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Treatment Resistant Depression: Review of its Therapeutic Interventions

Hani Raoul Khouzam[1,2*]

[1]Psychiatrist, VA Palo Alto Health Care System, Palo Alto, Marina Clinic, Monterey, California, USA

[2]Clinical Professor of Psychiatry, University of California San Francisco (UCSF) – Fresno Department of Psychiatry, California, USA

[*]**Corresponding author:** Hani Raoul Khouzam, Psychiatrist, VA Palo Alto Health Care System, Palo Alto, Marina Clinic, Monterey, California, USA; E-mail: frank.frimpong2012@gmail.com

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Abstract

Treatment-resistant depression (TRD) is a complex and challenging psychiatric condition. The selective serotonin reuptake inhibitors (SSRIs) and the serotonin and norepinephrine reuptake inhibitors (SNRIs) are considered first-line antidepressants treatment of TRD. Switching between various antidepressants and augmentation strategies of adding other pharmacological or non-pharmacological interventions to the first-line antidepressants treatment are usually implemented for the management of TRD. This review is a brief summary of the currently available therapeutic interventions that could be implemented to eventually improve TRD treatment outcomes.

Keywords: ***Major depression; Antidepressants; Psychotherapy; Brain stimulation; Switching; Augmenting; Pharmacology***

1. Prelude

Major depressive disorder (MDD) is considered one of the most prevalent and disabling mental illnesses worldwide. Left untreated MDD would precipitate severe personal and societal complications affecting almost every aspect of life and leading to loss of productivity, and the development of interpersonal, occupational and vocational difficulties subsequently aggravating economic and human sufferings. Additionally, MDD is also associated with several co-occurring medical and psychiatric conditions further impacting its detrimental effects on individuals, families and society at large. MDD has also been associated with increased suicide risk. The persistence of MDD despite appropriate and adequate treatment duration has been clinically described as treatment resistant depression (TRD).

2. Introduction

Treatment-resistant depression (TRD) is a complex and challenging psychiatric condition. Its accurate definition has not been standardized in the context of a generalized consensus [1]. In clinical settings it is usually described as a category of MDD that continues to persist despite appropriate comprehensive and integrated biopsychosocial treatment including pharmacological treatment with at least two different first-line antidepressants provided during an adequate period of at least six to eight weeks [2]. An alternative definition describes TRD as s lack of achieving remission of depressive symptoms despite adequate treatment with two or more antidepressant medications of different classes, at the appropriate recommended dose and duration, with a confirmation of consistent adherence [3].

3. General Evaluation

To confirm the presence of TRD, clinicians need to assure the following

- Acuracy of an initial diagnosis of MDD.
- A comprehensive assessment of co-occurring medical and or psychiatric conditions that are contributing to the persistence of MDD. Hypothyroidism, chronic pain, cardiovascular disease are among the medical conditions that could precipitate TRD [4]. Anxiety, substance use and personality disorders could also hinder MDD recovery [5].
- Adherence with the recommended treatment plan confirming compliance, with correct dosing and duration of pharmacological interventions.

4. Psychotherapeutic Interventions

Various psychotherapeutic modalities have been found to be beneficial in TRD especially when co-occurring with other psychiatric conditions such as anxiety disorder, posttraumatic stress disorder, personality disorders and substance use disorders. Studies have shown the combination of psychotherapy with psychopharmacology to improve TRD treatment outcome. Dialectical behavioral therapy, cognitive behavioral therapy, interpersonal therapy and intensive short-term dynamic psychotherapy could all contribute to an overall improvement in TRD depressive symptoms [6,7]. Individuals with TRD who are candidates for evidence-based psychotherapies (EBP) would benefits from Cognitive Behavioral Therapy, Acceptance and Commitment Therapy, Interpersonal Therapy, Behavioral Activation, Mindfulness-Based Cognitive Therapy and Problem-Solving Therapy. The combination of EBT with pharmacological interventions could improve TRD treatment outcome [8].

