Drug Augmentation for Treatment-refractory Major Depressive Disorder

Cynthia Yi-An Chen, M.D.¹, Yi-Hang Chiu, M.D.¹*, Winston W. Shen, M.D.¹,²

Major depressive disorder (MDD) is one of the most frequent psychiatric diseases seen in the clinic. Most MDD patients can be treated reliably and comfortably with the use of one antidepressant. But some patients have treatment-refractory depression (TRD), which needs to be managed with switch of the antidepressant or augmentation therapy with another antidepressant or other drugs. Therefore, managing TRD is a challenge for practicing psychiatrists. In this overview, the authors are focusing on treating TRD with augmentation therapy. First, clinicians need to be well-versed in behavioral and physiological classification of antidepressants as a logical basis of choosing an appropriate antidepressant for add-on therapy. Second, clinicians need to be familiarized with data of clinical drug trials for treating TRD with second-generation antipsychotic drugs such as aripiprazole, olanzapine, and quetiapine, approved by the Food and Drug Administration (FDA) of the United States. Third, clinicians need to recognize the use of lithium and thyroid hormone as an add-on drugs for treating patients with TRD. Finally, the patients need to be educated to adapt a healthy lifestyle such as having the habit of regular aerobic exercise, refraining from substance uses, etc. With all those tips, the authors believe that the goal of remission can be more easily achieved for patients with TRD.

Key words: a second antidepressant, second generation antipsychotic drugs, lithium, thyroid hormone


Introduction

MDD and definition of TRD

Major depressive disorder (MDD) is a rising concern of health burden, causing huge impact on life quality and economic loss [1]. Furthermore, functional impairments in MDD can be ranged from mild to completed incapacity that MDD individuals are unable to attend to their basic self-care needs or are mute or catatonic, having greater decreases in physical, social, and rôle functioning [2].

Lifetime prevalence of MDD in the United States is 16.2% [1], while 12-month prevalence is 6.6% [1, 2]. It is one of the most prevalent mental...
health disorders [1]. Among all the patients receiving treatment for MDD, only 41.9% are adequately treated [1]. Impaired functioning in household, career, interpersonal relationship, and social rôle is a significant problem among those patients [1].

Most MDD patients can benefit from antidepressant treatment [3]. But about 21% of patients cannot achieve remission after two years despite the use of antidepressants [4]. About 10% - 30% of patients have been reported to have chronic course of MDD even under adequate treatment [5]. Patients who show no response to treatment of two kinds of antidepressants with adequate dose and duration are defined as treatment-refractory depression (TRD) [6]. Moreover, Dunner has further adjusted the definition of TRD to first treatment failure to one adequate treatment trial, as the response rate drops along with treatment attempts [7].

The question of augmentation therapy or switching antidepressant in treating TRD

In 2006, US National Institute of Mental Health funded the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, enrolling 4,041 non-psychotic MDD outpatients at 23 psychiatric and 18 primary care sites [8, 9]. The STAR*D study has demonstrated the inadequacy of the first prescribed antidepressant, and was intended to obtain generalizable clinical wisdom to achieve the goal of remission of MDD patients step by step [9].

The STAR*D study showed that 14.7% of MDD participants have not eventually reached remission [5]. Among those who do, the rate of remission has also decreased with time [5]. With more treatment steps needed, the remaining remission rate of MDD is decreased and the relapse rate for MDD is also increased [8]. More severe symptoms, presence of melancholic or anxious features, psychiatric comorbidities, presence of psychotic symptoms, poorer physical health, poor adherence with treatments, unemployment, and impairment in rôle functioning are found to be related to higher risk of nonremission or longer time to remission [8]. Furthermore, age older than 40 years and longer duration of episode are associated with higher risk of non-remission [8]. But having college education is related to a lower risk of non-remission. Furthermore, marital status other than currently married or cohabiting, treatment in specialty mental health settings, atypical depressive features, previous suicide attempts, and poorer mental health functioning are associated with longer time to achieve remission among remitters [5].

