Major Depressive Disorder: A Review into Potential Alternative Treatments with Psychostimulants, Lifestyle Modifications, and Current Mainstream Treatments of Depression

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Abstract

Major depressive disorder (also known as MDD, clinical depression, or just "depression") is a mental illness characterized by a prolonged (at least 2 weeks) [1] depressed mood, loss of interest in activities, even ones that the patient found enjoyable, and a generalized feeling of anxiety and, for some, thoughts of suicide. It is, unfortunately, a too common of a mood disorder in the United States and the world, leading to many patients being either undertreated, having no treatment or put on a specific therapy to do little to alleviate the pain. As of now, it can be treated from several clinical approaches: a pharmaceutical approach, where certain antidepressants and other medications may help treat the disorder; a psychotherapeutic approach, where speaking to a therapist or a group of other patients in counseling may give a better understanding as to why the patient is behaving this way; a more unconventional approach, where techniques such as shock therapy have been proven to be quite effective in temporarily abating the negative feelings from this disease; or, a combination of all or some of the above approaches in whatever ensures each patients' needs, depending on the severity of the disorder. This paper will focus mainly on the pharmacological aspects of currently used antidepressants, their efficacy and how other alternatives may be better suited for certain patients during a regimen in treating this disorder. One group of drugs that are of particular interest are amphetamines and methamphetamines in the possible acute treatment of MDD. Although many of these drugs within this specific group of chemicals carry undesirable effects, it may be possible, in specific dosages, to safely treat patients suffering from MDD, especially those categorized in a severe state (i.e., suicidal

ideation, self-harm). The principle of the application of these drugs is to, hopefully, be able to treat patients suffering from acute episodes of MDD quicker than the standard antidepressants can, which generally take at least a month (4 to 6 weeks) before they start working—if they even work at all.

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List of Abbreviations

ADHD: Attention deficit hyperactivity disorder. A brain disorder characterized by a lack of attention or inability to remain attentive during specific times, such as learning. Symptoms mainly include hyperactivity of the patient, with difficulty to focus on certain tasks at hand.

CBT: Cognitive behavioral therapy. A type of psychotherapy which emphasizes changing a patient's way of thinking via modification of their cognitive thinking. The goal is to reduce negative behavioral symptoms associated with mental disorders, such as depression.

CNS: Central nervous system. The brain and spinal cord of the human body, including all specific neurons and synaptic connections that make up the primary nerves of the body.

ECT: Electroconvulsive therapy. A procedure which involves administering an electric stimulus through a patient's brain via electrodes that are placed upon specific areas around the patient's head. This reduces the symptoms of depression; the mechanism of action is unknown.

MDD: Major depressive disorder. A common mood disorder characterized by long-term feelings of melancholy, loss of interest in activities, and negative behavioral patterns in one's thinking, including suicidal thoughts. A disease that primarily targets the brain and spinal cord, affecting the central nervous system as whole.

SNRI: Selective noradrenaline (norepinephrine) reuptake inhibitor. A class of antidepressants that are commonly used in the treatment of depression and its symptoms. Function by inhibiting the reuptake of noradrenaline at the presynapse of a neuron and causing it to build up to fire onto the postsynaptic site.

SSRI: Selective serotonin reuptake inhibitor. A class of antidepressants that is commonly used in the treatment of depression and its symptoms. These drugs function by inhibiting the reuptake of serotonin at the presynapse of a neuron and causing it to build up neurotransmitter levels in the synaptic cleft.

