

Adverse Drug Events on the Use of Sertraline in Clinical Studies: A Review

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ABSTRACT

Major depressive disorder (MDD) and anxiety are known as a widespread public health problem treated with sertraline, a class of *Selective Serotonin Reuptake Inhibitor* (SSRI) drugs as first-line therapy. However, clinical evidence showed that MDD and anxiety therapy with sertraline has not been optimal due to patient non-compliance associated with *adverse drug events* (ADE) occurring. A literature search on sertraline clinical study was conducted on the PubMed and Science Direct electronic database in April 2020. A total of 12 articles from 5.664 articles have been selected at the initial screening. A total of 6 articles used sertraline as a testing drug in MDD patients, 2 articles used sertraline as a testing drug in anxiety patients, 2 articles with sertraline as a comparative drug, 1 article with sertraline as a positive control, and 1 article with sertraline as an adjuvant in MDD patients. Studies on these articles were carried out worldwide from 2010 to 2019. ADEs that occur due to the use of sertraline were: gastrointestinal disorders, nutritional and metabolic disorders, central nervous system disorders, sweating, sleep disorders, irritability, eye disorders, as well as disorders of the skin and subcutaneous tissues. Nausea is the most common ADE of sertraline. ADEs are affected by several factors such as age, sertraline combination therapy, and alcohol consumption.

Keywords: *Adverse Drug Event*; Anxiety; Major Depressive Disorder; Sertraline; SSRI

INTRODUCTION

Major Depressive Disorder (MDD) and anxiety are recognized as public health problems because of their significant whole impact on mortality and morbidity as well as high costs ¹. The proportion of the global population with depression in 2015 was estimated at 4.4% while the global population with anxiety in 2015 was estimated at 3.6% ². Depression is a chronic and recurring disease that requires lifelong medication with sertraline first-line therapy ³. Meanwhile, anxiety is a mental health disorder characterized by feelings of worry, anxiety, or fear that are strong enough to disturb with daily activities and can be treated with sertraline medication as the first line ⁴.

Sertraline is an SSRI (Selective Serotonin Reuptake Inhibitor) class antidepressant which works to increase serotonin activity and is used orally ⁵. However, evidence suggests that MDD therapy with SSRI class antidepressants is still not optimal, especially in primary care centers ^{6,7}. Non-adherence and premature discontinuation of medication are

major factors contributing to suboptimal medication outcomes ⁸.

Adverse Drug Event or ADE associated with the use of antidepressants is one of the factors responsible for non-adherence and medication discontinuation in patients ^{9,10}. Studies have shown that up to 43% of patients with MDD can stop antidepressants because of ADE ¹¹. ADE is a temporary medical event in the form of injury to certain organs related to drug use ¹². Mistakes in medication, adverse drug reactions, allergic reactions, and drug overdose can cause ADE in the patient's body ¹². In contrast to side effects, ADE is often not known beforehand except after the patient has used the drug ¹³.

In the medication of depression with sertraline, ADE has not been widely reported. Therefore, ADE related to the use of sertraline needs to be known further in order to improve patient medication adherence and provide written reports about ADE that can occur in patients. This article summarizes the ADE with sertraline in clinical studies around the world in the past ten years. In addition,

this study was conducted to raise awareness about reporting of ADE with sertraline among health workers such as pharmacists, doctors, and nurses.

METHODS

The research design is a literature study. Data search was carried out electronically on the electronic database PubMed and Science Direct with medical subject headings (MeSH) "Adverse Drug Events" and "Sertraline" in April 2020. The article inclusion criteria were searched based on the following keywords: "Sertraline" [MeSH Terms] AND "Adverse Drug Events" [All Fields]. Articles are published in the last 10 years, in the form of clinical trials, and in English. The exclusion criteria for this article were the protocol test and review articles. There were 5,664 articles related to keywords in search engines at the initial search, but only 12 articles met the inclusion criteria. In brief, the process of searching for articles can be seen in Figure 1.

