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

Sheng-Min Wang¹,², Changsu Han³, Won-Myoung Bahk¹, Soo-Jung Lee¹, Ashwin A. Patkar⁴, Prakash S. Masand⁵, and Chi-Un Pae¹,⁴,⁶,∗

¹Department of Psychiatry, The Catholic University of Korea College of Medicine, Seoul, ²International Health Care Center, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, ³Department of Psychiatry, Korea University, College of Medicine, Seoul, Korea, ⁴Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, ⁵Global Medical Education, New York, NY, USA, ⁶Cell Death Disease Research Center, College of Medicine, The Catholic University of Korea, Seoul, Korea

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

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

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 would be more efficacious and safer than TCAs, 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
“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. For example, up to 43% of patients with major depressive disorder (MDD) stopped taking antidepressants due to side effects. Thus, dropout rate and tolerability could be an important indirect hallmark of drug safety. A meta-analysis 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 SSRIs 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.

**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. 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. 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). Thereafter, numerous studies reported the risk of bleeding associated with SSRIs and venlafaxine, the most potent serotonergic drug among SNRIs, was associated with degree of serotonin reuptake inhibition property. Two studies even showed that SSRIs, but not TCAs, were associated with an increased risk of bleeding. Three studies further showed that the bleeding risk increased with low-dose aspirin or NSAID.

2. **Cardiovascular side-effects**

SSRIs were initially considered to have safer cardiac profiles than TCAs. 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. A meta-analysis, which included 16 prospective controlled studies, showed that SSRIs caused significantly greater QTc interval prolongation than did placebo by 6 milliseconds. 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.

A descriptive study, based on the continuous pharmacovigilance programs of German-speaking countries, assessed severe cardiovascular adverse reactions occurring in clinical situations. 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. Unfortunately, all antidepressants, except for SSRIs, were associated with increases in heart rate. They also decreased heart rate variability (HRV). 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. 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

|                | Basal Heart Rate (beats per minute) | Heart Rate Variability (lnRMSSD) |
|----------------|-------------------------------------|----------------------------------|
| 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, SSRI: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants.

Receptor contributes to cardiovascular problems. Among newer antidepressants, SNRIs are associated with an increased incidence of cardiovascular AEs, especially hypertension. Recent studies focused on the risk of SSRI induced QTc interval prolongation, especially for citalopram.

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. However, meta-regression analysis restricted to SSRIs and SNRIs did not indicate a significant association between M3 receptor affinity and risk of dry mouth. 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 antidepressants (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. 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. Thus, gastric motility is significantly influenced by drugs having effects on serotonin receptors or serotonin levels. Likewise, higher occurrence of gastrointestinal side effects with fluoxetine than with TCAs have been repeatedly documented in earlier meta-analyses. 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. Among second generation antidepressants, venlafaxine consistently showed a higher rate of nausea and vomiting than SSRIs. 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).

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. 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. 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. A quantitative signal detection analysis using pharmacovigilance data from the Uppsala Monitoring Centre from the WHO was conducted to compare the hepatotoxicity of antidepressants. 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. Milnacipran showed a higher risk of hepatotoxicity rather than duloxetine. Again, SSRIs did not show significant risk compared with other antidepressants (Table 2).
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.49 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).50 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 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 treatment. 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% each55 (Table 3 for summary of the 3 studies).

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% each56 (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) | Bloechliger (2015) | Köster (2013) |
|----------------|-------------|--------------------|--------------|
|                | HR¹ | p      | IR/10,000 person-years | OR² | 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                     |
| SSRI           | 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, OR: Odds ratio, SNRI: serotonin and noradrenaline reuptake inhibitor, SSRI: 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.

---

8. Safety in overdose

Depression is the most prevalent psychiatric disorder in people who die by committing a suicide. An increased risk of suicide 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). With limited data, it is not possible to 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. 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. 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. 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.

