Selective Serotonin Reuptake Inhibitors

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Selective serotonin reuptake inhibitors (SSRIs) are an essential pharmacological treatment for patients with unmanageable premenstrual syndrome (PMS) and premenstrual dysmorphic disorder (PMDD). SSRIs can be taken either continuously or in the luteal phase to reduce the symptoms of PMS and PMDD. Most SSRIs exhibit equal efficacy for the treatment of PMS and PMDD, so a provider's choice of SSRI should be based on anticipated side effects and the patient's response to the drug.

selective serotonin reuptake inhibitors | adverse effects | suicidality

1. Introduction

Depression is the most prevalent psychiatric disorder in the world, affecting 4.4% of the global population [1]. In the United States alone, the economic burden of the major depressive disorder increased by 21.5% from 2005 to 2015, when it was estimated to be USD 210.5 million/billion [2]. There are several types of depression and to differentiate there are specifiers that can be included. These are atypical features, anxious distressed, mixed features, melancholic features, psychotic features, catatonia, peripartum onset, and seasonal pattern [3]. Each different type of depression may respond better to a certain type of pharmacologic treatment than others. Despite an array of treatment modalities, depressive disorders remain difficult to manage due to many factors, including relatively high relapse rates while undergoing treatment and unfavorable side effect profiles of the medications available [4][5].

Preceding the discovery of selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (TCAs) were the only options for pharmacologic intervention in depressive disorders. These drugs, however, had unfavorable side effect profiles, resulting in poor patient adherence. Consuming too much tyramine while on an MAOI may cause a potentially deadly hypertensive crisis. TCAs can cause blockage of cardiac sodium channels and cardiac arrhythmias [6].

Beginning with the introduction of fluoxetine to the United States in 1988, SSRIs quickly became a mainstay of treatment for a variety of psychiatric disorders. They were originally studied to target depression, but further investigation has led to their use in many anxiety disorders. SSRIs were not more effective than TCAs but had increased rates of patient adherence [7], largely due to their more favorable side effect profile. Despite being an immense step forward in the management of psychiatric disorders, SSRIs still have a variety of adverse effects that need to be reviewed and monitored.

The primary mechanism of action of SSRIs is to inhibit the presynaptic reuptake of serotonin at the serotonin transporter, subsequently increasing serotonin at the postsynaptic membrane in the serotonergic synapse [8]. Interestingly, the therapeutic effects of SSRIs cannot be entirely summed up by simple inhibition of serotonin transporter (SERT), and as such further mechanisms of action must be at work. A current theory posits that the neuronal stress caused by SSRIs causes a shift in brain homeostasis that results in downregulation of SERTs in some areas of the brain and upregulation in others [9]. This mechanism may explain why the full therapeutic effects of SSRIs are not realized until four to six weeks after initiation, despite significant immediate alterations in serotonin flux. The aim of this review to educate clinicians on potential adverse effects of SSRIs.

2. Current Uses of SSRIs

Depression is a debilitating illness that often interferes with a patient's quality of life. It imposes a significant financial burden on a patient and the healthcare system, with both direct and indirect costs [10]. In 2018, a study reported increased use of outpatient services by patients with hypertension and/or diabetes with untreated depressive symptoms [11]. Along with addressing the patient's depressive symptoms, treatment with antidepressants in these patients may decrease secondary health costs [11]. Additional comorbidities associated with depression are alcohol use disorder, anxiety disorders, and even somatoform disorders [12]. Adequate treatment of depression is thought to decrease these associated comorbidities as well.

The individual and societal impacts of depression highlight the importance of effective treatments. In patients who have not had a medication trial of an antidepressant, SSRIs are usually the first medication used in depression treatment. While SSRIs are the mainstay of pharmacological treatment for patients with depression, some patients do not respond to initial monotherapy and require the addition of other treatments [13]. One strategy involves combining SSRIs with psychotherapy. In one study, 30% of SSRI users utilized psychotherapy [14]. A meta-analysis that looked at studies that examined the use of antidepressants, psychotherapy, and both used in combination found that the use of the combination of antidepressants and psychotherapy offered better treatment outcomes which were still sustained two years later [15].

Anxiety disorders, such as generalized anxiety disorder (GAD), social anxiety disorder (SAD), and panic disorder are some of the most common psychiatric disorders. SSRIs are currently the preferred medication for anxiety disorders due to an abundance of literature supporting their safety and effectiveness [16][17][18]. Compared to other anxiolytics, SSRIs have fewer side effects and treat depression, which is often comorbid with anxiety [19]. Results from a meta-analysis of 57 trials confirm that SSRIs are an effective treatment for anxiety disorders and that doses on the higher side of the therapeutic range are associated with greater symptom improvement [18].

