Review Article

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Addressing the Side Effects of Contemporary Antidepressant Drugs: A Comprehensive Review

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Randomized trials have shown that selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have better safety profiles than classical tricyclic antidepressants (TCAs). However, an increasing number of studies, including meta-analyses, naturalistic studies, and longer-term studies suggested that SSRIs and SNRIs are no less safe than TCAs. We focused on comparing the common side effects of TCAs with those of newer generation antidepressants including SSRIs, SNRIs, mirtazapine, and bupropion. The main purpose was to investigate safety profile differences among drug classes rather than the individual antidepressants, so studies containing comparison data on drug groups were prioritized. In terms of safety after overdose, the common belief on newer generation antidepressants having fewer side effects than TCAs appears to be true. TCAs were also associated with higher drop-out rates, lower tolerability, and higher cardiac side-effects. However, evidence regarding side effects including dry mouth, gastrointestinal side effects, hepatotoxicity, seizure, and weight has been inconsistent, some studies demonstrated the superiority of SSRIs and SNRIs over TCAs, while others found the opposite. Some other side effects such as sexual dysfunction, bleeding, and hyponatremia were more prominent with either SSRIs or SNRIs.

Key Words: *Antidepressive Agents; Depressive Disorder; Drug-related Side Effects and Adverse Reactions*

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INTRODUCTION

An important consideration in the choice of an antidepressant is its safety and tolerability. Before selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) were the mainstay of pharmacological treatment for depression. The TCAs were largely replaced by SSRIs from 1990s with the hope that SSRIs would be more efficacious and safer than TCAs.[1] Studies initially supported this hypothesis suggesting that, although SSRIs do not differ from TCAs in efficacy, they have superior side effect profiles such as less anticholinergic symptoms.[2] However, safety and tolerability concerns related to the newer generation of antidepressants including SSRIs and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) have increased with recent research.[3,4] In addition, side effects which are more specific to serotonin or norepinephrine also have become a concern.[5,6] Thus, the purpose of this review is to critically compare the side effects associated with the newer generation antidepressants, focused on SSRIs and SNRIs, with that of TCAs.

DATA SEARCH

Published articles were identified from PubMed, Embase, Medline, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Web of Science using the key words "antidepressant," "side-effects," and

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"tolerability." There is a countless number of studies regarding antidepressant-associated side-effects, which cannot all be included here due to space limitations. Thus, we focused on large-scale, observational studies and well-designed, randomized controlled trials (RCTs), and previous reviews and meta-analyses focused on comparing side effects of TCAs with those of newer generations of antidepressants including SSRIs, SNRIs, mirtazapine, and bupropion. We aimed to compare safety among different drug classes (i.e. SSRIs vs TCAs) rather than the individual antidepressants (i.e. fluoxetine vs imipramine). Thus, studies containing comparison data as to drug groups were prioritized. Multimodal antidepressants including vilazodone and vortioxetine were also included in the study in a separate section. The data searches and verifications were handled by lead authors (C-U Pae and C Han) and independently reassessed by coauthors (S-J Lee and S-M Wang).

TOLERABILITY AND DROPOUT RATE

Although tolerability might be considered different from side effects, the two could also be closely related because side effects from antidepressants are some of the most common factors responsible for the treatment discontinuation.[7] For example, up to 43% of patients with major depressive disorder (MDD) stopped taking antidepressants due to side effects.[8] Thus, dropout rate and tolerability could be an important indirect hallmark of drug safety. A meta-anlaysis containing 3 head-to-head studies compared dropout and adverse event rates of SSRIs and TCAs. The results showed that SSRIs had significantly lower dropout rates (OR=0.41; 95% CI: 0.19-0.86) and adverse events (adverse event: OR=0.48; 95% CI: 0.32-0.70; $p < 0.001$) than TCAs. In line with this study, a network meta-analysis showed that SSIRs including fluoxetine (OR=0.23; 95% CI: 0.04-0.78), citalopram (OR=0.27; 95% CI: 0.04-0.96), and paroxetine (OR=0.22; 95% CI: 0.08-0.87) were better tolerated than TCAs (imipramine) in children and adolescents with MDD.[9]

ADVERSE REACTIONS

1. Bleeding

It has been hypothesized that antidepressants might affect primary hemostasis by interfering with the uptake mechanism of blood serotonin by platelets. Serotonin causes platelet aggregation, but SSRIs inhibit the uptake of serotonin into platelets.[10] Thus, antidepressants with a high degree of inhibition of serotonin uptake might cause more bleeding abnormalities than antidepressants with a low degree of inhibition of serotonin uptake.[11] A study showed that the risk of GI bleeding increased with SSRIs (Risk ratio (RR)=3.0), but not in those with antidepressants having no serotonin reuptake inhibitor property (RR=0.8).[12] Thereafter, numerous studies reported the risk of bleeding associated with SSRIs and venlafaxine, the most potent serotonergic drug among SNRIs,[13-15] was associated with degree of serotonin reuptake inhibition property.[16] Two studies even showed that SSRIs, but not TCAs, were associated with an increased risk of bleeding.[17,18] Three studies further showed that the bleeding risk increased with low-dose aspirin or NSAID.[19-21]

