Selective Serotonin Reuptake Inhibitors
Relevance of Differences in Their Pharmacological and Clinical Profiles

Frans de Jonghe and Jan Swinkels
1 Psychiatrisch Ziekenhuis Amsterdam, University of Amsterdam, Amsterdam, The Netherlands
2 Academic Medical Centre, Amsterdam, The Netherlands

Contents
Summary .................................................................................................................. 452
1. Pharmacodynamic and Pharmacokinetic Profiles ........................................ 453
   1.1 Pharmacodynamics .................................................................................. 453
   1.2 Pharmacokinetics .................................................................................... 454
2. Clinical Profiles ............................................................................................... 455
   2.1 Paroxetine versus Fluoxetine .................................................................. 456
   2.2 Sertraline versus Fluoxetine ................................................................... 460
   2.3 Citalopram versus Fluoxetine ................................................................ 462
   2.4 Paroxetine versus Fluvoxamine ............................................................. 462
   2.5 Sertraline versus Fluvoxamine ............................................................... 463
   2.6 Citalopram versus Fluvoxamine ............................................................. 464
   2.7 Fluvoxamine versus Fluoxetine ............................................................. 464
3. Conclusion ....................................................................................................... 465

Summary

In this article, we raise the following question regarding the treatment of depression with the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs) citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline: are there clinically relevant differences between these SSRIs in terms of their (i) pharmacodynamic and pharmacokinetic and (ii) clinical (i.e. efficacy, tolerability, adverse events and safety) profiles?

In order to answer the first part of the question, the large body of literature on the pharmacodynamics and pharmacokinetics of SSRIs were examined. It can be concluded that, except for a few special situations (such as breast feeding), the many differences that the SSRIs show in their pharmacodynamic and pharmacokinetic profile are probably of limited importance in clinical practice.

In order to answer the second part of the question, the 16 head-to-head comparisons between SSRIs that were published before January 1997 were reviewed. These were double-blind randomised studies that directly compared the SSRIs using a parallel group design; however, they were limited, quantitatively as well as qualitatively. The data published do not reveal unequivocal, clinically relevant differences between the SSRIs in terms of general efficacy, profile of action (e.g.
Selective Serotonin Reuptake Inhibitors

453

effect on anxiety, agitation, sleep, suicidal ideation or cognitive function), speed of onset of action, total severity or profile of adverse events, or safety.

We conclude that the differences between the SSRIs may lead the clinician when making a choice in *individual* cases. However, at present, neither pharmacodynamic/pharmacokinetic considerations nor direct clinical comparisons between SSRIs provide data that can assist clinicians in making a rational *general* choice between these drugs.

In the last decade, a new class of antidepressants, the selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs), has become available to clinicians and their patients. What is the value of these drugs in the treatment of depression? This question, of course, has to be qualified: compared with what? Placebo and the tricyclic antidepressants (TCAs) seem natural choices. It is now well established that SSRIs are less well tolerated than placebo and that they are more effective. It also has been demonstrated that the SSRIs are as effective as TCAs, that they are probably better tolerated and that they are certainly safer in overdose. It may therefore be said that the SSRIs, taken as a class, have moderate efficacy, that their tolerability is reasonable and that they are relatively safe in overdose.

Given that the differences between SSRIs and placebo and TCAs are now well defined, interest has turned to possible intra-class differences. In this article, we raise the following question regarding the treatment of depression with citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline: are there clinically relevant differences between these SSRIs in terms of their (i) pharmacodynamic and pharmacokinetic and (ii) clinical (i.e. efficacy, tolerability, adverse events and safety) profiles? If clinically relevant differences appear, this could assist clinicians in making a rational choice between these agents.

### 1. Pharmacodynamic and Pharmacokinetic Profiles

In this section, we succinctly comment from a clinician’s point of view on the large amount of literature on the pharmacodynamics and pharmacokinetics of the SSRIs. Undoubtedly, the individual SSRIs do have different pharmacodynamic and pharmacokinetic profiles.

#### 1.1 Pharmacodynamics

The differences among the SSRIs in terms of potency at inhibiting amine uptake are shown in table I. It appears that sertraline is the most potent and citalopram the most selective serotonin reuptake inhibitor. Sertraline is a more potent dopamine reuptake inhibitor than the other SSRIs. The clinical relevance of these data is unclear.

The affinity of SSRIs for the receptors of various neurotransmitters is shown in table II. In general, the SSRIs have little affinity for the receptors. However, paroxetine has a higher affinity for cholinergic muscarinic receptors than the other SSRIs.

### Table I. Effects of selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors on the uptake of biogenic amines *in vitro*[^8^]

<table>
<thead>
<tr>
<th>Amine</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>citalopram</td>
</tr>
<tr>
<td>Serotonin</td>
<td>1.8</td>
</tr>
<tr>
<td>Noradrenaline (norepinephrine)</td>
<td>6100</td>
</tr>
<tr>
<td>Dopamine</td>
<td>40000</td>
</tr>
<tr>
<td>Selectivity[^7^]</td>
<td>3400</td>
</tr>
</tbody>
</table>

[^7^]: IC<sub>50</sub> noradrenaline/IC<sub>50</sub> serotonin.

[^8^]: Abbreviation: IC<sub>50</sub> = concentration of the drug that inhibited uptake by 50%.