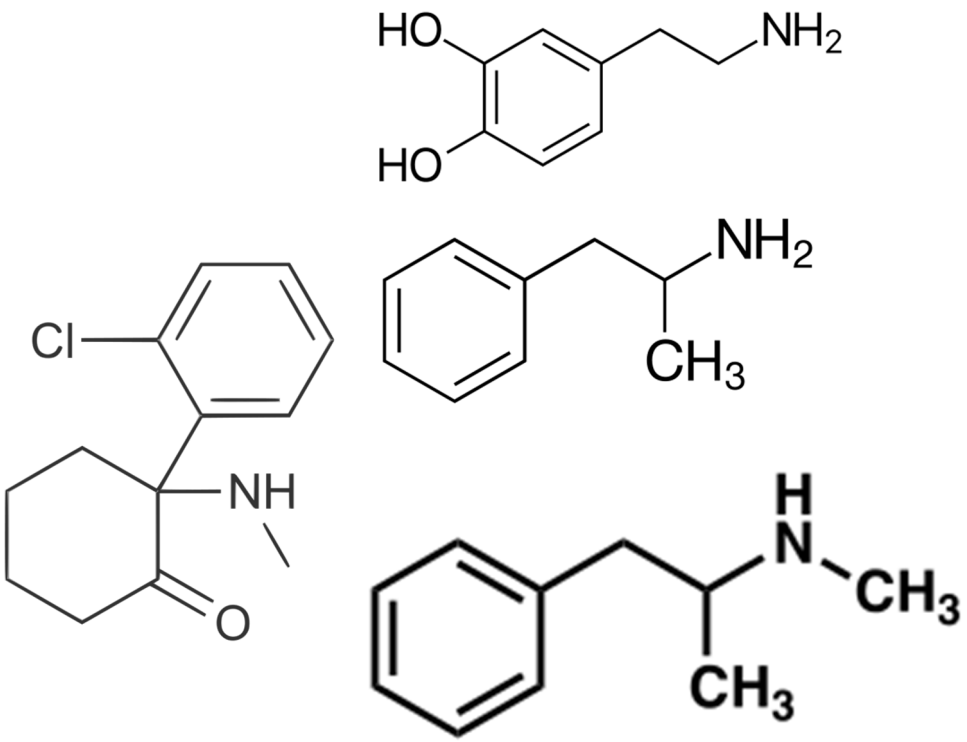

Figure 1: From top to bottom, the Lewis structure of dopamine, amphetamine, ketamine and methamphetamine. The structures are here to show and highlight the similarities the orientation and placement of the atoms, and how this affects the chemistry of the brain [63].

Introduction

Major depressive disorder defined

According to the United States National Institute of Mental Health (NIMH), major depressive disorder is defined as "a common but serious mood disorder… [which] causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating or working" [1]. It is the most common mental disorder in the United States [2], and the most common mood disorder affecting many children, adolescents and adults in the world, with an estimated amount of 350 million people affected, a statement made by the World Health Organization (WHO) [3]. It is a mental disorder that primarily affects the brain and hence the nervous system as whole, leading to the associated negative attributes of this disease. The specific causes of this disease are unknown and are associated with many factors that may cause it to appear over time, directly or indirectly. For example, stress factors such as losing a job or being in financial distress can attribute to feelings of depression, which can eventually lead to the symptoms commonly seen with MDD. Or, in the case of trauma, childhood abuse, for example, can lead to feelings of regret, defeat and blame, all of which can transition and come back to adulthood, manifested as MDD with its symptoms. No two patients are the same, and other factors such as genetics, a history of family depression, diet, other traumatic events, certain drugs and medications, or specific lifestyles for each patient may all cause or lead

up to MDD, regardless of the severity [1]. It should be noted that these are not the only factors that may contribute to the possible causation of depression; as stated before, no two patients are the same, and it is likely there are many more factors that have yet to be

found through clinical practice and scientific research [4]. One major and devastating symptom associated with MDD is suicidality, also known as thoughts of or ideations of suicide. Though most patients do not carry out suicidal intention, it remains a crux in this disease, further contributing to the symptoms and is still a leading cause of death among those with MDD [1]. In any case, treatment of this disorder must be done as efficiently and quickly as possible, especially in younger patients [5], as prolonged episodes of depression can further insinuate suicidal thoughts, rapidly decreasing quality of life of each patient. In other words, the longer the disease remains untreated, the worse it is going to get, and as such, immediate treatment must be made available after a thorough assessment from a clinician.

Available treatments for MDD

The three most common and relatively effective treatments for depression are pharmacotherapy, psychotherapy, and electroconvulsive therapy (ECT; also known as shock treatment or shock therapy). The most common and convenient treatment of these three is through pharmacotherapy, with the most prescribed medications being antidepressants. There are several classes of antidepressants, many of which have varying efficacy in patients; some patients respond well, some respond partially, while others do not respond at all. One of the most prescribed of these classes are the selective serotonin reuptake inhibitors (SSRIs) [8]. The current theory of depression mainly deals

with the dysfunction of the brain's neurotransmitters and metabolic systems, especially those involved in stress response, and postulates that these class of drugs act upon those systems and "correct" it [6]. This theory revolves around evidence that MDD may be

caused from a depletion and deficiency of mainly noradrenaline (NA; also known as norepinephrine) and 5-hydroxytriptamine (5-HT; the chemical name for serotonin) throughout the body, mainly in the brain (i.e. central nervous system) [7]. Although other monoamines such as dopamine may be involved in depression [7], for years NA and 5-HT were and still are of chief interest in the development of medicine that may treat depression. As the name implies, SSRIs function by inhibiting the reuptake of serotonin, a neurochemical that has been found to be highly involved in mood control. Although the exact mechanism of action is unknown [9], the inhibition of reuptake is said to occur at the presynaptic sight of a neuron, increasing the level of serotonin in the synaptic cleft and allowing the increased amount to bind to receptors on the postsynaptic sight. The principle of this drug is based on the previously mentioned theory, whereas reuptake inhibition—via what is described as a partial agonistic and antagonistic pattern—can compensate for the lost amount of serotonin (or noradrenaline and dopamine) that is commonly found in patients with MDD. In doing so, the hope is to achieve a "chemical balance" within the brain and thus throughout the entire nervous system, alleviating the negative mood and symptoms associated with depression **(see figure 1)**.