---

9. Sexual dysfunction

Sexual dysfunction in patients with MDD is very com-
**Review of Antidepressant Side Effects**

**Table 4. Safety after overdosing antidepressants**

|                  | Fatality¹ |             | Case fatality² |             | Hazard Index ³ |
|------------------|-----------|------------|----------------|------------|----------------|
|                  | Rate ratio (95% CI) | RTI⁴       | Rate ratio (95% CI) | RTI⁴        |                |
| **TCAs**         |           |            |                |            |                |
| 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             |            | 187            |
| Dosulepin        | 36.3 (33.4-39.3)            | 3.2                   | 23.3 (21.4-25.2)         | 2.7                   | 148            |
| Doxepin          | 28.1 (17.6-42.6)            | 2.5                   | 22.5 (14.1-34.0)         | 2.6                   | 136            |
| Imipramine       | 12.4 (8.1-18.4)             | 1.1                   | 12.8 (8.3-18.9)          | 1.5                   | 88             |
| Nortriptyline    | 9.9 (3.2-23.2)              | 0.9                   | 11.0 (3.6-25.5)          | 1.3                   | 56             |
| Maprotiline      | 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             |            | 97             |

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

**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-
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). 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). Within SSRIs, citalopram and escitalopram were constantly noted for higher incidences than other SSRIs. 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. 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. 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. Mirtazapine, an antidepressant promoting sleep, may do so not through a sedative action but through resynchronization of the circadian rhythm. Venlafaxine 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).

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

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. 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. Furthermore, mixed evidence suggests that antidepressants may increase the risk of cardiovascular and cerebrovascular events according to metaanalyses. 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-

TABLE 5. Effect of antidepressants on weight change

| Weight change after 4 months or longer of antidepressant | Mean weight difference, kg<sup>a</sup> | p | Blumenthal (2014)<sup>71</sup> | All Patients | Completers<sup>c</sup> |
|--------------------------------------------------------|-------------------------------------|---|---------------------|--------------|-----------------|
|                                                        |                                     |   |  (SE) p            |  (SE) p     |  (SE) p        |
| Amitriptyline                                          | 2.24                                | <.001 | −0.081 (0.025)      | .001         | −0.063 (0.028)  |
| Imipramine                                             | −0.04                               | NS  | NA                 | NA           | NA              |
| Nortriptyline                                          | 1.24                                | NS  | −1.147 (0.034)     | <.001        | −1.144 (0.038)  |
| Citalopram                                             | 1.69                                | NS  | 0                  |             | .001            |
| Escitalopram                                           | 0.65                                | NS  | −0.071 (0.038)     | .06          | −0.097 (0.043)  |
| Fluoxetine                                             | −0.31                               | NS  | −0.003 (0.022)     | .90          | 0.000 (0.025)   |
| Paroxetine                                             | 2.73                                | .001 | −0.046 (0.026)     | .08          | −0.057 (0.029)  |
| Sertraline                                             | −0.12                               | NS  | −0.044 (0.026)     | .09          | −0.032 (0.029)  |
| Duloxetine                                             | 0.71                                | NS  | −0.093 (0.049)     | .06          | −0.103 (0.055)  |
| Mirtazapine                                            | 2.59                                | .07  | −0.054 (0.056)     | .34          | −0.056 (0.064)  |
| Buproprion                                             | −1.87                               | <.001 | −0.063 (0.027)     | .02          | −0.077 (0.031)  |
| Venlafaxine                                            | NA                                  | NA  | −0.044 (0.033)     | .19          | −0.012 (0.038)  |

<sup>a</sup> vs placebo, <sup>c</sup>Citalopram as the reference, <sup>c</sup>Completers include only patients who had a weight measured at the 12-month point.
Review of Antidepressant Side Effects

patients, perhaps owing to the positive effects in the clotting process involving platelet cell activation.87,89 Similarly, 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 in-crease 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-HT1A receptor94 and vortioxetine has an antagonistic property on 5-HT3, 5-HT7 and 5-HT1D receptors, while it shows agonist activity at the 5-HT1A receptor as well as presenting a partial agonist profile at the 5-HT1B 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.](image-url)
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 SSRI s 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 or 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. 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. Various biases could have resulted in discrepancies between results from RCT and naturalistic studies.

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. 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. 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. Regardless of the cause, adverse effect profiles between SSRIs and TCAs are prone to systematic expectation influences.

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 patenty, so they are starting to be replaced with even more expensive drugs such as multimodal drugs (i.e. vilazodone and vortioxetine). 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. 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.

ACKNOWLEDGEMENTS

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HC15C1405).

