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So, Antidepressant Drugs have Serious Adverse Effects, but what are the Alternatives?

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Abstract

Background: Pharmacological treatments of depression underwent several refinements; relatively more effective ones exist nowadays. Nonetheless, dissatisfaction with depression treatments is widespread because of the poor response and resistance that is encountered by about 33% of patients. Further, concerns are raised regarding the disabling negative adverse effects of these medications (carcinogenic, cardiotoxic, diabetogenic, etc.). A search for safer and more effective treatments is highly encouraged.

Methods: This article reviews the most relevant studies that describe adverse effects of antidepressant drugs; it also briefly explores the literature for recent reports on alternative avenues for the treatment of depression. When possible, the mechanisms underlying the addressed adverse effects and alternative treatments were detailed.

Results: All antidepressants can cause adverse effects, but SSRIs are reported to have less adverse effects in relation to TCAs and MAOIs. Furthermore, antidepressants' contribution to oxidative stress, inflammation, and cytotoxicity increase the risk of obesity, cancer, diabetes, and cardiovascular diseases in some patients. Available natural alternatives are limited and understudied to some extent. However, Omega-3 fatty acids, herbal plants, flavonoids, bee honey, probiotics, and dietary modifications seem promising approaches that can be used alone, combined with each other, or even combined with SSRIs to enhance their therapeutic effect and overcome the drug-related adverse effects.

Highlight

i. The use of antidepressant drugs has increased recently.

ii. Drug resistance prevails in around one third of the depressed patients.

iii. Neurodegeneration and cognitive dysfunction are common among depressed patients despite of receiving treatment.

iv. The adverse effects of antidepressant drugs range from minor symptoms that cause discomfort e.g., dryness of mouth to serious physical problems such as increased blood pressure and severe bleeding.

v. Antidepressant drugs contribute to colontoxicity, which reduces the production of neurotransmitters and increases microbiota related neurotoxicity.

vi. Tricyclic antidepressants and monoamine oxidase inhibitors contribute to oxidative stress and inflammation and in turn worsen the prognosis of depression and contribute to physical health problems.

Promising alternatives to antidepressants include omega-3 fatty acids, herbal plants, flavonoids, bee honey, probiotics, and dietary modifications.

Keywords: Antidepressants, Depression, Drug Resistance, Metabolic Disorders, Herbal Plants, Flavonoids, Bee Honey, Omega-3 Fatty Acids, Probiotics, Dietary Modification

Abbreviations: ECG: Electrocardiograph; ES: Effect size; TCAs: Tricyclic Antidepressants ; SSRIs: Selective Serotonin Reuptake Inhibitors; MAOIs: Mono Amino Oxidase Inhibitors; GIT: Gastrointestinal Tract; ROS: Reactive Oxygen Species; PUFAs: Polyunsaturated fatty acids; IRR: Incidence Risk Ratio; RR: Relative Risk.

Introduction

Depression is a serious and recurrent disorder, which is characterized by heterogeneous symptoms of psychopathological sadness, inability to experience pleasure, insomnia or hypersomnia, psychomotor agitation or retardation,

fatigue, poor concentration; feelings of hopelessness, worthlessness or guilt, and frequent suicidal ideation [1]. It results from the interaction of several pathological pathways that include genetic tendencies, intrauterine environmental factors, neurotransmitter disturbances, chronic inflammation, oxidative and nitrosative stress, gut-brain axis interactions, and environmental factors such as stress and diet [2,3].

An Overview of Antidepressants

Antidepressants are considered the first line of treating depression [4]. They are also used to treat anxiety disorders (e.g., obsessive compulsive disorder) and neuropathic pain; they are used to prevent migraine[5]. Antidepressants are drugs that increase extracellular availability of monoamines [6]. They have been classified into several categories based on the patterns of neurotransmission regulation they induce. Monoamine oxidase inhibitors (MAOIs) are drugs that are less frequently used; they prevent the reuptake of biogenic amines in a nonselective fashion [7]. Tricyclic antidepressants (TCAs) are nonselective mixed serotonin and norepinephrine reuptake inhibitors that have distinct chemical structures known as tertiary amines (e.g., amitriptyline), which have greater serotonergic effect and secondary amines (e.g., nortriptyline), which have more noradrenergic effect [5]. The category of the second-generation antidepressant drugs involves drugs that selectively target one or two biogenic amines: selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) (e.g., venlafaxine), and the noradrenaline and dopamine reuptake inhibitors (NDRI) (e.g., bupropion).

