Available online on 15.12.2019 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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Review Article

A Review Article on Selective Serotonin Reuptake Inhibitors (SSRIS)

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A B S T R A C T

Depression, tension and mental health have been ignored as a serious issue since ages. Depression can be fatal or life-threatening, if not treated to this problem. Antidepressants are also regularly used to treat many other conditions, such as social phobia, fibromyalgia, panic disorder, anxiety/anxiety depression, PTSD, OCD, PMDD, and menopause. The major antidepressant used in the study followed oral prescribing trends. A "serious adverse reaction means an adverse reaction which is fatal, life-threatening, disabling, incapacitating, or which results in or prolongs hospitalization." Material method collect from Google, Wikipedia, Elsevier, PubMed, Google scholar, Sci-Hub etc. This is a meta-analysis study. Fluoxetine have the longest half-life, but Fluvoxamine have short half-life. SSRIs increase the serum concentrations of the latter two drugs, potentiating their effects and increasing the risk of toxicity. Fluoxetine and Paroxetine specifically, are known to cause a 5-fold increase in serum TCA concentration upon co-administration. By in the addition of combination therapy SSRIs associated many types of adverse drug reaction and some time it can cause serotonin syndrome also.

Keywords: Depression, Antidepressants, Adverse drug reaction, Serotonin syndrome, Combination therapy.

A R T I C L E I N F O: Received 26 Sept. 2019; Review Completed 15 Nov. 2019; Accepted 10 Dec. 2019; Available online 15 Dec. 2019

Cite this article as:

Devi Meena*, Chand S, Kumar D, A Review Article on Selective Serotonin Reuptake Inhibitors (SSRIS), Asian Journal of Pharmaceutical Research and Development. 2019; 7(6):72-75, **DOI:** http://dx.doi.org/10.22270/ajprd.v7i6.592

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INTRODUCTION:

All human beings, from children to elderly, take medicines at some point in their lives. Medicines have brought enormous benefits (such as lowering blood pressure, safe life threatening, curing infection, or relieving pain.), but no medicine are absolutely 100% safe. If we talk about Depression, this shocked to know that 300 million people worldwide are suffering from depression.

But now a day majority people of current scenario depression due to stress, mobile phone, social media sites, people isolate their family, someone loss of loved, official work load, college stress, many peoples have so many types of tension that's is the DEPRESSION. Causes of depression may be several, physical, biological, economic, social, and cultural factors, poor nutrition, which are triggered by an environmental factor.[1] A depressive mood is a normally temporary reaction to life events, such as loss of loved any one. It is too a symptom of physical diseases and an adverse effect of drugs and medical treatments.[2]

Antidepressants are also regularly used to treat many other conditions, such as social phobia, fibromyalgia, panic disorder, anxiety/anxiety depression, PTSD, OCD, PMDD, and menopause - (term used to describe the change in hormone production). Occasionally, SSRIs may also be prescribed to treat severe pain. SSRIs include drugs such as: Sertraline, Fluoxetine, Citalopram, Escitalopram, Paroxetine, and Fluvoxamine. [3-4]

Table 1: Drugs of SSRIs with brand name.

	Fluoxetine	Sertraline	Paroxetine	Citalopram	Escitalopram
Pharmaceutical forms	Capsules - soluble- or dispersible tablets, oral solution	Tablets - oral concentrate	Tablets - oral suspension	Tablets - oral solution	Tablets - oral solution
Brand name	**Fluoxetine** - Prozac, Depex, Fluctin, Seronil, Flutop, Fontex, Seromex	**Sertraline** -Sertral, Zoloft, Asentra, Lustral, Tresleen	**Paroxetine** – Paxil, Paxetin, Aropax, Seroxat, Paroxat, Deroxat	**Citalopram**- Cipramil, Celexa, Citox, Cipram, Sepram, Oropram	**Escitalopram**- Cipralex, Lexapro, Seroplex, Esopram
FDA approval date	29 December 1987[17]	30, December 1991[4]	29 December 1992[4]	17 July 1998	14August 2002[4]

Mechanism of action (MOA) of SSRIs

Selective serotonin reuptake inhibitors act as inhibit the action of the serotonin reuptake transporter (SRT), leading to an inflow of serotonin (5-hydroxytryptamine or 5-HT) at the neurotransmitter junction.[5] SSRIs predominantly maintained their effect on serotonin pathway and these show relatively less affinity on norepinephrine (NE), dopamine (D2), acetylcholine (Ach) and histamine receptors in comparison to other antidepressants classes because these drugs are selective for serotonin. SSRIs vary considerably in their chemical structure, which results in pharmacologic differences among drugs in this class and may affect various aspects of treatment, such as administration, dosing, side effect profile as well as discontinuation.[6] For example, sertraline has relatively more potency for dopamine receptors when compared to other SSRIs and patients may present with extra-pyramidal side effects.[7]The proper therapeutic effects of SSRIs occurs gradually and may take 2 to 6 weeks before it is optimum.[8] *The MOA of the SSRIs is exemplify in Figure 1*.[9]

