

Dr Houston and Colleagues Reply

To the Editor: De Leon and colleagues, in reference to our article,¹ suggest that, under certain conditions, subtherapeutic olanzapine concentrations may occur during divalproex coadministration. Specifically, they propose that a hypothetical smoker with a serum valproate concentration of 80 µg/mL who is taking olanzapine 10 mg/d might develop subtherapeutic olanzapine levels (<20 ng/mL)² of 6 and 10 ng/mL at 2 and 4 weeks.³ Their example suggests the need for 20 mg/d of olanzapine, within label-recommended dose ranges⁴ but with proportionately (2-fold) higher olanzapine concentrations just at the suggested lower limit of the therapeutic range at 4 but not 2 weeks. (Notably, these analyses assume therapeutic ranges are the same for augmentation of divalproex vs olanzapine monotherapy and bipolar disorder vs schizophrenia.)

We agree that further data may be useful regarding any potential effects of coadministration of divalproex on olanzapine concentrations. In a small case series,⁵ a clinically significant

mean 54% (range 32%–79%) decrease in dose-corrected olanzapine concentration occurred in 4 patients, none with bipolar disorder, treated with 1,000 to 2,700 mg/d of valproate, with larger decreases above 2,000 mg/d. In contrast, in 18 patients,³ a mean decrease in olanzapine concentration of only 18% occurred without clinical worsening in any patient, leading the authors to conclude that "...valproate, at doses of up to 2,000 mg/d, is associated with a minimal, presumably not clinically significant, decrease in plasma olanzapine concentrations, possibly as a result of induction of olanzapine metabolism."^{3(p758)} The available data are consistent with what occurs in many (but not all) patients, in whom effects on olanzapine concentration at divalproex doses up to 2,000 mg/d are clinically insignificant. It might be worthwhile to try to understand how to identify patients who have the potential for clinically significant decreases in olanzapine concentrations with divalproex coadministration. Moreover, it might be desirable to study olanzapine concentrations in patients taking divalproex (particularly at doses over 2,000 mg/d) who have adequate tolerability but inadequate efficacy, as they may be candidates for higher doses of olanzapine. However, in conventional clinical practice, olanzapine dose would be increased up to 20 mg/d in many patients to increase the likelihood of adequate dosing as assessed by clinical response rather than olanzapine concentration.

Our article¹ described numerically greater but statistically nonsignificant reductions in both depression and mania at high (≥ 90 $\mu\text{g/mL}$) mean serum divalproex concentrations rather than the low (< 90 $\mu\text{g/mL}$) concentrations suggested by the drug-drug interaction (DDI) in de Leon and colleagues' example. However, because our study was designed with flexible dosing of olanzapine 5–20 mg/d, to assess for evidence of reduced efficacy requiring higher olanzapine doses at higher divalproex concentrations, we compared high versus low divalproex concentration groups with regard to olanzapine mean (SD) modal dose (16.5 [5.1] vs 14.0 [9.7] mg/d, $P = .18$) and final dose (15.4 [6.9] vs 13.8 [10.3] mg/d, $P = .47$) and percentage of patients ever at maximum olanzapine dose (52.2% [12/23] vs 35.9% [28/78], $P = .16$). This suggests a modest (statistically nonsignificant) tendency toward higher olanzapine doses at higher divalproex concentrations. Our analyses are not inconsistent with modestly increased olanzapine dosing, which generally compensated for the potential reduction in olanzapine concentration and efficacy at higher divalproex concentrations. In our analyses, sample size and additional factors potentially contributing to variance in response, including individual differences in neuroreceptor site activities, neurotransmitter metabolism, and olanzapine transport across the blood-brain barrier, may have tended to reduce the statistical significance of the apparent clinical effect of divalproex on olanzapine dose increases.

Industry, as required by the US Food and Drug Administration, conducts DDI studies. Because there are many potential pharmacokinetic DDIs, focused studies address regulatory requirements or DDIs most likely to have clinically significant effects on efficacy or safety. The range of flexibly dosed olanzapine augmentation therapy for divalproex treatment permits dose increases of olanzapine, which may address potential concentration reductions with divalproex coadministration. This flexibility in olanzapine dosing and the demonstrated efficacy within the established dose range for olanzapine even at high divalproex concentrations suggest that titration of olanzapine dose based on efficacy and tolerability may limit the apparent overall usefulness of monitoring olanzapine concentrations in clinical settings unless there is insufficient efficacy with olanzapine 20 mg/d, in which case obtaining a serum olanzapine concentration could be considered.

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