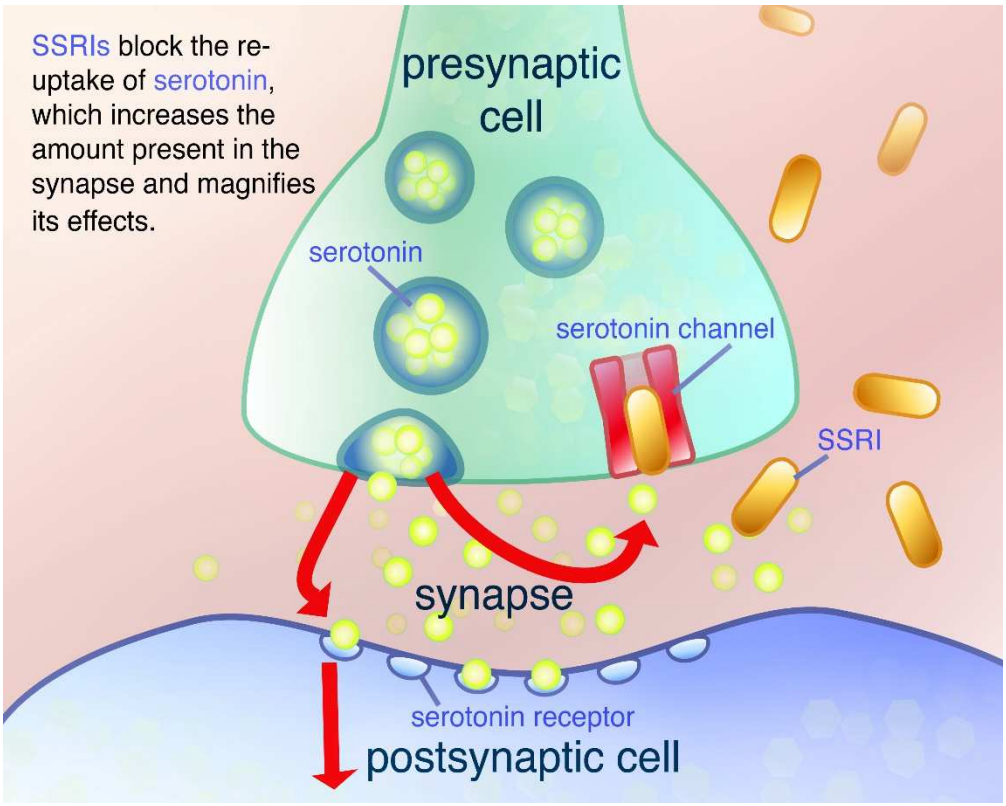

Figure 2: A simple illustration of how SSRIs function [61]. The presynapse of the neuron is where the supposed mechanism of action of reuptake inhibition occurs via blocking the target (in this case, the serotonin plasma membrane transporter). This leads to increase of serotonin in the extracellular space, which in turn activates receptors on the postsynaptic side. Thus, there is a significant change in the brain's chemistry, compensating for the lost amount of serotonin normally found in depression and providing the antidepressant effects found with these drugs. Other classes of antidepressants such as SNRIs work similarly but with different targets. Source: http://web.stanford.edu/group/hopes/cgi-bin/hopes_test/ssris/

Other classes of antidepressants such as selective noradrenaline reuptake inhibitors (SNRIs) work similarly, except that these drugs mainly target the noradrenaline transporter and not the serotonin transporter, with the intention to increase extracellular noradrenaline levels [10].

The second treatment for MDD that is used, especially in conjunction with pharmacotherapy, is psychotherapy, commonly called "talk therapy" [1]. The principle of this treatment is for patients to speak face-to-face with a therapist, usually a licensed

and certified clinical psychologist. In doing so, the patient hopefully learns a better understanding of her/his condition and what possible stressors may be triggering the symptoms and prolonging their episodes. Although psychotherapy has been effective with most patients, those suffering from MDD and seeking this treatment alone may not get any better with time, especially in pediatric patients (children and adolescents) [11]. This is not to say that different types of psychotherapy such as cognitive behavioral therapy (CBT) and psychodynamic therapy are wholly ineffective. In the case of CBT, its effectiveness is more geared towards patients seeking elimination of their symptoms by modifying their behavioral patterns [12], rather than the classical way of therapy, which is to find the underlying, insidious reason in a patient's psyche that is driving the depression to get worse [13]. In contrast, psychodynamic therapy deals with the more "traditional sense" of therapy, helping the patients understand why they are behaving in a certain way during their depressive episodes from a personal/emotional standpoint rather than a strictly scientific standpoint [14]. In the case of these two types of therapy, the former specializes in a more "in-your-face" kind of treatment when dealing with MDD in a clinical setting, while the latter takes a calmer and steady approach to analyze a patient's psyche and to find out how they can cope better with this disease through basic approaches in clinical psychology. These are not the only two types of psychotherapy that are practiced [15], and many patients may benefit more from one type of therapy than the other. In any case, a general consensus that psychotherapy alone is not as effective as having a combination of other treatments to influence the patient's behavior for the better is agreed upon by many experts in the field of psychiatry,

