

Disseminating Findings from a Drug Class Review: Using Best Practices to Inform Prescription of Antiepileptic Drugs for Bipolar Disorder

CATHY L. MELVIN, PHD, MPH
LEAH M. RANNEY, PhD
TIMOTHY S. CAREY, MD, MPH
W. DOUGLAS EVANS, PHD
AED DISSEMINATION PANEL

Evidence from drug class reviews is often not accessible to practicing clinicians nor is it presented in a way that allows clinicians to use the information to guide treatment and prescribing decisions. Nevertheless, information from such reviews can be very helpful to clinicians as they evaluate the “evidence” provided to them through marketing strategies implemented, primarily, by the pharmaceutical industry and designed to influence their prescribing behavior. Unfortunately, these marketing strategies can be used to promote the off-label use of drugs that may not be efficacious. One example is the pharmaceutical marketing to promote off-label use of gabapentin (Neurontin) for the treatment of bipolar disorder, the legality of which was later addressed in a major lawsuit by the National Association of Attorneys General. We describe an effort to use counter-marketing strategies to compete with those implemented by the pharmaceutical industry and to help clinicians, principally psychiatrists, make use of available evidence to inform their prescription of antiepileptic drugs (AEDs) in the treatment of bipolar disorder. A growing body of literature describes industry marketing practices designed to influence prescriber behavior. This literature suggests that use of competing approaches involving the same underlying strategies to deliver highly credible information from trusted sources can inform prescriber knowledge and prescribing practice. We describe our use of existing evidence to develop accurate and convincing messages and materials to be disseminated nationally to counter industry misinformation and promote evidence-based prescription of AEDs. (*Journal of Psychiatric Practice* 2007;14(suppl 1):44–56)

KEY WORDS: bipolar disorder, antiepileptic drugs, gabapentin, marketing, dissemination

Major advances have been made in the number and types of medications for psychiatric illness. As the number of medications within a class increases, so does the complexity of decision-making for the prescriber. Because the demands and rigors of clinical practice do not allow prescribers time to undertake their own research or literature reviews on drug effectiveness, they must often rely on other sources of information to guide their choice of medication. Such choices are informed by a number of sources, some evidence-based and some not, including peer reviewed and other publications, participation in continuing medical education (CME), computer-based clinical decision support systems, clinical practice guidelines, advertising, and consultation with peers.

Unfortunately, certain information available to prescribers has led to inappropriate use of various classes of drugs. One case in point is the use of antiepileptic drugs (AEDs) for bipolar disorder. Although approved in 1993 by the U.S. Food and Drug Administration (FDA) only for adjunctive treatment of partial complex

seizures, the manufacturer of the AED gabapentin (Neurontin) promoted its off-label use for treatment of psychiatric disorders, including bipolar disorder, even though its efficacy for psychiatric disorders had not been demonstrated. A recent publication outlined the tactics used in the industry promotion of gabapentin

MELVIN, RANNEY, and CAREY: Cecil G. Sheps Center for Health Services Research, The University of North Carolina at Chapel Hill; EVANS: RTI International, Inc. Washington, DC.

The AED Dissemination Panel is composed of Cathy L. Melvin, PhD, MPH, W. Douglas Evans, PhD, Gary Kreps, PhD, Thomas Linden, MD, John Oldham, MD, MS, and Leah Ranney, PhD.

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Please send correspondence and reprint requests to: Cathy L. Melvin, PhD, MPH, The Cecil G. Sheps Center for Health Services Research, The University of North Carolina at Chapel Hill, 725 Martin Luther King Jr. Boulevard, CB#7590, Chapel Hill, NC 27599-7590. cathy_melvin@unc.edu

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and documented its success in causing a remarkable increase in use of this agent in the treatment of psychiatric disorders, with over 900,000 prescriptions registered in the first quarter of 2000.¹ In fact more than 90% of the prescriptions for gabapentin were for off-label uses.²

Several studies published within the past few years outline the prevalent use of AEDs in the treatment of bipolar disorder. Although lithium remains the most commonly prescribed drug, with 50% of patients in one study and 38.4% in another receiving lithium,^{3,4} the reported use of AEDs was also high. Both standard anticonvulsants, valproate (40%³ and 36.8%⁴) and carbamazepine (11%³ and 5.8%⁴), and the novel anticonvulsants, lamotrigine (15.4%),⁴ gabapentin (14.0%),⁴ and topiramate (5.2%)⁴ were also prescribed frequently. Understanding these clinical patterns of care can identify areas for which there is insufficient evidence to support current clinical practice.

In May 2004, 50 attorneys general settled consumer protection claims regarding alleged deceptive "off-label" marketing practices of Pfizer subsidiary Warner-Lambert. At the same time, the Oregon Evidence-based Practice Center, with funding from a consortium of state Medicaid agencies, coordinated a Drug Effectiveness Review Project (DERP) with other organizations to compare the effectiveness and adverse event profiles of AEDs in the treatment of bipolar mood disorder, neuropathic pain, and fibromyalgia. The drug class review on AEDs (AED Review), which was one of a series of drug class reviews (<http://www.ohsu.edu/epc>), was released in draft form in December 2005, with the final report issued in April 2006.⁵ While a systematic review of a medication class can provide evidence to inform prescribers about appropriate and effective treatments, these complex and sometimes lengthy reviews are often not used by clinicians.

