# Psychopharmacology for the Clinician
# Psychopharmacologie pratique

*The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.*

**Using psychostimulants for treating residual symptoms in major depression**

Mrs. N. is a 44-year-old nurse with major depression who only had a partial response to venlafaxine 300 mg / day taken for 6 months. Upon referral, her symptoms were of mild-to-moderate intensity (Hamilton Depression Rating Scale [HAM-$D_{17}$] = 14). When interviewed, Ms. N. complained mostly of anergia, fatigue, and hypersomnia (12–16 hr/d sleeping), but denied the presence of depressive mood. She was then started on modafinil 100 mg twice daily and showed a 30% improvement within 3 days. After 1 week of treatment, her HAM-$D_{17}$ had decreased to 5 (i.e., remission of symptoms) and she was sleeping an average of 6–8 hours per night.

As shown by the clinical vignette, psychostimulants are being increasingly used as augmentation agents for conventional antidepressant drugs, particularly given their usually rapid onset of action (normally within 48 hr) and relative lack of major side effects (Huffman and Stern, *Prim Care Companion J Clin Psychiatry* 2004;6:44-6). The most commonly used stimulants are dextroamphetamine (10–40 mg/d) and methylphenidate (10–60 mg/d). Other more recent alternatives include atomoxetine (a selective norepinephrine reuptake inhibitor used in doses of 40–120 mg/d) and pramipexole (a dopamine $D_2/D_3$ receptor agonist used in doses of 0.25–1 mg 3 times daily).

This class of dopaminergic or noradrenergic agonists and reuptake inhibitors has produced interesting results in small open trials with subjects with depression resistant to tricyclics, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (Fava, *J Clin Psychiatry* 2001;62[Suppl 18]:4-11). However, to date, there are no controlled double-blind data on the effectiveness of these augmenting agents in treatment-resistant depression and, accordingly, they are not currently approved by the FDA for this indication.

Modafinil, a novel psychostimulant, has shown promising results (in doses up to 200 mg twice daily) in the management of residual symptoms of depression. Indeed, a preliminary double-blind, placebo-controlled, 6-week study involving 118 depression subjects (using a wide range of antidepressant drugs) found that modafinil rapidly improved fatigue ($p < 0.05$) and daytime sleepiness ($p < 0.01$), although no significant differences were found between modafinil and placebo at end point (DeBattista et al, *J Clin Psychiatry* 2003;64: 1057-64). A subsequent, placebo-controlled multicentre study in 311 patients with depression using selective serotonin reuptake inhibitors (SSRIs) monotherapy showed that modafinil (v. placebo) significantly improved patients' overall clinical condition, compared with placebo ($p = 0.02$). Only nausea and jitteriness were significantly more common with modafinil than with placebo (Fava et al, *J Clin Psychiatry* 2005; 66:85-93). A small, open-label study of modafinil in 29 subjects with depression receiving either paroxetine or fluoxetine has also suggested its potential usefulness in accelerating response and enhancing the chances of achieving remission (Ninan et al, *J Clin Psychiatry* 2004;65:414-20). Nevertheless, further studies are needed to confirm the effectiveness and safety of modafinil in major depression.

Typical side effects of psychostimulants are usually of mild-to-moderate intensity (reversible with drug discontinuation) and may include insomnia, exacerbation of anxiety or agitation, tremor, changes in appetite and palpitations (Huffman and Stern, *Prim Care Companion J Clin Psychiatry* 2004;6:44-6). Importantly, cardiovascular complications have not been prominent (even among patients with preexisting cardiac disease). Further, there is currently little evidence for habit formation or addiction (Fava and Rush, *Psychother Psychosom* 2006;75:139-53).

Some relatively contraindicated conditions for the use of psychostimulants include recent myocardial infarction, ongoing congestive heart failure, history of ventricular arrhythmia and hyperdynamic states (e.g., hyperthyroidism). Finally, their administration should be avoided in patients who have been treated with monoamine oxidase inhibitors in the previous 2 weeks and during pregnancy (for lack of safety data in humans).

In summary, although some trials have demonstrated benefits of psychostimulants as augmenting agents to standard antidepressant drugs, more rigorous controlled studies are needed before their routine use can be recommended. Moreover, the optimal duration for this augmentation remains to be determined.

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**Competing interests:** None declared.

*Psychopharmacology for the Clinician columns are usually based on a case report that illustrates a point of interest in clinical psychopharmacology. They are about 500–650 words long and do not include references. Columns can include a bibliography which will be available only at the journal Web site and can be accessed through a link at the bottom of the column.*

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