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PRIORITIZING FUTURE RESEARCH ON OFF-LABEL PRESCRIBING: RESULTS OF A QUANTITATIVE EVALUATION

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Abstract

Background—Drug use for indications not approved by the Food and Drug Administration exceeds 20% of prescribing. Available compendia indicate that a minority of off-label uses are well supported by evidence. Policy makers, however, lack information to identify where systematic reviews of the evidence or other research would be most valuable.

Methods—We developed a quantitative model for prioritizing individual drugs for future research on off-label uses. The base model incorporated three key factors, 1) the volume of off-label use with inadequate evidence, 2) safety, and 3) cost and market considerations. Nationally representative prescribing data were used to estimate the number of off-label drug uses by indication from 1/2005 through 6/2007 in the United States, and these indications were then categorized according to the adequacy of scientific support. Black box warnings and safety alerts were used to quantify drug safety. Drug cost, date of market entry, and marketing expenditures were used to quantify cost and market considerations. Each drug was assigned a relative value for

each factor, and the factors were then weighted in the final model to produce a priority score. Sensitivity analyses were conducted by varying the weightings and model parameters.

Results—Drugs that were consistently ranked highly in both our base model and sensitivity analyses included quetiapine, warfarin, escitalopram, risperidone, montelukast, bupropion, sertraline, venlafaxine, celecoxib, lisinopril, duloxetine, trazodone, olanzapine, and epoetin alfa.

Conclusion—Future research into off-label drug use should focus on drugs used frequently with inadequate supporting evidence, particularly if further concerns are raised by known safety issues, high drug cost, recent market entry, and extensive marketing. Based on quantitative measures of these factors, we have prioritized drugs where targeted research and policy activities have high potential value.

Keywords

off-label; drugs; FDA

Introduction

The United States (US) Food and Drug Administration (FDA) drug approval process requires clinical trials that demonstrate efficacy for an indication prior to marketing. Once approval is given, however, the FDA does not regulate whether drugs are prescribed for “off-label” indications.

Prior studies of off-label prescribing have focused on psychiatric disorders,^{1,2} bacterial infections,³ children,^{2,4} and “orphan” clinical conditions.^{5,6} These studies have demonstrated that off-label use is frequent, and that there is substantial variation in the evidence supporting such uses. The studies also identified disease- and patient-specific situations where off-label use may be beneficial.

Three prior studies have examined off-label use among more general patient populations in the US. Strom and others examined the 100 most common uses of marketed medications and found 31 indications that were not approved by the FDA.⁷ The Knight-Ridder news services estimated that 21% of prescription drug use in 2002–2003 and 22% in 1997–1998 was off-label by indication.⁸ Rates of off-label use varied widely across drug classes and were highest among anticonvulsants (74%), antipsychotics (60%), and antibiotics (41%). Radley and colleagues examined the frequency and uses of off-label prescribing for common medications as a function of the strength of scientific support for those uses.⁹ Of the estimated 21% of drugs uses that were off-label, 73% of these did not have good scientific support. Although several drug classes, including anticonvulsants, antipsychotics, and antibiotics, were associated with a higher frequency of off-label use, other drug characteristics such as manufacturer, and annual sales levels did not predict the likelihood of off-label prescribing. Collectively these studies highlight both the frequency of off-label drug use and lack of evidence supporting such prescribing.

Given that additional evidence on certain off-label drug uses is needed, we sought to develop a method for prioritizing future research based on the concept of value of information.¹⁰ Generally, information is valuable when little is known regarding a decision,

and when that decision impacts a large number of people in a meaningful way. Our primary purpose was to consider multiple dimensions of off-label use (i.e., extent of use and quality of existing evidence supporting that use, safety, drug cost, extent of marketing, and time on market) to identify areas where future off-label research initiatives would be likely to have the greatest value.

Methods

We developed a model for identifying drugs that are used off label for which additional research should be conducted. A nine-member technical expert panel was used to guide the development of the model and subsequent analyses. The panel included representatives from the FDA, the health insurance industry, the pharmaceutical industry, and academia (see acknowledgments) with expertise in off-label drug use.