psychology and pharmacology [16]. There is considerable complexity in treating patients from a strictly psychotherapeutic approach. Criticism and controversy revolving certain types of psychotherapy, including psychodynamics and CBT, are abundant, with many authors in peer-reviewed articles [17] [18] [19] often having conflicting views on how patients should be treated using this kind of approach. Such articles approach psychotherapy through meta-analytical studies, reviewing past journal articles and theories and evidence gathered from both clinical practice and psychological research, which, with an emphasis on basic science, mainly includes neurological and biochemical studies. With that being said, psychotherapeutics should not be disregarded and it is primarily the patient's personal experience that will influence decisions on whether or not to rely on this kind of treatment. If anything should be said about such approaches, it is that patients must be clinically evaluated (i.e. by a psychiatrist) before deciding if psychotherapy is right for them.

The third and final treatment of MDD to be considered is ECT, or shock therapy, as it is commonly called. The common name of this technique is misleading; the electrodes that are placed on the head of the patient do not actually "shock" them, but rather administer a small electric stimulus, similar to a static shock [20]. This type of therapy has been approved to be used for patients with MDD, seizures, catatonia and manic disorders [21]. In terms of MDD, ECT seems to be the most effective out of all treatments alone. For example, one article stated that half the patients in a study with unipolar depression (i.e. MDD alone) receiving ECT treatment went into remission with a higher rate of success compared to antidepressant or psychotherapy treatment alone [22].

Another meta-analytic article stated that ECT had "significant superiority" compared to aforementioned treatments, including treatments with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) [23]. Although not considered the "first-line" treatment for MDD, ECT does have promising results for a majority of patients that respond to it. As promising as it seems, interestingly, the underlying mechanism of action is still unknown. One theory states that ECT has a direct neurotrophic (neuro-enhancing) effect primarily on the frontal lobe, temporal lobe and hippocampus of the brain [24], and this is mostly based on neuroimaging studies that have found better blood flow from the brain post-ECT. Again, the exact mechanism of action is unknown, although some articles refer to this possible neurotrophic effect as "jumpstarting the brain", a nod to the electric stimuli used by this approach [24]. As for any side effects, the main concern for ECT is memory loss, specifically retrograde amnesia, especially for patients who are undergoing treatment for the first time [25]. A large concern using this treatment is for patients suffering from epilepsy. As postulated, ECT causes an enhanced neurotrophic effect to the brain, which may accelerate the chance of a seizure to happen, either during or after an ECT session [26]. Although quite effective in the treatment of MDD, the treatment is, like many of these approaches, temporary, with most patients relapsing back to negative mood and symptoms after 12 months post-ECT [27]. A more obvious problem is the inconvenience of ECTs, where patients must go to a trusted and certified operator of such devices, in order to maintain their positive mood and not have any ideations resurface, which can be much worse than the original symptoms unless the

patient is already under another type of therapy, especially pharmacotherapy with antidepressants [28].

These three treatments are the mainstay of current approaches in patients with MDD, but that is not to say there are no other ways of dealing with depression. Lifestyle changes have a strong impact on patients who are coping with MDD. Physical exercise has been shown to be apt in managing depression, especially in patients suffering from mild to moderate episodes [29]. Even less-strenuous activities such as walking have been shown to have an antidepressant effect on a patient with MDD, including severe cases [30]. Other approaches of treating MDD have been linked to a patient's diet, with some articles delineating specific nutrients that are connected to the brain's chemistry and how patients can take preventive measures by taking in such nutrients. One article stated that consuming large amounts of fish, which contains an abundant amount of omega-3 fatty acids, has an indirect effect on modifying the brain's chemistry that may prevent MDD from happening in the first place [31]. Though such articles talk about MDD from a preventive standpoint, the authors did state that more research was needed to conclude that nutrition may have an indirect or direct effect on prevention of depression. Other lifestyle changes such as cessation of smoking have been shown to have a positive effect on patients suffering from MDD, supporting the theory that nicotinic receptors throughout the brain and nervous system play a major role in patients with depression and who have been long-term smokers [32].

