A Research Review of Antidepressants for the Treatment of Major Depressive Disorder

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Abstract

The prevalence of major depressive disorder (MDD) in the U.S. has been significantly on the rise between 2015 and 2020, with adolescents and young adults (ages 18-34) contributing the most to this increase (Goodwin et al., 2022). The trend represents a disturbing downturn in the mental health of U.S. adults and warrants close attention and consideration.

As the case number of MDD has continuously risen in the recent past, medical practitioners have been searching for more effective solutions. The techniques for combating the symptoms and curing the disease have varied, but one option consistently respected throughout the literature has been antidepressant medication (ADM). Not only are ADMs a commonly administered treatment for MDD, but among certain demographics, particularly ages 12-17, prescription rates have more than doubled over the course of twenty years.

With such high prescription rates, the effectiveness of ADMs would naturally be assumed to be very strong. However, recent controversy has called into question the method of action of prominent ADMs and has cast doubt on their efficacy as a treatment option for MDD. Psychologist Irving Kirsch is largely credited with initiating and popularizing the controversy surrounding the drugs, claiming that antidepressants are no more effective than the placebo against which they are evaluated (Chen et al., 2023). If ADMs were to demonstrate clinically insignificant effects on symptoms of MDD, or if the method of action of these drugs were to deviate from that which was initially proposed, the implications on patients and the psychological community would be drastic. The purposes of this review are to evaluate the extent to which ADMs are effective in the treatment of MDD, define the method of action of various ADMs, account for the adverse effects commonly experienced by those administered ADMs, and consider alternative treatments if these prove insufficient.

A Research Review of Antidepressants for the Treatment of Major Depressive Disorder

MDD is one of many depressive disorders addressed with psychiatric medicine and is regarded by the DSM-5-TR as the archetype of disorders in this category (American Psychiatric Association, 2022). Candidates for diagnosis must exhibit for at least two weeks any five of the depressive symptoms, of which depressed mood, disinterest or anhedonia, abnormal food consumption, abnormal sleep duration, fatigue, and more are examples. The DSM distinguishes MDD from attention-deficit/hyperactivity disorder (ADHD) by the qualities of the mood disturbance; whereas the disturbance of ADHD is of an irritable nature, that of MDD is characterized by sadness and apathy. Additional qualification is given in that the symptoms cannot be the result of a medication or another medical condition. In these instances, a separate diagnosis would be appropriate, partly to accommodate the precise study of MDD and its treatment options.

MDD comes at a great expense to the quality of life for individuals, but the greater concern is directed at the common outcomes of depression. It is reported that approximately 60% of the suicides in the male demographic suffered from MDD and that globally, suicide is one of the most common causes of death for MDD patients (Kielan et al., 2021). Suicide risk in MDD patients is therefore of great concern and clinicians have designated categories for assessing the risk of suicide in these patients. Suicidal ideation (SI) is the preliminary stage, in which a patient begins thinking about or imagining suicide; suicide threat (ST) involves a communicated warning to commit self-harm, but without the intent to follow through; suicide plan (SP) entails actively planning out a specific means of committing suicide; suicide attempt (SA) is defined by a genuine act intended to complete suicide that fails; and completed suicide (CS) is a fatal act to take one’s life (Orsolini et al., 2020).

There are many contributing factors to MDD, both domestically and globally. Factors such as being of the female sex, divorce, and unemployment appear to be consistent correlates of MDD internationally, whereas factors such as socioeconomic status, drug use, child abuse experience, and diagnosis of personality disorders appear to vary in significance and effect size by region, race, and individual variation (Gutiérrez-Rojas et al., 2020). General psychological contributors to depression include neuroticism, a low view of self, and rejection sensitivity (Remes et al., 2021). A proposed "stress-induced" model of depression notes that chronic or childhood stressful events are significantly correlated with a later diagnosis of MDD, as are higher cortisol levels and certain genes associated with the hypothalamic-pituitary-adrenal axis and supposes that hyperactivity of cortisol production may be a prime contributor to depressive symptoms (Shadrina et al., 2018). This theory does initially receive some skepticism due to the fact that traits common to MDD, like neuroticism, demonstrate little to no significant correlation with cortisol levels (Limone et al., 2021). However, the other factors supporting this model lend the theory some plausibility.

A second model, often referred to as the serotonin theory, proposes that depressive symptoms result from either a chemical imbalance of serotonin or pathological serotonin regulation (Moncrieff et al., 2022). This theory remains very prevalent in the literature and is the justification for many treatments commonly prescribed for MDD. As will be discussed further, this model has lately undergone intense scrutiny, which has led to a large fracturing within the psychiatric field. Antidepressant medications (ADMs) have also come under scrutiny considering that they are one of the most popular MDD treatments and rely heavily on the validity of the serotonin model. To evaluate the claims made regarding the medications, it will be

necessary to discuss the relevant physiological processes, noting the various sites of inhibition by various ADMs and contributions to symptomology.

Neuron Physiology Overview and ADM Action

To discuss the physiological method of action of neurotransmitters, it is first crucial to understand the normal physiology that underlies neurotransmission and reuptake. In so doing, the physiological effect of ADMs will become more accessible, and the discussion of their clinical practicality will be more comprehensive.