To assure that the best evidence regarding the use of gabapentin was widely disseminated using strategies likely to influence prescriber behavior, the legal settlement also included funds to develop a corrective national counter-marketing program. The purpose of the program is to provide fair and balanced information to prescribers about the use of gabapentin and other AEDs in the treatment of bipolar disorder. A contract was awarded to the University of North Carolina at Chapel Hill (UNC) in 2005. We describe here work undertaken by UNC to design and implement a corrective marketing plan to compete with efforts implemented by the pharmaceutical industry and to help clinicians, principally psychiatrists, make use of available evidence to

inform their prescription of AEDs in the treatment of bipolar disorder.^{6,7}

CLINICAL RELEVANCE

Making evidence-based information regarding the use of AEDs in the treatment of bipolar disorder more accessible and usable for prescribers should improve the quality of care and resulting outcomes among patients with bipolar disorder. The incidence of bipolar disorder is between 2 and 21 per 100,000; however, the prevalence is much higher due to its chronic and recurrent nature.⁸ These rates more than likely represent underestimates because the figures do not include institutionalized patients in prisons or jails; moreover, there is also evidence of underdiagnosis in certain ethnic populations (e.g., African-Americans).⁹ Individuals with bipolar disorder are usually identified in general medical settings when they present with depressive symptomatology. However, long-term management typically occurs in a mental health setting by a psychiatrist or other mental health specialist. Studies have reported that this transition from general practice to psychiatric care can take over 10 years and may involve visits to more than four clinicians between onset of the first symptoms and the diagnosis of bipolar disorder.⁹ This is a seriously mentally ill population, in whom use of evidenced-based practices can improve screening and appropriate treatment and promote better care.

While efficacious treatments are available for bipolar disorder, symptom recurrence/relapse and non-response to treatment remain a problem, and long-term remission rarely occurs. This pattern of illness is due in large part to the chronic, episodic, and phasic patterns of the illness, which necessitate very complex treatment strategies. Without appropriate treatment, these patients experience functional impairment and an increased risk of morbidity and mortality. Appropriate treatment for bipolar disorder is multifaceted and addresses acute mania, depression, and maintenance. In an effort to treat acute symptoms and reduce their recurrence, many clinicians use combination therapy involving multiple agents rather than a single antimanic agent. Many evidence-based treatment guidelines for bipolar disorder include use of multiple medications in their recommendations and suggest the use of antipsychotic, antidepressant, and antiepileptic drugs.^{8,10,11} Not all drugs within these classes are included in the treatment algorithms, since researchers have not demonstrated the equivalency of all drugs in these classes. Maximizing the quality of medication use in patients with bipolar disorder can

reduce both acute symptoms and recurrence, improve patients' quality of life, and enhance the effectiveness of other treatments (e.g., psychotherapy) used in combination with pharmacotherapy.

Evidence is mixed concerning degree of adherence to treatment guidelines for bipolar and other psychiatric disorders within general clinical and mental health practices. In a 1998 study of adherence to American Psychiatric Association guidelines for depression, Banks et al. reported only 59% compliance; however, this study also showed that there were fewer hospitalizations among patients who did receive care according to guidelines.¹² Lehman and Steinwachs reported a wide range of adherence (9%–97%) to the Patient Outcomes Research Team (PORT) guideline for schizophrenia in both acute inpatient and continuing outpatient programs. This variation in adherence fell short of what would be recommended for treatment efficacy.¹³ The use of the PORT guidelines for schizophrenia was assessed again in 1998 by Young et al. in a VA community mental health setting, in which 38% of patients were found to have poor medication management through nonadherence to guideline treatment.¹⁴ These findings concerning variations in practice in the mental health environment warrant continued research involving the implementation of intense and diverse dissemination strategies, followed by subsequent testing of their effects.

PURPOSE OF THE NATIONAL DISSEMINATION ACTION PLAN

Researchers at the UNC Sheps Center for Health Services Research and their collaborators at UNC and at the Research Triangle Institute International (RTI) were awarded a contract in 2005 1) to create derivative products based on the final AED Review and the results of formative market research with relevant audiences, 2) to develop and implement a national dissemination strategy for the derivative products, and 3) to cooperate and assist in evaluating dissemination of the derivative products. A logic model was developed to describe plan inputs, the use of expert advice and audience research to drive product design and national dissemination strategies, and expected impacts such as changes in prescriber behavior (Figure 1).