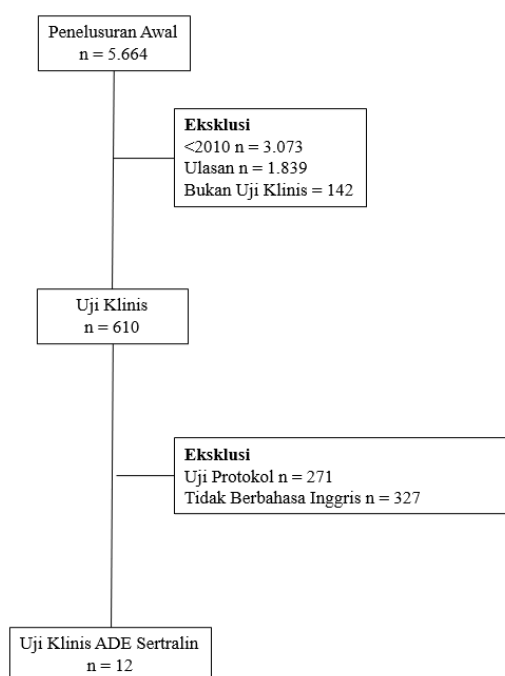


Figure 1. Search diagram for the article "Adverse Drug Events (ADE) Sertraline"

RESULTS AND DISCUSSION

The Results of the Clinical Trial of Sertraline

Table I shows 12 articles that discuss clinical trials of sertraline use. This study was conducted throughout the world, namely in the continents of Asia, America, Africa, Europe and Australia from 2010 to 2019. A total of 3,749 patients participated in this study. All articles employ the integrated randomized study type. There were 8 articles with sertraline as the drug tested (articles number 1, 2, 3, 5, 6, 7, 8, 10), 2 articles with sertraline as a comparison drug (articles number 4 and 11), 1 article with sertraline as positive control (article number 9), and 1 article with sertraline as adjuvant (article number 12).

Various Kinds of Adverse Drug Event (ADE) Sertraline

Table II shows several types of ADE arising from sertraline use in several patient groups. Twelve articles with sertraline as a test drug, comparison drug, positive control, or adjuvant therapy show that ADE in the gastrointestinal region is the most common ADE after sertraline use. Gastrointestinal ADE that occurs most often is nausea. Meanwhile, sertraline ADE which is used as a comparison drug for hypericum is not mentioned in article number 9. Based on Table II, ADE that is arising from the use of sertraline can be grouped as follows:

Gastrointestinal disorders

Serotonin plays a role in motor and sensory regulation of the gastrointestinal tract²⁶. Drugs that act on serotonin receptors and the amount of serotonin will affect gastric motility²⁷. In the same way, serotonergic drugs acting on 5-HT₃ receptors can cause nausea and vomiting²⁸. The ADE caused by sertraline as a serotonergic drug in the gastrointestinal area is nausea (article no. 1, 2, 4, 6, 8-12), vomiting (article no. 8-10), abdominal pain (article no. 6), constipation

Table Ia. Sertraline clinical test in the last ten years

Article number	Writer	Year	Country	Participant	Number of Participant	Drugs Tested	Sertraline Role
1	Pettinati <i>et al.</i> , ¹⁴	2010	USA	Depressed patient with alcohol dependence	170	Sertraline and Naltrekson	Test drug
2	Katz <i>et al.</i> , ¹⁵	2012	USA	Outpatient age 18-75 years old with major depressive disorder non-psychotic who failed with first line therapy citalopram and shifting to second line monotherapy with alternative anti-depressant	727	Sustained Release Bupropion, Sertralin, Extended release venlavaxine	Test drug
3	Blumberger <i>et al.</i> , ¹⁶	2013	Canada	18 years or older patients treated as inpatient or outpatient from 4 academic sites between December 2002 and June 2007, who suffered from major depression with tardive dyskinesia risk factor assessed with Abnormal Involuntary Movement scale initially, and 4 weeks, 8 weeks, and 12 weeks of therapy	259	Olanzapine and Sertraline	Test drug
4	Chen <i>et al.</i> , ¹⁷	2014	USA	Outpatient older than 18 years old who fulfilled major depression episode criteria based on structured clinical interview for DSM-V	277	<i>Hypericum</i>	Comparative drug

