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Novel and Investigational Drugs in Depression

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Authors' contributions

Authors collaborated in this review. Author SMS conceived of the review. Author DNS managed the literature search and wrote the first draft of the manuscript. Author SMS reviewed and edited the manuscript. Both authors read, edited, and approved the final manuscript.

Review Article

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ABSTRACT

Major depressive disorder is a serious medical illness associated with significant burden. Our current treatments for depression are limited, which has motivated researchers to explore novel targets. This article will highlight new psychopharmacological agents and investigational directions which may show promise in achieving better outcomes and symptom relief for those suffering from depression. This review will address key categories of novel therapeutic targets for depression. The newer and investigational agents involving monoaminergic transmission will be discussed, followed by those with glutamatergic, opioid, anticholinergic, and miscellaneous mechanisms. As the field continues to learn more about the pathophysiology of depression, there will be an emergence of additional innovative targets and investigational mechanisms, along with an improvement in our treatment outcomes.

Keywords: Antidepressants; novel; investigational; major depressive disorder.

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1. INTRODUCTION

Depression is a common psychiatric illness with significant disease, disability, economic, and psychosocial burden [1]. According to the 2010 Global Burden of Disease Study, depressive disorders were the second leading cause of years lived with disability (YLDs) and contributors to suicide and ischemic heart disease [2]. It is predicted that by 2030, depression will be the leading cause of disease burden globally [3]. Our current treatments and medications are suboptimal, only showing modest response and remission rates, which has motivated the development of new treatments for patients. It is critical to keep investigating new drug targets and mechanisms of actions in order to prioritize and promote the positive impact effective mental health treatments have on individual and societal levels. This article will highlight new agents and investigational directions which may show promise in achieving better outcomes and symptom relief for those suffering from depression.

First line pharmacotherapies for the treatment of depression mostly involve enhancing monoaminergic function, thereby increasing neurotransmitters such as serotonin, norepinephrine and dopamine. The early drug treatments for major depressive disorder include monoamine oxidase inhibitors (MAOI) and tricyclic antidepressants (TCA). The first selective serotonin reuptake inhibitor (SSRI) generated a revolution in the treatment of depression in the late 1980s. Additional SSRIs followed, along with selective norepinephrine reuptake inhibitors (SNRIs), norepinephrine dopamine reuptake inhibitors (NDRIs), serotonin reuptake inhibitors (SARIs), and norepinephrine antagonist serotonin antagonists (NASA) [4].

This review will focus on main categories of novel therapeutic targets for depression. The newer and investigational agents involving monoaminergic transmission will be discussed, followed by those agents with glutamatergic, opioid, and anticholinergic mechanisms of action. As the field learns more about the pathophysiology of depression, additional innovative targets and investigational mechanisms will emerge with a goal to improve our treatment outcomes.

2. MONOAMINE

2.1 Vilazodone

Vilazodone (Viibryd) was approved for depression by the FDA in 2011. Vilazodone potently inhibits the serotonin transporter and is a partial agonist at the 5-HT1A receptor [5-6]. Multiple studies have supported the efficacy of vilazodone in the treatment of depression [7-9]. Given its unique mechanism of action, vilazodone is often called a serotonin partial agonist reuptake inhibitor (SPARI) [4,10-13]. Theories of why this medication has shown to be effective include its 5-HT1A partial agonism which, in combination with serotonin transporter (SERT) inhibition, may lead to rapid and robust elevations of synaptic 5-HT. This partial agonist action may mitigate sexual side effects seen in antidepressants, in addition to the lesser degree of SERT inhibition and enhanced downstream dopaminergic action [4,10]. Vilazodone also appears to have a favorable weight gain and sexual side effect profile based on short-term studies [14]. However, additional research should explore the role of 5-HT1A agonism. As noted by Citrome, sexual side effects were not consistently reported using clinical rating scales in those taking vilazodone, but there was evidence of spontaneously reported adverse events related to sexual functioning [6]. Vilazodone should be administered with food to ensure adequate bioavailability. The adverse effects most commonly reported in

clinical trials were diarrhea, nausea, vomiting, and insomnia, and headaches [6,14]. It is advised that vilazodone not be used concomitantly with an MAOI or within 14 days of stopping or starting an MAOI. In addition, vilazodone dose should be reduced when co-administered with CYP3A4 strong inhibitors. The maximum recommended daily dose is 80 mg [15]. Vilazodone demonstrates a novel dual mechanism of action, tolerability, and potential for less weight gain and sexual side effects; in addition, there is no known cardiac toxicity [7]. However, given limited research and comparison with other agents, additional clinical trials are recommended to investigate vilazodone's efficacy.