INPUTS

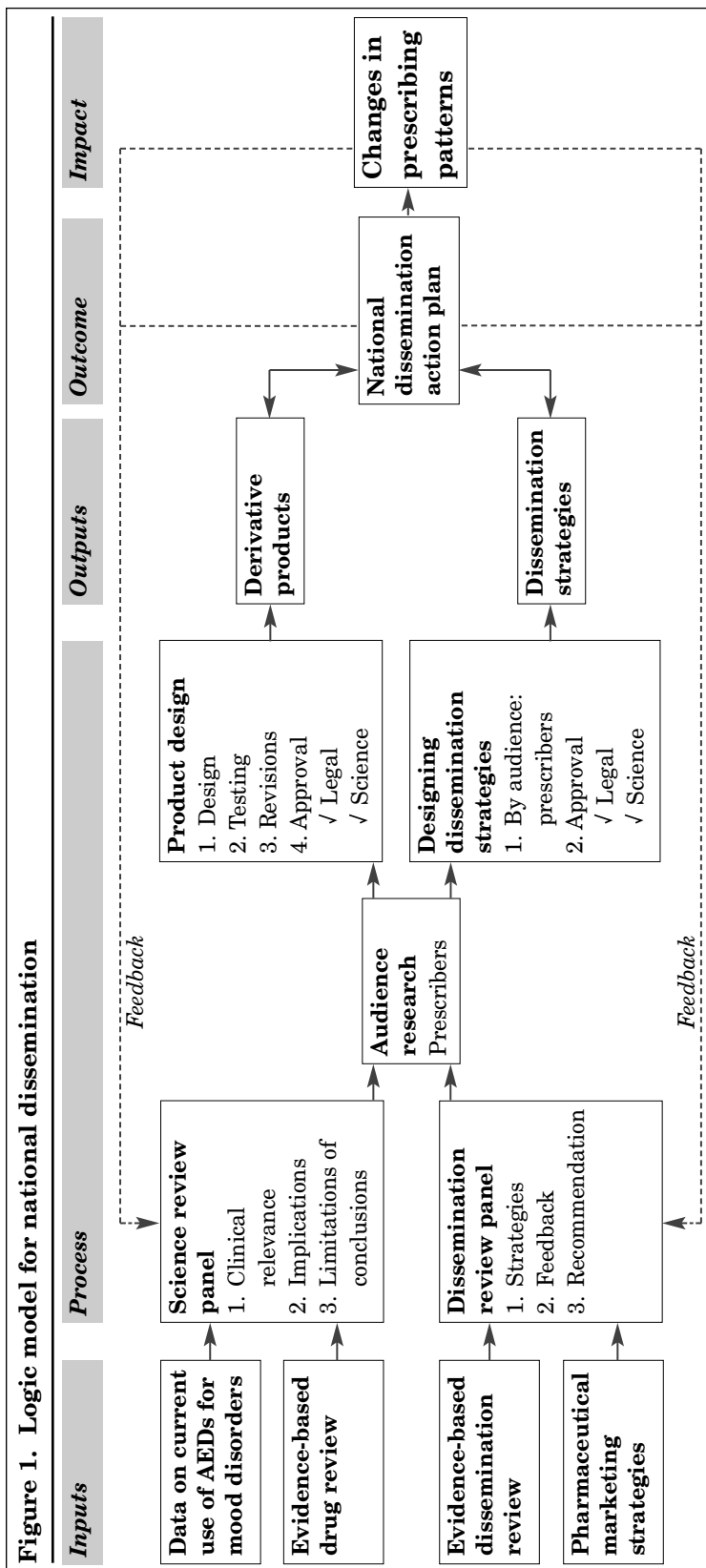
We identified four key inputs (Figure 1) for designing strategies for the national dissemination action plan:

1. Current data on prescribing patterns for AEDs, especially for bipolar disorder
2. The drug effectiveness report and subsequent updates of relevant literature
3. A review of the literature, including systematic reviews on evidence-based dissemination strategies
4. Pharmaceutical marketing strategies, based on recent publications of industry practices discovered in the legal suit.

Current Prescribing Patterns

In order to properly target key messages regarding prescription of AEDs for patients with bipolar disorder, we needed to identify the specialties prescribing these drugs to patients with bipolar disorder. We anticipated that the majority of prescriptions of AEDs for bipolar disorder would be written by psychiatrists, the specialty responsible for use of medication to treat patients with serious mental illness. However, some mental illnesses are also treated by other specialties, especially primary care physicians, family physicians, general internists, and general practitioners. This is especially true for conditions such as anxiety disorders and major depressive disorder, where primary care providers may initiate treatment and continue to manage the case. We therefore estimated the magnitude of AED use for bipolar disorder among primary care providers using two sources, the National Ambulatory Medical Care Survey (NAMCS) and the Medical Expenditure Panel Survey (MEPS).

NAMCS. The NAMCS, which is administered by the Centers for Disease Control and Prevention, involves random sampling of office-based healthcare providers on a nationwide basis. The sampling is stratified, so that the number of visits for each condition to each specialty can be estimated. Providers record each visit, documenting the reasons for the visit and treatments and consults recommended. NAMCS thus gives nationally representative estimates of the nature of problems seen by various providers, including psychiatrists and primary care providers. We examined NAMCS databases from 1999–2003 and found that the number of patients with bipolar disorder in the database for each year gradually increased, from 151 in 1999 to 237 in 2003, possibly reflecting increasing recognition of this disorder by providers. Of those patients diagnosed with bipolar disorder, a majority were receiving an AED. The proportion of bipolar patients prescribed an AED varied somewhat depending on the type of coding system used (drug class



code vs. generic), but the estimates were generally similar, ranging from 52% to 58% in the 2003 sample, for example, and these trends were consistent over time. The sample size was too small to allow examination of regional variation. We next examined the specialties of physicians treating individuals with bipolar disorder who were also taking an AED. Although the number of patients sampled in any one of the 5 years was modest (ranging from 84 to 138), the data were consistent over time. In 2003, only 5% of bipolar patients were prescribed an AED by a family physician, internist, or general practitioner. In 2002 the proportion was 6%, in 2001 2%, in 2000 6%, and in 1999 8%. No trend towards an increase in the proportion of visits over time in primary care was seen. The estimates for each year are likely unstable given that the number of observations of visits to internal medicine or family practice in some years was low (fewer than 5 visits). The relative consistency of estimates over time, however, indicates that the use of AEDs for bipolar disorder in primary care is relatively uncommon compared to use of these agents by psychiatrists.

