

Methylphenidate Augmentation of Fluvoxamine for Treatment-resistant Depression: A Case Report and Review Literature

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Abstract

Methylphenidate and other psychostimulants have received substantial attention for the management of depression in patients with medical co-morbidities as well as for the symptomatic palliation of various neuropsychiatric disorders. Despite having been of little use in the first-line treatment of depressive disorders, some evidence does suggest that they may be of potential benefit as an antidepressant augmentation strategy in patients who fail to respond to stand-alone antidepressant regimens. However, such claims appear to be based entirely on case reports and to date, no appropriate placebo-controlled studies have been carried out on healthy young subjects. We report a case of a woman with refractory depression who successfully responded to methylphenidate augmentation of fluvoxamine. Her clinical picture was dominated by significant biological symptoms, which included apathy, anergia, increased appetite, and somnolence, with marked secondary functional impairment. Several antidepressant treatment modalities were attempted, including electroconvulsive therapy, with little improvement in her symptomatology. Augmentation of fluvoxamine with methylphenidate ultimately brought about a rapid and sustained complete remission of her depression. We will highlight how methylphenidate and other psychostimulants, when used with caution and an appreciation of their potential risk for abuse, may prove to be remarkably effective agents for antidepressant augmentation, including that of partially-effective or ineffective selective serotonin re-uptake inhibitors. Evidence for such use of methylphenidate unfortunately remains largely empirical and adequate placebo-controlled studies are therefore required to support or refute this claim.

Key Words: Depression augmentation, refractory depression, fluvoxamine methylphenidate, psychostimulants

INTRODUCTION

Methylphenidate is a very short-acting psychostimulant with a structure similar to endogenous catecholamines (Biederman, 1998). Despite being one of the first psychotropic drugs to be used in the first-line treatment of depression alongside other psychostimulants, such as dextroamphetamine and pemoline (Schatzberg and Cole, 1991), its use as a primary antidepressant fell out of favor with the subsequent introduction of other antidepressant agents in the 1950s and 1960s, i.e. tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (Warneke, 1990). Thus, the clinical use of methylphenidate nowadays is primarily for the treatment of attention-deficit/hyperactivity disorder (ADHD) and narcolepsy, such indications bearing

the full approval of the Food and Drug Administration (FDA) (Thomas and Lipsky, 2000).

A large body of literature supported by adequate clinical evidence has nonetheless focused on the use of methylphenidate as a monotherapy in the treatment of major depressive disorder in elderly patients with medical co-morbidities, post-stroke depression, as well as for the palliation of neuropsychiatric symptoms in patients with cancer and human immunodeficiency virus (HIV) infection (Thomas and Lipsky, 2000). Notwithstanding, interest in the use of methylphenidate and other psychostimulants in primary depression has persisted, such that a very small number of authors have advocated its use as an augmentation strategy for increasing the efficacy of the standard antidepressant armamentarium for the

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treatment of refractory depression (Nierenberg et al., 1998). However, used on its own for the treatment of refractory depression in otherwise healthy patients, methylphenidate has not been shown to be superior to placebo (Warneke, 1990; Satel and Nelson, 1989). While recognizing the potential for abuse of methylphenidate, its prescription deserves consideration given its rapid onset of action, easy scheduling, and virtual lack of potentially serious drug interactions and adverse side-effects (Stoll et al., 1996).

Herein, we report a case of a middle-aged woman with treatment-resistant unipolar depression, which included resistance to electroconvulsive therapy, who successfully responded to the augmentation of fluvoxamine with methylphenidate. We will highlight the potential benefit of psychostimulants as an adjunctive therapy protocol in resistant depression, as supported by empirical evidence.

Case

Patient A is a 40-year-old Caucasian female with 2 offspring, with a DSM-IV-TR (American Psychiatric Association 2004) diagnosis of major depressive disorder since the age of 25. She subsequently had about 10 depressive recurrences, which were generally amenable to standard therapeutic modalities with complete remission within a community setting. Developmental history was unremarkable and social history has never been suggestive of any major adversity. Family psychiatric history was negative. She had no history of substance misuse.

