



Rapid resolution of depressive symptoms with methylphenidate augmentation of mirtazapine in an elderly depressed hospitalized patient: a case report

Practice points

- Treatment of elderly depressed patients is challenging because of concomitant medical conditions and changes in the pharmacokinetics and pharmacodynamics.
- The urgency of response is of paramount importance because of the fragility of the elderly and the pressures from third party payers.
- This calls for augmentation strategies of antidepressant treatment.
- Methylphenidate augmentation appears to be useful with regard to clinical improvement, morbidity reduction and shortening of hospital stay.
- Further controlled studies are recommended.

Elderly depressed patients pose a significant challenge in treatment due to pharmacokinetic and pharmacodynamic changes, and the concomitant medical conditions. In a hospital environment, the pressure from managed care companies and the length of stay considerations call for strategies that reduce hospital stay. We report an elderly patient admitted with severe depression and poor eating pattern who improved rapidly with augmentation treatment of the antidepressant mirtazapine with methylphenidate. Clinical Global Impression (CGI)-Severity (CGI-S) score on admission was 6. At midpoint, CGI-S score was 6 when methylphenidate 5 mg was added. CGI-Improvement at this time was 3. At the end point, CGI-S was 1 and CGI-Improvement was also 1. The patient tolerated the methylphenidate augmentation without any significant side effects. Our patient showed significant improvement justifying discharge in about 2 weeks of admission. Methylphenidate augmentation may be helpful in elderly depressed patients for clinical improvement, morbidity reduction and shortening of hospital length of stay. Further controlled studies are recommended.

Keywords: augmentation • methylphenidate • mirtazapine

Depression in older people remains an important public health problem. Unrecognized or inadequately treated depression is of major importance in clinical practice and subsequently leads to inappropriate use of healthcare resources. In order to minimize suffering and improve overall quality of life in depressed patients, early recognition and diagnosis are essential [1].

Despite continuing progress in antidepressant therapies, a significant number of depressed elderly patients develop a chronic

course of depression. In a prospective study of 124 elderly depressed patients, only a third had a good outcome. Poor outcome was associated with severity of initial illness. Patients with depressive delusions had a particularly poor outcome [2].

Elderly depressed patients with multiple medical conditions pose a challenge in treatment due to their age-related reduced homeostatic abilities and the fragility of their physical conditions. Delayed therapeutic action of all antidepressant drugs, partial and

Subramoniam
Madhusoodanan^{*,1,2}
& Diana Goia³

¹St John's Episcopal Hospital, 327 Beach
19th Street, Far Rockaway, NY 11691,
USA

²State University of New York, Brooklyn, NY, USA

³Department of Psychiatry, St John's Episcopal Hospital, Far Rockaway, NY 11691, USA

*Author for correspondence:

Tel.: +1 718 869 7375

Fax: +1 718 869 8532

sdanan@ehs.org

even no response to antidepressants, poor eating patterns and suicidal tendencies further complicate the management of depression in this population group.

In a hospital environment, the pressure from managed care companies and the length of stay considerations call for strategies that reduce hospital stay. Augmentation with a rapidly acting agent may help to accelerate and enhance the antidepressant response [3,4]. We report an elderly patient admitted with severe depression and poor eating pattern who improved rapidly with augmentation treatment of mirtazapine with methylphenidate.

Case report

Patient is a man in his 70s who was admitted because he refused to eat or open his mouth for a few days. He has been depressed on and off for the past 4 years, since he had a freak accident resulting in paralysis and subsequent nursing home placement. He has been under psychiatric care in the nursing home since his initial placement. He had mild depressive symptoms that did not warrant antidepressant treatment until 6–7 months before hospitalization, when he was started on mirtazapine 15 mg orally at bedtime, which was increased to 30 mg in 3–4 months. The patient showed improvement, however, he had periods of paranoid, jealous and delusional thoughts. He also periodically refused to eat, talk, or take medications. Two months prior to hospital admission the patient became more suspicious. He refused to talk to his children. He appeared more depressed and anxious and expressed suicidal thoughts. He was sleeping poorly, refused medications and food, and also would not open his mouth. Two weeks prior to admission he had visual hallucinations. His psychiatric diagnoses in the nursing home included adjustment disorder with depression, dementia Alzheimer's type with depression and histrionic personality disorder. He had no history of psychiatric hospitalizations, drug or alcohol abuse, or any suicide attempts.