Table Ib. Sertraline clinical test in the last ten years

Article number	Writer	Year	Country	Participant	Number of Participant	Drugs Tested	Sertraline Role
5	Cvjetko vic-Bosnjak <i>et al.</i> , ¹⁸	2015	Serbia	Man and woman, between 20-60 years old, diagnosed with GAD (based on JCD-X and DSM-IV), examined from 2011 October-2013 February.	107	Pregabalin and Sertraline	Test drug
6	Reid <i>et al.</i> , ¹⁹	2015	USA	Pair of adults - kids, 7-17 years old kids who had registered for controlled two-way random check to assess OCD medication	56	Sertraline	Test drug
7	Amidfar <i>et al.</i> , ²⁰	2016	Iran	Outpatient with medium-severe based on DSM-V diagnostic criteria	65	Sertraline	Test drug
8	Li <i>et al.</i> , ²¹	2017	People's Republic of China	Patients older than 18 years old fulfilling PTSD criteria with duration at least 6 months with CGI-S score more than 4 when visiting	147	Sertraline	Comparative drug
9	Liu <i>et al.</i> , ²²	2017	People's Republic of China	Patients with myocardial infarct and depression treated in department of cardiology of Harbin University Hospital	149	Shugan Jieyu	Positive control
10	Kamijima <i>et al.</i> , ²³	2018	Japan, Korea, Malaysia, Taiwan, Australia	Patient from 20 to 65 years old and fulfilled (DSM-5) MDD as primary diagnosis, with in scale Score ≥ 18 (HAM-D17)	412	Sertraline and Aripipazol	Test drug

Table Ic. Sertraline clinical test in the last ten years

Article number	Writer	Year	Country	Participant	Number of Participant	Drugs Tested	Sertraline Role
11	Papakostas <i>et al.</i> , ²⁴	2018	USA	Patient 18-75 years old with episodic major depression as primary diagnosis with score 95 or MDD relapse, MDE duration < 12 months, MADRS score more than 22, and apparent sadness more than 3 when visiting and screening	493	Vortioxetine and Agomelatine	Comparative therapy
12	Popova <i>et al.</i> , ²⁵	2019	Czech Republic, Poland, German, Spain, United States	Patients were 18 to 64 years old, have one-episode (more than 2 years) or relapsed major depression disorder (per DSM-5 criteria) without psychotic feature	435	Esketamine	Adjuvant

(article no. 2), and diarrhea (article no. 2, 3, 9, 10).

Nutritional and metabolic disorders

Change in appetite^{20,21} and dry mouth^{21,22} is one of the ADE after the use of sertraline as an antidepressant. Change in appetite can affect the patient's weight²⁹. Weight gain during acute antidepressant therapy or treatment may occur. Some of the interaction mechanisms that contribute to weight gain due to the use of antidepressants are: antidepressant action on specific neuroreceptors such as serotonin receptors, decreased calorie expenditure due to the sedative effect of antidepressants, shifting food preferences, and dry mouth or throat which leads to increased calorie intake³⁰.