MEPS. The MEPS, the second data source we examined, is a national probability sample of individuals. It differs from the NAMCS in that over 30,000 people from approximately 12,000 households are sampled. We examined individuals in MEPS from 2002 and 2003 with a self-reported diagnosis of bipolar disorder. There were sufficient differences in the coding for type of physician seen in previous years compared with the 2002–03 years that we were not confident in the comparability of recent to earlier data, and therefore we restricted our analysis of the MEPS data to those 2 years. There was partial overlap in subjects from 2002 to 2003, since the MEPS cohort is only partially replaced from year to year. Slightly over 200 patients with bipolar disorder were identified in 2002 and 183 in 2003. From these subjects, we identified a subset of individuals with bipolar disorder who were taking one of the AEDs, excluding patients with seizure disorder. We then examined care patterns among these individuals. The MEPS data allowed us to assess the full range of providers who provided care to the subjects over each year, and many of the patients saw multi-

ple providers, including psychiatrists, primary care providers, psychologists, and other specialists. We found that, of the patients with bipolar disorder who were taking AEDs, only 14% in 2002 and only 15% in 2003 did not see a psychiatrist. Only 5% of patients in each study year saw a primary care provider without also seeing a psychiatrist; 5%–7% of patients saw a psychologist during the year, but most of these individuals also saw a psychiatrist. Note that the MEPS data would not identify prescriptions provided by phone with no ambulatory visit, or prescriptions provided through the emergency room or after an inpatient hospitalization.

Summary. The conclusion from these analyses is that, among individuals with bipolar disorder, the very large majority of AED prescriptions are written by psychiatrists. While primary care providers do see patients with bipolar disorder, these patients are generally also seeing a psychiatrist, which supports the published evidence on pharmacotherapy in this population.

Drug Effectiveness Review for AEDs

The AED Review was conducted to compare the effectiveness and adverse event profiles of AEDs in the treatment of bipolar mood disorder, neuropathic pain, and fibromyalgia.⁵ We focus here only on dissemination of findings related to AED use in bipolar disorder. Three key questions were addressed by the AED Review:

1. Do AEDs differ in effectiveness for adult patients with bipolar disorder?
2. Do AEDs differ in safety or adverse events in adult outpatients with bipolar disorder?
3. Are there subgroups of patients with bipolar disorder for which one AED is more effective or associated with fewer adverse events based on demographics (e.g., age, race, gender), other medications being taken, or comorbid conditions?

As part of the AED review, articles relevant to the key questions were located on the Cochrane Central Register of Controlled Trials and the Database of Reviews of Effects (DARE), Medline/Pubmed (1966–2005), and Embase (1974–2005). While most of the studies in the review were conducted in outpatients, some of the studies involved patients with acute disease who were hospitalized for initiation of therapy. Both internal and external validity were assessed to determine the quality of the study reports. Grading of quality was done by using the standards outlined by the U.S. Preventive Services Task Force and the U.K. National

Health Service Centre for Reviews and Dissemination. Trials that had substantial shortcomings in their methodology were rated as “poor” quality and were not discussed in the effectiveness review. More information about the process and updated reports can be found at <http://www.ohsu.edu/drugeffectiveness/reports/final.cfm> or <http://www.prescribingforbetteroutcomes.org>.

The Science Panel for this project then summarized findings from the April 2006 AED Review on effectiveness and adverse event profiles of AEDs for use in adults with bipolar I and II mood disorder into key concepts and messages for dissemination. Table 1 presents an abbreviated summary of these Key Concepts (for a full summary see Carey et al.¹⁵ p. 28 or visit www.prescribingforbetteroutcomes.org). Along with dissemination of these Key Concepts and evidence-based findings from the AED Review, the four Key Messages shown in Table 2 will be delivered to prescribers.

Strategies to Improve Prescribing Practice

Results of studies that measure the impact of interventions designed to improve prescribing practices have been mixed. In their review of 51 published articles from 1988 through 1997, Figueiras et al. found that, even among the 8 studies with a high degree of evidence, only one demonstrated positive results from active interventions (e.g. group education, individual outreach visits).¹⁶ Majumdar and Soumerai¹⁷ suggested that the literature cited in this and other recent systematic reviews^{18,19} is plagued by the absence of common nomenclature, inadequate study designs, too short time horizons, and a focus on process rather than outcome.¹⁷ Despite these limitations, they suggested that three generalizations could be drawn from these systematic reviews:

- Interventions that rely solely on passive information transfer are relatively ineffective. This includes disseminating articles and delivering traditional lectures in CME, as well as providing unsolicited information such as clinical guidelines, medication profiles, or drug use reviews.
- Active knowledge translation strategies, such as audit and feedback involving comparison with peers and “real time” reminders, are usually effective, although the effects are modest. Educational outreach or academic detailing involves a number of principles, the purpose of which is to engage individual clinicians in activities designed to increase their awareness and use of specific products or interventions. It is the intervention that is most consistently reported to be effective in changing clinician pre-

Table 1. Summary of key concepts from the Drug Effectiveness Review Project Report on antiepileptic drugs (AEDs) for bipolar disorder

