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 costs1. 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 therapy3. 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 line4.

Sertraline is an SSRI (Selective Serotonin Reuptake Inhibitor) class antidepressant which works to increase serotonin activity and is used orally5. However, evidence suggests that MDD therapy with SSRI class antidepressants is still not optimal, especially in primary care centers6,7. Non-adherence and premature discontinuation of medication are major factors contributing to suboptimal medication outcomes8.

Adverse Drug Event or ADE associated with the use of antidepressants is one of the factors responsible for non-adherence and medication discontinuation in patients9,10. Studies have shown that up to 43% of patients with MDD can stop antidepressants because of ADE11. ADE is a temporary medical event in the form of injury to certain organs related to drug use12. Mistakes in medication, adverse drug reactions, allergic reactions, and drug overdose can cause ADE in the patient’s body12. In contrast to side effects, ADE is often not known beforehand except after the patient has used the drug13.

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 related to the use of sertraline in clinical studies around the world in the past ten years.
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.

**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 tract. Drugs that act on serotonin receptors and the amount of serotonin will affect gastric motility. In the same way, serotonergic drugs acting on 5-HT3 receptors can cause nausea and vomiting. 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,

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Figure 1. Search diagram for the article "Adverse Drug Events (ADE) Sertraline"
Table Ia. Sertraline clinical test in the last ten years

<table>
<thead>
<tr>
<th>Article number</th>
<th>Writer(s)</th>
<th>Year</th>
<th>Country</th>
<th>Participant</th>
<th>Number of Participant</th>
<th>Drugs Tested</th>
<th>Sertraline Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pettinati et al., 14</td>
<td>2010</td>
<td>USA</td>
<td>Depressed patient with alcohol dependence</td>
<td>170</td>
<td>Sertraline and Naltrexon</td>
<td>Test drug</td>
</tr>
<tr>
<td>2</td>
<td>Katz et al., 15</td>
<td>2012</td>
<td>USA</td>
<td>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 antidepressant</td>
<td>727</td>
<td>Sustained Release Bupropion, Sertraline, Extended release venlaxine</td>
<td>Test drug</td>
</tr>
<tr>
<td>3</td>
<td>Blumberger et al., 16</td>
<td>2013</td>
<td>Canada</td>
<td>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</td>
<td>259</td>
<td>Olanzapine and Sertraline</td>
<td>Test drug</td>
</tr>
<tr>
<td>4</td>
<td>Chen et al., 17</td>
<td>2014</td>
<td>USA</td>
<td>Outpatient older than 18 years old who fulfilled major depression episode criteria based on structured clinical interview for DSM-V</td>
<td>277</td>
<td>Hypericum</td>
<td>Comparative drug</td>
</tr>
<tr>
<td>Article number</td>
<td>Writer</td>
<td>Year</td>
<td>Country</td>
<td>Participant</td>
<td>Number of Participant</td>
<td>Drugs Tested</td>
<td>Sertraline Role</td>
</tr>
<tr>
<td>----------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td>5</td>
<td>Cvjetko vic-Bosnjak <em>et al.</em></td>
<td>2015</td>
<td>Serbia</td>
<td>Man and woman, between 20-60 years old, diagnosed with GAD (based on JCD-X and DSM-IV), examined from 2011 October-2013 February.</td>
<td>107</td>
<td>Pregabaline and Sertraline</td>
<td>Test drug</td>
</tr>
<tr>
<td>6</td>
<td>Reid <em>et al.</em></td>
<td>2015</td>
<td>USA</td>
<td>Pair of adults - kids, 7-17 years old kids who had registered for controlled two-way random check to assess OCD medication</td>
<td>56</td>
<td>Sertraline</td>
<td>Test drug</td>
</tr>
<tr>
<td>7</td>
<td>Amidfar <em>et al.</em></td>
<td>2016</td>
<td>Iran</td>
<td>Outpatient with medium-severe based on DSM-V diagnostic criteria</td>
<td>65</td>
<td>Sertraline</td>
<td>Test drug</td>
</tr>
<tr>
<td>8</td>
<td>Li <em>et al.</em></td>
<td>2017</td>
<td>People's Republic of China</td>
<td>Patients older than 18 years old fulfilling PTSD criteria with duration at least 6 months with CGI-S score more than 4 when visiting</td>
<td>147</td>
<td>Sertraline</td>
<td>Comparative drug</td>
</tr>
<tr>
<td>9</td>
<td>Liu <em>et al.</em></td>
<td>2017</td>
<td>People's Republic of China</td>
<td>Patients with myocardial infarct and depression treated in department of cardiology of Harbin University Hospital</td>
<td>149</td>
<td>Shugan Jieyu</td>
<td>Positive control</td>
</tr>
<tr>
<td>10</td>
<td>Kamijima <em>et al.</em></td>
<td>2018</td>
<td>Japan, Korea, Malaysia, Taiwan, Australia</td>
<td>Patient from 20 to 65 years old and fulfilled (DSM-5) MDD as primary diagnosis, with in scale Score ≥ 18 (HAM-D17)</td>
<td>412</td>
<td>Sertraline and Aripiprazol</td>
<td>Test drug</td>
</tr>
</tbody>
</table>
Nutritional and metabolic disorders

