Are Two Antidepressant Mechanisms Better Than One?

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**Issue:** A drug that combines two or more synergistic mechanisms of action may yield superior therapeutic efficacy or tolerability compared to a single therapeutic mechanism of highly selective agents.

The classical antidepressants, namely tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors, have multiple pharmacologic mechanisms, but only those increasing the availability of serotonin (5-HT) and norepinephrine (NE) explain antidepressant actions.1 Their other actions, such as anticholinergic properties, are responsible for side effects.1 This profile has given rise to the notion that multiple mechanisms mean “dirty drugs” and that the best drugs should be “smart bombs” attacking only a single receptor target. Thus, the classical antidepressants were replaced by the serotonin selective reuptake inhibitors (SSRIs), which have essentially only a single neurotransmitter action, namely on 5-HT.

Some of the newest antidepressants, however, challenge the notion that combining mechanisms is always undesirable. Two drugs in which multiple mechanisms reduce undesired actions rather than cause them are nefazodone and mirtazapine. Both agents increase serotonin, as do the SSRIs.1,2 However, the anxiety, sexual dysfunction, and sleep disturbance associated with SSRIs and mediated by stimulating 5-HT2 receptors can be prevented by the 5-HT2 antagonists nefazodone and mirtazapine; the nausea associated with SSRIs and mediated by stimulating 5-HT3 receptors can also be prevented by the 5-HT3 antagonist mirtazapine.1,3,4

New drugs with multiple mechanisms may not only be able to reduce side effects, they might even improve antidepressant efficacy. There is a troubling clinical notion, especially among some investigators, that the SSRIs are not as powerful as the TCAs for treating patients who have severe depression or who are resistant to prior trials of antidepressants. Looking at the pharmacology of the favorite Europe TCA clomipramine, we see that it is both a serotonin and a norepinephrine reuptake inhibitor.1 Is it possible that the SSRIs went too far by removing

**Take-Home Points**

- Classical antidepressants are “dirty drugs” because their multiple mechanisms cause side effects
- Newer antidepressants are clean compared with these dirty drugs and produce a much improved side effect profile, but not improved antidepressant efficacy
- “Designer” antidepressants with two or more mechanisms may reduce side effects, improve antidepressant efficacy, or both
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**Multiple Mechanisms = Improved Efficacy**

**Single Selective Mechanisms = Loss of Side Effects**

**Behavioral Changes**

**Traditional Drugs**

**Novel Drugs**

**REFERENCES**

10. Schatzberg AF. Treatment of severe depression with the selective serotonin reuptake inhibitors. Depression and Anxiety 1996;4:182–189