2. Cardiovascular side-effects

SSRIs were initially considered to have safer cardiac profiles than TCAs.[22] In recent years, newer classes of antidepressants were also suggested to have a high risk of cardiovascular adverse effects. For example, SSRIs were suspected to have the potential to induce QTc interval prolongation, and therefore increase the risk of ventricular arrhythmia.[23] A meta-analysis, which included 16 prospective controlled studies, showed that SSRIs caused significantly greater QTc interval prolongation than did placebo by 6 milliseconds.[24] The QTc prolongation was also dose dependent. Moreover, the study further showed that TCAs prolong the QTc to a greater extent than SSRIs. Among SSRIs, citalopram prolonged the QTc to the greatest extent. Thus, the FDA has put forth a recommendation regarding citalopram and the risk of abnormal heart rhythms.[25]

A descriptive study, based on the continuous pharmacovigilance programs of German-speaking countries, assessed severe cardiovascular adverse reactions occurring in clinical situations.[26] The overall cardiovascular adverse reactions were higher for TCAs (0.15%) and SNRIs than SSRIs (0.08%). The noradrenergic and specific serotonergic antidepressant mirtazapine (0.07%) had a significantly lower risk of cardiovascular adverse events. In terms of hypertension, SNRIs showed a significantly higher risk ($p < 0.001$) than other antidepressants did. Among SNRIs, venlafaxine (incidence rate 0.05%, median dosage 150 mg/day) was revealed to have a significantly higher risk of hypertension ($p < 0.001$). In contrast, hypertension associated with SSRIs was very rare.

Increases in resting-state heart rate and decreases in its variability are associated with substantial morbidity and mortality.[27] Unfortunately, all antidepressants, except for SSRIs, were associated with increases in heart rate. They also decreased heart rate variability (HRV).[28] These negative effects were highest in TCAs (mean=73.94 bpm, $p < 0.001$, Cohen's d, 0.72-0.81) followed by SNRIs (mean=71.00 bpm, Cohen's d, 0.42-0.95) compared to those not on antidepressants (mean=66.87 bpm). Interestingly, the basal heart rate was lower in patients taking SSRIs (mean=65.40 bpm, p=0.003, d=0.161) than in patients taking the placebo (Table 1).

In summary, evidence suggested TCAs are associated with higher cardiovascular risk even in the therapeutic doses. Mechanism behind cardiovascular side effect is very complicated, but TCAs' higher anticholinergic property may be the major cause.[29] While newer antidepressants have greater cardiovascular safety, they are not entirely without risk, because blockade of serotonin and norepinephrine transporters with or without monoamine re-

TABLE 1. Heart rate and variability associated with antidepressant[28]

	Basal Heart Rate (beats per minute)	Cohen's d, p	Heart Rate Variability (lnRMSSD)	Cohen's d, p
Control (No antidepressant)	66.87		3.23	
TCAs	73.94	d=0.721 p<0.001	2.71	d=0.810 p<0.001
SNRI	70.55	d=0.420 p=0.003	2.79	d=0.952 p<0.001
SSRI	65.40	d=0.161 p=0.003	3.08	d=0.280 p<0.001

lnRMSSD, log-transformed root mean square of successive difference. SNRI: serotonin and noradrenaline reuptake inhibitor, SSRIs: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants.

ceptor contributes to cardiovascular problems.[30,31] Among newer antidepressants, SNRIs are associated with an increased incidence of cardiovascular AEs, especially hypertension.[23] Recent studies focused on the risk of SSRIs inducing QTc interval prolongation, especially for citalopram.[32]

3. Dry mouth

Traditionally, TCAs were known to decrease salivary flow rate by blocking the effects of acetylcholine on muscarinic M3 receptors, which can lead to dry mouth.[33] However, meta-regression analysis restricted to SSRIs and SNRIs did not indicate a significant association between M3 receptor affinity and risk of dry mouth.[34] This recent meta-analysis which included 99 RCTs with SSRIs, SNRIs, and atypical antidepressants showed that all antidepressant increased dry mouth compared with placebo. Among them, SNRIs had a higher risk than SSRIs, and fluvoxamine and vortioxetine were not associated with an increased risk of dry mouth. The study further demonstrated that significant risk of dry mouth was associated with SSRIs (Relative risk: 1.64, $p < 0.001$), SNRIs (Relative risk: 2.24, $p < 0.001$), and, to some degree, atypical antidepressant bupropion (Relative risk: 2.0, $p < 0.001$). SNRIs exhibited a moderately higher risk of dry mouth compared to placebo than SSRIs did. The central accumulation of norepinephrine from SNRIs might have activated alpha-2 receptors and concurrent inhibition of parasympathetic salivary neurons in the brainstem, which lead to decreased salivary flow and dry mouth.[34,35] The SSRIs might have had less risk of dry mouth because of their lower affinity for muscarinic cholinergic receptors, alpha-2 receptors, and norepinephrine.

4. Gastrointestinal side effects

The role of serotonin in the gastrointestinal system is very complex, but one thing is very clear: serotonin and its receptors play an important role in gastrointestinal motility.[36] Thus, gastric motility is significantly influenced by drugs having effects on serotonin receptors or serotonin levels.[37] Likewise, higher occurrence of gastrointestinal side effects with fluoxetine than with TCAs have been repeatedly documented in earlier meta-analyses.[38,39] Nausea, vomiting, diarrhea, weight loss and anorexia were more frequent in fluoxetine-treated patients than other SSRIs. TCAs were found to be less often associated with nausea, anorexia and weight loss, but more with constipation and weight gain, in comparison with fluoxetine, which may be due to anticholinergic side effects.[38] Among second generation antidepressants, venlafaxine consistently showed a higher rate of nausea and vomiting than SSRIs.[40-43] A meta-analysis further showed that the relative risk of nausea and vomiting for venlafaxine was higher than those for SSRIs with RR of 1.53 (95% CI, 1.26-1.86).[44]