On admission the patient was calm and communicative. He appeared depressed. Speech was of normal rate, rhythm and well articulated. His thought process was goal directed. Poverty of thought was noted. He was not expressing any suicidal or homicidal ideation. He did not make any delusional statements. The patient denied hallucinations. He was oriented to person, place and time. His memory was mildly impaired, and his insight and judgment were poor. He was assessed with Clinical Global Impression (CGI) scale (Figure 1) [5]. The index for severity (CGI-S) score on admission (baseline) was 6 (severely ill).

He had a medical history of gastroesophageal reflux disease, glaucoma, diabetes mellitus, hypertension,

spinal cord injury, quadriplegia, megacolon and suprapubic catheter for neurogenic bladder. There was no history of allergies. A laboratory workup was carried out, which included complete blood count, chemistry, coagulation profile, type and screen, electrocardiogram, chest x-ray, cat scan of the abdomen and pelvis, urine analysis, hemoglobin A1C and lipid panel. The test results showed no significant findings.

The patient was on the following medications at the nursing home: docusate sodium 100 mg orally at bedtime, multivitamin 1 tablet orally daily, milk of magnesia 30 ml orally daily as needed for constipation, artificial tears 1 drop both eyes four-times a day, tap water enema rectal three-times a week, polyethylene glycol 3350 powder one pack orally three-times a week, diphenhydramine 25 mg orally at bedtime, latanoprost ophthalmic 1 drop both eyes at bedtime, fentanyl patch 50 mcg/h one patch to skin every 72 h, famotidine 20 mg orally twice a day, glimepiride 4 mg orally twice a day, baclofen 20 mg orally every 8 h, oxybutynin 10 mg orally daily and mirtazapine 30 mg orally at bedtime.

The patient was diagnosed with dementia Alzheimer's type, mild with depressive and delusional features and histrionic personality disorder. He was started on with risperidone 0.5 mg orally daily, in view of his history of periodic psychotic symptoms. Oral mirtazapine 30 mg at bedtime was continued. Diphenhydramine was discontinued because of anticholinergic side effect potential.

After 4 days of gradual improvement of depressive symptoms, the patient suddenly became uncooperative with care. He was found to be responding to internal stimuli and appeared to have visual hallucinations. He also refused to take medications that morning. Risperidone was increased to 1 mg, in liquid form, orally each morning. The patient was also refusing to open his eyes and mouth, and was refusing to communicate. He did not seem to be in pain and did not seem to be responding to internal stimuli. The following day the patient continued to refuse care, was not eating, and was keeping his eyes and mouth closed at all times. The patient was administered 25 mg of long-acting risperidone intramuscularly, in view of his refusal of oral medications. His mood became labile in the following days, had a broken sleep pattern, was not interested in activities and was not interacting with anyone. He was not agitated. Psychomotor retardation was noted and his mood was depressed. The CGI-S score after a week of admission was 6 (severely ill). The patient was started on methylphenidate 5 mg orally daily. The patient received the first dose in the morning. By afternoon he became more alert, verbally responsive, was taking medications, and ate more