Based on our review of past research and consensus from our technical expert panel, we identified three key factors to include in our prioritization model. These factors were 1) the volume of off-label drug use with inadequate evidence supporting that use, 2) the safety of the candidate drug, and 3) a composite factor representing cost, recency of market entry, and degree of promotion/marketing. This final factor was included as a composite because it was believed that cost, recency of market entry, and degree of promotion may be correlated and that including each separately might bias the model.

For each of the key factors above we created a quantitative relative index measure for inclusion in our prioritization model. Each drug was assigned a score for each of the three index measures. The scores were determined from objective data as described below.

Volume of Off-Label Prescribing with Inadequate Evidence

The first and most important factor in our model was volume of off-label prescribing with inadequate evidence. We used several data sources in a stepwise manner to measure this factor. First we quantified the volume of off-label uses for a specific drug using the National Disease and Therapeutic Index (NDTI) (IMS Health, Norwalk, CT).¹¹ Next we categorized the level of evidence for each drug-indication combination based on the Drugdex compendium (Micromedex, Greenwood Village CO).¹⁸ Based on the number of off label uses with inadequate evidence, a primary index representing the relative magnitude of such use (varying from 0.0 to 1.0) was constructed as the ratio of a particular drug's number of off-label uses with inadequate evidence to the drug with the greatest number of off-label uses with inadequate evidence. Each drug was scored on this index and that score was then included in our prioritization model. More detailed information on this process is provided below.

The NDTI is a physician survey that provides nationally representative diagnostic and prescribing information on patients treated by US office-based physicians. For each contact record, physicians record the medications used to treat any applicable diagnosis. The NDTI has been cross-validated against other national sources of information on outpatient practice.^{12,13} Using the data and information on labeled indications approved by the FDA, prescription uses were counted as off-label if the indication ICD-9 code did not match with

an FDA approved indication for the drug.^{14,15,16} We took a conservative approach in that if any indication was on-label as of June of 2007 it was considered as a labeled indication throughout the time period examined.

We also used the National Prescription Audit (IMS Health, Norwalk CT) to confirm that the most common drugs dispensed through pharmacies matched those reported by physicians at patient encounters in NDTI.¹⁷ These data provided national estimates of the volume of prescription orders received by pharmacies, physical prescriptions dispensed by pharmacies, and mean cost per dispensed prescription based on a national sample of approximately 25,000 retail, discount, and mail-order pharmacies.

To capture recent prescribing patterns, we analyzed 30 months of prescribing data (January 2005 through June 2007). This time period restriction was applied to all databases used in the study. We excluded children (age < 18 years) because of the distinctive nature of pediatric off-label use. We excluded vaccines, non-drug products (e.g., liquid nitrogen), and any medications available over-the-counter (whether or not a prescription formulation also was available). Finally, drug names were aggregated, so that generic and brand names for the same chemical entity administered by the same route were considered together.

For categorizing levels of existing evidence for each off-label use of a drug we used the Drugdex compendium, which contains readily available summaries of evidence-based information on both on- and off-label indications of specific drugs.¹⁸ Drugdex provides an assessment in three important evaluation dimensions: (1) efficacy (in four categories: “effective,” “evidence favors efficacy,” “evidence is inconclusive,” and “ineffective”), (2) strength of recommendation (in four categories: “Class I-recommended,” “Class IIa-recommended in most cases,” “Class IIb-recommended in some cases,” and “Class III-not recommended,” and (3) strength of evidence [in three graded categories: “A,” (good RCT evidence) “B,” (less consistent RCT evidence) and “C” (non-RCT forms of evidence)]. We used these three Drugdex evaluation dimensions to construct three ordinal levels of aggregate support for specific off-label indications. These were a) evidence-based off-label use, b) uncertain evidence base for off-label use, and c) inadequate evidence for off-label use. While similar to the algorithm of Radley,⁹ we sought to explicitly consider those indications where ambiguous evidence is available and therefore added the “uncertain evidence” category which we included in our sensitivity analysis. For some drugs we also used the US Pharmacopeia Drug Information (USP-DI) as an adjunct to Drugdex.¹⁹ USP-DI lists FDA approved indications, as well as “accepted” off-label uses.