2.2 Vortioxetine

Vortioxetine (Brintellix) was approved for major depressive disorder in September 2013. Vortioxetine has a multimodal mechanism of action which includes serotonin reuptake inhibition and direct action at serotoninergic receptors. Vortioxetine exerts 5-HT1D, 5-HT3, and 5-HT7 antagonism, 5-HT1B receptor partial agonism, 5-HT1A agonism, and SERT inhibition [4,16-17]. Vortioxetine modulates serotonin, noradrenaline, dopamine, acetylcholine and histamine neurotransmitter systems according to animal and in vitro studies. In addition, there is evidence of modulation of gamma-aminobutyric acid and glutamate neurotransmission [18]. Animal studies suggest that vortioxetine does have antidepressant effects; in addition, clinical studies indicate that vortioxetine is effective in the treatment of major depression. As reviewed in Katona's article, there have been placebo controlled studies to support clinical efficacy of vortioxetine, however none showing superiority over other agents. In some studies, "there was a trend for the SNRI active comparator to be associated with numerically superior outcomes to vortioxetine" [19]. Studies on vortioxetine provide support for a favorable cognitive profile with some research showing an improvement in cognitive functioning including memory enhancement [14,20-21]. It has been proposed that 5-HT3 receptor antagonism [22] and 5-HT1A receptor agonism [23-24] may play a role in enhancing memory function in rats. In clinical trials, vortioxetine was well tolerated with low sexual dysfunction and minimal weight gain. The most common adverse events were nausea, nasopharyngitis, headache, diarrhea, dry mouth and dizziness [25-26]. The recommended dosage for vortioxetine ranges from 5mg to 20mg a day. Vortioxetine should be used with care in strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, quinidine) as CYP2D6 is the likely main pathway for its metabolism [27].

2.3 Levomilnacipran

Levomilnacipran ER (Fetzima) is a serotonin and norepinephrine reuptake inhibitor indicated for the treatment of major depressive disorder which was approved by the FDA in July 2013. Levomilnacipran is an active enantiomer of milnacipran (Savella) which is used to treat fibromyalgia [28-29]. Levomilnacipran has greater potency for norepinephrine reuptake inhibition compared to serotoninergic reuptake inhibition, possibly contributing to its efficacy [30] and resulting in fewer serotonin mediated side effects [31-32]. Studies have concluded efficacy of the drug including a phase III study (NCT01034462) which was a multicenter, randomized, double-blind, and placebo controlled [33]. This study found a statistically significant difference between levomilnacipran ER and placebo in depression rating scales between baseline and 8 weeks [33]. Side effects included nausea, dizziness, constipation, tachycardia, urinary hesitation, hyperhidrosis, insomnia, vomiting, hypertension, and erectile dysfunction [33].

The recommended dose range is from 20mg to 120mg once daily with or without food. It is recommended to use caution with strong CYP3A4 inhibitors such as ketoconazole [34]. Overall, early studies have been encouraging in Levomilnacipran ER's efficacy and tolerability [35-36].

2.4 Brexpiprazole

Brexpiprazole (OPC-34712) is an agent in phase III clinical testing for adjunctive treatment of major depressive disorder. Chemically it is similar to aripiprazole, however it has more D2 antagonism as well as more potent 5-HT2A antagonism, 5-HT1A agonism, and alpha1 antagonism [4]. Antidepressant activity is thought to be related to its 5-HT1A partial agonism and 5-HT7 antagonism. In early trials, brexpiprazole demonstrated efficacy and was well tolerated as an adjunctive treatment for depressed patients with an inadequate response to antidepressant treatment [37]. This drug is hypothesized to have a more favorable tolerability compared to aripiprazole due to its mechanism. Brexpiprazole is a drug in development to watch in for the future.