Nonetheless, Patient A first required hospitalization in September 2004 at the age of 38 years, at which time we undertook her care. She then had a severe depressive episode, with increased daytime somnolence and increased appetite. She was unable to take care of her children, and her occupational and social activities were significantly impaired. Subsequently she made a suicide attempt by strangling herself, which precipitated her admission to hospital. At admission, she was profoundly subdued, apathetic, unmotivated, minimally engageable, asthenic, and hopeless. She also expressed intense suicidal ideation. Her baseline medication regimen was fluoxetine 40 mg/day and lorazepam 1 mg tid. Physical examination was unremarkable; laboratory investigations, including blood count, electrolytes, B12, folate, thyroid function tests, liver function tests, and urinalysis were normal. Fluoxetine was increased to a maximum of 60 mg/day with no subjective or objective affective improvement; so high-dose imipramine was introduced gradually up to 300 mg/day as an augmentation strategy.

Modest improvement in symptomatology was achieved after 5 weeks, thus allowing follow-up in the community to be resumed.

Patient A, however, discontinued imipramine after a few days because of increased appetite and morbid weight gain, and at her next out-patient clinic visit about 4 weeks later, her depressive symptoms recurred, yet again marked by neurovegetative symptoms with apathy, psychomotor retardation, hopelessness, and passive suicidal ideation. Lithium was therefore added to fluoxetine, until a plasma level of 0.6 mmol/l was achieved, with some amelioration in mood. However, Patient A never regained her pre-morbid functional level, and distressed by anergia, apathy, difficulty concentrating, and reversed eating and sleeping patterns, she quit her fulltime job as a care-worker in a residential home for the elderly and eventually required hospitalization, once again, a year later.

An underlying medical cause for her depression was again ruled out by normal laboratory findings, together with normal magnetic resonance imaging of the brain and electroencephalography. At this point, augmentation of fluoxetine with lamotrigine 200 mg/day was attempted, with no significant effect. Switching to venlafaxine 200 mg/day proved to be of little clinical benefit as well. The latter was discontinued and replaced by fluvoxamine, increasing to a maximum dose of 300 mg/day within 6 weeks. A noticeable reduction in depressive symptoms took place such that hospitalization was no longer required after an additional 4 weeks. Despite the high dose of fluvoxamine, Patient A slipped back into severe depression a month later without having experienced any clear-cut precipitating factor. She reported impaired concentration, apathy, lethargy, and increased appetite. Introduction of risperidone 0.5 mg bid as a means of augmentation brought about a mildly beneficial effect of short duration until hospitalisation was required. At this stage, a trial of electroconvulsive therapy (ECT), while keeping her on antidepressant therapy was inevitable, but only slight improvement was noted 5 weeks after the 10th treatment was administered.

Given that major debilitating components in Patient A's depressive episodes were apathy, low energy, decreased concentration, and increased appetite and daytime sleep, based on theoretical knowledge, a potentially beneficial adjunctive agent in the treatment regimen, methylphenidate was considered. Before introduction of methylphenidate, Patient A's baseline score on the 21-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton,

Table I. Summary of Published Reports of Psychostimulant Augmentation of Antidepressants.

Augmentation strategy	Type of study	Outcome	Reference
Fluoxetine + Pemoline	Case series	Rapid remission in 4 patients	Metz and Shadder, (1991)
MAOIs + Pemoline or Dextroamphetamine	Case series	Rapid, sustained improvement in 25 of 32 patients	Fawcett et al., (1991)
TCAs + Methylphenidate	Open-label	Full or near-remission in 63% of patients after 2 weeks	Gwirtsman et al., (1991)
Venlafaxine + Methylphenidate	Case report	Full remission in one patient after 5 days	Bader et al., (1998)
Sertraline + Methylphenidate	Double-blind placebo- controlled	No remission in 5 patients receiving combination; full response in 2 of 4 patients receiving placebo	Postolache et al., (1999)
Fluoxetine + methylphenidate Paroxetine + Methylphenidate	Open-label	Rapid, sustained symptom reduction in 5 patients	Stoll et al., (1996)
Citalopram + Methylphenidate	Double-blind placebo- controlled	Improvement in 50% receiving combination therapy; no change in those receiving placebo	Lavretsky et al., (2006)

