

## SELECTIVE SEROTONIN REUPTAKE INHIBITORS – MEDICATIONS NOT ONLY FOR DEPRESSION

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### **Abstract**

*Selective serotonin reuptake inhibitors (SSRIs) are the frontline class of antidepressant drugs. They are widely used because of their safety, tolerability, and demonstrated efficacy. In this review, we are pointing at other indications of SSRIs – apart from depression. This article is based on a selective review of the relevant literature retrieved by a PubMed search and ScienceDirect search. The results of electronic searches show SSRIs to be of great importance in pharmacotherapy of many conditions outside depression. Medical literature supports the use of SSRIs for the treatment of premature ejaculation (especially short-acting SSRI - dapoxetine), eating disorders (especially bulimia nervosa and binge eating disorder), obsessive-compulsive disorder and social anxiety disorder.*

**Keywords:** SSRI, premature ejaculation, dapoxetine, eating disorder, obsessive-compulsive disorder, social anxiety disorder.

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### **Introduction**

The selective serotonin reuptake inhibitors (SSRIs): fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram and escitalopram, are members of the frontline class of antidepressant drugs. SSRIs block the reuptake of serotonin at the presynaptic neuron (selectively block 5-HT transporters), with minimal or no effect on norepinephrine or dopamine [1]. Even though the first SSRI antidepressant drug on the market was Zimelidine, it has been banned worldwide due to serious, sometimes fatal, cases of central and/or peripheral neuropathy known as Guillain-Barré syndrome [2,3]. The introduction of SSRIs, starting with the approval of fluoxetine in 1987 revolutionized the behavioral pharmacology of antidepressant drugs [1]. There was no crossover of the hypersensitivity reaction between fluoxetine and zimeldine. The mechanism giving rise to the reaction was specific to zimeldine and, therefore, could not be the common mechanism of

the SSRIs of serotonergic reuptake blocking [2]. By comparison with older drugs, tricyclic drugs which inhibit the reuptake of monoamines and monoamine oxidase inhibitors (MAOIs) which inhibit their enzymatic degradation, fluoxetine reduced the frequency and severity of side effects that often required patients to withdraw from treatment. SSRIs became clinically successful and well-known for medical treatment of depression [1,4]. Especially fluoxetine which is the most frequently used worldwide antidepressant drug [5]. However, medical literature supports the use of SSRIs not only for the treatment of depression but also for many other conditions.

### **Premature ejaculation**

Premature ejaculation (PE) is a widely observed male sexual dysfunction with a major impact on quality of life for many men and their sexual partners. When rapid ejaculation occurs occasionally, especially among men who didn't have any sexual intercourses for a long time, it

can not be called a problem. The symptoms which can stand for sexual dysfunction are: premature ejaculation nearly every intercourse, with every sexual partner, most often within 1 minute, often within 30–40 seconds after penetration, sometimes during foreplay, before penetration. Many men who suffer from ejaculatory dysfunction try to develop all sorts of tricks just to delay ejaculation or even try to avoid sexual contact [6,7].

On the market there are many easily available topical agents, creams, sprays, and systemic therapies which are supposed to deal with PE [8]. The use of topical anesthetic creams was first described in 1943. The reduction of penile sensitivity would result in prolongation of sexual intercourse. The examples of popular agents are used off-license prilocaine/lidocaine cream (EMLA®) and a novel metered-dose aerosol spray of lidocaine/prilocaine (TEMPE®). These topical treatments may appear ideal for on-demand use in PE, but they have several disadvantages, including genital numbness for both the patient and partner, reduced ability to maintain an erection, and messy application. As a result, these topical therapies have never achieved widespread acceptability and induced search for an oral drug [9].

Delayed or inhibited ejaculation, a known side effect of SSRIs, has made SSRIs potentially useful in the treatment of this disorder. SSRI medication increases the latent period of intravaginal ejaculation and therefore to be beneficial in patients who prematurely ejaculate [10]. The off-label use of antidepressant SSRIs, including paroxetine, sertraline, fluoxetine, citalopram and fluvoxamine, and the serotonergic tricyclic clomipramine has revolutionized the approach to treatment of PE [11]. Unfortunately, because of commonly experienced adverse effects, including erectile dysfunction, loss of libido, mood changes, and discontinuation syndrome, they were not ideal for the treatment of PE either [9]. As a

matter of fact, these drugs were not developed to treat PE, in contrast with dapoxetine which was specifically developed for this purpose.