The synthesis of serotonin is a multi-step process involving two enzymes: L-tryptophan hydrolase (TPH) and L-aromatic amino acid decarboxylase (*Serotonin Synthesis and Metabolism*, n.d.). TPH performs the preliminary conversion of L-tryptophan to 5-hydroxytryptophan, which is a rate-limiting hydroxylation. Subsequently, L-aromatic amino acid decarboxylase converts 5-hydroxytryptophan to 5-hydroxytryptamine (or serotonin). Once synthesized, the neurotransmitters must be packaged into vesicles in the axon terminal in preparation for their release. The vesicular monoamine transporter (VMAT) is responsible for moving monoamine neurotransmitters from the cytoplasm to the inner space of the vesicle (Yaffe et al., 2018). This eight-step process involves the antiport release of two protons to the cytosol and one molecule of a monoamine to the luminal space of the vesicle.

Norepinephrine synthesis differs from that of serotonin, starting from the precursor. Whereas serotonin is produced from L-tryptophan, norepinephrine begins as L-phenylalanine (*Dopamine, Norepinephrine, and Ephinephrine Synthesis*, n.d.). Through two hydroxylation reactions via phenylalanine-4-hydroxylase and tyrosine-3-hydroxylase, L-phenylalanine is converted to L-dihydroxyphenylalanine. The rate-limiting step is the second hydroxylation, wherein l-tyrosine is hydroxylated at the 3 carbon. L-aromatic amino acid decarboxylase, as seen

in serotonin synthesis, then converts this to dopamine. Dopamine in turn is converted to norepinephrine via dopamine-Î²-hydroxylase, which hydroxylates the ß carbon.

Neurotransmitter release is an exocytic mechanism involving the fusion of synaptic vesicles (SV) to the outer membrane that occurs in the axon terminal of a neuron (Van den Eynde et al., 2022). When an action potential reaches the terminal, the wave of depolarization opens the voltage-gated sodium channels located in the outer membrane. Calcium ions, which are usually forced out of the cell by the sodium/calcium ion exchanger (NCX) and the plasma membrane calcium ATPase (PMCA), are permitted to freely diffuse back into the cell along a concentration gradient (Cooper and Dimri, 2021). Once inside, calcium initiates a myriad of biochemical processes.

Because it is necessary for the response of the axon terminal to the action potential to proceed as immediately as possible, the components of the presynaptic neuron that convey the neurotransmitter to the synapse wait in a pre-formed state at the plasma membrane. These components are soluble N-ethylamide-sensitive factor attachment protein receptor (SNARE) proteins (Ramakrishnan et al., 2020). On the plasma membrane, syntaxin/SNAP25 articulates with VAMP2 on the vesicle to naturally initiate the docking of the vesicle on the synaptic membrane. When calcium then influxes upon depolarization, the SNARE proteins are released, the vesicle becomes continuous with the outer membrane, and the neurotransmitters are released into the synapse.

Each neurotransmitter has a specialized effect on its post-synaptic neuron. Serotonin occupies both the ionotropic and metabotropic categories of effects on the postsynaptic neuron (Frazer and Hensler, 1999), with the 5-HT_1, 5-HT_2, 5-HT_4 5-HT_6, and 5-HT_7 receptors mediating the G-protein coupled metabotropic responses and the 5-HT_3 receptor mediating the ionotropic

ones. The ionotropic/metabotropic distinction is not the only one that is relevant to the 5-HT receptor types and sub-types; each is also distinguished by the intracellular second messenger that it affects, the localization within the body, and its physiological effects on a larger scale. 5-HT_1 receptors are all identified by their propensity to inhibit the adenylyl cyclase of the presynaptic neuron, complimenting their function as serotonergic auto-receptors. 5-HT_2 receptors each activate phospholipase C but demonstrate more diffuse excitation effects on the postsynaptic neuron. 5-HT_4, 5-HT_6, and 5-HT_7 each activate adenylyl cyclase and are primarily active in the central nervous system (CNS).

The reuptake of serotonin from the synapse by the presynaptic neuron is the primary target of most ADMs, save for MAOIs. Reuptake is prevented by the inhibition of the serotonin transporter SERT: a transmembrane protein consisting of twelve transmembrane domains (TMDs) that work in tandem to facilitate the symport of 5-HT and sodium ions (Na^+) into the cell (Baudry et al., 2019). The maximum transport rate of SERT, as well as the substrate concentration at which the enzyme reaches half its transport maximum and the turnover rate, have been demonstrated to be dependent on the binding of cholesterol to a residue CHOL1: a pocket of hydrophobic residues bordered by TM7, TM5, and TM1a (Baudry et al., 2019). As well, it is suggested based on LeuT and MhsT homologs that the symport function of SERT is dependent on the simultaneous binding of substrate to both a primary (sS1) and a secondary (sS2) substrate site (Quick et al., 2018). Further research has elucidated the roles of S1 and S2 in the cyclic mechanism of 5-HT/Na^+ symport by SERT. When the outermost substrate site (sS2) is occupied by 5-HT and SERT occupies the inward-open apo-state conformation, a potassium ion (K^+) enters the groove formed by TM1a and TM6b (Yang and Gouaux, 2021). This causes TM1a and TM6b to twist SERT into an occluded apo-state conformation and subsequently to an