The Newer Atypical Antidepressants (NAAs) (e.g., vilazodone) target the monoamine neurotransmitter systems similar to the other previously established antidepressants; in addition, they are thought to have a multimodal mechanism of action, which lowers the risk of sexual dysfunction that usually occur with MAOIs, TCAs, SSRIs, and SNRIs [6,8,9]. Based on the fact that antidepressants increase the levels of biogenic amines within hours from acute administration, and that the therapeutic effects occur after 2-4 weeks of lowers treatment, it has been hypothesized that the therapeutic action of antidepressants is mediated by intracellular signal transduction pathways. However, this hypothesis did not result in a compelling model for the action of these drug [10].

Problem Statement

The basic principle of guidelines of pharmacological treatment of depression focuses on helping patients attain remission [11]. However, it is not confirmed that the relatively trivial effect of these drugs (compared with placebo reported by clinical trials) are of clinical importance [4]. In addition, more than half the patients drop-out of treatment mainly because of adverse effects of antidepressants [12]. These drugs function mainly by targeting disturbances of neurotransmitters [6]. This solo mechanism of action leaves other depressive pathologies unaddressed. Hence, a considerable percentage of patients who receive antidepressants suffer persistence of depressive symptoms, deterioration of cognitive functions, and increased suicidality [7,13,14]. A current meta-analysis reported non-significant effect of antidepressant dose increase compared with antidepressant continuation in antidepressant resistant patients; the effect size (ES) was close to zero (ES = 0.053, 95% CI, -0.143 to 0.248) [15]. Accordingly, poor overall functioning and low quality of life is wide spread among victims of depression despite of receiving treatment. [16,17].

Theoretical Framework and Aim

It seems that the literature on the efficacy and adverse effects of antidepressants is dull. A widely cited systematic review indicates selective reporting of clinical trials of antidepressant drugs that favor positive results [18]. Another recent review reports that the majority of meta-analyses that assessed the adverse effects of antidepressants were funded by manufacturers of antidepressants or conducted by employees in these companies (N=147 study), and these studies were less likely to report adverse effects of antidepressants compared with studies conducted by independent research entities (N = 58 study) [19]. Therefore, masking adverse consequences of these drugs would in turn negatively affect patients and the health care system as a whole.

The current review aims to uncover the most important adverse consequences of antidepressant drugs: carcinogenic effect, obesity, diabetogenic effect, and cardiotoxic effect. Whenever possible mechanisms leading to such adverse effects would be illustrated. Another purpose of this review is to explore the literature for safer evidence-based alternatives—this review focused on interventions for which we could find review studies that reported positive effects such as omega-3, herbal plants, diet, and other alternative treatments for depression that involve oral intake, which is easier to take part in than long-term active treatments such as CBT, yoga, exercise, or other sophisticated procedures such as deep and synchronized transcranial magnetic stimulation. To achieve the aim of this paper a literature search of PubMed and Google Scholar was conducted using terms directly related with the targeted outcomes (adverse effects of antidepressants and alternative antidepressant treatments) to obtain the relevant research articles. A variety of studies were consulted: RCTs, systematic reviews, meta-analyses, observational studies, in addition to in vitro and animal studies.

Limited Efficacy of Antidepressants

Antidepressants have been prescribed to treat depression for several decades; their prescription rate has even increased in the last few years [19]. Yet, the burden of depressive disorders is increasing, which sets the efficacy of these drugs questionable [20]. A former meta-analysis reported no significant differences for remission and premature treatment discontinuation between antidepressants and placebo in long-term (treatment duration 6–8 months) parallel-arm efficacy trials [21]. A recent cohort study that involved repeated assessment of symptoms in

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a representative community sample of 4,547 patients over 30 years indicated that antidepressant use is associated with poorer long-term outcomes of depression relative to non-use [20].

Recent evidences indicate that antidepressant drugs may contribute to the deterioration of the prognosis of depression. The mechanism of action of these drugs negatively interferes with other several pathological pathways of depression. The effect starts locally from their intake sites in the gastrointestinal tract (GIT), which can affect both the neurotransmitters pathway and the gut-brain axis. In addition, their systemic effects involve activation of oxidative stress and inflammation, which enhance neurotoxicity (Figure 1).

