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A SHORT REVIEW ON SSRIs

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Abstract:

Selective Serotonin Reuptake Inhibitors (SSRIs) represent a class of drugs primarily used in the treatment of various mental health disorders, notably depression, anxiety disorders and certain other psychiatric conditions. This article aims to elucidate the history, pharmacological profile, therapeutic efficacy, adverse effects, and clinical considerations associated with SSRIs. SSRIs operate by selectively inhibiting the reuptake of serotonin in the synaptic cleft, thereby enhancing serotonin neuro transmission. This mechanism is pivotal in regulating mood, emotions, and behaviour. Thoroughly considering this action, SSRIs are recognized for their efficacy in alleviating symptoms of depression and managing anxiety disorders. The drugs within this class commonly prescribed include fluoxetine, sertraline, paroxetine, citalopram, and escitalopram. Despite their therapeutic benefits, SSRIs are associated with a spectrum of side effects, including gastrointestinal disturbances, sexual dysfunction, weight changes, and rarely emergent suicidal ideation, especially in individuals. Moreover, discontinuation of SSRIs may lead to withdrawal symptoms, To overcome this a gradual tapering regimen is performed under medical supervision. The clinical utility of SSRIs extends beyond psychiatric conditions, with emerging evidence suggesting their potential in treating conditions such as premature ejaculation, premenstrual dysphoric disorder, and certain pain syndromes. Individual variability in response to SSRIs underscores the importance of personalized medicine in prescribing these medications. Factors such as genetic predisposition, co-existing medical conditions, concomitant drug use, and patient-specific considerations significantly influence treatment outcomes.

Keywords: *Selective Serotonin Reuptake Inhibitors, Depression, Anxiety Disorders, sexual dysfunction, psychiatric conditions*

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INTRODUCTION:

History of SSRIs

Several scientists began presenting data in the late 1960s indicating serotonin plays a key role in major depressive disorders. The data is based on several postmortem accounts of individuals who killed themselves as a result of depression[1]. The pharmaceutical industry underwent radical transformations that directed in a new era of antidepressant development. Eli Lilly, a pharmaceutical company, started creating ligands that are intended to specifically inhibit the re-uptake of serotonin at serotonin transporters, therefore raising serotonin levels in the synaptic cleft, and stimulating postsynaptic serotonin receptors even more. In 1974, the first report on the SSRI LY110140 (fluoxetine) was published. The authors of that article proposed that fluoxetine functions as an antidepressant medication (Wong, Horng, Bymaster, Hauser, & Molloy, 1974)[2]. The following year, Wong and associates showed that fluoxetine, a phenoxyphenylpropylamine analogue of nisoxetine (LY94939), was a strong and selective serotonin reuptake inhibitor with a low affinity for the norepinephrine transporter. This finding allowed fluoxetine to be pharmacologically distinguished from other antidepressants. Wong, Bymaster, Horng, & Molloy, 1975)[3]. The FDA authorized fluoxetine in December 1987, and it was introduced on the market as Prozac® in January 1d988. Wong, Bymaster, & Engleman, 1995; Wong, Perry, & Bymaster, 2005 provide an excellent overview of the development of fluoxetine [4].Fluoxetine was the first approved SSRI in the United States market, it's clinical trials [Phase I-Phase III] Takes place more than 7 years . During this period the first SSRI named Zimeldine, was introduced in to the European market. Zimeldine was introduced by Astra AB. The major draw back of Zimeldine is severe side effects. The side effects include hypersensitivity reactions and Guillain -Baree syndrome. Guillain -Baree syndrome is a rare disorder in which body's immune system attacks the peripheral nervous system. Due to this reasons Zimeldine was dis continued[5] .

Reasons for choosing SSRIs over TCA's

TCA's have low safety of margin .They are hazardous in over dose and deaths are common .TCA's also produce cardiovascular and anti-cholinergic side effects very frequently .some patients doesn't respond for TCA's.

The high safety profile along with the wide acceptability, The SSRIs become 1st line drugs in depression and anxiety , panic disorder , OCD , several phobias , PTSD also[6].

How an SSRI works

SSRIs exert action by inhibiting the reuptake of serotonin, thereby increasing serotonin activity.[6]

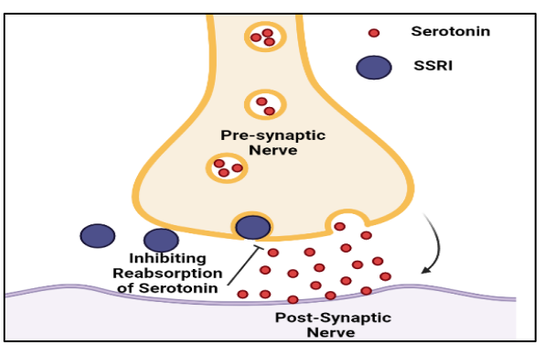

Figure 1 : MOA of SSRI

Pharmacological classification of SSRIs[6]

1.Fluoxetine
2.Fluvoxamine
3.Paroxetine
4.Sertraline
5.citalopramnn
6.Escitalopram

