Not So Selective Serotonin Reuptake Inhibitors

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Issue: *Since the pharmacologic selectivity of SSRIs (selective serotonin reuptake inhibitors) is* relative *rather than absolute, these agents can have clinically significant secondary properties that distinguish one drug in this class from another.*

Selective serotonin reuptake inhibitors (SSRIs) got this name from their greater selectivity (10-fold or more) for blocking serotonin reuptake rather than norepinephrine reuptake.[1] They also lack the sodium channel blocking properties of the tricyclic antidepressants, making them safe in overdose. In addition, SSRIs have less affinity for α_1-receptors, muscarinic cholinergic receptors, and histamine-1 receptors compared with the tricyclic antidepressants, leading to the greater tolerability profile of SSRIs.[2]

Now that the fifth SSRI, citalopram,[3] is being introduced into clinical practice in the United States (following fluoxetine, sertraline, paroxetine, and fluvoxamine), it may be useful to remember that these drugs are not just clones of each other. Most of the past decade's clinical literature emphasizes the similarities among these agents, including comparable overall efficacy in depression and, in most cases, obsessive-compulsive disorder and panic disorder.[1,2] After a decade of use, however, it is clear to physicians who prescribe these drugs that all SSRIs are *not* created equal, even though they all have the inalienable property of potent serotonin reuptake inhibition. The uniqueness of different SSRIs is most evident in the dramatic differences that individual patients can demonstrate in their clinical responses as well as side effects from one SSRI to another. These distinctions are obscured by clinical investigations that emphasize the similar mean responses that large groups of individuals have to every SSRI. Until recently, there has been no scientific hypothesis to explain why various patient subtypes might respond differently to one versus another individual agent within this therapeutic class. Since the 5 SSRIs have unique individual pharmacologic profiles of secondary binding properties (see table), it is possible that these secondary properties are responsible for the clinically detectable distinctions, especially at higher doses (for details, see references 4 through 7).

There are at least 10 such secondary properties as potent or within 1 order of magnitude of serotonin reuptake potency (see figure), and the list grows as new receptors and enzymes are better clarified. Thus, at

Secondary Binding Properties of the SSRIs and Venlafaxine

Citalopram	may be the only true SSRI
Fluvoxamine	sigma CYP1A2 CYP2C19 CYP3A4
Paroxetine	muscarinic cholinergic nitric oxide synthase CYP2D6
Fluoxetine	norepinephrine reuptake serotonin-2C CYP2D6 CYP3A4
Sertraline	dopamine reuptake norepinephrine reuptake sigma (CYP2D6 at high doses)
Venlafaxine	norepinephrine reuptake dopamine reuptake

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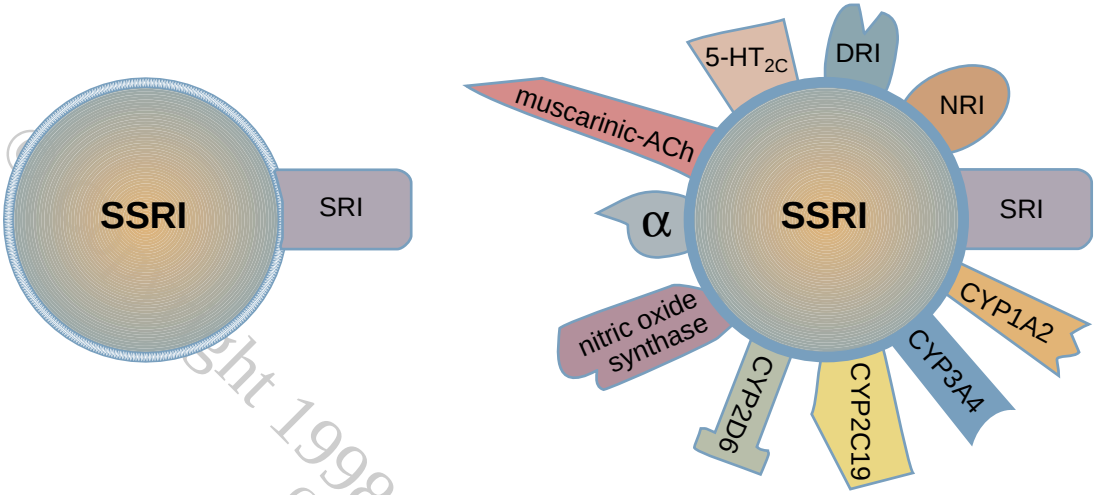
Conceptual vs. Actual Actions of SSRIs on Receptors and Enzymes



least 1 of the 5 SSRIs has potent enough activity at the following receptors and enzymes to create potentially clinically meaningful consequences: (1) norepinephrine reuptake, (2) dopamine reuptake, (3) serotonin-2C receptors, (4) muscarinic cholinergic receptors, (5) sigma receptors, (6) nitric oxide synthase, (7) cytochrome P450 2D6, (8) cytochrome P450 3A4, (9) cytochrome P450 1A2, and (10) cytochrome P450 2Cl9. No 2 SSRIs are identical, but sorting out which pharmacologic properties explain which clinical observation is just beginning.[4–7] The relevance of differences in the P450 enzymes has been much debated, often generating more heat than light. Differences in binding to various neurotransmitter receptors are now generating hypotheses to explain differences in tolerability in anxious patients, in cognitive effects, in anticholinergic effects, and many others. If the role of these ancillary pharmacologic actions can be understood, it may be possible to find individualized applications for each of the not-so-selective serotonin reuptake inhibitors. ◆

Take-Home Points

- The so-called SSRIs are at least 10-fold more selective for serotonin reuptake inhibition than for norepinephrine reuptake inhibition
- Selectivity for serotonin reuptake has tended to obscure the fact that most SSRIs bind to a large number of other receptors and enzymes that can contribute to their overall clinical actions
- Each SSRI has a unique portfolio of these multiple pharmacologic actions, which may explain the differences in efficacy and tolerability observed from one agent to another and from one patient to another

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