Clinical effects of pharmacological variations in selective serotonin reuptake inhibitors: an overview

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SUMMARY

Although the selective serotonin reuptake inhibitor (SSRI) class of antidepressants shares a common primary pharmacology, namely the inhibition of serotonin reuptake, their secondary pharmacology is remarkably heterogeneous. Inhibition of serotonin reuptake and the consequent increase in serotonin availability are responsible for the relief of depressive symptoms and for some of the adverse effects of this class of drugs. Transsynaptic effects such as modulation of signalling cascades, gene expression processes and neuroplasticity are also important in the mechanism of action of antidepressants. However, this review shows that secondary properties of the SSRIs may contribute to the differences in efficacy and tolerability between members of the class. For example, fluvoxamine has affinity for σ1-receptors – a property likely to be responsible for its particular efficacy in delusional depression. By understanding the properties of SSRIs and employing careful selection of agents for individual patients, physicians are more able to tailor antidepressant treatments to their patients’ particular circumstances.

Keywords: Selective serotonin reuptake inhibitors; antidepressants; pharmacology; variations; overview; review

INTRODUCTION

Now that there are six selective serotonin reuptake inhibitors (SSRIs) available worldwide for the treatment of depression and other disorders, it is pertinent to consider the similarities and differences among and between them. While it is clear that all the SSRIs share the key property of inhibiting the reuptake of serotonin and thereby increasing the synaptic availability of this neurotransmitter, it is equally clear that, otherwise, their pharmacology is quite heterogeneous. Although all of the SSRIs are effective antidepressants, this heterogeneous pharmacology offers more opportunities for the psychiatrist to tailor the choice of treatment to the particular circumstances of the individual patient. This review based on Medline publications will examine the properties that the SSRIs do and do not share and how those properties that they do not share can be deployed to provide a better outcome for individual patients.

PHARMACOLOGY OF THE SSRIs

The simplified concept of an SSRI is that of a serotonin reuptake inhibitor. It is true that SSRIs all have several things in common, not the least of which is the blockade of the serotonin transporter that leads to elevation of serotonin levels throughout the central nervous system (CNS) and also throughout the entire body. Increases in serotonin levels in specific regions of the brain result in the therapeutic actions of the SSRIs. Unfortunately, the action of SSRIs on the serotonin transporter is not regionally specific, and increases in serotonin levels in some regions of the CNS and peripheral nervous system lead to side effects. The most common adverse reactions to the SSRIs are gastrointestinal, specifically nausea, and neuropsychiatric, particularly headache and tremor (1). While recent systematic reviews of randomised controlled trials have suggested a possible association between suicide attempts and the use of SSRIs (2,3), the evidence currently available does not support the hypothesis that antidepressants, or more specifically SSRIs, cause increased suicidality in patients with depression, nor do they appear to do so in patients treated with these drugs for other reasons (4).

Because this class of drugs has been used for many years, much has been learned of their individual properties, in particular their actions on different receptors, enzymes or other biological systems as well as on the serotonin reuptake site. It is now clear that the SSRIs are not all the same. On the contrary, patients may experience side effects that are due to properties that are different between the different SSRIs. Some side effects are likely to be due to serotonin reuptake inhibition; indeed, some patients respond almost equally to all the SSRIs. However, the unique responses and side effects have more to teach us about how to use SSRIs most
effectively. SSRIs not only have serotonin reuptake inhibitory properties, but some of them may also show more noradrenergic reuptake inhibition (e.g. paroxetine) (5). One SSRI, namely sertraline, may even have some potency as a dopamine reuptake inhibitor (6), while another may have effects at 5-HT₂C receptors (fluoxetine) (7). Similarly, paroxetine has effects at muscarinic receptors (8). Finally, fluvoxamine has shown affinity for the σ₁-receptor, which may confer some specific clinical characteristics on this drug (9). These secondary pharmacodynamic properties therefore distinguish these drugs from each other.