Drug Safety

The presence of serious side-effects and/or drug-drug interactions was the second most important factor identified by our technical expert panel and included in our prioritization model. We used FDA safety warnings as means of quantifying serious side-effects and drug interactions. Again, an index from 0.0 to 1.0 was developed and applied to each drug. Specifically, a drug with an FDA black box warning was scored as 1.0 - for most concerning, those with other published safety alerts identified via the FDA Center for Drug Evaluation and Review website were scored as 0.5 - for moderately concerning, and drugs without black box warnings or safety alerts were scored as zero for this index.^{15,16}

Composite Measure of Cost, Recency of Market Entry, and Promotion

The final factor included in our prioritization model was a composite measure of drug cost, recency of market entry, and degree of drug promotion to consumers and physicians. For each of these factors we created a quantitative relative index measure (from 0.0 to 1.0) as described below.

Cost associated with off-label drug use was represented by the mean total cost of a single prescription of the medication.¹⁷ The ratio of a particular drug's prescription cost relative to the drug with the greatest cost formed the cost index (range 0.0 to 1.0). We measured recency of market entry by grouping drugs by years since first FDA approval (source: FDA website Orange Book, and FOIA report).^{20,21} Specifically, drugs approved within the past three years (based from 12/31/06) were coded as 1.0, drugs approved between 4–13 years as 0.5, and drugs approved over 13 years ago or available as generics coded as 0.^{20,21} Concerns about the intensity of drug promotion were represented by total expenditures on physician promotion plus expenditures on direct to consumer advertising.^{22,23} The ratio of a particular drug's total marketing expenditures relative to the drug with the greatest combined marketing expenditures formed the marketing index (range 0.0 to 1.0).

The scores for each component measure for each drug were assigned and then combined by taking an equal weighted average of the three components to create a single composite measure. Again, the reason for using the composite was to avoid the possibility of correlation between the three factors when used separately in our prioritization model.

Determination of Priority Scores and Priority Ranking

Priority scores and associated priority rankings of drugs were determined from a weighted model incorporating the three key factors described above: volume of use with inadequate evidence, safety concerns, and the composite of cost and market based characteristics. Note that each of these three key factor index scores is bounded between 0.0 and 1.0 and that any weighted average of these scores is also bounded between 0.0 and 1.0.

In our base analysis, we used a weighted average of the three scores with volume of use with inadequate evidence weighted at 0.5, safety at 0.25 and the combined cost and marketing factor at 0.25. We assigned the volume component a higher weight because it was considered by our expert panel as the most important factor in considering calculations of value of future research on off-label drugs. The underlying premise to ranking the drugs is that the value of research is proportional to the index score, so that drugs with a higher score are ranked higher in priority. Given that this was a ranking process, the relative levels of the scores are more important than the absolute levels for any drug.

To assess the robustness of the base case rankings we conducted sensitivity analyses by varying some of the fundamental assumptions used in assigning drug scores for the volume and evidence factor. The most important variation was to include the volume of off-label uses with both inadequate and uncertain evidence. We also examined a variety of priority lists based on alternative weighted combinations of the three primary indices described in the base model.

Results

There were 56,110 drug indication pairs, and a total of 1.8 billion reported drug uses with a mean number of 18 indications per drug in the NDTI data. Prescribing volume information from the IMS National Prescription Audit data verified that the NDTI data included all commonly prescribed medications. Table 1 shows the top 25 drugs in terms of total combined off-label uses with inadequate evidence and summarizes the number of on- and off-label uses as well as the number of off label uses in each evidence category for those drugs. Table 2 displays the index scores for each of the key factors used in forming the priority lists for the same 25 drugs found in Table 1. The pair-wise correlations between the three primary components was 0.09, -0.13, and 0.06 for volume and safety, volume and the composite cost and market index, and for safety and the composite index respectively. Among the three sub-factors in the composite index, the correlations were somewhat higher, ranging from 0.16 to 0.45.

The drugs listed in Tables 1 and 2 represent a broad range of drug classes and areas of clinical practice. Most prominent among the drugs in the top 25 are antidepressants (escitalopram, trazodone, sertraline, bupropion, amitriptyline, and venlafaxine), antipsychotics (quetiapine and risperidone), and anxiolytics/sedatives (zolpidem, lorazepam, and clonazepam).

