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Reply to F. Felix et al and M.F. Fay et al — Source link

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CORRESPONDENCE

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In our recent article in *Journal of Clinical Oncology* titled, "Does Valproic Acid or Levetiracetam Improve Survival in Glioblastoma? A Pooled Analysis of Prospective Clinical Trials in Newly Diagnosed Glioblastoma,"[1] we reported that drug repurposing has attracted a lot of interest, specifically in glioblastoma, given the disappointing results obtained with initially promising, but ultimately inactive novel treatments and the availability of large databases suitable for exploratory analyses. In that regard, the potential impact on survival of the anticonvulsant drug, valproic acid, has been in focus for more than a decade. Yet, the pooled analysis of several contemporary clinical trials that enrolled almost 2,000 patients, which set out to strengthen the rationale for testing valproic acid in a randomized definitive phase III trial in newly diagnosed glioblastoma, failed to provide an adequate signal to support such a hypothesis in an otherwise molecularly unselected group of adult glioblastoma.[1]

Felix and Fontenele[2] rightly raise the issue that patients in these trials were not enriched for any biomarker that predicted potential benefit from valproic acid and propose that valproic acid be tested specifically in pediatric patients with *H3F3A* mutation, mostly pontine gliomas. There is a possible biologic and molecular rationale to explore valproic acid in this subgroup of patients on the basis of the predicted epigenetic effects of valproic acid; however, three issues arise. First, such patients are relatively rare among those with glioblastoma and are underrepresented in the patient cohorts studied in the trials compiled for our analysis despite that our study included almost 2,000 patients (which underscores the rarity of this target). Second, the concentrations of valproic acid required to inhibit histone deacetylases may not be reached in human patients in vivo.[3] Third, is valproic acid truly the best histone deacetylase inhibitor to study in this context?

Fay et al[4] raise some methodological issues about our analysis. They express concerns that confounders were not sufficiently analyzed, but the analysis we presented was adjusted for known important confounding factors, including O^6-methylguanine DNA methyltransferase promoter methylation status, and probably represents one of the best efforts that could be done in the context of clinical trial database analysis. The issue that sicker patients with larger tumors were more likely to have received valproic acid due to associated seizures was not substantiated by our database; there were no particular clinical characteristics of valproic acid–treated patients that differed from those not receiving it. That physicians would be less inclined to give valproic acid to patients with larger tumors with a higher bleeding propensity would argue against the authors' hypothesis that we overlooked an effect of valproic acid because this would provide an even stronger bias in favor of superior survival in the valproic acid groups. As discussed in the present publication as well as in the initial report,[5] the major weakness we acknowledge is the lack of solid data on the dose and duration of valproic acid exposure. Yet, the analysis was repeated at clinically relevant time points (at baseline and after concomitant temozolomide/radiotherapy) with the same conclusions. It is conceivable that for a beneficial effect in glioblastoma, early and high-dose treatment with valproic acid would be required, although no categorical data truly support this contention. Thus, we contend that analyses such as those reported here are not suitable to completely rule out an effect of valproic acid on outcome, especially on minuscule subsets with unique biologic characteristics. However, our data are robust enough to exclude any major effect of valproic acid, especially in significant proportions of patients with glioblastoma. Furthermore, any beneficial effect would have to be weighed against the major toxicity associated with prolonged high-dose valproic acid treatment (eg, hematologic abnormalities, hair loss, weight gain) in a patient population already significantly affected by other treatments such as corticosteroids, irradiation, and alkylating agent chemotherapy.

We appreciate the interest of our colleagues in further studying this topic, and we agree that further retrospective studies are unlikely to resolve the issue unless we arrive at the conclusion that we have definitively ruled out a major benefit of valproic acid in molecularly unselected newly diagnosed glioblastoma. In fact, the European Organisation for Research and Treatment of Cancer Brain Tumor Group has arrived at the latter conclusion and will not further pursue the idea of a randomized phase III trial of valproic acid in newly diagnosed glioblastoma.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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