Drug Repurposing for the Management of Depression: Where Do We Stand Currently?

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Abstract: A slow rate of new drug discovery and higher costs of new drug development attracted the attention of scientists and physicians for the repurposing and repositioning of old medications. Experimental studies and off-label use of drugs have helped drive data for further studies of approving these medications. A deeper understanding of the pathogenesis of depression encourages novel discoveries through drug repurposing and drug repositioning to treat depression. In addition to reducing neurotransmitters like epinephrine and serotonin, other mechanisms such as inflammation, insufficient blood supply, and neurotoxicants are now considered as the possible involved mechanisms. Considering the mentioned mechanisms has resulted in repurposed medications to treat treatment-resistant depression (TRD) as alternative approaches. This review aims to discuss the available treatments and their progress way during repositioning. Neurotransmitters’ antagonists, atypical antipsychotics, and CNS stimulants have been studied for the repurposing aims. However, they need proper studies in terms of formulation, matching with regulatory standards, and efficacy.

Keywords: clinical trials; depression; major depressive disorder; new drugs; repurposing; repositioning; strategies

1. Introduction

Despite the high rate of technological progress and improvements in knowledge of different diseases, the discovery of new medications demonstrated a lower speed [1].

As the regulatory requirements for bringing a new medication to the market is becoming more challenging to meet, medication cost increases globally [2].

Drug repositioning, also called drug repurposing or re-tasking, is a promising strategy to introduce new indications for other therapeutic goals for an available drug in the market [3]. Since the safety profile of these medications was studied thoroughly before, the development of their formulation has been analyzed, and the medicines successfully passed the preclinical and clinical steps, the risk of failure decreases significantly [4]. To
apply a drug repositioning strategy, three main steps are needed to be concluded; first, a molecule/substance should be suggested for the mentioned indication; second, preclinical models, including animal and computational models, should be assessed and last the efficacy of medication should be analyzed [5].

As a significant mental disorder, major depressive disorder (MDD) affects approximately 264 million globally [6]. Due to the insufficient therapeutic response of patients to the available medications, the need for new medicines has attracted scientists worldwide [7]. Various mechanisms have been associated with the prevalence of MDD, and these mechanisms directly influence medication selection. Changes in inflammatory biomarkers, neurotransmitters, age-related, and genetic factors are among the mechanisms constituting the indications of medications [8]. Moreover, new antidepressant medications usually act on multiple intra- and extra-cellular markers, indicating their poly-pharmacology indications [9]. This review aims to provide a complete insight into the drug repositioning strategy, especially the candidates that could be beneficial in managing MDD.

2. Drug Repurposing

2.1. History

Drug repurposing is the procedure of finding new indications for approved or investigational medications [10,11]. Investigational medicines may have had a desirable safety profile in phase I/II clinical trials [12] but never reached the market [11,12] due to reasons unrelated to safety [12], such as lack of efficacy [11]. Drug repurposing can emerge in different forms like repositioning, reformulation, and combination [13,14]. Drug repurposing was serendipitous and accidental in the past; whenever a medication had shown an off-target or a new on-target effect, it was investigated for commercial exploitation [10]. So far, the most successful repurposed drugs have been found accidentally, and no systematic approach has been involved in the process [10,15]. Sildenafil citrate was an antihypertensive medication that got repurposed as retrospective clinical data analysis showed its positive effect on erectile dysfunction [10,16]. The year sildenafil got marketed by Pfizer for erectile dysfunction under the name Viagra® [17], it held a 47% share of this problem’s market, and the total sales were USD 2.05 billion worldwide [10]. Thalidomide is another well-known instance causing many severe skeletal birth defects in children whose mothers had taken this medication during the first trimester of pregnancy [1,10]. In consequence, thalidomide was withdrawn for four years [10]. In 1964, thalidomide was fortuitously recognized to be effective in erythema nodosum leprosum (ENL) [18]. Decades later, in 1999, thalidomide was discovered to be effective in multiple myeloma [19]. The positive outcome in multiple myeloma led to further derivative developments like lenalidomide [10]. Bupropion, an antidepressant medication got approved by the United States Food and Drug Administration (US-FDA) for smoking cessation [13], botulinum toxin A, the compound used for eye muscle disorders with cosmetic impacts [18] and minoxidil, the antihypertensive medication, became established for pattern hair loss in male and female [17,20] are some instances of well-known repurposed drugs [12]. Iproniazid, an antitubercular compound, was the first medication got reported for its antidepressant effect. This compound showed euphoria, psychostimulation, increased appetite, and improved sleep as the side effects [21]. The story of finding D-lysergic acid diethylamide (LSD) psychedelic effects is another exciting example of serendipitous discovery in the field of psychiatry. LSD was first synthesized in 1938, but it did not show considerable physiological effects in animal testing. LSD’s strong and extraordinary influences on the mind were accidentally discovered for the first time in 1943 [22]. Thirteen medications have been repurposed for depression or bipolar depression treatment by 2017 [13].
2.2. Different Types of Drug Repurposing

Drug reformulation, repositioning, and combination are counted as different drug repurposing/repositioning [13,14].

2.2.1. Drug Repositioning

It finds new indications for a medication that already has other therapeutic indications [13,14]. For instance, mifepristone, an anti-progesterone drug with an initial indication for abortion, was experimentally effective in psychotic depression [3,23].

2.2.2. Drug Reformulation

It is about using a medication in a new dosage form [13,14]. The new formulation can both be taken via the same old route or a different route of administration. An example of drug reformulation is formulating ketamine for intranasal and sublingual routes to treat MDD [13].

2.2.3. Drug Combination

It refers to using two or more medications together [13,14] to improve efficacy and safety [13]. For example, using quetiapine and antidepressants in combination leads to the increased effect of antidepressant medications in the elderly suffering from MDD and cerebrovascular deterioration. In addition, taking anti-inflammatory medicines with antidepressants enhances responses to first-line antidepressants [13].

2.3. Common Approaches

Before the development stage in drug repositioning, three levels should be considered. The first level is discovering appropriate molecules for the desired indication, wherein most drug repurposing approaches are related to it. The second one is evaluating effects in preclinical experiments. The last is the appraisal of efficacy in phase II clinical trials, given that safety has been approved in phase I clinical trials for the original use [10].

Repositioning approaches are divided into two major groups: computational and experimental strategies [10,12,16]. These are growingly being used together [10,16] and will be separately discussed as follows. Explanations, pros, and cons of the drug repurposing approaches are summarized in Table 1. In addition, examples of each separate approach are indicated in Table 2.

2.3.1. Computational Approaches

Computational approaches consist of data analysis. These data can be obtained from different resources. For example, gene expression, chemical structure [10,12], or electronic health records (EHRs) can all be kinds of data resources [10]. In comparison with experimental approaches, computational approaches have lower expenses and fewer barriers [3].

Signature Matching

This method compares exclusive features (signature) of medication with another medication or disease. Three different types of data could be used as resources for extracting medication characteristics: chemical structure, adverse event profiles, proteomics, transcriptomic, and metabolomics, which are explored aptly in the following [10]:

Transcriptomic: This technique compares gene expression in a healthy state, disease-associated state, and medication-using state. If a medication can reverse the expression pattern of the genes related to disease phenotype, it will probably also revert the disease phenotype itself [10,12,16,23–25]. An example of this approach is that ketamine improves mood by modulating miRNAs like miR-598-5p and miR-451 [13]. Histone deacetylase (HDAC) inhibitors like
vorinostat are promising drug repositioning targets for depression, anxiety and schizophrenia treatment due to their role in affecting gene expression [26]. Peroxisome proliferator-activator receptor (PPAR-γ) agonists, especially pioglitazone, have significant antidepressant outcomes in MDD and major depressive episodes of bipolar disorder due to their role in adjusting responsible gene expressions [13]. HMG-CoA reductase inhibitors (statins) are PPAR-α ligands that increase the expression of some neuronal growth factors. Randomized controlled trials have suggested that they possess beneficial effects in combination with selective serotonin reuptake inhibitors (SSRIs) [21].

**Metabolomics:** Metabolomics is the study of all chemical procedures in the body [27]. A drug can be shared between two different disease treatments with similar pathophysiology [5]. This approach helps us to gain a comprehensive idea about the molecular processes involved in disease pathophysiology and finding how close our preclinical models to reality are [28]. Nuclear magnetic resonance and mass spectrometry are two methods for analyzing the metabolome [29].

**Proteomics:** Most medications apply their therapeutic effects by interacting with protein targets, and it is crucial to understand these interactions for drug development [12].

**Chemical Structure:** In this method, networks are made based on the shared chemical features [10] as similarity in chemical structure may lead to the same biological activity [10,16]. As an example, chlorcyclizine belongs to the phenylpiperazine class. This class includes many antipsychotic and antidepressant medications and chemical structure similarities between these medications and chlorcyclizine make it likely to possess the same effects [26].

**Adverse Event Profiles:** A hypothesis suggests that two different medications showing the same adverse effects might affect a shared target, protein, or pathway [10,16]. As well, a medication’s adverse effect resembling a disease phenotype can imply a shared pathway or physiology between the drug and the illness [10,15,16]. In addition, if two treatments for one disease with different mechanisms demonstrate the same uncommon adverse effect, there may be a shared underlying mechanism that links adverse events and therapeutic effects [30]. Side effects are more helpful in predicting drug indications than chemical structure or protein targets. It is possible to extract adverse events data from chemical structures if a drug has not reached the clinical trial level [31].

Cabergoline, an ergot derivative dopamine agonist, showed delusion adverse events and got recognized to have antidepressant-like effects. Pergolide, another dopamine agonist, demonstrated antidepressant effects in Parkinson’s disease. Modafinil is a narcolepsy medication that may be effective in depression treatment in combination with fluoxetine. Phenytoin, the famous anticonvulsant medicine, can be efficient in depression. This effectiveness is a result of hyperacusis, the phenytoin adverse effect [15].

