Potassium bromide was the first antiseizure drug, recognized in 1857, and was the only agent used clinically until 1912, when phenobarbital was discovered. Since 1975, there have been 28,000 new chemical entities studied as antiseizure drugs, with approximately 30 (0.1%) of them ultimately being approved by the US Food and Drug Administration. Antiseizure drugs often have narrow therapeutic windows, and therapeutic drug monitoring is recommended during therapy. The International League Against Epilepsy began issuing guidance on therapeutic drug monitoring in 1993 and released their most recent iteration in 2008. Interestingly, the 2008 iteration included a single reference on pharmacogenetics.

Interpatient pharmacokinetic variability with antiseizure drugs has been appreciated for decades, but the underlying mechanisms for such disparity have been unclear. A delicate interplay between patient- and drug-specific factors likely explains some of the variability. Hepatic drug metabolism occurs in 2 phases, with the first phase mediated by a heterogeneous group of protein isoforms called the cytochrome (CYP) P450. Humans have 57 CYP genes arranged into 18 families and 42 subfamilies. Genetically determined polymorphisms in CYP450 genes may alter their function, resulting in various phenotypes. Recently, research into the clinical significance of these genetic polymorphisms has begun.

In this study, Milosavljević and colleagues reported the results of a systematic review and meta-analysis that quantified changes in antiseizure drug concentrations stratified by genes encoding drug metabolizing enzymes. Using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines, the investigators screened 1734 publications and ultimately included 98 studies with 12,543 participants. Carbamazepine, lamotrigine, phenytoin, and valproate were the only antiseizure drugs included, as they are heptatically metabolized by CYP isozymes or uridine diphosphate-glucuronosyltransferases (UGT) with a high frequency of functional allelic variants.

The included studies were heterogeneous; 69 studies were conducted in East Asian countries, and 59 studies included children and adolescents. For certain medications, like carbamazepine, 100% of the studies were conducted in non-White participants. Furthermore, only 16 participants (0.13%) identified as Black and just 8 studies (8%) included exclusively European participants. The racial makeup of the participants is important when interpreting the results of the meta-analysis by Milosavljević and colleagues. A recent study of 12 CYP genes in 56,945 unrelated individuals of 5 major human populations determined there is large interracial differences in the prevalence of polymorphisms.

Sufficient data were available to evaluate ranges of means, which are used by the US Food and Drug Administration for bioequivalence for phenytoin, valproate, carbamazepine, and lamotrigine. No clinically relevant differences in ranges of means were observed for valproate, carbamazepine, or lamotrigine. For phenytoin, CYP2C9 intermediate metabolizers had 46% (95% CI, 33%-61%) higher phenytoin concentrations compared with the CYP2C9 normal metabolizers. Similarly, CYP2C19 intermediate metabolizers and CYP2C19 poor metabolizers showed 20% (95% CI, 17%-30%) and 39% (95% CI, 24%-56%) higher phenytoin concentrations, respectively.

Applying the results of the systematic review and meta-analysis by Milosavljević and colleagues is akin to identifying a signal amidst near constant background noise. Multiple aspects of their results must be considered before taking definitive action. Importantly, all included studies reported total drug concentrations without consideration for free (unbound) antiseizure drug concentrations. This is especially important for phenytoin and valproate, which are both more than...
90% protein bound to albumin. Perturbations in protein binding, mostly due to uremia and hypoalbuminemia, can lead to altered free fractions and adverse drug effects. How genetic polymorphisms in CYP450 or UGT isozymes affect this is unknown.

An additional consideration when reading the systematic review and meta-analysis by Milosavljević and colleagues is the quality of evidence included. Only 7 of 22 (32%) ranges of means in unadjusted analyses had an I^2 statistic less than 50%, suggesting that there was homogeneity in just one-third of studies. Similarly, relative weight contributed by individual studies varied significantly, with some values as high as 44% and as low as 1.1%, resulting in a 40-fold difference. Such disparity in evidence quality cannot be overlooked.

Any reader of the systematic review and meta-analysis by Milosavljević and colleagues should ask themselves is there signal in the noise? The easy answer is yes, there is, but the hard part is identifying where the signal lies. The results of the systematic review and meta-analysis were most robust for phenytoin, even if the effect size was small. There is also value in the scope of their systematic review and meta-analysis, in that almost all relevant studies were included. This provides a foundation for where we have been and perhaps a roadmap for where we are going.