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Ioannidis JP. Effectiveness of antidepressants: an evidence myth constructed from a thousand randomized trials? Philos Ethics Humit Med 2008;3:14.
2. Peretti S, Judge R, Hindmarch I. Safety and tolerability considerations: tricyclic antidepressants vs. selective serotonin reuptake inhibitors. Acta Psychiatr Scand Suppl 2000;403:17-25.
3. Whiskey E, Taylor D. A review of the adverse effects and safety of noradrenergic antidepressants. J Psychopharmacol 2013;27:732-9.
4. Moret C, Isaac M, Briley M. Problems associated with long-term treatment with selective serotonin reuptake inhibitors. J Psychopharmacol 2009;23:967-74.
5. Dording CM, Mischoulon D, Petersen TJ, Kornbluh R, Gordon J, Nierenberg AA, et al. The pharmacologic management of SSRI-induced side effects: a survey of psychiatrists. Ann Clin Psychiatry 2002;14:143-7.
6. Kirwin JL, Gören JL. Duloxetine: a dual serotonin-noradrenaline reuptake inhibitor for treatment of major depressive disorder. Pharmacotherapy 2005;25:396-410.
7. Fortney JC, Pyne JM, Edlund MJ, Stecker T, Mittal D, Robinson DE, et al. Reasons for antidepressant nonadherence among veterans treated in primary care clinics. J Clin Psychiatry 2011;72:827-34.
8. Hung CI. Factors predicting adherence to antidepressant treatment. Curr Opin Psychiatry 2014;27:344-9.
9. Cipriani A, Zhou X, Del Giovane C, Hetrick SE, Qin B, Whittington
Review of Antidepressant Side Effects

1. van Walraven C, Mamdani MM, Wells PS, Williams JI. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a re
view for clinicians and a reconsideration of mechanisms. J Clin Psychiatry 2010;71:1565-75.

11. de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and im-
plications for use in elderly patients. Drugs Aging 2011;28:345-67.

12. de Abajo FJ, Rodriguez LA, Montero D. Association between se-
lective serotonin reuptake inhibitor antidepressants and upper gastrointestinal bleeding: population based case-control study. BMJ 1999;319:1106-9.

13. van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. BMJ 2001;323:655-8.

14. Ziegelstein RC, Meuchel J, Kim TJ, Latif M, Alvarez W, Dasgupta N, et al. Selective serotonin reuptake inhibitor use by patients with acute coronary syndromes. Am J Med 2007;120:525-30.

15. Targownik LE, Bolton JM, Metge CJ, Leung S, Sareen J. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. Am J Gastroenterol 2009;104:1475-82.

16. Meijer WE, Heerdink ER, Nolen WA, Herings RM, Leufkens HG, Egberts AC. Association of risk of abnormal bleeding with degree of serotonin reuptake inhibition by antidepressants. Arch Intern Med 2004;164:2367-70.

17. Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. Clin Gastroenterol Hepatol 2009;7:1314-21.

18. Opatrny L, Delaney JA, Bielski RJ, Ventura D, Chang CC. A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. Int J Neuropsychopharmacol 2014;17:537-45.

19. Hauta-Aho M, Tirkkonen T, Vahlberg T, Laine K. The effect of antidepressants on bleeding risk associated with warfarin therapy in hospitalized patients. Ann Med 2009;41:619-28.

20. Dalton SO, Johansen C, Mellemkjaer L, Norgård B, Sørensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Arch Intern Med 2003;163:59-64.

21. Wessinger S, Kaplan M, Choi L, Williams M, Lau C, Sharp L, et al. Increased use of selective serotonin reuptake inhibitors in patients admitted with gastrointestinal haemorrhage: a multicentre retrospective analysis. Aliment Pharmacol Ther 2006;23:937-44.

22. Glassman AH. Cardiovascular effects of antidepressant drugs: updated. Int Clin Psychopharmacol 1998;13 Suppl 5:S25-30.

23. Mago R, Tripathi N, Andrade C. Cardiovascular adverse effects of newer antidepressants. Expert Rev Neurother 2014;14:339-51.

24. Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, Noseworthy PA, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. J Clin Psychiatry 2014;75:e441-9.

25. Wang SM, Pae CU. How much to worry about the FDA warning in the use of citalopram? Expert Rev Neurother 2013;13:883-6.
43. Ballús C, Quiros G, De Flores T, de la Torre J, Palao D, Rojo L, et al. The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder or dysthymia. Int Clin Psychopharmacol 2000;15:43-8.

44. Gartlehner G, Thieda P, Hansen RA, Gaynes BN, Deaveugh-Geiss A, Krebs EE, et al. Comparative risk for harms of second-generation antidepressants: a systematic review and meta-analysis. Drug Saf 2008;31:851-65.

45. Lucena MI, Carvajal A, Andrade RJ, Velasco A. Antidepressant-induced hepatotoxicity. Expert Opin Drug Saf 2003;2:249-62.