1960) was 32. On the Apathy Evaluation Scale, Clinician Version (AES-C) (Marin 1996), she registered a baseline score of 54. Methylphenidate was started at a dose of 5 mg bid and was titrated gradually to 10 mg bid over 2 weeks. She made a remarkable rapid improvement, such that by the end of second week her mood greatly improved, suicidal ideations completely resolved, and she was considerably less apathetic and lethargic. No significant adverse effects were reported other than some irritability when the dose of methylphenidate was increased from 15 mg to 20 mg/day, but this resolved soon after. Her appetite also decreased, further contributing to her improved sense of well-being. Her scores on the HAM-D and AES-C decreased to 8 and 32, respectively, after 3 weeks. At a follow-up out-patient visit 4 weeks after discharge, she was in full remission with no symptomatology whatsoever, maintained on fluvoxamine 100 mg tid and methylphenidate 10 mg bid. After 6 months, she remains inarguably stable, has even resumed her normal social activities, including work, and is actively interested in life.

DISCUSSION

Successful augmentation of selective serotonin reuptake inhibitors (SSRIs) with methylphenidate in depressed patients without concomitant significant medical illnesses has been previously described, including paroxet-

ine and fluoxetine (Stoll et al., 1996). Early co-administration of methylphenidate with antidepressants has also been suggested to shorten the latency of response if introduced early enough in the course of treatment (Satel and Nelson, 1989). To the best of our knowledge based on a MEDLINE search (1966–April 2006), this is the first case report of successful augmentation of fluvoxamine with methylphenidate in the treatment of refractory major depressive disorder. Our patient with resistant depression failed to respond to several antidepressant regimens, including monotherapy with fluoxetine, fluvoxamine and venlafaxine, successive augmentation of fluoxetine with imipramine, lithium and lamotrigine, augmentation of fluvoxamine with risperidone, and ECT. She underwent a rapid and sustained improvement with near-complete resolution of symptoms following the addition of methylphenidate to a maximum recommended dose of fluvoxamine after a few weeks, as indicated by a reduction in the 21-item HAM-D score. Apathy, a major debilitating component of our patient's depression also made a rapid resolution after the introduction of methylphenidate, as expected, due to the nature of methylphenidate's stimulatory property and as confirmed by the AES-C. Moreover, neither major short-term adverse effect was noted, nor did tolerance to the drug develop once stabilization was achieved.

The exact mechanism by which methylphenidate exerts its action has not been completely elucidated, but a number of putative neurochemical effects have been postulated (Thomas and Lipsky, 2000). Studies on animals showed that methylphenidate promoted the acute release of dopamine from the presynaptic membranes of neurons (Chiuch and Moore, 1975) and further prevented its uptake from the synaptic cleft by binding to the dopamine transporters in the presynaptic membranes (Hurd and Ungerstedt, 1989). Methylphenidate may also be responsible for reversing the harmful dopamine-depleting effect of SSRIs (Steur, 1993). Furthermore, it may exhibit a pharmacodynamic effect by increasing blood levels of concomitantly administered antidepressants (Thase et al., 1998) through its inhibition of cytochrome P450 2D6 enzymes involved in the metabolism of other antidepressants (Lavretsky and Kumar, 2001).

Advocacy for the use of methylphenidate in depression has largely been restricted to geriatric patients with medical co-morbidities, as supported by a double-blind placebo-controlled study in which 75% of patients made a rapid recovery without reporting any significant adverse effects (Wallace et al., 1995). Yet, clinical research about the potential beneficial effect of methylphenidate and other psychostimulants as an augmentation strategy in healthy young patients with depression is generally lacking. Indeed, evidence is based entirely on a few cases and series of cases (Stoll et al., 1996), despite a theoretical basis for their potential in the treatment of depression.

The effectiveness of SSRI augmentation with methylphenidate has also been previously described. Stoll et al. (1996) reported an open-label trial using methylphenidate augmentation of SSRIs (fluoxetine or paroxetine) in 5 patients with unipolar major depressive disorder. In all patients, rapid and sustained symptom reduction was reported with methylphenidate dosages ranging from 10 to 40 mg/day. Remission of symptoms was independent of any co-morbid ADHD.

