The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature

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Abstract

Newer generation antidepressant drugs (ADs) are widely used as the first line of treatment for major depressive disorders and are considered to be safer than tricyclic agents. In this critical review, we evaluated the literature on adverse events, tolerability and safety of selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, bupropion, mirtazapine, trazodone, agomelatine, vilazodone, levomilnacipran and vortioxetine. Several side effects are transient and may disappear after a few weeks following treatment initiation, but potentially serious adverse events may persist or ensue later. They encompass gastrointestinal symptoms (nausea, diarrhea, gastric bleeding, dyspepsia), hepatotoxicity, weight gain and metabolic abnormalities, cardiovascular disturbances (heart rate, QT interval prolongation, hypertension, orthostatic hypotension), genitourinary symptoms (urinary retention, incontinence), sexual dysfunction, hyponatremia, osteoporosis and risk of fractures, bleeding, central nervous system disturbances (lowering of seizure threshold, extrapyramidal side effects, cognitive disturbances), sweating, sleep disturbances, affective disturbances (apathy, switches, paradoxical effects), ophthalmic manifestations (glaucoma, cataract) and hyperprolactinemia. At times, such adverse events may persist after drug discontinuation, yielding iatrogenic comorbidity. Other areas of concern involve suicidality, safety in overdose, discontinuation syndromes, risks during pregnancy and breast feeding, as well as risk of malignancies. Thus, the rational selection of ADs should consider the potential benefits and risks, likelihood of responsiveness to the treatment option and vulnerability to adverse events. The findings of this review should alert the physician to carefully review the appropriateness of AD prescription on an individual basis and to consider alternative treatments if available.

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Introduction

Major depressive disorder (MDD) has increasingly been recognized as a major global public health issue due to the significant overall impact on mortality and morbidity, as well as high economic and human costs attached to it [1]. The WHO predicts that MDD will become the second leading cause of disability worldwide by the year 2030 [2]. In addition, an estimate indicates that antidepressants were the most frequently prescribed drugs taken by individuals aged 18–44 years between 2005 and 2008 in the USA, and were the third most common among all ages [3].

Depression is a chronic and recurring illness that may require lifelong treatment with different modalities. Compelling evidence indicates that a significant proportion of patients with MDD remain inadequately treated, especially in primary care settings [4, 5]. Nonadherence and premature discontinuation of treatment are important factors that may significantly contribute to suboptimal outcomes [6]. Adverse effects associated with the use of antidepressant drugs (ADs) are some of the most common factors responsible for nonadherence and the discontinuation of treatment [7, 8]. Studies have shown that up to 43% of patients with MDD may discontinue antidepressants due to treatment-emergent adverse effects [9].

The introduction of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors in the 1950s revolutionized the treatment of MDD. Since then, the search for more selective and possibly better tolerated ADs has continued. This movement of rational drug development gave birth to selective serotonin reuptake inhibitors (SSRIs). The ensuing years have witnessed SSRIs becoming the first-line drugs for the treatment of MDD among several other indications [10]. Following the marketing success of SSRIs, many newer generation antidepressants have gained approval as treatments for MDD, including but not limited to serotonin and noradrenaline reuptake inhibitors (e.g. venlafaxine, desvenlafaxine and duloxetine), bupropion (a noradrenaline and dopamine reuptake Inhibitor), mirtazapine (noradrenaline and selective serotonin antagonist) and trazodone (serotonin antagonist and reuptake inhibitor). With the exception of agomelatine (melatonin receptor agonist with 5-HT$_{2C}$ receptor antagonist properties), all other agents primarily act through the modulation of monoaminergic neurotransmission [11, 12]. The aforementioned drugs along with SSRIs are so-called newer generation antidepressants [13]. More recently, over the past 4 years, the US Food and Drugs Administration (FDA) has approved

Table 1. Main adverse events related to use of newer generation ADs

1.	Gastrointestinal (nausea, vomiting, GI bleeding)
2.	Hepatotoxicity and hypersensitivity reactions (dermatologic and vascular manifestations)
3.	Weight gain and metabolic disturbances
4.	Cardiovascular (QT interval prolongation, basal heart rate and HRV, hypertension, orthostatic hypotension)
5.	Genitourinary (urinary retention, incontinence)
6.	Sexual dysfunction
7.	Hyponatremia
8.	Osteoporosis and fractures
9.	Bleeding
10.	Central nervous system (seizure threshold, extrapyramidal side effects, serotonin syndrome, headache, stroke)
11.	Sweating
12.	Sleep disturbances
13.	Affective (apathy, switching into hypomania or mania, paradoxical effects)
14.	Suicidality
15.	Safety in overdose
16.	Discontinuation syndromes
17.	Ophthalmic (glaucoma, cataract)
18.	Hyperprolactinemia
19.	Risk during pregnancy and breast feeding
20.	Risk of malignancies

three additional antidepressants for the treatment of MDD, namely vilazodone, levomilnacipran and vortioxetine [14].

Over the years, there has been a consistent effort to develop more efficacious ADs with better safety and tolerability profiles. There is no unequivocal evidence to support clinically significant differences in efficacy and tolerability among the various newer antidepressant agents and controversies remain in the literature [15–19]. In addition, in a meta-analysis that included 102 studies, no clinically significant differences were found in the efficacy of SSRIs and TCAs [10]. Differences in tolerability between TCAs and SSRIs appear to be modest [10, 20–23]. In addition, concerns about safety and tolerability related to the long-term use of newer generation antidepressants have been raising in the literature [24, 25].

Here we critically review the side effects associated with the long-term use of newer generation antidepressants. In this review, we evaluate a wide range of untoward effects (table 1), although some rare treatment-emergent adverse reactions (mostly described in anecdotal case reports) are not discussed due to space limitations. A PubMed/MEDLINE database search was conducted

with the search term 'antidepressive agents'[Mesh] cross-referenced with 'drug-related side effects and adverse reactions'[Mesh] OR 'specific side effect' (i.e. a separate targeted search for each side effect listed in table 1 was also conducted) from inception up until April 2, 2016. For this comprehensive review we considered for inclusion large-scale observational studies and randomized controlled trials (RCTs), as well as previous reviews, systematic reviews and meta-analyses, while case series and case reports were included if higher level evidence was not available. In this review, we primarily focus on data derived from populations with MDD.