**Computational Molecular Docking**

The basis of this approach is complementarity between ligand and target [10,23]. In conventional docking, the target involved in the disease is already known, and different medications get tested. In inverse docking, a set of targets are studied to check if they match particular medicines [10]. Computational molecular docking indicates that dextromethorphan shows an antidepressant effect with rapid onset of action during the first administration days due to involving glutamatergic receptors [13]. Cyproheptadine was hypothesized to improve depression based on its potential ability to be a serotonin receptor (5-HT2) antagonist [26]. Computational molecular docking suggests that mecamylamine, a nicotinic receptor antagonist, might be effective in depression treatment [23].
Genome-Wide Associated Studies (GWAS)

This method is proceeded on finding genetic variants associated with common diseases and understanding the biology of disease. In addition, these data can result in recognition of shared targets between conditions [10].

GWAS suggest pregabalin, gabapentin, nitrendipine, alizapride, mesoridazine, levonorgestrel, diethylstilbestrol, papaverine, scopolamine, ketoconazole, arcaaine sulfate, ifenprodil, cycloserine, risperidone, and sulpiride all can be repurposed for MDD [23].

Pathway or Network Mapping

This approach is building networks based on signature matching data, protein interactions [10,25,32], gene expression pattern [10,25], disease pathology, or GWAS data [10] to find similarity or relation between medication and disease [25]. Some disease-associated genes are not appropriate druggable targets. Therefore, constructing and analyzing such networks could be a way to find upstream or downstream genes which can be used for drug repurposing [10]. Pathway mapping based on disease pathogenesis showed that nimodipine, a calcium channel blocker, makes antidepressants effective in old patients suffering from vascular depression. Scopolamine, the muscarinic antagonist, possesses rapid antidepressant effects since the cholinergic system is responsible for the pathogenesis of mood disorders [13]. Cannabidiol is a propitious agent for MDD due to its effects on involved pathways in this disorder. Sho-saiko-to, a traditional Chinese medicine, showed antidepressant effects in mice upon its influence on the serotonergic system in the central nervous system. Medications that inhibit p38 mitogen-activated protein (p38-MAPK) signaling pathways such as neflamapimod may have desirable effects on depression as the p38-MAPK pathway is engaged in many cellular processes, especially neuro-inflammation. Spermine is useful in treatment-resistant depression (TRD), as it is a glutamatergic receptor modulator. N-acetyl-l-cysteine (NAC), the glutathione precursor, positively affects the different mechanisms involved in depression and is a beneficial nutraceutical for adding to antidepressant medications in MDD treatment [21].

2.3.2. Experimental Approaches

Retrospective Clinical Analysis

The main idea of this approach is reviewing and extracting valuable data from different resources such as EHRs, post-marketing surveillance, and clinical trials. This process would result in repositioning and using a medication for a dissimilar indication or finding an indication for a drug that had failed for its initial purpose [10].

**EHRs:** EHRs data are subdivided into structured (diagnosis and pathophysiology data, laboratory test results, and medication prescriptions) and unstructured (patients’ symptoms reports and imaging data) groups [10]. Analyzing data gained from the national health insurance of Taiwan research database showed metformin is a promising target for drug repositioning for depression and anxiety [26]. The results of observational or case-control studies indicated a lower risk of MDD in patients using angiotensin-converting enzyme inhibitors (ACEIs) like telmisartan in comparison with other antihypertensive medications. Case reports also demonstrated that pramipexole, a relatively new dopamine receptor agonist, has potential effects in treating MDD. An observational study on 82,643 women revealed the relation between higher flavonoid intake and lower risk of MDD. Last but not least, a meta-analysis of 17 observational studies suggested the association between depression and zinc deficiency [21].

**Post-Marketing Surveillance and Clinical Data:** Retrospective clinical data analysis showed that using anti-inflammatory medications, especially celecoxib, with antidepressants improves the responses to first-line antidepressants. Clinical data claims
that valproic acid enhances the effects of antidepressants in resistant depression patients. Based on clinical data, quetiapine co-administered with antidepressants improves the outcomes in patients with MDD and cerebrovascular deterioration [13]. Reviewing prior literature has shown that phenothiazines have anti-depressive effects resembling tricyclic antidepressants. Atypical antipsychotics can also help treat depression as adjunctive or primary therapy based on a meta-analysis [28]. Taking antidepressants combined with zinc caused decreased depressive symptoms than antidepressants alone in randomized control trials [21].

Novel Sources

This approach consists of three methods. The first one is using immortalized human cancer cell lines (CCLs) for screening different compounds to examine if pharmacological and genetic data match. The second method links EHR data to DNA biobanks; thereby, identifying the association between the patient’s genome and the patient’s illness. The third novel resource is patients’ online self-reported data about their condition while taking medicine [10].

Binding Assays

Binding assessments help us realize target and ligand interactions. For example, affinity chromatography, mass spectroscopy, and cellular thermos ability assay (CETSA) techniques are three methods used in this approach [10].

Phenotypic Screening

This approach attempted to identify compounds showing effects of disease consequences in model systems without any earlier information about targets they affect [10].

| Table 1. Explanations, advantages and disadvantages of approaches commonly used for drug repurposing. |
|---|---|
| **Explanation** | **Pros and/or Cons/Ref** |
| Signature Matching, Transcriptomic, Metabolomics, and Proteomics | Pros: finding new targets or off-target effects for existing medications [10], finding the new mechanism of action for drugs, involving more genetic level mechanisms in comparison to knowledge-based methods [25,32], low costs, public access to databases [23] Cons: medication-target genes not getting expressed in altered patterns and not being detectable [33] |
| Transcriptomic | Comparison of Gene Expression in Healthy, Disease-Associated and Medication-Using State |
| | Pros: gaining more molecular level mechanisms in comparison to knowledge-based methods [25] |
| Metabolomics | Recognizing potentially druggable targets in different diseases |
| Proteomics | Applying interaction between medication and proteome |
| Common Approaches | Computational Approaches |
| Method | Description                                                                 | Pros                                                                 | Cons                                                                                                                                                                                                                                                                                                                                 |
|--------|-----------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Toxicity, mode of action of small molecule medications | Developing networks based on shared chemical features | Cons: the difference between actual results and expectations, variety of physiological effects despite structure resemblance [10], possibility of happening alterations in structure due to biological activity [16] |                                                                                                                                                                                                                                                                                                                                 |
| Chemical structure | Finding shared targets, proteins, or pathways affected by different medications showing the same adverse effects | Pros: unlike animal models, both therapeutic and adverse effects are observable in humans [15] | Cons: problems in extracting information on medication package inserts, lack of proper adverse event profile and causality assessment [10]                                                                                                                                                                                                 |
| Adverse event profile | Finding shared targets, proteins, or pathways affected by different medications showing the same adverse effects | Pros: the ability to test all compounds with recognized structure [25] | Cons: difficulty in providing a 3D image of G-protein receptors, lack of eligible database providing appropriate information about targets’ structures, the difference between actual affinity between ligand and target and virtual results, different outcomes of different software packages [10], impossibility of identifying unknown mechanism beyond the known target in conventional docking [25] |
| Computational molecular | Testing different medications on a known target (conventional docking) or checking different targets |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                 |
| Docking | Match a particular medication (inverse docking) based on complementarity between ligand on target |                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                 |
| Genome-wide associated data (GWAS) | Finding genetic variants associated with common diseases and understanding the biology of disease | Pros: advances in technology, the accomplishment of |                                                                                                                                                                                                                                                                                                                                 |
Pros: narrowing the range of molecules from a large number to few targets [12]

Cons: ethical and legal obstacles, challenges in extracting unstructured data [1]

Pros: development of sequencing technologies, which helps ones collect more thorough information on each patient’s genetics (2), acceleration in the drug discovery process, reduction in research costs,
increase in patient involvement, ability to assess the effectiveness of the in-use medication (3)  
Cons: Happening alterations that make in vitro results better (1), challenges in using big data and technology for analysis (2), bias in collecting data, threat in patients’ safety in case of self-prescription (3) [10]

| Binding assays | Realizing interactions between target and ligand by using different methods as chromatography and mass spectrometry | - |
|----------------|--------------------------------------------------------------------------------------------------|---|
| Phenotypic screening | Identifying compounds showing disease consequences related effects in model systems, without any prior information about targets | Pros: testing many medications for a therapeutic effect over a complete range of concentration [34], high flexibility for administration to numerous drugs or diseases [32]  
Cons: not reaching a complete picture by in vitro assays [33] |

CCLs: Cancer cell lines; FAERS: Food and Drug Administration adverse event reporting system; HGP: Human genome project; Ref: Reference; WHO: World Health Organization.

2.4. Advantages

Drug discovery is a high-cost and lengthy process. Bringing a new medication to market takes 13–15 years and costs USD 2–3 billion [10,21,25]. Although the expenses are increasing, the number of approved medications has remained constant or even decreased through the past years [22,25]. Moreover, demands in therapeutic fields are growing, and traditional drug discovery cannot answer these needs [13]. In the case of psychiatric medications, it should be noted that this field has not been developed enough over time [26]. Drug repurposing is cost-effective and reduces the time taken to get a new medication to market [10,11,21] as it costs on average USD 300 million and takes about 6.5 years [10,21]. The preclinical tests [10,16] and phase I and II clinical trials can be skipped in drug repurposing if these steps have already passed for other indications and safety has been approved [10]. This is why drug repurposing may shorten the time needed and expenses as mentioned above [1,10].  

Furthermore, if the formulation is appropriate for the new indication, there is no need for formulation development. This can also be another helping hand for reaching the stated aims. Another great pro of drug repurposing is the lowered risk of failure due to approved sufficient safety [10,16]. At last, drug repurposing may uncover novel targets or pathways in treating a disease, which can be exploited further [10].
2.5. Barriers

Although toxicity and safety are not obstacles in drug repurposing, some barriers lead to failures, such as patent consideration, regulatory issues, and organization hurdles. In brief, many of the repurposed uses are already mentioned in the prior scientific literature or clinical data leading to limitations in patent protection. In addition, when an available generic formulation gets repurposed for a new indication, profitability reduces. This reduction happens due to off-label using the medication for novel indications. Governments make some rules for collaboration on patents that are near expiring to save public benefit. Creating a new formulation or dosage forms, developing new derivatives with the same therapeutic effects, or presenting medication in a new geographic region market are strategies for making a profit from the repurposed drugs [10]. Another trouble is that the effect of the medication is dependent on its dose. Therefore, it is necessary to identify the appropriate dose for novel indications during clinical trials [16]. Investments might be another obstacle in repurposing medications that have already failed during the drug development process. This trouble happens due to investors’ unwillingness as they see medication’s failure. In addition, medicines that failed in later stages of drug development have less time until patent expiration for repurposed try. Designing parallel development processes for different indications can lower the risk of failure [1] (Figure 1).