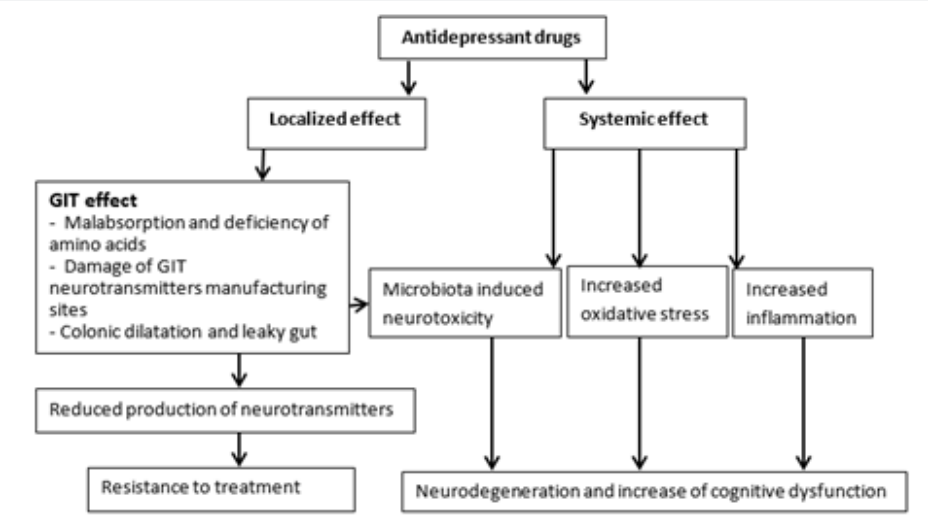

Figure 1: Effect of antidepressant drugs on the prognosis of depression.

Localized Effect on The GIT: Activation of The Gut-Brain Pathway

Some antidepressants such as TCAs have been reported to exert cytotoxic effects on the GIT by antagonizing prokinetic neurotransmitters, stimulating antikinetic neurotransmitters, relaxing smooth muscle, promoting dysmotility, and injuring enteric neurons. Colonic pseudo-obstruction is a form of antidepressants induced colonotoxicity, which is characterized by diffuse dilatation of the intestinal loops containing multiple air-fluid levels. It manifests with symptoms of constipation, abdominal pain, distention, etc. If untreated it progresses into necrotizing enterocolitis and colonic ischemia [22] . Colonotoxicity leads to further exacerbation of depression in a number of ways. On one hand, mal-absorption takes place as a consequence of drugs-induced GIT toxicity, which results in deficiency of the nutritional ingredients (amino acid precursors e.g., tryptophan and tyrosin) necessary for the formation of all neurotransmitters. Further, it is reported that 95% of serotonin is produced in the endocrine cells of the GIT; inflammation induced destruction of the GIT signals serious deficiencies in the body's serotonin formation infrastructures. It goes without saying that serotonin is the main neurotransmitter responsible for the regulation of mood [23]. In addition, drugs-induced GIT inflammation increases the possibility of leaky gut. A recent systematic review indicates that antidepressants have an antimicrobial activity, which alters microbiota composition and induces gut permeability [24]. Hence, the normally existing microflora get to the circulation, release their toxins (e.g., lipopolysaccharides produced by gram-negative bacteria). These processes, in turn, increment oxidative stress and inflammation, and causes serious neurotoxic effects [25].

Systemic Effect: Oxidative Stress, Inflammation, and Immune Modulation

The therapeutic effect of antidepressant drugs involves increasing levels of biogenic amines. On the contrary, the interaction between the monoamine oxidases (MAOs) and their monoamine substrates results in several byproducts that activate oxidative stress and further increases the turnover of biogenic amines. This strategy contributes to the generation of neurotoxic aldehydes, hydrogen peroxide, reactive oxygen species (ROS), increased 5-hydroxyindoleacetic acid/5-HT ratio, and nuclear factor-κB (NF-κB) activation. The effect of such oxidative stress and its associated inflammatory processes leads to alterations of neuroplasticity and neurotrophins in selective vulnerable cerebral areas, which is linked to alterations in mitochondrial function and neuronal bioenergetics, DNA damage, aptosis, and cell death. Such processes accelerate the course of neurodegeneration among depressed patients [10,14]. A study that tested the effect of 4 antidepressants amitriptyline, clomipramine (TCAs), citalopram and paroxetine (SSRIs) on the immune response of abalone hemocytes in vitro, reported that the four antidepressants exhibited different cytotoxicities. A significant dose-dependent stimulation of the hemocyte immune efficiency was noticed: destabilization of lysosomal membranes, phagocytosis, and production of reactive oxygen

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species increased at lower concentrations but decreased at higher concentrations. TCAs affected the immune response more strongly than SSRIs [26].

Adverse Effects of Antidepressants

Despite the marginal benefits they produce compared with placebo, antidepressants contribute to a wide range of psychological and biological adverse effects. In addition to the stigma associated with the prolonged use of these drugs, interpersonal adverse effects of antidepressants that involve aspects of sexual life, social life, work or study are high, up to 52% of participants of a former study [27]. This is probably associated with the high treatment drop out that in most instances takes place without consulting the physician [28]. A recent meta-analysis reports that different antidepressants (even within the same generation) vary considerably according to their efficacy, acceptability, and tolerability [29]. The biological adverse effects of antidepressants are also heterogeneous; they range from simple and tolerable side effects such as photosensitivity and mouth dryness to serious and life threatening complications such as cataract, arrhythmia, and intracranial hemorrhage [30-32]. Therefore, it is clear that antidepressant drugs may contribute to the pathologic mechanisms of several serious disorders. This manuscript sheds light on 4 of these conditions: cancer, obesity, diabetes, and cardiovascular diseases. Figure 2 illustrates the mechanisms through which antidepressants maybe associated with these disorders. The pathological mechanisms through which antidepressants produce adverse effects are related mainly to oxidative stress, immunomodulation, inflammation, and homeostatic imbalance [33-35]. However, several factors interact with the action of these drugs (the degree of depressive symptoms, presence of comorbidities, age, general condition, stress, diet, etc.), which may enhance or counteract their negative effects [32,36].