5. Pharmacological Treatment

The selective serotonin reuptake inhibitors (SSRIs) or the serotonin and norepinephrine reuptake inhibitors (SNRIs) are considered first-line antidepressants treatment due to their relative tolerable side effects profile compared to other antidepressants [2]. TRD pharmacological intervention could involve switching between different classes of antidepressants and when clinically indicated implementing augmentation strategies of adding other agents to the first-line antidepressants treatment [6,9]. The most widely studied TRD pharmacological interventions may include

- Antidepressants from different classes

- Lithium
- Thyroid hormone supplementation
- Atypical or Second-generation antipsychotics (SGAs)
- Stimulant Agents
- Glutamatergic N-methyl-D-aspartate (NMDA)receptor antagonists:
- Psychedelics

6. Antidepressants

The various antidepressant and adult doses are illustrated in TABLE 1.

TABLE 1. **Various antidepressants and reciprocal adult doses.**

Medications	**Initial daily dose in mg**	**Average maintenance daily dose in mg**	**Maximum daily dose in mg as tolerated**
SSRIs			
Citalopram	20	20 to 30	40
Escitalopram	10	10 to 20	30
Fluoxetine	20	20 to 60	80
Fluvoxamine	50	100 to 200	300
Fluvoxamine CR	100	100 to 200	300
Paroxetine	20	20 to 40	10 to 50
Paroxetine CR	25	25 to 50	62.5
Sertraline	50	50 to 200	300
SNRIs			
Desvenlafaxine	25 to 50	50 to 100	400
Duloxetine	30 to 60	60	120
Levomilnacipran	20	40 to 120	120
Milnacipran	25 to 50	100 to 200	300
Venlafaxine	37.5 to 75	75 to 375	375
Venlafaxine XR	37.5 to 75	75 to 225	375
Atypical antidepressants			
Bupropion	200	300 (maximum single dose 150 mg)	450
Bupropion SR	150	300 (maximum single dose 200 mg)	400
Bupropion XL	150	300	450
Mirtazapine	15	15 to 45	60

Serotonin modulators Nefazodone It can cause liver failure and has been withdrawn from the USA and other countries.	200	300 to 600	600
Trazodone	100	200 to 400	600
Vilazodone	10	20 to 40	40
Vortioxetine	10	20	20
TCAs Amitriptyline	25	150 to 300	300
Amoxapine	25	200 to 300	400
Clomipramine	25	100 to 250	300
Desipramine	25	150 to 300	300
Doxepin	25	100 to 300	300
Imipramine	25	150 to 300	300
Maprotiline	25	100 to 225	225
Nortriptyline	25	50 to 150	200
Protriptyline	10	15 to 60	60
Trimipramine	25	150 to 300	300
Isocarboxazid	10	10 to 40	60
Phenelzine	15	15 to 90	90
Selegiline transdermal	6 mg/24-hour patch	6 to 12 mg/24-hour patch	12 mg/24-hour patch
Tranylcypromine	10	30 to 60	60

CR: controlled release; SR: sustained release; XL: extended release/24-hour XR: extended release.

Selecting an antidepressant is primarily based on previous response to a particular class, family history of a favorable response, side effects profile, interactions with other medications, the cost and individual preferences. The following stepwise approach is clinically indicated for the management of TRD.

6.1 Dose adjustment

Increasing the dosage of a prescribed antidepressant is a common strategy to manage persisting TRD following an adequate treatment duration. Clinicians using this strategy will gradually increase the dose up to the maximum approved safe limit to achieve symptoms remission. The implementation of this strategy would require vigilance in monitoring the development of intolerable side effects thus warranting no further dose increases [10]. The next step would be switching to/ or augmenting with another antidepressant, when remission is not achieved after an adequate trial of antidepressant monotherapy. Agent selection will need to take into consideration side effects, drug interactions, and clinical characteristics of the individual.

6.2 Switching antidepressants

Switching strategies are recommended when there is a lack of response to the initial treatment, poor tolerance to the initial treatment or a history of a previous response to a different antidepressant. Studies show a wide variability in the effectiveness of switching antidepressants. Switching to a different SSRI; or changing to an SRNI or to a different class of antidepressants could achieve symptoms remission in TRD [11].

6.3 Combining and augmenting

The lack of TRD response to antidepressants switching may necessitate augmentation by the addition of various pharmacological and non-pharmacological interventions. In clinical settings it is recommended to initiate augmentation strategy in cases of partial response, to 4 to 6 weeks of adequate treatment.