These are not the only ways for treatment and preventive measures in MDD, and there are likely to be many more as research continues in this field of interest. The

current paper focuses primarily on pharmacological strategies for treating MDD. Specifically, I will discuss the therapeutic experience with using different classes of drugs. From a pharmacological standpoint, it is time to look at another approach for treating patients with MDD, and one that can hopefully provide acute benefits to MDD patients with little adverse effects.

Amphetamine and Methamphetamine

Mechanism of action

Amphetamine and methamphetamine are both very potent central nervous system (CNS) stimulants, with the latter being much more powerful than the former. Although notorious for their illicit (recreational) uses, both chemicals do have legitimate medical usage in their drug forms. The most common and popular usage of amphetamine and methamphetamine is in the treatment of attention deficit hyperactivity disorder (ADHD) [33]. They are also used, though in smaller amounts today, in the treatment of obesity and narcolepsy; amphetamines are the only chemicals approved for being used in narcolepsy. Both are stimulants of the CNS and as such, both primarily act upon the mesolimbic (reward) pathway of the brain [34]. The drugs increase extracellular levels of monoamines (i.e. serotonin, dopamine, noradrenaline), partly through the same reuptake inhibition mechanism by which conventional antidepressants function, and additional release of monoamine neurotransmitters and exposure of postsynaptic targets to them [35]. In turn, this effect causes the psychological and physical symptoms associated with amphetamine and methamphetamine use, such as euphoria, elevated heart rate, increased sex drive (libido), dry mouth (and sometimes salivating mouth, due to the dopaminergic

effects), muscle spasms and twitches, increased perspiration (sweating), and/or increased body temperature (hyperthermia) [36]. These effects are mainly due to the dopaminergic action of both chemicals, which is primarily the reason why most patients use these drugs for their recreational uses, as it gives a "high" and euphoric feeling directed from the reward pathway of the brain **(see figure 2)**.

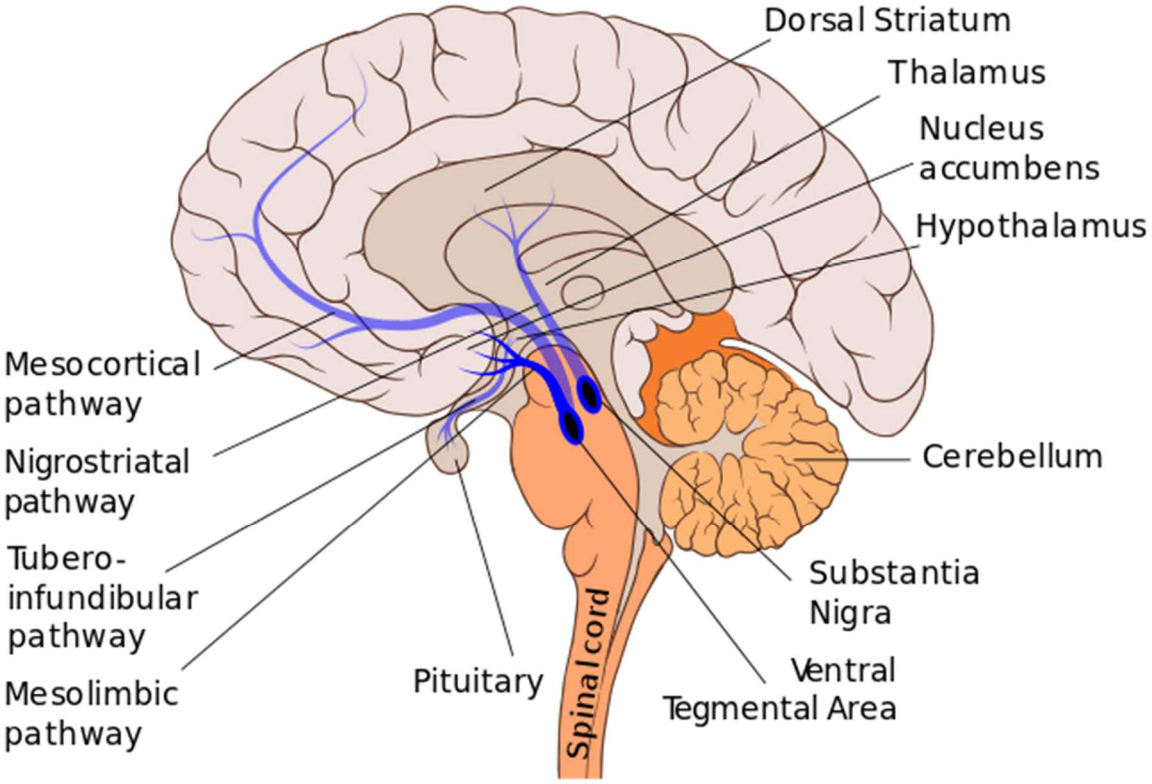

Figure 3: A schematic overlay of the mesolimbic (reward) pathway of the human brain [62]. The highlighted blue areas at the Ventral Tegmental Area (VTA) and Substantia Nigra (SN) show the largest origin of dopamine synthesis and shuttling throughout the cerebrum. Amphetamines and methamphetamines act as major dopaminergic agonists for these pathways, especially at these sites, causing the acute antidepressant effects.