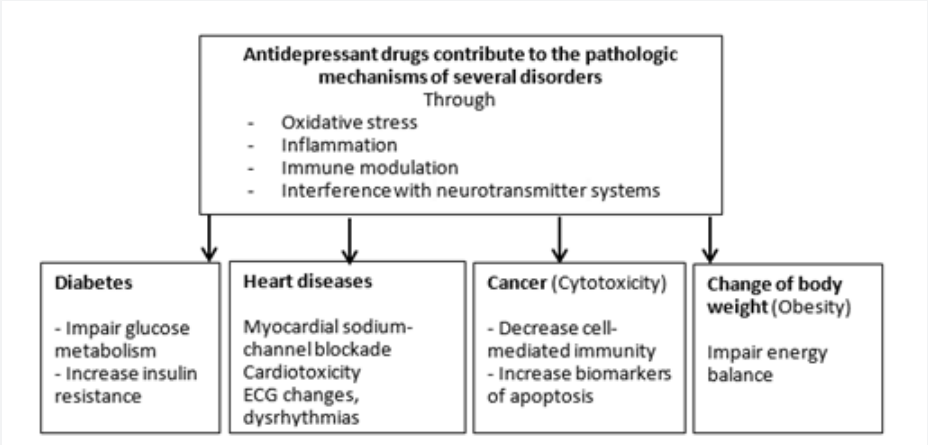

Figure 2: Antidepressants-related disorders and their associated mechanisms.

Antidepressants and Risk Of Cancer

Antidepressants are used to treat depressive symptoms in cancer patients; however, a recent Cochrane review reports no significant antidepressant effect of these drugs compared with placebo [37]. Furthermore, antidepressants are frequently prescribed concurrently with opioids in cancer patients to enhance their effect of neuropathic pain reduction [38]. However, such combinations with anti-cancer drugs (e.g. platinum) have synergistic cytotoxicity effect evidenced by increased biomarkers of apoptosis compared with cytotoxicity induced by solo anti-cancer [39]. A former systematic review and a recent meta-analysis reported that combining antidepressants with opioids in cancer is less likely to reduce pain intensity of greater than 1 point on a 0-10 numerical rating scale; the effect size for all drugs was much smaller than that in non-cancer patients with neuropathic pain. Meanwhile, such combination is associated with an increase in adverse events [38,40].

Several animal studies indicate that antidepressant drugs (TCAs, MAOIs, and SSRIs) stimulate carcinogenesis and promote the growth of neoplasms [41-43], even when administered at therapeutic doses [44]. Similarly, a number of large scale observational studies support an association between intake of antidepressants and incidence of different types of cancer [45-48]. However, TCAs and MAOIs are associated with higher risk than SSRIs [45]. The overdose of certain drugs e.g., bupropion encompasses a higher risk [49]. The mechanism involves dampening natural killer cell function and cell-mediated immunity (T and B lymphocyte proliferative responses) [35,41]. It is suggested that these drugs enhance tumor growth by binding to growth-regulatory intracellular histamine receptors-associated with anti-estrogen binding sites in microsomes and nuclei-stimulating catalytic activity of cytochrome P450 monooxygenases and inhibiting their binding to histamine receptors [43,44].

Antidepressants and Risk of Obesity

Use of antidepressants has been reported to cause considerable weight gain [50]. Nonetheless, antidepressants vary considerably in their association with weight gain [2]. Some antidepressants induce a weight gain of 20 kg over several months of treatment [51]. Obesity increases the risk of several

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related disorders such as diabetes mellitus, cardiovascular diseases, cancer, etc., which lowers life expectancy and increases mortality [52]. Nonetheless, the association of antidepressants with changes of body weight varies considerably based on the type and dose of the used drug as well as individuals' characteristics [2,51,53]. A large meta-analysis study reported that amitriptyline, mirtazapine, and paroxetine were associated with a greater risk of weight gain. On the other hand, SSRIs e.g., fluoxetine caused weight loss during the acute phase of treatment [51]. Sibutramine is an antidepressant that is widely used as an appetite suppressant, not as antidepressant in depression treatment. It effectively promotes weight loss (about 4-5 kg); however, its use is associated with an increase of blood pressure and pulse rate [54,55]. Phentermine, an appetite suppressant, is sometimes used in combination with antidepressants to counteract their negative effects on body weight; however, concerns are raised about its co-administration [56]. A large controlled trial that recruited 2487 obese participants who received a combination of phentermine and topiramate to lower their body weight indicated some acceptable levels of weight loss. Nonetheless, a trail of adverse effects was reported: dry mouth, constipation, insomnia, paraesthesia, depression-related and anxiety-related adverse events [52], which indicates that antiobesity drugs interfere with the regulation of mood.