Figure 1. Advantages and barriers of drug repurposing.
### Table 2. Examples of repurposed/suggested repurposing medications for different types of depression with their repurposing approach.

| Medication Name | Repurposing Approach/Ref | New Indication Suggested by Article, or Investigational/FDA Approved/Ref |
|-----------------|--------------------------|---------------------------------------------------------------------|
| Atypical antipsychotics | Retrospective clinical analysis (PM surveillances and CD) [13] | MDD, BP1 depressive episodes (FA) [8] |
| Quetiapine | NA | MDD (FA) [9] |
| Aripiprazole | NA | MDD (FA) [35] |
| Brexpiprazole | NA | MDD (FA) [35] |
| Mecamylamine | Computational molecular docking [23] | Depression (SA) [23]; MDD (INV) [17,19,20,36,37] |
| Cyproheptadine | Computational molecular docking [26] | NA |
| Dextromethorphan | Computational molecular docking [13] | MDD (INV) [36–41] |
| Pregabalin | GWAS [23] | MDD (SA) [23] |
| Gabapentin | GWAS [23] | MDD (SA) [23] |
| Cycloserine | GWAS [23] | BP depression (INV) [42]; MDD (SA, INV) [23,36] |
| Risperidone | GWAS [23] | Extrapyramidal symptoms, suicidal ideation (INV) [43] |
| Cannabidiol | Pathway or network mapping [21] | MDD (SA) [21] |
| N-acetyl-L-cysteine | Pathway or network mapping [21] | MDD (SA) [21] |
| Sho-saiko-to | Pathway or network mapping [21] | NA |
| Spermine | Pathway or network mapping [21] | TRD (SA) [21] |
| Nimodipine | Pathway or network mapping [21] | Vascular depression in old patients (SA) [13] |
| Scopolamine | GWAS, Pathway or network mapping [13] | MDD (INV) [44,45] |
| Anti-inflammatory medications | Retrospective clinical analysis (PM surveillances and CD) [13] | NA |
| Valproic acid | Retrospective clinical analysis (PM surveillances and CD) [13] | Resistant depression (SA) [13] |
| Zinc | Retrospective clinical analysis (PM surveillances and CD) [21] | MDD (INV) [46] |
| Pramipexole | Retrospective clinical analysis (EHRs) [21] | MDD (SA, INV) [21,47] |
| Telmisartan | Retrospective clinical analysis (EHRs) [21] | MDD (SA) [21] |
| Metformin | Retrospective clinical analysis (EHRs) [26] | MDD (INV) [48] |
| Phenothiazines | Retrospective clinical analysis (PM surveillances and CD) [26] | NA |
| Cabergoline | Signature matching (adverse event profile) [15] | NA |
| Modafinil | Signature matching (adverse event profile) [15] | MDD (INV) [49], depressive episode in BP1 disorder (INV) [50], major depressive episode in BP1 disorder (INV) [51] |
| Pergolide | Signature matching (adverse event profile) [15] | NA |
| Phenytoin | Signature matching (adverse event profile) [15] | NA |
| Chlorcyclizine | Signature matching (chemical structure) [26] | NA |
| Vorinostat | Signature matching (transcriptomic) [26] | Depression, anxiety, schizophrenia (SA) [26] |
| Statins | Signature matching (transcriptomic) [21] | NA |
| Ketamine (esketamine) | Signature matching (transcriptomic) [13] | MDD and bipolar depression, Depressive symptoms in adults with MDD with acute suicidal ideation or behavior (FA) [52] |
| Pioglitazone | Signature matching (transcriptomic) [13] | MDD, a major depressive episode in bipolar disorder (SA) [13] |

BP: Bipolar; CD: Clinical data; FA: FDA approved; GWAS: Genome-wide associated studies; INV: Investigational; MDD: Major depressive disorder; NA: Not available; PM: Post-marketing; Ref: Reference; SA: Suggested by articles; TRD: Treatment-resistant depression.

### 3. Management of Depression

In order to manage a patient diagnosed with MDD, two or three main options, including psychotherapy, pharmacotherapy, and somatic interventions, exist. Some guidelines suggest that those with moderate to severe depression would benefit from both psychotherapy and pharmacotherapy. In a mildly depressed person, treatment could be initially based on psychotherapy, and if needed, switching to medication could be applied after weeks [17]. Physical activity and exercise, balanced nutritional habits, improved sleep patterns, etc., can impact mental health and might be beneficial towards depressive...
disorders. Training like meditation, yoga, Tai chi, or daily journaling events is another helpful way to reduce stress, leading to the improved mental condition [53] (Figure 2).

| Step 1: Before starting antidepressant treatment |
|------------------------------------------------|
| • Lifestyle modifications: physical activity and exercise, balanced nutritional habits, smoking cessation, improved sleep pattern, meditation, yoga, Tai Chi |

| Step 2: Initial antidepressant treatment |
|-----------------------------------------|
| • Either psychotherapy or pharmacotherapy |
| • Combination of pharmacotherapy and psychotherapy |
| • Psychotherapy: Behavioral therapy, CBT and MBCT, IPT, psychodynamic therapies, and supportive therapy |
| • Pharmacotherapy |
| First line: SSRIs, SNRIs, atypical antidepressants, and 5-HT modulators |
| Second line: TCAs and MAO inhibitors |

| Step 3: Partial or nonresponders to initial antidepressant treatment |
|-------------------------------------------------------------------|
| • Switch from antidepressant medication alone or cognitive therapy alone to the combination |
| • Increase the dose of antidepressant treatment |
| • Switch from one class of antidepressant medication to another |
| • Combination therapy of different classes of antidepressants |
| • Augmentation therapy with repurposed agents |

| Step 4: Nonresponders to 2 or 3 adequate antidepressant trials |
|-------------------------------------------------------------|
| • Neurostimulations: ECT and rTMS (if possible) |

Figure 2. MDD management steps. Abbreviations: CBT: Cognitive behavioral therapy; IPT: Interpersonal psychotherapy; MAO: Monoamine oxidase; MBCT: Mindfulness-based cognitive therapy; MDD: Major depressive disorder; SSRI: Selective serotonin reuptake inhibitors.

In mild-to-moderate depression, psychotherapy has proved to be adequate and comparable to pharmacological therapies. Many experts suggest different types of psychotherapy like cognitive-behavioral therapy, behavioral activation therapy, and interpersonal psychotherapy. However, for severe forms of depressive disorder, antidepressant drugs have appeared to be much more effective by possessing a more rapid onset of action. Furthermore, psychotherapy is often used in those who have shown a response to antidepressants to prevent its relapse. Overall, the combination of both therapies is suggested and has been demonstrated to be more effective to either alone [48]. It is shown that the beneficial effects of different psychotherapy methods can last for at least one year after the treatment process. However, many people refuse this choice due to its high costs, lack of time, and the recent issue of Coronavirus disease-2019 (COVID-19). As solutions, attending some group psychotherapies to reduce the costs, setting online or over the phone sessions are valued, although all patients still do not believe in such ways [17]. Somatic intervention is another non-pharmacological option for the treatment of MDD. Electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulus (rTMS) are some noninvasive examples suggested to be beneficial for patients who have already failed at least one antidepressant trial. Vagus nerve stimulation is a US-FDA-approved surgical and invasive procedure for the management of TRD, which of course, carries its risks [53].
3.1. Pharmacotherapy

After a patient is diagnosed with MDD, a psychiatrist can start pharmacologic treatment to symptom remission. Antidepressants take approximately 3–4 weeks to exert their effects, although there is always the risk of relapse or recurrence of mood episodes even after the therapy. Choosing the first-line treatment for a patient depends on multiple factors, including age, concurrent medical conditions or psychiatric state, adverse effect profiles of the drug and its interactions, ease of access, cost, convenience and patient’s preference, safety in overdose, etc. Another essential issue is the patient’s initial responses to antidepressants (if taken) and the family history [53].

3.1.1. Current Antidepressant Medications

Today, according to Katzung Basic and Clinical Pharmacology’s last edition, five (or six) main antidepressant categories exist and exert their effects through various molecular targets and mechanisms of action. These categories include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) with two subgroups of selective serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants (TCAs), 5-HT2 receptor modulators, tetracyclic and unicyclic antidepressants, monoamine oxidase inhibitors (MAOs) [54]. The sixth category consists of some various antidepressant medications such as tianeptine (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors modulator) [55], reboxetine (a selective inhibitor of norepinephrine reuptake), agomelatine (an agonist for melatonin (MT1 and MT2) and serotonin (5-HT2C) receptors) [19], ademetionine (a major methyl donor, required for the synthesis of several neurotransmitters) [56] and agmatine (an NMDA receptor inhibitor) [57], etc.