Gastrointestinal

Serotonin plays a major regulatory role in the motor and sensory regulation of the gastrointestinal (GI) tract [26]. It is now well established that drugs with effects on serotonin receptors or serotonin levels can affect gastric motility [27]. Similarly, serotonergic agents that act on central 5-HT$_3$ receptors may lead to nausea and vomiting [28]. Some of the most frequently reported side effects associated with the use of SSRIs and serotonin noradrenaline reuptake inhibitors (SNRIs) include nausea, diarrhea, dyspepsia, GI bleeding and abdominal pain. Approximately half of all patients started on these agents experience GI side effects mainly in the first few days/weeks following treatment initiation [29, 30]. Short-term SSRI use (7–28 days) is significantly associated with upper GI bleeding, suggesting that the same precautions that are used with nonsteroidal anti-inflammatory drugs and aspirin are appropriate [31]. Some studies have found nausea and vomiting to be one of the most common reasons for treatment discontinuation [32, 33]. Among SSRIs, fluvoxamine was associated with the highest rate of GI side effects, whereas escitalopram was less likely to cause GI side effects [34]. Most of these results were derived from observational studies and from case series submitted to regulatory authorities. Thus, the comparative incidence rates of nausea across different antidepressant agents remain incompletely elucidated. A meta-analysis of adverse reactions reported during clinical trials indicated that when compared to SSRIs and duloxetine, the use of venlafaxine was associated with higher rates of nausea and vomiting, while sertraline appeared to be associated with a higher incidence of diarrhea when compared to other SSRIs and venlafaxine [35]. The extended-release formulations of venlafaxine and paroxetine may be associated with lower rates of nausea than their immediate-release formulations [36]. However, a recent meta-analysis did not find significant differences in the rate of adverse events (including nausea) between immediate versus extended-release venlafaxine [37]. The data for the most recently approved antidepressant agents (i.e. vortioxetine, vilazodone and levomilnacipran) remain limited. Nevertheless, similarly to other antidepressant agents, nausea was one of the most frequently reported side effects [38–40].

Hepatotoxicity and Hypersensitivity Reactions

The incidence of drug-induced liver toxicity among patients taking SSRIs and SNRIs ranges from 0.5 to 1% and this risk seems to be more elevated among patients exposed to nefazodone, bupropion, agomelatine and duloxetine [41]. The elevation of alanine aminotransferase levels above 3 times the upper normal limit provides an indication (i.e. a 'red flag') of clinically significant drug-induced liver injury (DILI) [41]. Liver toxicity may occur within days to about 6 months after antidepressant treatment initiation. It is noteworthy that symptoms of liver toxicity and neurovegetative manifestations of MDD including fatigue and loss of appetite may overlap. Antidepressant-induced liver injury is generally dose-dependent, with higher doses being more likely to cause liver injury [42]. In addition, polypharmacy, especially with the concomitant administration of multiple compounds metabolized by the same CYP450 isoenzymes, is an important risk factor for DILI. For example, the concomitant use of duloxetine plus trazodone, duloxetine plus fluoxetine, duloxetine plus mirtazapine, and venlafaxine plus trazodone have been associated with severe liver injury [for a review, see 41].

Two main mechanisms may be involved in antidepressant-induced liver toxicity, namely a metabolic component and/or an immuno-allergic pathway. A hypersensitivity syndrome with fever and rash as clinical manifestations, as well as with autoantibodies and eosinophilia, and a short latency period (1–6 weeks) point to a predominantly immunoallergic pathophysiological mechanism [43], whereas a lack of hypersensitivity syndrome and a longer latency period (i.e. 1 month to 1 year) points to an idiosyncratic metabolic mechanism [44].

Citalopram and escitalopram have been considered the safest among the SSRIs with respect to potential for liver injury [41]. On the other hand, the risk of liver toxicity for nefazodone was so high that it was subsequently withdrawn from the market [45]. A recent systematic review found

that the incidence of agomelatine-induced liver injury was as high as 4.6% and the risk of liver injury appeared to be dose dependent [46]. Case reports of life-threatening liver toxicity, in some cases requiring liver transplantation, have been described in the literature for nefazodone, duloxetine, venlafaxine and agomelatine [41]. Thus, clinicians should regularly monitor liver function while treating patients with antidepressants, particularly if using agomelatine and duloxetine. Baseline liver function tests should be tested prior to treatment initiation and thereafter following dose increments. Special care should be taken when treating patients with preexisting liver disease and, if possible, drugs with low liver toxicity (for example, citalopram and escitalopram) should be used in these patients [41].

Cutaneous adverse drug reactions may also occur among individuals using SSRIs; the evidence for these adverse skin reactions comes from prospective and retrospective cohort studies [47]. Most commonly, SSRIs have been associated with petechiae and ecchymosis, which occur secondarily to the effects SSRIs on platelet aggregation [48]. Some individuals can develop skin reactions on the face, neck and dorsum of the hands secondary to excessive exposure to sunlight [47, 48]. The long-term use of SSRIs can be linked to hyperpigmentation of hair, skin and nails [47]. Another adverse effect is alopecia which is most commonly seen with the use of fluvoxamine [47, 49]. In addition, SNRIs have not been associated with major cutaneous adverse reactions apart from hyperhidrosis, which is discussed below [47]. Finally, the use of mirtazapine has been associated with rash, acne, exfoliative dermatitis and alopecia [47].

