Dopaminergic Agents and Stimulants as Antidepressant Augmentation Strategies

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Dopaminergic agents and stimulants have been used to manage depression when conventional antidepressant treatments fail. We reviewed evidence for the role of dopaminergic dysfunction in depression, the use of dopaminergic agents as antidepressants, and the use of dopaminergic agents and stimulants as antidepressant adjuncts. Dopamine may be part of the pathophysiology of depression for a subset of patients. When used with caution and an appreciation of the potential risk of abuse, dopaminergic agents and stimulants may be useful for patients refractory to antidepressants alone.

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Dopamine has received less attention than either serotonin or norepinephrine as a factor in the pathogenesis and treatment of depression. In sharp contrast to the recent ascendancy of serotonin uptake inhibitors, few specific dopamine uptake inhibitors have been marketed as antidepressants. Nevertheless, preclinical and clinical evidence indicates that dopamine may have a role in the development and treatment of depression.[1] Furthermore, stimulants and dopaminergic agents are useful antidepressants either alone or as adjuncts for a subgroup of depressed patients. This paper will review evidence for the role of dopaminergic dysfunction in depression and the use of dopaminergic agents as antidepressants and then will focus on the use of dopaminergic agents and stimulants as antidepressant adjuncts.

EVIDENCE FOR THE ROLE OF DOPAMINE IN DEPRESSION

As reviewed elegantly by both Kapur and Mann[1] and Willner,[2] while some studies of depressed patients have found decreased cerebrospinal fluid (CSF) homovanillic acid (HVA), the major metabolite of dopamine, other studies have failed to detect a difference or have found increased CSF HVA compared with normal controls. Neuroendocrine studies that assess dopaminergic functional status (by measuring prolactin and growth hormone levels after the administration of dopaminergic agonists) have failed to indicate dopaminergic dysfunction. Overall, this evidence for dopaminergic dysfunction is mixed, but appears to favor diminished dopaminergic turnover and decreased CSF HVA in depressed patients.

Developing neuroimaging techniques may further elucidate the role of dopamine in depression. Three neuroimaging studies of in vivo dopaminergic function in patients with affective disorders have been reported. Pearlson et al.[3] demonstrated that bipolar patients with psychotic symptoms had elevated D_2 dopamine receptor densities while nonpsychotic bipolar patients did not differ from controls in this regard. This simply suggests that psychotic states, regardless of psychiatric diagnosis, are associated with changes in the dopaminergic system. Ebert et al.[4] studied D_2 receptor occupancy in depressed patients divided into two groups: total sleep deprivation responders and total sleep deprivation nonresponders. They found that responders showed a significant decrease in D_2 receptor occupancy following total sleep deprivation when compared with nonresponders. They interpreted this finding as evidence of enhanced dopamine release in responders and also as indirect evidence of dopaminergic involvement in the pathophysiology of depression. Both of the above studies, however, examine D_2 receptors, which are predominantly located in the striatum. In contrast to D_2 receptors, D_1 receptors are found in both the striatum and frontal cortex. Suhara et al.[5] found that although D_1 recep-

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tor binding potentials in the striatum of bipolar patients were similar to controls, D_1 binding potentials in the frontal cortex of bipolar patients were significantly lower. The authors postulated that these findings implicated frontal dopamine systems in the pathophysiology of affective disorders.

Neuroimaging studies of cerebral blood flow and glucose metabolism are reviewed elsewhere[6,7] and may provide indirect evidence of dopaminergic dysregulation. Consistent findings include decreased cortical glucose metabolism in the left prefrontal cortex and caudate and the bilateral anterior cingulate and temporal cortex. Interestingly, these structures lie within the basal ganglia-thalamocortical circuits, where dopamine is an important neurotransmitter,[8] that have been implicated in the pathophysiology of depression.[9]

One PET study[10] demonstrated that dopaminergic systems may be modulated following acute administration of the serotonin-releasing agent fenfluramine to normal subjects. In addition, therapeutic agents including antidepressants[1] and electroconvulsive therapy (ECT)[11–13] have been shown to increase dopamine transmission in mesolimbic pathways. Finally, antidepressants that affect dopamine, such as nomifensine, bupropion, and monoamine oxidase inhibitors (MAOIs), are regarded by clinicians to be effective for patients when other antidepressants fail.

DOPAMINERGIC AGENTS AS ANTIDEPRESSANTS

Dopaminergic agonists, uptake inhibitors, and stimulants have at least some antidepressant properties when given as single agents.