In the relentless pursuit of achieving remission for MDD patients suffering from TRD, we have learned that in STAR*D study, clinicians can use two basic managing strategies – drug switch or drug augmentation [8]. As a clinical intuition, clinicians just need to wait for more time or to increase the dose of the first antidepressant if patients show response to treatment (50% or more in severity of symptom improvement) with a rating scale or a symptom brief questionnaire in clinic interview [10] at clinic follow-up [11]. But drug augmentation is a preferred choice if the patients have 25% to 50% of symptom improvement at the clinic follow-up, whereas drug switch is usually advised if the patients have no response or only have a symptom response of less than 25% in severity of depression after they started to receive antidepressant therapy.

In drug switch, clinicians need to give up the existing unsatisfying antidepressant and/or other drugs completely; but drug augmentation means that patients receive extra add-on drugs on top of existing antidepressant. In other words, the clinicians using drug augmentation keep already
achieved treatment response, and expect to add more bonus treatment response after adding on another drug(s).

**Drug augmentation strategy for treating TRD**

Based on two previous publications [3, 11], we intend to briefly describe the treatment strategies in handling MDD patients with TRD. As a continuation of a previous paper [3], this overview is to be practical in dealing with patients with TRD. Due to space limitation for the size of this overview, we have to limit the scope by focusing on only the review of drug augmentation in treating patients with TRD.

This overview is by no means an exhaustive encyclopedic review on the topic of drug augmentation in treating TRD. For readers who are interested in studying any specific topic further, they are recommended to do more in-depth studies in the published papers cited in this overview. Table 1 is the outline of augmentation drugs to be covered in this overview.

**Table 1. Drugs used in augmentation in treatment-refractory depression**

<table>
<thead>
<tr>
<th>Drug Class</th>
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<tbody>
<tr>
<td>A second antidepressant</td>
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<tr>
<td>A second-generation antipsychotic drug</td>
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<tr>
<td>Lithium</td>
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<tr>
<td>Thyroid hormone</td>
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<td>Others</td>
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**Guidelines of choosing add-on antidepressants**

- Behavioral physiology has proposed that 5-HT is more related to impulse, NE to energy and interest, and DA to drive [12].
- Anxiety and irritability are mediated through both combined actions of 5-HT and NE; sex, appetite, and aggression through those of 5-HT and DA, as well as motivation through those of NE and DA [12].
- It does not make much clinical sense if one antidepressant is added to another antidepressant of the same category, e.g. paroxetine + sertraline, or venlafaxine + duloxetine.
- We need to keep in mind [3, 11] that the remission rate is higher in patients treated with a dual action antidepressant – a serotonin and norepinephrine reuptake inhibitor (SNRI), or mirtazapine – than those treated with a single action antidepressant – a specific serotonin reuptake inhibitor (SSRI) [13-16].
- Recently introduced vilazodone and vortioxetine (Figure 1) which are antidepressants with 5-HT partial agonists, can improve tolerability for certain side effects, such as sexual dysfunction. But they are still considered as single action antidepressants.
A 5-HT-related antidepressant (Figure 1) should be added as an add-on antidepressant if the patients who are not on a 5-HT related antidepressant, are comorbid with anxiety disorder symptoms, especially panic, phobic, or obsessive-compulsive symptoms.

A 5-HT-related antidepressant is an add-on treatment drugs of choice if patients who are not on an adequate 5-HT-related antidepressant, still have any kind of pain symptoms – migraine, diabetic peripheral neuropathy, gastrointestinal pain, muscle pain, arthritis pain, etc.

A DA-related antidepressant needs to be prescribed to augment the MDD treatment if the patients still have the predominant symptom of “fatigue or loss of energy,” the sixth symptom of MDD diagnosis in DSM-5 [2].

**Possible combinations of antidepressants**

**An SNRI or an SSRI and mirtazapine**

Among responding but non-remitted patients, some SNRI- or SSRI-treated MDD patients still have existing depressive symptoms. The top-five most residual symptoms, short of reaching remission, include sleeping disturbances, fatigue, lack of interest, guilt, and poor concentration, are listed here according to the occurring frequency [17]. In a randomized, double blind, comparative study on MDD inpatient drug trial, both groups of duloxetine doses (120 mg [4 pills] and 60 mg [2 pills]) have not been found to have any differences in response and remission rates in weeks 4 and 8 compared to week 0, measured with Montgomery-Åsberg Depression Rating Scale (MADRS) [18]. In another placebo-controlled, double blind, three-arm comparative study, both groups of patients on duloxetine doses (120 mg vs. 60 mg) do not have any differences in response and remis-
sion rates, measured with Hamilton Anxiety Rating Scale (HAM-A) [19]. The results of those two studies suggest that further increase of certain dose level of an SNRI or an SSRI does not necessarily give more efficacy of its antidepressive or antianxiety effects.