1.Fluoxetine

Fluoxetine [Prozac®] is a SSRI , which is a bicyclic derivate of phenyl propylamine . It lacks three fused ring system which is present in TCAs . This unique feature which Facilitates the advantage over the TCAs

Mechanism of action

- Fluoxetine acts as an antagonist at 5HT2C receptors. Fluoxetine works by inhibiting the reuptake of serotonin at serotonin transporters . There by it helps in treating patients with mild depression .It is used as a mood elevator and there by decrease the feeling of fear.
- Fluoxetine doesn't bind to the histamine and acetyl choline dopamine receptors .It doesn't have sedative effect

Clinical uses

- Mood Disorders – major depressive disorder , bipolar disorder
- Anxiety Disorders – Panic disorder , OCD
- Other – Bulimia nervosa and premenstrual dysphoric disorder[7]

Pharmacokinetics

- The fluoxetine has longest half-life among all the SSRIs i.e., [24-48 hours]
- Fluoxetine is metabolized in the liver by the CYP450 ANS CYP2D6 Systems
- Complete excretion of fluoxetine takes several weeks

Adverse Effects

Decreased libido,nausea,nervousness, pharyngitis, ab normal ejaculation, anorexia, anxiety, asthenia, urticaria

Along with this sexual dysfunction and QT prolongation syndrome and serotonin syndrome

Drug interactions

Mono Amino Oxidase inhibitors

This drug interaction is very dangerous and fatal sometimes, the symptoms include vitals variation, agitation, hyperthermia etc. The gap of at least 14 days for discontinuing SSRI and starting MOA inhibitors [8]

Contraindications

- Never combined fluoxetine with MOA inhibitors
- Never combine fluoxetine with other SSRIs
- Never combine fluoxetine with pimozide, thioridazine, or tamoxifen . It has a history of seizures
- Mostly fluoxetine doesn't use in pregnancy[9].

2.Fluvoxamine

- Fluvoxamine [Luvox, Faverin] is the first SSRI approved by US FDA for the treatment of OCD[10]
- It is a short acting SSRI and well tolerated and available widely.
- It's half-life is 18 hours

- It is mainly used in the treatment of OCD and GAD [11].

Mechanism of action

Fluvoxamine works by blocking the Reuptake of serotonin at the sodium dependent transporter [SERT] and improves the actions of serotonin on 5HT1A receptors.[12]

Clinical uses

- Major depressive disorders
- Anxiety
- Depression
- Generalized anxiety disorder
- OCD

Pharmacokinetics

When given through oral route it is completely absorbed through GIT . The absorption rate doesn't alter due to presence of food

- Peak plasma concentration: 2-8 hours
- Elimination half-life : 19-22 hours [13].
- It is metabolised in the liver by the cytochrome P450 system

Adverse effects

Head ache , nausea , diarrhea , Agitation, Anxiety, Abdominal pain , Insomnia , Palpitations , Tremors
Along with is a serious condition called as serotonin syndrome may occur in some patients. It is fatal.

Drug Interactions

Anti consultant's

Fluvoxamine increases the concentration of the anti convulsants in the blood
Ex: Phenytoin , valproic acid

Blood thinners: Increase the risk of bleeding
Ex : warfarin, Aspirin

Other Antidepressants: Lithium, Buspirone [14]

Contraindications

- Don't use MAOIs within 14 days of Fluvoxamine
- Don't co administer with alosetron , pimozide, tizanidine [15].

3.Paroxetine

Paroxetine [Aropax,Paxil, Pexeva , Seroxat , Sereupin , Brisdelle] is a SSRI . It is used to treat social anxiety disorder, panic disorder, posttraumatic stress disorder, Depression

Mechanism of action

As an SSRI drug , paroxetine's has the ability to inhibit the serotonin reuptake transporter, therefore increase in the synaptic serotonin concentration

Clinical uses

- Premature ejaculation
- Social anxiety disorder
- Obsessive – compulsive disorder
- Dysthymia
- Post partum depression

Pharmacokinetics

- Paroxetine is given through oral route.
- Plasma T1/2 is 21 hours
- It undergoes metabolism via hepatic CYPP4502D6
- Excreted through urine and feces

Adverse Effects

The most common side effects include drowsiness, dry mouth, loss of appetite, sexual side effects and disturbance in sleep, Dizziness , Diarrhea , Nausea[16].

Drug interactions

MOA Inhibitors

Concurrent use of paroxetine with MAOIs or with in 14 days of discontinuing leads to fatal condition called serotonin syndrome

- **NSAIDs**
- Increased risk of bleeding -Aspirin
- **Other SSRIs and SNRIs –** Risk of serotonin syndrome **.**
- **TCA'S**-serotonin syndrome
- **Lithium –** potential toxicity

Contraindications

Don't use MAO along with paroxetine
Concurrent use of thioridazine, pimozide is contraindicated
Paroxetine inhibit TCA metabolism leading to possible TCA toxicity
Contraindicated in pregnancy – Leads to cardiac vascular malformations [17]

4.Sertraline

Sertraline [Zoloft] is a SSRI which is used mainly in the treatment of panic disorder and depression in adults
It has an advantage over other SSRIs i.e., It does not cause weight gain

Mechanism of action

Sertraline works by inhibiting serotonin transporter [SERT] in striatum and it also have capability to act as dopamine Reuptake inhibitor
.