Dopaminergic Agonists

Bromocriptine, piribedil, and amantadine are dopamine agonists that are used to treat Parkinson's disease. Bromocriptine has been found to have antidepressant-like effects in the animal model of chronic exposure to mild unpredictable stress, but only when administered intermittently.[14] Furthermore, these effects are reversed when raclopride, a D_2 and D_3 antagonist, is added. As for the antidepressant efficacy of bromocriptine, four open trials showed that 57% (total N = 56) of a mixed group of mostly treatment-resistant depressed patients responded.[15–18] Three double-blind trials (total N = 125), reviewed by Wells and Marken,[19] found bromocriptine to be as effective as either imipramine or amitriptyline.[20–22] Piribedil, a postsynaptic dopamine agonist at high doses, was found to be clinically effective in 36% (total N = 11) of a group of unipolar, bipolar I, and bipolar II depressed inpatients.[23] Three patients continued to be improved following piribedil discontinuation and substitution with placebo. No studies have been published on the antidepressant efficacy of amantadine.

Stimulants as Antidepressants

Stimulants, such as dextroamphetamine, methylphenidate, and pemoline, are both dopaminergic and noradrenergic releasers and uptake inhibitors. Stimulants have been found to be no more effective than placebo in controlled, albeit flawed, studies of depressed patients without medical comorbidity.[24–26] Data from uncontrolled studies suggest, however, that stimulants may be useful for some patients who fail to respond to conventional antidepressants. To date, no stimulant-responsive subgroup of depressed patients has been identified.

MAOIs

The MAOIs have survived into the 1990s as a clinically useful class of antidepressants despite the requirement that patients maintain a tyramine-free diet and refrain from taking sympathomimetic agents to avoid a hypertensive crisis. The durability of this class of antidepressants is due to the substantial minority of patients who appear to respond to nothing else besides MAOIs. Why should these patients respond to MAOIs to the exclusion of all other antidepressants? One possibility is that the nonspecific irreversible MAOIs prevent the oxidation of not only serotonin and norepinephrine, but dopamine as well. Treatment with MAOIs consistently decreases CSF HVA in addition to 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG), the metabolites of serotonin and norepinephrine, respectively.

DOPAMINERGIC AGENTS AND STIMULANTS AS ANTIDEPRESSANT ADJUNCTS

Dopaminergic Agents

Pergolide, a dopamine agonist 20 to 30 times more potent than bromocriptine, was found to be an effective adjunct in 55% (total N = 20) of depressed patients (4 bipolar, 16 unipolar) who had failed to respond to either fluoxetine, tricyclics, MAOIs, or trazodone.[27] Adverse drug reactions included nausea, dizziness, anxiety, and mania. Other dopamine agonists such as bromocriptine, amantadine, and piribedil have not been studied as adjuncts to antidepressants.

Stimulants

Dextroamphetamine, methylphenidate, and pemoline have a high potential for abuse, but have been reported to be taken responsibly in stable doses for as long as decades by depressed patients who experienced initial benefit.[24] As for the use of stimulants as antidepressant adjuncts, few controlled trials have been published. Case reports and series have suggested that stimulants were effective when given to patients who failed to respond to, but continued to take, fluoxetine,[28–30] MAOIs alone, or MAOIs in combination with tricyclic antidepressants.[31,32] Both

Feighner's[31] and Fawcett's[32] groups reported their experience with the use of dextroamphetamine (dose range, 5–40 mg daily), methylphenidate (dose range, 10–15 mg daily), and pemoline (dose range, 18.75–112.5 mg daily) as adjuncts for severely treatment-resistant patients (combined N = 45). They found that 57% (total N = 14) responded to dextroamphetamine, 50% (total N = 26) responded to pemoline, and 60% (total N = 5) responded to methylphenidate added to failed aggressive trials of MAOIs alone and in combination with other psychotropic classes of medications. Of the 32 patients treated by Fawcett's group, 78% (N = 25) were considered to have a good response (CGI ≤ 2), but only 31% maintained their improvement. Lest one get the wrong impression that these trials of stimulant adjuncts were straightforward, note that only 12.5% (N = 4) had an initial response that was maintained. Either the other patients failed to respond to the first trial of one stimulant and then went on to respond to a second trial of another stimulant, or they lost their response to the first trial only to regain it when another stimulant was added. Adverse events that led to discontinuation included impotence, orthostatic hypotension, elevated blood pressure, and shakiness with pemoline, and memory difficulties, parkinsonian syndromes, and somnambulism with dextroamphetamine. Nuisance adverse events included fatigue, unsteady gait, and weight gain. Furthermore, six patients developed either mania or hypomania.