Table 3 displays the base model prioritization and five additional priority lists of the top 15 drugs each based on different weightings of the individual priority factors from our sensitivity analysis. Despite very different modeling assumptions, the top drug on each list was quetiapine and of the remaining drugs in the base model, warfarin, escitalopram, risperidone, montelukast, bupropion, sertraline, venlafaxine, celecoxib, lisinopril, duloxetine, trazodone, olanzopine, and epoetin alfa appear in the top 15 in the majority of lists. Further sensitivity analyses varying coding methods, not included in the table, did not lead to significant changes in the lists. Hence, we suggest that the top 14 drugs in the base model priority list are good candidates for future research systematically exploring the evidence base for off-label use.

Each of the drugs that appear in the base model is shown in Table 4 along with their top on-label use and their top three off-label indications categorized as having inadequate evidence. Table 4 provides explicit information on the indications driving our evidence ranking and identifies conditions that have prompted off-label use. In several instances among atypical antipsychotics, the most common off-label use is more frequent than the leading on-label use. Note that generally the top 1 to 3 indications represented the vast majority of the overall off-label uses of the drug. For example, for quetiapine, the on-label uses and the top three off-label uses account for 77% of all uses, while this proportion is 98% for escitalopram.

Discussion

Our findings identified high volume of off-label prescribing in the absence of good evidence for a substantial number of drugs, particularly antidepressants, antipsychotics, and anxiolytics/sedatives. Accounting for other important factors (safety, and cost/marketing)

yielded robust results that placed priority for future off-label drug research on antidepressants and antipsychotics.

These rankings correspond in many respects with past assessments of off-label use, although some important differences were noted. Our assessment has extended past studies by including drug characteristics other than volume of off-label use that may impact the level of concern or priority associated with a specific drug. Because of this, several drugs and drug classes identified by past researchers as having prevalent off-label use,^{1,3,8,9} particularly anticonvulsants and antibiotics, were not as prominent within our listing of priority drugs.

Our prioritization is formed from a general framework but limited to available quantitative measures included in our model. The factors selected by our expert panel were influential in the prioritization. For example, among any of the top 10 drugs across the lists, there is only one antibiotic (metronidazole). The generally better safety profile of antibiotics, their relatively lower cost, older age, and limited marketing may have resulted in these drugs being ranked lower than antipsychotics and antidepressants. However, consideration of microbial antibiotic resistance could be an argument for increasing the priority of antibiotics beyond the criteria used in our analysis.

Off-label use of the atypical antipsychotics has long been a source of concern. Radley,⁹ as well as the Knight-Ridder⁸ news series, identified members of this drug class as particularly noteworthy. We identified three antipsychotics (quetiapine, risperidone, and olanzapine) among our high priority drugs. The most common conditions prompting their use were bipolar disorder, depression, and dementia. This may result from the lack of entirely acceptable and effective treatments, as well as overlapping clinical characteristics.

In fact, although it is often assumed²⁴ that all antipsychotics are approved for chronic maintenance in bipolar disorder, the FDA-approval for quetiapine and risperidone is limited to manic or depressive presentations. Indeed, available evidence for these drugs focuses on short-term studies of acute decompensated bipolar disorder. Drugdex lists these two antipsychotics as being inadequately supported by evidence for unspecified bipolar disorder. However, we recoded bi-polar disorder in quetiapine and risperidone in a sensitivity analysis and found little impact on the results. Most atypical antipsychotics are used for depression in the absence of strong scientific evidence. Similarly, support is lacking for their use in dementia where safety concerns have been raised about cardiovascular adverse events and included in an FDA Black Box warning for all atypical antipsychotics.

Gabapentin has been highlighted recently in discussions of off label use.^{1,8,9} Although relatively prominent in our analysis, it was not a top priority because it lacks a black box warning, has limited ongoing promotion, and has been on the market for some time.

Among the top priority drugs, six were antidepressants, including two serotonin reuptake inhibitors (escitalopram and sertraline), two serotonin- and norepinephrine-reuptake inhibitors (venlafaxine and duloxetine), and two other class (bupropion and trazodone). Bipolar disorder was the most common condition prompting off-label use. There is only limited support for the use of these drugs in this condition, particularly as maintenance therapy. Even as an adjunct to other therapies in depressive episodes, antidepressants do not

appear to be effective in bipolar disorder.²⁵ Hence, we view these medications as valuable focal points for future research.