Weight Gain and Metabolic Disturbances

Weight gain during antidepressant therapy may occur during both acute and maintenance phases of treatment [50]. In addition, weight gain may be a sign of improvement or even a residual symptom of atypical depression [50]. Notwithstanding the complexity of the clinical scenario, compelling evidence indicates that the use of most antidepressants may increase weight in a significant proportion of patients [51]. The interaction of several mechanisms may contribute to antidepressant-induced weight gain, including but not limited to: (i) the action on specific neuroreceptors (e.g. antagonism to histaminergic H1 receptors and serotonin 5-HT$_{2C}$ receptors); (ii) a decrease in caloric expenditure due to the sedative effects of certain antidepressants; (iii) a shift in food preference, and (iv) dry mouth/throat may lead to an increased intake of caloric beverages [50, 52]. Recently, it has been suggested that an increase in exposure to antidepressants via a multitude of mechanisms may be a driving force for the obesity pandemic [53].

Despite the fact that SSRI use has been associated with weight loss during acute treatment, several studies have indicated that long-term use (more than 6 months) is associated with weight gain [53]. In addition, evidence indicates that paroxetine may be the worst SSRI when it comes to weight gain [51, 52]. In addition, a prospective population-based study indicates that the use of ADs may be associated with a higher risk of obesity [54]; it is possible that the oppositional model of tolerance may also apply to the emergence of weight gain following long-term AD treatment [55]. According to this model, continued drug treatment may recruit processes that oppose the initial acute effects [55].

Mirtazapine is the newer generation antidepressant most consistently associated with significant weight gain in the initial phases of treatment [51]. Some studies showed a paradoxical reduction in weight gain in doses ranging from 75 to 90 mg and above [56]. Unlike mirtazapine, the use of bupropion may promote weight loss in a subgroup of patients who may lose up to 12.9% of their body weight after 24 weeks of treatment [57]. In addition, despite its structural similarities to sibutramine, significant weight change has not been associated with the use of venlafaxine [58]. The limited evidence to date suggests that vortioxetine and vilazodone do not promote significant weight gain in patients with MDD [59, 60].

Some antidepressants that may promote weight gain (e.g. TCAs and mirtazapine) may also impact on serum lipid parameters, whereas a direct weight-independent effect on serum cholesterol has not been consistently reported [61, 62]. The association between antidepressant use and incident diabetes mellitus (DM) remains inconclusive [62]. Some reports point to a higher risk of DM [63–65] whereas others do not [66, 67]; however, a recent systematic review and meta-analysis found that antidepressants (mainly SSRIs and TCAs) increase the risk of DM (OR = 1.5, 95% CI 1.08–2.10; HR = 1.19, 95% CI 1.08–1.32) [68]. As the included studies were observational, this association may not be causal [69].

Cardiovascular

A substantial body of evidence indicates that the cardiovascular safety profile of newer generation antidepressants is significantly improved compared to the TCAs,

with a lower degree of anticholinergic side effects along with better safety in the setting of acute overdose. Most SSRIs have been associated with a reduction in basal heart rate [70–72], even though a recent large study has found the opposite (an increase in heart rate associated with the use of SSRIs) [73]. On the contrary, the use of SNRIs (e.g. venlafaxine and duloxetine) has been associated with an increase in basal heart rate [25, 74]. In addition, SSRIs and SNRIs may promote a decrement in heart rate variability (HRV) [73, 75]. Although the impact of the effects of antidepressants on HRV remains to be established, data indicate that a lower HRV is a significant predictor of incident cardiovascular events [76]. Levomilnacipran (perhaps as a consequence of its noradrenergic effects) promotes increments in basal heart rate, whereas adequate data are missing as to the cardiovascular effects related to the use of vilazodone and vortioxetine [40, 77].

The effects of SSRIs on QT interval prolongation have also emerged as a significant source of concern [78]. The QT interval is defined as the period elapsed between the onset of a Q wave and the end of a T wave in the electrocardiogram. The QT interval can vary with heart rate and becomes shorter as the heart rate increases. The QTc refers to the corrected QT interval (i.e. after adjustment to basal heart rate). Among the SSRIs, citalopram may cause a clinically significant increase in the QTc interval and has also been associated with cases of torsades de pointes [79]. A few case reports have suggested an association whereby the use of fluoxetine and sertraline may lead to QTc prolongation in individuals with preexiting risk factors for QTc prolongation. Paroxetine can be considered the least likely SSRI to cause QTc prolongation [79]. A recent meta-analysis also confirmed that among SSRIs, citalopram appears to be the agent most significantly associated with QTc prolongation [80].

Venlafaxine use has been associated with clinically significant increases in diastolic blood pressure of up to 15 mm Hg from baseline. This risk was lower among individuals receiving doses of less than 200 mg daily [25, 81]. Duloxetine may also increase blood pressure [82] and levomilnacipran may increase both systolic and diastolic blood pressure, although the magnitude of the effect seems to be small and its clinical significance is yet to be determined [38]. The SNRIs have not been consistently associated with clinically significant cardiac conduction defects or arrhythmias [25].

Studies investigating the risk of orthostatic hypotension secondary to the use of ADs have employed different definitions of orthostatic hypotension ranging from clinical symptoms of postural dizziness to predefined postural changes in blood pressure and heart rate. It is well established that TCAs may cause orthostatic hypotension due to their well-known antagonistic α$_1$-adrenergic receptor activity [83, 84]. The main mechanisms associated with SSRI-induced orthostatic hypotension remain unknown. Postural hypotension associated with the use of SSRIs is most commonly observed in elderly populations [83]. Paroxetine seems to be the SSRI most frequently associated with orthostatic hypotension at least partly due to its anticholinergic effects [85]. This increased anticholinergic effect may help explain the increased risk of orthostatic hypotension especially in the elderly [86]. Similarly, fluoxetine use has also been associated with an increased incidence of orthostatic hypotension among the elderly [87].