46. Tripp AC. Bupropion, a brief history of seizure risk. Gen Hosp Psychiatry 2010;32:216-7.

47. Gartlehner G, Thieda P, Hansen RA, Gaynes BN, Deaveugh-Geiss A, Krebs EE, et al. Comparative risk for harms of second-generation antidepressants: a systematic review and meta-analysis. Drug Saf 2008;31:851-65.

48. Alper K, Schwartz KA, Kolts RL, Khan A. Seizure incidence in people aged 20 to 64 years: cohort study using a primary care practice research datalink. Drug Saf 2016;39:307-21.

49. Montastruc F, Scotto S, Vaz IR, Guerra LN, Escudero A, Sáinz M, et al. Hepatotoxicity associated with agomelatine and other antidepressants: Disproportionality analysis using pooled pharmacovigilance data from the Uppsala Monitoring Centre. J Clin Pharmacol 2015;55:768-73.

50. Tufts NS, Painold A, Holl AK, Vergin H, Engel R, et al. Risk factors for suicide completion in major depression: a case-control study of impulsive and aggressive behaviors in men. Am J Psychiatry 2005;162:2116-24.

51. Friedman RA. Antidepressants’ black-box warning—10 years later. N Engl J Med 2014;371:1666-8.

52. Ye, Wang Y, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry 2010;196:354-8.

53. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol 2009;29:259-66.

54. Reichenpfader U, Gartlehner G, Morgan LC, Greenblatt A, Nussbaumer B, Hansen RA, et al. Sexual dysfunction associated with second-generation antidepressants in patients with major depressive disorder: results from a systematic review with network meta-analysis. Drug Saf 2014;37:19-31.

55. Valla M. Weight gain and antidepressants. J Clin Psychiatry 2000;61 Suppl 11:37-41.

56. Sansone RA, Wiederman MW, Shrader JA. Naturalistic study of the weight effects of amitriptyline, fluoxetine, and sertraline in an outpatient medical setting. J Clin Psychopharmacol 2000;20:272-4.

57. De Picker L, Van Den Eede F, Dumont G, Moorkens G, Sabbe BG. The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder or dysthymia. Int Clin Psychopharmacol 2000;15:43-8.

58. Frieden RA. Antidepressants' black-box warning—10 years later. N Engl J Med 2014;371:1666-8.

59. Stone MB. The FDA warning on antidepressants and suicidality—why the controversy? N Engl J Med 2014;371:1668-71.

60. Stone MB. The FDA warning on antidepressants and suicidality—why the controversy? N Engl J Med 2014;371:1668-71.
Review of Antidepressant Side Effects

