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SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS: AN OVERVIEW

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SUMMARY

Selective serotonin re-uptake inhibitors (SSRIs) are front-line pharmacotherapies in the treatment of major depressive disorder (MDD), a disorder characterized by a persistent low mood, anhedonia and feelings of worthlessness. Since their formulation over 40 years ago, there have been several conflicting studies exploring the efficacy of these highly prevalent drugs. The nature of their therapeutic effect has also remained elusive, with several hypothesises pertaining to neurotransmitter and endocrine modulation proposed. While the medications are better tolerated than their predecessors, the tricyclic antidepressant family (TCAs), the side effect profile of SSRIs is not insubstantial and novel cases have highlighted adverse effects enduring past the cessation of drug treatment. Data gathered from clinical practice also highlights that the prevalence of these side effects is often underestimated, leading to patient frustration and non-compliance. This report will seek to outline the rise of SSRI usage in the last half century while exploring possible avenues of pharmacotherapeutic action, with a particular focus on the side effect profile of these drugs.

Key words: *selective serotonin re-uptake inhibitor (SSRI) - major depressive disorder (MDD) - psychopharmacology*

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INTRODUCTION

The role of serotonin (5-HT) itself in the aetiology of major depressive disorder (MDD) was initially brought to light in the form of the monoamine hypothesis of depression, which in its simplest form postulated that MDD was a consequence of chemical imbalances' of serotonin, noradrenaline (NA) and dopamine (DA) levels in limbic areas (Smart 2015). Initial studies lent weight to this argument, with decreased 5-HIAA levels being reported in suicide attempters diagnosed with MDD compared to healthy controls (Mann 1997). Further evidence for depression precipitating as a result of aberrant monoamine modulation stemmed from data collected from the use of reserpine, a potent anti-hypertensive used extensively in the mid 20th century (Achor 1955). While animal studies had demonstrated the efficacy of reserpine in depleting 5-HT and NA from the mammalian hypothalamus (Holzbauer 1956), it was also noted that the use of reserpine had led to the unwanted of effect of inducing depression in humans undergoing therapy for hypertension. One such example, involving a 54-year old woman being treated with reserpine for severe hypertension, recovered fully from her depression upon withdrawal of the offending drug (Freis 1954).

The effect of the monoamine hypothesis was to spur the development of compounds that could artificially augment multiple monoamine systems simultaneously. The answer to this came in the form of the tricyclic antidepressant (TCA) class of drugs. Derived from the structure of the antihistamine promethazine (Domino 1999), the first drug of the class, imipramine, was shown to cause pharmacological blockade at the pre-synaptic NA and 5-HT uptake channels, thus increasing the concentration of these monoamines in the synaptic cleft (Preskom 1982). The TCAs however, while efficacious for depression, had an unpleasant side effect profile as a result of their near-ubiquitous off-target activity; symptoms including dry mouth, hypotension and urinary retention were frequent complaints among TCA users (Furukawa 2002).

While the monoamine hypothesis has since been shown to be overly simplistic (Salomon 1997), the underlying rational that modulating 5-HT would improve MDD symptoms has endured. Indeed, this has been corroborated by animal studies which have kept afloat the argument for the role of serotonin in depression, with SERT deficient mice expressing depressive phenotypes (Ansorge 2004). The pharmaceutical giant Eli Lilly eventually shone the spotlight exclusively on serotonin, and in 1986 the first selective serotonin reuptake antidepressant fluoxetine was approved in the USA as a novel treatment for MDD (Wong 2005). Several decades on, it is clear that the SSRI class of drugs have revolutionised the treatment of depression; indeed, they remain a first line pharmacotherapy for MDD to this day (NICE 2009).

PSYCHOPHARMACOLOGY

Therapeutic effect

SSRI drugs exert their therapeutic effect by causing regional blockade of the presynaptic serotonin transporter (SERT) located abundantly in dorsal raphe-originatingneurons (DRN) and in the hippocampi, amygdala and prefrontal regions (Descarries 1975). These structures play critical roles in mediating the response to rewarding and emotionally salient stimuli,

and as such it is likely that the pathogenesis of depression has a neural basis amongst the limbic circuitry and its associated cortical connections (Goldin 2008). Initially, this blockade facilitates an increase in the extracellular concentration of 5-HT, thereby activating inhibitory auto-receptors which open G-protein-coupled potassium channels, causing neuronal hyperpolarisation and an attenuation of 5-HT neurotransmission (Nutt et al. 1999). Microdialysis studies have revealed that these auto-receptors can be classified into two types; 5-HT_{1A} somatodendritic receptors which mediate Gi-coupled neurotransmission (particularly in forebrain regions which receive projections from the DRN) and 5-HT_{1B} receptors, which also mediate Gi-coupled inhibition, leading to adenylyl cyclase inhibition and a subsequent dampening in serotonergic transmission (Stahl 1998). 5-HT_{1B} stimulation on non-serotonergic neurons in the medial prefrontal cortex (mPFC) also has the effect of reducing theta oscillations in layer V pyramidal neurons by suppressing hippocampal and contralateral mPFC inputs (Kjaerby 2016). These theta oscillations arise in the ventral hippocampus and are thought to encode anxiolytic signals, and as such SSRI treatment can lead to consistent 5-HT_{1B} stimulation by 5-HT located in the synaptic cleft (Adhikari 2010).