1. Current evidence supports the conclusion that three AEDs (carbamazepine, valproic acid/valproate, and lamotrigine) are efficacious in maintaining remission for adult outpatients with primary diagnoses of *bipolar I disorder with recent mania or mixed episodes*.
2. Current evidence provides only modest support for the efficacy of carbamazepine, valproic acid/valproate, and lamotrigine in achieving and maintaining remission in adult outpatients with *bipolar I disorder with a recent depressive episode or bipolar II disorder*.
3. Efficacy of these agents in maintaining remission is generally based on the percentage of patients who do not experience symptomatic recurrence or prematurely discontinue study treatment because of symptoms.
4. Carbamazepine, valproic acid/valproate, and lamotrigine appear to have similar magnitudes of benefit in inducing remission, although the risk of recurrence is substantial for all agents. These conclusions should be considered tentative because the magnitudes of benefit in inducing remission were based on indirect comparisons.
5. The rates of achieving and maintaining remission during treatment with carbamazepine, valproic acid/valproate, and lamotrigine are similar to those obtained with lithium treatment for *bipolar I disorder*. For adult outpatients with acute mania, carbamazepine and valproate were similar, relative to lithium, in terms of response rates.
6. The overall risk of adverse events resulting in medication discontinuation is similar among carbamazepine, valproic acid/valproate, and lamotrigine, and the overall risk of adverse events for AEDs is similar to that for lithium across all clinical subtypes of bipolar disorder. However, the types of adverse events encountered differ among the three AEDs and lithium.
7. The risk of suicide or suicide attempt is present in bipolar disorder. Compared with placebo, patients treated with AEDs for psychiatric conditions may have a small increase in suicidal ideation (<http://www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm>).
8. There is some evidence (although not extensive) showing that gabapentin is no more, and perhaps less, efficacious than placebo in the treatment of bipolar I disorder with recent mania and rapid cycling bipolar disorder. No acceptable evidence was found to support the use of gabapentin in achieving remission or preventing relapse in bipolar disorder.
9. The available evidence regarding the potential differential efficacy among AEDs in the treatment of patients with rapid cycling and other patient subgroups is extremely limited. Available evidence does not allow prediction of which patient subpopulations will respond to any given AED.
10. Little evidence is available regarding differential efficacy of the three AEDs in subpopulations defined by gender, age, ethnicity, or comorbidity.

scribing and other behaviors. The principles underlying educational outreach and academic detailing are listed in Table 3.

- Multifaceted interventions that incorporate two or more distinct strategies are more likely to work than single interventions.¹⁷

In spite of these cautionary findings, we know from observation that prescribers do change their prescribing behavior. Pharmaceutical companies and others have been successful in their endeavors to bring this about,

using a variety of methods. A recent Cochrane Review on the effect of educational outreach or academic detailing on professional practice and healthcare outcomes concluded that, when outreach visits are combined with additional interventions, they appear to have effects on prescribing that are small to modest, but still potentially important.²⁰ The review examined six studies that evaluated different types of visits in head-to-head comparisons.²⁰ When individual visits were compared to group visits, results were mixed. While in-person visits are effective, they are also quite expensive. When in-per-

Table 2. Key Messages about antiepileptic drugs (AEDs) derived from AED Key Concepts (Table 1)*

<i>Key Messages</i>	<i>Refers to Key Concept #</i>
1. There remains no scientifically acceptable clinical trial evidence which supports use of either gabapentin or topiramate in bipolar mood disorder, either as monotherapy or as an adjunct to other therapies.	8
2. Research supports the use of three AEDs—1) carbamazepine, 2) valproic acid/valproate, and 3) lamotrigine—in achieving and maintaining remission for adult outpatients with primary diagnoses of bipolar I disorder. Evidence of efficacy is less clear for these treatments for bipolar II disorder.	1, 2, 3, 4
3. Carbamazepine, valproic acid/valproate, and lamotrigine work as well as lithium in achieving and maintaining remission in bipolar I disorder, but the strength of the evidence supporting this conclusion is low, and additional research is needed to clarify the relative roles of these agents in bipolar disorder.	5
4. The types of adverse events vary among AEDs and lithium. There is insufficient evidence to determine if the overall risk of adverse events differs among AEDs. Unlike the AEDs, lithium poses a significant risk when taken in an overdose.	6, 7

**Key Concepts 9 and 10 refer to specific subpopulations that are not included in the Key Messages.*

son or in-office visits are not feasible, the next most effective approach to changing clinician behavior is the concurrent or phased implementation of multiple interventions that reinforce the principles of pharmaceutical detailing (Table 3).²¹

The literature also identifies potentially significant barriers associated with changing prescribing behavior. These barriers may occur at a variety of levels, including structural (e.g., financial disincentives), organizational (e.g., inappropriate skill mix, lack of facilities or equipment), peer group (e.g., local standards of care not in line with desired practice), individual (e.g., knowledge, skills, information overload within busy consultations leading to acts of omission or error), and patient expectations (e.g., created by direct-to-consumer pharmaceutical advertising).²² Even with these barriers, it is possible to successfully change provider behavior by employing active dissemination approaches such as those outlined above.

