disorder; Antidepressants; Second generation antipsychotics; Dopamine-agonists

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Core tip: According to the available evidences and

our personal experience we suggest to treat patients non-responders: to one selective serotonin reuptake inhibitors antidepressants (SSRI), bupropion or mirtazapine trial by switching to venlafaxine; to one venlafaxine trial by switching to tricyclic antidepressants (TCA) or, if TCA are not tolerated, by combining mirtazapine with SSRI or venlafaxine; to two or more adequate antidepressant (AD) trials (including TCA if tolerate) by AD augmentation with lithium (mainly in patients with bipolar depression or suicidality), second generation antipsychotics (SGAs) (mostly aripiprazole) or dopamine-agonists (mostly pramipexole); to combination and augmentation strategies and electroconvulsive therapy (ECT), if workable, by combination plus augmentation strategy. Combining the available evidences and our personal experience we suggest: for non-responders to one SSRI (bupropion or mirtazapine) trial switching to venlafaxine for non-responders to one venlafaxine trial switching to TCA, if TCA are not tolerated, combining mirtazapine with SSRI or venlafaxine. For non-responders to two or more AD trials (including TCA if tolerate) we suggest AD augmentation with lithium (bipolar depression or suicidality), SGAs (aripiprazole) or dopamine-agonists (pramipexole) for non-responders to combination and augmentation strategies and ECT, if possible, we suggest a combination plus augmentation strategy.

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INTRODUCTION

Major depressive disorder (MDD) is a widespread disease, with a lifetime prevalence of 15% and an annual incidence of approximately 7%. It is associated with a high risk of mortality (RR = 1.81 compared with non-depressed individuals) and is predicted to be the leading cause of disability in Western countries by 2030^[1]. Antidepressants (ADs) are the first-line treatment for depression. Nevertheless, despite advances in the understanding of the psychopharmacology of major depression and the introduction of never-generation ADs, 10%-15% of patients do not respond to an adequate pharmacological therapy and an additional 30%-40% have only a partial remission^[2]. Before defining these patients as treatment-resistant clinicians should ascertain that: (1) the diagnosis is correct; (2) the AD has been selected according to diagnosis specifiers^[3]; (3) the patient has taken the treatment for an adequate duration of time (usually 6-12 wk) and dosage (up to two thirds of the manufacturer's maximum recommended dose, if tolerated); and (4) the medical or psychiatric comorbidity has been assessed and, if present, adequately treated. After excluding these conditions, individuals who are still non-responders or

partial responders to AD are defined as suffering from treatment-resistant depression (TRD). TRD is very often associated with lack of efficacy feelings, suicidal risk, poor prognosis, impairment in work, social and family life, physical health decline, and increased health care utilization^[4,5].

Management of TRD is a hard challenge for physicians because the topic has been poorly investigated and data providing evidence in support of each proposed treatment are sparse and contradictory^[6]. The main confounding factor is the absence of a validated, systematic and common definition for TRD, so each research team adopts different criteria in staging type and number of pharmacological trials failure to define diagnosis^[7]. Others confounding factors are the difference between studies in the definition of response, remission and recovery, and the exclusion in some studies of patients with high risk of non-response to treatment, *e.g.*, with Axis II comorbidity or alcohol/substance abuse or dependence.

Given the controversial findings of the trials, clinicians find difficult to decide how to proceed if the patient does not improve or shows only a partial response to the initial AD treatment.

The aim of this study is to review available evidence supporting the pharmacological options for treating TRD and to discuss each option according to the long-standing personal experience of the senior author (AT) in treating TRD.

MATERIALS AND METHODS

Literature searches were conducted using PubMed, Google Scholar e Quertle Searches for the years 1990-2013 and the terms: "treatment resistant depression", "treatment refractory depression", "partial response depression", "non responder depression", "optimization strategy", "switching strategy", "combination strategy", "augmentation strategy", selective serotonin reuptake inhibitors antidepressants (SSRI), tricyclic antidepressants (TCA), serotonin norepinephrine reuptake inhibitors antidepressants (SNRI), mirtazapine, mianserine, bupropione, monoamine oxidase inhibitor antidepressant (MAOI), lithium, thyroid hormones, second generation antipsychotics (SGA), dopamine agonists, lamotrigine, psychostimulants, dextromethorphan, dextropropranolol, ketamine, omega-3 fatty acids, S-adenosyl-L-methionine, methylfolat, pindolol, sex steroids.