Several complex mechanisms are involved in the regulation of energy balance and body weight. Drugs that cause body weight change interfere with a number of neurotransmitter systems (e.g., antagonism of the 5-HT2C receptors) that act in several hypothalamic nuclei to regulate the stores of body fat [36,53]. One possible mechanism involves inhibition of the gene expression of several enzymes that are essential for the transcriptional regulation of adiponectin—a protein derived from adipocytes, which regulates insulin sensitivity and glucose homeostasis. This consequently leads to obesity that is associated with insulin resistance [33]. The anorexiant role of these drugs involves reduction of appetite, induction of satiety, and thermogenesis [54]. Given the fact that all trials of antiobesity drugs (including antidepressants e.g., sibutramine) have been limited by their high attrition rates and lack of long-term morbidity and mortality data, the safety of these drugs is not established especially as thermogenesis is associated with enhancement of oxidative stress [55].

Antidepressants and Risk of Diabetes

Use of antidepressants has been associated with both hyperglycemic and hypoglycemic effects [2]. Serotonin plays a vital role in glucose regulation; most antidepressants increase the neurotransmission of serotonin. In particular, antagonism of 5-HT2C receptors and M3 muscarinic receptor is associated with obesity (a risk factor of diabetes) and diabetogenic effects: reduced insulin secretion from beta cells due to inhibition of cyclic adenosine monophosphate (cAMP) in the pancreas, reduced sensitivity to insulin, and impaired glucose tolerance [33,36]. In an in vitro study that tested the effect of 3 antidepressants on murine and human cell-line models of pancreatic β-cells, antidepressants (even at therapeutic doses) decreased the redox, oxidative respiration, and energetic potential of β-cells. This effect was associated with inhibition of mitochondrial complex I and III, increased lactate output, and decreased insulin secretion. Chronic administration of antidepressants increased oxidative stress and activated caspases, 3, 8, and 9 [34].

A Diabetes Prevention Program that followed 3187 participants on 3 treatments (intensive lifestyle, metformin, and placebo) for an average of 3.2 years reported a significant diabetogenic effect of continuous and intermittent use of antidepressants in the placebo and the intensive lifestyle groups compared with no use of antidepressants; hazard risks ranged between 2.25 and 3.48 [57]. A former review reported that noradrenergic antidepressants and TCAs impair the metabolism of glucose in non-diabetics and cause deterioration of the metabolic situation in diabetics. Meanwhile, SSRIs are thought to improve glucose regulation in the short run although their long term effect is under dispute [58]. However, the effect may depend on the dose and duration of administration. A large scale nested case-control study identified the incidence of 2,243 cases of diabetes mellitus in a cohort of 165,958 depressed patients who received at least one new prescription of an antidepressant. Compared with no use of antidepressants, use of TCAs and SSRIs for more than 2 years in moderate to high daily doses was associated with an increased risk of diabetes (IRR =1.77, 95% CI=1.21-2.59) and (IRR=2.06, 95% CI=1.20-3.52), respectively. Meanwhile, no risk was associated with treatment with lower daily doses or for shorter periods [50].

Antidepressants and Risk of Cardiovascular Diseases

Several review reports indicate that TCAs and MAOIs cause cardiotoxicity i.e., they induce a variety of cardiovascular disorders and worsen the prognosis in established cardiovascular conditions [59-61]. Combined use of antidepressants and heart medications, especially in recent cardiac conditions, increases the risk of recurrence and cardiac re-hospitalization [8,61]. TCAs e.g., imipramine at therapeutic doses are associated with electrocardiographic (ECG) changes that involve T-wave changes, abnormally prolonged PR and QRS intervals [62]. Such ECG changes can be diagnostic of TCAs toxicity [63]. Further, drugs such as reboxetine, duloxetine and venlafaxine can increase blood pressure [64]. A big cohort study reported an association between use of TCAs with an increased risk of myocardial infarction (RR= 2.2, 95% CI 1.2 to 3.8) compared with no use of antidepressants in an analysis that was adjusted for age, gender, baseline heart disease, diabetes, hypertension, hyperlipidemia, anxiety, and cancer [60].