In conclusion, passive dissemination strategies, such as conferences or mailing unsolicited educational materials, while potentially important for increasing awareness, have little impact, while academic detailing (e.g., educational outreach) in combination with additional interventions such as performance audit and feedback, sometimes with financial incentives, reminder systems (e.g., flowsheets, stickers, and checklists), and participa-

Table 3. Principles of pharmaceutical detailing²¹

Defining specific problems and objectives
Establishing credibility
Involvement of “opinion leaders”
Promoting active learner involvement
Brief graphic print materials
Market research
Targeting “high-potential” physicians
Two-sided communication
Repetition and reinforcement
Offering practical alternatives

tory CME are moderately effective in changing prescribing behavior.^{17,22,23}

Pharmaceutical Marketing Strategies

A growing body of literature describes industry marketing practices designed to influence prescriber behavior. Steinman et al.¹ used documents discovered in the suit against Warner Lambert to report on pharmaceutical

marketing strategies to promote the AED gabapentin. Warner Lambert used strategies such as physician speakers promoting off-label use of gabapentin through CME events, advisory board and consultant meetings at which physicians would participate in informal information gathering that amounted to Pfizer “exploratory research,” and dissemination of prescription recommendations through a publication program that promoted off-label use. As stated in press releases from the National Association of Attorneys General and the U.S. FDA, the methods used by Warner Lambert to deceptively promote gabapentin for off-label uses included many strategies that would be considered “best practice” based on dissemination literature. They included CME classes that included providing “perks” to attending physicians, a publication strategy, financial incentives for use of gabapentin, providing information to a drug reference compendium, one-on-one sales pitches to physicians, and use of scientific experts. The use of these dissemination strategies did not constitute deceptive “off-label” marketing practice but the content of the materials presented as part of these strategies did. For example, CME classes lacked fair balance and misrepresented the nature of the CME while providing expensive “perks” to attending physicians; a “publication strategy” subsidized the production and dissemination of anecdotal reports favorable to “off label” use of gabapentin and were of no scientific value; payments were made to prescribers for “research” that was, in effect, a kickback for “off-label” prescribing; and incomplete information about gabapentin was provided to the drug reference compendium known as Drugdex.² These effective industry marketing tactics suggest that use of competing approaches utilizing the same underlying strategies—delivery of highly credible information from trusted sources—can inform prescriber knowledge and prescribing practice.

We decided to use social marketing dissemination strategies, specifically counter-marketing to industry strategies, to increase the use of evidence-based prescribing of AEDs for bipolar disorder. Andreasen²⁴ defines social marketing as “the application of proven concepts and techniques drawn from the commercial sector to promote changes in diverse socially important behaviors such as drug use, smoking, and sexual behavior. This marketing approach has an immense potential to affect major social problems if we can only learn how to harness its power....” Recent research has shown that social marketing strategies can be highly effective in changing discrete behaviors, especially when messages are targeted for specific populations. Snyder and Hamilton²⁵ reviewed recent mass media campaigns in the United States and

found that the average campaign accounted for 9% of favorable changes in health risk behavior. Among the most effective classes of campaigns have been tobacco control counter-marketing campaigns aimed at preventing and controlling youth smoking through use of commercial (often industry inspired) marketing strategies.^{7,26} “Non-coercive” campaigns (simply delivering health information) accounted for about 5% of the observed variation in behavior. Grilli et al.²⁷ studied 17 recent European campaigns on several topics (e.g., HIV, nutrition) and found that behaviors that require a one-time change or only a few changes are easier to promote, show greater effect sizes, and result in longer term maintenance than those that must be repeated and maintained. Snyder and Hamilton²⁵ and Evans et al.⁷ reviewed the effectiveness of social marketing in healthcare settings, as a strategy both to influence physician behavior and to reach patients through physicians (mediated communication), and concluded that there are substantial opportunities to translate proven effective applications of social marketing of public health to healthcare settings.

Summary

Our consideration of inputs helped us to identify psychiatrists as our primary target audience, key concepts and messages based on available evidence concerning the use of AEDs for bipolar disorder, and alternative and evidence-based approaches to consider as a basis for our national dissemination action plan to counter industry marketing of gabapentin for the treatment of bipolar disorder.

METHODS

The process of preparing our national dissemination action plan included consideration of expert advice on the clinical relevance, limitations, and implications of our evidence base and the feasibility and likelihood of success associated with use of proven dissemination strategies as well as the perceptions, knowledge, and attitudes of our primary target audience of psychiatrists. This expert advice and audience research have driven our product design and our choice of dissemination strategies for those products.

Expert Advice

We supplemented our knowledge of dissemination strategies and evidence-based practice by establishing

an expert Science Panel to advise us on clinical issues related to product development and dissemination and an expert Dissemination Panel to advise us on how to develop and implement an evidence-based dissemination strategy for select audiences. The Science Panel consists of key opinion leaders with expertise in the treatment of bipolar disorder and drug-effectiveness reviews; members of the panel were drawn from the practices of psychiatry, internal medicine, and pharmacy. The Science Panel is chaired by Dr. Tim Carey, an internist and director of the Sheps Center at UNC. Members include John Oldham, MD, MS, psychiatrist (Menninger Clinic), John Williams, MD, MHS, internist (Duke University), Francine Goodman, PharmD, clinical pharmacy specialist (Veterans Administration Health System), and Cathy L. Melvin, PhD, MPH (Sheps Center at UNC). Their work to distill the AED Review and other related literature into key concepts and messages was briefly reviewed above and has been described in more detail elsewhere (p. 28¹⁵).

The Dissemination Panel is chaired by Dr. Cathy Melvin (Principal Investigator for the AED Project and researcher on health services and dissemination). Members include W. Douglas Evans, PhD (communications specialist), Gary Kreps, PhD (health communications researcher), Thomas Linden, MD (national medical journalist), John Oldham, MD, MS (psychiatrist and psychiatric faculty), and Leah Ranney, PhD (Study Director for the AED Project). Panel members have published extensively on a wide range of topics such as protection of persons with mental disorders from research risk, the effects of social marketing on behavior change, and communicating harm and benefits to vulnerable populations. The work of the Dissemination Panel is described later in this article.