Change in appetite\textsuperscript{20,21} and dry mouth\textsuperscript{21,22} is one of the ADE after the use of sertraline as an antidepressant. Change in appetite can affect the patient’s weight\textsuperscript{29}. 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 intake\textsuperscript{30}.

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), drowsy (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.\textsuperscript{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 pathways\textsuperscript{32}.

### Table Ic. Sertraline clinical test in the last ten years

<table>
<thead>
<tr>
<th>Article number</th>
<th>Writer</th>
<th>Year</th>
<th>Country</th>
<th>Participant</th>
<th>Number of Participant</th>
<th>Drugs Tested</th>
<th>Sertraline Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Papakos\textit{tas et al.,}\textsuperscript{24}</td>
<td>2018</td>
<td>USA</td>
<td>Patient 18-75 years old with episodical major depression as primary diagnosis with score 95 or MDD relapse, MDE duration &lt; 12 months, MADRS score more than 22, and apparent sadness more than 3 when visiting and screening</td>
<td>493</td>
<td>Vortioxetine Comparative and Agomelatine Therapy</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Popova\textit{et al.,}\textsuperscript{25}</td>
<td>2019</td>
<td>Czech Republic, Poland, Spain, United States</td>
<td>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</td>
<td>435</td>
<td>Esketamine Adjuvant</td>
<td></td>
</tr>
</tbody>
</table>
Table IIa. Harmful Effect caused by sertraline use

<table>
<thead>
<tr>
<th>Article Number</th>
<th>Writer</th>
<th>Drugs Tested</th>
<th>Drug Role</th>
<th>Side effect/ADE</th>
<th>Other result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pettinati et al., 14</td>
<td>Sertraline and Naltrexon</td>
<td>Test drug</td>
<td>Anxiety/irritability, fatigue, headache, and nausea</td>
<td>Serious side-effect rate was significantly less than combination of sertraline and naltrexone</td>
<td>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</td>
</tr>
<tr>
<td>2</td>
<td>Katz et al., 15</td>
<td>Sustained Release Bupropion, Sertraline, Extended release venlaxavine</td>
<td>Test drug</td>
<td>Constipation, diarrhea, dizziness, headache, insomnia, nausea, and drowsiness</td>
<td>-</td>
<td>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</td>
</tr>
<tr>
<td>3</td>
<td>Blumberger et al., 16</td>
<td>Olanzapine and Sertraline</td>
<td>Test drug</td>
<td>Tardive dyskinesia (TD)</td>
<td>Clinically only 1 subject who experienced TD as ADE</td>
<td>TD incident was relatively low for younger and older patients with psychotic major depression disorder who used acute olanzapine therapy</td>
</tr>
</tbody>
</table>
Table IIb. Harmful Effect caused by sertraline use

<table>
<thead>
<tr>
<th>Article Number</th>
<th>Writer</th>
<th>Drugs Tested</th>
<th>Drug Role</th>
<th>Side effect/ADE</th>
<th>Other result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Cvjetkovic-Bosnjak et al., 18</td>
<td>Pregabaline and Sertraline</td>
<td>Test drug</td>
<td>Dizziness, drowsiness, nausea, diarrhea, vertigo, insomnia</td>
<td>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</td>
<td>Pregabalin showed good efficacy and tolerability effect with a very fast onset in GAD (Generalized Anxiety Disorder) therapy without potency of withdrawal</td>
</tr>
<tr>
<td>5</td>
<td>Reid et al., 19</td>
<td>Sertraline</td>
<td>Test drug</td>
<td>Irritability, mania, dangerous to self, akathisia, and disinhibition</td>
<td>Escalation of irritability happened only from session to session causing increase of obsessive-compulsive symptoms session to session</td>
<td>ADE hinder treatment of pediatric OCD.</td>
</tr>
<tr>
<td>6</td>
<td>Amidfar et al., 20</td>
<td>Sertraline</td>
<td>Test drug</td>
<td>Dizziness, abdominal pain, raise of appetite, decreased appetite, nausea, headache, sedation, rash, insomnia</td>
<td>There was no serious ADE and no death. No specific difference between memantine and placebo in the occurrence of ADE</td>
<td>Adjuvant therapy of memantine and sertraline for 6 weeks showed security and efficacy for MDD patient</td>
</tr>
</tbody>
</table>
### Table IIc. Harmful Effect caused by sertraline use