2.5 Tedatioxetine

Tedatioxetine (Lu 24530) is another agent in clinical development for the treatment of depression. It can be classified as a triple reuptake inhibitor (TRI) or a serotonin-norepinephrine-dopamine reuptake inhibitor with additional pharmacological properties including 5-HT2C, 5-HT3, 5-HT2A, and alpha-1a antagonism [4,38]. This class of drug holds promise for a robust response by targeting three main neurotransmitters without requiring high occupancy of the serotonin transporter, thus potentially reducing some serotonin mediated side effects [11]. According to a Lundbeck release, in vivo rat studies involving tedatioxetine demonstrated increases in acetylcholine, noradrenaline, dopamine, and serotonin levels in brain regions involved in mood regulation. In addition, Lundbeck reported that Lu 24530 was well tolerated and performed well in phase II clinical trials with significant improvement compared to placebo along with low dropout rates [39-40].

3. GLUTAMATERGIC

3.1 Ketamine

Ketamine, a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist, is another novel agent for treatment resistant depression. While it does not hold FDA approval for treatment refractory depression, it is an approved anesthetic. Initial findings of its rapid onset and short duration instigated more research to find a longer acting agent similar in mechanism [4,41-44]. Animal studies have examined the antidepressant mechanism of action of ketamine finding that ketamine acts potently on NMDA receptors, increasing glutamate signaling with downstream action including synaptogensis and enhanced synaptic functioning [38,45-46]. Downstream release of glutamate leads to stimulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and mGluR subtypes of glutamate receptors. Other agents and pathways linked to the antidepressant action of ketamine include brain derived neurotrophic factor, tropomyosin related kinase B, phosphatidyl inositol-3 kinase, Akt and Ras–mitogen-activated protein kinase, glycogen synthase kinase, and mammalian target of rapamycin [45-50]. In addition, ketamine also acts, albeit less potently, on the sigma, mu opioid, norepinephrine, and serotonin receptors [38]. It is hypothesized that action at the sigma 1 receptors could be a main contributor to ketamine's antidepressant effects.

In studies, ketamine has been given at subanesthetic doses with slow onset and offset IV infusion which has prevented substantial dissociative and hallucinogenic responses. Many patients have experienced rapid relief from depression, suicidal thoughts, as well as pain [41,44,51-52]. According to one 28-day, open-label, proof-of-concept trial of daily oral ketamine administration in patients receiving hospice care, there was significant improvement of both depressive and anxiety symptoms in all patients which lasted the full 28 days [53]. Of significance, the time to response using oral ketamine was noted to be more protracted compared to IV administration. There were minimal side effects which included diarrhea, trouble sleeping, and trouble sitting still [53]. Another small study found favorable results for depression, mood stabilization, and cognition [54]. These are hopeful early studies, but there is a need for continued investigation with randomized, controlled clinical trials to confidently establish the efficacy and safety of ketamine. There is limited data on the recommended dosage of ketamine. Currently, infusions of ketamine in sub-anesthetic doses have been linked to anti-depressive effects. In the research literature, improvement in mood has been demonstrated with intravenous infusions of 0.5mg/kg ketamine over 40 minutes. In order to enable practical clinical usage of ketamine, researchers are investigating administration routes other than the intravenous one, including intramuscular, intranasal, sublingual, and oral formulations with varying doses. It seems that frequent and repeated infusions may extend time in remission [52]. However, there is a need for continued research in order to obtain recommended routes of administration, dosage, and drug (racemic vs. isomers). Some of the potential side effects of ketamine include urinary tract symptoms, increases in blood pressure, heart rate, and cardiac output, and lowering of the seizure threshold. There is also concern for any hallucinogenic effects or abuse potential given illicit use of the substance for recreational purposes. Future direction should be focused on investigating different dosages, routes, predictors of response, as well as clearly identifying any risks and/ or contraindications, and establishing the mechanism of action of its proposed antidepressant activity.