Dapoxetine (Priligy, Janssen-Cilag), which is selective serotonin reuptake inhibitor, is the first and currently the only approved oral drug to treat PE in men aged 18–64 years [8,9,12]. Dapoxetine is significantly different from other SSRIs [9,12]. Conventional SSRIs are intended for chronic use in the treatment of depression and are designed to have pharmacokinetic profiles that would allow them to provide constant systemic concentration with long-term administration in order to exhibit efficacy. It has been suggested that on-demand treatment with SSRIs possessing a short half-life and short T<sub>max</sub> would be equally effective, more convenient, and exhibit fewer serotonergic side-effects than observed with daily treatment [12]. Different pharmacological profile to other SSRIs, makes dapoxetine suitable for on-demand dosing of PE, an effective and safe treatment for PE and represents a major advance in sexual medicine [9,11].

Dapoxetine attains its peak plasma concentration in about 1.5 hours after dosing, which is much faster than fluoxetine, paroxetine, or sertraline [12]. It is rapidly absorbed and eliminated, resulting in minimal accumulation, and has dose proportional pharmacokinetics which are unaffected by multiple dosing [11]. The recommended starting dose is 30 mg (administered with water) as needed, 1–3 hours prior to sexual intercourse (with a maximum dosing frequency of once every 24 hours). The dose may be increased to 60 mg (the maximum recommended dose) based on efficacy and tolerability. Each film-coated tablet contains either 30 mg or 60 mg dapoxetine hydrochloride, and may be administered with or without food [9].

Dapoxetine – a short-acting SSRI, with its unique pharmacokinetic profile, is an ideal compound for the treatment of PE [12]. However, it can also cause adverse effects such as nausea

(11.0% for 30 mg, 22.2% for 60 mg), dizziness (5.9% for 30 mg, 10.9% for 60mg), and headache (5.6% for 30 mg, 8.8% for 60 mg) [11].

What is interesting, some clinical trials have demonstrated that approved by FDA an analgesic drug – tramadol can be also an effective treatment for PE, providing an option for managing mild to severe PE [8].

### Eating disorders

Eating disorders such as bulimia nervosa (BN), binge eating disorder (BED) and anorexia nervosa (AN), are serious problems of not entirely profiled etiology. While culture and society may be an influence, it is now widely recognized that there exists a biological basis to these disorders. Food intake is mediated, in part, through brain pathways for motivation and reinforcement. Several neurotransmitter systems have been proposed to be involved in these disorders with much attention given to the role of monoamine systems, particularly dopamine (DA) and serotonin (5-HT) but also acetylcholine (ACh) and opioid systems [13]. The results of electronic searches of the PubMed and Science Direct show SSRIs to be of great importance in pharmacotherapy of eating disorders, especially bulimia nervosa and binge eating disorder.

Bulimia nervosa is characterised by recurrent episodes of binge eating and secondly by compensatory behaviour (vomiting, self-induced vomiting, purging, fasting, exercising or misuse of laxatives, diuretics, thyroxine, amphetamine or other medication or combination of these) in order to prevent weight gain. Binge eating is accompanied by a subjective feeling of loss of control over eating [14]. Food restriction has been linked with decreased levels of 5-HT driven by a low rate of synthesis as well as down-regulates the density of 5-HT transporters, leading to the clinical use of fluoxetine (Prozac), a selective serotonin reuptake inhibitor, for the treatment of

bulimia [13]. For children and adolescents with BN, fluoxetine is the first line pharmacological option. The results of electronic searches suggest that fluoxetine should be the first line agent for BN also for adults. Not only because of well-established efficacy of fluoxetine, but also because of its better side effect profile, which makes it superior to other drugs in treating BN [15]. Early pharmacological treatments focused on tricyclic antidepressants, and showed efficacy in decreasing binge episodes compared to placebo. However, these medications were associated with adverse side effects [16]. The effective daily dose of fluoxetine is 60 mg and is more effective than a dose of 20 mg [15,16].