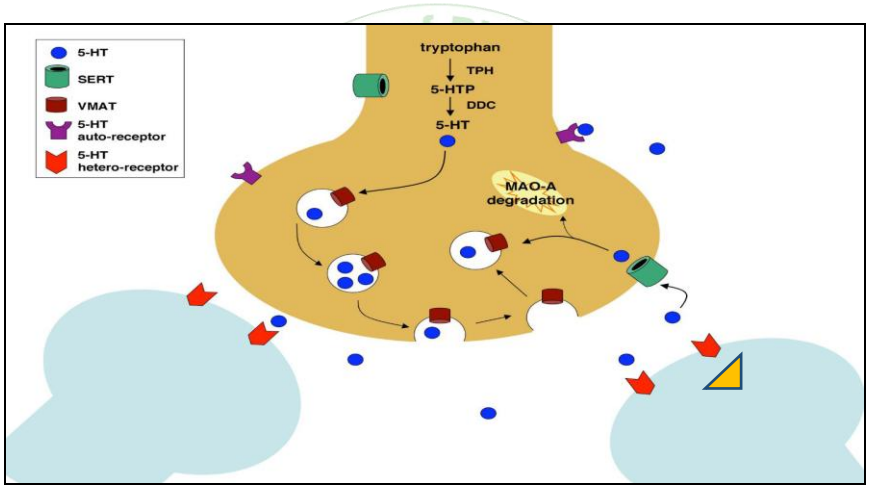

Figure: 1 Blockade of Serotonin reuptake

Pharmacokinetics

SSRIs are rapidly metabolized by the liver and administration is not affected by food. Co-administration with food would thus have an additional benefit in preventing the gastro-intestinal side effects associated with SSRI use. The half-life of SSRIs varies across the different drug classes. Fluoxetine have the longest half-life (72-96 hours) other than drugs & its steady state is reached after 2-3 weeks of treatment.[10]

Table 2: Currently available SSRIs with dose and mean of half - life.[10-11]

Drug name	Examples	Dosage	Mean half-life (hours)
Citalopram hydrobromide	Adco-Talomil®, Arrow Citalopram®, Austell-Citalopram®, Bio Citalopram®, Cilate®, Cilift®, Ciloram®, Cipramil®, Depramil®, Recita®	20mg once daily; Maximum dose: 60mg daily	Medium (30 hours)
Escitalopram oxalate	Aspen Escitalopram®,Accord Escitalopram®, Cipralex®, Citraz®, Dolin®, Escitalopram Lexamil®, Zytomil® Marprem®, Mylan Escitalopram®,	10mg once daily; Maximum dose: 20mg daily	Medium (30 hours)
Fluoxetine hydrochloride	Deprozan®, Lilly-Fluoxetine®, Lorien®, Nuzak®, Prohexal 20®, Prozac®, Ranflocs®	20mg once daily; Maximum dose: 60mg daily	Long (96 hours)
Fluvoxamine maleate	Faverin®, Fluoxetine Actor 20®, Luvox®	100mg once daily; Maximum dose: 300mg daily; Doses >150mg should be given in 2-3 divided doses	Short (15 hours)

Paroxetine hydrochloride	Adco-Paroxetine®, Aropax®, Deparoc®, Lenio®, Paroxetine Unicorn 20®, Paxil®, Serrapress®, Texine®, Xet 20®	20mg once daily; Maximum dose: 50mg daily (gradual 10mg increments) Controlled release formulation: 25mg once daily; Maximum dose: 62.5mg daily (gradual increments of 12.5mg)	Short (21 hours)
Sertraline hydrochloride	Austell-Sertraline®, Dyna-Sertraline®, Serlife, Sertra®, Winthrop®, Zolid®, Zoloft®, Zylin®	50mg once daily; Maximum dose: 200mg daily	Short (26 hours)