3.1.2. Repurposed Drugs for MDD

Plenty of repurposed agents for depression are studied or have gotten US-FDA approval for use in the clinic from different pharmacological categories. These categories vary from some central nervous system (CNS)-related medications like the second generation (atypical) antipsychotics, NMDA receptor antagonists and anesthetics, GABA receptor modulators, dopamine agonists, anticholinergic agents, CNS stimulants, anticonvulsant agents, histamine antagonists and ergot derivatives to even some unrelated ones such as thyroid products, anti diabetic agents, anti-inflammatory agents, antibiotics, HMG-CoA reductase inhibitors, calcium channel blockers, angiotensin-converting enzyme inhibitors, antineoplastic agents and some nutritional supplements. These agents exert their antidepressant effects through various pathways due to their pharmacological category. The complete list of repurposed drugs for MDD with a particular focus on their mechanism of action, significant adverse effects, contraindications, and dosages (if available) are provided in Table 3. Moreover, related clinical trials studying their effects on MDD in real-world settings are summarized in Table 4.

| Medication/Active Compound/Brand Name/Ref | US-FDA Approval | Pharmacological Category/Mechanism of Action | Dosage | Significant Adverse Effects | Contraindications |
|------------------------------------------|-----------------|---------------------------------------------|--------|----------------------------|-------------------|
| Aripiprazole Abilify® [58]               |                 | Bipolar disorder, irritability associated with autistic disorder, MDD, TRD, schizophrenia, Tourette disorder | MDD and TRD as an adjunctive treatment. Oral: 2 to 5 mg/day Increase dose based on response in 5 mg increments up to a maximum of 15–20 mg/day | >10%: decreased HDL-C, increased LDL-C, increased serum cholesterol, increased serum TG, weight gain, akathisia, headache, increased serum glucose, constipation, nausea, and vomiting | Hypersensitivity to aripiprazole or any component of the formulation |

Table 3. Pharmacological and clinical profile of repurposed medications for MDD.
| Treatment | Indications | Mechanism of Action | Dosage | Adverse Effects | Contraindications |
|-----------|-------------|---------------------|--------|----------------|------------------|
| **Brexanolone**<br>Zulresso®<br>[59] | Postpartum depression (PPD) in adults | The mechanism of action is not fully understood, but is thought to be related to its positive allosteric modulation of GABA<sub>A</sub> receptors/GABA<sub>A</sub> receptor-positive modulator | Postpartum depression. IV: 0 to 4 h: 30 mcg/kg/h 4 to 24 h: 60 mcg/kg/h 24 to 52 h: 90 (or 60) mcg/kg/h 52 to 56 h: 60 mcg/kg/h 56 to 60 h: 30 mcg/kg/hour | >5%: sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush | No contraindications were listed in the US-FDA monograph |
| **Brexpiprazole**<br>Rexulti®<br>[60] | MDD, schizoaffective disorder | Partial agonist activity for 5-HT<sub>1A</sub> and D<sub>2</sub> receptors and antagonist activity for 5-HT<sub>2A</sub> receptors/Second-generation (atypical) antipsychotic | MDD as an adjunct therapy to antidepressants. Oral: 0.5 mg or 1 mg once daily; titrate to 1 mg once daily, followed by 2 mg once daily; maximum daily dose: 3 mg | >10%: increased serum TG, weight gain, akathisia | Hypersensitivity (e.g., anaphylaxis, facial swelling, rash, urticarial) to brexpiprazole or any component of the formulation |
| **Cabergoline**<br>Dostinex®<br>[61] | Hyperprolactinemic disorders | Long-acting dopamine receptor agonist with a high affinity for D2 receptors, a potent 5-HT2B-receptor agonist/Ergot derivative | NA | Headache, dizziness, nausea | Known hypersensitivity to cabergoline, ergot derivatives, or any component of the formulation, uncontrolled hypertension; history of cardiac valvular disorders, history of pulmonary, pericardial, or retroperitoneal fibrotic disorders |
| **Cannabidiol**<br>Epidiolex®<br>[62] | Treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients with 2 years of age and older | The precise mechanisms of its anticonvulsant effect in humans are unknown; however, it does not appear to exert its effects through interaction with cannabinoid receptors/Anticonvulsant, cannabinoid | NA | >10%: somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, malaise and asthenia, rash, insomnia, sleep disorder and poor quality sleep, infections | Hypersensitivity to cannabidiol or any of the ingredients in Epidiolex® |
| **Celecoxib**<br>CeleBREX®<br>[63] | Acute pain, ankylosing spondylitis, juvenile idiopathic arthritis, osteoarthritis, primary dysmenorrhea, rheumatoid arthritis | Inhibits prostaglandin synthesis by decreasing COX-2 enzyme/Analgesic, nonopioid, NSAID, COX-2 selective | NA | Serious cardiovascular thrombotic events, myocardial infarction, and stroke increased the risk of serious gastrointestinal adverse events, including bleeding, ulceration, and perforation of the stomach or intestines | Hypersensitivity to celecoxib, sulfonamides, aspirin, other NSAIDs, or any component of the formulation |
| **Cycloserine**<br>Seromycin®<br>[64] | Tuberculosis, UTI | Inhibits bacterial cell wall synthesis by competing with amino acid (D-alanine) for incorporation into the bacterial cell wall/Antibiotic, antitubercular agent | NA | Cardiac arrhythmia, cardiac failure, coma, confusion, dizziness, drowsiness, dysarthria, headache, hyperreflexia, paresis, paresthesia, psychosis, restlessness, seizure, vertigo, skin rash, cyanocobalamin deficiency, folate deficiency, increased liver | Hypersensitivity to cycloserine or any component of the formulation, epilepsy, severe anxiety, or psychosis, severe renal insufficiency, excessive concurrent use of alcohol |
| **Cyproheptadine** | **Dextromethorphan** | **Esketamine** | **Etanercept** | **Gabapentin** | **Infliximab** |
|-------------------|-------------------|---------------|---------------|---------------|---------------|
| Euro-Cyproheptadine®, PMS-Cyproheptadine® [65] | Cough suppressant | TRD, MDD with suicidality | Ankylosing spondylitis, plaque psoriasis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, rheumatoid arthritis | Ankylosing spondylitis, Crohn disease, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis | |
| **Allergic conditions** | Decreases the sensitivity of cough receptors and interrupts cough impulse transmission by depressing the medullary cough center through sigma receptor stimulation/Antittusive, NMDA receptor antagonist | TRD. Intranasal: induction: 56 mg (may increase to 84 mg) twice weekly for 4 weeks Maintenance: on week 5, the previously established dose (56 or 84 mg) once weekly—on week 9 and onward continue effective dose (56 to 84 mg) once weekly or every 2 weeks MDD with suicidality; Intranasal: 84 mg twice weekly for 4 weeks; may reduce dosage to 56 mg twice weekly | Binds TNF-α and blocks its interaction with cell surface receptors/ Antirheumatic disease-modifying, TNF-α blocking agent | Modulates the release of excitatory neurotransmitters which participate in epileptogenesis and nociception/Anticonvulsant, GABA analog | Binds to human TNF-α and interfere with endogenous TNF-α activity/Antirheumatic, disease-modifying, gastrointestinal agent, immunosuppressant agent, monoclonal |
| **Potent antihistamine and serotonin antagonist with anticholinergic effects competes with histamine H1 receptors/First, generation histamine H1 antagonist, a piperidine derivative** | NA | TRD. Intranasal: induction: 56 mg (may increase to 84 mg) twice weekly for 4 weeks Maintenance: on week 5, the previously established dose (56 or 84 mg) once weekly—on week 9 and onward continue effective dose (56 to 84 mg) once weekly or every 2 weeks MDD with suicidality; Intranasal: 84 mg twice weekly for 4 weeks; may reduce dosage to 56 mg twice weekly | Binds TNF-α and blocks its interaction with cell surface receptors/ Antirheumatic disease-modifying, TNF-α blocking agent | Modulates the release of excitatory neurotransmitters which participate in epileptogenesis and nociception/Anticonvulsant, GABA analog | Binds to human TNF-α and interfere with endogenous TNF-α activity/Antirheumatic, disease-modifying, gastrointestinal agent, immunosuppressant agent, monoclonal |
| **Cytotoxic effects** | **Cytotoxic effects** | **Cytotoxic effects** | **Cytotoxic effects** | **Cytotoxic effects** | **Cytotoxic effects** |
| **Cough suppressant** | **Cough suppressant** | **Cough suppressant** | **Cough suppressant** | **Cough suppressant** | **Cough suppressant** |
| **Dizziness, drowsiness, nausea, stomach pain, vomiting** | **Dizziness, drowsiness, nausea, stomach pain, vomiting** | **Dizziness, drowsiness, nausea, stomach pain, vomiting** | **Dizziness, drowsiness, nausea, stomach pain, vomiting** | **Dizziness, drowsiness, nausea, stomach pain, vomiting** | **Dizziness, drowsiness, nausea, stomach pain, vomiting** |
| **Concurrent administration with or within two weeks of discontinuing MAO inhibitor** | **Concurrent administration with or within two weeks of discontinuing MAO inhibitor** | **Concurrent administration with or within two weeks of discontinuing MAO inhibitor** | **Concurrent administration with or within two weeks of discontinuing MAO inhibitor** | **Concurrent administration with or within two weeks of discontinuing MAO inhibitor** | **Concurrent administration with or within two weeks of discontinuing MAO inhibitor** |
| **Increased blood pressure, tachycardia, palpitations, tachycardia, ataxia, chills, confusion, dizziness, drowsiness, euphoria, excitement, fatigue, hallucination, headache, hystera, insomnia, irritability, nervousness, neuritis, paresis, restlessness, sedation, seizure, vertigo, etc.** | **Increased blood pressure, tachycardia, palpitations, tachycardia, ataxia, chills, confusion, dizziness, drowsiness, euphoria, excitement, fatigue, hallucination, headache, hystera, insomnia, irritability, nervousness, neuritis, paresis, restlessness, sedation, seizure, vertigo, etc.** | **Increased blood pressure, tachycardia, palpitations, tachycardia, ataxia, chills, confusion, dizziness, drowsiness, euphoria, excitement, fatigue, hallucination, headache, hystera, insomnia, irritability, nervousness, neuritis, paresis, restlessness, sedation, seizure, vertigo, etc.** | **Increased blood pressure, tachycardia, palpitations, tachycardia, ataxia, chills, confusion, dizziness, drowsiness, euphoria, excitement, fatigue, hallucination, headache, hystera, insomnia, irritability, nervousness, neuritis, paresis, restlessness, sedation, seizure, vertigo, etc.** | **Increased blood pressure, tachycardia, palpitations, tachycardia, ataxia, chills, confusion, dizziness, drowsiness, euphoria, excitement, fatigue, hallucination, headache, hystera, insomnia, irritability, nervousness, neuritis, paresis, restlessness, sedation, seizure, vertigo, etc.** | **Increased blood pressure, tachycardia, palpitations, tachycardia, ataxia, chills, confusion, dizziness, drowsiness, euphoria, excitement, fatigue, hallucination, headache, hystera, insomnia, irritability, nervousness, neuritis, paresis, restlessness, sedation, seizure, vertigo, etc.** |
| **MAO inhibitor therapy, close angle glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction, elderly, debilitated patients** | **MAO inhibitor therapy, close angle glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction, elderly, debilitated patients** | **MAO inhibitor therapy, close angle glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction, elderly, debilitated patients** | **MAO inhibitor therapy, close angle glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction, elderly, debilitated patients** | **MAO inhibitor therapy, close angle glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction, elderly, debilitated patients** | **MAO inhibitor therapy, close angle glaucoma, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction, elderly, debilitated patients** |

