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HYPERSALIVATION ASSOCIATED WITH OLANZAPINE AND VALPROATE COMBINATION: *A CASE REPORT*

To the Editor:

Severe cases of bipolar disorder often require polypharmacy regimens in order to achieve symptom remission.[1] Nevertheless, polypharmacy has the drawback of augmenting potential undesirable consequences. Hypersalivation related to antipsychotic use has been described most frequently as a clozapine adverse effect. We here report a case of hypersalivation associated to concomitant use of olanzapine and valproate in a patient with bipolar disorder.

A 75-year-old female was referred in December 2008 to our University Hospital inpatient unit because of agitation and grandiosity. At admission, the patient fulfilled *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for a manic episode without psychotic features, with a Young Mania Rating Scale (YMRS) score of 33. She was on a daily dose of haloperidol 10 mg, chlorpromazine 300 mg, paroxetine 20 mg, and olanzapine 2.5 mg. Immediately after admission, all drugs except olanzapine were discontinued, which was progressively increased up to 10 mg/day. The patient was also taking alendronate 70 mg weekly and acetylsalicylic acid 100 mg/day. Due to the persistence of mood symptoms, olanzapine was increased up to 15 mg/day and valproate 1,000 mg/day was introduced. After four days using both medications, the patient began to complain about hypersalivation. This side-effect became prominent, impairing the patient's ability to speak during interviews and requiring her to continuously hold a cloth. Excessive hypersalivation was not associated with sleeping periods, and no further extrapyramidal signs were detectable upon neurological examination. After 10 days of combined use of olanzapine and valproate, the patient persisted with manic symptoms and hypersalivation.

Electroconvulsive therapy (ECT) was initiated, conforming to the protocol instituted by our service[2] and valproate was discontinued, with a complete remission of hypersalivation during the following week. Manic symptoms remitted after 8 sessions of ECT, presenting only a transient short term memory deficit as a side effect. The patient was discharged euthymic, with a YMRS score of 1, and was receiving olanzapine 5 mg/day and of valproate 1,000 mg/day (re-introduced after ECT sessions), and presenting no signs of hypersalivation.

Reports of hypersalivation associated to olanzapine and/or valproate use are rare. In a MEDLINE search using the expression "(hypersalivation OR sialorrhea) AND (olanzapine OR valproate)" 19 papers were found. An initial case report[3] described a patient who presented hypersalivation after an increase in olanzapine dose (10–15 mg/day). The authors suggested that olanzapine, due to its structural analogy and similar receptor-binding profile to clozapine, could increase saliva production by sympathetic αadrenergic antagonism as well as by parasympathetic cholinergic agonism.

Since hypersalivation occurred only when olanzapine was increased to 15 mg/day and after the introduction of valproate 1,000 mg/day, this side effect could be secundary to the olanzapine dose itself, to valproate introduction, or to the interaction of both psychopharmacs. Thus, hypersalivation may have been occurred due to any of these mechanisms. Another possibility is the existence of a pharmacokinetic interaction between olanzapine and valproate, which is a potent hepatic enzymes inhibitor. We found no reports regarding alterations in the pharmacokinetic of olanzapine and valproate when administered together.

A Cochrane meta-analysis, despite confirming the reduced incidence of hypersalivation among patients treated with olanzapine in comparison with those using clozapine (risk ratio 0.08; 95% CI 0.02-0.31), registered two cases of hypersalivation during olanzapine use.[4]

A more recent study confirmed a low occurrence of hypersalivation[5] among patients treated with olanzapine (10% vs. 80%, in comparison with clozapine). Together with the previous reports, the case here described should encourage physicians to monitor patients taking olanzapine for the occurrence of hypersalivation.

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REFERENCES

1. Gazalle FK, Hallal PC, Tramontina J, et al. Polypharmacy and suicide attempts in bipolar disorder. *Rev Bras Psiquiatr*. 2007;29(1):35-38.
2. Fernandes B, Gama CS, Massuda R, et al. Serum brain-derived neurotrophic factor (BDNF) is not associated with response to electroconvulsive therapy (ECT): a pilot study in drug resistant depressed patients. *Neurosc Lett*. 2009;453(3):195-198.
3. Perkins DO, McClure RK. Hypersalivation coincident with olanzapine treatment. *Am J Psychiatry*. 1998;155:993-994.
4. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication versus clozapine for schizophrenia. *Cochrane Database Syst Rev*. 2000;2: CD000966.
5. Kelly DL, Conley RR, Richardson CM, et al. Adverse effects and laboratory parameters of high-dose olanzapine vs. clozapine in treatment-resistant schizophrenia. *Ann Clin Psychiatry*. 2003;15(3-4):181-186.

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