5. Hepatotoxicity

Classical antidepressants such as monoamine oxidase inhibitors (MAOIs) or TCAs were suspected to have higher potential to induce liver damage than SSRIs. The potential for severe hepatotoxicity associated with nefazodone was also stressed.[45] Recent research supported this early hypothesis, and further showed that among new antidepressants nefazodone, bupropion, duloxetine, and agomelatine have higher risk of liver damage whereas citalopram, escitalopram, paroxetine, and fluvoxamine had lower risks.[46] More importantly, experts believe that it is impossible to prevent idiopathic drug induced liver injury, but the severity of the reaction may be minimized with prompt recognition and early withdrawal of the agent.[46,47]

A quantitative signal detection analysis using pharmacovigilance data from the Uppsala Monitoring Centre from the WHO was conducted to compare the hepatotoxicity of antidepressants.[48] The results showed that agomelatine was statistically associated with an increased risk of hepatotoxicity with a reporting odds ratio of 6.4. Among second generation antidepressants, duloxetine had a higher risk of causing hepatotoxicity. Among TCAs, clomipramine and amitriptyline also had higher hepatotoxicity than SSRIs. Pharmacovigilance data from Europe also showed similar results demonstrating that agomelatine has the highest risk of hepatotoxicity.[49] Milnacipran showed a higher risk of hepatotoxicity rather than duloxetine. Again, SSRIs did not show significant risk compared with other antidepressants (Table 2).

TABLE 2. Antidepressants and Hepatotoxicity

Agents	Gahr (2015)[48]		Montastruc (2014)[49]							
			Spain		France		Italy		Portugal	
	Cases (%)	ROR (95%CI)	Cases (%)	ROR (95%CI)	Cases (%)	ROR (95%CI)	Cases (%)	ROR (95%CI)	Cases (%)	ROR (95%CI)
Agomelatine	334 (19.0%)	6.4 (5.7-7.2)	9 (12.0)	4.9 (2.4-9.7)	22 (16.7)	2.4 (1.5-3.7)	31 (16.1)	5.1 (1.7-4.1)	1 (3.2)	0.9 (0.1-6.4)
Amitriptyline	857 (5.2%)	1.5 (1.4-1.6)	NA	NA	NA	NA	NA	NA	NA	NA
Bupropion	591 (1.2%)	0.3 (0.3-0.4)	6 (0.8)	0.3 (0.1-0.7)	NA	NA	NA	NA	1 (2.1)	0.6 (0.1-4.2)
Citalopram	797 (3.2%)	0.9 (0.8-0.10)	27 (3.9)	1.4 (1.0-2.1)	201 (9.2)	1.2 (1.1-1.4)	10 (3.4)	1.0 (0.5-1.8)	0 (0.0)	-
Clomipramine	608 (7.2%)	2.3 (2.1-2.5)	NA	NA	NA	NA	NA	NA	NA	NA
Duloxetine	2341 (9.0%)	2.7 (2.6-2.8)	10 (2.2)	0.8 (0.4-1.5)	48 (11.4)	1.5 (1.1-2.0)	5 (1.7)	0.5 (0.2-1.2)	2 (3.5)	0.9 (0.2-3.9)
Escitalopram	379 (2.7%)	0.8 (0.7-0.8)	18 (2.8)	1.0 (0.6-1.6)	75 (9.1)	1.2 (0.9-1.5)	6 (2.8)	0.8 (0.3-1.8)	9 (5.5)	1.5 (0.8-3.0)
Fluoxetine	1854 (3.0%)	0.8 (0.8-0.9)	36 (2.5)	0.9 (0.6-1.6)	388 (12.2)	1.6 (1.5-1.8)	6 (2.6)	0.7 (0.3-1.6)	5 (2.2)	0.6 (0.2-1.4)
Fluvoxamine	297 (3.4%)	1.0 (0.9-1.1)	3 (1.3)	0.5 (0.2-1.5)	98 (13.1)	1.8 (1.4-2.2)	NA	NA	0 (0.0)	-
Milnacipran	74 (2.6%)	0.7 (0.6-0.9)	8 (3.6)	1.3 (0.6-2.7)	345 (19.9)	2.9 (2.6-3.3)	4 (16.0)	5.1 (1.5-5.6)	1 (4.6)	1.3 (0.2-9.3)
Mirtazapine	778 (5.2%)	1.5 (1.4-1.6)	23 (3.6)	1.3 (0.8-1.9)	75 (11.8)	1.6 (1.2-2.0)	4 (3.6)	1.0 (0.3-2.8)	1 (2.0)	0.5 (0.0-3.9)
Nefazodone	930 (10.6%)	3.2 (3.0-3.5)	4 (10.8)	4.3 (1.5-12.1)	NA	NA	NA	NA	NA	NA
Paroxetine	1306 (2.2%)	0.6 (0.6-0.7)	41 (2.8)	1.0 (0.8-1.4)	331 (10.1)	1.3 (1.2-1.5)	14 (2.8)	0.8 (0.3-1.8)	4 (1.8)	0.5 (0.2-1.3)
Sertraline	1398 (2.9%)	0.8 (0.8-0.9)	35 (4.5)	1.7 (1.2-2.4)	99 (9.3)	1.2 (1.0-1.5)	11 (3.1)	0.9 (0.4-1.6)	7 (4.1)	1.1 (0.5-2.4)
Tianeptine	124 (13.9%)	4.4 (3.6-5.3)	NA	NA	140 (16.1)	2.3 (1.9-2.7)	NA	NA	NA	NA
Trazodone	386 (3.6%)	1.0 (0.9-1.1)	16 (4.8)	1.8 (1.1-3.0)	NA	NA	1 (1.2)	0.3 (0.0-2.1)	6 (3.5)	1.0 (0.4-2.2)
Venlafaxine	1297 (3.2%)	0.9 (0.86-1.0)	18 (2.5)	0.9 (0.6-1.5)	223 (12.4)	1.7 (1.5-1.9)	7 (2.1)	0.6 (0.3-.1.2)	2 (1.4)	0.4 (0.1-1.5)