3.2 Dextromethorphan

Another innovative agent targeting the glutamate system is dextromethorphan. Similar to ketamine but with different affinities, dextromethorphan has actions on the sigma receptors, mu opioid receptor, norepinephrine transporter (NET), and SERT [4]. Lauterbach et al. highlight similarities between ketamine and dextromethorphan including “sigma-1 (σ(1)) agonist and NMDA antagonist properties, calcium channel blockade, muscarinic binding, serotonin transporter (5-HTT) inhibition, and μ receptor potentiation” [55]. When combined with quinidine, a cytochrome P450 2D6 inhibitor, the bioavailability of dextromethorphan is increased. Combination dextromethorphan/quinidine (Nuedexta) has FDA approval for pseudobulbar affect; and given its mechanism of action, it has the potential to treat mood disorders [55-56]. There is animal evidence indicating that at least some of dextromethorphan’s antidepressant actions involve sigma-1 receptors [57]. Explaining the exact science behind the potential mood effects of dextromethorphan is unclear at this time, but hypotheses include involvement of the NMDA receptor, sigma-1 receptor, mTOR activation, AMPA receptor, and possibly alpha-2 receptors [55]. More studies and investigation should be done in determining the potential use for dextromethorphan in treatment resistant depression.

3.3 Traxoprodil (CP-101,606)

The NMDA receptor is composed of different subunits with various subtypes and actions. Traxoprodil (CP-101 606) is an innovative drug in development that is an NR2B subunit-

selective NMDA receptor antagonist. The NMDA receptors containing the NR2B subunit are localized primarily in the forebrain [58]. In addition, NR2B containing receptors seem to be related to “pathological processes linked to overexcitation of glutamatergic pathways” [59]. Preskorn et al. [58] conducted a randomized, placebo-controlled, double-blind study to evaluate traxoprodil as an antidepressant in patients with treatment refractory depression. In this study, the NMDA antagonist was added to SSRI therapy. Using the Montgomery-Asberg Depression Rating Scale (MADRS), traxoprodil produced a greater decrease in score than did placebo when compared to baseline scores. Using the Hamilton Depression Rating Scale, response rate was 60% for traxoprodil and 20% for placebo. Response lasted at least a week in 78% of traxoprodil treated responders [58]. Of note, there was report of dissociative reactions in this study which occurred more frequently at the higher dose of infusion, emphasizing the need for further research to determine the appropriate dosing that does not cause psychomimetic effects. In summary, this novel agent targeting the N2RB may be promising for those patients suffering from treatment refractory depression.

3.4 MK-0657

Similar to traxoprodil in mechanism, MK-0657 is another NR2B antagonist. However in a randomized, placebo-controlled trial, it did not reproduce similar results on the Montgomery-Asberg Depression Rating Scale in treatment resistant patients, but did show significant antidepressant effect as per the Hamilton Depression Rating Scale and Beck Depression Inventory. This novel agent was discontinued by the manufacturer, and only 5 of 21 patients completed this crossover study [60].

3.5 GLYX-13

Continuing to explore the glutamatergic system as a target for depression, GLYX-13 is a NMDA receptor glycine-site functional partial agonist currently in clinical trials [61]. This novel agent may enhance cognition and decrease depressive symptoms without psychotomimetic side effects. It is thought that the antidepressant effects of this agent can be explained by “NMDAR triggered synaptic plasticity” [62]. In a Phase IIA double-blind, placebo-controlled, proof-of-concept trial, a single IV dose of GLYX-13 improved depressive symptoms at the 5 and 10 mg/kg dose, but not at the 30mg/kg dose. These effects were only short term, 3-7 days depending on the scale used, and importantly they were without psychotomimetic effects which may be related to GLYX-13’s partial agonist properties. Of note, dizziness was reported by approximately 10% of subjects [62]. Additional studies are needed given the limitations in these early studies. Greater knowledge about the glutamatergic system will contribute to the development of effective future therapeutic agents.

