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### **Pharmacokinetic Drug-Drug Interactions Between Olanzapine and Valproate Need to Be Better Studied**

**To the Editor:** We read with interest the study by Houston et al<sup>1</sup> of olanzapine versus placebo in bipolar patients taking divalproex for at least 2 weeks. The authors did not mention the lack of published pharmacokinetic drug-drug interaction (DDI) studies of these drugs. According to olanzapine prescribing information,<sup>2</sup> 10 mg/d of olanzapine for 2 weeks did not influence valproate concentrations. Divalproex prescribing information<sup>3</sup> does not mention olanzapine.

Olanzapine is mainly metabolized by the cytochrome P450 (CYP) 1A2 and uridine diphosphate glucuronosyltransferases (UGTs), possibly UGT1A4,<sup>4</sup> with minor roles played by CYP2D6 and the flavin monooxygenase system.<sup>4</sup> Valproate is mainly metabolized by several UGTs and  $\beta$ -oxidation and less so by some CYPs (probably CYP2C9).<sup>5</sup> Olanzapine is probably not a clinically relevant inducer or inhibitor.<sup>4,6</sup> However, valproate is definitely a clinically relevant inhibitor of some metabolic enzymes including some UGTs (valproate increases lamotrigine levels) and CYP2C9.<sup>5</sup> Valproate may potentially induce some metabolic enzymes, its own  $\beta$ -oxidation,<sup>7</sup> and, according to an in vitro study, CYP3A and the P-glycoprotein.<sup>8</sup>

Psychiatrists skeptical of the clinical relevance of mood stabilizer DDIs should remember Yatham and colleagues' study,<sup>9</sup> which failed to demonstrate that risperidone was better than placebo for mania in patients taking carbamazepine. When considering the study design, the risperidone marketer forgot that carbamazepine is a powerful inducer of risperidone metabolism, which had previously been hypothesized<sup>10</sup> and demonstrated.<sup>11</sup> Pharmaceutical companies are apparently not particularly interested in mood stabilizer DDIs. The frequent clinical use of valproate-olanzapine combinations should have prompted their marketers to use their abundant resources to conduct pharmacokinetic DDI studies.

In the absence of such studies, Bergemann et al<sup>12</sup> found a halving of olanzapine concentrations in 4 patients who received valproate, and we<sup>13</sup> completed a preliminary study in which a valproate dose ranging from 600 to 2000 mg/d was administered for 4 weeks to 18 patients stabilized on treatment with olanzapine (5–20 mg/d). During valproate coadministration, mean plasma olanzapine concentrations in our sample decreased significantly from  $32.9 \pm 9.7$  ng/mL at baseline to  $27.4 \pm 9.8$  ng/mL at week 2 ( $P = .02$ ) and  $26.9 \pm 9.2$  ng/mL at week 4 ( $P = .001$ ). Thus, valproate was associated with minimal average decreases in olanzapine concentration, possibly due to induction of olanzapine metabolism.<sup>13</sup> A small increase in olanzapine concentration between weeks 2 and 4 in patients with high valproate levels suggested competitive inhibition. A statistical model of a hypothetical smoker aged 40 years and taking 10 mg/d of olanzapine was used to provide some idea of the clinical relevance of valproate-olanzapine interactions. If this patient had a valproate level of 30  $\mu$ g/mL, respective olanzapine concentrations of 24 and 21 ng/mL would be obtained at weeks 2 and 4. If the patient's valproate level were 80  $\mu$ g/mL, the respective predicted concentrations would be 6 and 10 ng/mL,<sup>13</sup> which may be lower than the therapeutic range.<sup>14</sup>

New valproate-olanzapine DDI studies with longer duration and more repeated measures are needed to establish our preliminary finding<sup>13</sup> that valproate induces olanzapine metabolism in a mild way, because, in extreme situations (high valproate concentrations or low olanzapine doses), the effect could be clinically relevant. These DDI studies should provide practical dosing recommendations for clinicians.<sup>15</sup>

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