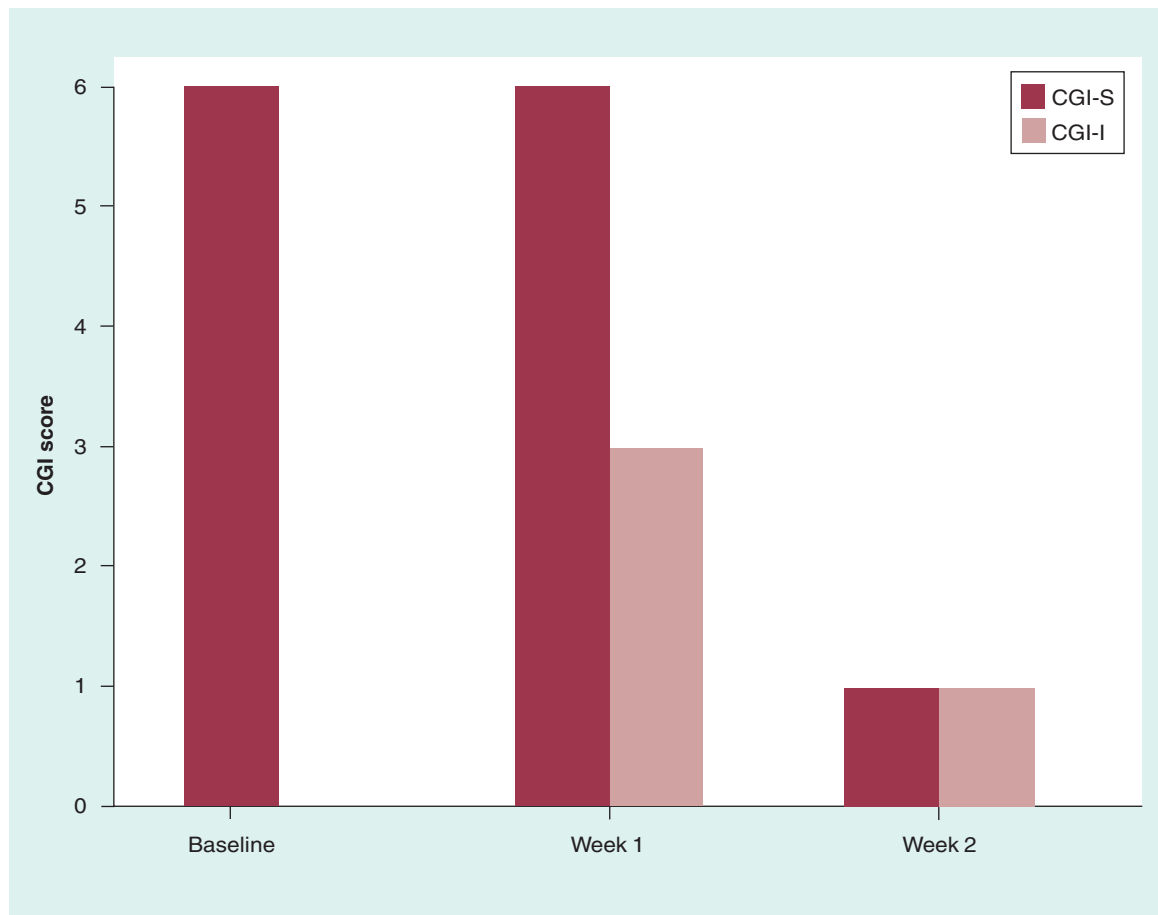


Figure 1. Clinical Global Impression scale assessments.

CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity.

than 60% of lunch. His mood and affect started to improve. The CGI-I at this time was 3 (minimally improved).

Patient was also being evaluated for bladder stones and was scheduled for cystoscopy. The patient was reporting delusional thoughts again. He was noted to be depressed with a labile affect. The patient was also reported to be hallucinating. Risperidone was increased to 1 mg in the morning and 1.5 mg by in the evening, orally.

His mood and affect gradually improved and became euthymic, and the delusions resolved. He was cooperating with care and was compliant with medications. His appetite and sleep pattern were good. The CGI-S done at 2 weeks after admission was 1 (normal, not ill at all) and CGI-I was also 1 (very much improved). The patient tolerated the methylphenidate augmentation without any significant side effects and was discharged after 2 weeks of admission. His discharge psychiatric medications included risperidone 1 mg orally every morning and 1.5 mg at bedtime, methylphenidate 5 mg daily and mirtazapine 30 mg at bedtime, all orally.

Discussion

The diagnosis and treatment of this patient is complicated by multiple factors, such as his refusal to communicate or adhere to medications or food intake, concurrent medical illnesses and concomitant medications. The patient's depressive symptoms and delusions have a strong correlation to his paralyzed state from a freak accident. The possibility of a primary delirium or delirium superimposed on his dementia also need to be considered particularly in view of the fact that the patient was on two anticholinergic medications – diphenhydramine and oxybutynin. However, the patient's symptoms were present on and off for 4 years, only the intensity worsened in the weeks prior to hospitalization. The laboratory test results and lack of associated clinical symptoms ruled out infective or metabolic causes for delirium. Diphenhydramine was discontinued on admission and the patient has been on oxybutynin for 4 years. Even though many of the patient's symptoms will fit into the broad category of 'Behavioral and psychological symptoms of dementia', since it is not included in the DSM or ICD systems, we have used the diagnosis of

dementia Alzheimer's type with depressive and delusional features and histrionic personality disorder. Use of risperidone for control of psychotic symptoms in dementia is supported by current literature [6–8]. Since augmentation treatment with methylphenidate is an off-label use and not without potential side effects it should be supervised by an expert clinician specialized in the treatment of elderly patients.

We have not come across any published reports of methylphenidate augmentation of mirtazapine in elderly patients. There have been other case reports of modafinil augmentation of mirtazapine [9] and methylphenidate augmentation of fluvoxamine [10].