Our model suggests how future research efforts could be focused on a small set of high priority off-label uses where in-depth evaluation can be expected to provide the greatest value. Such evaluations would begin with a systematic review and synthesis of all available information on the use of a drug to assess the extent and quality of the available evidence. Such a review may in turn prompt new evidence generation from retrospective database queries to prospective randomized trials. In addition, the policy implication of our finding may include a requirement for comparative effectiveness studies, greater scrutiny of marketing for particular off-label drugs, efforts by payers to require physician justification of off-label uses, and a range of post-market pharmacovigilance activities, as appropriate. Our top priority drugs, quetiapine, warfarin, escitalopram, risperidone, montelukast, bupropion, sertraline, venlafaxine, celecoxib, lisinopril, duloxetine, trazodone, olanzapine, and epoetin alfa, and their associated off-label uses are strong candidates such for further investigation.

We offer a few additional considerations associated with the quality of data on off-label drug use. A fundamental issue in the future assessment of off-label utilization, and indeed in assessment of pharmaceutical utilization generally, is the availability of data that relates a prescribed drug to its indication for use. This question is directly related to existing policy surrounding the writing of prescriptions. Currently, physicians are not required to document the indication for which a drug is prescribed. Furthermore, existing systems of coding (e.g., ICD-9) do not capture a variety of important nuances of clinical indication from the perspective of optimal care. Policy surrounding data collection, coding, and the prescription mechanism, need to be updated, particularly in the current environment where many health systems are moving to electronic health records and electronic prescribing. Documentation of a diagnosis for each drug prescribed is likely to be increasingly useful and feasible while at the same time could reduce medication errors.²⁵

Limitations

A number of limitations associated with our analysis should be considered. We assessed off-label use involving drugs used for indications not approved by the FDA. We did not evaluate other forms of off-label use (e.g., prescribing to children and other special population, or drug use in dosages beyond those approved). We did not attempt to conduct a systematic review of the clinical literature on specific drugs, because such a review was one avenue of research that might be influenced by our study findings. We instead relied on the synthesis available from the Drugdex compendium despite its potential limitations. Further, in coding off-label uses, our strategy was to apply our methods systematically to the available data on individual drugs. We did not consider whether another drug in the same class was approved nor did we give special consideration as to where a drug's use may be miscoded, as when an unusual label (e.g., hypertensive heart disease) might be used for a common related, but diagnostically distinct, condition (e.g., atrial fibrillation).

Although NDTI is designed to reflect outpatient physician visits in the US, the sample of physicians is not strictly random, as past respondents may continue their participation from

year to year. Clinical information available in NDTI is limited and additional details would have been useful for ambiguous diagnoses (e.g., bronchitis) or where past drug therapy history was important. Although NDTI links a drug's use to a clinical condition, this feature may not account for instances where a cluster of conditions or symptoms prompt use of a particular drug.

Matching the ICD-9 codes from NDTI with the indications listed by the FDA and Drugdex is challenging because of differences in terminology, degrees of specification, and clinically imprecise diagnoses. Drugdex may not always provide an optimal synthesis of available evidence. Not only are recent reports often not included,¹² but Drugdex often refers to unpublished studies cited in package inserts. Alternative compendia, however, often lack information on common off-label indications altogether.

In extending past research, our process of prioritizing individual drugs for further research necessarily involves several assumptions. Although we received substantial input from our technical expert panel, the framework we developed included subjective elements. However, our sensitivity analysis indicated that the framework was quite robust to substantial changes in model assumptions. We also were limited in the availability of reliable metrics for drug characteristics to include in our model. For example, Black Box warnings may not always reflect an equal magnitude of concern about drug safety and drug interactions. In prioritizing a list of drugs for future attention, we recognize that different forms of research and evaluation may be needed for different drugs on our list.

Conclusion

Future research into off label drug use should focus on drugs currently being prescribed widely with little or no evidence, particularly if the drugs are known to have safety issues, and/or are costly or being marketed heavily. We have identified 14 such drugs that merit priority for future research. While past research has highlighted the substantial frequency of off-label use without good evidence, we have identified and prioritized specific medications warranting attention. Future research to evaluate the efficacy and safety of off-label use should focus on these medications.

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A fully copy of the report associated with this study, with more fully described methods, additional results, and discussion can be found at the AHRQ Effective Health Care website, <http://effectivehealthcare.ahrq.gov/>.

