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-HT_2 receptors can be prevented by the 5-HT_2 antagonists nefazodone and mirtazapine; the nausea associated with SSRIs and mediated by stimulating 5-HT_3 receptors can also be prevented by the 5-HT_3 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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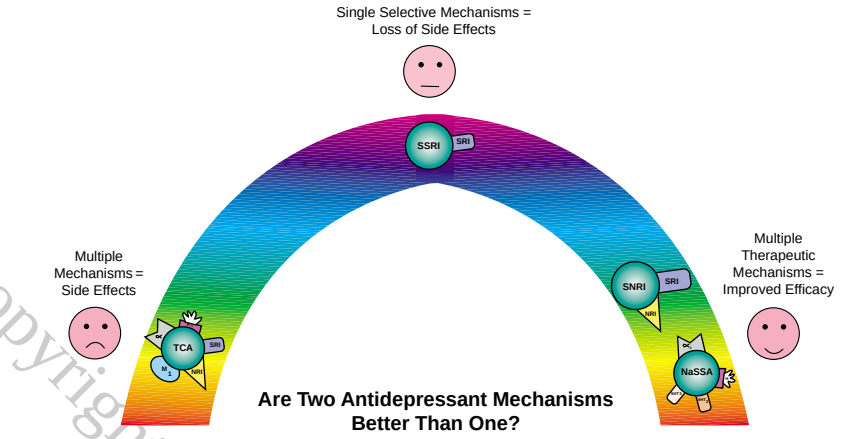

the NE-enhancing properties of the TCAs?

Some evidence indeed suggests that this is so,[5–9] although not everyone agrees.[9–10] The dual 5-HT/NE-action TCA clomipramine has proved to be superior to various single 5-HT-action SSRIs in several trials (e.g., references 5 and 6). The dual (5-HT/NE)-action agent venlafaxine preserves both the NE- and 5-HT-enhancing properties (especially at high doses) of the TCAs while cleaning up their undesired pharmacology.[1] One study suggests enhanced efficacy or more rapid onset of action for venlafaxine compared with an SSRI.[7] Similarly, the dual (5-HT/NE)-action agent mirtazapine may also have enhanced efficacy over an SSRI.[8] Although more research is clearly needed for all dual-acting drugs, it would not be surprising if these observations eventually hold up in more rigorously designed studies, because experienced clinicians have often combined antidepressants with independent therapeutic actions to effect a therapeutic response when single agents fail. Why couldn't the same benefit happen if a single molecule combined two actions in a form of "intramolecular augmentation"?

Such a notion simply reinforces what skilled clinicians have been doing for a long time to treat patients unable to respond to or tolerate different antidepressants. That is, they have been combining therapeutic mechanisms by using multiple simultaneous therapeutic agents. This brings to mind the old saying that there are three types of psychopharmacologists: those who can count and those who can't. Wise clinicians suggest that the best ones are those who can't count: that is, combining therapeutic agents may yield much more efficacy than either agent alone. In other words, sometimes 1 + 1 = 10. On the other hand, combining therapeutic agents may also reduce the side effects of each agent. In that case, 1 + 1 = 0.

Where this all leads no one knows for sure, but the clear mandate for future antidepressants will be to enhance efficacy, not just tolerability. Perhaps bad mathematics is the answer. ◆

REFERENCES

1. Stahl SM. Essential Psychopharmacology. New York, NY: Cambridge University Press; 1996
2. de Boer T. The effects of mirtazapine on central noradrenergic and serotonergic neurotransmission. Int Clin Psychopharmacol 1995;10(suppl 4):19–23
3. Stimmel GL, Dopheide JA, Stahl SM. Mirtazapine: an antidepressant with noradrenergic and specific serotonergic effects. Pharmacotherapy 1997;17:10–21
4. Pedersen L, Klysner R. Antagonism of selective serotonin reuptake inhibitor-induced nausea by mirtazapine. Int Clin Psychopharmacol 1997;12:59–60
5. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine: a controlled multicenter study. Psychopharmacology (Berl) 1986;90: 131–138
6. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990; 18:289–299
7. Clerc GE, Ruimy P, Verdeau-Pailles J, on behalf of the Venlafaxine French Inpatient Study Group. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for minor depression and melancholia. Int Clin Psychopharmacol 1994;9:139–143
8. Wheatley D, Kremer C. A randomized, double-blind comparison of mirtazapine and fluoxetine in patients with major depression. In: New Research Program and Abstracts of the American Psychiatric Association; May 17–22, 1997; San Diego, Calif
9. Shader RI, Fogelman SM, Greenblatt DJ. Newer antidepressants: hypotheses and evidence [editorial]. J Clin Psychopharmacol 1997;17:1–3
10. Schatzberg AF. Treatment of severe depression with the selective serotonin reuptake inhibitors. Depression and Anxiety 1996;4:182–189