Valproate and Weight Gain:

A New Look at an Old Problem

Joseph F. Goldberg, MD

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.[1] 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,[2] but also in the aftermath of randomized trials failing to show its prophylactic value as a core monotherapy.[3,4] 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.[5] Among SGAs, weight gain appears to be a dose-related side effect for some (notably, olanzapine and clozapine) but not all agents.[6] Predictors of valproate-associated weight gain have received comparatively less study.

In this issue of the *Journal*, Grosu et al[7] 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 ½ 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.[8]

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).[9] 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,[10] age,[11] ethnicity,[11] symptom improvement,[12] and pharmacogenetic correlates.[13] 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

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.[14] 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.[15] 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

Published Online: March 27, 2024. https://doi.org/10.4088/JCP.23com15213

J Clin Psychiatry 2024;85(2):23com15213

Submitted: December 6, 2023; accepted December 7, 2023.

To Cite: Goldberg JF. Valproate and weight gain: a new look at an old problem. *J Clin Psychiatry.* 2024;85(2):23com15213.

Author Affiliations: Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York.

Corresponding Author: Joseph F. Goldberg, MD, 128 East Ave, Norwalk, CT 06851 (joseph.goldberg@mssm.edu).

Relevant Financial Relationships: None.

Funding/Support: None.

References

1. Rhee TG, Olfson M, Nierenberg AA, et al. 20-year trends in the pharmacologic treatment of bipolar disorder by psychiatrists in outpatient care settings. *Am J Psychiatry*. 2020;177(8):706–715.
2. Freeman MP. Prescribing guideline for valproic acid and women of reproductive potential: forget it exists. *J Clin Psychiatry*. 2022;83(6):22ed14609.
3. Bowden CL, Calabrese JR, McElroy SL, et al; Divalproex Maintenance Study Group. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Arch Gen Psychiatry*. 2000;57(5):481–489.
4. BALANCE Investigators and Collaborators. Geddes JR, Goodwin GM, Rendell J, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet*. 2010;375(9712):385–395.
5. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry*. 2003;160(7):1263–1271.
6. Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. *J Clin Psychiatry*. 2009;70(7):1041–1050.
7. Grosu C, Hatoum W, Piras M, et al. Associations of valproate doses with weight gain in adult psychiatric patients: a 1-year prospective cohort study. *J Clin Psychiatry*. 2024;85(2):23m15008.
8. Kinon BJ, Basson BR, Gilmore JA, et al. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. *J Clin Psychiatry*. 2001;62(2):92–100.
9. Lipkovich I, Citrome L, Perlis R, et al. Early predictors of substantial weight gain in bipolar patients treated with olanzapine. *J Clin Psychopharmacol*. 2006;26(3):316–320.
10. Kang D, Lu J, Liu W, et al. Association between olanzapine concentration and metabolic dysfunction in drug-naive and chronic patients: similarities and differences. *Schizophrenia (Heidelb)*. 2022;8(1):9.
11. Lipkovich I, Jacobson JG, Caldwell C, et al. Early predictors of weight gain risk during treatment with olanzapine: analysis of pooled data from 58 clinical trials. *Psychopharmacol Bull*. 2009;42(4):23–39.
12. Luckhoff H, Phahladira L, Scheffler F, et al. Weight gain and metabolic change as predictors of symptom improvement in first-episode schizophrenia spectrum disorder patients treated over 12 months. *Schizophr Res*. 2019;206:171–176.
13. Zhang J-P, Lencz T, Zhang RX, et al. Pharmacogenetic associations of antipsychotic drug-related weight gain: a systematic review and meta-analysis. *Schizophr Bull*. 2016;42(6):1418–1437.
14. Nierenberg AA, Friedman ES, Bowden CL, et al. Lithium Treatment Moderate-Dose Use Study (LiTMUS) for bipolar disorder: a randomized comparative effectiveness trial of optimized personalized treatment with and without lithium. *Am J Psychiatry*. 2013;170(1):102–110.
15. Goldberg JF. Personalized pharmacotherapy for bipolar disorder: how to tailor findings from randomized trials to individual patient-level outcomes. *Focus Am Psychiatr Publ*. 2019;17(3):206–217.