References

1. Chen H, Deshpande AD, Jiang R, Martin BC. An epidemiological investigation of off-label anticonvulsant drug use in the Georgia Medicaid population. *Pharmacoepidemiol Drug Saf.* 2005; 14:629–38. [PubMed: 15597329]
2. Ma J, Lee K-V, Stafford RS. Depression treatment during outpatient visits by U.S. children and adolescents. *J Adolesc Health.* 2005; 37(6):434–442. [PubMed: 16310120]
3. Linder JA, Huang ES, Steinman MA, Gonzales R, Stafford RS. Fluoroquinolone prescribing in the United States, 1995–2000. *Am J Med.* 2005; 118:259–68. [PubMed: 15745724]
4. McIntyre J, Conroy S, Avery A, Corns H, Choonara I. Unlicensed and off-label prescribing of drugs in general practice. *Arch Dis Child.* 2000; 83:498–501. [PubMed: 11087285]
5. Loder EW, Biondi DM. Off-label prescribing of drugs in specialty headache practice. *Headache.* 2004; 44:636–41. [PubMed: 15209684]
6. Donofrio PD, Busis NA. Regulatory and reimbursement issues in treating patients with immune-mediated neuropathies. *Neurology.* 2002; 59:S41–5. [PubMed: 12499470]
7. Strom BL, Melmon KL, Miettinen OS. Post-marketing studies of drug efficacy: why? *Am J Med.* 1985; 78:475–80. [PubMed: 3976706]
8. Adams, C.; Young, A. Risky Rx: A Knight Ridder Investigation. Newspaper article series. Nov 2–4. 2003 http://www.realcities.com/mld/kirwashington/news/special_packages/riskyrx/
9. Radley D, Finkelstein S, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med.* 2006; 166:1021–1026. [PubMed: 16682577]
10. Claxton K. Bayesian approaches to the value of information: implications for the regulation of new pharmaceuticals. *Health Econ.* 1999 May; 8(3):269–74. [PubMed: 10348422]
11. IMS Health. National Disease and Therapeutic Index, Medication Reference File, 2001. Plymouth Meeting; PA: IMS Health; 2001.
12. Zell, ER.; McCaig, LF.; Kupronis, BA.; Besser, RE.; Schuchat, A. A comparison of the National Disease and Therapeutic Index and the National Ambulatory Medical Care Survey to evaluate antibiotic usage. Proceedings of the Section on Survey Research Methods American Statistical Association; Alexandria, VA. 2000. p. 840-845.
13. Stafford RS, Radley DC. The underutilization of cardiac medications of proven benefit, 1990 to 2002. *J Am Coll Cardiol.* 2003; 41:56–61. [PubMed: 12570945]
14. International Classification of Diseases, Ninth Revision, Clinical Modification. Washington DC: Public Health Service, US Dept. of Health and Human Services; 1988.
15. PDR® Electronic Library™ [Internet database]. Greenwood Village, Colo: Thomson Micromedex; Updated periodically
16. Food and Drug Administration. [Accessed April 26, 2007] Center for Drug Evaluation and Review. www.fda.gov/cder
17. IMS National Prescription Audit Data; Plymouth Meeting; PA. IMS Health;
18. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex; Updated periodically
19. USP DI® Volume I: Drug Information for the Health Care Professional [intranet database]. Version 5.1. Greenwood Village, Colo: Thomson Micromedex;
20. [Accessed April 24, 2007] FDA Orange Book. <http://www.fda.gov/cder/ob/>
21. Electronic report obtained by Randall S. Stafford under a Freedom of Information Act request that the FDA provide information on all drugs approved prior to 1982.
22. IMS Health Office Promotion Report; Plymouth Meeting; PA. IMS Health;
23. TNS Media Intelligence. Ad\$ponder Survey. TNS; New York, New York:
24. Antman, EM.; Anbe, DT.; Armstrong, PW., et al. A report of the Am Coll of Cardiol/Am Heart Assoc Task Force on Practice Guidelines (Committee to revise the 1999 guidelines). Bethesda (MD): American College of Cardiology, American Heart Association; 2004. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; p. 211
25. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med.* 2007; 356:1711–22. [PubMed: 17392295]

26. Kennedy A, Littenberg B. A modified outpatient prescription form to reduce prescription errors. *Jt Comm J Qual Saf.* 2004; 30(9):480–7. [PubMed: 15469125]