3.6 AZD6765

AZD6765 (Lanicemine) is a low to moderate affinity open channel NMDA channel blocker with less psychotomimetic effects than ketamine [63]. Zarate et al. [64] conducted a double-blind, randomized, crossover study with 22 subjects who received single infusion of either AZD6765 (150 mg) or placebo. There was notable improvement in the AZD6765 group at 80 minutes which lasted until 110 minutes using the MADRS. There was no significant difference between groups on psychotomimetic or dissociative adverse effects, and there were no serious adverse events in the study. Sancora et al. [65] reviewed placebo-controlled data of AZD6765 showing an antidepressant response with single and multiple drug

infusions without significant dissociative symptoms. Other trials have been completed per clinicaltrials.gov, but have not been published yet [66-67].

4. OPIOID

The role of mu, delta, and kappa opioid receptors in mood disorders has been receiving more attention [68]. Opioid receptor involvement has been linked to modulation of multiple neurotransmitter systems including serotonin, catecholamine, dopamine, corticosteroid, glutamate, and NMDA which all play a role in mood regulation [69]. Interestingly, opioids are not a novel treatment for psychiatric illness. This class of medications has been used during parts of the 19th and 20th centuries, until tricyclic antidepressants and monoamine oxidase inhibitors became established. Past research supports the use of opioids as an effective treatment for refractory depression [70].

4.1 Buprenorphine

In 1982, Emrich et al. [71] published a paper showing that buprenorphine exhibited antidepressant properties in treatment resistant depression. Another study by Bodkin et al. supported this finding with a small sample of 10 subjects suffering from treatment refractory depression. Seven subjects showed improvement in subjective and objective measure of depression [72]. Dosage of buprenorphine was initiated at 0.15 mg each day, intranasally or sublingually; the maximum daily dosage was 1.8mg [72]. In another small study, all 6 patients with treatment refractory depression showed some improvement with buprenorphine treatment over 1 week [73]. Five of 6 patients reached complete remission according to the Hamilton Depression Rating Scale (HAMD), and 4 of 6 reached remission according to the Beck Depression Inventory (BDI) [73]. In this particular study, patients received doses ranging from 0.8-2.0 mg once daily of sublingual buprenorphine. Patients were started at 0.4 mg a day with dose increases every 1 to 2 days. Most side effects were mild and short lived [73].

4.2 ALKS 5461: Buprenorphine + samidorphan (ALKS 33)

ALKS 5461 is an investigational opiate agent for the treatment of depression. It is a combination of buprenorphine, a mu opioid receptor partial agonist, and samidorphan (ALKS 33), a potent mu opioid antagonist. This combination was designed to lessen the mu agonist effects of buprenorphine, and therefore limit the potential for drug abuse. Per developer report, their phase II randomized, double-blind, placebo-controlled study of the agent in 142 subjects with major depressive disorder who did not sufficiently respond to an SSRI or SNRI, showed it was well tolerated and significantly reduced depressive symptoms in the HAMD, MADRS, and the Clinical Global Impression–Severity Scale (CGI-S). Given these reported findings, ALKS 5461will proceed to Phase III trials [74-75].

5. CHOLINERGIC/NICOTINIC

Another direction in drug development has focused on cholinergic transmission. The cholinergic system is known to be involved in cognition and dementia [76]. Cholinesterase inhibitors represent first-line medication therapy for patients with mild to moderate Alzheimer's disease [77]. Patients with dementia and older depressed patients both suffer from cognitive impairment, though the mechanism and therefore treatment is likely different. Unfortunately, cholinergic stimulation which has been shown to help in cases of dementia

has not been shown to improve mood [78]. In 1974, it was hypothesized that acetylcholine may actually be involved in the etiology of affective disorders given depressive responses to physostigmine administration [79]. While both nicotinic and muscarinic acetylcholine receptors are able to bind acetylcholine, they have different properties. The muscarinic acetylcholine receptor is G protein coupled and the nicotinic acetylcholine receptor is ligand-gated [80]. Related to drug development, Zurkovsky et al. [81] comment that there is potential specifically for nicotinic treatments as nicotinic stimulation may improve cognition and neural functioning without a detriment to mood, and muscarinic stimulation may exacerbate depressive symptoms.

