Divalproex sodium leading to sustained significant improvement in tardive dyskinesia in a patient with bipolar disorder

Sir,

Not many therapeutic options are available to treat tardive dyskinesia (TD). Usual algorithm involves a reduction of antipsychotic dosage, clozapine, or tetrabenazine.[1] Apart from that, available literature is scant and inconclusive.[2] We report a case where divalproex sodium at a relatively higher serum concentration lead to improvement in TD.

A 35-year-old married male with no family history first visited the outpatient clinic in August 2014 with irritable behavior, “racing thoughts,” referential ideas for 1 week. He had been a known case of bipolar affective disorder[3] (four episodes between 1994 and 2009) and cannabis dependence for 6 months in 2009 (as per subjective and objective corroboration). Between 2009 and 2013, he maintained largely euthymic and occupationally functional while on unknown medications. In December 2013, patient stopped all medications, maintained well for subsequent 8 months until current presentation.

He was prescribed aripiprazole 5 mg/day by the treating doctor (pending a detailed assessment), with which remission was achieved. After being on low-dose aripiprazole for 2 months, patient started to experience involuntary movements involving lips, mouth, and jaw. As a result, patient reported feeling inhibited while attending to customers at workplace.

Patient presented again in November 2014 for a detailed work-up. He was euthymic. However these movements were present consistently for a month. The movements were noticeable during the interview and an impression of TD was made. On Abnormal Involuntary Movement Scale (AIMS),[4] these were rated as 3 for lips and perioral area (0–4) and 3 for jaw (0–4), three for awareness (0–4) with moderate distress. During that visit, tablet valproate 1000 mg/day was added as prophylaxis for bipolar disorder. Aripiprazole was continued with a plan to stop it later. The patient was compliant to both medications.

During his next visit after 10 days, patient and informants reported a significant improvement (of more than 90%) in TD. It was now barely noticeable during the interview. The AIMS rating was 1 for lips/perioral movements (0–3) and 0 for jaws (0–3), and 1 for awareness (0–3) with no accompanying distress.[5] Serum valproate level (12-h postdose) was 134 µg/ml. Clinically, neurological examination was within normal limits.

Considering that level was on somewhat higher side, an attempt was made to reduce divalproex sodium to 750 mg/day. However, TD re-surfaced almost at previous intensity, as observed after 2 weeks. Consequently, the dosage was increased to 1000 mg/day, which was well tolerated. During the next 4 months, he continued on both divalproex sodium and aripiprazole, with no TD, and periodic review every 2–4 weeks. Aripiprazole
was discontinued in early April 2015. In the same visit, he was shifted to tablet valproate sodium 1000 mg/day (free of cost at hospital’s pharmacy). The urinalysis (thin layer chromatography) was negative for cannabis. He was euthymic and free of movements during his recent visit in August 2015.

In this patient, TD showed a relatively rapid (7–10 days), significant (>90%) and sustained (over 4 months) improvement after addition of divalproex sodium. The efficacy was associated with a dosage of 1000 mg/day yielding a serum trough level of 134 µg/ml, higher than target range of 50–125 µg/ml.[5] On attempted dose reduction to 750 mg/day, the movements resurfaced at almost previous frequency and amplitude.

On a brief review (PubMed; using Mesh terms – “Valproic Acid,” “Dyskinesia, Drug-induced;” human studies; and cross-references), we found only ten small-sample, mostly older (1976–1987), studies. These had methodological heterogeneities such as using valproate in dosages between 400 and 2400 mg/day for a variable duration (1–12 weeks maximum) with mixed results.[2,6–8] No report is yet available for use of di-valproex sodium in TD.

Di/valproate use may have treatment implications in cases with persistent TD, especially in bipolar disorder where it is used for prophylaxis. The presence of TD might be one of the points to guide the selection of mood stabilizer (of course, in conjunction with other clinical considerations).

The precise pathophysiology of TD remains unknown. Chronic dopamine receptor blockade has been proposed to induce their overgrowth in nigrostriatum, leading to an inactivity of brain cells employing gamma-aminobutyric acid (GABA). Sodium valproate resembles GABA structurally. The anti-dyskinetic effect of sodium valproate (or GABA agonists) may be related to this supplementation of the function of underactive GABA cells.[2]

Finally, the efficacy of di/valproate needs to be studied further through well-controlled studies before any firm conclusions are drawn.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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How to cite this article: Pattanayak RD, Charan D. Divalproex sodium leading to sustained significant improvement in tardive dyskinesia in a patient with bipolar disorder. Indian J Psychiatry 2016;58:103-4.