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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should amphetamines be added to SSRI therapy to enhance the antidepressant effect?

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A: IT IS DIFFICULT to make any definite conclusions about the role of psychostimulants in enhancing the antidepressant effect of selective serotonin reuptake inhibitors (SSRIs). Although anecdotal reports and case series have suggested that psychostimulants can augment the efficacy of SSRIs in patients with major depression, we have no data from prospective controlled trials.

PSYCHOSTIMULANTS AND DEPRESSION

The theory is attractive, but we have few data

In the past, amphetamines were used more extensively to treat depression than they are now.[1] Physicians began to use them less after more-effective drugs were introduced, ie, tricyclic antidepressants and monoamine oxidase inhibitors.[2]

Selective serotonin reuptake inhibitors—the newest class of antidepressants—are effective in treating major depressive episodes. However, major depression does not respond satisfactorily to an SSRI in 21% to 55% of cases.[3]

Amphetamines are currently used to augment therapy with standard antidepressants (tricyclics and monoamine oxidase inhibitors).[2,4] Ample evidence also suggests that they are effective when added to SSRIs in patients with depression caused by a medical illness.[5] Therefore, it seems logical to add amphetamine to an SSRI when a partial response occurs.

Researchers assume that an additive effect occurs because the two drugs work on different systems—amphetamine on the dopamine and norepinephrine systems and SSRIs on the serotonin system. It has also been postulated that psychostimulants decrease the response latency—the lag time from when an SSRI is started until a response can be observed—when given early in the course of treatment.

WHAT THE LITERATURE SHOWS

Although the theory is promising, research has not provided definitive proof that adding a psychostimulant to SSRI therapy is beneficial. We conducted a MEDLINE search of studies published between 1980 and 2000 and found only four that looked at this issue:

Cohen[6] added dextroamphetamine to fluoxetine in three patients with anergic depression and found that it resolved their persistent anergia. He suggested that amphetamine-induced enhancement of dopamine and noradrenergic activity improves mood, decreases fatigue, and increases psychomotor activity.

Metz and Shader[7] described four patients with treatment-refractory depression who responded to a combination of fluoxetine and pemoline.

Stoll et al[5] found that adding methylphenidate to SSRI therapy rapidly resolved symptoms in five patients with major depression.

Postolache et al,[8] in a randomized, double-blind, placebo-controlled, parallel-design study, evaluated whether adding methylphenidate to sertraline would decrease the response latency. Response to therapy was determined using the Hamilton Rating Scale for Depression—a 21-item, clinician-administered rating scale used to assess both the severity of a patient's depressive symptoms and response to treatment.

This paper discusses treatment that is "off label," ie, not FDA-approved for the use under discussion.

The trial had to be stopped, however, after a preliminary analysis of the initial nine patients revealed that the therapy had not decreased their Hamilton Rating Scale scores or improved their global functioning.

Therefore, despite the hint of a relationship between improvement in depressive symptoms and the addition of psychostimulants in three of these four studies, no firm conclusions can be drawn. We also have to wonder whether a placebo effect may be at work, whether the perceived antidepressant effect may have been due to additional time on SSRIs, or whether the psychostimulants somehow increased the serum levels of the SSRIs.

SIDE EFFECTS OF PSYCHOSTIMULANTS

The use of psychostimulants in general is controversial because of the potential for abuse and risk of physical dependence.[5]

Psychostimulants can also cause substantial side effects. According to one report, subjective side effects occur from most to least often in the following order: insomnia, nausea, tremor, appetite change, palpitations, blurred vision, dry mouth, constipation, and dizziness.[9] Patients may also experience objective side effects such as blood pressure changes, dysrhythmias, and tremor.[9] In addition, confusion, exacerbation of preexisting anxiety, agitation, hypomania, paranoid delusions, and changes in sensorium can occur.[9]

AMPHETAMINES IN MEDICALLY ILL PATIENTS

It is unknown why amphetamines help depression in the medically ill but not in the non-medically ill population. In the non-medically ill, even if there is an initial response it is not maintained.

When treating patients with depression caused by a medical illness, dextroamphetamine or methylphenidate can be used to augment antidepressant therapy. Dextroamphetamine is started at a dose of 5 to 10 mg per day. Methylphenidate can be started at a dose of 2.5 to 5 mg twice a day. The daily maximum dosage of dextroamphetamine is usually 5 to 30 mg per day. The maximum dose of methylphenidate is between 5 to 40 mg per day.

To prevent insomnia, these drugs should not be given after 3 PM. Because medically ill patients are particularly vulnerable to the multiple side effects of psychostimulants, these drugs should be used cautiously in this patient population.

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Amphetamine can be added to an SSRI for depression caused by medical illness