The title and abstract of the retrieved articles were reviewed by the first two authors (AT and RdF), independently and non-pertinent papers were excluded. Only papers including original studies, clinical trials, systematic reviews, and meta-analyses, which directly addressed pharmacological treatment or pharmacological treatment strategies for TRD on adult patients were retained for extensive review and inclusion in this study. Some exceptions were made with regard to small case series, and related mainly to new therapies.

Other citations of interest were further identified from references reported in the accessed articles. Selected publications were grouped by treatment strategy: switching, combination, augmentation and new treatments. The statistical review of the study was performed by biomedical statistician.

RESULTS

The combined search strategy yielded a total of 140 articles. Seventy-three paper were eligible and 67 were excluded. Agreement on exclusion of non-pertinent articles was good, with a Cohen's kappa for inter-rater agreement of 0.83.

Switching

This strategy consists in switching from an ineffective AD to a new AD from a similar or different class. Most of the studies on this topic are open trials and regard non-responders to one AD trial.

The usefulness of switching from a TCA to another TCA is limited by a modest response rate (9%-27%)^[8]. Only one study reports a clinically significant result, with response and remission rates of 40% and 12%, after switching from an ineffective TCA to nortriptyline (study duration 7 wk)^[9].

Some studies found a benefit, with a response rate of up to 75%, of switching from a SSRI to another SSRI^[10-13], but the better results have been reported when switching was caused by intolerance instead of resistance to previous treatment^[10,11,14].

As regard between class switch, evidence sufficiently supports the usefulness of switching from SSRI to venlafaxine, TCA, and MAOI.

Two open studies report that the response rate to venlafaxine in non-responders to SSRI is 58%-87%^[15,16] and one double blind trial reports that venlafaxine is significantly more effective than paroxetine (response rates 52% and 33%, remission rates 42% and 20%, respectively) in patients with a history of resistance to two ADs treatments^[17]. Venlafaxine proved to be better than citalopram (response rate 42% and 22%, respectively) in a double blind study including 406 SSRI non-responders, even if the difference did not reach statistical significance in the overall sample (primary outcome), but only in the subgroup with more severe depression [Hamilton Depression Rating Scale-21 items (HDRS-21) total score > 31]^[18]. Moreover, one third of 84 patients with severe TRD (non-responders to at least three adequate trials of ADs from at least two different ADs classes or electroconvulsive therapy, plus at least one attempt at augmentation) responded to 12 wk of venlafaxine treatment^[19]. In a more recent study the remission rate after 8 wk of treatment with venlafaxine (42%) did not differ significantly from those with mirtazapine (36.4%) and paroxetine (46.7%) in 150 patients who did not respond to two consecutive AD trials^[20].

Despite a long history of good efficacy as antide-

pressant, trials regarding the efficacy of TCA in TRD, are surprisingly scanty. The first study on this topic was a double-blind trial where 15 paroxetine non-responders were switched to imipramine with a response rate of 73%^[21]. In a crossover study in which non-responders to imipramine or sertraline were switched in the other drug, a significant improvement was found (response rate of 60% in sertraline group and 44% in imipramine group)^[22]. To our knowledge only one study reaches the opposite conclusions. In this study 189 patients with TRD received citalopram or desipramine for a 4-wk period and those who failed to respond were treated for a further 4-wk period with the same AD or switched to the other one (citalopram vs desipramine and *vice versa*). There was no difference in the phase one between patients receiving citalopram or desipramine, whereas in the phase two remission rates were higher among non-switched patients^[23].

Two studies report a response rate of 50%-60% with phenelzine or tranylcypamine after failure of TCAs^[24,25], with a higher response rate in patients with atypical features. Data regarding the efficacy of switching from SSRI to bupropion, duloxetine and mirtazapine are conflicting.

A meta-analysis of four trials, including 1496 SSRI non-responders, showed a significant advantage of switching to bupropion, mirtazapine or venlafaxine over switching to a second SSRI (28% of remission vs 23.5%, risk ratio 1.29)^[26].

