Economic Outcomes Associated With Atypical Antipsychotics in Bipolar Disorder: A Systematic Review

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Received Jan. 8, 2007; accepted April 2, 2007. From United BioSource Corporation, Bethesda, Md. (Dr. Fleurence and Ms. Dixon); MLG Consulting Services, Inc., Chadds Ford, Pa. (Dr. Chatterton); and AstraZeneca, Wilmington, Del. (Dr. Rajagopalan). Dr. Rajagopalan is now with Biogen Idec (Cambridge, Mass.).

This study was funded by a grant from AstraZeneca (Wilmington, Del.).

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The authors thank Alexander Wade from United BioSource Corporation for his contribution to the data collection for this study. Mr. Wade has served as a consultant for Bristol-Myers Squibb, AstraZeneca, Pfizer, Janssen, and Eli Lilly.

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Objective: Bipolar disorder is a serious condition that is costly to the health care system. Atypical antipsychotics are more expensive than conventional treatments. From a policy-making perspective, the additional cost must be justified by improved outcomes. The objective of this study was to conduct a systematic review to determine the relative costs and cost-effectiveness associated with atypical antipsychotics in bipolar disorder.

Data Sources: We conducted a systematic review of the literature in PubMed and EMBASE from January 1985 through October 2005, including published studies and conference proceedings. Databases were searched using predefined terms.

Study Selection: Studies were included if they were claims data analyses, trial-based economic evaluations, or cost-effectiveness analyses using models. Data were extracted using predefined tables.

Data Synthesis: Fourteen studies were identified. Seven were medical claims database analyses, 4 were trial-based economic evaluations, and 3 were cost-effectiveness models. Eight of these studies were conference proceedings. The studies did not provide sufficient information to determine any ranking of interventions in terms of least to most costly in overall resource consumption or in terms of their relative cost-effectiveness. Where comparable, results tended to be inconsistent.

Conclusion: There is a scarcity of economic studies in this field. A reference case outlining how to address the complex interplay between effectiveness, safety, adherence, and quality of life and their impact on resource use and costs is needed to contribute to improving the treatment of patients with bipolar disorder while making the best use of scarce health resources.

(Prim Care Companion J Clin Psychiatry 2007;9:419–428)

Bipolar disorder affects approximately 2.6% of the United States population.[1] Patients with bipolar disorder may experience manic, mixed, or depressed episodes, and the disorder is characterized by patterns of stability and relapse throughout the patient's lifetime. Bipolar disorder has a significant impact on the psychological and social welfare of patients, and it greatly impairs their quality of life.[2] Onset of mania typically occurs in late adolescence or early adulthood. Impaired quality of life and functioning persist, even during asymptomatic periods.[3] The suicide rate may be as high as 15%, and a third of patients admit to having made a suicide attempt.[4]

Bipolar disorder is extremely costly to the health care system.[5,6] For example, one study has shown that patients with bipolar disorder incurred over 4 times greater costs per patient that nonbipolar patients ($7663 vs. $1962 per patient per year).[7] While prescription drugs contribute to the overall cost of the disease, because patients will often be prescribed a variety of drugs in combination,[8] the primary cost drivers have been shown to be hospitalizations and emergency room visits, followed by physician visits.[7,9]

Atypical antipsychotics, a relatively recent class of drug, are used for the treatment of acute manic episodes.[10–17] In remission, patients may also be prescribed a form of maintenance therapy with an atypical antipsychotic in order to prevent relapse into manic or depressive episodes. Some of these agents may prove useful in the treatment and management of bipolar depression and rapid cycling.[18] These agents typically show an improved

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safety and tolerability profile compared to conventional antipsychotic agents. There are currently 6 atypical drugs on the market (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone). All but clozapine are currently approved for the treatment of acute manic and/or mixed episodes associated with bipolar disorder. They may be prescribed as monotherapy or in combination with other agents such as lithium and valproate.

Atypical antipsychotic drugs are more expensive than lithium and conventional antipsychotics such as haloperidol. From a policy-making perspective, the additional cost must be justified by improved outcomes. For example, reduced medical resource utilization may offset the costs of drug therapy in the long term. The objective of this study was, therefore, to conduct a systematic review of the literature to determine the relative costs and cost-effectiveness of atypical antipsychotics in the treatment of patients with bipolar disorder.