outward-open apo-state conformation as K^+ escapes to the extra-cellular fluid (ECF) by the movement of TM1b and TM6a. From here, the 5-HT molecule in the S2 site is displaced to the S1 site (nearer to TM1a) and is replaced by a second 5-HT. Two Na^+ and one Cl^- influx, with each Na^+ associating with the midline of TM1 and TM6 and Cl^- associating with both TM1b and TM6a, forming the outward-open holo-state. TM1 and TM6 temporarily realign vertically to form the occluded state before quickly reconfiguring to the inward-open holo-state. As one 5-HT escapes from S1 and one Na^+ influxes from TM6 to the intracellular fluid (ICF), SERT returns to the inward-open apo-state.

The other key transporter for ADM targeting is the norepinephrine transporter (NET). Until recently, the structure of NET has remained obscure. However, x-ray crystallography has revealed several key functional components of the protein that further inform its reuptake function (Góral et al., 2020). Much like SERT, NET has twelve TMDs, and the main transport mechanism primarily involves TM1 and TM6, with a lower affinity secondary substrate binding site (nS2) and a subsequent higher affinity primary binding site (nS1). In what appears to be an expansion of the model set by SERT, successful NET function is at least minorly dependent on the appropriate interaction of the substrate with extracellular loop 4 (EL4). EL4 is the first segment of NET to interact with inhibitors, and thus serves as the first line of selectivity for transport.

Upon reuptake of the neurotransmitter, whether norepinephrine or serotonin, the amine is commonly degraded via enzymatic reaction with MAOA. The rate-limiting step of this reaction involves the transfer of a hydride to the flavin adenine dinucleotide (FAD) factor of MAOA from the methylene group of the amine (Prah et al., 2020).

Antidepressants

When discussing the use of antidepressants in the clinical setting, it is important to note the various classifications and varieties therein. This allows for a discussion regarding the utility of targeting specific physiological processes while also allowing a comparison of the various medications within those ADM categories. Antidepressant medications (ADM) are generally classified under four categories: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs).

SSRIs

The category "SSRIs" encompasses a large swathe of medications including fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, and vilazodone (Chu and Wadhwa, 2022). SSRIs are identified by their unique antagonistic action, inhibiting the reuptake of serotonin by the pre-synaptic neuron and prolonging the duration of serotonin availability in the synaptic cleft for excitation of the postsynaptic neuron.

Of the ADMs prescribed for the treatment of MDD, SSRIs tend to be the most commonplace, with sertraline leading within the category (Marasine et al., 2021). As proposed above, the temporary occlusion of SERT by an SSRI results in a prolonged action of serotonin on the postsynaptic neuron with the intent to attenuate the depressive symptoms though to result from inadequate serotonin.

SNRIs

SNRIs relevant to the treatment of MDD, including desvenlafaxine, duloxetine, levomilnacipran, and venlafaxine, provide an additional function compared to SSRIs, in that they inhibit the reuptake of an additional monoamine, norepinephrine (Fanelli et al., 2021). This

additional effect is not as prevalent at low doses, however, which explains why the effects of SNRI treatment at lower doses closely resemble those of SSRIs (Fasipe, 2019). An advantage of SNRIs over certain other ADMs, such as TCAs, is that they display a high degree of specificity for their target receptors and thus are limited in their indirect adverse effects.

TCAs

TCAs cannot be distinguished from SNRIs save for their diminished selectivity. While it should be noted that TCAs are not currently widely prescribed, they are still often used as a tertiary medical option when the patient exhibits a poor response to both SSRIs and SNRIs (Vos et al., 2021). Their diminished use over time since their inception in the 1950s is due in large part to their severe adverse effects, especially when compared to their more modern alternatives. As TCAs by nature are basic due to the free valence electrons on the nitrogens, the protic extracellular environment maintained by the Na^+/K^+ ATPase antiporter can often cause the ADM to ionize and initiate neuropathies (Khalid & Waseem, 2020). These often entail the occlusion of several key channels and transporters at the synapse that impedes neurotransmission. Among the TCAs commonly prescribed for MDD are amitriptyline, clomipramine, doxepin, trimipramine, desipramine, nortriptyline, protriptyline, maprotiline, and amoxapine (Sheffler & Abdijadid, 2020).

MAOIs

Rather than targeting the transporters responsible for reuptake, MAOIs target the enzymes responsible for catabolizing the neurotransmitters after reuptake. MAO is a deamination enzyme that is located on the outer mitochondrial membrane and specifically targets monoamines (Cho et al., 2021). MAOIs target either isoform of monoamine oxidase (MAO), whether that be MAOA (responsible for catabolizing norepinephrine, dopamine, tyramine, and

serotonin) or MAOB (responsible for catabolizing tryptamine, dopamine, tyramine, methylhistamine, and phenylethylamine) (Sub Laban and Saadabadi, 2022). It is evident based on the proposed serotonergic model of MDD that MAOA will be of more significance than MAOB to the discussion on ADMs. MAOIs are generally categorized according to two criteria: reversibility (the extent to which the MAO can be recovered after the interaction with the inhibitor) and selectivity (the capacity of the inhibitor to target a specific isoform of MAO) (Rege, 2021). Because those addressing MDD are generally concerned with specifically targeting serotonin catabolism and desire for MAO to be reusable after initial inhibition, those in the selective-reversible category are of special interest.