Bupropion and duloxetine did not differ significantly in remission (70% and 60%, respectively) and response rates (40% and 30%, respectively) in 49 non-responders to 2 trials with SSRI^[27]. In another study only 28% of patients with previous fluoxetine non-response did respond to bupropione^[28].

For patients not responding to SSRIs the switch to mirtazapine showed to be a valid therapeutic option in one study (remission rate 48%)^[29], but not in two other studies in which the remission rate for mirtazapine did not differ significantly from that of a second SSRI and was lower than that of venlafaxine^[30,31].

STAR*-D study reported that one out of four citalopram non-responders responded to within-class switch (from citalopram to sertraline) and between-class switch (from citalopram to venlafaxine or bupropione) without significant differences between the two strategies^[32]. These results were consistent with the findings of three reviews showing no differential benefit between intra-class and across-class switch^[33-35]. In patients resistant to 3 AD trials, STAR*-D study found that remission rate with tranylcypromine and venlafaxine-mirtazapine combination was low and did not differ between the 2 treatment groups (6.9% and 13.7%, respectively) in the overall sample as well as in the subgroup of patients with atypical features^[36].

In our practice the switch is the first strategy employed for patients with less severe TRD, *i.e.*, with non-responders to one AD trial. Usually, we switch SSRI, mirtazapine or bupropione non-responders to

venlafaxine and patients who do not respond to other classes including SNRI to TCA. As regard within-class switch, in our experience only the switch from a TCA to nortryptiline could be sometimes useful, while the switch from an SSRI to another SSRI should be reserved to intolerance more than to resistance.

The switch strategy is safe, well tolerated and reduces medication costs. We restrict the wash-out period, frequently reported as one of the major concern of this strategy^[37], to the switch from MAOI to an AD of another class (two weeks of wash-out) or from fluoxetine to MAOI (one month of wash-out). In the other cases we temporarily (on average 1 wk) overlap the old - at decreasing doses - and new - at increasing doses - antidepressant to reduce the risk of withdrawal symptoms and of the lost of therapeutic gain from original AD. During the overlap period we closely monitor patients for potential pharmacokinetics or pharmacodynamic interaction.

Combination

This strategy consists in adding to the current therapeutic regimen a second AD, usually from a different class, in optimum doses and for an adequate time.

Data on the efficacy of TCA-SSRI combination are conflicting. A series of old studies, usually including small samples of patients who did not respond to either TCA or SSRI, showed that combining a TCA and a SSRI allows depressive symptomatology reduction in 27%-87% of cases^[38-40]. One study, comparing fluoxetine-TCA combination, fluoxetine dose increase and fluoxetine-lithium augmentation, failed to show a significant superiority of SSRI-TCA combination over increasing the dosages or augmentation strategy (response rates 29%, 42%, and 23%, respectively)^[41].

Findings of the studies evaluating the efficacy of mirtazapine, or of its analogue mianserine, in combination with ADs of different classes are mostly positive. In one study, including 32 patients with persistent depressive illness, the response rate to mirtazapine-venlafaxine combination was 44% at 4 wk, 50% at 8 wk, and 56% at 6 wk^[42]. A response rate of 82% and a remission rate of 27% have been reported in another study including 22 patients with TRD treated with the same combination for 8 wk^[43]. Adjunctive mirtazapine to a previous ineffective regimen in 26 nonresponders to one AD trial showed significantly higher response and remission rates (63% and 45%, respectively) than placebo (20% and 13%, respectively)^[44]. These positive results confirm the findings of one previous open-label study where mirtazapine augmentation produced a 55% response rate in 20 patients with refractory depression^[45]. Different results were obtained by STAR*D study, that compared the effectiveness and tolerability of mirtazapine-venlafaxine combination with those of tranylcypromine mono-therapy in 109 patients with a depressive episode not responding adequately to three prior AD trials. In this study both treatments showed a modest and not significantly different remission rate

(6.9% in the combination sample and 13.7% in the tranylcypromine sample)^[36]. As regards mianserine, in a randomized trial, including 104 nonresponders to six weeks of fluoxetine at 20 mg, mianserine-fluoxetine combination showed response and remission rates (62% and 44%, respectively) higher than those of mianserine alone (48% and 36%, respectively) and significantly higher than those of fluoxetine alone (37% and 18%, respectively)^[46]. A second study, including patients with incomplete response to six weeks of sertraline 100 mg, found no significant difference between mianserine-sertraline combination and sertraline at increased doses (200 mg) (response rate 67% and 56%, respectively; remission rate 44% and 29%, respectively)^[47].