For eating disorders psychological treatment is also a factor of great importance. For BN, both 60 mg fluoxetine and cognitive behavioral therapy have well-established efficacy. For BED, selective serotonin reuptake inhibitors, cognitive behavioral therapy, and interpersonal psychotherapy [16]. There is one open trial of fluoxetine in ten adolescents aged 12 to 18 years. These patients received 8 weeks of fluoxetine at a daily dose of 60 mg along with supportive psychotherapy. Frequencies of weekly binge episodes decreased significantly from about 4 to 0, and weekly purges decreased from about 6 to almost none [17]. There has been mixed support for fluoxetine's efficacy in reducing depressive symptoms in patients with BN, with some studies finding no differences between fluoxetine and placebo and others favoring fluoxetine. What is important, 52 weeks of 60 mg fluoxetine significantly reduced relapse rate compared to placebo (33% vs. 51%, respectively) and increased time to relapse [16].

The SSRIs are not of great importance in pharmacotherapy of anorexia nervosa. Admittedly, some data suggest that SSRI medication is useful in preventing relapse in weight-restored anorexics [18,19], but first of all it

remains uncertain [15,20], and secondly SSRI medication have no effect on clinical symptoms of malnourished underweight anorexics [18,20]. Antidepressants have not been effective in improving the primary outcome for AN: weight. Further, there is limited evidence for whether antidepressants are effective in improving secondary outcomes, such as anxiety and depression, in underweight patients with AN [16,20].

Anorexia nervosa is significantly different from BN. It is a syndrome in which the patient maintains a low weight as a result of a pre-occupation with body weight, construed either as a fear of fatness or pursuit of thinness [14]. Animal models as well as clinical research indicates an interesting relationship between DA and 5-HT in anorexia. For this reason, atypical antipsychotics, which have effects on both DA and 5-HT receptors, might be effective in treating anorexia [13]. It appears that olanzapine may prove to be promising for AN at low body weights [15,20].

### **Obsessive-compulsive disorder (OCD)**

Because of the fact that serotonin is thought to be implicated in the pathophysiology of obsessive-compulsive disorder (OCD), selective serotonin reuptake inhibitors are also useful in treating this disorder [2].

OCD is characterized by obsessions (unwanted, intrusive thoughts, impulses or images) and compulsions (mental or physical acts undertaken to relieve the anxiety of the obsession) that cause distress [21]. It usually has an onset in childhood or early adulthood and what is worrying - disability and quality-of-life impairment in people suffering from OCD have been comparable with that of serious mental illness like schizophrenia [22]. Early-onset obsessive-compulsive disorder is one of the more

common mental illnesses of children and adolescents, with prevalence of 1% to 3% [23].

Prior to the 1960s, OCD was considered an untreatable condition. Fortunately, a tricyclic antidepressant, namely clomipramine, more potent than other antidepressants serotonin reuptake inhibitor, revolutionized the treatment of OCD [22]. Due to the adverse effects commonly observed in people treated with clomipramine and a greater specificity of fluoxetine, selective serotonin reuptake inhibitors (SSRIs) have taken over clomipramine. The effect of the SSRIs in OCD can be explained by a specific inhibition of serotonin reuptake [2]. Currently, pharmacotherapy with SSRIs (eg. escitalopram, fluvoxamine, fluoxetine, paroxetine or sertraline) in conjunction with cognitive behavioral therapy are the first-line treatments for OCD [21,23,24,25]. Both of them are highly effective and well tolerated. The SSRI's do not differ from each other in their efficacy at improving the manifestations of the disease.

Depression in children and adolescents appears to be more responsive to SSRIs than OCD. That is why, the recommended doses for children and adolescents with OCD are higher than the recommended doses of the same medications in the treatment of depressive disorders and largely correspond to those for adults [23]. It is also demonstrated that higher doses of SSRI are more effective than lower doses and that all doses of SSRI pharmacotherapy were more effective than placebo. These suggest that the increased side-effect burden of SSRIs at higher doses may be counterbalanced by the increased treatment efficacy [21]. The acute treatment is recommended to last at least 3 months [25].