Nicotinic acetylcholine receptors are implicated in depression given their location in the brain as well as their associated effects on key neurobiological systems including neurotransmitters, HPA axis, and inflammation [82]. An increasing number of researchers have considered modulation of nicotinic acetylcholine receptors, specifically those containing the beta2 subunit, in the treatment of major depressive disorder [83-84]. Using single photon emission computed tomography (SPECT) analysis of the beta2 subunit containing nicotinic acetylcholine receptor (nAChR), Saricicek et al. [84] showed lower availability across all brain regions in acutely ill and recovered depressed subjects compared to controls. This finding gave support to the idea that depressed patients may have lower nAChR availability than do healthy subjects. Researchers continue to explore the role of nicotinic receptors in depression.

5.1 Varenicline and TC-5214

Varenicline, an alpha4-beta2 partial agonist at nicotinic acetylcholine receptors and alpha7 full agonist, has been studied in depressed patients. Patterson et al. conducted a double-blind, placebo, crossover smoking cessation study and found that during abstinence, smokers on varenicline demonstrated significantly lower levels of negative affect and significantly greater levels of positive affect [85]. In an open label study of varenicline augmentation in 18 adult smokers with depression, 44% of patients met criteria for response and 33% achieved remission using the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) [86]. Of note, some case reports of varenicline reporting worsening mood led to a boxed warning from the Food and Drug Administration highlighting the “risk of serious mental health events including changes in behavior, depressed mood, hostility, and suicidal thoughts” [87]. However, not all follow-up studies have shown this to be true. In a study by Anthenelli et al. smokers who were given varenicline had higher continuous abstinence rates without exacerbating depression or anxiety [88]. The dose of varenicline in participants was titrated to 1mg twice a day [88]. Some participants had their dose decreased to 0.5mg twice daily due to tolerability issues [88]. The medication had to be reduced or discontinued due to adverse events in 8.6% and 3.7% of varenicline and placebo participants, respectively [88]. The most frequent adverse events in this study were nausea, headache, abnormal dreams, irritability, and insomnia. Other side effects may include constipation, flatulence, and vomiting. Serious warnings include rare angioedema and hypersensitivity reactions, skin reactions, cardiovascular events, and accidental injury [89]. Of note, more research is required when combining varenicline with other smoking cessation therapies. Transdermal nicotine in combination with varenicline has been associated with higher rates of discontinuation [89].

Unfortunately, a drug with a related mechanism, TC-5214, performed no better than placebo in the treatment of depressive symptoms in a Phase III trial. TC-5214 is a form of mecamylamine, a blood-pressure drug introduced in the 1950s that targets nicotinic alpha4-

beta2 receptors [90]. Of important consideration, varenicline and TC-5214 do not have exact effects on nAChRs, as the latter is a nonspecific antagonist and the former is a partial agonist.

5.2 CP-601927

Another agent recently in development is CP-601927, a selective alpha4-beta2 nicotinic acetylcholine receptor partial agonist developed by Pfizer. Clinical trials evaluating the efficacy of CP-601927 compared to placebo in the augmentation of antidepressant therapy in patients with major depressive disorder were stopped as criteria for futility were met. No safety concerns were raised [91].

6. OTHER AGENTS TO CONSIDER

This article is unable to review all novel drugs as well as drugs in development to treat depression and other mood disorders. However, this last section will give a brief overview of some additional agents to consider and watch for in the future.