Effectiveness

A recent meta-analysis of commonly prescribed ADMs compared the effectiveness and acceptability of each medication against its placebo and against each other ADM (Cipriani et al., 2018). The researchers reported that the five most effective ADMs among those assessed were amitriptyline (a TCA), mirtazapine (a tetracyclic antidepressant), duloxetine (an SNRI), venlafaxine (an SNRI), and paroxetine (an SSRI) in order of descending efficacy. Consistent with the literature, the more effective antidepressant medications tend to reside in the TCA and SNRI categories. As the study notes, the efficacy of an ADM is irrelevant to its prescription if the acceptability and tolerability are low.

Only two ADMS, agomelatine (a melatonin agonist) and fluoxetine (an SSRI) demonstrated statistically significantly higher acceptability from placebo. While in head-to-head comparisons the two drugs demonstrated comparable efficacy and acceptability, general trends in the United States from 1996 to 2015 show fluoxetine was more frequently prescribed than all other monotherapy ADMs (Luo et al., 2020). In fact, SSRIs generally remain the most common

ADMs prescribed, due in part to their milder side effects when compared to TCAs. As a matter of fact, the consideration for adverse effects constitutes major pushback against a careless interpretation of the study. Often, the effectiveness of an ADM is outweighed by the consideration of the concurrent administration of other medications, which can have devastating effects on the patient (Kendrick et al., 2019). Additionally, researchers note that limitations of the Cipriani study arise from its design as a network meta-analysis, reasoning that indirect comparisons of drugs are not as reliable as head-to-head comparisons (Kendrick et al., 2019). However, this criticism seems to fail given that the study includes data and significance for head-to-head studies of different antidepressants.

As the literature on ADMs develops, the understanding of the factors that affect the outcomes of drug administration continues to evolve. Novel research even goes so far as to suggest that the external environment may play a primary role in determining the treatment response. A study conducted on the efficacy of fluoxetine in enriched and stressful environments demonstrated that depressive symptoms improved in enriched environments, but worsened in stressful environments (Alboni et al., 2017). The implications of this finding for the clinical setting are a few-fold. Primarily, the practice of combining ADM prescription with CBT for the purpose of controlling the living environment may need to be emphasized. Secondly, it may be necessary for a practitioner to use discretion when prescribing ADMs to patients at high risk for suicide, considering the administration may worsen the depressive symptoms.

Despite developments that recontextualize the practice of ADM administration, the treatments appear to at least have a positive effect. Escitalopram, an SSRI, demonstrates a consistently significant reduction in depressive symptoms over an 8-week period (Wang et al.,

2021). In order to be consistent with the literature, proposed reinterpretations of MDD etiology and pathophysiology will need to account for the significant effect of ADMs.

Considering that the ADM in the previous study is an SSRI, it is possible that the efficacy and adverse effects thereof do not reflect those of ADMs generally. To assess this, an evaluation of other ADMs is necessary. Meta-analysis of duloxetine, an SNRI, demonstrates mixed reports of efficacy with respect to a placebo (Rodrigues-Amorim et al., 2020). In most cases, approximately 80%, duloxetine demonstrated a statistically significant effect with respect to a placebo or another ADM. The study highlights this as a significant finding, but the details of the study and the researchers involved cast doubt on the validity of these results. To start, the researchers note having either direct employment or indirect amicable associations with major pharmaceutical companies, calling into question the selection process for the articles incorporated into the meta-analysis. A survey of the sources included does not foster confidence in the research's integrity. It is reported that 19 of the 85 articles (22%) did not report sufficient data to calculate Hedges's g, which would seemingly call into question to what extent the findings can be assessed for significance, both statistically and clinically. In seeming confirmation of this inability, the data are presented as percentages, without assessment holistically for statistical significance and certainly no assessment of effect size. For this reason, it remains inconclusive to what extent the findings can be extrapolated to the clinical setting. If these were not sufficient, another issue for the meta-analysis arises. This study relies upon the validity of the monoaminergic hypothesis, often referred to as the serotonergic model, of MDD in which a deficiency of 5-HT or pathological signaling thereof. As will be noted later, the consensus of the literature on this conclusion has been questioned in recent years, potentially undermining the premise of this study. In summary, the efficacy of duloxetine and SNRIs largely

remains obscured based on the questioned validity and the failure to provide significance values for the data as a whole.

Further research into the disparity in efficacy between SSRIs and SNRIs supports the use of the former over the latter. While both sertraline and desvenlafaxine demonstrated a statistically significant reduction in depressive symptoms, as assessed by the Beck Depression Inventory and Hamilton Depression Rating Scale, sertraline demonstrated a greater reduction in symptoms (Ch et al., 2022). This finding must be taken with some scrutiny, however, as the researchers failed to report statistical analysis that assessed whether the difference in symptom reduction between the groups was statistically significant. Simple differences in improvement may be deceptive when attempting to assess whether either treatment is superior to a significant degree. Further research should prioritize reporting such analysis as statistical significance and effect size to allow practitioners to evaluate the data themselves.