Metz and Shader[29] reported on combining pemoline (dose range, 9.375–37.5 mg daily) with fluoxetine in 21 patients with treatment-resistant depression, 76% of whom responded. Adverse drug reactions included agitation, insomnia, anxiety, anorexia, and weight loss. Linet[28] published another case of a patient who had failed robust treatment and who subsequently responded to a combination of fluoxetine 60 mg/day and dextroamphetamine 45 mg t.i.d. Stoll and colleagues[30] reported five cases of depressed patients who had failed either fluoxetine or paroxetine and then responded to the addition of methylphenidate 10 to 40 mg daily.

Diagnostic Issues: ADHD Comorbidity

Is there a diagnostic subtype of depression that would require the addition of a stimulant? One possibility is that a subgroup of patients who have a history of childhood attention-deficit/hyperactivity disorder (ADHD) themselves, or in their family, and then develop a major depression may require the addition of a stimulant to an antidepressant (Wilens T. Oral communication). One study found that 16% of patients with major depressive disorder met full or subthreshold criteria for childhood ADHD, with 12% who endorsed persistence of ADHD symptoms into adulthood.[33] Systematic treatment studies of patients with major depression who have comorbid ADHD have not been done.

GUIDELINES FOR THE USE OF DOPAMINERGIC AGENTS AND STIMULANTS AS ANTIDEPRESSANT ADJUNCTS

While it should be apparent that the database supporting the use of dopaminergic agents and stimulants as antidepressant adjuncts is limited, clinicians have been using these drugs for their patients when more conventional therapies have failed.[34,35] Guidelines for how to prescribe dopaminergic agents and stimulants are based, therefore, more on clinical experience than controlled trials.

Dose

Pergolide, bromocriptine, amantadine, and piribedil can be started in low doses and increased to the maximum dose recommended for use in Parkinson's disease.[36] Pergolide should be started at 0.05 mg daily and increased by 0.1 to 0.15 mg every 2 to 3 days up to a maximum of 5 mg daily in divided doses. Bromocriptine is started at 1.25 mg daily or b.i.d. and increased every 2 weeks by 1.25-mg increments up to 20–30 mg daily, although some patients may require up to 100 mg. Amantadine can be started at 25 to 50 mg daily and increased up to 200 mg.[37]

Dextroamphetamine and methylphenidate should be started at doses of 2.5 to 5.0 mg daily, respectively, with gradual increases up to 60 mg/day in divided doses. Pemoline can be started at 18.75 mg daily and increased up to 112.5 mg daily.[37]

Duration of Treatment

How long should either a dopaminergic agent or stimulant be tried before a clinician decides that the trial was long enough? In contrast to the 3 to 6 weeks necessary for both lithium and thyroid augmentation, the dopaminergic and stimulant agents seem to be effective within days. Once patients respond to the dopaminergic agents, no data are available to guide clinicians as to the duration of continuation or maintenance treatment.

Adverse Drug Reactions and Precautions

Limited information is available to assess the risk of developing serious adverse drug reactions when dopaminergic agents and stimulants are combined with antidepressants. Dopaminergic agents by themselves can cause nausea, vomiting, and orthostatic hypotension and can cause confusion, delusions, hallucinations, and dyskinesias at higher doses.

Stimulants can result in nervousness, insomnia, anorexia, weight loss, restlessness, tachycardia, and psychosis. Addiction and tolerance are problems with long-term administration. Stimulants may increase blood levels of other drugs, and monitoring of blood levels of antidepressants may be necessary. Extreme caution should be used when stimulants are combined with MAOIs, and patients should be instructed about the symptoms of a hypertensive

crisis. Starting with stimulants at very low doses with gradual increases is most appropriate.

CONCLUSIONS

Stimulants and dopaminergic agents may be effective as antidepressant adjuncts, but controlled data are lacking. Physicians should reserve the use of these drugs for those patients who fail to respond to more conventional therapies. In the spirit of informed consent, patients should be warned about the potential to develop tolerance and addiction with this class of drugs. Meticulous documentation of the rationale for using stimulants needs to be included in the chart to manage the medicolegal consequences of using this class of medications. How long to treat depressed patients with dopaminergic and stimulant adjuvants after they respond remains to be determined, but should be periodically reevaluated with the patient.

Drug names: amantadine (Symmetrel), amitriptyline (Elavil and others), bromocriptine (Parlodel), bupropion (Wellbutrin), dextroamphetamine (Dexedrine and others), fenfluramine (Pondimin), fluoxetine (Prozac), imipramine (Tofranil and others), methylphenidate (Ritalin), paroxetine (Paxil), pemoline (Cylert), pergolide (Permax), trazodone (Desyrel and others).

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DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated as antidepressants or augmentors of antidepressants: amantadine, bromocriptine, dextroamphetamine, methylphenidate, pemoline, piribedil.