Without further increase of dose of the SNRI or SSRI, clinicians can augment with mirtazapine to the existing SNRI or SSRI to make above-listed symptoms, especially sleep disturbances, improved, or even disappeared in about 2-3 days. In fact, the trial of the combination of venlafaxine and mirtazapine was carried out as level 4 of the STAR*D study, achieving 13.7% more patients into remission [20]. This combination trial, patient had lower side effect burden, and lack of dietary restrictions, and the daily mean doses of venlafaxine and mirtazapine were 210.3 mg and 35.7 mg, respectively. In clinical practice, we suggest that the add-on dose of mirtazapine is 15 mg (a half of a pill) per night in the beginning. If not quite enough, the dose can be gradually titrated up to 30 mg (1 pill), or even 45 mg (1.5 pills) nightly. Of course, the dose of mirtazapine can be reduced after the patients’ residual MDD symptoms or anxiety disorder symptoms are improved and stabilized.

Depending on preference or avoidance of specific side effects from two categories of antidepressants, patients can be kept on 30 mg of mirtazapine plus daily 75 mg (1 pill) of venlafaxine, instead of 150 mg (2 pills) of venlafaxine; or daily 30 mg of duloxetine plus mirtazapine in any dose level of 15-45 mg (0.5 -1.5 pills) instead of 60 mg of duloxetine per day. The minimal required daily doses of each antidepressant are not needed [3], after the goal of remission is achieved because we are counting the total accumulated amount of neurotransmission of all antidepressants that the patients are receiving.

**An SNRI or an SSRI and bupropion or agomelatine**

In level 2 of STAR*D study, the investigators added bupropion on top of the existing daily 50 mg or 100 mg of citalopram, showing that bupropion add-on produces 29.7% more of remission rate measured with 17 items of Hamilton Depressive Rating Scale (HAMD<sub>17</sub>) in a 10-week augmentation therapy [8]. As shown in Figure 1, bupropion is involved in neurotransmission of DA and NE. Bupropion works particularly well if the patients have predominant symptom of fatigue or loss of energy in the residual symptoms [17]. In this case, the addition of bupropion makes above-listed symptoms, especially fatigue or loss of energy, improve or even disappear in about 2-3 days.

Like bupropion, agomelatine [21] is an antidepressant producing eventual neurotransmissions of DA and NE (Figure 1). The use of agomelatine is similar to that of bupropion in the context of augmentation strategy. Both medications have favorable side effect profile for not causing weight gain.

In level 2 of STAR*D study, buspirone, together with bupropion, was also used as an arm of an add-on therapies, producing 30.1% more of remission rate in a 10-week trial [8]. Buspirone is a 5-HT<sub>1A</sub> partial agonist with DA agonistic property [3, 22]. Buspirone does not have antidepressant efficacy when is used alone [3]. Therefore, the use of buspirone in the context of augmentation strategy for TRD patients is not popular because of easy availability of DA-transmitting antidepressants (bupropion and agomelatine).

**Mirtazapine and bupropion**

Bupropion can be used as an add-on antidepressant if patients with TRD do not get remitted after treated with adequate dose of mirtazapine. It is clinically meaningful if the patients’ predomi-
nate residual symptoms consist of both sleeping disturbances and fatigue or loss of energy, or if the patients do not tolerate any SNRI- or SSRI-induced side effects of nausea and/or vomiting.

**Drug Augmentations for TRD with Second-generation Antipsychotic Drugs**

Use of antipsychotics in MDD patients has a long history. With the developments of antidepressants, use of antipsychotics, especially the first-generation (conventional) antipsychotics (FGAs), was decreased due to the possible risks of extrapyramidal symptoms and tardive dyskinesia. But the advent of second-generation (atypical) antipsychotics (SGAs) has changed the situation. SGAs have many indications approved by the Food and Drug Administration of the United States, and off-label uses in clinical psychopharmacotherapy [23].