METHOD

Data Sources and Search Strategy

The literature search was conducted in MEDLINE, EMBASE, and the National Health Service Economic Evaluation Database (NHS EED) from January 1, 1985, to October 4, 2005. Conference proceedings from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) were searched from 1999 through 2005. Conference proceedings from the American Psychiatric Association (APA) were searched from 2000 through 2005. Because of the potentially inferior quality of conference proceedings compared to studies published in peer-reviewed publications, we indicate clearly in the reporting of results which studies were conference proceedings.

Databases were searched using predefined terms. The terms related to bipolar illness were *bipolar III disorder*, *unipolar mania*, *rapid cycling disorder*, *bipolar*, *bipolar disorder*, *bipolar I disorder*, *bipolar II disorder*, *cyclothymic disorder*, *hypomania*, *mania*, *manic-depressive*, *manic disorder*, *manic episode*, *bipolar affective disorder*, *dysphoric mania*, *manic symptoms*, and *bipolar spectrum disorder*. Terms related to treatment were *atypical antipsychotics*, *aripiprazole or Abilify*, *clozapine or Clozaril*, *olanzapine or Zyprexa*, *quetiapine or Seroquel*, *risperidone or Risperdal*, *ziprasidone or Geodon*, *lithium or lithium carbonate*, *divalproex or Depakote*, and *lamotrigine or Lamictal*. Terms related to economics were *burden of illness*, *costs*, *cost-benefit*, *cost-effectiveness*, *cost of illness*, *economics*, *expenditure*, *quality-adjusted life years*, *resource utilization, models*, and *decision—analysis*.

Study Selection

Studies were included if they were claims data analyses, trial-based economic evaluations, or cost effectiveness analyses using models. There are significant differences in the types of costs collected and outcomes reported in these 3 study designs. It would, therefore, be inappropriate to present the results of these studies together. Claims database analyses are useful sources of data because they reflect resource utilization patterns in actual clinical practice, in which a wide range of patients outside of the rigid environment of a clinical trial use a treatment. However, it is always difficult to identify any possible confounding factors, since these patients do not undergo random assignment. Trial-based economic evaluations provide valuable data because of the randomization of the treatments. However, they may overestimate costs due to the protocol-related costs, and there may be issues of generalizability, since patients are selected using the strict criteria for entry into a clinical trial. Finally, cost-effectiveness models combine data from a number of different sources in order to obtain the incremental costs and effects and cost-effectiveness of interventions. While useful as decision-making tools, models often have to extrapolate data beyond what is clinically available and use a number of different sources of data.[19] Therefore, explicit reporting and model validation are important criteria for assessing the validity of the model.[20]

Further inclusion criteria were as follows. Participants in these studies were individuals with bipolar disorder treated for acute mixed or manic episodes (with or without psychotic features, and with or without a rapid-cycling course) or depressive episodes or treated for maintenance to prevent future manic or depressive episodes. The interventions included atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone), in monotherapy or in combination with mood stabilizers such as lithium, valproate, lamotrigine, or haloperidol. The search was limited to articles in English, articles published after 1985, and original research.

Abstracts were manually reviewed and assessed for potential inclusion in the review according to the predefined inclusion and exclusion criteria. Full length articles of potentially relevant publications were reviewed for final assessment. Bibliographies of articles and review articles were searched to identify any potential additional studies. For conference proceedings, authors of abstracts were contacted via e-mail to obtain further information on the study, such as the corresponding poster or presentation.

Data Extraction

Table shells for data extraction were predefined and contained the following information: objective, treatment, comparator, population, methods, economic outcomes, and conclusions. For claims data and economic trials, we extracted annual total charges, annual mental charges, outpatient charges, inpatient charges, and prescription drug charges. For cost-effectiveness studies, we extracted

costs and incremental cost-effectiveness ratios where these were reported.