With all that being said, the drugs have the potential to provide an alternative way of treating depression when used as prescription drugs. As the reuptake inhibition

process for amphetamine and methamphetamine is similar yet more aggressive than that of antidepressants, it is of interest to look into how exactly these drugs could deliver an acute treatment in patients with MDD.

Amphetamine usage as an antidepressant

Off-label use of drugs is prescribing a medication to a patient with a different indication than what the "on-label" indications of the drug state. This means that, from previous research and studies, certain drugs have been wholly or somewhat effective in treating specific ailments which they were originally never intended for. In this case, amphetamines are examined for their off-label use in treating patients with MDD, and to see how their efficacy stands in relation to current on-the-market antidepressants, which can take weeks before any change is seen—if it is seen at all.

As abundant and available antidepressants such as SSRIs are, there are always patients, unfortunately, who do not respond well to these drugs. In doing so, these patients are said to be "resistant" to such drugs, with MDD being reclassified as treatment-resistant depression, which one article defines as follows: "…unipolar major depression [MDD] is considered resistant or refractory when at least two trials with antidepressants from different pharmacologic classes (adequate in dose, duration, and compliance) fail to produce a significant clinical improvement" [37]. Most patients diagnosed with MDD are first given a loading (starting) dose of an antidepressant, usually an SSRI (i.e. fluoxetine, also known as Prozac), with the dose increasing steadily after the first week. If there is no response from the patient, the dosage is increased for the next month until there is either a positive response, or a negative one, in which case

the prescription is halted and the patient is given another antidepressant or other options to alleviate the symptoms [38]. The main problem with antidepressants is that it can take a while for a positive response to occur, and even when there is a response, there is a chance for the depression to relapse into an even worse state than before the treatment [1]. This may due to the slow reuptake inhibition effect that antidepressants elicit on the brain, with the CNS slowly adapting to the enhanced amount of serotonin, dopamine and/or noradrenaline to which neurons are exposed. Serotonin deficiency is primarily of chief concern in patients with MDD, and it was thought that elevation of serotonin via a pill or tablet could counteract this deficiency easily, thus effectively treating patients with depression. Unfortunately, the human brain has a potential blocking mechanism for this seemingly simple treatment: the blood-brain barrier. This structure prevents certain chemicals from entering the brain, including serotonin. Only the serotonin precursor tryptophan and its metabolite 5-hydroxytryptophan (5-HTP), from which serotonin is synthesized, cross the blood–brain barrier.. To circumvent such limitations, it was later established via tricyclic antidepressants that reuptake inhibition could indirectly affect the nervous system by interfering with how neurons clear serotonin from the synapse. This enabled the development of conventional antidepressants like SSRIs and SNRIs [5].

Amphetamines behave similarly to antidepressants partly through reuptake inhibition effects on dopamine [39]. Common formulations of amphetamine such as Adderall are the most prescribed in the United States [39], with this drug containing a mixture of its left-handed and right-handed enantiomers, with a 1:3 ratio of levoamphetamine and dextroamphetamine salts, respectively [40]. For the purpose of

treating MDD, Adderall and other amphetamine-based formulations were, once upon a time, in use. Unfortunately, like many recreational drugs, amphetamine-based products carry a high potential for abuse due to its effects on dopamine release in the brain. Despite this, one article stated that usage of psychostimulants in the form of Adderall or methylphenidate increased the efficacy in treating patients with refractory MDD, when they did not respond well to SSRIs or SNRIs [41]. Although the authors did not go into detail if psychostimulants could be used at the onset of MDD (they stated it was an uncontrolled trial), the results reflected a positive outcome for most patients, though a temporary one due to the addiction factor. It is also stated in other articles and the one cited above that patients undergoing off-label use of amphetamines for the treatment of MDD are more likely to benefit from it if they are lacking addictive personality traits or heart problems [41] [42]. In terms of addictive personality traits, it is extremely difficult to assert whether or not a patient is "prone" to an addictive substance compared to another patient. It is a hypothesis that stems from both older [43] and recent sources [44] that try to give a psychological, physical and societal explanation as to why different patients are more or less likely to have an addiction-prone personality. Adderall and its amphetamine-based products do carry addictive properties, but in the treatment of a patient who is suffering from MDD and is already in a melancholic state, the overall outcome of drug-induced dopaminergic and serotonergic effects may benefit the patient's treatment [41] [42]. This ambivalence makes treatment with such drugs quite complex; notwithstanding that these compounds have the potential to provide seemingly easier, alternative MDD therapies than the conventional antidepressants. Indeed, it is a

challenge to look into more acute pharmaceutical treatments for patients suffering from MDD, considering that the mainstay of conventional treatment options are antidepressants that can take a while to work. Previous work cited has stated that the efficacy of amphetamines such as Adderall for off-label use in patients with MDD is high and enables a positive outcome, but this is strictly in terms of treating the depression while ignoring other factors such as addiction and other adverse effects associated with psychostimulants such as possible withdrawal symptoms, irritability and aggressive behavior.