[1]based on 9,383,954 adverse drug reactions reports in VigiBase™. ROR: reporting odds ratio. Spain: adverse drug reactions recorded between January 1, 1990, and December 31, 2011, France: ADRs recorded between January 1, 1985, and January 23, 2012, Italy: ADRs recorded between January 1, 2001, and December 31, 2011, Portugal: ADRs recorded between January 1, 1992, and November 8, 2012.

6. Seizure

When we talk about seizure, bupropion readily comes to mind. The use of bupropion immediate release (IR) in dosages more than 450 mg may cause a 10-fold increase of the estimated seizure incidence.[50] However, with the development of bupropion sustained release (SR), the incidence of seizure was decreased to 0.1% in a study containing 3,094 patients (50-300 mg).[51] The seizure incidence was similar to that of the general population (0.07-0.09%) as well as that of other antidepressants including SSRIs (0.1%).[52]

Classical studies showed that epileptogenic potential is higher for TCAs than for bupropion, so TCAs are still contraindicated for individuals with seizure disorders.[53] However, recent studies concerning seizure were contradictory. A retrospective study containing 238,963 patients extracted from the primary care database of the UK showed that all antidepressants increased risk of seizure.[54] For the first 5 years of prescription, trazodone (Hazard Ratio 5.41, 95 % confidence interval (CI) 3.05 to 9.61, number needed to harm (NNH) 65) had the highest risk compared with no antidepressant, followed by lofepramine (HR 3.09), venlafaxine (HR 2.84), and combined treatment (HR 2.73). Although TCAs as a class had higher risk (HR: 2.32) than SSRIs (HR: 1.92), the study included trazodone as a TCAs. Thus, if trazodone was not included as TCAs, then HR for SSRIs and TCAs might be very similar. Among SSRIs, paroxetine and citalopram had a higher risk whereas escitalopram and sertraline had a lower risk of seizure.

Another retrospective follow-up study, with a nested case-control analysis between 1998 and 2012, further showed that the risk of seizure was higher for SSRIs (odds ratio: 1.98) than for TCAs (OR: 0.99). Among SSRIs, sertraline had the highest risk (OR: 2.53). As a whole both sertraline and venlafaxine (for both, OR: 2.53) had the highest risks.[55] Furthermore, within the case-control analysis, relative risk estimates for seizures were increased in current users of SSRIs (OR: 1.98) and SNRIs (OR: 1.99), but not in TCAs (OR: 0.99).

A study sought to investigate seizures during antidepressant drug treatment in a "real-life" setting of routine psychiatric treatment in a psychiatric inpatient population by analyzing data of the pharmacovigilance project from 1993 to 2008. The study showed that 77 seizure grand mal seizure were identified among 142,090 inpatients under surveillance. The TCAs had a 2-fold risk to develop a seizure as compared to other antidepressants (0.10%). For SSRIs, the seizure risk was not enhanced relative to our reference population with a seizure rate of 0.05%. The SNRIs and noradrenergic and specific serotonergic antidepressants (NaSSAs) showed the lowest subgroup seizure rates with 0.02 % each[56] (Table 3 for summary of the 3 studies).

7. Suicidality

The FDA has issued a black box warning concerning the risk of suicidality associated with the use of antidepressants in children and adolescents from 2004. Despite this fact, whether or not antidepressants truly increase suicidality is up for debate because depression itself is associated with

TABLE 3. Seizure and antidepressants

	Hill (2015)[54]		Bloechliger (2015)[55]		Köster (2013)[56]	
	HR[1]	p	IR/10,000 person-years	OR[2]	AD imputed for GMS (case/exposed)	AD imputed for GMS (%)
No antidepressant	1			1	28/52,887	0.05
TCAs	2.32	<0.001	8.33	0.99	43/43,602	0.10
Amitriptyline	1.94	<0.001	12.18	1.48	6/10,721	0.06
Dosulepin	2.19	0.001	NA	NA	NA	NA
Lofepramine	3.09	<0.001	NA	NA	NA	NA
Trazodone	5.41	<0.001	NA	NA	4/3,904	0.10
SSRIs	1.92	<0.001	12.44	1.98	28/52,887	0.05
Citalopram	2.03	<0.001	14.11	1.69	9/14,682	0.06
Escitalopram	1.49	0.171	9.90	1.28	3/11,931	0.03
Fluoxetine	1.92	<0.001	10.51	1.51	3/4,074	0.07
Paroxetine	2.02	0.003	9.12	1.04	6/8,680	0.07
Sertraline	1.56	0.045	16.97	2.53	4/10,067	0.04
SNRI			15.44	1.99	5/23,233	0.02
Venlafaxine	2.84	<0.001	16.73	2.53	5/19,401	0.03
Others	2.33	<0.001	NA	NA	NA	NA
Mirtazapine	1.72	0.028	17.06	1.53	6/32,179	0.02
Combined use	2.73	0.001	NA	NA	NA	NA