Costs Conversion

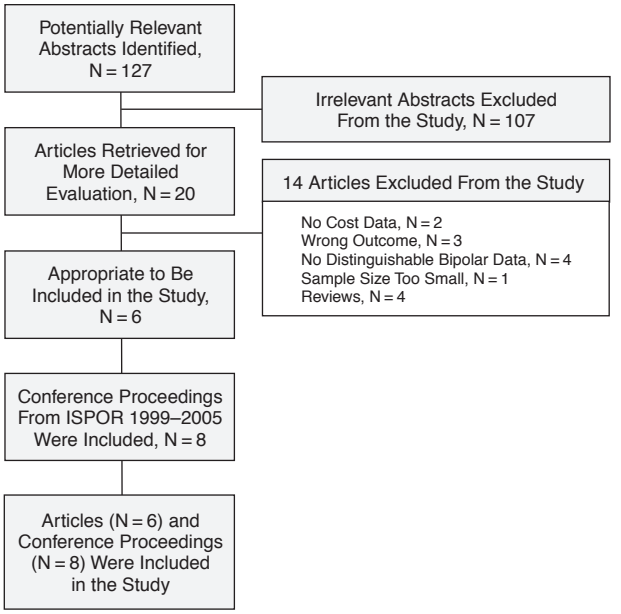
Costs were not converted to a common time unit (e.g., annual) due to the possibility of overestimating or underestimating costs in this way. When in foreign currencies, costs were converted to U.S. dollars, using appropriate exchange rates. Costs were not updated to a common price year to account for inflation, because a number of studies did not report price year. It was decided to report costs as they were reported in each publication.

This study was supported by AstraZeneca. AstraZeneca collaborated in helping set the specifications for the study but had no role in methodological decisions or interpretation of results. They were also allowed to review and comment on this manuscript, with editorial control resting with the first author (R.L.F.).

RESULTS

The search yielded 127 potential abstracts. Based on the abstracts, 20 potential articles for inclusion were ordered and reviewed manually. Of these 20 articles, 6 met our eligibility criteria for this research. In addition, 8 conference proceedings from ISPOR met our inclusion criteria. We did not identify additional abstracts from the APA database. Figure 1 shows the flow chart for the identification of studies. Of the 14 economic studies comparing atypical antipsychotic treatments among patients with bipolar disorder, 7 were medical claims database analyses (2 peer-reviewed publications and 5 conference proceedings), 4 were trial-based economic evaluations (3 peer-reviewed publications and 1 conference proceeding), and 3 were cost-effectiveness models (1 peer-reviewed publication and 2 conference proceedings) (Table 1).

Figure 1. Studies Identified for the Economic Search



Economic Outcomes Obtained From Claims Databases

The 7 claims database analyses of atypical antipsychotics were conducted in U.S. populations and investigated the atypical antipsychotics olanzapine, quetiapine, risperidone, and ziprasidone. We extracted complete data (total annual charges, mental health annual charges, outpatient charges, inpatient charges, atypical drugs, and other drug costs) from only 3 studies.[21–23] These data are presented in Table 2. We included 4 additional studies even though they did not report costs broken down into the categories that were described above.[24–27] Two studies investigated rates of hospitalization for patients with bipolar disorder, and 2 studies investigated rates of adherence with atypical antipsychotic treatment. These studies were included because they reported data that directly impact resource utilization (hospitalization and adherence).

Gianfrancesco et al.[21] (2005) performed a retrospective analysis of claims data from commercial health plans covering the period from 1998 to 2002. Patients (N = 6625) with a diagnosis of bipolar disorder who were not being treated concurrently with multiple antipsychotics and had not switched from a prior antipsychotic were included in the study. Results indicated that mental health care charges (excluding study drug) per patient per month did not differ substantially for the 3 antipsychotics (olanzapine, $527; quetiapine, $492; risperidone, $544). This result did not change after adjusting for patient characteristics. However, the drug costs of olanzapine appeared to be significantly higher than those for quetiapine or risperidone.