Central Nerve System

In table II, there are ADE caused by sertraline in the central nervous system, including: akathisia (article no. 5 and 7), headaches (articles 1, 2, 6, 7, 8), dizziness (article no. 2, 4, 6, 8), pain (article no. 10), fatigue (article no. 1, 8, 10), drowsiness (article no. 2, and 4), vertigo (article no. 10), tardive dyskinesia (article no. 3), tremors (article no. 7), anorexia (article no. 10), dissociation (article no. 12), and dysgeusia or tasting disorders (article no. 12). Akathisia and tardive dyskinesia are extrapyramidal symptoms caused by sertraline.³¹ The mechanism of extrapyramidal symptoms affected by sertraline is related to excess amounts of serotonin which can harm dopaminergic neurons in the nigrostriatal and tuberoinfundibular pathways³².

Table IIa. Harmful Effect caused by sertraline use

Article Number	Writer	Drugs Tested	Drug Role	Side effect/ADE	Other result	Conclusion
1	Pettinati <i>et al.</i> , ¹⁴	Sertraline and Naltrekson	Test drug	Anxiety/irritability, fatigue, headache, and nausea	Serious side-effect rate was significantly less than combination of sertraline and naltrexone	alcohol dependence patients who were more depressed receive combination of sertraline and naltrexone became no longer dependent on alcohol, experiencing deferment to excessively consume alcohol, experiencing less ADE and tend to be less depressed at the end of medication
2	Katz <i>et al.</i> , ¹⁵	Sustained Release Bupropion, Sertraline, Extended release venlavaxine	Test drug	Constipation, diarrhea, dizziness, headache, insomnia, nausea, and drowsiness	-	Selecting second generation anti-depressant for patients who failed to respond on the beginning of treatment because of ADE was difficult to be provided. There was similarity of ADE occurrence risk
3	Blumberger <i>et al.</i> , ¹⁶	Olanzapine and Sertraline	Test drug	Tardive dyskinesia (TD)	Clinically only 1 subject who experienced TD as ADE	TD incident was relatively low for younger and older patients with psychotic major depression disorder who used acute olanzapine therapy

Table IIb. Harmful Effect caused by sertraline use

Article Number	Writer	Drugs Tested	Drug Role	Side effect/ADE	Other result	Conclusion
4	Cvjetkovic-Bosnjak <i>et al.</i> , ¹⁸	Pregabalin and Sertraline	Test drug	Dizziness, drowsiness, nausea, diarrhea, vertigo, insomnia	ADE was reported on two groups of patient with mild intensity, prolonged short-term duration, and dependent on the dose. There was no withdrawal phenomenon on this study	Pregabalin showed good efficacy and tolerability effect with a very fast onset in GAD (<i>Generalized Anxiety Disorder</i>) therapy without potency of withdrawal
5	Reid <i>et al.</i> , ¹⁹	Sertraline	Test drug	Irritability, mania, dangerous to self, akathisia, and disinhibition	Escalation of irritability happened only from session to session causing increase of obsessive-compulsive symptoms session to session	ADE hinder treatment of pediatric OCD.
6	Amidfar <i>et al.</i> , ²⁰	Sertraline	Test drug	Dizziness, abdominal pain, raise of appetite, decreased appetite, nausea, headache, sedation, rash, insomnia	There was no serious ADE and no death. No specific difference between memantine and placebo in the occurrence of ADE	Adjuvant therapy of memantine and sertraline for 6 weeks showed security and efficacy for MDD patient

Table IIc. Harmful Effect caused by sertraline use

Article Number	Writer	Drugs Tested	Drug Role	Side effect/ADE	Other result	Conclusion
7	Li <i>et al.</i> , ²¹	Sertraline	Test drug	Nausea, headache, insomnia, drowsiness, dry mouth, asthesnia, constipation, decreased appetite, diarrhea	The prominent ADE was nausea, there was no death caused by sertraline ADE	Use of sertraline for 12 weeks was proven to be efficacious and well-tolerated for PTSD patients
8	Kamijima <i>et al.</i> , ²³	Sertraline and Aripripazol	Test drug	Nasopharyngitis, akathisia, tremor, headache	MDD patients who received sertraline 100 mg/day did not showed sufficient medication response; combination of sertraline and aripripazol was efficacious and well-tolerated	Rate of ADE severity cause by combination of sertraline-aripripazol was on mild-moderate rate
9	Chen <i>et al.</i> , ¹⁷	Hypericum	Comparative drug	Type was not mentioned	-	ADE severity cannot be measured
10	Liu <i>et al.</i> , ²²	Shugan Jieyu	Positive Control	Nausea and vomiting, diarrhea, insomnia, fatigue, sore, vertigo, skin rash, edema, loss of sight, dry mouth, and hyperhydrosis	Sertraline and Shugan Jieyu have similar drug safety for heart	Shugan Jieyu flow of ADE was lower than Sertraline