Chronic treatment with SSRIs is believed to mediate PKC-dependent desensitisation of presynaptic $5HT_{1A}$ receptors, thereby disinhibiting the DRN neuron and thus increasing basal 5-HT neurotransmission. This was reflected in the fall in Gi/Go proteins in the mammalian midbrain with repeated fluoxetine administration, alongside reduced $5HT_{1A}$ mRNA transcription in the anterior raphe (Li 1997). However, it is often reported that the antidepressant effect of SSRIs is only evident after several weeks, a finding which may be explained by the time taken to gradually desensitise the inhibitory $5HT_{1A}$ receptors. This is supported by the evidence that pindolol, a $5HT_{1A}$ antagonist, augmens the antidepressant effect when given in conjunction with SSRIs (Blier 2001). Changes in the SERT protein may also be seen with chronic SSRI treatment, with sustained treatment radiolabelled paroxetin eleading to a decrease in 5-HT binding sites on the transporter itself (Pineyro 1994).

Effectiveness

While the molecular mechanism of SSRIs is slowly being unravelled, there still exists a large gap between the neurobiological understanding of MDD and the therapeutic effect of SSRIs.

Initial studies conducted have concluded that the drugs within the class are equipotent in the treatment of severe MDD yet not “interchangeable”, and as such patients can be easily switched onto another SSRI (Nurnberg 1999). However, the lack of direct placebo-controlled results published during the time the drugs were undergoing regulatory approval has led to several authors revisiting the efficacy of these compounds.

A landmark review that analysed the pharmaceutical data collected by the FDA about SSRIs between 1983 and 2008 revealed that placebo conditions led to a significant improvement in moderate MDD phenotypes for over 80% of the cohort (Kirsch 2014). Further probing revealed a SSRI effect size of approximately two points on the Hamilton Scale for Depression, contravening the NICE guidelines that require a minimum of a 3-point difference between placebo and active compound for it to be considered as therapeutically significant (Moncrieff 2005). In addition, systematic reviews of RCTs involving antidepressants were found to show a hyperinflated judgment of SSRI efficacy and a poor benefit to risk ratio when assessed alongside the potential side effects incurred by patients (Jakobsen 2017). However, major criticisms of this paper have since surfaced including the “misleading classification” of any adverse effects detailed in Jakobsen’s method’s section (Hieronymus 2017).

The current stance has attempted to undo some of the negativity surrounding antidepressant efficacy, with a 2018 network meta-analysis uncovering that SSRIs were indeed more effective than placebos at ameliorating MDD (Cipriani 2018). However, it is imperative to consider that this review analysed multiple other classes of antidepressants, some of which were shown to be significantly more efficacious than SSRIs. The overall picture about the extent of SSRI efficacity therefore, remains unclear.

It is important to note that the indecisiveness caused by multiple conflicting pieces of literature on SSRI efficacy has a profound effect on the lives of the general public, of which almost 20% will experience some form of depression in their lifetime in the UK (MIND 2018). Headlines such as “Anti-Depressants: Major study finds they work” (BBC 2018) are able to shape the ideas and expectations of thousands of patients that may require pharmacotherapy for MDD. Therefore, it is evident that there remains further work until the public are left with a single answer as to the true nature of the effectiveness of SSRIs.

COMPLICATIONS

While SSRIs are incredibly selective for the SERT transporter, they do also have varying degrees of off target activity, which gives rise to some common side effects shared by all members of the drug family. Indeed, it is believed that over 80% of individuals beginning SSRI therapy experience at least one side effect, with over half experiencing multiple adverse effects (Hu 2004). These side effects appear to be dose dependent and resolve within a few weeks of beginning drug treatment. However, there appears to be new evidence that more persistent and serious side effects may occur, which in turn has implications for patient compliance and treatment efficacy.

Nausea

Nausea is one of the chief complaints with antidepressant usage and is often a leading cause for early discontinuation of SSRI pharmacotherapy. They are thought to be as a result of excessive 5-HT_3 receptor signalling in the solitary nucleus and in vagal terminals embedded along the length of the gastric tract (Tyers 1992). In addition, there is clear impetus of the role of the 5-HT_3 receptor in SSRI-induced nausea as ondansetron, a 5-HT_3 antagonist, was able to alleviate nausea in SSRI-treated individuals (Bailey 1995).