6.4 Selective serotonin reuptake inhibitors (SSRIs)

Arranged by their alphabetical order SSRIs include Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Fluvoxamine, Paroxetine, Paroxetine, Sertraline. SSRIs are a class of antidepressants that share many similarities in the context of their effectiveness in TRD. When prescribed as initial agents for TRD or as augmenting agents, clinicians need to be mindful about their pharmacokinetics differences, particularly on the CYP450 enzyme systems, which will subsequently influence their safety profile, their clinical indications, and dosing recommendations [6].

6.5 Serotonin-norepinephrine reuptake inhibitors (SNRIs)

Arranged by their alphabetical order they include Desvenlafaxine, Duloxetine, Levomilnacipran, Milnacipran, Venlafaxine and Venlafaxine XR. SNRIs are commonly described as “dual action agents”; however, the degree to which reuptake of serotonin and norepinephrine inhibition usually depends upon the prescribed dose. Statistically the SNRIs appear to be more effective than SSRIs in the treatment of TRD, however this effectiveness was not significantly different in clinical settings, the choice of SNRIs in TRD would be then based on the initial response and the long term treatment outcomes [6].

6.6 Atypical antidepressants

Arranged by their alphabetical order they include Bupropion, Bupropion SR, Bupropion XL and Mirtazapine.

6.7 Bupropion

Bupropion with its various available formulations could offer a broad advantage in TRD management by allowing individuals to select the formulation with lesser side effects based on their prior treatment episodes of depression. Additionally, each formulation, could be amenable to a tolerable and faster dose titration. Individuals may experience a stimulating effect with bupropion which could be perceived as anxiety and as a precipitant for sleep difficulties if administered close to bedtime. The stimulating effects of bupropion could improve TRD symptoms of low energy level, excessive daytime sleepiness, and cognitive functioning [12].

6.7 Mirtazapine

Individuals with TRD and co-occurring anxiety, sleep disturbances, and agitation could benefit from mirtazapine due to its mechanism of action and relative tolerable side effects profile [13]. The overall pharmacological antidepressant activity of mirtazapine has been attributed to its possible dual action, on noradrenergic and 5-HT1 receptor-mediated serotonergic neurotransmission, and its blockade of 5-HT2 and 5-HT3 receptors [14]. This unique mechanism of action of mirtazapine could place it as a primary alternative agent for TRD treatment or as an augmenting agent to either an SSRI or an SNRI. Further studies are still needed in order to confirm the potential effectiveness of mirtazapine as a sole or an augmenting agent in TRD [15].

6.8 Serotonin modulators

Arranged by their alphabetical order they include Nefazodone, Trazodone, Vilazodone, and Vortioxetine. There are fewer studies comparing the efficacy of serotonin modulators with other classes of antidepressants in TRD. Some comparison studies have shown similar efficacy to the SSRIs and SNRIs in TRD with vortioxetine being well tolerated than vilazodone, the SSRI sertraline and the SNRI venlafaxine [16]. Vortioxetine is an agonist of the 5-HT1A receptor, a partial agonist of 5-HT1B, and an antagonist of 5-HT3, 5-HT1D, and 5-HT7 [17]. Vilazodone is a partial 5-HT1A agonist [18]. Similar to SSRIs, vortioxetine and vilazodone are also inhibitors of the pre-synaptic serotonin transporter, increasing the synaptic concentration of serotonin [17,18]. The serotonin modulators antidepressant effects have not been compared with other antidepressants and they need to be thoroughly studied in adequately-powered and well-designed clinical trials [18]. Although trazodone is FDA-approved for the treatment of MDD [19], it has shown mixed results in TRD treatment [20]. Nefazodone was withdrawn from the market in most countries by 2004 due to concerns over liver toxicity. However, the generic version of nefazodone, which continues to be available in the United States, was not removed from the market by the FDA for safety or effectiveness reasons. The brand-name medication Serzone was discontinued by its manufacturer, Bristol-Myers Squibb, in 2004, influenced by declining sales and mounting concerns over rare but severe liver toxicity. Despite the brand-name's withdrawal, the generic version remains available, although it is not a first-line treatment and is typically prescribed only for patients who have not responded to other antidepressants.