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Table 1

Top 25 drugs by number of uses off-label with inadequate evidence.^a

Rank	Generic name	On-label uses	Total off-label Uses	Off label uses with adequate evidence	Off label uses with uncertain evidence	Off label uses with inadequate evidence
1	quetiapine	2120	6507	0	0	6507
2	warfarin	13000	5325	0	0	5325
3	clonazepam	1297	4235	0	0	4235
4	escitalopram	21376	3580	0	0	3580
5	gabapentin	446	6334	84	3423	2827
6	promethazine	208	2732	0	0	2732
7	risperidone	2366	4034	0	1465	2569
8	digoxin	4701	2561	0	0	2561
9	lorazepam	3841	2490	0	0	2490
10	lisinopril	32140	2601	227	0	2374
11	prednisilone	6024	2359	0	0	2359
12	trazodone	2858	2166	0	0	2166
13	zolpidem	5114	2085	0	0	2085
14	sertraline	16617	2071	0	0	2071
15	bupropion	12196	1929	0	0	1929
16	acetaminophen / tramadol	2925	1802	0	0	1802
17	dexamethasone	784	2455	0	803	1652
18	metronidazole	2644	1648	0	0	1648
19	amitriptyline	848	1918	70	308	1540
20	albuterol	11749	8373	6881	0	1492
21	venlafaxine	11475	1472	0	0	1472
22	vancomycin	1089	1394	0	0	1394
23	esomeprazole	10237	1385	0	0	1385
24	montelukast	8201	1353	0	0	1353
25	celecoxib	6998	1296	0	0	1296

^aUses are in thousands, ranked in decreasing order of number of off-label uses with inadequate evidence, data from United States, July 2005–June 2007, IMS Health National Therapeutic and Disease Index.

Table 2
Individual index scores for top 25 drugs used in base model and sensitivity analysis^a

Rank	Generic Name	Volume with inadequate evidence	Volume with inadequate plus uncertain evidence ^b	Drug Safety	Drug cost	Corporate promotion	Recency of market entry	Composite of cost + promotion + + recency of market entry ^c
1	quetiapine	1.00	1.00	1.00	0.24	0.19	0.50	0.31
2	warfarin	0.82	0.82	1.00	0.03	0.01	0.00	0.01
3	clonazepam	0.65	0.65	0.00	0.03	0.01	0.00	0.01
4	escitalopram	0.55	0.55	1.00	0.09	0.47	1.00	0.52
5	gabapentin	0.43	0.96	0.00	0.12	0.01	0.50	0.21
6	promethazine	0.42	0.42	0.00	0.02	0.00	0.00	0.01
7	risperidone	0.39	0.62	1.00	0.25	0.12	0.50	0.29
8	digoxin	0.39	0.39	0.00	0.01	0.00	0.00	0.00
9	lorazepam	0.38	0.38	0.00	0.03	0.00	0.00	0.01
10	lisinopril	0.36	0.36	1.00	0.03	0.00	0.00	0.01
11	prednisilone	0.36	0.36	0.00	0.01	0.00	0.00	0.00
12	trazodone	0.33	0.33	1.00	0.02	0.00	0.00	0.01
13	zolpidem	0.32	0.32	0.00	0.10	0.73	0.50	0.45
14	sertraline	0.32	0.32	1.00	0.11	0.44	0.00	0.18
15	bupropion	0.30	0.30	1.00	0.13	0.57	0.00	0.23
16	acetaminophen/tramadol	0.28	0.28	0.00	0.05	0.06	0.50	0.20
17	dexamethasone	0.25	0.38	0.00	0.02	0.00	0.00	0.01
18	metronidazole	0.25	0.25	1.00	0.04	0.00	0.00	0.01
19	amitriptyline	0.24	0.28	1.00	0.01	0.00	0.00	0.00
20	albuterol	0.23	0.23	0.00	0.04	0.05	0.00	0.03
21	venlafaxine	0.23	0.23	1.00	0.15	0.36	0.50	0.34
22	vancomycin	0.21	0.21	0.00	0.36	0.00	0.00	0.12
23	esomeprazole	0.21	0.21	0.00	0.19	1.00	0.50	0.56
24	montelukast	0.21	0.21	1.00	0.12	0.74	0.50	0.45
25	celecoxib	0.20	0.20	1.00	0.14	0.49	0.50	0.38

^aThe values shown in the table are the parameter index calculated for each drug (range 0.00 to 1.00)

^bThe index combining volume with inadequate evidence and volume with uncertain evidence is used in the sensitivity analysis only.

c, The composite index which combines cost, promotion, and recency of market entry was used in the model because of concerns of correlation between the separate indicies.