Members of both panels, including the UNC investigators, are “conflict free,” having accepted no funding from the pharmaceutical industry in the 2 years prior to their appointment to the panel.

Audience Research

Audience research was conducted in mid to late 2007 to drive the design of derivative products and strategies for widespread dissemination to prescribers. The principal findings of this research, which are described in detail elsewhere, (p. 35),²⁸ were the following:

1. Psychiatrists report knowing about the suit brought by the attorneys general regarding the off-label marketing of gabapentin.

2. While they prescribe AEDs for off-label use, psychiatrists report not using gabapentin as a primary treatment for bipolar disorder.
3. Psychiatrists obtain their information about AEDs from professional journals, colleagues, and pharmaceutical representatives.

As part of the audience research, the sample of psychiatrists reviewed the four key messages developed by our Science Panel and identified misconceptions about the efficacy of the draft messages as they were written. The wording of the messages was then revised based on this participant feedback, although their content remained entirely consistent with the key findings from the AED Review and other evidence.^{15,28,29}

Development of Product Design and Dissemination Strategy

Based on input from the Science Panel and from literature on proven approaches for changing clinician prescribing behavior, the Dissemination Panel undertook the following actions:

1. Identified efficacious approaches for reaching clinicians, whether psychiatrists or not, and influencing their prescribing behavior
2. Recommended specific strategies for reaching psychiatrists
3. Worked with the Science Panel to review findings from concept testing focus groups with psychiatrists and use those findings to assure accurate and informative wording of the ten key concepts and four key messages³⁰
4. Provided feedback and comment on product design to assure suitability for widespread dissemination
5. Assisted in the development of information and tracking systems to document the dissemination process.

To jump start the development and implementation of a national dissemination action plan, the Dissemination Panel met in Washington, DC in July 2007 with the UNC and RTI research teams. They reviewed additional findings from our audience research on psychiatrists' preferences for receiving and reacting favorably to information on prescribing. The panel decided, as a first line strategy, to increase awareness about the evidence on prescribing AEDs for bipolar disorder among psychiatrists by targeting their usual and preferred sources of prescribing information: newsletters, journals, conferences, and websites. To assure that evidence-based

information was widely available to psychiatrists and that this information reached large numbers of them as quickly and efficiently as possible, our dissemination strategies focused on three target audiences:

1. Thought leaders, or those individuals in organizations perceived as credible sources of psychiatric information
2. Psychiatric residency program directors given their role in recruiting and training psychiatrists and in designing psychiatric curricula and other learning activities
3. Psychiatrists in general since psychiatrists rely on consultation with each other in making decisions about prescribing.

For each of these audiences, the panel identified specific communication channels and vehicles of dissemination (Table 4). A preliminary plan was developed to explore the possibility of reaching specific targeted organizations, including the American Psychiatric Association, the American College of Psychiatrists, the American Association of Chairs of Departments of Psychiatry, the American Association of Community Psychiatrists, and the American Association of Directors of Psychiatric Residency Training. The panel adopted a strategy of providing information tailored to each audience and appropriate for inclusion in each vehicle used by that audience to assure the availability of consistent evidence-based information concerning prescribing of AEDs for bipolar disorder wherever an individual psychiatrist might go for information.

Recognizing that providing this information was necessary but not sufficient for widespread adoption of evidence-based prescribing of AEDs for bipolar disorder, the Dissemination Panel focused on the following activities: establishing the UNC project as a credible and unbiased source of evidence on prescribing AEDs for bipolar disorder; publicizing the availability of options to learn about the role of AEDs and other medications in the treatment of bipolar disorder; and offering ongoing sources of information and support for psychiatrists and other clinicians. To achieve those goals, the panel recommended the development of five specific products:

<i>Audience</i>	<i>Channels of dissemination</i>	<i>Vehicles of dissemination</i>
Thought leaders	American Psychiatric Association (APA)	Membership list Website Publications (<i>FOCUS/Psychiatric News</i>) Conferences Online CME
Thought leaders	American College of Psychiatrists (ACP)	Website Newsletter Annual meetings
Thought leaders	American Association of Chairs of Departments of Psychiatry (AACDP)	Public membership list Website
Thought leaders	American Association of Community Psychiatrists	Website Offers online CME Conferences Newsletter
Residency Program Directors	American Association of Directors of Psychiatric Residency Training (AADPRT)	Publications (journal/newsletters) Website Annual meetings
Psychiatrists	<i>Psychiatric Times</i>	Journal publication
Psychiatrists	<i>Psychiatric News</i>	APA biweekly newspaper
Psychiatrists	<i>Clinical Psychiatry News</i>	Monthly newsletter

1. Journal supplement to inform target audiences
2. *Prescribing for Better Outcomes* website
3. Exhibit panel board to promote the website and other products at major conferences and meetings of psychiatrists
4. Interactive CME program offered through the *Prescribing for Better Outcomes* website
5. Press release and media event to simultaneously launch the *Prescribing for Better Outcomes* website and announce publication of the journal supplement.