The second claims database analysis by Gianfrancesco et al.[22] (2005) looked at 3-month costs in patients with a diagnosis of bipolar disorder who initiated quetiapine monotherapy between 1999 and 2002 and were treated for at least 4 consecutive months (N = 2421). This study compared a higher dose of quetiapine with a lower dose of quetiapine and did not include any additional drug comparators. It was included in this review since it did provide data on the economic outcomes of interest. Total mental health charges (excluding antipsychotic drug charges) for 3 months ranged from $1683 to $1973, depending on the initial dose of quetiapine. Inpatient costs were higher for patients initiating a higher dose of quetiapine than for those initiating a lower dose of quetiapine ($955 vs. $643, respectively), reflecting the difference in patient populations between those who initiated high doses versus those who initiated low doses.

The third claims data analysis by Gutierrez et al.[23] (2005 conference proceedings) matched 2 bipolar cohorts

Table 1. Economic Studies of Atypical Antipsychotics

Study	Comparators	Population	Cost Time Frame
Claims database analyses			
Gianfrancesco et al[21] (2005)	Olanzapine, quetiapine, risperidone	Bipolar disorder identified by ICD-9 codes	Duration of treatment episode ranged from 6.9–7.8 mo
Gianfrancesco et al[22] (2005)	High-dose quetiapine, low-dose quetiapine	Bipolar disorder identified by ICD-9 codes	3 mo
Gianfrancesco and Rajagopalan[24] (2005)[a]	Olanzapine, quetiapine, risperidone, ziprasidone, typical antipsychotics	Diagnosis of bipolar or manic disorder identified by ICD-9 codes	NA[b]
Gianfrancesco and Rajagopalan[25] (2005)[a]	Olanzapine, quetiapine, risperidone, ziprasidone, typical antipsychotics	Diagnosis of bipolar or manic disorder identified by ICD-9 codes	NA[b]
Gutierrez et al[23] (2005)[a]	Olanzapine, quetiapine, risperidone	Diagnosis of bipolar disorder	12 mo
Lazarus et al[26] (2004)[a]	Olanzapine, quetiapine, risperidone + MS	Diagnosis of bipolar disorder	NA[b]
White et al[27] (2002)[a]	Olanzapine, quetiapine, risperidone, haloperidol	Diagnosis of bipolar disorder	NA[c]
Trial-based economic evaluation			
Zhu et al[28] (2005)	Olanzapine, valproate	Diagnosis of bipolar I disorder with an acute or manic episode using DSM-IV criteria	Annual costs based on 47-wk economic trial
Price et al[30] (2004)[a]	Olanzapine, lithium	Diagnosis of bipolar I disorder	52-wk economic trial
Revicki et al[29] (2003)	Olanzapine, valproate	Diagnosis of bipolar I disorder using DSM-IV criteria and hospitalization for an acute manic episode	Average 12-wk costs based on economic trial
Namjoshi et al[31] (2002)	Olanzapine, unspecified previous therapy	Diagnosis of bipolar I disorder with an acute or manic episode randomly assigned to 3-wk acute trial	Average cost/mo based on 49-wk economic trial data and prior 52-wk resource use
Cost-effectiveness models			
Bridle et al[32] (2004)	Olanzapine, quetiapine, valproate, haloperidol, lithium	Patients with bipolar disorder experiencing acute mania requiring hospitalization	3-wk model
McGarry et al[34] (2004)[a]	Olanzapine, risperidone, haloperidol	Patients with bipolar disorder experiencing acute mania requiring hospitalization	24-wk and lifetime model
McGarry et al[33] (2003)[a]	Olanzapine + MS, risperidone + MS, haloperidol + MS, lithium monotherapy, valproate monotherapy	Patients with bipolar disorder experiencing acute mania requiring hospitalization	24-wk and lifetime model

[a]International Society for Pharmacoeconomics and Outcomes Research conference proceedings.
[b]Costs not reported.
[c]Only estimated cost differences reported.
Abbreviations: ICD-9 = International Classification of Diseases, Ninth Revision, MS = mood stabilizer, NA = not applicable.

of risperidone patients (N = 951) with olanzapine (N = 1660) and quetiapine patients (N = 699), using administrative claims from a national managed care organization (2000–2002). Patients initiated treatment with one of the 3 atypicals and had a bipolar disorder diagnosis. Subjects treated with more than one antipsychotic were excluded. The study found that risperidone patients had similar annual mental health costs compared to patients receiving olanzapine ($5728 vs. $5908, respectively; not statistically significant), and significantly lower mental health costs compared to those treated with quetiapine ($5666 vs. $6579, respectively; p = .007). In addition, quetiapine had higher inpatient costs compared to risperidone ($1354 compared to $963). Annual psychotropic drug costs were significantly lower for risperidone versus both olanzapine and quetiapine.