Among SNRIs, some studies suggest that venlafaxine may cause orthostatic hypotension in more than 50% of patients aged over 60 years, most likely secondary to its strong noradrenergic action [88]. Although there have been no formal studies, a few case reports suggest a risk of orthostatic hypotension also for patients who were prescribed duloxetine [85]. In addition, mirtazapine may cause orthostatic hypotension in up to 7% of patients [89].

Genitourinary

Urinary retention secondary to the use of SSRIs appears to be a rather rare event and is supported only by case reports [90]. In most cases, SSRIs have been implicated only when used in combination with benzodiazepines and/or antipsychotics. These case reports have particularly concerned fluvoxamine, while fewer studies have implicated fluoxetine [90]. SSRIs can cause urinary retention by acting on central micturition pathways. Serotonin may increase the central sympathetic outflow leading to urinary storage, and at the same time inhibits parasympathetic flow, which affects voiding [91]. On the other hand, SNRIs may cause urinary retention via actions on α$_1$-adrenoreceptors. There have been case reports which have shown that the use of venlafaxine and reboxetine has led to cases of urinary retention [25]. There have also been a few reports to suggest that venlafaxine can also cause urinary incontinence. Even though the exact underlying mechanism is unknown, the action of venlafaxine on 5-HT$_4$ receptors appears to cause incontinence [92]. Likewise, duloxetine appears to be associated with both urinary retention and hesitancy [25].

A large retrospective study found that the relative risk of incontinence associated with the use of SSRIs was approximately 1.61, with sertraline having the highest relative risk. However, causal inferences linking SSRIs and urinary incontinence remain to be established [93]. It is noteworthy that most cases which reported urinary incontinence or retention related to the use of either SSRIs or SNRIs involved individuals who were on a wide variety of drugs, which could have contributed to the reported incontinence or retention.

Sexual Dysfunction

The prevalence of sexual dysfunction is considerably higher among individuals with MDD compared to the general population. For instance, loss of libido has been reported to affect 25–75% of patients with MDD, and its prevalence may correlate with the severity of depressive symptoms [94], while a decrease in desire and arousal may affect >50% of patients who have received a diagnosis of MDD [95]. In addition, a significant body of data shows that antidepressants may differentially affect sexual function in multiple aspects, leading to reductions in libido, arousal dysfunction (erection in males and vaginal lubrication in females) and orgasmic dysfunctions [95, 96].

These side effects are some of the most underreported adverse effects associated with the use of antidepressants, and a growing body of evidence indicates that clinicians should actively monitor for such side effects. The use of validated instruments to assess sexual dysfunction seems to enhance the identification and quantification of these adverse events [97]. These adverse reactions are a major contributor of treatment discontinuation and lack of adherence [98, 99]. Several mechanisms may contribute to antidepressant-induced sexual dysfunction, including but not limited to psychosocial factors and comorbid medical diseases, as well as the use of other medications that may affect sexual function [95]. According to one hypothesis, the serotonergic action of SSRIs and SNRIs reduces dopaminergic transmission in the mesolimbic area, which in turn is known to regulate orgasm and sexual desire [100].

The prevalence of sexual side effects can be as high as 50–70% among individuals taking SSRIs. These effects are reduced or absent among individuals taking medications with a predominant effect on dopamine or noradrenaline reuptake (e.g. bupropion). All SSRIs along with SNRIs have been shown to have significant sexual side effects. There are minor individual variations among these drugs but, according to a recent network meta-analysis, these differences were not statistically significant [101]. Bupropion appears to have a favorable tolerability profile with regards to sexual side effects [102]. In fact, it has established itself as the drug of choice for patients who have experienced sexual side effects from other antidepressants [103]. In addition, mirtazapine and agomelatine have been associated with lower risks of sexual side effects [104]. Preliminary data suggest that vortioxetine and vilazodone might have some advantage over SSRIs with regards to sexual side effects [59, 60, 105].

During the course of antidepressant therapy, clinicians should continuously monitor for the possibility of sexual side effects. Several strategies have been investigated for the management of sexual dysfunction associated with antidepressants [for a review, see 106]. For example, clinicians may attempt a switch to an antidepressant with a lower rate of sexual dysfunction. In addition, tricyclic antidepressant agents have long been implicated in the emergence of sexual side effects. Clomipramine, imipramine and amitryptiline are particularly troublesome, whereas nortriptyline may be less so [107, 108].

Some antidotes (e.g. bupropion) have been proposed as effective strategies for a subgroup of patients [109]. The use of type 5 phosphodiesterase inhibitors (e.g. sildenafil, tadalafil and vardenafil) may also alleviate antidepressant-induced erectile dysfunction [106]. Finally, it is worth mentioning that for a small group of patients sexual dysfunction may either persist after treatment discontinuation or be a transitory phenomenon during AD treatment [110].

Hyponatremia

Most of the evidence pointing towards an increased risk of hyponatremia with the use of antidepressant medications is based on multiple case reports and a few observational studies. The SSRIs and venlafaxine appear to be the antidepressants most commonly associated with hyponatremia [111]. Among the SSRIs, the incidence of hyponatremia varies based on the definition of hyponatremia used. For studies which defined hyponatremia as serum sodium levels <135 mmol/l, the incidence ranged from 9 to 40%. The incidence decreased to 0.06–2.6% when hyponatremia was defined as serum sodium levels <130 mmol/l [111]. There were no consistent difference in the incidence of hyponatremia among different SSRI

members, but available data indicate that the incidence could be slightly higher for fluoxetine, citalopram and escitalopram, whereas incidence rates may be lower for paroxetine and sertraline [112–114]. The data looking at the risk of hyponatremia associated with the use of SNRIs are even more limited [111]. Most studies have found incidence rates of hyponatremia comparable to the ones reported for SSRIs. Incidence figures for mirtazapine and TCAs appear to be lower [111].