Fluvoxamine

Preclinical studies suggest that fluvoxamine has effects at σ₁-receptors (9). Recent research also shows that the σ-receptor modulates the N-methyl-D-aspartate (NMDA)/glutamate receptor (10). The most studied subtypes are the σ₁- and σ₂-receptors. In marked contrast to receptor systems such as serotonin and dopamine, σ-receptors are endoplasmic reticulum proteins (11) that probably interact with intracellular second messenger systems, particularly in the mobilisation of calcium (10). In addition, σ-receptors may exist in organs other than the brain (12–14). The σ₁-receptor is more abundant in the dentate gyrus of the hippocampal formation, facial nucleus and various thalamic and hypothalamic nuclei (15). σ₂-Receptor density is highest in various cranial nerve nuclei, followed by certain hippocampal subfields and laminae, the red nucleus, the interpendicular nucleus and midlayers of primary and secondary motor cortices (15). The distribution of σ₁- and σ₂-receptors, as well as their different ontogenetic patterns, suggests that they are distinct entities (16).

σ-Binding sites regulate dopamine release in some areas of the brain (17), modulate NMDA-type glutamate receptors (18) [which has a knockon effect in regulating dopamine (19)] and are even involved in modulating substance P (20). These receptors have been shown to have important antiamnesic effects and a positive role in memory impairments (21–25).

Indeed, selective σ₁-receptor agonists may have potential as cognitive enhancers during ageing (23). Moreover, the σ₁-receptor also exerts a potent neuromodulatory role in the brain that may have relevance in the response to anxiety and stress (6,26,27), depression (28,29), learning and cognitive process (23,24,30), neuroprotection (27,31) and antipsychotic activity (32). Among the SSRIs, fluvoxamine has the highest affinity for the σ₁-receptors (9) (Figure 1), suggesting that this drug may have particular benefits in the treatment of depressed patients who show features of anxiety/stress (33), and for whom memory impairment is particularly undesirable (34,35) [such as in depressed elderly patients (36,37)], and also in treating psychotic depression (38,39).

The most common adverse event reported for fluvoxamine is nausea, which tends to disappear after some days of treatment (40). The overall incidence of nausea is similar for all SSRIs (41). Other side effects include somnolence, asthenia and headache (42).

Fluvoxamine has no active metabolites to continue the pharmacological effects once fluvoxamine has been metabolised.

Paroxetine

Muscarinic effects are generally responsible for the unpleasant side effects of the tricyclic drugs that made compliance with drugs of this class so difficult for many patients. By contrast, a modest degree of anticholinergic sedation could promote a short-term amelioration of insomnia and anxiety and might even reduce the activating actions that some SSRIs possess (43). Routine clinical experience suggests that paroxetine (which is the SSRI with the highest affinity for the cholinergic receptor) appears to have such properties (Figure 2) (44). By contrast, anticholinergic activity can cause dry mouth, fatigue, tremor, weight gain and cognitive impairment (45–48).
A study by Pollock and colleagues (49) investigated the anticholinergic effects of paroxetine and the tricyclic agent nortriptyline in 61 elderly depressed patients. As expected, paroxetine had significantly less anticholinergic properties than nortriptyline; paroxetine was responsible for around 20% of the anticholinergic effects of nortriptyline. However, paroxetine was not devoid of anticholinergic effects.

Randomised controlled clinical studies comparing paroxetine with other SSRIs have also shown that paroxetine possesses a significantly greater propensity to induce anticholinergic effects than other substances of the same class (50). By contrast, the lack of activating properties of paroxetine, or even some sedation, can be used to advantage in patients with insomnia (43).

Paroxetine also inhibits the reuptake of noradrenaline more than other antidepressants (51,52). This effect is substantially less potent than that of the tricyclic drugs such as desipramine and amitriptyline but is a full order of magnitude more potent than that of other SSRIs or nefazodone and venlafaxine (Figure 3) (53). Several case reports suggest that paroxetine has the highest incidence of withdrawal symptoms of all the SSRIs (54,55).

Paroxetine has no active metabolites to continue the pharmacological effects once paroxetine has been metabolised.

Fluoxetine

Although a member of the SSRI class, fluoxetine is in fact a more potent inhibitor of 5-HT$_{2C}$ receptors than other serotonin reuptake inhibitors (56). Inhibition of 5-HT$_{2C}$ receptors modulates brain norepinephrine and dopamine systems (57), which, in turn, cause activation and weight loss (58). It is well known that fluoxetine has activating properties, and this can lead to problems, such as insomnia and agitation, in anxious patients (59,60). By contrast, this property can be used to good effect in patients who have a lack of energy.