**Note:** MDD = major depressive disorder; TRD = treatment-resistant depression; ANA = antinuclear antibody; ALT = alanine aminotransferase; NA = not available.
| **Ketamine** Ketalar® [70] | Induction and maintenance of general anesthesia | Noncompetitive NMDA receptor antagonist (blocks glutamate)/General anesthetic | Depressant episodes and MDD. IV: 0.5 mg/kg administered over 40 min; 1 to 3 times weekly; may increase dose to 0.75 to 1 mg/kg. Treatment up to 6 weeks (optimal duration of therapy is unknown) | >10%; prolonged emergence from anesthesia (includes confusion, delirium, dreamlike state, excitement, hallucinations, irrational behavior, vivid imagery) | Hypersensitivity to ketamine or any component of the formulation, conditions in which an increase in blood pressure would be hazardous |
| **Liothyronine** Cytomel®, Triostat® [71] | Thyroid disorders, a myxedema coma Manufactured form of the thyroid hormone triiodothyronine (T₃) and exerts its many metabolic effects through control of DNA transcription and protein synthesis/Thyroid product | Antidepressant augmentation. Oral: 25 mcg/day; may be increased to 50 mcg/day after ~1 week. Dose ranges of 20 to 62.5 mcg/day have been studied in clinical trials. | 1% to 10%; cardiac arrhythmia, tachycardia, hypotension, myocardial infarction | Hypersensitivity to liothyronine sodium or any component of the formulation, uncorrected adrenal insufficiency, untreated thyrotoxicosis, concurrent use with artificial rewarming of the patient |
| **Lisdexamfetamine** Vyvanse® [72] | ADHD, binge eating disorder Converts to the active component dextroamphetamine, a noncatecholamine, sympathomimetic amines that cause a release of dopamine and NE from their storage sites/central nervous system stimulant | NA | >10%; insomnia, decreased appetite, xerostomia, upper abdominal pain | Hypersensitivity to amphetamine products or any component of the formulation, concurrent use of MAO inhibitor, or within 14 days of the last MAO inhibitor dose |
| **Lithium** Lithobid® [73] | Bipolar disorder Influence the reuptake of serotonin and/or NE and inhibit 2nd messenger systems involving phosphatidylinositol cycle, increasing glutamate clearance, enhancing the expression of neurotrophic factors (BDNF)/Antimanic agent | MDD and TRD as an adjunctive treatment. Oral: 300 to 600 mg/day in 1 to 2 divided doses; may increase every 1 to 5 days to a target dose of 600 mg to 1.2 g/day in divided doses. Clinical improvement may take up to 6 weeks. | The most significant adverse reaction is lithium toxicity; signs: diarrhea, vomiting, drowsiness, muscular weakness, and lack of coordination | Hypersensitivity to lithium or any component of the formulation |
| **Metformin** D-Care DM2®, Fortamet®, Glucophage®, Glumetza®, Riomet® [74] | Type 2 diabetes mellitus Decreases hepatic glucose production, reduces intestinal absorption of glucose and improve insulin sensitivity, increases peripheral glucose uptake and utilization/Antidiabetic agent, biguanide | NA | >10%; diarrhea, flatulence, nausea and vomiting, dyspepsia, abdominal pain, lactic acidosis, vitamin B12 deficiency | Hypersensitivity to metformin or any component of the formulation, severe renal dysfunction, metabolic acidosis |
| **Mecamylamine** Vecamyl® [75] | Hypertension Inhibits acetylcholine at the autonomic ganglia/Ganglionic blocking agent | NA | Orthostatic hypotension, syncope altered mental status, convulsions, fatigue, paresthesia, sedation decreased libido, anorexia, constipation, glossitis, intestinal | Hypersensitivity to mecamylamine or any component of the formulation; mild, moderate, labile hypertension, coronary insufficiency or recent myocardial infarction, uremia, glaucoma, |
| **Minocycline**<br>CoreMino®, Minocin®, Minolira®, Solodyn®, Ximino® [76] | Inhibits bacterial protein synthesis by binding with the 30S and possibly the 50S ribosomal subunit/Antibiotic, tetracycline derivative | NA | 1% to 10%: pruritus, urticaria, dizziness, fatigue, malaise, drowsiness, arthralgia, tinnitus | Hypersensitivity to minocycline, other tetracyclines, or any component of the formulation |
|---|---|---|---|---|
| **Modafinil**<br>Provigil®, Alertec® [77,78] | Increase dopamine in the brain by blocking dopamine transporters/Central nervous system stimulant | NA | Headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, dyspepsia | Contraindicated in patients with known hypersensitivity to modafinil, armodafinil or its inactive ingredients |
| **N-acetyl cysteine**<br>Acetadote®, Cetylev®, Parvolex® [79] | Restoring hepatic glutathione, serving as a glutathione substitute, exerts mucolytic effects through its free sulphydryl group, which opens up the disulﬁde bonds in the mucoproteins/Antidote, mucolytic agent | NA | >10%: autoimmune disease, anaphylactoid reaction | Hypersensitivity to acetylcysteine or any component of the formulation |
| **Nimodipine**<br>Nymalize®, Nimotop® [80] | Inhibits calcium ion from entering the slow channels/Calcium channel blocker, dihydropyridine | NA | 1% to 10%: decrease blood pressure, bradycardia, headache, nausea | Concomitant use with potent CYP3A4 inhibitors |
| **Olanzapine**<br>ZyPREXA® [81] | Combination of dopamine and serotonin type 2 receptor antagonism/Antimanic agent, second-generation (atypical) antipsychotic | MDD and psychotic depression as an adjunctive therapy. Oral: 5 mg once daily; may increase the dose in increments of 5 mg up to 20 mg/day. TRD as an adjunctive therapy. Oral: 5 mg once daily; may increase dose up to 20 mg/day. A fixed-dose of olanzapine/fluoxetine combination may be used instead of separate components. | Postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia, sedation, headache, increased appetite, abdominal pain, pain in extremity, fatigue, dry mouth, asthenia, drowsiness, tremor | No contraindication with ZyPREXA® monotherapy, caution in combination therapy with fluoxetine, lithium or valproate |
| **Pergolide**<br>Permax®, Prascend® [82] | Potent dopamine receptor agonist/Ergot derivative | NA | Dyskinesia, hallucinations, somnolence, insomnia, nausea, constipation, diarrhea, dyspepsia, rhinitis | Hypersensitivity to pergolide mesylate or other ergot derivatives |
| **Pioglitazone**<br>Actos® [83] | Improving target cell response to insulin, a potent and selective agonist for | NA | >10%: edema, hypoglycemia, upper respiratory tract infection | Hypersensitivity to pioglitazone or any component of the formulation, NYHA |
| Drug | Class | Indication | Side Effects |
|------|-------|------------|--------------|
| Phenytoin | Class III/IV heart failure | Antidiabetic agent, thiazolidinedione | Hypersensitivity to phenytoin, other hydantoins, or any component of the formulation, concurrent use of delavirdine, history of prior acute hepatotoxicity attributable to phenytoin |
| Phenytoin Dilantin®, Phenytek® [84] | | Stabilizes neuronal membranes and decreases seizure activity by modulating efflux or influx of sodium, shortens action potential in the heart/Anticonvulsant, hydantoin | Nystagmus, ataxia, slurred speech, decreased coordination, somnolence, mental confusion |
| Pramipexole Mirapex® [85] | Parkinson disease, restless legs syndrome | Nonergot dopamine agonist with specificity for the D3 and D4 receptors/Antiparkinson agent, dopamine agonist | >10%: orthostatic hypotension, drowsiness, extrapyramidal reaction, insomnia, dizziness, hallucination, headache, restless leg syndrome, abnormal dreams, nausea, constipation, dyskinesia, asthenia, accidental injury |
| Pregabalin Lyrica®, Lyrica CR® [86] | Fibromyalgia, neuropathic pain associated with diabetic peripheral neuropathy or spinal cord injury, partial-onset seizures, postherpetic neuralgia | Modulates calcium influx at the nerve terminals, thereby inhibits excitatory neurotransmitter release, may also affect descending noradrenergic and serotonergic pain transmission pathways from the brainstem to the spinal cord/Anticonvulsant, GABA analog | Peripheral edema, Dizziness, drowsiness, headache, fatigue, weight gain, xerostomia, visual field loss, blurred vision |
| Quetiapine SEROquel® [87] | Bipolar disorder, unipolar MDD schizophrenia | Antipsychotic activity through a combination of dopamine type 2 (D2) and serotonin type 2 (5-HT2) antagonism/Second-generation (atypical) antipsychotic | MDD or nonpsychotic depression as an adjunctive therapy. Oral: 50 mg/day on days 1 and 2; increase to 150 mg/day on day 3. Usual dosage range: 150 to 300 mg/day. Doses up to 600 mg/day may be needed in psychotic depression. Nonpsychotic depression, monotherapy. Oral: 20 mg once daily; may be gradually increased up to 300 mg/day. | Hypersensitivity to quetiapine or any component of the formulation |
| Risperidone Perseris®, RisperDAL®, RisperDONE® [88] | Bipolar disorder, schizophrenia, bipolar mania, irritability associated with autistic disorder | High 5-HT2 and dopamine-D2 receptor antagonist activity/Antimanic agent, second-generation (atypical) antipsychotic | MDD and TRD, as an adjunctive therapy. Oral: 0.25 to 0.5 mg/day; may increase dose in increments of 0.25 to 1 mg/day every 3 to 7 days up to 3 mg/day. Usual effective dose: 1 to 1.5 mg/day. | Activating/sedating effects, angioedema, dyslipidemia, extrapyramidal symptoms, hematologic abnormalities, hyperglycemia, weight gain, hyperprolactinemia, neuroleptic malignant syndrome, orthostatic hypotension, QT |

