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Case Report Open Access

Add-on Memantine Treatment for a Complicated Case of Juvenile Bipolar Mood Disorder with Co-morbid Obsessive-compulsive Disorder

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Abstract

Comorbid Bipolar Mood Disorder (BMD) and Obsessive-Compulsive Disorder (OCD) is not a rare clinical scenario as was once thought. Treatment of such cases poses a pharmacologic conundrum as the serotonin reuptake inhibitors (SRIs), constituting the mainstay of treatment in OCD, can destabilize BMD.

No guidelines are currently available to dictate the most appropriate course of action in these cases. Memantine, a drug that is approved for Alzheimer's Disease (AD) with putative antiglutamate activity has been reported in successful management of some refractory cases of OCD as well as BMD. Here, we report a pharmacologically-challenging case of an adolescent with comorbid BMD and OCD masquerading as school refusal behaviour (SRB) , that ultimately improved with add-on memantine to her treatment combo with great tolerability.

This could open new treatment venues for such complicated cases.

Keywords: Bipolar mood disorder comorbidities; Obsessive compulsive disorder comorbidities; Memantine

Introduction

Comorbidity of Bipolar Mood Disorder (BMD) and Obsessive-Compulsive Disorder (OCD) is not a rare clinical scenario as once was thought. Circa 20% of BMD patients have a comorbid OCD [1]. This comorbidity renders pharmacologic treatment of such cases really puzzling. Serotonin reuptake inhibitors (SRIs) are the mainstay of treatment in OCD at especially high doses but can readily destabilize BMD [2]. No guidelines are available to dictate the pharmacologic approach to such challenging cases. This is coupled with dearth of data on that topic in literature, notably in child and adolescent population [3]. Only a single systematic review of the topic was recently conducted, concluding that mood stabilization should be the primary goal in these patients and that adding SRIs seems unnecessary in most cases [4]. Here, we are portraying a case of comorbid juvenile BMD and OCD that presented to us as school refusal behaviour (SRB). We were caught in a limbo, when we introduced SSRI to tackle her bothersome OCD symptoms, she incurred a manic shift and when we attempted avidly stabilizing her shooting mood swings with a combo of atypical antipsychotic, two conventional mood stabilizers (lithium and anticonvulsant) and benzodiazepine, she plunged into depression with resurfacing of distressing OCD symptoms. Instead of rechallenging her with SSRI, which remains a viable option though, we thought of trying anti-glutamate pharmacotherapy, given the growing body of evidence highlighting role of glutamate dysfunction in neurobiology of OCD [5] and hence successful use of the anti-glutamate, memantine (Ebixa®) in refractory OCD [6] which would also address refractory BMD as heaps of papers abound in the literature describing utility of memantine as a 'mood stabilizer' [7-11]. What was also encouraging to embark on that trial is to help with the cognitive problems incurred by the illness itself [12] and negative impact of psychotropic drugs in this student by virtue of its cognitive enhancer activity resonating with reports of using it as add-on to stimulants in adult ADHD [13]. Memantine pharmacology dictates no major pharmacokinetic interactions and reasonably safe option which guided our choice in this case [14]. After consent by parents and assent by patient, we followed dosing tips of memantine as in Alzheimer's Disease (AD). Two weeks later, both mood and OCD symptoms markedly improved as clinically shown, patient's and parents' reporting and objectively on YMS (Young Mania Scale), BDI (Beck's Depression Inventory) and C-YBOCS (Yale-Brown Obsessive-Compulsive Scale). After another two weeks, with escalating memantine dose, further improvement was noticed both subjectively and objectively. Two months later, the response was sustained and patient was faring very well for the first time.

Multiple drug trials, together with lengthy hospital stay, would defy any placebo response in that case.

Case Report

A 15 y old Iraqi female youngster was casualty petitioned in accompaniment of her parents for suicidal gestures. The condition dated few months back with school refusal behaviour, apprehension, low dampened mood, fragmented sleep and some morbid ideations of visual imagery mostly revolving around sexual themes with subsequent guilt feelings given the kid strict religious family background. Parents sought private psychiatric consult at that time whereby a diagnosis of social anxiety disorder with secondary depression was entertained and paroxetine (Seroxat CR®) was prescribed for only a week before she presented to us. She came across the interview ambulant, lucid and alert. She was lanky with coarse features, appeared fretful, with gaze-aversion and average grooming and hygiene. She reported hollowed mood and demonstrated restricted affectivity. Her speech was responsive albeit hesitant. Her thought was dominated with depressive cognitions and notable for suicidality. She denied any hallucinatory experience by then. She was intellectually insighted with poor judgment. She had no