6.1 Lurasidone

Lurasidone, a novel antipsychotic, has been recently approved for the treatment of bipolar depression. Lurasidone is an antagonist at D2 and 5-HT2A receptors; it also is a partial agonist at 5-HT1A receptors and has affinity for 5-HT7 and alpha receptors [4]. The minimal affinity for muscarinic M1 and histamine H1 receptors may explain fewer reports of weight gain, sedation, and cognitive impairment compared to other antipsychotics. The effect lurasidone has on 5-HT7, 5-HT1A, and alpha 2 receptors may explain its antidepressant effects [4]. Loebel et al. investigated lurasidone in a placebo controlled, double-blind study for bipolar depression. Monotherapy with lurasidone in the dosage range of 20-120 mg/day significantly reduced depressive symptoms in patients with bipolar I depression. The medication was well tolerated with minimal effect on weight, lipids, and measures of glycemic control. The most frequent adverse events were nausea, headache, akathisia, and somnolence [92]. The usual dose range for lurasidone is from 40-80mg a day. Some patients may benefit from doses up to 160mg a day. Absorption of lurasidone is greater when it is taken with food [4]. There are possible drug interactions with CYP3A4 inhibitors and inducers. It is recommended that lurasidone not be used in combination with strong CYP3A4 inducers (eg. rifampin) or strong CYPA3A4 inhibitors (eg. ketoconazole). In moderate CYP3A4 inhibitors, the dose should be restricted [93]. As with some other antipsychotics, lurasidone carries warnings of tardive dyskinesia, neuroleptic malignant syndrome, extrapyramidal symptoms, blood count abnormalities, metabolic side effects, hyperprolactinemia, orthostatic hypotension, seizures, and increased risk of mortality in elderly patients. As mentioned above, lurasidone may be less likely to cause weight gain and development of diabetes [93].

6.2 L-methylfolate

There is a strong association between folate deficiency and depression [94]. L-methylfolate, or deplin, is a “medical food” and only available by prescription. It is thought to act as an augmenting agent in patients with depression given its role in increasing the synthesis of dopamine, norepinephrine, and serotonin via influence on tetrahydrobiopterin (BH4), a co-factor needed for neurotransmitter synthesis [95]. Many, but not all, trials concluded positive

results on the effectiveness of adjunctive antidepressant response using L-methylfolate, the active and more bioavailable form of folic acid [94-97]. Two recent placebo controlled, double-blind studies showed greater efficacy for 15mg a day of adjunctive L-methylfolate, but not 7.5mg a day of adjunctive L-methylfolate, administered for up to 30 days with continued SSRI therapy compared with continued SSRI therapy plus placebo [98]. In these trials, L-methylfolate showed rates of adverse events similar to those reported with placebo [98]. Of note, one patient taking L-methylfolate was withdrawn from the study due to the development of manic symptoms [98]. L-methylfolate was well tolerated in the study with 80% of patients completing 60 days of the double-blind treatment [98]. L-methylfolate has minimal reported side effects; the package insert includes possible non specified allergic reaction [99]. Although there have been concerns about folate increasing the risk of cancer, masking vitamin B12 deficiency, and decreasing monoamines which may lead to depression, Fava et al. discuss that folate is generally well tolerated and some of these early concerns are not well supported. In addition, L-methyfolate may be "less likely to incur some of these risks" [100]. L-methylfolate may be most beneficial to those patients with suboptimal folate levels including those with the C677T variant of the enzyme methylene tetrahydrofolate reductase and subsequent inefficient synthesis of L-methylfolate [101-104]. L-methylfolate is usually prescribed from 7.5mg to 15mg daily. Interactions with L-methylfolate should be checked prior to prescription. There may be interactions with antiepileptic drugs, fluoxetine, NSAIDs, metformin, warfarin, dihydrofolate reductase inhibitors, pancreatic enzymes, pentamidine, and methylprednisolone, among others [105]. Many of these medications reduce serum folate levels; however, interactions with certain antiepileptic agents may lead to enhanced drug metabolism, thereby lowering the antiepileptic drug level and putting patients at risk for seizures. Therefore, patients should be monitored closely for any seizure activity [105].

6.3 Cariprazine

Cariprazine is a dopamine D2 and D3 receptor partial agonist pending approval from the US Food and Drug Administration. In addition to dopamine modulation, it has potent actions at 5-HT2B and 5-HT1A receptors [4]. It is in testing for schizophrenia, mania, bipolar depression, and treatment resistant depression. Early studies have shown efficacy and tolerability for the treatment of bipolar disorder (manic/mixed and depressive episodes) [106]. Per early investigation, cariprazine may have a favorable weight gain, metabolic, and EPS profile; furthermore, there may be potential for long acting formulations given its two long acting metabolites [4]. However, more well-designed clinical trials are needed to determine its future treatment role in mood disorders. As of November 2013, the FDA has requested more clinical data from its developers Forest/Gedeon Richter [107].