One other popular drug of this class is methylphenidate, with the brand name of Ritalin, or its alternative formulation, Concerta. Ritalin and Concerta have the same indications as Adderall in the treatment of ADHD and narcolepsy, but are considered to be "weaker" (i.e. lower binding affinity to the neurotransmitter transporter) than Adderall [45]. Investigators of one article [45] were particularly interested in the psychostimulant effects of Ritalin on patients suffering from depression and bipolar disorder. Amphetamines have been shown to modify the brain's structure and chemistry in the treatment of ADHD [46]; this modification is hypothesized to be the same mechanism in the treatment of MDD, although the authors did note that it is important to recognize depression as a mental illness firstly and not necessarily as a disease that can simply be treated through the same drugs that can seemingly change behavior in patients with ADHD. They further concluded that these data should not be compared to the drugs' primary indication without further research [45]. It should be noted that amphetamines cause enhanced focus and concentration in their users [47], leading most patients to have,

as described by some, more self-confidence while under the influence of these formulations [40]. It is perhaps for this reason that amphetamines can be used in the treatment of acute MDD, with the hope that the "alertness" induced by these drugs can abate the suicidality and depressive episodes, potentially shifting focus on seeking improved mental health and finding other ways to maintain a healthy mind, including the option to use conventional antidepressants for long-term treatment.

Methamphetamine usage as an antidepressant

Unfortunately, data for methamphetamines as potential antidepressants are far and few between. The only related drug approved by the United States Food and Drug Administration (FDA) that comes close to methamphetamine and amphetamine regarding its chemistry and effects is bupropion, commonly known as Wellbutrin and Zyban. The drug is approved as an antidepressant but unlike most conventional antidepressants, it acts as both a dopamine and noradrenaline reuptake inhibitor (NDRI) [48]. This makes it more akin to the tricyclic antidepressants, with the exception that it has little to no binding affinity to serotonin receptors at the synapse. Further studies have shown that bupropion has the potential to release dopamine and noradrenaline actively from the synaptic sites in addition to the chemical's reuptake inhibition activity [49], though this release activity in patients with MDD seems to be related to the severity of each case [49]. This makes bupropion behave more like a psychostimulant from a mechanistic viewpoint. Patients suffering from severe forms of MDD may benefit greatly from taking bupropion given its "balanced" response that is counteracted by the reuptake inhibition. However, bupropion does not have the same addictive properties that are associated with

amphetamines and true methamphetamines, on account of their immediate release of monoamines throughout the CNS resulting in instant euphoric feeling. To consider this drug as an acute treatment for MDD is, therefore, very unlikely [50]. The silver lining is that bupropion cannot be abused in the same recreational sense that applies to amphetamines and methamphetamines, yet it still cannot be considered for patients with severe or refractory cases of depression.

Ketamine and its antidepressant activities

Although neither an amphetamine or methamphetamine, ketamine is one drug that is becoming of particular interest in the treatment of MDD and bipolar disorder and, as one article states, could be used in an emergency for patients suffering from immediate thoughts of suicide (i.e. acting out ideations) [51]. Originally, ketamine was and is still used as an anesthetic in hospitals (specifically emergency rooms) and veterinary hospitals to alleviate pain, cause sedation and induce memory loss [52]. It has also been used in the management of patients suffering from acute pain, especially those induced by debilitating diseases such as rheumatoid arthritis and specific types of cancer, usually ones involving bone tissue [53]. This makes it an ideal chemical for research into the treatment of MDD, and because of its fast-acting time (average 5 minutes until effect onset) and low to moderate potential for abuse [54], it may be better suited for patients suffering from severe cases of MDD and suicidal crises. In terms of its antidepressant effects, ketamine has been shown to have a generally positive effect on patients with MDD within 2 hours or less, via intravenous (IV) injection, with the symptoms of depression abated for about 1 to 2 weeks, half the time needed for conventional