76. Houghton WC, Scammell TE, Thorpy M. Pharmacotherapy for cataplexy. Sleep Med Rev 2004;8:355-66.
77. Yeung WF, Chung KA, Yung KP, Ng TH. Doxepin for insomnia: a systematic review of randomized placebo-controlled trials. Sleep Med Rev 2015;19:75-83.
78. Wichniak A, Wierzbicka A, Jernajczyk W. Sleep and antidepressant treatment. Curr Pharm Des 2012;18:5892-17.
79. Ng QX. A systematic review of the use of bupropion for attention-deficit/hyperactivity disorder in children and adolescents. J Child Adolesc Psychopharmacol 2017;27:112-6.
80. Rye DB, Dihenia B, Bliwise DL. Reversal of atypical depression, sleepiness, and REM-sleep propensity in narcolepsy with bupropion. Depress Anxiety 1998;7:92-5.
81. Marcy TR, Britton ML. Antidepressant-induced sweating. Ann Pharmacother 2005;39:748-52.
82. Garber A, Gregory RJ. Benztropine in the treatment of venlafaxine-induced sweating. J Clin Psychiatry 1997;58:176-7.
83. Mago R, Thase ME, Rovner BW. Antidepressant-induced excessive sweating: clinical features and treatment with terazosin. Ann Clin Psychiatry 2013;25:186-92.
84. Kolli V, Ramaswamy S. Improvement of antidepressant-induced sweating with as-required benztropine. Innov Clin Neurosci 2013;10:10-1.
85. Butt MM. Managing antidepressant-induced sweating. J Clin Psychiatry 1989;50:146-7.
86. Brouwers C, Christensen SB, Damen NL, Denollet J, Torp-Pedersen C, Glissoon GH, et al. Antidepressant use and risk for mortality in 121,252 heart failure patients with or without a diagnosis of clinical depression. Int J Cardiol 2016;203:867-73.
87. Maslej MM, Bolker BM, Russell MJ, Eaton K, Durisko Z, Hollon SD, et al. The mortality and myocardial effects of antidepressants are moderated by preexisting cardiovascular disease: a meta-analysis. Psychother Psychosom 2017;86:268-82.
88. Hansen RA, Khodneva Y, Glasser SP, Qian J, Redmond N, Safford MM. Antidepressant medication use and its association with cardiovascular disease and all-cause mortality in the reasons for geographic and racial differences in stroke (REGARDS) study. Ann Pharmacother 2016;50:253-61.
89. Sharma T, Guski LS, Freund N, Getzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 2016;352:i65.
90. Cuijpers P, Vogelzangs N, Twisk J, Kleinboer A, Li J, Penninx BW. Differences in mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. Br J Psychiatry 2013;202:22-7.
91. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Norman PE, Flicker L. Depression, frailty, and all-cause mortality: a cohort study of men older than 75 years. J Am Med Dir Assoc 2015;16:296-300.
92. Holwerda TJ, van Tilburg TG, Deeg DJ, Schutter N, Van R, Dekker J, et al. Impact of loneliness and depression on mortality: results from the Longitudinal Ageing Study Amsterdam. Br J Psychiatry 2016;209:127-34.
93. Laursen TM, Musliner KL, Benros ME, Vestergaard M, Munk-Olsen T. Mortality and life expectancy in persons with severe unipolar depression. J Affect Disord 2016;193:203-7.
94. Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, Pae CU. Vilazodone for the treatment of major depressive disorder: focusing on its clinical studies and mechanism of action. Psychiatry Investig 2015;12:155-63.
95. Pae CU, Wang SM, Han C, Lee SJ, Patkar AA, Masand PS, et al. Vortioxetine, a multimodal antidepressant for generalized anxiety disorder: a systematic review and meta-analysis. J Psychiatr Pract 2015;64:88-98.
96. Mathews M, Gommoll C, Chen D, Nunez R, Khan A. Efficacy and safety of vilazodone 20 and 40 mg in major depressive disorder: a randomized, double-blind, placebo-controlled trial. Int Clin Psychopharmacol 2015;30:67-74.
97. Wagner G, Schultes MT, Titscher V, Teufer B, Klerings I, Gartlehner G. Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: A systematic review and network meta-analysis. J Affect Disord 2018;228:1-12.
98. Mahableshwarkar AR, Jacobsen PL, Chen Y, Serenko M, Trivedi MH. A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. Psychopharmacology (Berl) 2015;232:2061-70.
99. Mahableshwarkar AR, Zajecka J, Jacobsen W, Chen Y, Keefe BS. A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. Neuropsychopharmacology 2015;40:2025-37.
100. Grady MM, Stahl SM. Practical guide for prescribing MAOIs: debunking myths and removing barriers. CNS Spectr 2012;17:2-10.
101. Remick RA. Anticholinergic side effects of tricyclic antidepressants and their management. Prog Neuropsychopharmacol Biol Psychiatry 1988;12:225-31.
102. Rosenbaum TG, Kou M. Are one or two dangerous? Tricyclic antidepressant exposure in toddlers. J Emerg Med 2005;28:169-74.
103. Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psychother Psychosom 2016;85:270-88.
104. Every-Palmer S, Howick J. How evidence-based medicine is failing due to biased trials and selective publication. J Eval Clin Pract 2014;20:908-14.
105. Wang SM, Han C, Lee SJ, Jun TY, Patkar AA, Masand PS, et al. Efficacy of antidepressants: bias in randomized clinical trials and related issues. Expert Rev Clin Pharmacol 2018;11:15-25.
106. Rief W, Nestoriuc Y, von Lilienfeld-Toal A, Dogan I, Schreiber F, Hofmann SG, et al. Differences in adverse effect reporting in placebo groups in SSRI and tricyclic antidepressant trials: a systematic review and meta-analysis. Drug Saf 2009;32:1041-56.
107. John MM. The “Pygmalion Effect” and surgical mentoring. Indian J Surg 2016;78:79.
108. Davidson OB, Eden D. Remedial self-fulfilling prophecy: two field experiments to prevent Golem effects among disadvantaged women. J Appl Psychol 2000;85:386-98.
109. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. Exp Clin Psychopharmacol 2015;23:1-21.