SGAs are mostly prescribed for MDD patients who have shown psychotic symptoms and signs (hallucinations and delusion) besides MDD symptoms. Although they provide partial relief in MDD patients in previous studies, they have not been found to be effective to treat two core symptoms of MDD – loss of interest and psychomotor retardation. Therefore, SGAs have never been recognized as antidepressants [24]. The meta-analysis by Nelson et al. on efficacy of several SGAs as adjunctive therapy of MDD with TRD showed that the overall response rate of SGAs is 44.2%, while that of placebo is 29.9% [25].

**Aripiprazole**

Aripiprazole was approved by the US FDA as an augmentation treatment of MDD in 2006 (www.fda.org). It is the first antipsychotic being approved by the US FDA as an adjunctive treatment of MDD. Its partial agonist activity at the D_{1}/D_{3} receptors and that at the 5-HT_{1A} receptors may contribute to its synergic antidepressant effect [24]. But there is still no adequate evidence to support this hypothetical mechanism. The initial dose suggested by the US FDA as adjunctive treatment for MDD is 2-5 mg/day, while the target dose is 5-10 mg/day. For this indication, the maximum dose recommended is 15 mg/day (www.fda.org).

For patients not responding to antidepressants treatment, multiple studies have proven the efficacy of aripiprazole as an add-on treatment [24]. In the studies by Berman et al. [26] and Marcus et al. [27], remission rates in both studies have been reported higher in the aripiprazole adjunctive group as compared with the placebo group. In a large, multicenter, randomized, doubleblind, placebo-controlled trial, the investigators enrolled patients with inadequate response to previous treatment in a six-week, doubleblind phase [28]. Study participants were randomized to receive their original antidepressant with an adjunctive placebo or aripiprazole with dose of 2-20 mg/day. For participants who were taking fluoxetine or paroxetine, the maximum dose was 15 mg/day. As a result, participants receiving aripiprazole experienced greater improvement in symptoms from the first week to the endpoint of study. The aripiprazole group has shown higher response rate and remission rate. In side effects, 18% of participants in the aripiprazole group have been reported to have akathisia. About 40% of akathisia have been resolved by the endpoint of the study. The two groups have shown no difference in weight gain, as well as serum levels of total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and fasting glucose [28].

In general, aripiprazole is a safe, well-tolerated, and effective option of augmentation therapy.
for MDD patients with TRD. The treatment response has often been described as “robust,” which is a term rarely used in literature of psychiatric clinical drug trials. Its metabolic effect is minimal. The side effect of akathisia should be kept in mind, although the severity is usually mild to moderate. To improve patients’ tolerability of akathisia, we suggest that extreme small dose of aripiprazole should be started, e.g. 2.5 mg in the first dose, then 2.5 mg as the second dose three days later. Then, the dose can be titrated up slowly to receive 2.5 mg/day in week 2, 5 mg in week 3, 10 mg in week 4...

**Olanzapine**

Olanzapine is an SGA not only antagonizing the dopamine D₂ receptor, but also strongly antagonizes the 5-HT₂A receptor. The combination of olanzapine and fluoxetine was approved by the US FDA for the treatment of TRD. The recommending starting dose is 5 mg of oral olanzapine and 20 mg of fluoxetine daily (www.fda.org).

In the study by Corya et al., the olanzapine/fluoxetine combination has shown higher remission rate for TRD than olanzapine alone, or fluoxetine, and venlafaxine. The improvement of symptoms in the olanzapine/fluoxetine combination group is greater than other groups [29]. In another randomized doubleblind trial by Shelton et al., participants with TRD were divided into fluoxetine group, olanzapine group, and fluoxetine plus olanzapine group [30]. The mean dose of olanzapine use as adjunctive therapy was 13.5 mg/day. As a result, the fluoxetine/olanzapine group has provided greater improvement in symptomatology than the other two groups [30]. It has also achieved higher remission rate than the olanzapine group, but not the fluoxetine group. Moreover, side effects reported most included somnolence, increased appetite, asthenia, weight gain, headache, dry mouth, and nervousness. But the overall tolerance rate was high [30].

Olanzapine is a well-tolerated option of augmentation therapy for MDD patients with TRD. But the possible risks include the side effects of increased appetite, weight gain, and metabolic symptoms.