The risk of hyponatremia is significantly higher in elderly patients and among individuals using diuretics. The mechanisms of SSRI-induced hyponatremia remain incompletely elucidated, but these agents can act by either increasing the release of antidiuretic hormone (ADH) or increasing the sensitivity to ADH resulting in a clinical picture similar to the syndrome of inappropriate secretion of ADH [62, 111]. The discontinuation of the antidepressant, fluid restriction and diuresis are possible measures that can be taken to treat antidepressant-induced hyponatremia [115].

Osteoporosis and Fractures

Multiple studies and a subsequent meta-analysis have associated depression with an increased risk of fractures and a reduction in bone density among patients [116]. Furthermore, a recent meta-analysis of 10 studies found a significant reduction in lumbar and hip mineral density in adults aged 60 years and older [117]. This reduction in bone density and a metabolic state which favors bone resorption has been attributed to a complex interplay between the hypothalamic-pituitary-adrenal (HPA) axis and inflammation [118]. Patients with depression tend to have increased secretion of cortisol and also display elevation in markers of inflammation, especially, IL-1, IL-6 and TNF-α (which in turn can also increase cortisol secretion) [119].

The use of SSRIs has been associated with a reduction in bone mineral density (BMD) and a consistent higher risk of fractures [118]. A recent meta-analysis found that the relative risk of fractures associated with the use of SSRIs was 1.72 (95% CI 1.51–1.95), and this risk could not be accounted for by variations in BMD [120]. In a large-scale case-control study, among the SSRIs, high doses of citalopram, fluoxetine, paroxetine and sertraline carried an odds ratio of 1.98 (95% CI 1.82–2.16) with respect to risk of fractures. The same analysis did not find significant increase in the risk of fractures related to the use of mirtazapine, venlafaxine and reboxetine [121].

In summary, MDD and the use of antidepressants have been individually associated with an increased risk of fractures and a reduction in BMD. However, based on extant data it seems difficult to precisely determine whether these observations are due to an exposure to antidepressants, a result of the disease process or a combination of both.

Bleeding

All serotonergic antidepressants have been associated with an increased risk of bleeding [122]. The most likely mechanism responsible for these adverse reactions is a reduction of serotonin reuptake by platelets, although other mechanisms have also been implicated [122, 123]. In fact, serotonin influences platelet aggregation induced by adenosine diphosphate, epinephrine and collagen [124]. Among the SSRIs, fluoxetine, paroxetine and sertraline have been related to a higher risk of platelet dysfunction when compared to other SSRIs [122]. Among other antidepressants, venlafaxine and mirtazapine also have been associated with an increased risk of bleeding [122]. SSRIs have been associated with an increased risk of bleeding during surgical procedures [125]. The risk of bleeding appears to be higher with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin, preexisting platelet dysfunction, or a concomitant use of heparin [124]. A recent observational cohort study pointed towards an increased risk of intracranial bleeds in patients concomitantly using NSAIDs and SSRIs [126].

The use of SSRIs could be associated with an increased risk of upper GI bleeding [31, 127]. The overall risks are substantially higher among individuals on concomitant use of nonsteroidal anti-inflammatory agents [127, 128]. The association between the use of SNRIs and upper GI bleeding is less compelling with inconsistent results across studies [129–131]. The role of proton pump inhibitors against this increased risk of GI bleeding when used with SSRIs has not been firmly established [15, 130, 132, 133].

Central Nervous System

ADs can lower the seizure threshold; the epileptogenic potential is higher for TCAs than for bupropion, which is still contraindicated for individuals with seizure disorders [134]. Over the years many case reports have associated extrapyramidal symptoms (EPS) with the use of an-

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tidepressants. All kinds of EPS are seen in patients taking antidepressants, but akathisia appears to be the most common presentation followed by dystonic reactions, parkinsonian movements and tardive dyskinesia [135]. Akathisia appears to be more common in younger patients as compared with the other EPS symptoms [136]. Among antidepressants, SSRIs have the highest number of case reports of EPS [137, 138]. The mechanisms responsible for EPS may be related to excessive levels of serotonin, which may disrupt dopaminergic neurons in the nigrostriatal and tuberoinfundibular pathways [139]. The incidence of EPS appears to be highest among patients taking duloxetine, followed by sertraline, escitalopram, paroxetine, fluoxetine, bupropion and citalopram in decreasing order of incidence [140]. The elderly and individuals who carry the A1 allele of the dopamine D_2 receptor *(DRD2)* gene Taq1A polymorphism were at increased risk of developing EPS with the use of SSRIs [141]. In addition, a few case reports of neuroleptic malignant syndrome have been attributed to the use of antidepressants, and even to the withdrawal of SSRIs [134, 142].

The widespread use of SSRIs may result in the so-called serotonin syndrome, which is a highly heterogeneous and life-threatening condition characterized by a triad of mental-status changes, autonomic hyperactivity and neuromuscular abnormalities, but not all of these manifestations are universally present in patients presenting with this disorder [143]. The concomitant use of SSRIs and monoamine oxidase inhibitors may pose a significant risk [144], while the serotonin syndrome may occur in up to 16% of individuals who overdose on SSRIs [145]. The recognition of milder cases of this syndrome may be challenging and, although the diagnosis must be made on clinical grounds, the assay of urinary levels of serotonin may prove to be useful [146].

The achievement of cognitive remission has emerged as a novel yet unmet objective of AD treatment [147]. Antidepressants may have a small beneficial effect upon certain cognitive domains (e.g. delayed recall and psychomotor speed) [148]. However, the use of antidepressants may also lead to cognitive side effects [149]. For example, in one study a significant impairment of executive function was related to the use of SSRIs [150]. In addition, the use of antidepressants was associated with inattentiveness, forgetfulness, word-finding difficulty and mental slowing in depressed individuals reaching partial or full remission [151].

Headache was one of the most common side effects associated with the use of antidepressants in a large retrospective cohort of adolescents and adults [152]. Finally,

a meta-analysis of observational studies indicated that the use of SSRIs could be associated with a 40% increased risk of stroke [153]. However, this association was significant only in older age groups. In addition, a recent cohort study conducted in UK primary care settings did not confirm this association [154].