Exceptions to the rule of SSRI superiority are often context-specific. An example of this can be found in the superiority of venlafaxine efficacy over that of fluoxetine in post-menopausal women (Zhou et al., 2021). This finding should not be taken to invalidate the overall trend demonstrated for the general population. Instead, it should serve as a precaution for practitioners that encourages a consideration of the impact that certain atypical demographic features of a patient might have on their response to ADM administration.

Having discussed the efficacy of SSRIs and SNRIs, the question remains as to the efficacy of other ADMs. Interestingly, while MAOIs are generally not promoted for clinical use on account of the adverse effects associated, research suggests that in monotherapy MAOIs significantly outperform TCAs (Kim et al., 2019). However, this difference in efficacy did seem to diminish among patients displaying longer-term treatment-resistant depression (TRD). These

results may need to be evaluated individually based on the specific ADM, considering that tranylcypromine (an MAOI) demonstrates equal efficacy when compared to TCAs (Ulrich et al., 2020). While it is certainly the case that neither MAOIs nor TCAs is prescribed as a first line of defense against symptoms of MDD, the research may support, at least in some instances, MAOI prescription as the primary alternative in place of TCAs.

While the effectiveness of ADMs in isolation may be ambiguous in some studies, the literature continues to affirm in multiple contexts that the combination of cognitive behavioral therapy (CBT) with ADM provides an overall more positive treatment response and successfully targets residual symptoms when monotherapy fails (Dunlop et al., 2019). This effect was also not dependent on the order of administration (i.e., either CBT or ADM could be introduced first with the subsequent addition of the other). Considering this, it seems practitioners seeking to maximize the decrease in the depressive symptoms of their patients should consider CBT ADM combination therapy as an option. This, of course, does exclude considerations of monetary commitment for both treatments, which may be a valid criticism of this recommendation.

To address this potential criticism, an evaluation of the cost-effectiveness of ADMs and therapeutic options is in order. It has been demonstrated that the combination of ADMs and preventative cognitive therapy (PCT) is the more cost-effective strategy when compared to either ADMs or PCTs in isolation (Klein et al., 2019). The same study also suggested that ADM monotherapy offers greater cost-effectiveness over a 24-month period than PCT monotherapy. While these results may require re-evaluation for periods extending into the future, it nonetheless remains that combination therapy provides patients with the most cost-effective treatment approach and is a suitable approach for patients concerned with maximizing symptom reduction and with spending wisely.

More contentious findings in the recent literature arise from the assessment of serotonergic variations among healthy individuals and those with depressive symptoms. The general presupposition of ADM physiology is that MDD symptoms arise from a serotonergic imbalance or dysregulation. However, multiple studies attest that there remains no significant correlation between serotonin levels and depressive symptoms (Moncrieff et al., 2022). Seemingly in support of this, systematic reviews of genetic polymorphism candidates for the depressive phenotype reveal that those polymorphisms proposed to result in the depressive phenotype are no more correlated with depressive symptoms than any other polymorphism, nor are interactions between the polymorphisms and the environment significantly likely to result in depression (Border et al., 2019). The implications of these findings are profound. As the method of action of every ADM outlined herein is specifically designed to prolong the action of serotonin on the postsynaptic neuron by some means, it becomes difficult considering these findings to justify the true benefit of ADMs from the serotonergic model. If, indeed, the depletion or dysregulation of serotonin is not the main driver or even minor influence behind the presentation of depressive symptoms, then the effect of the ADMs enhancing serotonergic excitation only indirectly addresses the underlying pathology.

This is seemingly confirmed by the decrease in the availability of serotonin over time in individuals treated with ADMs, which, in tandem with the severe paradoxical reactions experienced by certain patients, supports an oppositional model of tolerance for ADMs (Fava, 2020). If the body were to demonstrate compensation for the increase in serotonin, it would support the notion that serotonin depletion is not the most active or underlying pathology in MDD.

If the research is to be believed, then Schpancer is vindicated; while ADMs may have statistically and even clinically significant effects on the depressive symptoms of certain individuals, these effects are unrelated to the proposed serotonergic model of depression. While practitioners may continue to administer ADMs as appropriate for the management of symptoms, this should be done with the acknowledgment that the biochemical processes underlying the improvement remain largely unknown.

Given that the prescription rate of ADMs for adolescents is increasing (Jack et al., 2020), it remains especially important to remain vigilant in evaluating the efficacy of the treatment methods provided for this demographic. A meta-analysis on ADM efficacy in the treatment of acute MDD found that fluoxetine was the only ADM more effective than a placebo (Boaden et al., 2020). To make matters worse, along some categories the meta-analysis found that the ADMs proved worse than the placebo. Duloxetine, venlafaxine, and imipramine were found to be significantly less tolerable and nortriptyline significantly less effective than the placebo. If the focus of the meta-analysis on RCTs as a more valid measure of ADM efficacy is indeed meritorious, serious questions arise about the ethics of the literature on ADMs wholistically. Naturally, it would warrant questioning how individual publications may find compelling evidence for ADM superiority over placebo, whereas some major meta-analyses find no such evidence (Cipriani et al., 2018; see also Jakobsen et al., 2017).