Drug interactions

Combination therapy of SSRIs with other therapeutic agents is common in the management of psychiatric conditions. This is due to SSRI inhibition of the cytochrome P450 enzymes (CYP2D6) which is responsible for the metabolism of TCAs, leading to elevated serum concentrations of TCAs and possible toxicity. Fluoxetine and Paroxetine specifically, are known to cause a 5-fold increase in serum TCA concentration upon co-administration. In addition, fluoxetine causes an elevation of lithium levels warranting the need for monitoring lithium levels during treatment. Studies have also shown serotonin toxicity associated with concurrent use of SSRIs and the TCA linezolid.[11-12]A similar effect is experienced with concurrent use of SSRIs and the anticonvulsants, carbamazepine and phenytoin. SSRIs increase the serum concentrations of the latter two drugs, potentiating their effects and increasing the risk of toxicity. Compared to the other SSRIs drugs Sertraline, Citalopram, and Escitalopram have a lesser potentially to cause drug interaction, as they are weaker inhibitors of the cytochrome P_{450} enzymes.[13]

Table 3: Summary of the major pharmacokinetic and pharmacodynamics interaction that involve SSRI drugs.[11,14]

Drug	Effect on drug metabolizing enzymes	Examples of drug-drug interactions	Pharmacodynamics interactions (All SSRIs)
Fluvoxamine	Potent inhibitor of CYP 1A2, 2C19	Leads to increased levels of the following, which may result in toxicity (avoid concomitant use): • Agomelatine • Benzodiazepines • Clonazepam • Clozapine • Risperidone • Duloxetine • Haloperidol • Melatonin • Olanzapine • Proton pump inhibitors • Phenytoin • Quetiapine • Theophylline • Tricyclic antidepressants • Warfarin	Potential serotonin syndrome when combined with the following: • Mono amine oxidase inhibitors e.g. linezolid, moclobemide, phenelzine, tranylcypromine • Serotonin releasing agents e.g. amphetamine , imipramine, tramadol, St John's wort, SNRIs • Other agents e.g. lithium, buspirone Increased risk of bleeding with NSAIDs, antiplatelet agents and Other interactions: • Antipsychotics: Sexual side effects • Acetyl cholinesterase inhibitors: Gastrointestinal side effects
Fluoxetine Hydrochloride Paroxetine Hydrochloride	Potent inhibitor of CYP 2D6	• Atomoxetine • Beta blockers (e.g. Carvedilol, metoprolol) • Clozapine • Propranolol	• Thiazide diuretics: Hyponatraemia • Alcohol, benzodiazepines, antihistamines: Increased effect on central nervous system
Sertraline	Potent inhibitor of CYP 2D6 (at doses >200mg/day	• Flecainide • Phenothiazine neuroleptics • Tamoxifen • Warfarin • Risperidone • Tricyclic antidepressants	• Neuromuscular blockers e.g. pancuronium, suxamethonium: SSRIs reduce plasma cholinesterase activity resulting in prolonged neuromuscular blocking action
Citalopram Escitalopram	None	Contraindicated with other medicines that can prolong QT interval	

Discontinuation syndrome

Discontinuation syndrome occurs on abrupt withdrawal of SSRIs, and is experienced by at least a third of patients who have been on long-term SSRI therapy (longer than four weeks). The onset of symptom is usually within 3 days of stopping treatment and usually resolves spontaneously within two - weeks, however, the syndrome can persist for up to six - weeks after drug withdrawal. When the drug's pharmacological effects diminish after dose decrease or discontinuation occur withdrawal symptoms of SSRI. Discontinuation syndrome can be mistaken for a relapse of the underlying psychiatric condition and can often be misdiagnosed by the clinician.[15-17] The discontinuation syndrome is common, particularly with more-potent and shorter-acting SSRIs, such as Paroxetine, and can generally be prevented by tapering off the drug over a period of four - weeks.[17]

DISCUSSION:

Depression is a major mental health problem worldwide, contributing to significant morbidities, deaths, reduced quality of life, and societal burden along with significant socioeconomic losses. Though various pharamaco-therapeutic agents are used for the treatment and management of mental health issues, yet the incident burden of mental problems are increasing with an alarming rate. SSRIs class of anti-depressant drugs are frequently prescribed for treatment of depressive disorders. The proper therapeutic effects or action of SSRIs occurs gradually and may take 2 to 6 weeks before it is optimum. These drugs show there effect slowly because SSRIs works with Neurotransmitter. Adverse drug reactions are intrinsic to every drug therapy. Discontinuation syndrome occurs on abrupt withdrawal of SSRIs, because if any patients stop to take medication so that it show there withdrawal symptoms and is experienced by at least a third of patients who have been on long-term SSRI therapy. In addition of combination therapy, fluoxetine causes mood elevation of lithium so that warranting to the need for monitoring lithium levels during the treatment. Studies have also shown serotonin toxicity associated with concurrent use of SSRIs and the TCA linezolid drug. The discontinuation syndrome is common, particularly with more-potent and shorter-acting SSRIs, such as Paroxetine, and can generally be prevented by tapering off the drug over a period of four – weeks. Sertraline if combine with Clonazepam than this associated sexual dysfunction and weight gain. And some adverse drug reaction like as- Tardive dyskinesia, Orofacial-dyskinesia, muscle stiffness, allergic reaction and blurred vision.