Sweating

Sweating is a compensatory mechanism used by the body to keep its temperature within a physiological range. Excessive sweating is an uncomfortable and often embarrassing side effect of antidepressant medications. The action of TCAs on muscarinic receptors may lead to excessive sweating in approximately 14% of the patients who take them [155]. Among the newer antidepressants, bupropion and venlafaxine have been more frequently associated with excessive sweating, while fluvoxamine and trazodone may be associated with lower incidence rates [156]. Most studies indicate that approximately 10% of patients on SSRIs may develop excessive sweating, although the incidence may be higher for paroxetine [25, 156]. The use of benztropine and cyproheptadine for the alleviation of antidepressant-induced sweating has been attempted with success, although the quality of the evidence is limited [156–158].

Sleep Disturbances

Sleep disturbances are one of the hallmark manifestations of depressive illnesses. Studies have shown that patients suffering from depression have reduced rapid eye movement (REM) latency and a reduction in the non-REM phases in the first sleep cycle [159]. However, there are significant sources of heterogeneity across studies [160]. The SSRIs and venlafaxine are associated with increased REM sleep latency and a reduction in the overall time spent in the REM phase while sleeping. These effects on REM sleep are mostly associated with the initial days/weeks of treatment, and may return to baseline levels after 8 weeks of treatment. A rebound in REM sleep can be measured upon discontinuation of SSRIs. These effects on REM sleep could be due to an increase in synaptic serotonin levels. Mirtazapine can increase latency to REM sleep. In addition, trazodone and mirtazapine have been associated with improving sleep continuity in patients with MDD [161]. Evidence indicates that a subgroup of patients may intensify dreaming and report troublesome

nightmares when they begin taking SSRIs or SNRIs, and even more so when they discontinue their use [162].

In addition, SSRIs and venlafaxine may cause and exacerbate restless leg syndrome. Among the newer antidepressants, mirtazapine followed by paroxetine and sertraline have been associated with the highest incidence of restless leg syndrome [163]. Furthermore, some case reports have related the use of venlafaxine to the emergence of periodic limb movement disorder [164]. Unlike other antidepressants, bupropion has been known to ameliorate the symptoms of restless leg syndrome [165].

Affective Disturbances

Many patients taking SSRIs have reported experiencing emotional blunting. They often describe their emotions as being 'damped down' or 'toned down', while some patients refer to a feeling of being in 'limbo' and just 'not caring' about issues that were significant to them before [166]. Evidence indicates that these adverse affective manifestations may persist even after the symptoms of depression have improved and can occur in patients of all ages [151, 167]. Some authors hypothesize that AD-induced emotional blunting occurs as a result of a down-regulation of dopamine neurotransmission in neural circuits that regulate reward processing, secondary to an activation of 5-HT2$_C$ receptors in the nucleus accumbens [168]. These changes in emotional processing are not limited to SSRIs, and have also been reported for patients taking mirtazapine, agomelatine and reboxetine [167]. In addition, cases of apathy, lack of motivation and frontal lobe syndrome have been described in patients taking SSRIs in adults, adolescents and children [24].

Treatment with ADs has been associated with mania or other forms of excessive behavioral activation [169, 170]. These responses may unveil unrecognized bipolar illness or may be drug induced since they may also occur in allegedly unipolar patients. A meta-analysis indicates that the treatment of juvenile patients for both anxiety and depressive disorders may lead to excessive arousal activation and even hypomania, which calls for a proper clinical monitoring for the emergence of bipolar disorder [171]. Furthermore, an activation syndrome in which patients taking antidepressants may experience anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness and impulsivity in the first 3 months of treatment may ensue [172].

The use of ADs may be associated not only with the return of depressive symptoms during maintenance treatment, but also with the appearance of new symptoms and exacerbation of the baseline clinical picture (paradoxical effects). Improvement may result from AD discontinuation [173]. The occurrence of paradoxical effects was reported in RCTs with fluoxetine [174] and sertraline [175].

Suicidality

The emergence of suicidality and self-injurious behavior upon treatment with ADs represents one of the most debated and controversial risks associated with antidepressant use [176–179]. Since 2014, the US Food and Drug Administration (FDA) issued a black box warning regarding the risk of suicidality related to the use of antidepressants in children and adolescents [179]. The incidence of suicide and attempted suicide has been a frequently underreported adverse outcome across antidepressant RCTs [180]. The first association between the use of SSRIs and suicidality was reported in 1990 [181]. The risk-to-benefit assessment of the use of antidepressants in children and adolescents considering the potential risk of suicidality is complex [182]. The potential therapeutic benefits have modest to moderate effect sizes, while a recent meta-analysis found a significant risk of suicide (OR = 2.79; 95% CI = 1.62–4.81) [183], although the underreporting of data limits the establishment of causal inferences. The risk of suicidality in pediatric populations treated with antidepressants could be a source of greater concern when higher doses are used [184]. Therefore, clinical monitoring regarding the emergence of suicidality throughout treatment is a necessary step.

Two recent meta-analyses have not identified a clear increased risk of treatment-emergent suicidality in adult individuals treated with antidepressants in RCTs [180, 183]. Notwithstanding that the use of antidepressants is efficacious for the treatment of MDD in adults, there is no clear evidence for either specific protective effects or increased risk related to suicidality. An expert statement issued by the European Psychiatric Association (EPA) mentions that antidepressants decrease suicidality [185], but there is no consistent evidence to support this statement.