Clinical uses

- Depression in elderly
- Obsessive-compulsive disorder
- Premenstrual dysphoric disorder
- Generalized anxiety disorder
- Premature ejaculation

Pharmacokinetics

- Sertraline is given through oral route; it is absorbed slowly. For achieving peak plasma concentration, it takes up to 4-6 hours
- Sertraline half-life is 13-45 hours
- Sertraline is metabolized in the liver by cytochrome 450 isoforms.
- Excreted through urine .

Adverse effects

- Nausea, diarrhea, decreased libido, Akathisia
- Sertraline can prolong the QT interval
- Serotonin syndrome.
- Concurrent use of sertraline with MAOIs or within 14 days of discontinuing leads to fatal condition called serotonin syndrome [18].

Contraindications

- It is contraindicated in patients who are using MAOIs
- It is contraindicated with thioridazine, pimozide. methylene blue.
- Sertraline solution contraindicated with disulfiram [19].

5.Citalopram

- Citalopram [Celexa] is a SSRI which is used to treat anxiety, panic , OCD , social phobia .
- It is S-enantiomer of the racemic citalopram
- It is a bicyclic Pthalane derivative

Mechanism of action

- Citalopram shows it's action by potentiating serotonergic activity in the central nervous system
- Citalopram shows less effect to norepinephrine and dopamine receptors

Clinical uses

- Treatment of depression in adults
- Panic disorder
- Generalized anxiety disorder
- Premature ejaculation
- Social anxiety disorder

Pharmacokinetics

- Citalopram given through oral route
- The onset of action for depression is about 1 to 4 weeks
- Bioavailability is 80%
- Half-life is 24-48 hours
- Citalopram is metabolized by cyp4503A4 and 2c19.[20]

Adverse effects

- Nausea , vomiting , constipation , diarrhea
- CNS: Drowsiness , dizziness , insomnia
- Sexual – Delayed ejaculation
- Hyponatremia
- Serotonin syndrome
- Suicidal ideation

Drug Interactions

- Citalopram has risk of bleeding
- Citalopram may interact with proton pump inhibitors . They increase the concentration of the proton pump inhibitors. Patients should be monitored carefully .
- Citalopram combining with MAOIs leads to serotonin syndrome [21].

contraindications

- Citalopram is contraindicated in patients who are using monoaminoxidase inhibitors, at least 15 days gap is required while shifting form SSRI to MAOI [22]

- Citalopram should not combine with thioridazine

6.Escitalopram

Escitalopram (Cipralex, Lexapro) , it is the s-enantiomer of the racemic selective serotonin reuptake inhibitor citalopram.

Escitalopram has rapid on set of action i.e., antidepressant activity

Mechanism of action

Escitalopram shows it's a action by binding to the SERT in the pre synaptic neuron

SERT is responsible for reuptaking serotonin from the synaptic cleft in to the presynaptic neuron [23].

Clinical Uses

- Major depressive disorder
- Anxiety
- Panic attacks
- Obsessive compulsive disorder
- Posttraumatic stress disorder
- Premature ejaculation

Pharmacokinetics

- Escitalopram is given through oral route of administration
- Peak plasma concentration is attained for 5 hours
- Steady-state plasma concentration within 1-2 weeks [24].
- Escitalopram undergoes hepatic metabolism via CYP3A4 and CYP2C19
- Elimination Half Life Is 27-33 Hours [25].

Adverse effects

- Insomnia
- Sleep disturbances
- Sexual dysfunction
- Ejaculatory disorders
- QT prolongation [26].

Drug interactions

- Anti platelet - Risk of bleeding [27]
- Amiodarone – prolong QTc intervals[28].

Contraindications

- Escitalopram combines with MAOI is strictly contraindicated due to the risk of causing serotonin syndrome
- escitalopram is contraindicated Rasagiline with pimozide.[29]

CONCLUSION:

In conclusion, Selective Serotonin Reuptake Inhibitors (SSRIs) stand as a pivotal cornerstone in modern psychiatric care. Through their ability to modulate serotonin levels in the brain, SSRIs have proven to be effective in alleviating symptoms associated with various mental health conditions, such as depression, anxiety disorders, obsessive-compulsive disorder (OCD), and more. Throughout this article, we've explored the mechanism of SSRIs, their potential side effects, and their role in mental health treatment. While acknowledging that individual responses to SSRIs can vary, their widespread use underscores their importance in providing relief to millions of individuals worldwide. Despite their efficacy, it's crucial to highlight the importance of responsible and informed use of SSRIs. Consulting with healthcare professionals, discussing potential side effects, and being vigilant about any changes during treatment are vital aspects of ensuring their safe and effective usage.

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