Evidence regarding the bupropion-SSRI combination, a strategy widely used in the United States, is contradictory. Three open series, including 65 patients, support the beneficial effects of this combination^[48-50], while two double-blind, placebo-controlled trial, including 221 patients, failed to confirm the superiority of bupropion-SSRI combination over continuing SSRI^[51,52]. In a trial including 565 citalopram non-responders, bupropion-citalopram combination showed a modest efficacy (remission rate 29.7%) and did not differ significantly from that of buspirone-citalopram augmentation (remission rate 30.1%)^[53].

Compared with the switching approach, combination strategy does not require titration and has the advantage that initial improvements are maintained and that the response is more rapid. However, side effects due to drug-drug interactions could emerge, so careful drug surveillance is needed.

After several years of extensive use, recently the TCA-SSRI combination has been replaced in our clinical practice with augmentation strategies. However, we still use the combination strategy in some conditions.

First, SSRI and SNRI non-responders who could not be treated with TCA because of comorbid medical conditions should benefit from mirtazapine and SSRI or venlafaxine combination before trying an augmentation strategy.

Second, patients with depression and obsessive compulsive symptoms or disorder comorbidity previously non-responders to both SSRI and clomipramine might benefit from clomipramine and SSRI or nortryptiline and SSRI or nortryptiline and clomipramine combination. All these combinations should be tried only in selected patients and need caution to avoid potential dangerous pharmacokinetics or pharmacodynamics interactions^[54], as well as serotonin syndrome^[55]. Special caution and surveillance is needed in combining TCA and paroxetine or fluoxetine. These SSRIs, blocking CYP2D6, increase TCA levels in plasma and consequently the risk of toxicity^[56].

Finally, we tried combination plus augmentation strategies in a small number of selected patients with highly resistant depression, *i.e.*, who failed to respond to combination and augmentation strategies as well as

to electroconvulsive therapy if workable.

Augmentation

Augmentation strategy involves the adding a second agent, not thought to be an antidepressant itself, to an antidepressant regimen in order to improve efficacy. Various agents, including lithium, thyroid hormone, second-generation antipsychotics, dopamine agonists, pindolol, omega-3 fatty acids, S-adenosil-L-methionine, methylfolate, lamotrigine and sex steroids have been used in patients with treatment-resistant depression with different evidences in term of efficacy and safety.

Lithium

Some old studies supported the efficacy of lithium augmentation to a TCA, at least when the lithium plasma level is > 40 mEq/L. A meta-analysis including ten controlled trials ($n = 269$) showed that the response rate was significantly higher in TCA non-responders augmented with lithium (2 to 6 wk, plasma level 0.5-1.0 mEq/L) than with placebo (OR = 3.3)^[57]. The number needed to treat to achieve one clinical response in this meta-analysis was 4.

The available evidences on lithium augmentation in SSRI responders are surprisingly few and contradictory. Baumann *et al.*^[58] found an advantage of lithium-citalopram augmentation (response rate 60%) over placebo-citalopram augmentation (response rate 14%) in a study involving 24 citalopram non-responders (40-60 mg, 4 wk). On the other hand, two studies, conducted by Fava *et al.*^[41,59], failed to show an advantage of lithium augmentation over both fluoxetine increased dose and desipramine combination in fluoxetine non-responders.

In the STAR*-D trial the efficacy of lithium augmentation showed to be modest (16% of remission) and not significantly different from that of thyroid hormone (25% of remission) in 142 outpatients who did not achieve remission after a treatment with citalopram and a second switch or augmentation trial^[60]. Methodological limits, including low lithium dosage, might have influence the results of STAR*D trial.