Safety in Overdose

Patients with MDD are at increased risk of suicide and overdosing of prescribed medications is a common method used to attempted suicide [186]. Therefore, the safety

Carvalho/Sharma/Brunoni/Vieta/Fava

of distinct antidepressants in overdose is a matter of concern [23]. One study reviewed records in the UK and found that among antidepressants the case fatality rate (ratios of deaths to nonfatal overdose) was highest for TCAs (1.6) followed by venlafaxine (0.29) and mirtazapine (0.22), and was lowest for SSRIs (0.06). Among the SSRIs, citalopram was found to be associated with the highest case fatality rates in overdose [187]. Another study investigated poison control data in the USA from 2000 to 2004. Likewise, TCAs were associated with the highest mortality rates due to overdose. Among the newer antidepressants, bupropion and venlafaxine were associated with the highest case fatality rates. In addition, among SSRIs, citalopram and fluvoxamine appeared to be related to higher mortality rates in overdose, whereas fluoxetine and sertraline were the safest [188]. Due to the limited available evidence, it seems clear that TCAs are associated with higher case fatality rates compared to SSRIs, while the relative ranking of different SSRIs deserves further investigation.

Discontinuation Syndromes

An often underappreciated clinical problem associated with the use of almost all SSRIs and SNRIs is the emergence of withdrawal symptoms of varying degrees of severity upon treatment discontinuation and/or interruption [189, 190]. These symptoms include flu-like symptoms, tremors, tachycardia, shock-like sensations, paresthesia, myalgia, tinnitus, neuralgia, ataxia, vertigo, sexual dysfunction, sleep disturbances, vivid dreams, nausea vomiting, diarrhea, worsening anxiety and mood instability [190]. A recent review suggested that dependence and withdrawal symptoms associated with newer antidepressants were comparable, if not worse, to those experienced with benzodiazepines [190]. These reactions have been defined as 'discontinuation syndromes', with the aim of avoiding any hint to a potential for dependence that may affect marketing [190, 191]. Due to the severity and unpredictability of these manifestations, it has been recently suggested that the term 'discontinuation syndrome' should be replaced by 'withdrawal syndrome' [190]. Symptoms typically appear within 3–4 days of stopping an antidepressant or initiating a medication taper. They may be mild and resolve spontaneously within 1–3 weeks; in other cases, they may persist for months or even years, leading to what has been defined as 'persistent postwithdrawal disorder' [192]. In addition, following the abrupt interruption of antide-

pressants, a manic or hypomanic episode may occur [193]. These symptoms can start within a few days to weeks (partly depending on the half-life of the agent used). Withdrawal symptoms are most prominent in agents with shorter half-lives and high potency, such as venlafaxine and paroxetine [190, 194]. Interestingly, most studies show that although tapering the drug over a period of weeks to months may confer some advantages, it does not eliminate the probability of developing withdrawal symptoms [190].

Alternative strategies for the management of antidepressant-related withdrawal syndrome are scarce, and the quality of the evidence is limited [189]. A combination of cognitive behavior therapy and well-being therapy has been reported to be successful in a case series for managing persistent postwithdrawal disorders [195].

Ophthalmic Effects

A subset of patients taking SSRIs reports nonspecific visual disturbances [196], which may be a cause of AD withdrawal [197]. A subsequent review indicates that the use of different SSRIs may increase intraocular pressure and lead to the emergence of angle-closure glaucoma [198], which case reports have also indicated may be caused by venlafaxine [199, 200]. In addition, a nested case-control study found that that the risk of angle-closure glaucoma was doubled among patients younger than 50 years taking bupropion [201]. Two analyses were performed using data derived from the Taiwan National Health Insurance database [202, 203]. While the use of SSRIs was associated with a substantial independent risk of acute angle-closure glaucoma (OR = 5.80; 95% CI = 1.89–17.9) [203], there was no apparent risk of either primary angle-closure glaucoma or primary open-angle glaucoma in patients with depression on long-term SSRI use [202]. Available evidence indicates that baseline and follow-up ophthalmic consultations may be warranted in patients taking SSRIs with a higher risk for glaucoma (e.g. the elderly and those with a familial high risk of glaucomatous diseases) [204].

A nested case-control study found a higher likelihood of cataracts after exposure to newer generation antidepressants, including fluvoxamine (RR = 1.39, 95% CI = 1.07–180), followed by venlafaxine (RR = 1.33, 95% CI = 1.14–1.55) and paroxetine (1.23, 95% CI = 1.05–1.45) [205]. These findings were replicated in another case-control registry study [206].

Hyperprolactinemia

Prolactin release is primarily regulated by tuberoinfundibular dopamine pathways, but it is also modulated indirectly by serotonin via the activation of 5-HT_{1C} and 5-HT_2 receptors [207]. Long-standing increases in peripheral prolactin levels are occasionally observed in patients using ADs, including SSRIs [208]; hyperprolactinemia may have deleterious health consequences (e.g. a decrease in BMD and hypogonadism) [209]. The routine monitoring of prolactin levels is not recommended, but the measurement of plasma prolactin is necessary when symptoms suggest the possibility of hyperprolactinemia. Where hyperprolactinemia is confirmed, a switch to mirtazapine may be a good therapeutic choice, although a switch to another SSRI may also stop this abnormality [210]. Finally, there are case reports of normoprolactinemic galactorrhea related to the use of ADs [211, 212].

Risks during Pregnancy and Breast Feeding

Pregnant women have an increased risk of developing depressive illness and about 10–15% of them experience depression during pregnancy. The risk of depression appears to be highest in the second and third trimester and almost half of these women continue to have symptoms after the end of pregnancy [213]. It is important to treat MDD during pregnancy as it has been associated with an increased risk of complications during pregnancy, including increased risk of preeclampsia, preterm birth, abnormal bleeding, miscarriages and even fetal death [214]. Even though an extensive discussion about the potential benefits and harms associated with the use of different ADs during pregnancy and breast feeding is beyond the scope of our review, we will briefly discuss key clinical issues. We refer the reader to a recent review on the topic for a wider debate [215].

Studies examining the effect of exposure to SSRIs during pregnancy and its association with birth defects have been marred by several confounders, such as the detrimental effects of MDD itself, maternal age, smoking and use of other medications (e.g. anticonvulsants) [214]. After controlling for these factors, SSRIs have not been unequivocally associated with an increased risk of major birth defects [216]. Most of the data describing the presence of birth defects associated with SSRI use have been based on observational studies and drug registries. Therefore, the clinical significance of these data is questionable.

