



# Suicidality: Once Again, Don't Blame the Drug Class

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## Abstract

**Importance:** Most antiseizure medications (ASMs) carry a US Food and Drug Administration–mandated class label warning of increased suicidality risk, based on a meta-analysis comparing suicidality between individuals treated with medications vs placebo in randomized clinical trials done before 2008. ASMs approved since then carry this warning although they were not similarly studied.

**Objective:** To review all placebo-controlled phase 2 and 3 studies of 10 ASMs approved since 2008 to evaluate the risk of suicidality of these drugs compared with placebo.

**Data Sources:** Primary publications and secondary safety analyses in PubMed of all phase 2 and 3 randomized placebo-controlled epilepsy trials of ASMs approved since 2008, using keywords *epilepsy*, *antiepileptic drugs*, *seizures*, *suicidality*, *suicidal ideation*, and the names of individual drugs.

**Study Selection:** All phase 2 and 3 randomized clinical trials of adjunctive treatment of drug-resistant epilepsy and their secondary safety analyses.

**Data Extraction and Synthesis:** Articles were reviewed for frequency of suicidality (ideation, attempts, and completed suicides). Mode of suicidality ascertainment included treatment-emergent adverse event reports, Standardized Medical Dictionary for Regulatory Activities queries for events in prespecified categories including suicidal ideation and behavior, prospective collection of suicidality data as a prespecified safety outcome using the Columbia-Suicide Severity Rating Scale, and retrospective evaluation by blinded review using the Columbia-Classification Algorithm of Suicide Assessment. A meta-analysis compared risk for drugs vs placebo of each outcome for all drugs overall and by individual drugs and trials.

**Main Outcomes and Measures:** Suicidality (total and by ideation), attempts, and completed suicides.

**Results:** Excluding studies that did not evaluate suicidality (everolimus and fenfluramine) or did not evaluate it prospectively (lacosamide, ezogabine, and clobazam), 5 drugs were analyzed: eslicarbazepine, perampanel, brivaracetam, cannabidiol, and cenobamate. Suicidality was evaluated in 17 randomized clinical trials of these drugs, involving 5996 patients, of whom 4000 patients were treated with ASMs and 1996 with placebo. There was no evidence of increased risk of suicidal ideation (drugs vs placebo overall risk ratio, .75; 95% CI, .35–1.60) or attempt (risk ratio, .75; 95% CI, .30–1.87) overall or for any individual drug. Suicidal ideation occurred in 12 of 4000 patients treated with ASMs (.30%) vs 7 of 1996 patients treated with placebo (.35%) ( $P = .74$ ). Three patients treated with ASMs and no patients treated with placebo attempted suicide ( $P = .22$ ). There were no completed suicides.

**Conclusions and Relevance:** There is no current evidence that the 5 ASMs evaluated in this study increase suicidality in epilepsy and merit a suicidality class warning

## Keywords

epilepsy, antiseizure medications, suicide, metanalysis

Klein and coauthors have reported a metanalysis of suicidality associated with the use of 5 newer antiseizure medications (ASMs) using data from the randomized clinical trials (RCTs), and have concluded that there was no statistical association of any of these drugs with suicidality.<sup>1</sup> They were able to do so with confidence because all clinical trials of ASMs after 2008 were required to measure suicidality specifically and prospectively, usually with the Columbia suicidality risk scale. Many earlier RCTs included no specific measurements of suicidality before or after drug assignment, and suicidality was thus detectable only from open-ended enquiry about side effects.

Few government reports have generated as much negative feedback from physicians as the 2008 FDA report entitled “Statistical Review and Evaluation-Antiepileptic Drugs and Suicidality”.<sup>2</sup> The FDA panel concluded that there is an association between antiepileptic drugs and suicidal ideation or behavior, based on RCT data from before 2008. Warnings were then added to the labeling of all ASMs, for example, this wording from a package insert: “*Suicidal behavior and ideation: antiepileptic drugs increase the risk of suicidal behavior or ideation*”. This FDA report has been critiqued in detail in this journal and others,<sup>3–6</sup> but it is important to review the main objections in order to understand the results from Klein et al.<sup>1</sup> A



central criticism of the FDA report is that it was illogical to combine results from trials of drugs of very different chemical classes and mechanisms of action. Other criticisms were based on perceived statistical flaws.<sup>6,7</sup> Indeed, there is an apparent misstatement of fact in the conclusion section of the FDA report: “Results were consistent for all of the drugs.”<sup>2</sup> They were not. Only topiramate, taken by a plurality-28% -of subjects, had a significant association with suicidality, after additional lamotrigine data were included. Confidence intervals for all the other drugs were wide and permit the null hypothesis. It is only when data from all the drugs are combined that a significant association can be stated. Epilepsy subspecialists are advised to read the actual report.<sup>2</sup>