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previous psychiatric history, uneventful developmental trajectories and a distinguished scholastic achievement. She emanates from non-consanguineous monogamous family, ranks the 3rd in order with her eldest brother suffered uncharacterized short-lived psychotic illness that responded favourably to treatment with risperidone (Risperdal®). She had no medical history of note. No history of head trauma, epilepsy or toxic exposures. She had her menarche at age of 12 with now regular menstruation. Apart from psychotropic drugs she was dispensed, no other meds are currently being taken. No known drug allergies. No smoking or illicit drug use. No ongoing legal problems. Her physical examination was totally unremarkable. She was admitted to our inpatient service for safety concerns. During hospitalization, paroxetine was discontinued, full lab investigations including thyroid function, prolactin, growth hormone (to rule out endocrinopathy given her apparent coarse features), ECG, neuro-imaging, EEG and toxic screen were performed and were all within normal. She was observed to have compulsive studying in the ward. Then she began to accuse other inmates of casting magic spells upon her and intending to harm her. She also became shut-in, covering her face with a veil to avoid looking at others lest she could hurt them as she reported. A psychotic prodroma vs. psychotic depression was the differential and quetiapine (Seroquel®) monotherapy was instituted. At 800 mg quetiapine, she was more serene but her morbid thought content was totally unwavering coupled with compulsive reciting of Quran in the ward. With further digging, she admitted to have images of sexual nature that she cannot get rid of, causing her distress while acknowledging its irrationality. She had to hide her face then as she felt she would otherwise seduce others and this is a big sin. OCD diagnosis surfaced at that time and sertraline (Zoloft®) was introduced. At 50 mg, she started to be more brightened and a little bit activated. At 75 mg escalation, she incurred a full-fledged manic shift. Sertraline was ceased, but she kept euphoric. Risperidone was substituted to quetiapine, given pharmacogenetics, with additional clonazepam (Rivotril®). She started to settle at 4 mg risperidone, but at the expense of asymptomatic hyperprolactinaemia (3000 U). Soon, she plunged into depression with OCD re-emergence. Risperidone was decreased to 2 mg and lamotrigine (Lamictal®) was added, uptitrated to 200 mg to tackle the depressive phase but with no improvement. Lithium (Camcolit®) was instituted in lieu of lamotrigine upto 800 mg with serum level of 1.1 mmol/l. She typically remained endorsing OCD symptoms with morphing themes (sexual mainly but also auto-aggression), notable mood swings coupled with frequent prankish behaviours and some oddities acting-out her morbid thoughts. She started to have nocturnal enuresis on lithium and to have insight scotomas. However, she had a favourable response on lithium in terms of fewer mood swings but adamant OCD core. Psychomotor sluggishness with continuous subjective aprosexia was noted. She incurred mild lithium toxicity with probably some dehydration while fasting during the holy month of Ramadan whereby lithium was decreased and plenty of fluids were allowed. Back to lithium 1000 mg/d with serum level of 1 mmol/l, valproate (Depakine chrono®) was combined for a tight mood stability to enable rechallenge with SSRI for OCD later on. Valproate was rapidly titrated to 1000 mg/d with adequate therapeutic level S. Prolactin was declining (1500 U). She put on much weight. TFT showed subclinical hypothyroidism, mostly lithium-induced and thyroxin (Eltroxin®) 25 micro was added. Aripiprazole (Abilify®) was cross-titrated against risperidone upto 30 mg/d. She had more or less reasonable mood stability on aripiprazole, lithium, valproate and clonazepam combo and S. prolactin normalized. We were divided whether or not to rechallenge her with SSRI for OCD. And because, she had a lengthy hospital stay (9 months only interrupted with some escorted leaves) struggling to accomplish adequate mood-stabilization, reinstitution of serotonergic agents was detracting. Instead, we thought of adding memantine for putative anti-gluatmate actions that has been reported to help with OCD, for cognitive complaints and above-all the encouraging reports of its mood-stabilizing effects. Y-BOCS, YMS and BDI were conducted to have baseline to measure against the response of memantine, if any. 5 mg was given in the morning, escalated to 20 mg/d over a whole month and a dramatic response was achieved both subjectively and on measured scales. Exhaustive psychopharmacologic trials and long hospital stay militate strongly against a placebo response on memantine.