Thyroid hormone

Thyroid hormones supplementation [usually triiodo-tironine (T3), 50 µg/d] is an augmentation strategy extensively studied in the past. In a meta-analysis including 8 studies with a total of 292 TCA non-responders, patients treated with T3 augmentation were twice as likely to respond as controls for an NTT of 4.3^[61]. As for lithium augmentation, it remains questionable whether these results could be generalizable to SSRI non-responders. Some open label studies showed the effectiveness of T3-SSRI augmentation^[62-64], while one controlled study failed to show an advantage of this augmentation over lithium augmentation, lithium plus T3 augmentation and placebo^[65]. As previously reported, in the STAR*D trial T3 augmentation proved

to have an advantage over lithium augmentation, but the difference was not statistically significant^[60].

Second-generation antipsychotics

In the last years a large number of studies verified the efficacy of AD augmentation with second-generation antipsychotics (SGAs) for TRD. Three large double-blind placebo controlled trials ($n = 1092$) showed that aripiprazole augmentation (average dose 10 mg) is significantly superior over placebo in patients who failed to adequately respond to at least one and no more than three trials with ADs^[66-68]. The pooled analysis of two out three of these studies^[66,68] showed a higher decrease in Montgomery-Asberg Depression Rating Scale (MADRAS) symptoms score in patients treated with ADs plus aripiprazole (8.7 points) than in patients treated with ADs plus placebo (5.7 points) with a modest but statistically significant difference^[69]. Two studies reported that a dose of aripiprazole lower than that used in the double blind trials (5 mg/d instead of an average of 10 mg/d) was also effective and well tolerated as augmentation with both SSRI (sertraline and paroxetine) and TCA (clomipramine)^[70,71]. Nevertheless, a very low dose (2 mg/d) is ineffective or only marginally superior to placebo, as reported in a recent double blind, placebo-controlled study^[72]. Currently, aripiprazole has a Food and Drugs Administration (FDA) indication for adjunctive treatment of major depression.

Two large double-blind, placebo-controlled trials ($n = 939$) showed that quetiapine extended release (XR) augmentation is more effective than placebo as treatment for TRD^[73,74]. In both studies response rates (57.8% and 58.9%, respectively) and remission rates (31.1% and 42.5%, respectively) to quetiapine administered at 300 mg/d were significantly higher than response rates (46.3% and 48%, respectively) and remission rates (23.8% and 24.5%, respectively) to placebo. A third double blind, placebo-controlled study comparing quetiapine augmentation with placebo in 58 patients with "residual depressive symptoms" after SSRI or venlafaxine treatment showed response (48% and 28%, respectively) and remission (31% and 17%, respectively) rates in the quetiapine group, while the difference did not reach the statistical significance^[75]. Quetiapine XR was approved for adjunctive therapy of major depressive disorder by the FDA.

In 2001 Shelton *et al.*^[76] demonstrated that olanzapine/fluoxetine combination is more effective than olanzapine monotherapy and fluoxetine monotherapy (remission rates 60%, 25% and 20%, respectively) in 28 non-responders to two consecutively trials of AD therapy. These positive results were replicated in a subsequent controlled trials^[77], conducted with an identical methodology, but not in three trials where olanzapine/fluoxetine combination was not more effective than fluoxetine or olanzapine monotherapy^[77,78], and not more effective than fluoxetine or venlafaxine monotherapy^[79]. In a recent open study, augmentation with a low dose of olanzapine (2.5-5 mg/d) showed to

be effective (64% response rate) and safe in patients who failed to respond to milnacipran^[80]. Olanzapine, in combination with fluoxetine, has received FDA indication for the acute treatment of TRD.

Two placebo-controlled studies showed that a 4-wk risperidone augmentation (remission rates 24.5% and 51.6%) was significantly more effective than placebo (remission rates 10.7% and 24.2%) in 365 non-responders to at least one AD trial^[81,82]. In a third double-blind trial risperidone proved to be superior to placebo in the reduction of suicidality though but not of other MADRAS symptom scores in patients with TRD^[83]. Another study, that investigated the long-term efficacy of risperidone augmentation, failed to confirm the sustained benefit of this augmentation (53.3% of relapses) over placebo (54.6% of relapses) at the end of a 24 wk follow-up^[84].

A review including all English-language, peer-reviewed publications reported that the doses of risperidone used as augmentation ranged from 0.25 to 2 mg/d^[85].