**Quetiapine**

Quetiapine is an SGA involving both DA and 5-HT receptors. It was approved by the US FDA for acute treatment of bipolar depression, with recommended dose of 300 mg/day (www.fda.org). In previous studies, quetiapine has shown antidepressive effects in patients with diagnosis of schizophrenia spectrum.

In the study by Dorée et al., study participants with TRD were randomized into two groups, receiving adjunctive intervention of lithium and quetiapine, respectively. The target dose of quetiapine was 400 mg/day, with maximum dose of 800 mg/day. Both groups have shown improvement in symptomatology, but improvement in the quetiapine group is greater [31]. In another multicenter, doubleblind, randomized, placebo-controlled trial by El-Khalili et al., patients with MDD showing inadequate response to previous antidepressant treatment were randomized into three groups for adjunctive intervention – quetiapine 150 mg/day, quetiapine 300 mg/day, and placebo [32]. As a result, the quetiapine 300 mg/day group has shown greater efficacy than the placebo group. The improvement in the quetiapine 150 mg/day group is less obvious. The overall remission rate is highest in the quetiapine 300 mg/day group (52.7%) as compared with the 150 mg/day group (42.0%) or placebo group (32.9%). During the study, the most frequently reported side effects which led to discontinuation are sedation and
somnolence. Most of the side effects reported are mild to moderate in intensity [32].

Quetiapine has been proven recently as a safe, effective, and well-tolerated option as an add-on intervention for patients with TRD. Although lithium is the most investigated first-line suggestion for augmentation strategy for TRD, more and more evidence has shown the possibility of quetiapine providing better efficacy and less concerns about safety.

**Drug Augmentations for TRD with Lithium**

Lithium has been prescribed for the treatment of bipolar disorder for decades [33]. But it can also be one of the choices of augmentation for MDD with TRD. In fact, lithium used to be one of the first-line treatment strategies for treating resistant unipolar or bipolar depression. Animal studies of augmentation with lithium have reported enhanced serotonin neurotransmission, as well as an increase in the presynaptic formation, storage, and release of serotonin, suggesting synergistic effect of lithium and antidepressants through the serotonergic pathway [34].

Many studies have provided evidence of improvement after using lithium as augmentation therapy of TRD. It is one of the most frequently investigated treatment strategies for TRD, many of them through placebo-controlled, double blind studies. Price et al. have reported 56% of patients with TRD showing positive response after the add-on therapy of lithium, with daily dose of 900-1,500 mg with its serum levels of 0.5-1.3 meq/L [35]. Furthermore, the positive response rate for unipolar depression is higher than that of bipolar depression, which is contrary to other studies. The marked positive response rate of melancholic patients is higher than that of non-melancholic patients [35]. Sugawara et al. studied the predictors of efficacy in lithium augmentation for TRD, they have reported no correlation between efficacy of treatment to sex, age, suicide attempts, serum lithium level, class of antidepressants, psychotic symptoms, or atypical depressive symptoms. [36]. Other than that, patients with three recurrent major depressive episodes and patients with family history of MDD or bipolar disorder in a first-degree relative have shown higher response rate to lithium augmentation therapy [36].

In level 3 of the STAR*D study, a proportion of the participants who did not have satisfactory response during the previous treatments in levels 1 and 2 were randomly assigned to augmentation with lithium or T3 [37]. The dose of lithium for augmentation was 450-900 mg/day, or 225-450 mg/day if the participant could not tolerate the initial dose. The median blood level of lithium was 0.6 meq/L. Lithium group has remission rate of 15.9%, that is not different from that of T3 group (24.7%), but greater proportion of participants in the lithium group cannot reach the target dose because of side effects [37]. The inadequate dose of lithium may affect the efficacy of treatment [37].

Although the positive effect of lithium augmentation therapy has been consistently reported, clinicians are concerned about the risk of intoxication, and the narrow gap between the therapeutic blood level and potentially toxic blood level while prescribing lithium. Dunner has advocated that lithium is a mainstay for treating bipolar depression, but has discouraged the use of lithium in treating patients with TRD [7]. As shown in STAR*D study, we need to keep in mind that lithium and T₃ augmentations have similar efficacy, but T₃ augmentation has more favorable side effect compared to that of lithium add-on [37]. After the advent of post-tricyclic antidepressants and SGAs, lithium augmentation is less popular be-
cause more tolerable drugs for augmenting treatment for TRD are readily available.