AD: Antidepressant, GMS: Grand Mal Seizure, HR: Hazard ratio, IR: Incidence rate, SNRI: serotonin and noradrenaline reuptake inhibitor, SSRIs: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants. [1]Adjusted for age, sex, year of diagnosis of depression, severity of depression, deprivation, smoking status, alcohol intake, ethnic group (white/not recorded or non-white), and diverse medical histories. [2]Adjusted for alcohol consumption, other antidepressant drugs, benzodiazepines, antipsychotics, opioids, schizophrenia, affective disorders other than depression, compulsive disorders, suicidal ideation, dementia, Parkinson's disease, transient ischemic attack, and stroke.

an increased risk of suicide.[57] Moreover, the meta-analysis which lead to the black box warning in fact showed that rate of suicidal thinking or suicidal behavior was 4% among patients being prescribed an antidepressant, as compared with 2% among those being taken placebo.[58] A network meta-analysis, which included 34 trials with 5260 participants and 14 antidepressants, was recently conducted to compare efficacy and tolerability of antidepressants in children and adolescents having MDD. A significantly increased risk of suicidal behavior or ideation was found with the use of venlafaxine than placebo (OR 0·13, 95% CI: 0·00-0·55) and five other antidepressants (escitalopram, imipramine, duloxetine, fluoxetine, and paroxetine).[9] With limited data, it is not possible conclude that newer antidepressants have a higher risk of causing suicidality. However, more importantly, it is also obvious that the newer antidepressants are not necessarily more beneficial.

8. Safety in overdose

Depression is the most prevalent psychiatric disorder in people who die by committing a suicide.[59] It has been estimated that a quarter of patients diagnosed with major depression attempt suicide in their lifetime, and 15% of those patients ultimately die from suicide.[60] Therefore, the safety of antidepressants in overdose is a matter of concern.

A study done in the US investigated poison control data of 25 antidepressants from 2000 to 2004.[61] The hazard index (number of major or fatal outcomes per 1000 reported antidepressant ingestions) was used to compare safety after suicidal overdose of antidepressants. Amoxapine (292), maprotiline (211), and desipramine (187) had the highest hazard indices. Moreover, all newer antidepressants including SSRIs, SNRIs, and mirtazapine (but bupropion) had much lower hazard indices than the TCAs.

Another study, using a retrospective chart review, conducted in the UK assessed the relative toxicity of TCAs with that of SSRIs, a serotonin and noradrenaline reuptake inhibitor (SNRIs) venlafaxine, and mirtazapine.[62] The study used two methods for assessing relative toxicity of antidepressants, the fatal toxicity index (mortality rate divided by prescription rate) and the case fatality index (mortality rate divided by self-poisoning rate). The case fatality index was used to minimize bias from selective prescribing. The results showed that the case fatality rate ratio was significantly less with SSRIs (0.5, 95% CI 0.4-0.7) than with TCAs (13.8, 95% CI 13.0-14.7). Venlafaxine (2.5, 95% CI 2.0-3.1) and Mirtazapine (1.9, 95% CI 1.1-2.9) were also safer than TCAs, but the case fatality rate ratio was higher than that of SSRIs. The fatal toxicity index was also greatest for TCAs compared to Venlafaxine, Mirtazapine, and SSRIs (Table 4).

9. Sexual dysfunction

Sexual dysfunction in patients with MDD is very com-

TABLE 4. Safety after overdosing antidepressants

	Hawton (2010)[62]				White (2008)[61]
	Fatal toxicity[1]		Case fatality[2]		Hazard Index[4]
	Rate ratio (95% CI)	RTI[3]	Rate ratio (95% CI)	RTI[3]	
TCAs	18.8 (17.7-20.0)	1.7	13.8 (13.0-14.7)	1.6	NA
Amitriptyline	11.4 (10.3-12.6)	1.0	8.6 (7.8-9.5)	1.0	154
Amoxapine	NA		NA		292
Clomipramine	14.1 (10.0-19.3)	1.2	12.5 (8.9-17.0)	1.4	74
Desipramine	NA	NA	NA		187
Dosulepin	36.3 (33.4-39.3)	3.2	23.3 (21.4-25.2)	2.7	
Doxepin	28.1 (17.6-42.6)	2.5	22.5 (14.1-34.0)	2.6	148
Imipramine	12.4 (8.1-18.4)	1.1	12.8 (8.3-18.9)	1.5	136
Nortriptyline	9.9 (3.2-23.2)	0.9	11.0 (3.6-25.5)	1.3	88
Maprotiline	NA	NA	NA		187
Trimipramine	15.0 (8.0-25.6)	1.3	14.2 (7.8-24.3)	1.7	56
SSRIs	0.9 (0.7-1.1)	0.08	0.5 (0.4-0.7)	0.06	
Citalopram	1.7 (1.3-2.3)	0.15	1.1 (0.8-1.4)	0.12	27
Fluoxetine	0.5 (0.3-0.9)	0.05	0.3 (0.2-0.5)	0.03	4
Fluvoxamine	0	0	0	0	22
Paroxetine	0.5 (0.2-0.9)	0.04	0.3 (0.1-0.5)	0.03	5
Sertraline	0.7 (0.3-1.3)	0.06	0.4 (0.2-0.8)	0.05	4
Venlafaxine	5.3 (4.2-6.6)	0.46	2.5 (2.0-3.1)	0.29	27
Mirtazapine	3.6 (2.1-5.7)	0.32	1.9 (1.1-2.9)	0.22	12
Bupropion	NA	NA	NA	NA	97