Table IId. Harmful Effect caused by sertraline use

Article Number	Writer	Drugs Tested	Drug Role	Side effect/ADE	Other result	Conclusion
11	Papakostas <i>et al.</i> , ²⁴	Vortioxetine and Agomelatine	Comparative therapy	Nausea	7,9% of Participants who used SSRI resigned from Vortioxetine/ Agomelatine	Vortioxetine was more prominent than agomelatine in MDD therapy for patients who used to have SSRI medication
12	Popova <i>et al.</i> , ²⁵	Esketamine	Adjuvant	Dissociation, nausea, vertigo, <i>dysgeusia</i> , and dizziness	Combination of esketamine with sertraline was more efficacious than only esketamine	Combination of esketamine and sertraline more frequently caused ADE which appeared after the end of and last for 1.5 hours after administration of dose

In addition, the use of sertraline can cause cognitive side effects. This happens because sertraline can affect cognitive areas in the brain³³. Cognitive side effects affected by the use of sertraline is dissociation²⁵. Dissociation is a time lag that occurs when a person processes information. People with dissociation will feel disconnected from their thoughts, feelings, memories, and surroundings³⁴. Dissociation is a mental mechanism with a very important role in adapting people. In addition, dissociation is an underlying mechanism in a number of defense mechanisms. Repression, intellectualization, isolation, and other defense mechanisms depend on dissociation to accomplish their specific tasks. Dissociation is believed to be the basis of many aspects of mental functioning³⁵.

Perspired

Perspired is the body's compensatory mechanism for keeping the temperature within a physiological range³². Excessive perspiration is one of the ADE's of sertraline use (article no. 10). Some research have shown that about 10% of patients on SSRIs experience excessive perspiration³⁶.

Sleep Disorders

The use of sertraline as an antidepressant also has another ADE, called insomnia (article no. 2, 4, 6, 8, 10). Insomnia can be affected by activation of the 5-HT₂ receptor and increased noradrenergic and dopaminergic neurotransmission.³⁷ Based on testing data conducted by the FDA, the average prevalence of insomnia due to the use of SSRIs is 17%.³⁸

Irritability

Irritability is one of the ADEs that occurs due to the use of sertraline (article no. 1, 5, 8). Symptoms of irritability have been reported in both psychiatric and nonpsychiatric MDD patients. This symptom occurs in adult patients, adolescents, and children³⁹.

Eye disorders

The ophthalmic effect that affected by the use of sertraline is blurred vision (article no. 10). One of the causes of blurred vision that affected by the use of sertraline is excessive dilation of the pupil. This situation potentially narrow the angle of view resulting in increased intraocular pressure and angle-closure glaucoma⁴⁰.