Most studies assessing efficacy, including the majority of those herein, measure improvement by a decrease in depressive symptoms. While this may be suitable for the analysis of ADM prescriptions for adults, this may not be the case for children. Some have suggested that for assessing children, the functioning and quality of life measures are also necessary in order to accurately reflect the outcome of administration. In a recent meta-analysis, an investigation into

the functioning and quality of life outcomes for children and adolescents with MDD found that ADMs did significantly improve functioning, but not the quality of life, perhaps further revealing the need for combination therapy (Teng et al., 2022).

One potential explanation for the discrepancy between meta-analyses and individual journal articles regarding efficacy is publication bias. It is reported that the literature is significantly polluted with research remodeled to find significant support for psychotherapeutic drugs and that such studies either are demonstrated to change their method of statistical analysis or their primary outcome measure after approval of the proposal, resulting in a favorable outcome for the drug in question in two-thirds of cases (Bowcut et al., 2021). If remodeling is to blame for the meta-analysis discrepancy with ADMs, one would expect to see the data that goes unpublished in major journals, yet is recorded in databases accessible for meta-analysis, to find less compelling overall significance for their effectiveness, which Bowcut et al. demonstrate. This bias potentially explains why the individual studies discussed herein demonstrate effective ADM results when compared to placebo, yet the meta-analyses do not.

Perhaps the most crucial, and vocal, opposition to the administration of ADMs comes from American psychologist Irving Kirsch. In a 2019 article in *Mental Health*, Kirsch and his peers outline what they believe to be a damning case against ADMs and the psychopharmaceutical industry regarding their handling and reporting of statistical analysis. It may surprise the reader that the systematic review published by the researchers previously did in fact find a statistically significant difference between antidepressants and their placebo counterparts (Jakobsen et al., 2017). However, the researchers argue that this finding is almost irrelevant to the discussion of efficacy, considering that the effect size of the difference is a better representation of clinically significant differences (Jakobsen et al., 2019). As an

application of this, the researchers note that while the acceptable minimum clinical difference in depressive symptoms is marked by a 7-point reduction on the HRDS scale, the systematic review produced by Jacobsen et. al. found only a 1.94-point reduction (Jakobsen et al., 2019). By this understanding, while individual studies may attest to the statistically significant efficacy of individual ADMs, and if the meta-analyses are to be believed this is also questionable, the clinical relevance of ADMs is seriously called into question. Additionally, the use of combination therapy yielded similar insignificance with an SMD of 0.35, far below the accepted clinically significant value of 0.875 (Jakobsen et al., 2019). Overall, if Kirsch and his colleagues are to be believed, ADMs are clinically insignificant in the treatment of MDD and should cease administration so long as the adverse effects outweigh the minimal improvement they offer. As well, the statistical reporting commonly practiced in the industry would also warrant questioning, and the level of interference and bias presented by pharmaceutical companies must be more vigilantly assessed.

Adverse Effects

Particularly disappointing is the continued struggle of the literature to find consistently valid reports amid bias and flawed methodology. This phenomenon is particularly prevalent in studies assessing the side effects and efficacy of ADMs. A systematic literature review of the withdrawal effects of commonly prescribed ADMs demonstrated several conflicts of interest involving pharmaceutical company funding, which in some cases was thought to contribute to failures in experimental design that produced uncharacteristically low incidence rates for withdrawal presentation after cessation of ADM administration (Davies and Read, 2018). Unfortunately, such influence is inevitable but remains within the scope of correction given the diligence of review. Disregarding the bias, the review found that 56% of patients experienced

withdrawal symptoms, with 46% of these withdrawal symptoms being reported as severe. If the numbers are to be believed, then practitioners can expect that approximately 26% of patients who cease ADM administration will experience severe withdrawal symptoms. This demonstrates yet another reason for caution when prescribing ADMs for the treatment of MDD.

The psychological implications of ADMs are not the only adverse effects that warrant monitoring. Research suggests that fluoxetine treatment amplifies the formation of plaque in atherosclerosis (Rami et al., 2018). While for most patients this enhancement represents a relatively insignificant adverse effect, it may be an important consideration for patients already at risk for cardiac events and other circulatory system pathologies.

The discussion of general gastrointestinal (GI) symptoms, which are related to and affected by serotonin regulation and administration, is similarly worthy of consideration. In some instances, ADMs appear to have the double effect of improving both depressive and GI symptoms simultaneously. Venlafaxine, for example, has been demonstrated to significantly improve the quality of life, stress, GI symptom severity, and depressive symptoms of patients suffering from irritable bowel syndrome (IBS) (Adhamian et al., 2020). While it is possible that the depressive symptom relief was influenced by the GI relief of the IBS patients, it nonetheless remains the case that GI symptom relief is significant with venlafaxine. For patients suffering from GI reactions to other ADMs, venlafaxine may be a suitable alternative.