The content of these products will focus on how to review evidence objectively and identify evidence-based sources of information. Suggestions from our audience research with prescribers included providing information on the use of AEDs for bipolar disorder as well as information about the FDA approved uses of gabapentin and other AEDs. Another suggestion was to add a personal tone to our messages by, for example, creating scenarios to illustrate the key messages, having a frequently asked questions (FAQ) page, and conducting

key informant interviews with credible sources such as members of APA guideline working groups. It was also suggested that the *Prescribing for Better Outcomes* website could provide tips on how psychiatrists can help educate residents and other trainees on how to make good prescribing decisions and how psychiatrists can communicate with other health professionals wanting to prescribe appropriate medications. The content of the messages will also stress an aspect of our work that the psychiatrists in our audience found particularly valuable, which was the focus on providing fair and balanced scientific review of the evidence that is not associated with or influenced, either directly or indirectly, by the pharmaceutical industry. By providing unbiased summaries of available evidence, we hope to move psychiatrists and other prescribers away from their reliance on pharmaceutical detailing or, at least, to make them more aware of the inherent biases present in such detailing.

To achieve that goal, the Dissemination Panel also recommended that, after the publication of this *Journal of Psychiatric Practice* supplement, a number of reinforcing events and products for dissemination be implemented for each of the target audiences listed in Table 4. A copy of this supplement will be mailed to approximately 38,000 psychiatrists, including those listed as members of the following organizations: American Psychiatric Association, American Psychiatric Association Residency Training Directors, National Association of State Mental Health Program Directors, and the American Association of Chairs of Departments of Psychiatry. We plan to exhibit at the annual meeting of as many of the organizations listed in Table 4 as possible, to submit abstracts for symposia at annual meetings, to prepare and submit articles on the clinical implications of our key messages for inclusion in routine correspondence (i.e., journals, newsletters, and newspapers) to members of each psychiatric professional organization, and to publicize the CME and offer targeted technical assistance to those requesting further information or assistance in interpreting our key messages for their clinical practice and/or educational efforts.

Assessing Impact

To assess our success in reaching our target audiences, we plan to focus on specific primary and intermediate outcome indicators. The primary outcome is the proportion of psychiatrists who prescribe AEDs inappropriately. Intermediate outcome measures include exposure and reaction to counter-marketing information (e.g., recall of information or confirmed awareness, ratings of

information, persuasive appeal and message receptivity, recall of receipt, frequency of reading, frequency of accessing Internet materials, reactions to materials, use of suggestions in materials), and attitudes and beliefs (e.g., ratings of information provided by pharmaceutical companies, ratings of pharmaceutical industry, depth of knowledge) (Table 5). The primary sources of data to inform these measures will include surveys or focus groups of psychiatrists, national survey data such as the MEPS and the NAMCS, web hits and downloads, and completed CME.

CONCLUSIONS

In this article, we have described an evidence-informed approach to developing a national dissemination plan for drug class review. Since evidence from drug class reviews is often not accessible to clinicians or presented in a way that allows clinicians to use that evidence-based information to guide treatment and prescribing decisions, dissemination of these findings must include a process for distilling this information into more concise messages,¹⁵ evaluating audience perceptions,²⁸ and creating an evidence and audience-informed dissemination plan. The process we used involved developing counter-marketing strategies that were intended to compete with those implemented by the pharmaceutical industry to help clinicians, principally psychiatrists, make use of available evidence to inform their prescribing of AEDs, including gabapentin, in the treatment of bipolar disorder.^{6,7} Our logic model describes inputs and processes designed to create a dissemination plan using what we currently know about effective industry marketing tactics. We used evidence from systematic reviews, including the drug class review, industry marketing documents, national data on prescribing practices, and audience research to develop accurate and convincing messages and materials and to disseminate them nationally to counter industry misinformation and promote evidence-based prescription of AEDs. These products and strategies are designed to match the critical principles underlying pharmaceutical detailing: defining specific problems and objectives through market research, establishing credibility by targeting “high potential” psychiatrists, involving opinion leaders in two-sided communication, promoting active learner involvement through repetition and reinforcement, and supplying brief, graphic print and alternative materials. We also described measures to be used to assess our success in reaching and informing our target audience of practicing psychiatrists. This evidence-informed process

Table 5. Potential intermediate and outcome measures

<i>Measure</i>	<i>Rationale</i>
<i>Exposure and reactions to counter-marketing information</i>	
Recall of message information (confirmed awareness)	Ability to corroborate exposure to counter-marketed information, to be related to changes in drug-related attitudes and dispensing practices
Ratings of information	Assess reactions to and believability of counter-marketed message information
Persuasive appeal and message receptivity	Assess persuasive process through which counter-marketed messages affect social cognitions; based on elaboration likelihood model (e.g., argument credibility, argument rationality, source credibility)
<i>Access and use of consumer marketing information</i>	
Recall of receipt Frequency of reading Frequency of accessing booster material Internet website Reactions to materials Use of suggestions in materials	Exposure to booster materials will enhance knowledge, increase recall, and reinforce counter-marketed messages
<i>Attitudes and beliefs</i>	
Ratings of information provided by pharmaceutical companies	Assess reactions and believability of information from pharmaceutical companies
Ratings of pharmaceutical industry	Assess attitudes and beliefs about the pharmaceutical industry
Items to form a scale of knowledge of the appropriate use of AEDs based on evidence-based review (e.g., AEDs are more efficacious in treating bipolar I disorder with recent mania than bipolar I disorder with a recent depressive episode.)	To assess awareness of appropriate AED use guidelines and knowledge of evidence on the appropriate use of AEDs

can serve as a model for others who are interested in translating drug class and other systematic reviews into clinically relevant, actionable messages, materials, and processes for changing clinician behavior.

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