Skin and subcutaneous network disorders

Skin and subcutaneous network disorders that occur due to the use of sertraline, as to include: itching, skin rashes, and edema (article no. 8 and 10). ADE occurs because sertraline works by inhibiting serotonin uptake by the Central Nervous System. Serotonin that is not taken by the SSP has effects on the skin, including: pruritogenic, proinflammatory, and proedema. Skin reactions are usually slight, although life-threatening reactions can also occur. As you get older, female gender, African-American ethnicity, polypharmacy, and serious illness can increase your risk for ADE.⁴¹

Factors Affecting the Sertraline Adverse Drug Event (ADE)

There are several factors that can affect adverse drug events due to the use of sertraline, including: age, alcohol consumption, sex, pregnancy, breastfeeding, kidney disorders, liver dysfunction, drug dosage, and frequency of drug administration, as well as multitherapy⁴². In this review article, several factors have been identified that can affect the Adverse Drug Event for sertraline use, including: ages^{14, 15, 16, 19}, the combination of sertraline with certain drugs^{14, 16, 18, 20, 23, 25}, and alcohol consumption.¹⁴

Age

Every drug can produce ADE, but not all patients experience the same levels and types of ADE. Age is a very important factor affecting the occurrence of ADE. Elderly patients with multiple medical problems who use multiple drugs, have a history of ADR, and have decreased drug elimination capacity are at high risk of developing ADR. As we get older, the liver loses the ability to metabolize drugs. In addition, the kidneys' ability to excrete drugs into the urine is reduced⁴². In the article reviewed (article no. 2 and 3), elderly is a factor that can increase the risk of ADE in patients with MDD and anxiety who consume sertraline.

Multitherapy

The combination of sertraline and naltrexone can reduce the risk of serious ADE in patients. However, ADE can still occur in small numbers. The combination of these two drugs also reduces alcohol dependence in depressed patients¹⁴.

In addition, the use of sertraline with olanzapine for the treatment of patients with the major depressive disease has a lower incidence of tardive dyskinesia than just using sertraline monotherapy. It has been reported that the incidence of tardive dyskinesia in patients taking the combination sertraline with olanzapine is relatively rare compared to patients with sertraline monotherapy.¹⁶

Slighter but dose-dependent ADE can also occur in patients taking the combination sertraline and pregabalin. The combination of these two drugs is used by patients who have Generalized Anxiety Disorder (GAD). Pregabalin is reported to have good efficacy and tolerability in patients with GAD¹⁸.

In addition, serious ADE did not occur in patients on combination therapy with sertraline and memantine. The combination of these two drugs has been reported to be safe and efficacious in patients with moderate-severe major depression disease²⁰.

Another research mentioned that combining sertraline with aripiprazole in patients with major depressive disease had a

risk of developing light-moderate ADE. This risk is lower than only using sertraline monotherapy. Furthermore, this combined therapy could be well-tolerated by patient.²³

Alcohol Consumption

Alcohol affects metabolism of various drugs and increases likelihood of ADE. Interaction of drugs and alcohol is based on possibility that alcohol could change ADE development's intensity to be more toxic or hazardous for patient pharmacokinetically as well as pharmacodynamically. Alcohol could affect liver function which could cause liver cirrhosis and liver hepatitis, subsequently, affecting liver's ability to metabolize drugs especially drugs metabolized by liver and drugs which undergo first pass metabolism. Consuming alcohol with certain drugs would cause various ADE such as nausea, vomit, headache, drowsiness, fainting, loss of coordination, hypotension, and other ADEs⁴². Based on article number 1, alcohol consumption would increase rate of ADE in sertraline use for depressed patient, such as: anxiety, fatigue, headache, and nausea¹⁴.

CONCLUSION

This article summarizes several types of ADE caused by use of sertraline in 12 articles within last 10 years from 2010 to 2019. Generally, clinical test was conducted for patients with major depression and anxiety. The sum of participants during testing was 3,749 patients. It was discovered that several ADEs affecting patients include: gastrointestinal disorder, nutrition and metabolism disorder, central nervous system disorder, sweating, sleep disorder, irritability, eye disorder, as well as skin and subcutaneous disorders. Gastrointestinal disorder was an ADE frequently occurred on patient who used sertraline. The most common gastrointestinal disorder was nausea. Sertraline ADE is affected by several factors, such as: age, therapy combination, and alcohol consumption.

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