6.4 SSR149415

Treatments that act on the hypothalamic-pituitary-adrenal axis are another potential target for novel drug development, but there are no current FDA approved treatments. Vasopressin and corticotropin-releasing factor (CRF) are involved in the stress response. By acting on pituitary and central vasopressin V1b receptors, vasopressin has effects on the hypothalamic-pituitary-adrenal axis and mood. There is evidence that plasma levels of this peptide may be elevated in patients with depression [108-109]. Researchers have considered that changes in vasopressin levels may be associated with vasopressin receptor activity, therefore exploring novel agents that alter receptor activity [110-111]. SSR149415 is a vasopressin V1b receptor antagonist recently studied for depression [112]. SSR149415 was studied in randomized, double-blind, placebo-controlled trials and results were not

convincing to support strong efficacy. Its potential as an antidepressant calls for further evaluation [113].

6.5 Agomelatine

The hormone melatonin is a serotonin precursor and is involved in the circadian system. It has been hypothesized to help treat depression. Agomelatine, a melatonergic receptor agonist of MT1 and MT2 and a 5-HT2C antagonist, is approved in Europe but is not approved in the US [114-115]. Comprehensive reviews of the studies done on agomelatine indicate that it does not have clinically significant advantages compared with other antidepressant drugs, and it has certain limitations and disadvantages including hepatic concerns [115]. Guiana et al. [114] commented that there are no firm conclusions which can be drawn regarding the efficacy and tolerability of agomelatine.

7. CONCLUSION

In conclusion, there is a substantial need for additional psychopharmacological treatments given the significant and rising burden associated with major depression. However, this task is associated with years of research, trials, and often disappointment. According to Belzung, a challenge the field faces in finding new therapies involves the inadequate dialogue between neuroscientists and psychiatrists [116]. Belzung appropriately calls for an integrated and collaborative effort to bridge the gap between basic and clinical science in order to drive the field forward [116]. Other barriers to advancement of clinical care include lack of awareness and advocacy, minimal incentives for continued drug development, unfortunate stigma, and limited access to modern technologies including pharmacogenetic testing, largely due to cost and insurance coverage.

This article has outlined various new and novel medication therapies for the treatment of depression across various mechanisms of action. Key categories of novel therapeutic targets were reviewed including monoaminergic, glutamatergic, opioid, anticholinergic, and other various systems. Unfortunately, not all trials have been clear and convincing or even successful; however, there are promising targets that warrant continued development and trials. After years of focusing on monoamines, we are branching out into new directions which will hopefully result in effective treatments for mood disorders. As our field advances, we also hope to develop more objective ways of predicting and monitoring psychiatric illnesses, such as utilizing biomarkers and genomics. In addition to psychopharmacological interventions, holistic and personalized treatment plans should include non-pharmacological approaches, especially psychotherapy, to optimize response and recovery.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Dr. Shapiro has declared that no competing interests exist.

In the past 12 months, Dr. Stahl has served as a consultant for Acadia, AstraZeneca, Avanir, Biomarin, Bristol-Myers Squibb, CeNeRx, Dey, Eli Lilly, Forest, Geno Mind, GlaxoSmithKline, Johnson & Johnson, Jazz, Lundbeck, Merck, Neuronetics, Novartis, Noven, ONO, Orexigen, Otsuka, PamLabs, Pfizer, RCT Logic, Rexahn, Roche, Servier, Shire, Solvay, Sunovion, Trius, and Valeant. He has served on speakers' bureaus for Arbor Scientia, AstraZeneca, Eli Lilly, Forest, J&J, Merck, Neuroscience Education Institute, Pfizer, Servier, and Sunovion. He has received research and/or grant support from AstraZeneca, CeNeRx, Eli Lilly, Forest, GenOmind, Merck, Neuronetics, Pam Labs, Pfizer, Roche, Schering Plough, Sepracor, Servier, Shire, Sunovion, Torrent, and Trovis.

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