Despite the hurricane of criticism, objections to the FDA report are not altogether convincing. It is theoretically possible that ASMs could share a common mechanism promoting suicidality which has nothing to do with antiseizure mechanisms. In some persons, the antiseizure effect itself could enhance suicidality. If the new ASM reduces seizures but does not eliminate them—the common result in most RCTs—there could be a dampening of hope. Is it possible that there is a systematic difference in suicidality effects between the drugs considered in the FDA report<sup>2</sup> and the newer drugs considered in the Klein et al publication?<sup>1</sup> That is unlikely. No excess risks of suicide attempt nor completed suicide were discovered among patients taking ASMs, including many patients taking one of the same 5 newer ASMs, in an analysis of medical records in the United Kingdom (“suicidality” could not be measured from these medical records).<sup>8</sup>

After the FDA panel results were publicized, neurologists feared that this would lead to dangerous physician hesitancy in prescribing ASMs for epilepsy. This worry is repeated by Klein et al.<sup>1</sup> but the evidence is anecdotal. No difference in prescription frequency of ASMs was found before vs after the 2008 warning among a cohort of Medicaid patients.<sup>9</sup> Patient hesitancy is also a concern. An ILAE Task Force stated: “When starting an AED or switching from one to other AEDs, patients should be advised to report any changes in mood and suicidal ideation to their treating physician.”<sup>6</sup> Each coauthor of the Klein et al article<sup>1</sup> asserted that he or she had seen a patient who was reluctant to take an ASM because of the suicidality warning. This has not been my experience. In every patient encounter, the physician is faced with balancing the patient’s need for the drug with full disclosure of adverse possibilities. We should vary this discussion for each specific drug. However, we should not vary it much between patients; that would be paternalistic. The exceptions are patients who are at extra risk for an adverse effect. If there is a history of suicidality, which we ought to know, of course it is prudent to tell such a patient explicitly that an ASM can precipitate depression or suicidal thoughts.

Klein et al.<sup>1</sup> argue strongly that the FDA should remove the “class label” warning of suicidality from these 5 new drugs, and many neurologists believe that it should do so for most of the older drugs as well. I agree, with the caveat that we may need more data for some drugs. Epilepsy organizations should

spearhead a request for the FDA to revisit the labeling language for ASMs. The ILAE report<sup>6</sup> should be updated; because as it reads it seems to make use of the words “suicide” or “suicidal thoughts” mandatory (actually the report is of “suicidal ideation”, a phrase which most patients will not understand) when counseling each patient starting a new ASM. This sandbags physicians and indeed may make occasional patients refuse a life-protecting treatment.

These results from Klein et al.<sup>1</sup> are welcome and encouraging, but should not divert attention away from the very real issue of suicidality. Suicide is a definite risk with epilepsy. Neurologists should screen verbally, if not with a formal instrument, for depression and for a history of suicidal behavior or thoughts in every new patient with epilepsy. It is a reasonable, though not required, practice to repeat this screen when starting a new CNS-active drug, as you would for a history of a drug allergy. “Have you ever had a rash from a drug? Have you ever felt suicidal or wanted to hurt yourself?” are phrases that are gentle but sufficient. It is, in my opinion, not necessary to say, “This drug may make you want to kill yourself”. Full disclosure: I do not do it.

It should surprise no one that the risk of depression is greater among persons with uncontrolled seizures than in persons who are seizure-free.<sup>10,11</sup> This surely outweighs the risk of depression from an ASM. The risk to life from seizures is overwhelmingly greater than the risk to life from taking any ASM. Are there rare patients in which an ASM precipitates suicidality? Of course, but that may be true for any neuroactive drug, and in fact for the events of any day in each of our lives.

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