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Table 3

Priority rankings for top 15 drugs based on base model and sensitivity analyses.

Model	Base model ^a	Sensitivity analyses A-D A. Inadequate plus uncertain evidence	B. Weights equal for each factor	C. Weighted by volume and safety only	D. Weighted by volume only
Weighting Schemes					
Inadequate Evidence Uses	0.50	0.25	0.33	.50	1.00
Uncertain Evidence Uses	0.00	0.25	0.00	0.00	0.00
FDA Safety Concerns	0.25	0.25	0.33	.50	0.00
Cost + Promotion + Entry	0.25	0.25	0.33	0.00	0.00
Rank					
1	quetiapine	quetiapine	quetiapine	quetiapine	quetiapine
2	warfarin	divalproex	escitalopram	warfarin	warfarin
3	escitalopram	warfarin	warfarin	escitalopram	clonazepam
4	risperidone	escitalopram	risperidone	risperidone	escitalopram
5	montelukast	epoetin alfa	montelukast	lisinopril	gabapentin
6	bupropion	risperidone	duloxetine	trazodone	promethazine
7	sertraline	gabapentin	epoetin alfa	sertraline	risperidone
8	venlafaxine	montelukast	celecoxib	bupropion	digoxin
9	celecoxib	bupropion	aripiprazole	metronidazole	lorazepam
10	lisinopril	sertraline	venlafaxine	amitriptyline	lisinopril
11	duloxetine	venlafaxine	bupropion	venlafaxine	prednisilone
12	trazodone	celecoxib	sertraline	montelukast	trazodone
13	olanzapine	lisinopril	olanzapine	celecoxib	zolpidem
14	epoetin alfa	duloxetine	olmesartan	levothyroxine	sertraline
15	aripiprazole	olanzapine	meloxicam	olanzapine	bupropion

Table 4

Clinical indications associated with approved and off-label uses with inadequate evidence for top 15 drugs.

Rank	Generic Name	Most Common On-Label Use	Most Common Off-label Use	Second Most Common Off-label Use	Third Most Common Off-label Use
1	quetiapine	Schizophrenia	Bipolar, maintenance <i>a,c</i>	Depression	Anxiety
2	warfarin	Atrial fibrillation	Hypertensive heart disease	Coronary heart disease	III-defined acute CVA
3	escitalopram	Depression	Bipolar <i>b</i>	OCD	Adjustment reaction
4	risperidone	Schizophrenia	Bipolar, maintenance <i>a</i>	Depression	Psychosis
5	montelukast	Asthma	COPD	Sinusitis	
6	bupropion	Depression	Bipolar <i>b</i>	Unspecified affective psychoses	
7	sertraline	Depression	Bipolar <i>b</i>	Adjustment reaction	
8	venlafaxine	Depression	Bipolar <i>b</i>	Schizophrenia	
9	celecoxib	Joint Sprain/Strain	Fibromatosis	Enthesopathy	
10	lisinopril	Hypertension	Coronary artery disease	Diabetes	
11	duloxetine	Depression	Anxiety	Bipolar <i>b</i>	
12	trazodone	Depression	Sleep disturbance	Anxiety	Bipolar <i>b</i>
13	olanzapine	Schizophrenia	Depression	Dementia	Anxiety
14	epoetin alfa	Chronic renal failure	Anemia of chronic disease	Myelodysplastic syndrome	

^aExcludes those diagnoses of Bipolar Affective Disorder (Manic-Depressive Disorder) listed as including Mania, Depression, or Mixed Presentation.

^bIncludes all diagnoses listing Bipolar Affective Disorder.

^cThe number of uses for this off-label drug indication exceeded that for its most common on-label indication.

Abbreviations

CVA = cerebral vascular accident

OCD = obsessive compulsive disorder

COPD = chronic obstructive pulmonary disease