6.9 Tricyclic antidepressants (TCAs)

Arranged by their alphabetical order they include Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin, Imipramine Maprotiline, Nortriptyline, Protriptyline and Trimipramine. The TCAs could be prescribed as monotherapy for TRD. Their side effects usually emerge prior to their therapeutic effects resulting in early discontinuation prior to experiencing TRD remission [21]. They are considered lethal in overdose suicidal attempts due to their cardiotoxicity especially in individuals with underlying cardio- vascular diseases [22].

6.10 Monoamine Oxidase Inhibitors (MAOIs)

Arranged by their alphabetical order they include Isocarboxazid, Phenelzine, Selegiline transdermal and Tranylcypromine. MAOIs may be effective in individuals with TRD especially in those with atypical features such as fatigue or agitated behaviors [23]. Irreversible MAOIs such as isocarboxazid, phenelzine, and tranylcypromine would require dietary restrictions due to their

effects on tyramine containing food which could precipitate a hypertensive crisis when MAOIs are combined with tyramine containing products. Reversible MAOIs such as transdermal selegiline would not require dietary restrictions at the 6 mg/24-hour dose [24]. When switching to or from an MAOI, washout periods for at least 2 weeks are required. For antidepressants with long half-life such as fluoxetine, a longer 5 weeks washout period would be required [25]. Despite MAOIs potential effectiveness in TRD, their increased level of interaction with several pharmacological agents, their required dietary restrictions and their side effects profile, narrows their wider use in clinical practice.

7. Lithium

Lithium is considered an effective augmenting agent for the management of TRD [26,27]. It possesses anti-suicidal properties which are of utmost clinical importance in the overall management of mood disorders including TRD [28]. Due to its narrow therapeutic/toxic blood level, lithium would require timely checking of its blood level and vigilant monitoring of its interactions with many pharmacological and non-pharmacological agents that would either lower or increase its therapeutic blood level [26].

8. Thyroid Hormone Supplementation

Triiodothyronine (T3) has been reported to improve remission rates in patients with TRD when added to SNRIs, TCAs, or MAOIs. even in euthyroid individuals. T3 supplementation seems to be well tolerated in most of the studies that documented its effectiveness. The appropriate timing of T3 supplementation still needs to be further explored in more studies especially in the context of its appropriate dosing and treatment duration in TRD [29].

9. Atypical, Second-Generation Antipsychotics (SGAs)

SGAs have shown effectiveness as augmenting agents in reducing depressive symptoms in TRD within the span 1 to 2 weeks [30,31]. Arranged by their alphabetical order the SGAs that could be considered as augmenting agents in TRD include Aripiprazole, Brexpiprazole, Cariprazine, Olanzapine, Olanzapine + Fluoxetine, Quetiapine, Risperidone, and Ziprasidone. SGAs could be associated with several side effects that clinically warrant thorough psychoeducation to highlight their risks versus their potential benefits [32].

Most studies recommend SGAs augmentation in TRD as a short-term treatment intervention [6]. Long-term treatment with the SGAs could lead to the emergence of tardive dyskinesia (TD) and metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, body weight gain and type 2 diabetes [33,34]. Laboratory testing, EKG monitoring and using a rating scale such as the Abnormal Involuntary Movement Scale (AIMS) would allow the early detection of these adverse effects.

10. Stimulant Agents

In individuals with anergia, anhedonia, fatigue and hypersomnia the augmentation with a stimulant may be considered to improve these atypical depressive symptoms [10]. The use of a stimulant is usually implemented for a short-term treatment duration to achieve remission of TRD depressive symptoms, then gradually tapered over several days and ultimately discontinued. It may be necessary to restart the stimulant that achieved symptoms remission at the lowest effective dose in

those individuals who experienced recurrence of depressive symptoms in the aftermath of its discontinuation. Stimulants treatment is contraindicated in individuals with anxiety, chronic cardiovascular disease, sleep disorders, psychosis and those with substance use disorders. Cardiology consultation would be warranted prior to prescribing stimulants in individuals with comorbid cardiovascular disease. There is still a scarcity of evidence supporting the long-term use of various stimulant medications in TRD [35].

11. A Novel Agent - Dextromethorphan/Bupropion

The combination of the antidepressant bupropion with the stimulant dextromethorphan formula *dextromethorphan/bupropion* has been FDA approved for the treatment of MDD due to its effective earlier onset of action, and well tolerated side effects profile, however it has not been approved or widely utilized in TRD treatment [36].