antidepressants to start working (which takes 4 to 6 weeks on average) [55]. One study stated that the biggest challenges in introducing ketamine as a new class of antidepressant were its legal status as a controlled substance and that the positive effects seem to wear off over time in using the drug [55]. In terms of legality, ketamine is classified as a schedule III drug in the United States [56]. Ketamine fits the following definitions: "the drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II [less abusive drugs]; the drug or other substance has a currently accepted medical use in treatment in the United States; abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence" [57]. Yet ketamine still is a strictly regulated substance by federal law. It is especially controlled in hospitals and pharmacies where facilities licensed to carry ketamine are subject to inspections by the United States Drug Enforcement Agency (DEA) in any suspected or confirmed illicit use or trafficking of the drug [57]. Legality aside, its chemistry on the brain, including patients with MDD, is still unknown. One theory is that ketamine, in depressed patients, works directly on glutamatergic NMDA and AMPA brain receptors, acting as an antagonist and inducing mood-changing effects found in patients under the influence of the drug [55]. Unfortunately, evidence for such observations is limited, with the main problem being ethical constraints in the use of ketamine in controlled trials and the low number of subjects willing to participate [55] [58]. Pharmacological augmentation of ketamine has been looked into, but so far no investigators (to this writer's knowledge) have found anything of significance to circumvent its addictive properties or to enhance its potential neural effects [55] [58].

The only apparent way of increasing the effect, as it stands, is to increase dosage, but doing so will lead to anesthesia [52] [59]; higher dosage is dangerous and can lead to seizures and coma [59]. Finally, a more practical problem with ketamine is that its current form in the treatment of MDD is through IV injection, a procedure which can only be (legally) performed by a trained and licensed clinician [59]. In the future, it may be beneficial and convenient for patients to receive ketamine in the form of a tablet or pill but such formulations are not available to date.

Discussion

Major depressive disorder is a debilitating disease that can and should be considered as significant as any other physical ailment. The complexity and difficulty of tackling such mental illness stems from the diagnosis, treatments and social stigma associated with depression [60]. Examining the three most common approaches in patients with depression and looking into other possible approaches in the form of psychostimulants, it is indeed an ongoing challenge for patients, clinicians and investigators. MDD is not caused by a single factor in a patient's psyche, but underlying factors are multiple and complex. Amphetamines, methamphetamines and derivatives like ketamine have been shown to be promising in their pharmacological activity, but these drugs do not cure depression, they simply treat it when used as therapeutics. Psychostimulants have a potential to treat patients with acute MDD or breaking through patients who are suffering from resistant or refractory-type depression, but research is still too vague and preliminary to even consider these options as a mainstream treatment.

Safety is and should always be the top priority for the development of any medication, even if it has been previously approved for another indication. From the articles and investigators' expert opinions that are summarized in this report, there is still much work to be done before any consideration of longer term off-label use of these drugs for the treatment of MDD can be made—and, maybe one day, on-label usage for a new indication in the treatment of depression and other mood disorders could be approved. Off-label usage, especially for psychostimulants, is something that is strictly between patient and doctor, and from an ethical standpoint it should remain this way before considering the benefits for scientific research. A combination of treatments should always be considered in tackling and coping with depression, as no one treatment alone is very effective. If anything is to be taken from this analysis, it should be that no matter what the drug is or how its antidepressant efficacy stands to be, patients with MDD should be encouraged to modify and change their lifestyle. This is easier said than done, of course, and it is up to the patient's and clinician's judgement and comfort whether they should feel ready to make this change for the better. The current theories on the biology of depression point to a depletion and/or downregulation of important monoamine neurotransmitters of the CNS. If this is indeed how the pharmaceutical route of treating depression should go, then it is a small wonder that there has been limited interest in considering psychostimulants such as ketamine and amphetamines for the treatment of MDD. The severity of disease in each patient should always be taken into consideration on a case-by-case basis, to evaluate how antidepressants and psychostimulants may affect each patient [5]. Factors to be considered include gender, diet, age, genetics, lifestyle and

other possible mental or mood disorders that may be present as co-morbidities [1]. MDD is a painful and exhausting disease, one that claims the lives of many patients with suicidal intentions and weighing down on one's mental fortitude. It is my hope that society recognizes MDD, and mental illness in general, as something to be taken seriously and not to be frowned upon or scoffed at. It is a medical problem, and like any medical problem it requires medical attention and assistance. It is my hope to see more investigations into pharmaceutical agents that may be used in the treatment of depression, regardless of whether they are based on conventional or innovative hypotheses or involve psychostimulants. It is also my hope that patients are to be more encouraged to seek treatment and not hide in the shadows where their symptoms can worsen.

Materials and methods

A majority of the sources were found via PubMed and the United States National Center for Biotechnology (NCBI). With a few exceptions, most citations were taken from the 21st century articles. Keywords for searching were, "major depressive disorder", "amphetamines", "methamphetamines", "ketamine", "mental illness", "MDD treatments", and "psychostimulants", all of which were related to researching MDD and its associated peer-reviewed articles and other sources.

Conflict of interest

This author declares no conflicts of interest.

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