SSRIs have been associated with a modest increase in risk of congenital cardiac malformations, with a relative risk of about 1.4, as well as with an increased risk of postpartum hemorrhage [217, 218]. In addition, paroxetine has been associated with an increased risk of congenital cardiac defects and should not be used during pregnancy [217, 219]. A recent meta-analysis indicated that exposure to SSRIs in late pregnancy may confer an increased risk of persistent pulmonary hypertension [220]. However, the absolute risk was small, and thus the clinical significance of this finding seems rather limited. Fluoxetine has the largest amount of data; however, this drug is slowly eliminated by the newborn (see below).

Exposure to SNRIs (e.g. duloxetine and venlafaxine) during pregnancy does not seem to be consistently associated with an increased risk of birth defects, but use of these medications has been associated with an increased risk of postpartum hemorrhage, and venlafaxine in particular has been associated with an increased risk of hypertension during pregnancy [221–223]. However, it is important to remember that the data investigating the safety of exposure to SNRIs during pregnancy are not as extensive as those for SSRIs. Similarly, most data suggest that the risk associated with the use of bupropion, mirtazapine and trazodone during pregnancy is low, while some studies have shown equivocal results regarding the potential risk cardiac malformation related to bupropion use [224–227].

The placental transfer of different antidepressant medications varies [228]. The use of SSRIs and SNRIs during late pregnancy has been associated with withdrawal reactions characterized by irritability, excessive crying, tremor and even seizures [229]. These reactions at least to a certain extent may be conceptualized as discontinuation or withdrawal syndromes [230]. In fact, paroxetine and venlafaxine, two antidepressants with relatively short half-lives, have been especially associated with withdrawal reactions [223].

The benefits of treating depression during pregnancy and lactation should be balanced against the risks associated with the treatment itself. Depending on the severity and degree of recurrence of the underlying illness, if the patient is already stabilized on a specific antidepressant, a recent expert panel advises that the patient should be maintained on the same medication, except in the case of paroxetine [215]. Whenever the patient is drug-naïve, sertraline and citalopram appear to be the best therapeutic option [215]. The use of TCAs (with the exception of doxepin) is also a relatively safe option during breast feeding [231].

Risk of Malignancies

Evidence which links antidepressants with increased risk of different types of cancer originates from animal studies and the results from clinical studies appear to be mixed. Most observational studies have been limited by confounders (e.g. age, the use of other medication and smoking). Preclinical studies have found that antidepressants can increase the growth of fibrosarcomas and melanomas, and may also promote mammary carcinogenesis [232]. However, other animal studies have reported the opposite trend (i.e. antidepressant use has been shown to have protective effects in tumor models) [233–235].

A review has found that the associations between the use of SSRIs and TCAs with either breast or ovarian cancer have been mixed across studies [236]. Similarly, a previous meta-analysis of eighteen studies did not support an association between the use of TCAs and SSRIs with breast cancer [237]. However, it should be mentioned that the concomitant use of SSRIs which inhibit the CYP450 2D6 isoenzyme (e.g. paroxetine) and tamoxifen may increase breast cancer-related mortality [238]. In summary, limitations in the overall quality of available evidence do not allow the establishment of causal inferences linking exposure to antidepressants and carcinogenesis [239]. Although clinicians might need to be vigilant when treating female patients with a high risk of breast/ovarian cancer with ADs [240], there is no absolute contraindication to the use of ADs in women with breast cancer [241].

Conclusions

It is a common belief that newer generation antidepressants (and particularly SSRIs) have fewer side effects than TCAs. This assumption only pertains to the safety of ADs in overdose. On the contrary, the long-term use of SSRIs and SNRIs is likely to yield important side effects, which are summarized in table 1. The likelihood of treatment-emergent adverse effects are related to the duration of AD treatment, which has been found to be the case regarding weight gain [53], diabetes [64, 242] and osteoporosis [243].

Some AD-related side effects may persist long after treatment discontinuation. These latter phenomena led to the introduction of the concept of iatrogenic comorbidity in adults [244, 245]. ADs, particularly following long-term use, may increase the risk of experiencing additional psychopathological (e.g. treatment emergent affective switches and paradoxical symptoms), or medical (e.g. obesity and bleeding) problems that do not necessarily subside after discontinuation of the drug, and that may modify responsiveness to subsequent treatments [173]. An issue of concern is that other newer generation ADs have not been used as extensively as SSRIs, SNRIs and TCAs. As Karch and Lasagna [246] note, the history of toxicology reminds us vividly of the lag that often occurs between the first approval of a drug for use in humans and the recognition of certain adverse events from that drug.

There is a tendency to protract treatment for long periods of time, with a widely held belief that it may be protective against recurrences. A meta-analysis indicates that the use of ADs may reduce the risk of recurrences in the maintenance phase [247]. However, patients with multiple major depressive episodes may experience significantly less benefit from long-term AD treatment compared to patients with single episodes [247]. This finding indicates that in patients with chronic recurring MDD, recurrences are difficult to prevent with AD use only. Furthermore, an extensive body of evidence, reviewed in detail elsewhere [173], suggests that the likelihood of relapse increases as a function of the duration of AD treatment. Hence, it has been suggested that the use of ADs should be limited to those patients with the more severe and chronic forms of MDD, for the shortest possible period of time.

The findings of this review suggest that long-term treatment with new generation ADs should be avoided if alternative treatments are available. The sequential use of pharmacotherapy in the acute phase of depression and of psychotherapy in its residual stage may allow the tapering and discontinuation of ADs, with significant clinical advantages [248].

It is thus important to place clinical decisions concerning the use of ADs in the framework of risk (the likelihood of poor outcomes from an index disorder if therapy is withheld), responsiveness to the treatment option, vulnerability to the adverse effects of treatment and availability of nonpharmacological options [173, 249].

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