NA: Not available, TCAs: tricyclic antidepressants. [1]Fatal toxicity=mortality rate/prescription rate. [2]Case fatality=mortality rate/self-poisoning rate. [3]RTI: Relative toxic index, index of toxicity relative to amitriptyline. [4]hazard index=number of major or fatal outcomes per 1000 reported antidepressant ingestions.

plex because it is associated with both the condition and the antidepressant used.[63] Despite the controversy, antidepressant induced sexual dysfunction is an important concern because up to 80% of depressed patients from randomized clinical trials reported treatment-emergent sexual side effects.[64] All antidepressants exhibiting serotonin and/or norepinephrine reuptake properties are known to cause sexual dysfunction. There are minor individual variations among these drugs, but no studies have confirmed that newer antidepressants have lower rates of sexual dysfunction than TCAs. In contrast, a study showed that the antidepressants with high serotonin selectivity such as citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine showed the highest rates of total sexual dysfunction. Although imipramine showed significantly higher sexual dysfunction than placebo, the rate was lower than the previous 5 antidepressants.[65] In line with this hypothesis, another network meta-analysis showed that bupropion, an antidepressant with no serotonergic effect but dopaminergic effect, had a statistically significantly lower risk of sexual dysfunction than other second generation antidepressants.[66]

10. Weight gain

Early studies have suggested that newer antidepressants, SSRIs and SNRIs still have a risk of weight gain, but mirtazapine have less risk of causing weight gain than TCAs.[67] It was generally accepted that paroxetine has a higher risk of weight gain amongst the SSRIs, and amitriptyline was thought to cause the most potent weight gain among TCAs.[68] In contrast, a retrospective study showed that the mean weight change among patients receiving amitriptyline (N=284), sertraline (N=180) and fluoxetine (N=80) did not differ.[69] A meta-analysis further showed that SSRIs including citalopram, escitalopram, fluoxetine, sertraline, paroxetine and SNRIs including venlafaxine and duloxetine were associated with weight loss compared with placebo. However, weight losing effects disappeared with longer term (>4 months) therapy, and paroxetine conversely caused significant weight gain. Amitriptyline and mirtazapine consistently showed weight gaining effects throughout acute and long-term treatment. Imipramine and bupropion showed significant weight loss effects for both acute and long term treatment (Table 5).[70] A more recent study using electronic health records showed even more conflicting results. The study included 22,610 patients with 19,244 patients prescribed an antidepressant for at least 3 months. The primary outcome measure included a rate of change in weight over 12 months following index prescription using a regression with mixed effects. All antidepressants caused weight gain rather than weight loss. After adjusting for socio-demographic and clinical features, bupropion, amitriptyline, and nortriptyline caused significantly less weight gain than citalopram. Among pa-

TABLE 5. Effect of antidepressants on weight change

	Serretti (2010)[70]		Blumenthal (2014)[71]			
	Weight change after 4 months or longer of antidepressant		Weight change compared With citalopram in mixed-effects models (12 months)			
	Mean weight difference, kg[a]	p	All Patients		Completers[c]	
			β (SE)	p	β (SE)	p
Amitriptyline	2.24	<.0001	−0.081 (0.025)	.001	−0.063 (0.028)	.02
Imipramine	−0.04	NS	NA	NA	NA	NA
Nortriptyline	1.24	NS	−0.147 (0.034)	<.001	−0.144 (0.038)	<.001
Citalopram	1.69	NS	0[b]		0	
Escitalopram	0.65	NS	−0.071 (0.038)	.06	−0.097 (0.043)	.02
Fluoxetine	−0.31	NS	−0.003 (0.022)	.90	0.000 (0.025)	.99
Paroxetine	2.73	.006	−0.046 (0.026)	.08	−0.057 (0.029)	.05
Sertraline	−0.12	NS	−0.044 (0.026)	.09	−0.032 (0.029)	.27
Duloxetine	0.71	NS	−0.093 (0.049)	.06	−0.103 (0.055)	.06
Mirtazapine	2.59	.07	−0.054 (0.056)	.34	−0.056 (0.064)	.39
Buproprion	−1.87	<.0001	−0.063 (0.027)	.02	−0.077 (0.031)	.01
Venlafaxine	NA	NA	−0.044 (0.033)	.19	−0.012 (0.038)	.76

[a]vs placebo, [b]Citalopram as the reference, [c]Completers include only patients who had a weight measured at the 12-month point.

tients who completed the study and had a weight measured at the 12-month point, in addition to the above three antidepressants, escitalopram also caused significantly less weight gain than citalopram. As controls, they also included weight loss agents including orlistat, phentermine, and sibutramine, which all resulted in decrease in weight (Table 5).[71]

11. Others - hyponatremia, sleep, and sweating

The first reports of antidepressant-induced hyponatremia concerned the tricyclic antidepressant class, but most studies suggested SSRIs (OR: 1.5-21.6) have a higher risk than TCAs (OR: 1.1-4.9).[72] A head-to-head comparison of these two classes in the large population-based Coupland cohort study confirmed this by showing lower HR for TCAs than for SSRIs (1:1.44, p=0.002).[73] Within SSRIs, citalopram and escitalopram were constantly noted for higher incidences than other SSRIs.[74,75] Studies also suggested that hyponatremia incidence with venlafaxine was equal to or higher than that of SSRIs, but studies regarding duloxetine are yet to be defined.[72] Above all, older age (OR: 6.3) and concomitant use of (thiazide) diuretics (OR: 11.2-13.5) increased the risk of antidepressant induced hyponatremia.