**Drug Augmentations for TRD with Thyroid Hormone**

The thyroid hormones have been used to augment the effect of antidepressant treatment for over 50 years. Active thyroid hormones include T₃ and T₄. T₃ has greater bioavailability in the plasma and greater affinity for thyroid receptors. Past studies have supported the association of hypothyroidism and mood disturbances. Comparing to non-depressed population, patients with MDD show a tendency of higher rate of subclinical hypothyroidism [38].

In the study by Agid and Lerer [39], T₃ augmentation was given to participants who did not respond to treatment of SSRI with adequate dose after 6 weeks. The dose administered was 25-50 μg depending on the response of participants. After 2 weeks, the response rate among participants is 40%. All of the responders are female. None of the male participant has shown positive response to T₃ augmentation [38].

In level 3 of the STAR*D study, daily dose of 25-50 μg of T₃ was prescribed as augmentation treatment to participants who did not achieve remission during the previous stages [37]. The mean duration of augmentation therapy is 9.6 weeks. As a result, 24.7% of participants in the T₃ group achieve remission. Although the only difference is the number of participants quitting the treatment due to side effects, the T₃ group is still suggested to have slight advantages over the lithium group, due to better treatment tolerance rate although the remission rates of lithium and T₃ augmentation are similar (15.9% vs. 24.7%, respectively) [37].

Current studies have shown a positive result of using T₃ as a choice of augmentation of antidepressant for TRD patients. It is a safe and well-tolerated option. Under monitoring of thyroid function, adverse effects are less concerning. But we need to be sensitive to T₃-related side effect – atrial flutter. As stated previously, T₃ augmentation becomes less popular because more tolerable drugs for augmenting treatment for TRD are readily available after the advent of post-tricyclic antidepressants and SGAs.

**Drug Augmentations for TRD with Others**

In 2010, American Psychiatric Association published a treatment guideline for patients with MDD [40]. In having reviewed a total of 1,170 papers, the work group members made a list of drugs having potential to augment the efficacy of MDD on top of antidepressant. The list includes St. John wort, S-adenosyl methionine, omega 3 fatty acid, and folate. But we have not seen any promising data on those drugs on treating TRD.

Interestingly, we have also found that two studies [41, 42] have reported the efficacy of ketamine in the context of augmentation therapy rather than the switch of using ketamine in treating TRD. We are also looking forward to have more definitive reports.

**Conclusion**

Major depressive disorder (MDD) is one of the most frequent psychiatric diseases seen in the clinic. Most MDD patients can be treated reliably and comfortably with the use of one antidepressant. But some patients have treatment-refractory depression (TRD), which needs to be managed with switch of the antidepressant or augmentation therapy with another antidepressant or other drugs.
Managing TRD is a challenge for practicing psychiatrists. In this overview, the authors have focusing on treating TRD with augmentation therapy. We recommend:
- Clinicians need to be well-versed in behavioral and physiological classification of antidepressants as a logical basis of choosing an appropriate antidepressant for add-on therapy.
- Clinicians need to be familiarized with data of clinical drug trials for treating TRD with second-generation antipsychotic drugs such as aripiprazole, olanzapine, and quetiapine, approved by the Food and Drug Administration of the United States.
- Clinicians need to recognize the use of lithium and thyroid hormone as an add-on drugs for treating patients with TRD.
- We are still await some other drugs with the potential for augmenting treatment for patients with TRD. More clinical efficacy data are needed.

In this topic of drug augmentation therapy, we have excluded all switch therapies in treating patients with TRD here. As a reminder, the patients need to be motivated to participate actively and work cooperatively with their psychiatrists in the endeavor to pursue TRD treatment. At the same time, the TRD patients are also educated to adopt a healthy lifestyle – such as having the habit of regular aerobic exercise [3], and refraining from substance uses [43, 44], etc. With all those tips, the authors believe that the goal of remission can be more easily achieved for patients with TRD.

Acknowledgements

The contents of this review contain information on off-label use of released licensed medications. The readers need to read package insert on dosages and side effects of each drug mentioned in this review before the prescribing them to their patients. All authors declare no potential conflicts of interest in writing this overview.

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