

# Valproate and Weight Gain: A New Look at an Old Problem

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The once-central role for antimanic mood stabilizers such as lithium and valproate to treat bipolar disorder has steadily declined amid the increasing use of second generation antipsychotics (SGAs), both short- and long-term, regardless of psychosis.<sup>1</sup> Use of valproate, in particular, may have declined in bipolar disorder not just as an artifact of promotional nonsupport since losing its patent exclusivity, or growing awareness about its teratogenicity,<sup>2</sup> but also in the aftermath of randomized trials failing to show its prophylactic value as a core monotherapy.<sup>3,4</sup> However, given the substantial liability for weight gain and metabolic dysregulation associated with many SGAs, one might ask whether valproate is metabolically more neutral, as either an alternative or adjunctive therapy, both short- and long-term. That question was briefly posed empirically two decades ago: a 47-week industry-sponsored bipolar relapse prevention trial found—in addition to no differences in relapse rates between groups—a slower rate of weight gain with divalproex than olanzapine for the first 15 weeks which then became indistinguishable from weeks 19–47.<sup>5</sup> Among SGAs, weight gain appears to be a dose-related side effect for some (notably, olanzapine and clozapine) but not all agents.<sup>6</sup> Predictors of valproate-associated weight gain have received comparatively less study.

In this issue of the *Journal*, Grosu et al<sup>7</sup> newly demonstrate a dose relationship with weight gain liability for valproate. Their retrospective,

naturalistic study of 215 patients with diverse major psychiatric disorders during 1-year treatment with valproate adds nuance to prior studies of valproate weight gain by further quantifying dose-related risk (about 1/2 of 1% weight increase per 500 mg dose, and particularly when total dosing is above 1,300 mg/d). Raw univariate correlations between valproate dose and weight gain were statistically significant but modest. Treatment duration and valproate dose were significantly associated with weight gain in men but not women. Most rapid weight gain occurred within the first 3 months than later but nevertheless persisted throughout the study period. No associations were observed between valproate use and glycemic or lipid parameters.

While the basic message of this report is helpful to clinicians (“If feasible, try to keep valproate dosing under 1,300 mg/d to minimize weight gain”), more pragmatic questions remain. One wishes that the authors would have provided a survival curve showing the time course to weight gain and its absolute magnitude, an estimate of eventual time until its plateau, and a parsing of valproate’s weight-gaining effects stratified by the presence or absence of coprescribed SGAs. The latter point is a particular conundrum, since it is hard to know how to apportion iatrogenic weight gain solely to valproate versus concomitant SGAs versus their synergy. Parsing such distinctions is also especially important for treatment planning when one considers that

for some SGAs (notably, olanzapine), weight gain may continue for nearly a year before reaching a plateau.<sup>8</sup>

One might also wonder if an algorithm could be constructed to gauge the probability of significant weight gain with valproate based on the amount of change occurring in the first few weeks or months (again, following patterns seen with olanzapine, in which gains of more than 4–5 lb in the first few weeks were shown to predict substantial long-term weight gain).<sup>9</sup> Also uncertain is whether valproate’s weight gain liability and dose relationship may differ across diagnoses (eg, epilepsy versus bipolar disorder, or mood disorders versus psychotic disorders). And finally, many other unaccounted-for features besides dose and sex can influence potential iatrogenic weight gain with some psychotropic drugs, such as drug-naïve versus chronically ill status,<sup>10</sup> age,<sup>11</sup> ethnicity,<sup>11</sup> symptom improvement,<sup>12</sup> and pharmacogenetic correlates.<sup>13</sup> Future “big data” studies might usefully assess and quantify, through multifactorial modeling, more sophisticated profiles for estimating weight gain risk with drugs such as valproate while taking into account such comprehensive risk factors.

Should Grosu and colleagues’ reappraisal of valproate’s lesser weight liability at low doses prompt a renaissance for its wider use in the treatment of bipolar disorder? Particularly in patients for whom its teratogenicity may not pose a relative contraindication? Probably not so much as the metabolically lesser evil

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to an SGA, but perhaps it is worth rethinking its potential utility as a low-dose augmentation option. Notably, in the case of lithium, low-dose augmentation in bipolar disorder has been shown to alleviate some of the burden and extent of SGA exposure.<sup>14</sup> Might renewed interest in adjunctive valproate similarly help to lessen the need for chronic SGA use, particularly in nonpsychotic mood disorder patients, or in patients for whom optimally dosed long-term SGAs may be metabolically or neurologically undesirable? It is reasonable to consider the possibility that antimanic mood stabilizers such as valproate may be efficacious at lower doses when used adjunctively than as monotherapies, minimizing the potential for weight gain and possibly other dose-related adverse effects.

Valproate has a distinct spectrum of pharmacodynamic activity that bears on the presence of mixed features, impulsive aggression, rapid cycling, multiple episodes, and alcohol use comorbidity.<sup>15</sup> When clinical features suggest value for its inclusion within a pharmacotherapy regimen, renewed awareness of dosing considerations for adjunctive therapy may help to optimize the proverbial balance between efficacy and tolerability.

## Article Information

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