Gastrointestinal (GI) disorders are frequently comorbid in patients with depression and anxiety disorders [20][21][22]. Serotonin transporters are located on neurons, glial cells, blood platelets, and enterocytes, and altered signaling of serotonin in the gut may contribute to the symptoms associated with GI disorders [23][24]. Antidepressants have shown to have anti-ulcerative effects and have been increasingly prescribed in those with GI disorders [25]. Multiple animal studies have shown that the SSRI fluvoxamine protects against the development of peptic ulcers through

antioxidant and anti-inflammatory mechanisms [26][27]. Certain SSRIs may improve symptoms of irritable bowel syndrome (IBS); however, their efficacy is controversial, so they should only be prescribed in IBS patients with comorbid depression or anxiety [28][29].

3. SSRIs and Adverse Effects

SSRIs are generally better tolerated than other antidepressants, but common side effects may include nausea, vomiting, insomnia, drowsiness, headache, decreased sex drive, and agitation [8][30]. Here, we will discuss some of the less common adverse effects of SSRIs reported in literature, with a focus on extrapyramidal symptoms (EPS), serotonin syndrome, QT prolongation, rash, birth defects, hyponatremia, and cataracts.

Although uncommon, EPS in patients treated with SSRIs has been observed in numerous studies [31][32][33]. One study identified 86 case reports connecting the use of SSRIs with the development of dystonia, parkinsonism, dyskinesia, and akathisia. Most of these cases occurred within 30 days of treatment initiation or dose increase, with citalopram, escitalopram, fluoxetine, and sertraline most frequently involved [31]. This association highlights the importance of monitoring patients during SSRI therapy for the development of EPS [31][32][33].

Serotonin syndrome is a potentially fatal consequence of serotonergic overactivity in the peripheral and central nervous systems [34]. Though rare, incidence is increasing due to widespread SSRI use [34]. The majority of cases involve a combination of serotonergic drugs, though SSRI monotherapy may also lead to serotonin syndrome [35][36]. One case reported moderate serotonin syndrome involving hyperreflexia and ankle clonus in an adult male on sertraline monotherapy [37]. Most other cases of serotonin syndrome with SSRI monotherapy have involved overdose or switching SSRI therapy without cross-titration [38][39][40]. To prevent serotonin syndrome in patients on SSRIs, providers should exercise caution when combining, switching, or discontinuing these drugs [41].

Among all antidepressants, SSRIs carry the highest risk of hyponatremia, especially in the initial weeks of treatment [42][43]. Although the mechanism is unknown, serotonin may increase antidiuretic hormone, thereby inducing syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [43][44]. Most cases of hyponatremia due to SSRIs involve elderly patients, but other risk factors include concomitant use of hyponatremia-inducing drugs, low body weight, female gender, low serum sodium, and severe illness [44][45][46].

4. Suicidal Ideation

In 2004, the US Food and Drug Administration (FDA) added a black box warning level 5 to all antidepressants of suicidality for children and young adults aged 18–24 years [47]. Anxiety, agitation, hostility, restlessness, or impulsive behavior in adolescents after starting an antidepressant may be the natural course of worsening depression or TESI [48]. Following this, physicians began to underdiagnose MDD in adolescents and prescribed them fewer antidepressants, and patients under age 18 were often not included in studies.

In 2014, a retrospective cohort study investigated 36,842 children aged 6 to 18 years old, with a mean age of 14 [49]. The children were enrolled in Tennessee Medicaid between 1995 and 2006 and were all new users of one antidepressant medication, including fluoxetine, sertraline, paroxetine, citalopram, escitalopram, or venlafaxine [49]. Four hundred nineteen cohort members who had a medically treated suicide attempt with explicit or inferred attempt to die, confirmed through medical record review, including four who completed suicide [49]. Compared to the national suicide average in adolescents, there was no evidence of increased risk for serious suicide attempts on any of the individual antidepressants [49]. One limitation of this study was the focus on suicide attempts, thereby possibly missing some SI.

Given the completed development of the brain, and therefore, the greater social acceptability of studies in adults, the relationship between SI and SSRIs in adults is better characterized.

In 2018, the Arzneimittelsicherheit in der Psychiatrie (AMSP) program for Drug Safety in Psychiatry studied 219,635 patients from 1993 to 2014 to determine the correlation between SI and antidepressants, including SSRIs, TCAs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonergic antidepressants (NaSSAs). There were 83 documented suicidal cases during the study—44 cases of SI, 34 attempted suicides, and 5 fatal suicides—with an incidence rate of 0.04% [50]. Increased restlessness, ego-dystonic thoughts or urges, and impulsivity contributed to suicidality [50]. This study found a rare and not clinically significant association between antidepressant use and SI [50].

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