CONCLUSION:

Antidepressants are the medications primarily used to treat depression, clinically referred as ‘major depressive disorder’ or MDD. SSRIs help to block the reuptake of serotonin in brain as well SSRIs mainly affect the level of serotonin so they referred as “Selective”. In all situations it may be some adverse effects, serotonin syndrome/symptoms of the drugs, so for this reason we have to need for the study of clinical trials. Mostly serotonin is found in the digestive system, although it’s also in blood platelets and throughout the central nervous system. The discontinuation syndrome is common, particularly with more-potent and shorter-acting SSRIs, such as Paroxetine, and can generally be prevented by tapering off the drug over a period of four – weeks. If you want to stop with SSRIs therapy so first of all you have to discuss with your doctor.

CONFLICTS OF INTEREST

The authors declare that they have no complicts of interests.

REFERENCES:

1. Depression and other common mental disorders: global health estimates. Geneva: World Health Organization; 2017 (http://apps.who.int/iris/handle/10665/254610, accessed 25 March 2017).
2. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). American Psychiatric Association. 2013.
3. Volkomer MM. Adolescent Mindfulness Interventions: A Meta-Analysis of the Effects on Anxiety and Depression.
4. Lederman S, Harris H, inventors; Tonix Pharma Holdings Limited, assignee. Methods and compositions for treating fatigue associated with disordered sleep using very low dose cyclobenzaprine. United States patent US 9,474,728. 2016; 25.
5. Slaton RM, Champion MN, Palmore KB. A review of paroxetine for the treatment of vasomotor symptoms. Journal of pharmacy practice. 2015; 28(3):266-74.
6. Siepmann T, Penzlin AI, Kepplinger J, Illigens BM, Weidner K, Reichmann H, Barlinn K. Selective serotonin reuptake inhibitors to improve outcome in acute ischemic stroke: possible mechanisms and clinical evidence. Brain and behavior. 2015; 5(10):e00373.
7. Rossiter D, editor. South African medicines formulary. Health and Medical Publishing Group; 2016.
8. Albert PR, Vahid-Ansari F, Luckhart C. Serotonin-prefrontal cortical circuitry in anxiety and depression phenotypes: pivotal role of pre-and post-synaptic 5-HT1A receptor expression. Frontiers in behavioral neuroscience. 2014 Jun 6;8:199.
9. Daubert EA, Condron BG. Serotonin: a regulator of neuronal morphology and circuitry. Trends in neurosciences. 2010 Sep 1; 33(9):424-34.
10. Sarkar S, Harihar S, Patra BN. Sexual dysfunction due to SSRI antidepressants: How to manage?. Apollo Medicine. 2016; 13(2):97-101.
11. Chigome AK, Matsangaise MM, Chukwu BO, Matlala M, Sibanda M, Meyer JC. Review of selective serotonin reuptake inhibitors. SA Pharmaceutical Journal. 2017; 84(6):52-9.
12. Woytowish MR, Maynor LM. Clinical relevance of linezolid-associated serotonin toxicity. Annals of Pharmacotherapy. 2013; 47(3):388-97.
13. Ducasse D, Boyer L, Michel P, Loundou A, Macgregor A, Micoulaud-Franchi JA, Courtet P, Abbar M, Leboyer M, Fond G. D2 and D3 dopamine receptor affinity predicts effectiveness of antipsychotic drugs in obsessive-compulsive disorders: a metaregression analysis. Psychopharmacology. 2014; 231(18):3765-70.
14. Manolopoulos VG, Ragia G, Alevizopoulos G. Pharmacokinetic interactions of selective serotonin reuptake inhibitors with other commonly prescribed drugs in the era of pharmacogenomics. Drug metabolism and drug interactions. 2012; 27(1):19-31.
15. Bérard A, Zhao JP, Sheehy O. Sertraline use during pregnancy and the risk of major malformations. American journal of obstetrics and gynecology. 2015; 212(6):795-e1.
16. Kaplan YC, Keskin-Arslan E, Acar S, Sozmen K. Prenatal selective serotonin reuptake inhibitor use and the risk of autism spectrum disorder in children: A systematic review and meta-analysis. Reproductive Toxicology. 2016; 66:31-43.
17. Wilson E, Lader M. A review of the management of antidepressant discontinuation symptoms. Therapeutic advances in psychopharmacology. 2015; 5(6):357-68.