The cardiotoxicity induced by antidepressants results mainly from myocardial sodium-channel blockade and autonomic function changes, which result in cardiovascular collapse:

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ventricular dysrhythmias, decreased cardiac output and cardiac contractility, changes in platelet activity, hypotension or hypertension—peripheral vascular resistance increases as a compensatory mechanism to maintain blood pressure [30,62,64]. TCAs, especially at high doses, are associated with sudden death—a characteristic feature of cardiovascular disease [62]. In line, a 3-year period medicolegal autopsy survey in Finland indicated that sudden death of 49 persons was associated with the use of antipsychotic and antidepressant drugs [65]. It is noteworthy that the cardiac effects of individual antidepressant drugs vary considerably; some antidepressants (e.g., fluoxetine, citalopram, bupropion) have neutral effects and are considered safe to use in patients with established coronary artery disease [64]. SSRIs are thought to have cardio-protective effects as they inhibit the reuptake of serotonin into thrombocytes which affects platelet reactivity and endothelial reactivity [31,66]. However, a number of meta-analyses indicate that such property of SSRIs increases the risk of severe bleeding and stroke [31,46,66,67].

Evidence-Base Effective Alternatives to Antidepressants

It is equally important that the potential benefits of antidepressant treatments outweigh their potential adverse effects. Thus, there is an increased need for safe and creative treatments that can target different neurobiological systems in order to restore functioning, promote resilience, and reduce the long-term vulnerability to recurrence of depressive episodes [7]. Evidence notes that metabolic and dietary factors play a major role in the pathology of depression [68]. Therefore, the new trends in depression management have recently moved from the use of synthetic drugs toward the use of natural and safer alternatives that can be easily incorporated into daily regimen—making food our medication. A recent review reported that a large number of nutrients can exert antidepressant effects such as long-chain omega-3 fatty acids, magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc [69]. In this respect, we searched PubMed and Google Scholar for studies on omega-3, herbal plants, diet, and the like. We selected treatments for which we could find review studies in the available literature that reported positive effects. Herein, we discuss some of these treatments.

Omega-3 Polyunsaturated Fatty Acids

Long-chain omega-3 polyunsaturated fatty acids (PUFAs) exist in fish oils. PUFAs are of importance to people with mood disorders since their metabolism in the brain results in several active products. Of particular interest the eicosanoids, which is a group of oxygenated C20 compounds that include prostaglandins, thromboxanes, leukotrienes and a variety of hydroxy and hydroperoxy fatty acids [70-72]. These products act in the intracellular environment as neuronal secondary messengers; they enhance cellular activity and preserve membrane fluidity by decreasing the level of cholesterol. They are involved in cholinergic, serotoninergic and catecholaminergic synaptic transmission. They contribute to neuromodulation, synaptic plasticity, and synaptogenesis mainly by interacting with extracellular G-protein-coupled receptors on neurons and glial cells. PUFAs positively influence cell migration and apoptosis [70]. Several meta-analyses have reported significant antidepressant effect of omega-3 fatty acid treatment [71-74].

Evidence indicates that omega-3 fatty acids work best in cases with a clinical diagnosis of depression not in healthy people who may experience depressive symptoms [73,74]. Interestingly, concurrent use of PUFAs with antidepressants (fluoxetine or mirtazapine) at both therapeutic and low ineffective doses induced additive antidepressant effects in rats [75]. Combining PUFAs with citalopram has been reported to speed the initial antidepressant response compared to solo antidepressant treatments [71]. Further, use of low dose of eicosapentaenoic acid, a common PUFA, as an adjunctive treatment in patients with mild-to-moderate depression who were non-responsive to medication resulted in better response to antidepressants as evidence by significant lowering of depression scores [76]. In addition, PUFAs can be beneficial for obesity and the metabolic side effects of antidepressants [71]. However, PUFAs may exhibit few negligible risks [71,72].

Herbal plants

Herbal plants are polyphenols that possess strong antioxidant properties [77]. They positively affect depression, and they have minimal adverse effects compared with conventional antidepressants [1]. Animal studies indicate that curcumin increases brain derived neurotrophic factor levels and activates the signaling pathways of 5-HT1A/cAMP/PKA/CREB [78,79]. In two clinical trials involving depressed human subjects curcumin was effective reducing depressive symptoms comparable to antidepressants [77,80]. Similarly, a hydro-alcoholic extract of Nigella sativa was successfully used to treat and prevent LPS-induced depression-like behaviors in mice [81]. Further, Nigella sativa was reported to provide a DNA protection under use of cytotoxic agents [82].

Terpene constituents of ginger's extract have moderate inhibitory properties against the MAO-A enzyme in vitro [83]. Cinnamon has been noted to affect regulatory proteins antioxidant and antiproliferative activity in a positive fashion. Cinnamon extract also has antihyperglycemic and antihyperlipidemic effects [84]. A recent systematic review indicates that black cohosh, chamomile, chasteberry, lavender, passionflower, and saffron have the most favorable risk–benefit profiles for anxiety and depression; these herbs may benefit cancer patients in particular by minimizing medication load and side effects [1]. Despite claims that herbal plants might be contaminated with toxic substances e.g., Pyrrolizidine alkaloids, a recent risk-benefit analysis review indicates that quantified Saint John's Wart extract is a safe and effective treatment option, and its potential of treating depression outweighs the hypothetical risk of its contamination [85]. It is worth noting

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that more rigorous RCTs are needed to establish the efficacy of antidepressant herbs.