Recently Lavretsky et al. (2006) reported the first double-blind, placebo controlled trial of augmentation of the SSRI citalopram with methylphenidate in the treatment of major depression, but once again, this study specifically targeted geriatric patients. This 10-week study focused on 16 otherwise healthy out-patients > 65 years of age, many of who had treatment-resistant chronic major depression or a history of recurrent depression. A rapid response was observed in 5 out of 10 patients that received combination treatment as early as the third week, compared to none of the patients that received citalopram and

a placebo. Three of the responders achieved full remission by the third week of treatment. Unfortunately, it is not clear whether this preliminary data can be extrapolated to young patients. On the other hand, less encouraging were the results of a short, double-blind, placebo-controlled trial of sertraline augmentation with methylphenidate among 9 subjects with major depression, who were followed at an out-patient clinic (Postolache et al., 1999). By the end of this 9-week study, none of the 5 patients that received combination therapy met the criteria for full remission, whereas 2 of the 4 patients that received sertraline plus placebo fully responded. Further clinical follow-up revealed that all patients who had not previously fully responded achieved full remission after switching to another antidepressant or following the introduction of another augmentation agent.

Augmentation of other classes of antidepressants with methylphenidate has also been reported with satisfactory results. In an open-label trial, Gwirtsman et al. (1991) reported rapid improvement of symptoms in subjects with depressive disorders who were co-administered methylphenidate with TCAs. Full or near-remission was achieved in 63% of subjects by the end of the second week. Bader et al. (1998) also reported successful augmentation of venlafaxine with methylphenidate in an elderly patient with treatment-resistant .

Apart from methylphenidate, other psychostimulants have also been used as augmentation agents. Metz and Shader (1991) described successful use of pemoline as an adjunct to fluoxetine in a series of 4 patients with major depressive disorder. In a series of 32 patients with treatment-resistant bipolar or unipolar depression, Fawcett et al. (1991) reported a rapid and sustained clinical improvement for at least 6 months in 78% of patients after augmentation of MAOIs with either pemoline or dextroamphetamine. Adverse effects were minimal, although 6 patients went on to switch to mania or hypomania. Table 1. summarizes these reports.

Several other augmentation strategies have been described to target the symptoms of the approximate 33% of patients who fail to respond to the recommended dose of standard pharmacotherapy (Stimpson et al., 2002). These include the use of an established antidepressant together with another agent not usually used as a monotherapy, such as lithium, thyroxine, and pindolol, as well as the use of 2 licensed antidepressants, such as SSRIs plus TCAs (Craig Nelson, 1998). Such augmentation regimens, albeit generally clinically effective, are not devoid of side-effects, including the risk of toxicity (Stoll et

al., 1996); therefore, psychostimulants, including methylphenidate, can be considered a plausible alternative to motivated patients bearing in mind their negligible side-effects in clinical practice and their ease of use. The sole issue that warrants attention is their potential for misuse by some patients, thus keeping careful records of prescriptions is mandatory (Goldman et al., 1998). No data is available with respect to the recommended duration of maintenance treatment with methylphenidate; however, patients who warrant methylphenidate augmentation are most likely to have suffered from severe forms of chronic treatment-resistant depression. It is thus envisaged that methylphenidate should be continued throughout the maintenance period of antidepressant-treatment. Again, such prolonged use should not be hindered by concerns

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about the remote possibility of divergent use as long as careful prescription data is maintained.

In summary, our report sheds further light on the use of psychostimulants as an augmentation strategy for antidepressant non-responders. The empirical addition of methylphenidate to partially effective or ineffective SSRI regimens may prove to be a rapid, effective, and generally safe solution when prescribed carefully in appropriately motivated and compliant patients. Moreover, it may play a significant role in alleviating anergia and apathy. Adequate evidence from placebo-controlled studies is lacking, and therefore, further formal studies, particularly in non-geriatric patients, are required to support or contest such claims.

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