The effect of antidepressants on sleep is very complicated, and patients with depression may experience both decreased and / or increased sleep. Thus, it is not wise to simply conclude whether or not newer antidepressants Are safer in terms of sleep. For example, venlafaxine is associated with increased rapid eye-movement (REM) sleep latency and a reduction in the overall time spent in the REM phase while sleeping, which is why it is one of the first line drugs for cataplexy and narcolepsy with or without depression.[76] Many TCAs, including doxepin, have a very strong sedating effect. Thus, low doses of doxepin (3 and 6 mg) were approved by the FDA for the treatment of insomnia.[77] Mirtazapine, an antidepressant promoting sleep, may do so not through a sedative action but through resynchronization of the circadian rhythm.[78] Bupropion is well known to cause insomnia, but it is also effective in patients with attention deficit hyperactivity disorder (ADHD) or atypical depression (patients with hypersomnia).[79,80]

Excessive sweating has been associated with antidepressants including TCAs, SSRIs, and SNRIs. Studies showed approximately 10% of patients on SSRIs may develop excessive sweating.[81] Venlafaxine and TCAs also showed similar incidence rates.[82] Benztropine, cyproheptadine, and terazosin could be used to alleviate antidepressant-induced sweating, but its effects have not yet been confirmed.[83-85]

12. Mortality

As partly described in previous section, all antidepressants may have some potential to increase mortality in relation to their use. Evidence has been consistent in relation with the increasing risk of all causes of mortality due to antidepressants use.[86] According to the recent meta-analyses, antidepressants' use was associated with a 33% increase in mortality corresponding to estimated additional 2.64 deaths per 1,000 person-years.[87] Furthermore, mixed evidence suggests that antidepressants may increase the risk of cardiovascular and cerebrovascular events according to metaanalyses.[88] Some studies have found that antidepressant use was associated with a small increase in all-cause mortality, while other meta-analysis has suggested potential differences based on population characteristics. Antidepressants may be hazardous in the general population, but are less so in cardiovascular pa-

tients, perhaps owing to the positive effects in the clotting process involving platelet cell activation.[87,89] Similarily, the class effects of antidepressants on all cause mortality are also still elusive, although the widespread use of SSRIs is partly based on the belief that they are safer than the older TCAs.[87] However, MDD itself is also-well-known to increase the mortality of patients regardless of disease severity (relative risk of MDD=1.58 vs. subthreshold depression=1.33)[90] continuously supported by a number of cohort studies.[91-93] Therefore we have to keep in mind that the use of antidepressants may have an increased risk of all cause mortality related to myocardial infarction, stroke, falls, upper gastrointestinal bleeding, seizures, bold dyscrasia, and adverse drug reactions, and thereby antidepressants use should be prescribed depending on risk/benefit assessment particularly in vulnerable patients in clinical practice at clinicians' careful discretion.[73]

SAFETY OF EVEN NEWER RECENTLY FDA APPROVED DRUGS: MULTIMODAL ANTIDEPRESSANTS

Among the latest approved novel antidepressants (antidepressants having distinct chemical structural and mechanisms of action rather than metabolites of a parent drug), vilazodone and vortioxetine are considered multi-modal drugs. For example, in addition to the SSRI activity, vilazodone is a partial agonist at the serotonergic 5-HT_{1A} receptor[94] and vortioxetine has an antagonistic property on 5-HT_3, 5-HT_7 and 5-HT_{1D} receptors, while it shows agonist activity at the 5-HT_{1A} receptor as well as presenting a partial agonist profile at the 5-HT_{1B} receptor.[95]

In regards to vilazodone, there was only one RCT which compared it with SSRIs (citalopram). The two had a similar discontinuation rate in general and from adverse events. However, significantly more patients treated with vilazodone experienced diarrhea (26.5% vs. 10.6%; RR 2.49, 95% CI 1.69-3.67) and vomiting (6.6% vs. 1.8%; RR 3.73, 95% CI 1.41-9.86) than patients treated with citalopram.[96,97]

In regards to vortioxetine, some side effect profiles were better than those of other second-generation antidepressants. For example, patients on vortioxetine experienced a lower risk of decreased appetite, fatigue, sexual dysfunction, and somnolence than patients on duloxetine.[98,99] However, in the other RCT, significantly more patients treated with vortioxetine experienced nausea (37.5% vs. 16.7%; RR 2.25, 95% CI 1.12-4.53) than patients treated with paroxetine.[97] Although the studies reported here only included RCT, with its primary aim as investigating the efficacy and tolerability of vortioxetine and vilazodone with placebo rather than comparator, the available evidence does not indicate fewer negative effects of vilazodone and vortioxetine as compared with other second-generation antidepressants.

DISCUSSION

Initially, monoamine oxidase inhibitors (MAOIs) were used to treat depression. Safety was a big concern with MAOIs because fatal hypertensive crises could occur if large amounts of tyramine was obtained from food.[100] Thus, patients taking MAOI had to change their diets to limit or avoid foods and beverages containing tyramine which largely decreased the tolerability and compliance related with antidepressant treatment. With TCAs, fatal hypertensive crisis was no longer an issue, so the patients did not have to limit their diets. However, many side effects related to the antimuscarinic properties arose.[101] Furthermore, fatal cardio- and neuro-toxicity when over used, could be attributed to the antimuscarinic properties, which still remained as a safety concern.[61,102] With the development of newer generation antidepressants with high selective action mechanisms, such as SSRIs and SNRIs, hypertensive crises no longer were an issue. However, the high serotonin selectivity may be related to higher risk of bleeding and hyponatremia in SSRIs than in TCAs (Fig. 1).[103]