Flavonoids and glycosides

Flavonoids and glycosides are natural products that can be used to treat depression. They are naturally occurring metabolites that exist in a variety of herbal plants, fruits, vegetables, bee products (e.g., propolis and honey), and other natural products. They confer color, flavor, and aroma, as well as nutritional and health benefits [14,17,86]. A large cohort study followed 82,643 midlife women (with no history of depression) for 10 years reported that intake of total flavonoids and subclasses-flavonols, flavones, flavanones, anthocyanins, flavan-3-ols, polymeric flavonoids, and proanthocyanidins—was significantly associated with lower risk of depression (HR = 0.83; 95% CI: 0.77, 0.90) [87].

Polyphenol flavonoids exhibit several pharmacological properties since they affect various physiological and biochemical functions in the body. A former review supports the antidepressant activity of several flavonoids such as Chrysin, rutin, quercetin, and hesperidin. Their therapeutic effect ensues from a variety of biological activities such as altering oxidative/antioxidant defenses and altering inflammatory responses [14]. Evidence supports their action of inhibiting monoamine oxidases; however, individual flavonoids vary according to the monoamine oxidase they target. Of particular note are results from two animal experiments suggesting that flavonoids isolated from the whole plant of Viola odorata L decreased depressive-like behaviors by interacting with the serotonergic system (5HT1A, 5HT2A, and 5HT3 receptors), and in particular the 5HT3 receptor subtype [88]. Meanwhile, the other model reported an antidepressant effect of flavonoids in Scutellariae Radix, and the mechanism involved activation of the nigra-striatal dopaminergic system and brain reward center [89]. A current review of preclinical studies indicates that glycosides exert their antidepressant effect by modulating the brain-derived neurotrophic factor (BDFN) in the hippocampus, which promotes synaptic efficacy, neuronal connectivity and neuroplasticity [88]. Further investigations of the antidepressant effect and mechanism of flavonoids and glycosides is warranted.

Bee Honey

Bee honey has been proposed as an effective treatment of depression. Honey is rich in several components known to counteract oxidative stress and inflammation e.g., flavonoids, steroid, alkaloids, saponins, tannins, etc. [90,91]. It has an inhibitory effect on more than 60 species of bacteria: aerobes and anaerobes, Gram-positives, and Gram-negatives [92,93]. Thus, it can also act through the gut-brain axis by treating gut leakage given that it possesses proven gastroprotective effects [94,95]. In addition, honey can exert its effect directly on the gut microbiota, which extends its benefit through the gut-brain axis' neuronal, humoral and the cell signaling. Of interest, mice treated with aflatoxin that received bee honey experienced a significant increase of the colon counts of bifido bacteria and lactobacilli—microbiota that are known as protective against depression [96]. Similarly, honey can limit the growth of harmful microflora which support a balanced microbiota [92]. A recent review that summarized findings from animal and human studies that involved use of different types of bee honey to treat depression revealed that administration of honey lowered depressive symptoms in humans and depressive-like behaviors in animals [17]. Animal studies portrayed positive effects of honey on biomarkers of depression in the blood, brains and livers of the treated animals: the levels of serum ACTH, corticosterone levels, oxidation and antioxidation markers, brain-derived neurotrophic factor [97], and monoamines in the liver [98]. Given the fact that human trials that tested the effect of bee honey are limited, it is necessary to examine the antidepressant effect of honey and its phenolic components in larger and more representative samples.

Probiotics

Probiotics are treatments that target the gut-brain pathway either by implanting live microorganisms in specific doses or nurturing beneficial gut microflora to produce health benefits to the host—Lactobacilli and Bifidobacteria are the most commonly used [99,100]. Intestinal microbiota produce their beneficial effects by increasing mucin expression which increases stability of the mucosal barrier, inhibiting over growth of pathogens, stimulating mucosal immunity (secretory IgA), activating xenobiotic metabolism system, and synthesizing beneficial substances such as antioxidants, vitamin K, and short-chain fatty acids [99].

In an experimental model, treatment of stressed mice with a combination of fructo-oligosaccharides and galacto-oligosaccharides for 3 weeks reduced stress-induced corticosterone and proinflammatory cytokine levels as well as depression-like and anxiety-like behavior. Probiotics normalized the effects of stress on the microbiota; it positively affected short-chain fatty acid concentrations e.g., increased cecal acetate and propionate and decreased isobutyrate concentrations. It also modified specific gene expression in the hippocampus and hypothalamus [101].

