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CORRESPONDENCE

Valproate in Adjuvant Glioblastoma Treatment

TO THE EDITOR: We are a group of clinicians and researchers who have been studying the effect of sodium valproate (VPA) in glioblastoma (GBM) since 2010. The study recently published in *Journal of Clinical Oncology* by Happold et al[1] pooled a number of trial data sets to study a variety of interventions for glioblastoma in which patients had taken anticonvulsants, including VPA. The study concluded that VPA showed no benefit on survival.

The motivation for the publication may be to dissuade clinicians from using VPA in the absence of a randomized prospective phase III trial that shows evidence of progression-free or overall survival benefit. However, the analysis may prematurely discourage other groups from studying the interaction between VPA and chemoradiotherapy as well as clinical outcomes with older drug therapies.

This type of analysis typically suffers from bias because the included trials were not equipped to answer the question of whether VPA improves survival in GBM. Without identification and control of confounders, the significance of the findings is compromised. An example of a biased GBM study that led to potentially poor practice is the recommendation to avoid VPA as an anticonvulsant around the time of surgery based on reports of increased incidence of bleeding. However, sicker patients with larger or more aggressive tumors were more likely to have received VPA because of their increased likelihood of having seizures. A large tumor cavity itself,

Table 1. Previous Literature That Examined VPA

First Author	Included Here	Cohort Size: VPA Positive	Cohort Size: VPA Negative	HR (95% CI)	Definition: VPA Negative	Definition: VPA Positive	Notes
Felix[4]	No	22	22	0.31 (0.14 to 0.7)	To 2006 No VPA	2007 onward 10-15 mg/kg/day as prophylactic anticonvulsant (routinely)	Multiple childhood tumors No TMZ Sometimes RT
	No	16	15	0.42 (0.16 to 0.97)	To 2006 No VPA	2007 onward 10-15 mg/kg/day as prophylactic anticonvulsant (routinely)	As above but brainstem tumors only
Felix[5]	No	13	6	0.6 (0.37 to 0.98)	To 2006 No VPA	2007 onward 10-15 mg/kg/day as prophylactic anticonvulsant (routinely)	DIPG No TMZ Conformal RT Cohort split on time period
Barker[6]	No	29	374	0.67 (0.27 to 1.07)	Five other AEDs Phenytoin Levetiracetam Carbamazepine Phenobarbital	VPA during RT Dose unknown	GBM with seizures RT TMZ use and nonuse Controlled confounders: RTOG RPS class, concurrent TMZ, seizure history
Barker[6]	Yes	12	122	0.54 (0.09 to 1.17)	Five other AEDs Phenytoin Levetiracetam Carbamazepine Phenobarbital	VPA during RT Dose unknown	GBM with seizures TMZ + RT
Kerkhof[7]	Yes	108	57	0.63 (0.43 to 0.92)	No VPA or VPA < 3 months with or without LEV and other therapies	VPA > 3 months Maintenance dose of 1,000 mg Raised but usually < 2,000 mg for ongoing seizures	Primary and recurrent GBM with seizures TMZ + RT for primary TMZ + chemotherapy for recurrent Controlled confounders: age, resection extent, and MGMT status
Obendorfer[8]	No	43	125	Survival data only	No AED (n = 88) or EI-AED (n = 43)	600-1,500 mg VPA (n = 32) or other non-EI-AED (n = 13). Sometimes with LEV	GBM Chemotherapy + RT
Weller[9]	Yes	97	277	0.67 (0.53 to 0.9)	No AED	VPA only Dose unknown	GBM TMZ only MGMT recorded but not controlled for
	No	97	252	0.39 (0.24 to 0.63)	EI-AED (four agents) and other comparisons	VPA only Dose unknown	GBM TMZ + RT MGMT recorded but not controlled for
Guthrie[10]	No	24	138	Cox-Mantel log-rank test	No AED EI-AEDs	VPA Dose unknown	GBM Chemotherapy + RT Controlled confounders: age, KPS, resection extent, location
Jaeckle[11]	No			Compare EI-AED *v* none	N/A	N/A	GBM Controlled confounders: age, sex, function, resection extent, steroid use (n = 620) 2% non-EI-AEDs

Abbreviations: AED, antiepileptic drug; DIPG, diffuse intrinsic pontine glioma; EI-AED, enzyme-inducing antiepileptic drug; GBM, glioblastoma multiforme; HR, hazard ratio; KPS, Karnofsky performance status; LEV, levetiracetam; MGMT, O6-methylguanine-DNA methyltransferase; N/A, not available; RPS, recursive partitioning analysis; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; TMZ, temozolomide; VPA, valproate