Dopaminergic effects

Neurophysiological studies have revealed that excessive synaptic 5-HT can lead to the modulation of dopaminergic signalling downstream of the target-neuron pool. DRN neurons project to the striatum, an area abundant with dopaminergic cells and are thought to mediate 5-HT_2 receptor dependent inhibition of DA cell firing (Zangen 2001). Indeed, positron-emission tomography studies in female baboons have demonstrated that altansterin, a 5-HT_2 receptor antagonist, enhanced striatal DA transmission (Dewey 1995). As such, it is hypothesised that SSRIs may exacerbate dopaminergic inhibition as a result of excessive serotonin receptor stimulation.

This notion is reflected in case reports of SSRI-treated patients experiencing extrapyramidal symptoms (EPS) and akathisia, which is of grave concern. Initially believed to be a by-product of long-term high potency neuroleptic use, these debilitating adverse effects have a poor prognosis, and can severely impair day-to-day functioning. One such case, of a female being treated for MDD, reports how she began to exhibit severe akathisia upon commencing 20 mg/day fluoxetine treatment, with a profound inability to sit still. Upon titrating the dose to 5 mg/day, the symptoms lessened, only to remerge weeks later alongside suicidal intent (Hamilton 1992). The mechanism behind SSRI-induced akathisia is unclear, as it appears to occur without the dystonic features seen in neuroleptic-induced akathisia. Animal studies have tentatively pointed at the role of the mesolimbic DA system in being complicit in the pathophysiology of akathisia. Indeed, lesions of the A10 cell fields, in which the mesolimbic projections originate, have induced persistent hyperactivity and 'restlessness' in rodents (Tassin 1978). SSRI treatment may therefore mirror the effect of fine lesions by causing 5-HT_2 receptor-dependent inhibition of these cell fields, giving rise to the akathisia phenotype in patients. Management of this condition primarily involves titrating the dose (or discontinuing the drug) until symptoms improve, however beta-blockers have also been shown to be efficacious in alleviating symptoms, perhaps as a consequence of the complex interplay of monoamine transmitters in the basal ganglia (Lipinski 1989).

Tardive dyskinesia, a condition which involves the abnormal movement of the orofacial and upper body areas, may also be a manifestation of aberrant signalling caused by SSRIs. A common presentation of this is in the form of bruxism, a disorder characterised by repeated grinding of the teeth with accompanying mandibular dystonia. Neuroanatomical mapping experiments in the 1980s highlighted that motor neurons responsible for the control of the face and jaw had a comparatively large density of 5-HT input from the DRN, thus pointing to a drug-induced effect for bruxism (Steinbusch 1981). The disorder has been shown to be successfully treated by buspirone, a 5-HT_{1A} agonist, however further research is required before commenting on its efficacy in clinical practice (Bostwick 1999).

Sexual effects

Decreased libido and sexual pleasure are characteristic features of MDD and often improve upon remission of the depressive episode. However, evidence points to the nature of a pharmacological origin to the distinctive sexual dysfunction seen in those undergoing SSRI treatments as a consequence of neurotransmitter modulation in CNS areas responsible for desire, arousal, orgasm and resolution. These modulations include the serotonergic inhibition of dopamine release discussed previously, which may contribute to the erectile difficulties experienced by over 35% of patients (Montejo-González 1997).

In a similar fashion, the control of prolactin secretion is under dynamic reciprocal control by serotonin (stimulatory) and dopamine (inhibitory) (Advis 1979). As SSRIs enhance serotonin signalling and supress dopaminergic neurotransmission one may assume the occurrence of hyperactivity in the prolactin-secreting hypothalamic regions in SSRI-treated individuals. Indeed, SSRIs have been shown to cause hyperprolactinemia, a condition associated with sexual dysfunction, with raised plasma concentrations of prolactin observed after citalopram administration (Laine 1997). Furthermore, the aspects of orgasm and ejaculation are believed in part to be mediated by descending spinal autonomic pathways (Stein 1994). These pathways are rich in the 5-HT_{2C} receptor, and thus dysfunction of these intrinsic pathways may contribute to the global picture of sexual dysfunction observed in SSRI-treated patients. While direct treatment options are limited (e.g. sildenafil for erectile dysfunction), dose titration is often the preferred method for combatting SSRI-induced sexual dysfunction.

CONCLUSION

Given the high prevalence of MDD and the increasing use of SSRIs in conditions such as anxiety, further study of these front-line drugs is necessary. Overall, it can be concluded that SSRIs remain effective drugs in

the treatment of severe MDD however their efficacy in mild to moderate depression is still unclear. Pertaining to their extensive side effect profile, some of which may remain as persistent, post-exposure effects, life-style remedies (e.g. exercise, mindfulness) should be considered as alternative first-line therapies where possible. The role of the 5-HT_{1A} and 5-HT_{2C} receptors, while currently under investigation, may eventually shed light on the wide range of both positive and negative effects of SSRIs and facilitate the development of novel-generation antidepressants with fewer off-target effects.

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