In terms of safety after overdose, the common belief that newer generation antidepressants have fewer side effects than TCAs appears to be true. TCAs were also associated with higher drop-out rates and lower tolerability. TCAs were associated with higher cardiovascular risk, such as acute toxicity, but SSRIs and SNRIs were not entirely

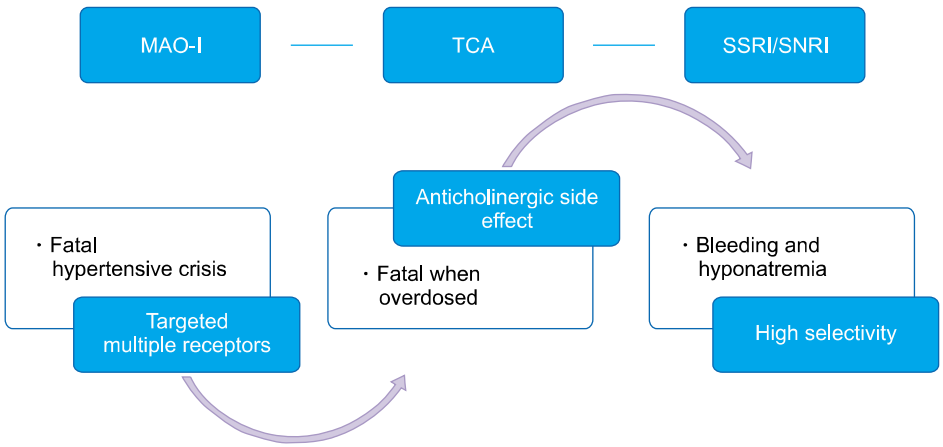

FIG. 1. Evolution of antidepressants and safety profile. MAO-I: Monoamine oxidase inhibitor, SSRI: Selective serotonin reuptake inhibitor, SNRI: Serotonin norepinephrine reuptake inhibitor, TCA: Tricyclic antidepressants.

risk-free. SNRIs are especially associated with increased incidence of cardiovascular AEs, such as hypertension. QTc interval prolongation was consistently shown to be a problem for citalopram. Classically, TCAs were known to have a higher risk of seizure than bupropion. However, our review suggested that the risk is the highest for trazodone, and the benefit of SSRIs over TCAs in seizures has not been confirmed. Similarly, studies regarding SSRIs and SNRIs in dry mouth, gastrointestinal side effect, hepatotoxicity, and weight were contradictory, some showing their superior over TCAs and some illustrating the opposite. In contrast, sexual dysfunction, bleeding, and hyponatremia were more prominent in antidepressants with high serotonin selectivity (SSRIs > SNRIs > TCAs).

Classically, double blinded RCT was known to be the golden standard for assessing safety and efficacy of an antidepressant. However, the ethical and feasibility aspects of the use of placebo in clinical trials are increasingly being debated.[104] Likewise, in general many short-term studies, such as RCT, suggested that SSRIs and SNRIs have a better safety profile than the TCAs. On the contrary, the long-term studies, such as naturalistic/retrospective and pharmacovigilance studies, showed that the use of SSRIs and SNRIs is likely to yield important side effects.[103] Various biases could have resulted in discrepancies between results from RCT and naturalistic studies.[105]

An interesting meta-analysis compared reports of adverse effects in the placebo groups in SSRIs and TCAs among RCTs. Interestingly, significantly more profound adverse effects were reported in TCA-placebo groups compared with SSRI-placebo groups.[106] For example, dry mouth (odds ratio [OR] = 3.5; 95% CI: 2.9-4.2), drowsiness (OR = 2.7; 95% CI: 2.2-3.4), constipation (OR= 2.7; 95% CI: 2.1-3.6), sexual problems (OR =2.3; 95% CI 1.5-3.5) were more frequent in the placebo group with the TCAs study than the placebo group or the SSRIs study. The clinicians or investigators may have expected a better safety profile for SSRIs than TCAs causing the placebo group within the SSRIs study to have less reported side effects.[107] Likewise, the researchers may have expected the placebo group within the TCA group to have a poorer safety profile which is called the Golem effect.[108] Regardless of the cause, adverse effect profiles between SSRIs and TCAs are prone to systematic expectation influences.[106]

A simple solution to this complicated problem is conducting more long-term head-to-head RCT directly comparing the safety of TCAs and SSRIs/SNRIs. In the industry's perspective, conducting such studies would result in more loss than gain. However, such studies will represent a large financial and chronological burden, so it is almost impossible for investigators to undertake such studies without industry's support. The ethical burden is another important obstacle. More importantly, many SSRIs and SNRIs have lost their patency, so they are starting to be replaced with even more expensive drugs such as multimodal drugs (i.e. vilazodone and vortioxetine).[109] Thus, there is even less impetus for industry to support such safety studies.

An alternative solution is using increasing public grants aimed at investigating longer-term safety of TCAs with other newer generation antidepressants. In order to prevent a publication bias or reduce the pressure of producing positive studies, the grant could be linked to a certain renowned journal ensuring publication regardless of data results.[105] There is a large discrepancy in patient characteristics between subjects enrolled in RCT and in real clinical practice. Thus, another realistic solution is undertaking more naturalist studies and registry studies using big-data analysis. Once again, public grants will help ease with the financial burden related to conducting research. More balanced data regarding, not only efficacy, but also the safety of antidepressants is needed for better selection of antidepressants based on clinically useful evidence. In order to so, more unsolicited research is needed in the near future.

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CONFLICT OF INTEREST STATEMENT

None declared.

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