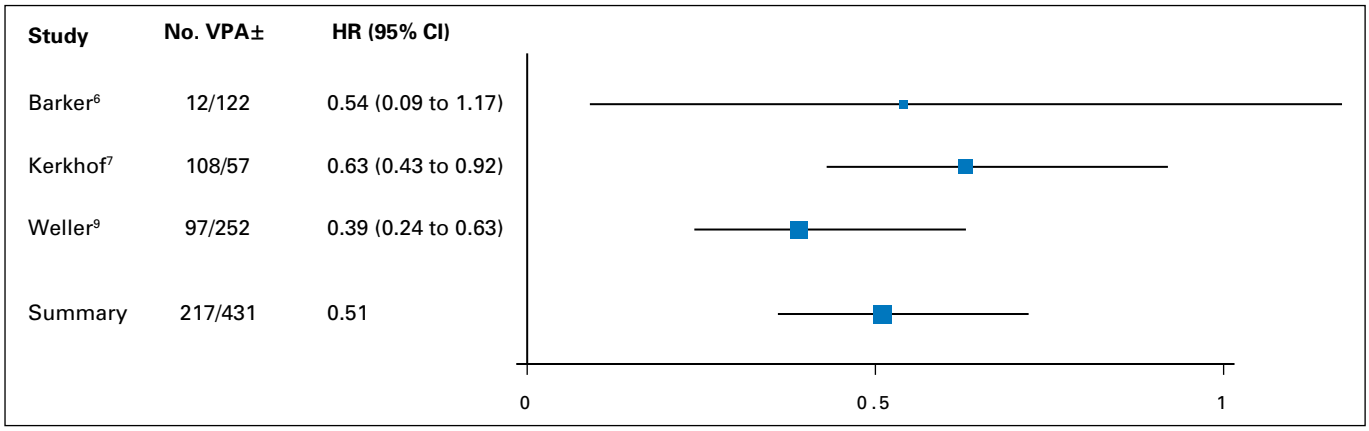

Fig 1. Forest plot that shows a meta-analysis of three studies of VPA use (specifically with the exclusion of enzyme-inducing antiepileptic drugs) in glioblastoma multiforme with concurrent temozolomide and radiotherapy. HR, hazard ratio; VPA+/−, taking/not taking valproate.

irrespective of therapy, predisposes to bleeding. More data do not remove bias, even if prospectively collected.

In addition, the dose and duration of VPA is neither reported nor controlled for. Dose-response curves for the initial effect can be quite different when used for a new application when repurposing drugs. Our in vitro experimental studies on established cell lines and primary human glioblastoma cells clearly showed an interaction between VPA and chemoradiotherapy[2,3] but only at the upper end of recommended doses for seizure prevention. VPA dose does not directly relate to CSF concentration in humans, and studies using subtherapeutic doses are of limited clinical relevance.

From reported results (Table 1), three studies that considered patients with GBM treated with temozolomide, and reported hazard ratios were used in a meta-analysis. Some are cited by Happold et al.[1] The studies are not without issue. The analysis is retrospective, and definitions for positive VPA use vary (data source was an included factor). Like Happold et al, dose and protocol were not always reported. Unlike other antiepileptic drugs,[6,9,10] VPA consistently had a small, but detectable benefit (Fig 1), not dissimilar to Table A2 in Happold et al.

The definition of VPA positive is critical to avoid obscuring or even eliminating observed beneficial effects (if any) of VPA, especially if mild. The obscuring effect of misallocation was simulated based on reported Kaplan-Meier curves.[12] From 138 patients taking VPA, increasing numbers were randomly reassigned to the 24 VPA-positive patients to simulate inclusion of other antiepileptic drugs. From a baseline hazard ratio of 0.9, which indicated benefit, the hazard ratio decreased to 0 (no benefit) when 32 patients had been reassigned.

We would consider that by controlling for protocol, the types of patients recruited and reasons for taking VPA is critical to analysis. The debate around the use of VPA cannot be resolved by further retrospective studies. There are clearly difficulties in investigating therapies in this uncommon disease ($<$ 1% of cancer diagnoses) and in a heterogeneous patient group.[12,13] However, a prospective analysis is not onerous because it simply requires the use and dose of VPA to be reported in forthcoming prospective studies with a placebo group and matched for confounders such as promoter status, histology, stage, age of patient, and comorbidities. Although less ideal than a randomized controlled trial, it certainly would provide better evidence than the work to date.

In conclusion, we suggest that the clinical effectiveness of VPA in adjuvant glioblastoma treatment has yet to be definitively investigated. A research bias exists toward new molecules over new applications of old drugs, many with proven anticancer efficacy and safety.[14] Given our limited progress in improving GBM survival, it would be regrettable to eliminate these by holding them to the higher standard of demonstrating efficacy in the face of uncontrolled confounders.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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