ADM effects on GI symptoms are not always positive, however. Sertraline, desvenlafaxine, and vortioxetine all demonstrated a significant correlation with nausea and vomiting symptoms when compared to a placebo (Kishi et al., 2022). In the case of sertraline, the adverse effects were such that there was a statistically significant correlation between the administration of the drug and the discontinuation rate (Kishi et al., 2022). These would clearly

be serious concerns for the patient, and if the effects were such that they outweighed the small positive effect produced by ADMs one might consider alternative methods of treatment.

While some ADMs may have a positive effect on general somatic symptoms, these seem to be the exception and not the rule. Vilazodone administration results in several treatment-emergent adverse effects (TEAEs), most notably diarrhea (occurring in ~27% of patients), nausea (~23%), and general sexual TEAEs (~13%) in men (Chauhan et al., 2022). While some risk factors are more consequential than others, with suicidality remaining chief among the risk factors for those with MDD, the quality of life of the patient should not be ruled out as a valid concern for the practitioner.

The relationship between suicide rates and ADMs has not gone uninvestigated in the psychiatric literature. A more recent meta-analysis compiling data on this relationship found that among children and adolescents, the ADM administration condition yielded higher suicide risks than the condition without (Li et al., 2022). This would serve as a precaution for practitioners treating patients at risk for completing suicide, perhaps suggesting a withholding of ADMs until suicidality can be reduced. These data must admittedly be viewed modestly considering the data was purely observational. This, while not invalidating the finding, does merit its confirmation using randomized control trials. This presents a unique challenge for studying suicidality, however, as it would suggest subjecting participants to conditions that might reasonably result in death.

It should be noted that this trend is almost reversed among adults. Adherence to ADMs has demonstrated a significant reduction in suicidal ideation, which was especially the case for SSRIs and not so for SNRIs (Henein et al., 2016). This further emphasizes the value that

demographic-specific prescriptions have on patient outcomes, simultaneously elucidating the value that research on these discrepancies has in clinical practice.

Alternative Treatment Methods

Considering the recent research focused on obtaining an updated understanding of antidepressant efficacy, it becomes imperative to evaluate this understanding against the efficacy of other MDD treatment options. In so doing, it is first necessary to outline the current conversation regarding the evaluation of statistical and clinical significance.

Traditionally, determining the effectiveness of a drug can be accomplished by examining the p-value. A p-value < 0.05 identifies a condition that successfully produces a result that significantly differs from the predicted result of random chance. While this may be suitable for simply determining that an effect exists, it is often insufficient evidence that a medication will be effective in clinical practice (Citrome, 2014). Instead, measures of effect size, such as the commonly used Cohen's d, are used to assess the magnitude of the effect of treatments and better serve as the basis for clinical use.

To utilize a relevant example of this distinction, a recent individual patient data meta-analysis (IPDMA) sought to evaluate the efficacy of ADM against that of CBT in the treatment of specific depressive symptoms, using a compilation of scores on the Hamilton Depression Rating Scale (HRDS) from multiple studies (Boschloo et al., 2019). While the authors correctly report that a statistically significant difference in improvement was observed along five categories (those being psychic anxiety, suicidal thoughts, feelings of guilt, and general somatic symptoms) they also note that Cohen's d values for these differences fall within the range of 0.13 - 0.16. Because even a small effect size for Cohen's d is at least 0.2, the difference between ADM and CBT is hardly clinically relevant. In light of this finding, it would seem more

appropriate for practitioners to consider the side effects associated with each treatment option and prioritize maximizing the quality of life for the patient. For most, this will likely mean choosing to administer CBT over ADM, but this choice may be dependent on individual severity of reaction to ADM.

This study, while potentially demonstrating a lack of distinctive efficacy between ADM and CBT for MDD treatment, does serve as further confirmation that ADM does significantly reduce the symptoms of MDD as assessed by the HRDS. Claims that ADMs do not have clinically significant effects on MDD symptoms would seem to risk also asserting that CBT is equally lacking in efficacy.

Further comparisons of therapeutic options and ADMs continue to support the notion that both are statistically viable treatments for MDD, even if the superiority of one over the other continues to be elusive. Metacognitive therapy (MCT), "a novel and promising transdiagnostic psychotherapy intervention based on the Self-Regulatory Executive Function model of conceptualizing emotional disorders" (Sharma et al., 2022, para. 1), is a technique targeted at improving mental health by addressing the patterns of thoughts in a patient rather than the mere thoughts themselves. A recent comparison of citalopram and MCT revealed that while both statistically reduced depressive symptoms, MCT had the additional benefit of improving metacognition and cognitive-emotional regulation (Gholam Reza Kheirabadi et al., 2020). This fits within other reports that negative metacognitions and brooding are significant predictors of depressive symptoms (Pedersen et al., 2022). Both findings suggest that MCT is a promising alternative to ADMs, providing not just relief from depressive symptoms, but the traits necessary to stave off depression relapse.

Complementary alternative medicine (CAM) includes any treatment method or practice intended to improve the symptoms of a disorder that differs significantly from the conventional approach (Liu et al., 2021). A recent meta-analysis has suggested that among patients choosing to engage in CAM, herbal remedies were by far the most frequently used medicines with pray therapy occupying a lower secondary status (Ashraf et al., 2021). Borage and yellow chamomile were found to be the most frequently used herbal remedies.