**Notes:**
- NA: Not applicable
- MDD: Major Depressive Disorder
- TRD: Treatment-Resistant Depression
| Drug/Trade Name | Description | Indications | Adverse Effects | Notes |
|-----------------|-------------|-------------|----------------|-------|
| Rosiglitazone <br> Avandia® [89] | Type 2 diabetes mellitus | Improving target cell response to insulin, a potent and selective agonist for PPARγ/Antidiabetic agent, thiazolidinedione | >10%: increased HDL-C, increased LDL-C, increased total serum cholesterol, weight gain | Hypersensitivity to rosiglitazone or any component of the formulation; NYHA class III/IV heart failure |
| Scopolamine (hyoscine) <br> Transderm Scop®, Buscopan® [90] | Prevention of nausea and vomiting associated with motion sickness, recovery from anesthesia, and surgery | Blocks the action of acetylcholine; increases cardiac output, dries secretions, antagonizes histamine and serotonin/anticholinergic agent | >10%: drowsiness, dizziness, xerostomia | Hypersensitivity to scopolamine, other belladonna alkaloids, or any component of the formulation, narrow-angle glaucoma |
| Statins, for example, Lovastatin <br> Altoprev®, Mevacor® [91] | Adjunctive therapy to diet to reduce elevated total cholesterol, LDL cholesterol, Apo B and TG and to increase HDL-C in patients with primary hypercholesterolemia | Competitively blocking the active site of HMG-CoA reductase/Antilipemic agent, HMG-CoA reductase inhibitor | >10%: Increased creatine phosphokinase | Hypersensitivity to lovastatin or any component of the formulation, active liver disease or unexplained persistent elevations of serum transaminases, concomitant use of potent CYP3A4 inhibitors |
| Telmisartan <br> Micardis® [92] | Cardiovascular risk reduction, hypertension | Nonpeptide ATI angiotensin II receptor antagonist/Anti hypertensive | 1% to 10%: intermittent claudication, chest pain, hypertension, peripheral edema, dizziness, fatigue, headache, pain, dermal ulcer, diarrhea, abdominal pain, dyspepsia, nausea, UTI, back pain, myalgia, upper respiratory tract infection, sinusitis, cough, flu-like symptoms, pharyngitis | Known hypersensitivity (e.g., anaphylaxis, angioedema) to telmisartan or any component of the formulation, concurrent use of aliskiren in patients with diabetes |
| Valproic acid [93] | Bipolar disorder, focal (partial) onset and generalized onset seizures, migraine prophylaxis | Increased availability and enhance the action of GABA, blocks voltage-dependent Na channels/Anticonvulsant, antimanic agent, histone deacetylase inhibitor | >10%: headache, drowsiness, dizziness, insomnia, pain, nervousness, alopecia, nausea and vomiting, abdominal pain, diarrhea, dyspepsia, anorexia, thrombocytopenia, infections, tremor, weakness, diplopia, visual disturbance, flu-like symptoms, accidental injury | Hypersensitivity to valproic acid, divalproex, derivatives, or any component of the formulation, hepatic disease, urea cycle disorders, mitochondrial disorders caused by mutations in mitochondrial DNA |
| Vorinostat <br> Zolinza® [94,95] | Cutaneous T-cell lymphoma | Inhibits HDAC enzymes, HCAC1, HDAC2, HDAC3, and HDAC6, which catalyze acetyl group removal from protein lysine residues/Antineoplastic agent, histone deacetylase inhibitor | >10%: peripheral edema, fatigue, chills, dizziness, headache, alopecia, pruritus, hyperglycemia, weight loss, dehydration, diarrhea, nausea, dysgeusia, anorexia, xerostomia, constipation, vomiting, decreased appetite, proteinuria, thrombocytopenia, anemia, muscle spasm | Severe hepatic impairment |
Table 4. Clinical trials which study the effects of repurposed medications on MDD since 2015.

| Treatment (T<sub>x</sub>) | Phase/Year First, Posted Ref | Dosage (Duration of Therapy) | Subjects/F/M Condition Groups | Study Design | Results | Non-Serious AEs (Treatment-Related) | Serious AEs (Treatment-Related) |
|--------------------------|-------------------------------|-------------------------------|-----------------------------|-------------|---------|---------------------------------|--------------------------------|
| **General anesthetics**   |                               |                               |                             |             |         |                                 |                                |
| Ketamine                 | NA/2016 [97]                  | Experimental: 1 mg/kg IV ketamine for the duration of their ECT index course over 2–3 weeks Active comparator: 1 mg/kg of IV methohexitol for the duration of their ECT index course over 2–3 weeks | 52/NA/NA MDD | R, PG, DB | NA | NA | NA |
| Ketamine                 | Early phase I/2015 [98]       | Experimental: ketamine + TAU Active comparator: midazolam + TAU | 9/NA/NA MDD, BP1 disorder, BP2 disorder, BP depression, suicidal ideation | R, PG, DB | NA | NA | NA |
| Ketamine                 | Phase I/2017 [99]             | Experimental: 4 ketamine infusions at 0.05 mg/kg—once weekly Active comparator: 4 infusions at 0.045 mg/kg—once weekly | 25/NA/NA A major depressive episode, unipolar depression, BP depression | R, PG, QB | NA | NA | NA |
| Ketamine                 | Phase IV/2016 [100]           | Placebo: saline 0.9%, IV administration of 0.2 mg/kg or 50 mg Medication: ketamine (1st phase) IV administration of 0.2 mg/kg or 50 mg Medication: ketamine (2nd phase) additional 4 sessions (twice a week, 2 weeks) of 0.5 mg/kg over 40 min | 45/NA/NA MDD | R, PG, QB | NA | NA | NA |
| Ketamine                 | Phase IV/2015 [101]           | Medication: ketamine 0.5 mg/kg over 40 min IV Other: MRI technology will be used before and after ketamine for patients with depression | 16/8/8 MDD, anxious depression, depression | SG, OL | NA | None | Not reported |
| Ketamine                 | NA/2021 [102]                 | Received IV ketamine in 2014–15 and will be evaluated in 5 years | 11/NA/NA MDD, medication abuse, medications, relapse | Retrospective | NA | NA | NA |
| Study | Design | Comparator | Primary End Points | Adverse Events |
|-------|--------|------------|-------------------|----------------|
| Ketamine NA/2017 [103] | Experimental: ketamine and 16 CBT sessions over 14 weeks <br>Active comparator: ketamine and psychoeducation all sessions over 14 weeks | 28/NA/NA MDD | R, PG, SB | NA | NA | NA | Hyperacusis, photophobia, vision blurred, dry mouth, nausea, fatigue, feeling of relaxation, gait disturbance, increased systolic blood pressure, decreased platelet count, dizziness, dysgeusia, headache, paresthesia, sciatica, somnolence, anxiety, depersonalization/derealization disorder, disinhibition, irritability, alopecia, pruritus |
| Ketamine Phase II/2018 [104] | Experimental: different dosages and regimens for MIJ821 <br>Active comparator: ketamine infusion 0.5 mg/kg weekly <br>Placebo Comparator: placebo infusion | 70/35/35 TRD | R, PG, DB | NA | None | Angina pectoris, tinnitus, vision blurred, diarrhea, dry mouth, coordination abnormal, dizziness, dysmetropsia, hypoesthesia, sedation, restlessness, depression, suicidal ideation, acute kidney injury, dry skin, hypertension |
| Ketamine Phase II/2016 [105] | Experimental: NRX-101 oral capsule + ketamine IV infusion + saline solution IV infusion <br>Active comparator: lurasidone oral capsule + ketamine IV infusion + saline solution IV infusion | 22/16/6 BP depression, suicidal ideation, suicide attempts | R, SG, QB | NA | None | |
| Antimanic agents | | | | | |
| Lithium Phase III/2015 [106] | Experimental: 40 mg ITI-007 administered orally as capsules once daily for 6 weeks <br>Experimental: 60 mg ITI-007 administered orally as capsules once daily for 6 weeks <br>Placebo Comparator: placebo administered orally as visually-matched capsules once daily for 6 weeks | 529/NA/NA BD | R, PG, QB | NA | NA | NA | |
### Risperidone 2011 [68,107]

| Groups: olanzapine users, quetiapine users, risperidone users, all other antipsychotic users |
|---|
| Comparison between quetiapine and olanzapine: quetiapine is associated with lower extrapyramidal symptoms and diabetes mellitus. |
| Comparison between quetiapine and risperidone: quetiapine is associated with lower extrapyramidal symptoms, but higher failed suicide attempt rates. |

| 17743/9692/8051 |
| SCH = 475 |
| MDD = 798 |
| BP disorder = 270 |
| Generalized anxiety disorder = 17 |
| Other mental health disorders = 637 |
| Unknown indication = 15546 |
| Quetiapine = 4658 |
| Olanzapine = 5856 |
| Risperidone = 7229 |

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### Atypical antipsychotics

#### Aripiprazole Phase II/2016 [108]

| Oral tablet (2.5,10,15,20, or 30 mg) with an IEM QD (8 weeks) |
|---|
| 49/31/18 |
| BP1 (n = 22) |
| SCH (n = 15) |
| MDD (n = 12) |
| T = 49 |
| SG, OL, multi-center |
| NA |

Rash, erythema, pruritus skin irritation, upper respiratory tract infection, sinusitis, headache, Not reported

#### Quetiapine Phase III/2016 [109]

| Experimental: 1 capsule of 20 mg JNJ-42847922 and 1 capsule of placebo once daily for 14 days. Then, JNJ-42847922 dose can be increased to 40 mg (2 capsules) until day 167 |
|---|
| Active comparator: 1 capsule of quetiapine XR 50 mg along with 1 capsule of placebo once daily from day 3–14. Then, the dose can be increased to 300 mg (2 capsules) until day 167. |
| 60/NA/NA |
| MDD |
| R, PG, TB |
| NA |
| NA |
| NA |

#### Quetiapine Phase II/2017 [110]

| Experimental: 1 capsule of 20 mg JNJ-42847922 and 1 capsule of placebo once daily for 14 days. Then, JNJ-42847922 dose can be increased to 40 mg (2 capsules) until day 167 |
|---|
| Active comparator: 1 capsule of quetiapine XR 50 mg along with 1 capsule of placebo once daily for 2 days, followed by 1 capsule of 150 mg along with 1 capsule of placebo once daily from day 3–14. Then, the dose can be increased to 300 mg (2 capsules) until day 167. |
| 107/NA/NA |
| MDD |
| R, PG, DB |
| NA |
| NA |
| NA |
Patients should continue to take their baseline SSRI/SNRI.