Unfortunately, despite the proven efficacy of SSRIs in OCD about 40% to 60% of patients show no or just partial symptom improvement to a treatment with a first-line drug [22,25]. It is

important that if one SSRI is ineffective, another SSRI should be tried next [23]. Due to the adverse effects, clomipramine is generally recommended when treatment with at least two SSRIs have failed. In people who show partial response to SSRI treatment or poor response to multiple SSRIs are recommended augmentation strategies [22]. The combination of the antipsychotics risperidone, haloperidol, olanzapine, aripiprazole, or quetiapine with SSRI was shown to be more effective than SSRI monotherapy in treatment-resistant cases. In most studies, response occurred within 1 month of augmentation. Augmentation with atypical antipsychotics is an established second-line drug treatment strategy. Alternatives include intravenous serotonergic antidepressants and combination with or switch to cognitive behavioral psychotherapy [25].

The selective serotonin reuptake inhibitors again turn out to be extremely essential in treatment of serious psychiatric disorder. Even though patients in remission from OCD may not function as well as people who have no history of psychiatric disorders, they appear to be able to function better than OCDs [26].

#### *Social anxiety disorder (SAD)*

When talking about important indications of SSRI, undeniably it is worth to mention SAD. Social anxiety disorder (SAD), also known as social phobia, is the most common anxiety disorder, usually with no remission, and is commonly associated with significant functional and psychosocial impairment [27]. It is the fourth most common mental disorder in the USA [28]. SAD is characterized by extreme fear of embarrassment in social situations involving performances or interactions. If left untreated, SAD is associated with the subsequent development of major depression, substance abuse, higher rates of divorce, suicide risk and other mental health problems [29,30].

Fortunately, there are several efficacious treatments for SAD. Studies show that the first-line pharmacological treatment for adults and children are serotonin selective reuptake inhibitors (sertraline, fluvoxamine and paroxetine) and serotonin and norepinephrine reuptake inhibitors (venlafaxine), whereas cognitive behavioral therapy is considered the best psychotherapeutic treatment [27]. Apart from SSRIs and SNRIs, several other medications have demonstrated short-term efficacy for SAD: monoamine oxidase inhibitors (MAOIs) and to a somewhat lesser degree, benzodiazepines [28].

The efficacy of SSRIs and moclobemide is similar. However, MAOIs require patients to follow strict diet restrictions in order to avoid severe hypertensive crisis after ingestion of tyramine-rich food [31]. Due to the dietary restrictions and adverse side effects, MAOIs are not ideal treatment for SAD. Benzodiazepines neither. It has been well documented that these medications have a high risk for abuse, as well as a high risk for relapse once they are discontinued. Unfortunately, despite recommendations discouraging their use, they continue to be commonly prescribed for individuals with SAD [28].

SSRIs have a relatively flat dose-response curve. Nevertheless, evidence suggests that a superior response may be obtained with higher doses of SSRIs. Clinical experience also suggests that some patients may require higher than normal starting doses to achieve an optimal response, and may even require maximal doses. SSRI administration should last for at least 12 weeks before its efficacy is assessed [29].

As mentioned above, cognitive behavioral therapy (CBT) is the most studied psychotherapy for SAD. Several studies have demonstrated its efficacy both in the short term and long term [28]. For cases that fail to respond to the initial treatment with SSRIs, CBT has consistently been

shown to be effective as first-line treatment [29]. The strong evidence base for cognitive behavioral therapies has led to their inclusion in treatment guidelines issued by professional group. Generally, the best choice for the treatment of adults is a combination of cognitive behavioral psychotherapy with serotonin selective reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors. Other options as benzodiazepines or monoamine oxidase inhibitors must be used as second and third choices, respectively [27].

### Resumo

Selektaj Serotoninino-Reenpreninhibitoroj (SSRI) estas moderna speco de antidepresiaj farmakoj. Ili estas vaste uzata kaŭze de iliaj secureco, tolerebleco kaj pruvita efiko. En tiu ĉi reviza artikolo ni indikas aliajn indikaciojn de la SSRI krom depresio. La artikolo estas bazita sur selekta revizo de la tiurilata literaturo, kiun ni trovis per serĉoj en PubMed kaj ScienceDirect. La rezultoj de tiuj elektronikaj serĉoj montris, ke SSRI ege gravas koncerne la farmakoterapion de multaj malsanoj krom depresioj. La medicina literaturo subtenas la uzadon de SSRI por la kuracado de ejakulo antaŭtempa (speciale la mallonge aganta SSRI dapoksetino), malsanoj de manĝado (speciale nervoza bulimio kaj la malsano kun diboĉa manĝado), obsesia-deviga malsano kaj sociala fobio.

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