Borage (*Echium amoenum*) has been suggested to have a more significant effect on depressive symptom reduction than placebo, but the small sample size of the study demonstrating this means more research is required before any concrete consensus regarding their efficacy can be reached (Sayyah et al., 2006). Similar conclusions were reached for yellow chamomile (*Matricaria chamomilla L*). Chamomile was demonstrated to significantly reduce HDRS scores, but the finding is limited by the fact that participants were selected for generalized anxiety disorder with depression being merely comorbid (Amsterdam et al., 2019). Future studies are required to assess with a higher degree of certainty to what extent borage and chamomile reduce depressive symptoms, as well as how these compare to ADMs. Additionally, it is important to note that the somatic nature of herbal remedies presents the potential for adverse drug interactions if the patient is concurrently taking ADMs. As researchers examine the efficacy of herbal remedies, they should also account for the pharmacodynamic interactions of these treatments with ADMs. As with ADM analysis, special care should be taken to determine whether the effects of the medication represent a clinically significant reduction in depressive symptoms rather than a simple statistical difference.

The effects of religious beliefs and religious involvement on depressive symptoms also demonstrate initial potential for clinical relevance. Whether because of the closely inter-related

social components of religiosity or the time needed to solidify certain cognitive aspects of religious faith, it has been demonstrated that at six months after initiation, intrinsic religiousness (desiring communion with God) and non-organized religious activities are both successful in attenuating the negative cognitive impact that stressful life events might otherwise have on patients with depressive episodes or adjustment disorder (Lorenz et al., 2019). Religious involvement may be an ethically ambiguous treatment to introduce in the clinical setting given the sensitive nature of religious beliefs, but if the effect of religious involvement provides clinical significance without introducing adverse effects comparable to those of ADMs, then the results should be allowed to stand on their own merit.

Of course, there are a significant number of studies that suggest religious involvement may not attenuate depressive symptoms, and in some cases, it may appear to worsen them. A longitudinal study found that prayer was correlated with more depressive symptoms when compared with no prayer, but that weekly or more frequent participation in a religious organization might reduce symptoms (Van Herreweghe & Van Lancker, 2019). However, the researchers note that correcting for within-person variability yields a positive correlation between public religious involvement and depressive symptoms and no correlation between symptoms and prayer. This would seem to suggest that at best religious involvement has no effect on depressive symptoms and at worst the symptoms are worsened. Assessing the bi-directionality of the relationship between religion and depressive symptoms, it is clear that while in older adult demographics poor mental health is associated with later religious attendance, there was no relationship between religious attendance and mental health (Kaushal et al., 2021). At first glance, this would seem to suggest that religious involvement altogether is an ineffective treatment option for MDD.

However, certain limitations arise in the evaluation of religious involvement effects. For one, the heterogeneity of beliefs categorically labeled as "religious" presents the possibility that meaningless distinctions are being made in the research. In some articles, religions such as Christianity and Buddhism are assessed together as though their effects on certain variables such as intimate partner violence should be comparable (Kim, 2018), even though these religions are comprised of incredibly different beliefs and practices. Thus, an underlying presupposition regarding the comparability of different religions potentially undermines the findings. Additionally, it is difficult to assess to what extent professing members of a religious organization actually internalize and adhere to the belief systems of the religion. For this reason, an analysis of religious involvement and its effects on certain outcomes ought to control for specific beliefs within each religion in order to address false positives within the religious subgroup and to qualify exactly which beliefs within the larger religious group actually impact mental health, if indeed any do.

Conclusion

In summary, the literature review herein finds no compelling evidence that the serotonergic model of depression adequately accounts for the pathology that undergirds MDD. While some ADMs such as fluoxetine may demonstrate some statistical advantage over placebo, no such advantage is meaningfully reflected in the clinical implementation of these drugs. Accounting for the adverse effects, ADMs provide an ambiguous to negative overall effect on the health of the patient and should therefore be administered with extreme caution or be ruled out entirely. In the case of an adolescent patient at high risk for suicidality, it is recommended that ADMs be viewed as a last resort due to paradoxical effects.

In addition, the physiological basis for depression is found to be more complex than originally conceived, with factors such as environmental stress and metacognitive patterns affecting the outcomes of other treatments as well as the overall depressive symptoms themselves.

The review also finds that dishonest reporting practices and funding biases on the part of the pharmaceutical industry, which are evident in the discrepancy between reported journal article data and those of meta-analyses, are potentially responsible for significant inflation of the perceived efficacy of ADMs. Future studies should focus on addressing this influence and reporting it, while also ensuring that publications that fall prey to this influence are not incorporated into larger reviews.

Finally, the review finds that although ADM efficacy is questionable, the alternative treatment options available either provide little promising clinically significant effects or fail to accumulate enough attention in research to definitively qualify their efficacy. More research is required to determine which, if any, treatments exist that might supersede the effectiveness of ADMs in practice. This research should adhere to the same rigorous standards proposed for that of ADMs, qualifying effectiveness not merely by the statistical advantage over placebo, but also the clinical significance of the effect.

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