| Brexpiprazole Phase III/2018 [35] | Experimental: brexpiprazole, 2–3 mg/day, once daily for 6 weeks, oral administration | Placebo Comparator: placebo, 2–3 mg/day, once daily for 6 weeks, oral administration | 65/NA/NA MDD | R, PG, TB | NA | NA | NA |
|---|---|---|---|---|---|---|---|
| Pramipexole Phase IV/2014 [47,111] | Started at 0.125 mg BD PO and increased by 0.25 mg/day every 3–4 days to a target range of 1.0–2.5 mg/day (6 weeks) | 51/25/26 MDD (n = 26) Healthy (n = 25) Healthy control patients did not receive study medication and only have baseline measures | Non-randomized, PG, OL | Symptom’s improvement | Not reported |
| Armodafinil Phase III/2011 [50,112] | Tablet, PO, QD in the morning, started at 50 mg/day; the dosage was increased by 50 mg/day on days 2 and 4, up to 150 mg/day (8 weeks) | 399/241/158 depressive episode despite maintenance therapy for BP1 disorder P = 199 T = 200 | R, PG, DB, PC, multi-center | ↓ Severity of depression, ↓ depressive symptoms, Improved functioning | Headache, nausea |
| Armodafinil Phase III/2010 [51,113] | Tablet, PO, QD in the morning, started at 50 mg/kg and titrated up in the first week to 150 or 200 mg/kg. Treatment with 200 mg/kg dose was discontinued via a protocol amendment. (8 weeks) | 492/273/219 major depressive episode despite BP1 disorder maintenance therapy P = 230 T = (150 mg/kg) = 232 T = (200 mg/kg) = 30 | R, PG, DB, PC, multi-center | ↓ Depressive symptoms | Nausea, diarrhea, dry mouth, toothache, dyspepsia, headache, dizziness, insomnia, anxiety, suicidal ideation, nasopharyngitis, cough | Mania, psychotic disorder, suicidal ideation, pulmonary embolism, abortion, spontaneous, accidental overdose, non-cardiac chest pain, coronary artery disease |
| Treatment | Phase | Year | Dosing | Duration | Efficacy | Side Effects | Transgender MDD | Primarily MDD | Nondistress | Depression | Non Depression | Outcomes |
|-----------|-------|------|--------|----------|----------|--------------|----------------|---------------|-------------|------------|--------------|----------|
| Armodafinil | Phase III/2010 | [40,114] | Tablet, PO, QD in the morning, started at 50 mg/kg and titrated up in the first week to 150 or 200 mg/kg. Treatment with 200 mg/kg dose was discontinued via a protocol amendment. (8 weeks) | 433/288/145 | major depressive episode while taking at least 4 weeks of conventional maintenance medication | Improvement in depressive symptoms | R, PG, DB, PC, multi-center | | | | | Diarrhea, nausea, headache, migraine, insomnia, feeling jittery |
| Modafinil with D-cycloserine (DCS) | Phase III/2015 | [7] | 250 mg DCS before two weekly sessions, 100 mg modafinil before two weekly sessions | 36/20/14/2 | (transgender) MDD | | R, PG, DB, PC | NA | | | †Energy/concentration, fatigue/low motivation | Not reported |
| Omega-3 PUFA | Not applicable/2018 | [115] | One capsule (EPA 300 mg and 200 mg DHA) QD were given antidepressant (citalopram, escitalopram, paroxetine 1 tablet at night time). (12 weeks) | 70/NA/NA | Taking antidepressants | | R, PG, SB, PC | NA | NA | NA | |
| n-3 Polyunsaturated fatty acid | Not applicable/2017 | [116] | 2 g of EPA and 1 g of DHA (12 weeks) | 60/NA/NA | MDD and cardiovascular disease | | R, PG, DB, PC | NA | NA | NA | |
| Zinc | Not applicable/2020 | [46] | Oral 30 mg zinc sulfate QD with SSRIs (8 weeks) | 100/NA/NA | MDD | | R, PG, DB, PC | NA | NA | NA | |
| NMDA receptor antagonist | Dextromethorphan hydrobromide | Phase I/2016 | Two 75 mg capsules PO, separated by 4 h | 4/NA/NA | MDD | | R, PG, DB, PC | NA | NA | NA | Dizziness, headache, somnolence, dysgeusia, hypoesthesia, sedation, dizziness, depression, postural, nausea, constipation, vomiting, dissociation, insomnia, anxiety, † blood pressure, blurred vision, vertigo |
| Esketamine | Phase III/2017 | [117,118] | 84 mg intranasal, twice a week (on days 1,4,8,11,15,18,22 and 25) along with the standard of care antidepressant treatment initiated on day 1 (4 weeks) | 225/139/86 | MDD and have suicidal ideation with intent but without psychotic features | † MADRS total score (improved), improvement in the severity of suicidality measured by CGI-SS-r | R, PG, DB, PC, multi-center | | | | | Suicidal depression, suicide attempt, diabetic ketoacidosis |
| Study | Design | Dose | Conditions | MADRS Total Score Improved | CGI-SS-r Improved | Adverse Events |
|-------|--------|------|------------|--------------------------|------------------|----------------|
| Esketamine Phase III/2017 [119,120] | 84 mg intranasal, twice a week (on days 1,4,8,11,15,18,22 and 25) along with the standard of care antidepressant treatment initiated on day 1 (4 weeks) | 227/136/91 MDD and having suicidal ideation with intent, but without psychotic features | P = 113 T<sub>x</sub> = 114 | ↓ in the severity of suicidality measured by CGI-SS-r | Dizziness, dysgeusia, somnolence, headache, paresthesia, sedation, hypoaesthesia, dizziness postural, nausea, vomiting, paresthesia oral, dry mouth, constipation, hypoaesthesia oral, dissociation, anxiety, euphoric mood, depersonalization/derealization disorder, insomnia, vision blurred, diplopia, nasal discomfort, oropharyngeal pain, throat irritation, vertigo, ↑ blood pressure, hyperhidrosis, feeling drunk | Suicide attempt, suicidal ideation, depersonalization/derealization disorder |
| Esketamine Phase II/2019 [121] | Four low, medium, or high doses (three different groups) on days 1,4,8 and 11 via dry powder inhaler (2 weeks) | 88/NA/NA TRD in the course of MDD | P = NA T<sub>x</sub> = NA | | Dissociation, dizziness, dysgeusia, paresthesia, fatigue, hypoaesthesia oral, nausea, headache, feeling abnormal, nasal discomfort, vision blurred, feeling drunk, dyshartria, feeling of relaxation, illusion, hypoaesthesia, altered time perception | |
| Esketamine Phase I/2016 [122,123] | Treatment A: intranasal placebo on day 1 and oral placebo on day 2 Treatment B: intranasal placebo on day 1 and oral alcohol on day 2 Treatment C: 84 mg of intranasal esketamine on day 1 and oral placebo on day 2 Participants will receive one of the ABC, BCA, CAB, CBA, ACB, or BAC treatments in part A and intranasal placebo on day 1 and 84 mg of intranasal esketamine on days 4,8,11,15,18,22 and 25 in part B | 23/16/7 MDD | P = 20 T<sub>x</sub> = 23 | Improvement in overall depression scores in MADRS | | |
| Combined medications | AXS-05 Phase III/2019 [40,124] | Oral tablets of 45 mg dextromethorphan and 105 mg bupropion, BID (6 weeks) | 327/215/112 Moderate or severe MDD | P = 164 T<sub>x</sub> = 163 | ↓ MADRS total score, improvement in daily functioning, improvement in mouth quality of life | Dizziness, nausea, headache, diarrhea, somnolence, dry Not reported |
| Study | Phase | Treatment | Duration | Sample Size | Comparator | CoA | Adverse Effects |
|-------|-------|-----------|----------|-------------|------------|-----|-----------------|
| AXS-05 Phase II/2018 [39,125] | | 45 mg dextromethorphan and 105 mg bupropion BID and Bupropion as AC (6 weeks) | | 80/51/29 | Moderate or severe MDD AC = 37 T = 43 | R, PG, DB, active-controlled, multi-center | ↓ MADRS total score, improvement in dry mouth, ↑ Not reported core symptoms | Nausea, dizziness, ↑ Not reported |
| AXS-05 Phase III/2019 [41,126] | | Oral tablets of 45 mg dextromethorphan and 105 mg bupropion, BID (12 months) | | 876/380/496 | MDD including TRD T = 876 | SG, OL, multi-center | ↓ Depression symptoms, improvement in functioning | Dizziness, nausea, headache, dry mouth, ↓ appetite |
| Anticholinergic agents | | Experimental: scopolamine (0.3 mg/1 mL, IM) BID; escitalopram (10 mg/d PO) QD | | 66/NA/NA | MDD | R, PG, QB | NA | NA | NA |
| | | Experimental: scopolamine (0.3 mg/1 mL, IM) QD; placebo (1 mL saline, IM) QD; escitalopram (10 mg/d PO) QD | | 14/NA/NA | Depression | R, PG, DB, DB | NA | NA | NA |
| | | Placebo comparator: placebo (1 mL saline, IM) BID; escitalopram (10 mg/d PO) QD | | |
| | | Experimental: participants will receive active medications scopolamine and naltrexone | | 10/NA/NA | MDD | Non-randomized, SG, OL | NA | NA | NA |
| | | Placebo comparator: participants will receive placebo medication | | |
| Mucolytic agents | | Experimental: sertraline and N-acetyl cysteine for 7 weeks | | 115/NA/NA | MDD | R, SG, QB | NA | NA | NA |
| | | Experimental: citalopram and N-acetyl cysteine for 7 weeks | | |
| | | Experimental: existing depression medication treatment and N-acetyl cysteine for 7 weeks | | |
| Antibiotics | | Experimental: minocycline 50 mg/day on week 1, 50 mg/BID on week 2, and 100 mg/BID weeks 3–8. For tapering, the dose will be reduced to 50 mg BID for a week and then stopped | | 115/NA/NA | MDD | R, SG, QB | NA | NA | NA |
| | | Placebo comparator: the number and appearance of the pills would be identical to those in the minocycline arm | | |
| | | Experimental: minocycline and standard antidepressant treatment | | 168/NA/NA | MDD | R, PG, TB | NA | NA | NA |
| Study | Treatment | comparator | Efficacy | safety | notes |
|-------|-----------|------------|----------|--------|-------|
| Cycloserine Not applicable/2017 [130,131] | Group A: placebo + placebo: placebo 8 mm pill, single dose Group B: fludrocortisone + placebo: fludrocortisone Astonin H 0, 1 gm, single-dose + placebo 8 mm pill, single dose Group C: D-cycloserine + placebo: cycloserine 250 mg capsule, single-dose + placebo 8 mm pill, single dose Group D: fludrocortisone + D-cycloserine: fludrocortisone Astonin H 0, 1 gm, single-dose + cycloserine 250 mg capsule, single dose | | ↑ Cognitive empathy in the group with stimulated mineralocorticoid receptor, ↓ cognitive empathy only for positive emotions in MDD patients with NMDA-R stimulation, | | |
| D-cycloserine Phase IIb/III/2016 [42,105] | Experimental: NRX-101 (D-cycloserine + lurasidone) oral capsule with fixed-dose (administered to subjects who respond to an intravenous infusion of ketamine—0.5 mg/kg administered over 40 min; on Day 0) ketamine intravenous infusion (Randomized administration of Ketamine or Placebo in a 3 to 1 ratio), saline solution intravenous infusion (Randomized administration of Ketamine or Placebo in a 3 to 1 ratio) Active comparator: Lurasidone in the same dosage as lurasidone in NRX-101 ketamine intravenous infusion (Randomized administration of Ketamine or Placebo in a 3 to 1 ratio), saline solution intravenous infusion (Randomized administration of Ketamine or Placebo in a 3 to 1 ratio) (6 weeks) | | R, SA, QB, multicenter | NA | Not reported |
| Metformin Phase I and II/2019 [132] | Experimental: fluoxetine 20 mg capsule once daily for 12 weeks + metformin 1000 mg XR tablet once daily for 12 weeks Placebo comparator: fluoxetine 20 mg capsule once daily for 12 weeks + placebo tablet once daily for 12 weeks | | R, PG, DB | NA | NA |
### Ganglionic blocking agents