Discussion

Apparent comorbidity between BMD and OCD is commonplace in psychiatry. According to Epidemiologic Catchment Area study and National Comorbidity Survey Replication, 21% and 25% of patients with BMD showed lifetime comorbidity for OCD respectively [15]. Pharmacotherapy of such clinical scenarios is a moot topic [16]. It poses a great treatment challenge for two reasons. First, SSRIs, of higher-than-usual doses and for longer duration, the mainstay of OCD treatment, can readily destabilize mood in BMD, induce manic shift or increase cyclicity [17]. Secondly, there is dearth of data in the literature to guide clinicians with a treatment roadmap for such cases [3]. Recently, a systemic review of topic was conducted , concluding , given scantiness and heterogeneity of available literature, the best interpretation of available evidence appears to be that mood stabilization should be the primary goal in treating BD-OCD patients. Addition of SRI agents seems unnecessary in most cases, although it may be needed in a minority of BD patients with refractory OCD [4]. Patients with BMD are notorious to be kept on complex polypharmacy regimens [18]. This is paradoxical in a sense that it jeopardizes adherence to critically-required long-term mood-stabilizing treatment. Nonetheless, a significant proportion remains refractory with gloomy outlook [19,20]. Apart from Electroconvulsive Therapy (ECT), a host of medications were anecdotally attempted in such cases of treatment-resistant BMD, and beyond standardised guidelines including, inter ali, clozapine, omega-3, high-dose thyroid and verapamil [21]. In cases, like the one we are presenting herein, it was our premise that 'tight' mood stabilization is mandatory before attempting to reinstitute SSRIs for residual OCD. This is akin to our practice when treating comorbid ADHD and BMD [22]. However, in our case, in particular, it took her (and us!) ages to get euthymic and she was tormented with OCD symptoms coupled with suicidality. Her frenetic manic flare on introducing SSRI initially discouraged us from rechallenging her, although, we split over this option. ECT and clozapine were thought of, but declined for futility in OCD, short-lived response for the former and heinous side effects of the latter. We do believe, atypical cases require atypical treatment, hence, we thought of embarking an add-on trial with memantine. Memantine is non-competitive NMDA-glutamate partial antagonist, FDA-approved for moderate-to-severe dementia of Alzheimer's disease (AD) [23]. Memantine does not significantly affect hepatic microsomal system which would translate into minimal drug-drug interactions; a major concern given the complex polypharmacy regimen in this case [14-24]. It selectively blocks extrasynaptic receptors, the excitotoxic, and hence, devoid of psychedelic or amnestic effects [25,26]. Memantine was our choice for a multitude of reasons. First, glutamate dysfunction in OCD has been postulated [5,27,28] and ergo successful treatment of refractory OCD with anti-glutamate agents including memantine [6,29-31]. Secondly, clinical utility of memantine as a mood-stabilizer has been widely

demonstrated in literature [7-12]. It was suggested that memantine by blocking NMDA receptors prevents the up and down regulation of mesolimbic dopamine D2 receptors and the neurodegeneration that results from excessive glutamatergic neurotransmission during mania which might underlie the following depressive phase [7]. Importantly, memantine would expectedly be of help mitigating the cognitive problems incurred by the disorder itself [31,32] and negative impact of psychotropic drugs in this student due to its cognitive enhancer activity resonating with reports of using it as add-on with stimulants in adult ADHD [13] and as an effective monotherapy in paediatric ADHD too [33]. Dosing of memantine in this case was similar to that of AD, that is, 20 mg divided on 2 doses and escalated over 4 weeks. Tangible improvement was appreciated clinically, patient and parents' reporting and objectified using YMS, BDI, and C-YBOCS, together with high tolerability. Long impairing course along with multiple drug trials would assuredly militate against any possible placebo response in this case. Response was well-sustained during subsequent follow-ups and the most rewarding outcome was the patient being able to join her school back.

To our knowledge, this might be one of the first cases reporting successful add-on memantine therapy to a complicated case of juvenile bipolar disorder with comorbid OCD.

Conclusion

Clinicians should be vigilant to the comorbidity between BMD and OCD, which is commonplace in stark contrast to previous contention. These cases are eventually difficult-to-treat and thus far, there is no roadmap to guide clinicians to gauge best course of action. Tailoring of treatment, on an individualized basis, with a priority to 'tight' mood stabilization, helps in most of cases. Given the atypicality and frustratingly refractoriness of these cases, atypical psychopharmacological approaches might be warranted. One of such approaches is add-on treatment with the anti-dementia agent, memantine with putative anti-glutamate activity which might target neurobiology underlying both OCD and BMD.

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