Fluoxetine has an active metabolite, norfluoxetine, which has a pharmacologic activity similar to the parent compound, with a half-life of 4–16 days (61).

Sertraline

Like the structurally related nomifensine, sertraline has significant dopamine uptake blocking effects, although these are considerably weaker than its serotonin uptake blocking properties. Nevertheless, sertraline is sufficiently potent at blocking dopamine uptake (62) to anticipate some clinical effects. On the negative side, some cardiovascular or extrapyramidal effects might also be expected (63,64). Sertraline might, however, be useful in patients with melancholic and retarded types of depression.

Together with fluoxetine, sertraline is one of the SSRIs with highest dopaminergic (D$_2$) affinity (65). Besides causing extrapyramidal symptoms, dopaminergic effects may account also for complaints of sexual dysfunction (66).

Sertraline has one active metabolite, which may continue to exert pharmacological effects once sertraline has been metabolised (67).

Citalopram

Citalopram is one of the most selective SSRIs and notably lacks activating and sedating properties. Citalopram has essentially no effect on noradrenergic receptors (65) but has the highest affinity for histamine H$_1$ receptors among the SSRIs (Figure 4) (44). The affinity of citalopram for H$_1$ receptors is, for example, over 100-fold higher than the affinity of fluvoxamine for H$_1$ receptors (44).

Citalopram has recently been associated with craving for carbohydrate (68) with patients experiencing consequent weight gain. Other reported side effects are sexual dysfunction and difficulty in concentration (69,70).
Citalopram has three active metabolites, which may continue to exert pharmacological effects once citalopram has been metabolised (71).

**Escitalopram**

Escitalopram is the active S-\((+\))-enantiomer of citalopram. Preclinical studies suggest that the R-\((-\))-enantiomer present in citalopram may counteract the effects of escitalopram (72), and there is evidence to suggest that escitalopram may have a faster onset of action than citalopram (73,74). Escitalopram has no effects on noradrenaline or dopamine uptake (75). Nevertheless, escitalopram has less affinity for \(\mathrm{H}_1\) receptors than citalopram, although its \(\mathrm{H}_1\) receptor affinity is higher than that demonstrated by other SSRIs (44).

The tolerability profile of escitalopram is similar to that of citalopram, with the most common adverse events being nausea, ejaculation disorder and insomnia (76).

Although less potent than the parent drug, two active metabolites have been observed (77). Some specific pharmacological data for escitalopram are still lacking in the literature.

**CONCLUSIONS**

Each of the SSRIs has a characteristic profile of positive and negative effects, and whilst the primary pharmacology (serotonin reuptake inhibition) is undoubtedly responsible for the antidepressant effects and some of the adverse effects (such as gastrointestinal disturbances), it is their other pharmacological actions that distinguish between the drugs and provide opportunities for the physician to choose the optimal antidepressant treatment for individual patients.

The SSRIs should be considered as distinctive therapeutic agents, and not as ‘almost identical’ drugs in the same therapeutic class. In addition to inhibition of serotonin reuptake, the SSRIs may also have a high \(\sigma_1\)-affinity (fluvoxamine),

**Figure 3** Relative potency of antidepressants for binding at noradrenaline transporter receptors based on \(K_i\) values. Potency of antidepressants at noradrenaline transporter based on IC\(_{50}\) values: citalopram: 6100; demethylcitalopram: 740; fluvoxamine: 620; venlafaxine: 620; fluoxetine: 370; sertraline: 160; paroxetine: 81 (65). *Active metabolite of citalopram

**Figure 4** Potency of antidepressants on binding of \(\mathrm{H}_1\) receptors based on \(K_i\) values [based on the affinity (\(K_i\) nmol/l) for binding to histaminergic receptors (fluvoxamine: 29,250; paroxetine: 23,740; sertraline: 6528; escitalopram: 1973; fluoxetine: 1548; citalopram: 283)] (44)
anticholinergic and noradrenergic properties (paroxetine), 5-HT$_2C$ effects (fluoxetine), dopamine activation (sertraline and fluoxetine) and histaminergic affinity (citalopram).

Pharmacological variations in the SSRIs distinguish one drug from the other and may explain why some patients respond better to one SSRI than another or tolerate one SSRI better than another.

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