

# Introduction: Antiepileptic Medications for Bipolar Disorder

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In recent years, clinicians and policymakers have embraced evidence-based medicine (EBM) as the best way of providing patients with care derived from up-to-date scientific data. Used appropriately, EBM gives providers and the public unbiased information on efficacy and effectiveness of tests and treatments, by generating systematic reviews of research on clinical and policy questions. With clinical practice too often overly influenced by dissemination of poor quality or biased research by groups with vested interests in the results of that research, EBM can help improve provision of care.

Several antiepileptic drugs (AEDs) (e.g., carbamazepine, valproate, lamotrigine) have been approved by the U.S. Food and Drug Administration (FDA) for use in specific phases of bipolar disorder, with efficacy supported by placebo-controlled randomized trials. This supplement describes a project by academic researchers and practicing clinicians to identify fair and balanced evidence on the efficacy of the class of AEDs in bipolar disorder. This project, supported by resources resulting from legal action by 50 state attorneys against Pfizer subsidiary Warner-Lambert for alleged deceptive off-label marketing of gabapentin (Neurontin), was free of pharmaceutical industry influence.

Originally approved by the FDA in 1993 only for adjunctive treatment of partial complex seizures, the AED gabapentin was promoted by its manufacturer for off-label use for psychiatric disorders, including bipolar disorder, although its efficacy for that indication had not been demonstrated either in FDA submissions or peer-reviewed publications. A recent publication outlined industry tactics used to promote gabapentin and documented their success in producing a remarkable increase in its use for psychiatric disorders, with over 900,000 prescriptions for gabapentin in the first quarter of 2000.<sup>1</sup> More than 90% of gabapentin prescriptions in that period were for unapproved indications.<sup>2</sup>

In May 2004, a consortium of 50 state attorneys general reached a settlement with Pfizer regarding allegations that Warner-Lambert marketed gabapentin for "off-label" indications, including psychiatric disorders, back pain, and headache, even though 1) scientific evidence for its use in these conditions was lacking and 2) it was approved by the FDA only for secondary treatment of epilepsy and pain from shingles. As a result of the settle-

ment, the Neurontin Executive Committee was created, which was empowered to allocate up to \$6 million from the settlement for a corrective national countermarketing program to provide fair and balanced information to prescribers about gabapentin and other AEDs in the treatment of bipolar disorder.

At about this same time, a consortium of state Medicaid agencies funded a drug class review by the Oregon Evidence-based Practice Center's Drug Effectiveness Review Project (DERP) to compare the effectiveness and adverse event profiles of AEDs in bipolar disorder, neuropathic pain, and fibromyalgia. The final report was issued in May 2006.<sup>3</sup> The goal of the DERP reviews is to enable states to utilize the best available evidence to inform formulary and payment decisions.

The Neurontin Executive Committee was very interested in the AED Review, since it specifically addressed on- and off-label use of AEDs in bipolar disorder. However, the full Review is over 700 pages and very technical, so that the format is not conducive for reaching large numbers of healthcare providers, who generally want brief, easy-to-use materials on issues they face in daily practice. Therefore, the Office of the Attorney General of Vermont, on behalf of the Executive Committee, issued a Request for Proposals in January 2005 for assistance in adapting fair and balanced information on use of AEDs for mood disorders from the AED Review and other sources and disseminating it to prescribers in all 50 states and the District of Columbia. Researchers at the University of North Carolina at Chapel Hill (UNC) and colleagues at Research Triangle Institute International (RTI), a nonprofit research firm, successfully responded to this RFP, proposing to:

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1. **Create derivative products for the use of AEDs for bipolar and mood disorders** based on 1) the AED Review,<sup>3</sup> 2) other sources of fair and balanced information that might be helpful to prescribers, 3) advice from a Science Panel on clinical implications of the report, 4) current patterns of AED prescribing, and 5) results of market research with relevant audiences. The products would be designed for widespread dissemination through various media to prescribers in all 50 states and the District of Columbia.
2. **Develop and implement a dissemination strategy for the derivative products** based on systematic reviews of interventions for improving physician prescribing and compliance with practice guidelines and advice from an expert Dissemination Panel.
3. **Cooperate and assist in evaluating the effectiveness of the dissemination of the derivative products** by 1) creating and maintaining databases for project monitoring, 2) documenting all methods and processes used to create and disseminate derivative products and 3) collaborating with an evaluation team to develop appropriate outcome and impact measures.

As noted above, Science and Dissemination Panels were formed to assist in adapting and disseminating information from the AED Review. The Science Panel, composed of five experts in systematic review, clinical psychiatry, and pharmacy, including the primary author of the AED Review, was charged with the following tasks:<sup>4</sup>

- Reviewing the AED Review
- Determining clinical implications of the report
- Providing feedback to ensure that derivative products would be fair and balanced and accurately reflect information in the published review.

The Dissemination Panel, composed of six members, including psychiatrists and experts in communications, dissemination, and marketing, was charged with:

- Reviewing evidence-based approaches for reaching audiences and influencing their prescribing behavior
- Providing feedback on derivative products to assure they are suitable for widespread dissemination
- Recommending dissemination strategies for each audience segment
- Assisting in development of information and tracking systems to document the dissemination process.
- Assisting in identifying appropriate professional organizations and other clinical groups for disseminating the information.

Members of both panels and the UNC researchers were carefully vetted to be sure they met stringent conflict of interest criteria outlined by the Executive Committee, in

order to assure those using the AED materials that there was no industry influence in their development—i.e., that not only was there no industry funding for the materials presented in this supplement, but that panel members received no industry funding for the duration of the project. The principal investigator, co-principal investigators, members of the Science and Dissemination Panels, and other healthcare or decision-making professionals working on the project had to disclose any payments over \$100 received from January 2002 to the present. Many prospective panel members were not eligible to participate in this project because of conflict of interest issues. The Neurontin Executive Committee, which funded the project, had no role in determining the content of the systematic review of the derivative products.

This supplement includes five papers that highlight steps taken to provide fair and balanced information to prescribers. The first paper describes findings from the AED Review. The second paper reviews studies of the efficacy of gabapentin in bipolar disorder. The third paper describes work of the Science Panel and UNC researchers in distilling practice-based messages from the AED Review and subsequent literature on use of AEDs in bipolar disorder. The fourth paper describes audience research and qualitative analysis methods used to determine psychiatrists' current use of AEDs, actual and preferred sources of information on AEDs, knowledge about the lawsuit, and reactions to sample marketing materials. The final paper describes approaches for using countermarketing strategies to compete with those of the pharmaceutical industry and for helping prescribers, especially psychiatrists, use available evidence to inform their use of AEDs in the treatment of bipolar disorder.

## References

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