A study of ten elderly depressed patients examined, in an open trial, the augmentation of citalopram with methylphenidate. The study demonstrated that augmentation was not only effective but may also have accelerated the onset of action of selective serotonin reuptake inhibitors [11]. A follow-up, double-blind, placebo-controlled pilot trial showed accelerated and enhanced antidepressant response observed by week 3 [12].

A multicenter, double-blind, randomized, placebo-controlled study of 145 subjects with major depressive disorder examined methylphenidate augmentation of antidepressants. The patients included were male and female between 18 and 65 years old who had failed at least one, but no more than three previous antidepressant monotherapies. Methylphenidate was added to their current antidepressant monotherapy. The antidepressants included were citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. The study concluded that apathy and fatigue were significantly improved with methylphenidate treatment, which was well tolerated with minimal side effects [13].

A large double-blind, randomized, placebo-controlled trial looked at the efficacy and tolerability of methylphenidate as add-on therapy of mirtazapine in cancer patients with depression. The patients included in this study were over 18 years of age, had been diagnosed with major depressive disorder and had a confirmed diagnosis of cancer. The results demonstrated that methylphenidate augmentation reduced depressive symptoms as early as day 3 of treatment. It also showed a significant greater number of responders from week 2 onward, as well as a placebo level of safety and tolerability. The major benefit of methylphenidate augmentation is rapid onset of antidepressant activity. This has a major impact on the quality of life in terminally ill patients and a major benefit in clinical practice [14].

Two other studies that examined the augmentation of methylphenidate to various selective serotonin

reuptake inhibitors showed that patients who were previously unresponsive to antidepressants showed an enhanced response when psychostimulants were added to the treatment regimen [15,16]. Both methylphenidate and antidepressants block the dopamine reuptake transporter in the presynaptic neuron. The pharmacodynamic difference between a stimulant and an antidepressant is that the stimulant acts much faster and occupies a greater number of transporters compared to an antidepressant [17].

Psychostimulants have three major effects at the monoaminergic synapse: inhibition of monoamine oxidase, blockade of dopamine reuptake and facilitation of release of dopamine into the synaptic cleft. The central stimulating effect is thought to be due to adrenergic response. Dopamine receptor agonism leads to increased motivation and reward-seeking behaviors. It also has the capacity to induce psychosis [17]. One important pathway for rapid antidepressant response is the mesolimbic dopaminergic pathway, which has been shown to be affected by low doses of amphetamine. A high dose of stimulant tends to affect the nigrostriatal dopaminergic pathway [12].

Methylphenidate has a shorter response latency compared with pemoline, and improved safety features compared with dextroamphetamine. For these reasons it has been most commonly used in elderly patients [15]. Methylphenidate blocks the norepinephrine reuptake transporter in the prefrontal cortex and the dopamine reuptake transporter in the nucleus accumbens [17]. The main reported adverse effects of stimulant use in elderly patients include insomnia, tachycardia, nausea, tremor, appetite changes, palpitation, blood pressure fluctuations, confusion, agitation and psychosis [18].

Mirtazapine is sometimes called a noradrenergic and specific serotonergic antidepressant. Its primary therapeutic action is α -2 antagonism. This causes noradrenergic neurons to become disinhibited, since norepinephrine can no longer block its own release. Thus, enhancement of noradrenergic neurotransmission by mirtazapine and methylphenidate, even though by different mechanisms, may contribute to the augmentation effect. Mirtazapine also blocks three serotonin receptors: 5HT_{2A}, 5HT_{2C} and 5HT₃. Finally, it blocks histamine-1 receptors [17].

Our study has its limitations. This is a single case report. The mirtazapine dose, even though adequate, was not maximized because of his labile mood and mental status. The augmentation effects of risperidone in depression also need to be considered. We could not use any depression scales since the patient was frequently noncommunicative and uncooperative.

Conclusion

Our patient showed significant improvement justifying discharge in approximately 2 weeks of admission. Methylphenidate augmentation may be helpful in elderly depressed patients for rapid clinical improvement, morbidity reduction and shortening of hospital length of stay. Further controlled studies are recommended.

Future perspective

With the rapid development in the pharmacogenomics and neurochemistry we may be able to improve the diagnosis and treatment selection more accurately in advance, thereby shortening treatment time and improving efficacy.

Disclosure

The abstract of this manuscript was presented as a poster at the 2013 annual meeting of the American Psychiatric Association in San Francisco and the 2013 meeting of Institute of Psychiatric Services held in Philadelphia.

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