11.1 Glutamatergic N-methyl-D-aspartate (NMDA)receptor antagonists

Ketamine and Esketamine could be considered in individuals with TRD who remain unresponsive to other alternative treatment interventions.

11.2 Intravenous (IV) Ketamine

The use of IV Ketamine as monotherapy or as an augmenting agent to an antidepressant, has shown noticeable effects on improving TRD depressive symptoms [37]. Side effects such as dissociative symptoms, hypertension, and confusion/agitation-appear to be tolerable and limited to the time of treatment. Longer -term IV ketamine use remains unknown, including the potential risk of abuse or dependence [38].

11.3 Intranasal (IN) Esketamine

IN Esketamine has been FDA approved in conjunction with an oral antidepressant, for the treatment of TRD in adults [39]. There is still a paucity of data to support its long-term efficacy and safety and there is no available data supporting its use in individuals who are 65 years or older. Based on clinical practice feedbacks IV ketamine appeared to be more efficacious than IN Esketamine for the treatment of MDD [40].

11.4 Psychedelics: Psilocybin

Studies have shown a noticeable decrease in depressive symptoms following psilocybin administration when assisted with psychotherapy. These findings have provided preliminary results suggesting the antidepressant efficacy of psilocybin-assisted psychotherapy, however, further studies are needed to evaluate the safety and the long-term efficacy of this intervention in TRD [41]. Understanding psilocybin antidepressant mechanism of action would be of crucial importance to confirm its therapeutic effects when combined with antidepressants in the general treatment of mood disorders including TRD [42].

12. Non -Pharmacological Treatment Strategies for TRD

Brain Stimulation interventions which may include

- Electroconvulsive therapy (ECT)
- Repetitive transcranial magnetic stimulation (rTMS)
- Deep magnetic stimulation (DMS)
- Vagus nerve stimulation (VNS)

12.1 Electroconvulsive therapy (ECT)

Compared with the available brain stimulation interventions, ECT has the most evidence supporting its beneficial effects in TRD [43]. The relative fast onset of ECT in reducing the severity of the depressive symptoms has also been associated with reduced risk of suicide in TRD [44]. ECT potential side effects may include cognitive impairments in the domains of short-term memory, autobiographical memory recall, attention and acquisition of new learning [45]. The cognitive adverse effects are usually transient in nature. Some individuals may experience long lasting retrograde amnesia especially those who received bilateral ECT [46]. While ECT has immediate effects on improving TRD, depressive symptoms could emerge following the initial course of treatment [47]. Maintenance ECT and pharmacological interventions would be indicated to prevent the recurrence of TRD [48].

12.2 Repetitive transcranial magnetic stimulation (rTMS)

This magnetic stimulation modality involves placing an electromagnetic coil near the head and stimulating the nerves in the areas of the brain that play a role in mood regulation and depression and has been approved for the treatment of MDD. rTMS effectiveness in TRD has been also documented [49]. Although rTMS requires a long duration with several sessions of treatment and does not have a prolonged lasting effect on reversing TRD compared to ECT, its favorable side effects profile makes it practically advantageous over ECT [50].

12.3 Deep magnetic stimulation (DMS)

This intervention is an extension of application of stimulus with rTMS coils of different designs, which allow pulses to target locations that are deeper into subcortical areas of the brain that could lead to increased effect in improving TRD [51]. Due to the paucity of studies confirming DMS lasting effects, it is not commonly used as a beneficial intervention in TRD [52].

12.4 Vagus nerve stimulation (VNS)

The mood effects of VNS lead to its FDA approval for TRD. Its invasive nature and serious side effects such as voice alteration, dysphagia, dyspnea, infection, dizziness, asthenia, chest pains, palpitations, and vocal cord paralysis made it a less desirable option for TRD [53]. Advances in modifying and improving noninvasive VNS could allow its frequent use in TRD [54].

12.5 Novel neuromodulation strategies

Magnetic seizure therapy, Transcranial direct-current stimulation and Transcranial Photo biomodulation are also being studied as possible brain stimulation interventions for TRD. The use of these modalities has not been yet approved by the FDA but they do offer a new horizon and could be added to the armamentarium of treating MDD and TRD [55].