<table>
<thead>
<tr>
<th>Article Number</th>
<th>Writer</th>
<th>Drugs Tested</th>
<th>Drug Role</th>
<th>Side effect/ADE</th>
<th>Other result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Li et al., 21</td>
<td>Sertraline</td>
<td>Test drug</td>
<td>Nausea, headache, insomnia, drowsiness, dry mouth, asthesnia, constipation, decreased appetite, diarrhea</td>
<td>The prominent ADE was nausea, there was no death caused by sertraline ADE</td>
<td>Use of sertraline for 12 weeks was proven to be efficacious and well-tolerated for PTSD patients</td>
</tr>
<tr>
<td>8</td>
<td>Kamijima et al., 23</td>
<td>Sertraline and Aripipazol</td>
<td>Test drug</td>
<td>Nasopharyngitis, akathisia, tremor, headache</td>
<td>MDD patients who received sertraline 100 mg/day did not showed sufficient medication response; combination of sertraline and aripipazol was efficacious and well-tolerated</td>
<td>Rate of ADE severity cause by combination of sertraline-aripipazol was on mild-moderate rate</td>
</tr>
<tr>
<td>9</td>
<td>Chen et al., 17</td>
<td>Hypericum</td>
<td>Comparative drug</td>
<td>Type was not mentioned</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Liu et al., 22</td>
<td>Shugan Jieyu</td>
<td>Positive Control</td>
<td>Nausea and vomiting, diarrhea, insomnia, fatigue, sore, vertigo, skin rash, edema, loss of sight, dry mouth, and hyperhydrosis</td>
<td>Sertraline and Shugan Jieyu have similar drug safety for heart</td>
<td>-</td>
</tr>
</tbody>
</table>
In addition, the use of sertraline can cause cognitive side effects. This happens because sertraline can affect cognitive areas in the brain. Cognitive side effects affected by the use of sertraline is dissociation. Dissociation is a time lag that occurs when a person processes information. People with dissociation will feel disconnected from their thoughts, feelings, memories, and surroundings. 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 functioning.

Perspired
Perspired is the body’s compensatory mechanism for keeping the temperature within a physiological range. Excessive perspiration is one of the ADE’s of sertraline use. Some research have shown that about 10% of patients on SSRIs experience excessive perspiration.

Sleep Disorders
The use of sertraline as an antidepressant also has another ADE, called insomnia. The use of sertraline can be affected by activation of the 5-HT2 receptor and increased noradrenergic and dopaminergic neurotransmission. Based on testing data conducted by the FDA, the average prevalence of insomnia due to the use of SSRIs is 17%.

Table II. Harmful Effect caused by sertraline use

<table>
<thead>
<tr>
<th>Article Number</th>
<th>Writer</th>
<th>Drugs Tested</th>
<th>Drug Role</th>
<th>Side effect/ADE</th>
<th>Other result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Papakostas et al., 24</td>
<td>Vortioxetine and Agomelatine</td>
<td>Comparative therapy</td>
<td>Nausea</td>
<td>7.9% of Participants who used SSRI resigned from</td>
<td>Vortioxetine was more prominent than agomelatine in MDD therapy for patients who used to have SSRI medication</td>
</tr>
<tr>
<td>12</td>
<td>Popova et al., 25</td>
<td>Esketamine</td>
<td>Adjuvant</td>
<td>Dissociation, nausea, vertigo, dyseusia, and dizziness</td>
<td>Combination of esketamine with sertraline was more efficacious than only esketamine</td>
<td>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</td>
</tr>
</tbody>
</table>
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 children 39.

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 glaucoma 40.

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 multitherapy 42. 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 reduced 42. 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 patients 14.

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 GAD 18.

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 disease 20.

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 patients. 21.

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 ADEs 42. Based on article number 1, alcohol consumption would increase rate of ADE in sertraline use for depressed patient, such as: anxiety, fatigue, headache, and nausea 14.

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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