To our knowledge, data on augmentation with other SGAs are very limited (ziprasidone) or absent (paliperidone, iloperidone, asenapina)^[86-88].

Dopamine agonists

In the last years two dopamine agonists approved for the treatment of Parkinson's syndrome and restless legs syndrome, pramipexole and ropinirole, have been proposed as adjunctive treatment in unipolar and bipolar TRD. Some case series and open label trials showed that both drugs are relatively well tolerated and effective with a response rate to pramipexole (the most tested) from 60% to 74% and to ropinirole of about 40%-44%^[89-95]. Pramipexole augmentation showed to be significantly more effective than placebo (response rate 48% and 21%, respectively) in one double-blind placebo-controlled trial^[96]. A more recent double-blind placebo-controlled study support the superiority of pramipexole augmentation over placebo (response rate 40% and 27%, respectively; remission rate 33% and 23%, respectively) but the difference did not reach statistical significance^[97].

Other miscellaneous

Some controlled studies^[98-101] and a systematic review^[102] that examined the efficacy of traditional psychostimulants and modafinil as augmentation for TRD have generally been negative.

Some other drugs have been suggested as augmentation for TDR: omega-3 fatty acids^[103], S-adenosil-L-methionine^[104], methylfolate^[105], pindololo, lamotrigine, sex hormone (testosterone for men, estrogen for women)^[106]. Evidences on the efficacy of these compounds are insufficient, contradictory or negative so, to date they does not appear to have a role in the treatment of TRD.

Future treatments

Recently, some studies examined the role of N-methyl-

D-aspartate (NMDA) receptor antagonists for TRD. In open-label and randomized double-blind studies single- or multiple subanesthetic doses of intravenous ketamine induced a rapid (with hours) improvement (response rate up to 100%, remission rate up 72%) and a reduction of suicidal ideation in patients with very severe TRD^[107-115].

The clinical relevance of these impressive results is limited by the short duration of the tests and the potential psychomimetic side effect of ketamine.

Other NMDA receptor antagonist drugs (*e.g.*, dextromethorphan and dextrophan) have been proposed and/or are currently studied for a potential use in TRD^[116,117] as well as some drugs that affect the acetylcholine receptor system (*e.g.*, scopolamine, mecamlamine, varenicline)^[118-120].

As for combination, augmentation strategy does not need of titration, so the early achieved improvement is maintained and the response may appear rapidly. The augmentation approach requires a careful monitoring of patient because it can increase the side effects burden. It is generally held that the poly-pharmacy decrease treatment adherence^[106], but our personal data do not confirm this hypothesis.

In our experience augmenting the current AD regimen with lithium, SGA (mainly aripirazole) or DA-agonist (mainly pramipexole) could be an effective approach for patients resistant to two or more AD (including at least one TCA, if tolerate) trials. We preferentially use lithium-TCA augmentation for patients suffering from bipolar resistant depression or with suicidal ideation. Clinicians should carefully examine the pros and cons of prescribing a SGA or a DA-agonist in patients with TRD and should take into account the potential risk of the using these drugs: neurological (acute extrapyramidal syndrome, tardive dyskinesia), metabolic (weight gain, lipid abnormality, and impaired glucose tolerance) and cardiovascular (QTc interval prolongation) complications for SGA, gambling disorder for DA-agonist.

As previous reported, we use combination (*e.g.*, TCA and SSRI or SNRI) plus augmentation strategies (*e.g.*, AD and lithium, SGA or DA-agonist) in selected patients with a highly resistant depression non-responder or partially responder to TCA (if tolerated), to both combination and augmentation strategies and to electroconvulsive therapy (if workable). Our experience in the management of TRD with thyroid hormone, lamotrigine, omega-3 fatty acid, S-adenosil-L-metionine and methylfolate are negative or scanty.

At least 10% to 30% of patients with major depression fail to adequately respond to initial AD therapy^[2] and need special treatment-resistant depression management strategy. A wide variety of options for pharmacological treatment of TRD have been proposed: switching from an ineffective AD to a new AD from a similar or different class, combining the current AD regimen with a second AD from a different class, and augmenting the current AD regimen with a second

agent. Clinicians should know which of these strategies is most likely to be effective, but the empirical evidences supporting these various approaches are limited and often contradictory and none of these strategies is always efficient. Furthermore, almost no studies compared alternative strategies and data on predictors of response to specific interventions are lacking.