13. Complementary Therapy- Nutraceutical Interventions

There are many nutraceutical interventions that target neurotransmitter pathways leading to the investigation of the role specific nutrients and herbal preparations in the treatment of MDD [56]. These nutraceuticals included St John's wort, S-adenosyl methionine (SAM-e), omega-3 fatty acid, and probiotics.

13.1 St John's wort

St John's wort (Hypericum perforatum) is an herbaceous plant containing many bioactive molecules including naphthodianthrones, phloroglucinol derivatives, flavonoids, bioflavonoids, proanthocyanidins, and chlorogenic acid. It is available over the counter in many pharmacies and health food stores in the United States. Studies have shown therapeutic effects of St. John's wort, on different psychiatric and mood disorders including MDD [57,58]. Although it may have some merit in treating MDD, its use in TRD has not been confirmed and may not be indicated due to its relative high potential of its interaction with multiple agents [59]. It could increase the metabolism of oral contraceptives and the protease inhibitors, thus reducing their intended therapeutic effects. St. John's wort could also minimize the effectiveness of cyclosporine and contributes to the rejection of organ transplants. It has also been associated with photosensitivity precipitating skin burning during sunlight exposure [59].

13.2 S-adenosyl methionine SAM-e

Production of SAM-e could be impaired in individuals with MDD. The daily intake of food supplements containing SAMe for a period of three months was reported to improve depressed mood and quality of life in those individuals with MDD [60]. It has been hypothesized that supplementation with SAM-e increases levels of 5-HT, DA, and phosphatides, and enhances 5-HT- and DA-receptor site binding, thus leading to amelioration of depression [58]. SAM-e breaks down into homocysteine, elevated levels of which have been correlated with increased incidence of cardiac disease [61].

13.3 Omega-3 fatty acid

There is no sufficient high-certainty evidence to confirm the effectiveness of Omega-3 fatty acid as a treatment for MDD [62]. Although it has been reported to alleviate depression, omega-3 fatty acid may exert a dose-related effect on bleeding time [63].

13.4 Probiotics

The microbiota–gut–brain diet axis is a promising target that could be modified via dietary and nutraceutical intervention, such as prebiotics, high-fiber diets and fiber supplements, and probiotics in fermented foods or supplements [64]. Few studies reported significant improvements in MDD with probiotics in food supplements [65].

Complementary nutraceutical interventions have all been used to treat MDD, they need to undergo rigorous randomized -placebo-controlled-double -bind studies confirming their effectiveness in TRD. Individuals considering these interventions are encouraged and advised to consult their health care providers prior to using these agents due to their potential risks for causing serious irreversible adverse effects [58].

13.5 Light therapy

Light therapy, phototherapy or bright light therapy, is a therapeutic intervention where the individuals are exposure to direct sunlight or artificial light at controlled wavelengths. It has been effective in the treatment of seasonal affective disorder (SAD) [66]. Studies have shown light therapy to be an effective adjunctive therapy in non-seasonal MDD [67]. Light therapy could be used as adjunctive intervention in TRD, its therapeutic effect is only transient since it does not persist after its discontinuation [68].

14. Summary

TRD remains a major and complex challenge for mental health professionals. It is difficult condition to treat, with frequent recurrence, and high impact on individuals and the society at large. TRD frequently develops in individuals with multiple recurrences of MDD who are treatment refractory and in those with co-occurring medical and psychiatric conditions. A wide variety of options for pharmacological treatment of TRD have been proposed including switching from one SSRI or SNRI to another within the same class of agents. Adding and, or augmenting with other classes of antidepressants. The TCAs, the atypical antidepressants, and the MAOIs are options to consider when augmenting treatment with antidepressant agents. Other augmenting agents include lithium, thyroid hormone supplementation, atypical or second-generation antipsychotics, stimulants, glutamatergic agents such as ketamine and esketamine and psychedelics. Brain stimulation interventions could also be initiated including ECT, rTMS, DMS and VNS. Complementary therapy with nutraceutical supplements such as St John's wort, S-adenosyl methionine (SAM-e), omega-3 fatty acid, and probiotics could also be considered. Despite the many difficulties that are attributed to TRD, therapeutic interventions could lead to symptoms remission and the restoration of a functioning and rewarding quality of life. Future studies are needed to compare the various pharmacological and non-pharmacological interventions effectiveness and efficacy in the management of TRD.

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