**Mecamylamine (TC-5214)**  
Phase III/2012  
[132,133]

| Experimental: SSRI/SNRI + TC-5214, 0.1 mg BID  
| SSRI/SNRI + TC-5214, 1 mg BID  
| SSRI/SNRI + TC-5214, 4 mg BID  
| Placebo comparator: SSRI/SNRI + placebo BID  
| (8 weeks)  |
| --- | --- | --- | --- | --- |
| 696/498/198 MDD with inadequate response to no more than one antidepressant R, PG, DB, PC, multi-center  |
| 0.1 mg = 174  
| 1 mg = 174  
| 4 mg = 174  |
| No significant difference between the two groups  |
| Headache, dizziness, somnolence, dysgeusia, constipation, dry mouth, nausea, abdominal pain upper, diarrhea, vomiting, insomnia, agitation, nightmare, nervousness, fatigue, hyperhidrosis, influenza, UTI, ↑ alanine aminotransferase, nasopharyngitis, orthostatic hypotension, hypertension, vertigo, ↑ appetite  |
| Suicide attempt, suicidal ideation, depression, pneumonia, UTI, toxicity to various agents, food poisoning  |

**Mecamylamine (TC-5214)**  
Phase III/2010  
[37,134]

| Experimental: SSRI/SNRI + oral tablet TC-5214, 1–4 mg BID  
| Placebo comparator: SSRI/SNRI + oral tablet placebo BID  
| (8 weeks)  |
| --- | --- | --- | --- |
| 319/200/119 MDD or depression with inadequate response to no more than one antidepressant R, PG, DB, PC, multi-center  |
| P = 160  
| T<sub>s</sub> = 159  |
| No significant difference between the two groups  |
| Constipation, diarrhea, nausea, dry mouth, vomiting, headache, dizziness, somnolence, dizziness postural, abnormal dreams, insomnia, anxiety, agitation, headache, nightmare, upper respiratory tract infection, nasopharyngitis, fatigue, ↑ weight, orthostatic hypotension, hyperhidrosis, musculoskeletal stiffness  |
| No significant difference between the two groups  |
| Mecamylamine (TC-5214) | Phase III/2010 [132,134] |
|-------------------------|-------------------------|
| **Experimental:** SSRI/SNRI + oral tablet TC-5214, 1–4 mg BID | 295/189/106 MDD or depression with inadequate response to no more than one antidepressant P = 148 T = 147 |
| **Placebo comparator:** SSRI/SNRI + oral tablet placebo BID (8 weeks) | No significant difference between the two groups |

- Constipation, nausea, dry mouth, diarrhea, abdominal distention, abdominal pain upper, headache, dizziness, somnolence, dizziness postural, sedation, tremor, orthostatic hypotension, hypertension, nasopharyngitis, sinusitis, influenza, fatigue, asthenia, insomnia, anxiety, back pain, vertigo, hyperhidrosis, vision blurred, ↑ appetite, ↑ aspartate aminotransferase
- Uterine cancer

| Mecamylamine (TC-5214) | Phase III/2010 [132,133] |
|-------------------------|-------------------------|
| **Experimental:** SSRI/SNRI + TC-5214, 0.5 mg BID | 641/355/276 MDD or depression with inadequate response to no more than one antidepressant P = 161 0.5 mg = 160 2 mg = 160 4 mg = 160 |
| SSRI/SNRI + TC-5214, 2 mg BID | R, PG, DB, PC, multi-center |
| SSRI/SNRI + TC-5214, 4 mg BID | No significant difference between the two groups |
| **Placebo comparator:** SSRI/SNRI + placebo BID (8 weeks) | |

- Blurred vision, constipation, nausea, dry mouth, diarrhea, abdominal distention, vomiting, dyspepsia, flatulence, fatigue, pyrexia, asthenia, pain, nasopharyngitis, bronchitis, upper respiratory tract infection, sinusitis, ↑ aspartate aminotransferase, ↑ appetite, back pain, muscle spasms, muscle tightness, myalgia, headache, dizziness, somnolence, dizziness postural, akathisia, insomnia, nightmare, agitation, abnormal dreams, pollakiuria, orthostatic hypotension, hypertension
- Major depression, suicidal ideation, clavicle fracture, rib fracture, scapula fracture, obstructive uropathy, renal failure acute, upper respiratory tract infection, benign prostatic hyperplasia, pulmonary fibrosis, convulsion
| Mecamylamine (TC-5214) | Experimental: SSRI/SNRI + oral tablet TC-5214, 1–4 mg BID | Placebo comparator: SSRI/SNRI + oral tablet placebo BID (52 weeks) |
|------------------------|-----------------------------------------------------------|---------------------------------------------------------------|
| AC: Active comparator; ADT: antidepressant therapy; AEs: Adverse events; BD: bipolar depression; BID: twice a day; BP: Bipolar; CBT: Cognitive behavioral therapy; CGI-SS-r: Clinical Global Impression–Severity of Suicidality—revised; DB: Double blind; DHA: Docosahexaenoic acid; EPA: Eicosatetraenoic acid; F: Female; FA: factorial assignment; IEM: Ingestible event marker; IM: intramuscular; ITI-007: Lumateperone LE: Leukocyte esterase; M: Male; MADRS: Montgomery-Asberg depression rating scale; MDD: Major depressive disorder; NA: Not available; NMDA: N-methyl-D-aspartate receptor; OL: Open label; P: Placebo; PC: Placebo-controlled; PG: Parallel-group; PO: by mouth; PUFA: Polyunsaturated fatty acid; QD: once a day; QB: Quadruple blind R: Randomized; SA: Sequential Assignment; SB: single blind; SCH: Schizophrenia; SG: Single group; SNRI: serotonin norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor; TAU: Treatment as usual; TB: Triple blind; TRD: Treatment-resistant depression; Tx: Treatment; WBC: White blood cell; UTI: Urinary tract infection. | Constipation, nausea, dry mouth, diarrhea, abdominal pain, vomiting, abdominal pain upper, flatulence, abdominal distension, fatigue, seasonal allergy, nasopharyngitis, bronchitis, upper respiratory tract infection, sinusitis, influenza, UTI, gastroenteritis, gastroenteritis viral, confusion, muscle strain, ↑ weight, ↑ blood pressure, ↑ appetite, arthralgia, back pain, muscle spasms, musculoskeletal pain, neck pain, pain in extremities, myalgia, headache, dizziness, somnolence, dizziness postural, sedation, memory impairment, migraine, paresthesia, tremor, insomnia, abnormal dreams, agitation, anxiety, bruxism, cough, nasal congestion, oropharyngeal pain, wheezing, hyperhidrosis, rash, hypertension, orthostatic hypotension. | 813/566/247 MDD or depression with inadequate response to no more than one antidepressant R, PG, DB, PC, multi-center. P = 203 Tc = 610 No significant difference between the two groups. Bradycardia, abdominal hernia, diverticulum, hemorrhoids, small intestinal obstruction, cellulitis, oral infection, pneumonia, brain contusion, cerebral vertebral fracture, contusion, facial bones fracture, fibula fracture, tibia fracture, toxicity to various agents, musculoskeletal chest pain, abortion spontaneous, alcohol withdrawal syndrome, psychotic disorder, suicidal ideation, suicide attempt, ovarian torsion, hypertensive crisis. |
4. Conclusions

MDD, as a severe mental disorder declining the quality of life of the patient, requires on-time screening and management. Psychotherapy, pharmacotherapy, and somatic interventions are among the suggested managements. However, due to the incomplete response of the patients to the approved medications, physicians tend to prescribe medications on their off-label use. Hence, a great need for a drug repositioning method took place for the MDD management medications. Drug repositioning is a cost-effective method that decreases the required time to introduce medicine to the market.

Moreover, as there are available data on the safety profile of the medications, the risk of failure decreases significantly, and this method is capable of uncovering novel targets to treat a disease. Various pharmacological categories, including neurotransmitters’ antagonists, atypical antipsychotics, and CNS stimulants, have been studied for the repurposing aims. However, proper studies on the formulation, regulatory, and efficacy of the medication are required to better this approach.

Author Contributions: Conceptualization, M.A. and S.N.; methodology, H.M.S. and I.A.; software, H.M.S. and I.A.; validation, T.M.; formal analysis, M.D.; data curation, H.M.S. and I.A.; writing—original draft preparation, H.M.S. and I.A.; writing—review and editing, T.M. and M.D.; supervision, M.A. and S.N. All authors have read and agreed to the published version of the manuscript.

Funding: This research was not funded.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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