Therefore, although many guidelines, treatment regimens and treatments algorithms have been proposed^[5], in every day clinical practice, the most appropriate treatment for each patient with TRD still needs to be identified balancing the available evidences and the clinical characteristics of patient as general health conditions, diagnosis specifiers, severity of symptoms, Axis I and II comorbidity and, mainly, the level of resistance.

In principle, most complex therapies, with the larger side effects and potentially more dangerous, should be reserved to those cases strictly needed and just after evaluating pros and cons. As clinicians we need to keep always in mind that our first aim is not to cause harm to the patient and that, for professional reliability, most of adopted strategies consider the off-label use of drugs or combinations.

To sum up, combining the available evidences and our experience we usually treat non-responders to one SSRI bupropion or mirtazapine trial switching to venlafaxine, and non responder to one venlafaxine trial switching to a TCA or, if TCA are not tolerated, combining mirtazapine with SSRI or venlafaxine. In non-responders to two or more AD (including at least one TCA if tolerate) trials we augment the current AD regimen with lithium salts (mainly in patients with bipolar depression or suicidality), SGAs (mostly aripirazole) or DA-agonists (mostly pramipexole). In patients with severe TRD, *i.e.*, non responder to combination and augmentation strategies as well as to electroconvulsive therapy if workable, we try a combination plus augmentation strategy.

Our study has some limitations that should to be taken into account: (1) the high number of study published on TRD is difficult to summarize and a possible selection bias might have affected this review; (2) the review does not include data on somatic and psychotherapeutic treatments of TRD; and (3) it is not clear if proposed suggestions, based on the personal experience of senior author as a chief of an Italian private outpatients clinic specialized in mood and anxiety disorders, are generalizable to different settings. Despite these limitations, however, we believe that the present work, combining empirical findings and "real word" experience, provide useful information for clinicians selecting the treatment for patients with TRD, a frequent, severe and difficult to treat condition.

Further large observational multicenter studies are needed to examine the effectiveness of available pharmacological options for TRD in more homogeneous samples selected according the stage of AD resistance (*i.e.*, number and duration of previous AD trials as well

class and dosages of AD employed), the presence of Axis I and II comorbidity and of alcohol/substance abuse comorbidity. Double-blind controlled study, directly comparing the efficacy of different pharmacological strategies, should be conducted too.

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COMMENTS

Background

Ten-fifteen percent of patients with depression do not respond to an adequate antidepressant (AD) trial and an additional 30%-40% have only a partial remission. Treatment resistant depression (TRD) is associated with suicidal risk, poor prognosis, impairment in work, social and family life, physical decline, and increased health care utilization. Management of this condition is a hard challenge for physicians because the topic has been poorly investigated.

Research frontiers

Pharmacological treatment strategies for TRD include switching from an ineffective AD to a new AD from a similar or different class, combination of two ADs of different class and augmentation of current AD treatment with a second agent not thought to be an AD itself (mainly lithium, second generation antipsychotics and dopamine agonists). The evidences supporting these strategies are sparse and contradictory.

Innovations and breakthroughs

The present article aim to review available evidences supporting the pharmacological options for treating TRD and to discuss each option according to the long standing personal experience of the senior author (AT) in treating TRD.

Applications

This review suggests treating patients non-responders to one selective serotonin reuptake inhibitors antidepressants (SSRI), bupropione or mirtazapine, trial by switching to venlafaxine, and non-responders to one venlafaxine trial by switching to tricyclic antidepressants (TCA) or, if TCA are not tolerated, by combining mirtazapine with SSRI or venlafaxine. In patients non-responders to two or more ADs (including at least one TCA if tolerated) current AD regimen could be augmented with lithium salts, second generation antipsychotics or dopamine-agonists. In patients non-responders to combination and augmentation strategies as well as to electroconvulsive therapy (if workable) combination plus augmentation strategies could be tried.

Terminology

The definition of TRD is controversial, although it is often defined as a major depressive episode with a poor or unsatisfactory response to two adequate (optimal dosage and duration) ADs trials.

Peer-review

This is a comprehensive review of the literature.

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