Probiotics use in humans is limited, but results are promising. A recent meta-analysis that evaluated the effect of probiotics on depressive symptoms revealed no effect of probiotics on mood. A subgroup analysis indicated significant improvements in the mood of individuals with mild to moderate depressive symptoms compared with healthy adults. It is worth noting that subjects in most of the included studies were healthy and the meta-analysis addressed no outcomes other than mood change [100]. A double blind RCT examined the effects of supplementing probiotic (Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium bifidum) to depressed patients for 8 weeks. Probiotic treatment significantly decreased depressive

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symptoms, serum insulin levels, homeostasis model assessment of insulin resistance, and serum high sensitivity C-reactive protein concentrations compared with the placebo. Probiotics positively affected level of antioxidants, which was evidenced by a significant elevation of plasma 53 total glutathione levels [102]. Further investigations of the antidepressant effects of probiotics would be of value.

Nutritional Modification

A recent systematic review indicates that certain foods can effectively prevent and treat depression such as sea foods, meat of animal organs such as liver, green leafy vegetables, lettuces, peppers, and cruciferous vegetables [69]. While consuming healthy diet (e.g., Mediterranean diet) is associated with decreased odds for depression, unhealthy (sugar and fat-rich) diet can dramatically alter the composition of the gut microbiota and heighten the risk of depression [103,104]. Consuming a healthy diverse diet promotes more diversity of gut microbiota [105]. Thus, use of diet to modify the gut microbiome can be helpful in preventing and treating depression [103]. In this respect, a significant association has been found between habitual consumption of the Mediterranean diet and Prevotella genus—indicative of the microbiome family of Prevotellaceae, which is considered protective against depression [106]. In fact, food can be not only a source of amino acids that are needed for neurotransmitter formation but also a source of probiotics: around 35% of all lactic acid bacteria that exist in raw fruits and vegetables can survive gastric conditions [99].

Discussion

This review focused on investigating the carcinogenic effects, obesity, diabetogenic effects, and cardiotoxic effects of antidepressants. Despite availability of pharmacological treatment guidelines, the literature highlights inadequate recognition and treatment of the adverse effects of antidepressant drugs [11,12]. It is reported that more than half of those who use antidepressants discontinue treatment because of lack of efficacy and adverse effects such as weight gain and sexual dysfunction [107,108]. Treatment discontinuation in more than half the patients takes place without consulting the prescribing doctor [28], which indicates a communication gap and ignorance of health professionals of patients' perceptions and painful experiences related to prolonged use of antidepressants. In addition, patients who receive these medications are rarely screened for cardiac problems, diabetes or dyslipidemia; clinicians' lack of knowledge regarding the adverse effects of these drugs is considered a main factor [33].

Both lack of efficacy of antidepressants and their vast adverse consequences necessitate the search for other effective treatments that can be more acceptable. In our search, we selected natural interventions for which we could find review studies that reported positive effects. We retrieved a bunch of meta-analyses and systematic reviews on the antidepressant effects of omega-3 fatty acids [71-73,76], herbal plants (e.g., Saint John Wart) [1,85] and their extracts such as flavonoids and glycosides [86]. Strong evidence supports the antidepressant effect of these nutrients. We formerly reviewed the literature for the effect of bee honey on depression both in humans and in preclinical models, and therefore included honey on the list [17]. What is reassuring about most of the offered treatments is that they are natural products that are in most instances foods that are safe. Nonetheless, some of these treatments such as probiotics are under-tested—though investigated in animal models, few human studies are available. Therefore, further efficacy researches concerning the offered treatments are necessary.

Strengths and Limitations

One of the merits of this study is that it involved a wide range of evidence that ranged from metanalyses of well-designed randomized trials to animals and in vitro studies; the latter allow manipulations and investigation of vital outcomes that cannot be explored in the most rigorous randomized trials. Hence, this review might represent a full description of the current state of knowledge of adverse effects of antidepressants and the available alternative treatments. Nonetheless, for lack of fund we could not do a systematic review since systematic search, screening, and extraction of data are rather costly. So, we alternatively discussed the topic in a narrative fashion.

Conclusion

Most antidepressants drugs—from all categories and generations—exhibit a range of adverse effects that differ from one medication to another. Furthermore, antidepressants' contribution to oxidative stress, inflammation, and cytotoxicity leads to deterioration of the prognosis of depression and contributes to an array of highly morbid health problems in some patients. Available natural alternatives are limited and understudied to some extent. However, omega-3 fatty acids, herbal plants, flavonoids, bee honey, probiotics, and dietary modifications seem promising approaches that can be used alone, combined with each other, or even combined with SSRIs to enhance their therapeutic effect and overcome the drug-related adverse effects. Further rigorous investigations are needed to test the cost-effectiveness of these alternatives.

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