Two medical claims studies limited their analyses to hospitalizations among the comparator atypical antipsychotics.[24,26] Gianfrancesco and Rajagopalan[24] (2005 conference proceedings) evaluated a large database (1999–2003). Patients with a diagnosis of bipolar disorder were included if they had not switched from a prior antipsychotic and were not receiving multiple treatments. Treatment episodes were as follows: olanzapine (N = 5128), risperidone (N = 4301), quetiapine (N = 2459), ziprasidone (N = 377), and typical antipsychotics (N = 570). The study found that olanzapine and risperidone had higher risks of hospitalization than quetiapine or ziprasidone.

Lazarus et al.[26] (2004 conference proceedings) used a medical claims database (1998–2001) and identified 977 individuals who had a diagnosis of bipolar disorder and

Table 2. Costs for Atypical Antipsychotics Using Claims Data

Study	Costing Method	Drug	Cost Type	Total Costs ($)	Outpatient Costs ($)	Inpatient Costs ($)	Study Drug Costs ($)	Other Drug Costs ($)
Gianfrancesco et al[21] (2005)	Duration: 1 mo	Risperidone	Mental health	691	210	266	147	68
	Cost year: unspecified	Olanzapine	Mental health	802	193	263	275	71
		Quetiapine	Mental health	663	179	223	171	90
Gianfrancesco et al[22] (2005)	Duration: 3 mo	High-dose quetiapine	Mental health	1,973	795	955	NR	223
	Cost year: unspecified	Low-dose quetiapine	Mental health	1,683	815	643	NR	225
Gutierrez et al[23] (2005)								
Cohort 1	Duration: 12 mo	Olanzapine	Mental health	5,908	1,389	979	3,363	NR
	Cost year: 2004		Total	10,366	NR	NR	NR	NR
		Risperidone	Mental health	5,728	1,581	1,023	2,969	NR
			Total	10,212	NR	NR	NR	NR
Cohort 2	Duration: 12 mo	Risperidone	Mental health	5,666	1,605	963	2,929	NR
	Cost year: 2004		Total	10,033	NR	NR	NR	NR
		Quetiapine	Mental health	6,579	1,551	1,354	3,492	NR
			Total	12,165	NR	NR	NR	NR

Abbreviation: NR = not reported.

received combination therapy with an atypical antipsychotic (olanzapine, quetiapine, or risperidone) and a mood stabilizer. The study found that, in the year following the start of combination therapy with a mood stabilizer, patients receiving quetiapine were 44% less likely to be hospitalized than those receiving olanzapine ($p = .035$) and were no more likely to be hospitalized compared to those receiving risperidone ($p = .58$).

Two studies investigated adherence to treatment.[25,27] White et al.[27] (2002 conference proceedings) examined adherence with atypical antipsychotics (risperidone, quetiapine, and olanzapine) and haloperidol using claims data (1997–2000). The cohort of 220 quetiapine patients was matched to the other 3 comparator groups. The median duration of adherence was 225 days for quetiapine compared with 158 days for olanzapine ($p < .01$), 154 days for risperidone ($p < .01$), and 98 days for haloperidol ($p < .01$). The study shows that quetiapine may have the highest level of therapy adherence; however, there was a scarcity of information provided in the conference abstract on patient population characteristics.

Gianfrancesco and Rajagopalan[25] (2005 conference proceedings) investigated adherence with atypical antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) or conventional antipsychotic treatment using a claims database (1999–2003). A total of 18,158 treatment episodes for bipolar or manic disorder met the inclusion criteria: 17,346 for the atypicals (5754 for risperidone, 6894 for olanzapine, 3901 for quetiapine, and 797 for ziprasidone) and 812 for the typical antipsychotics. Quetiapine and ziprasidone were more likely to have been initiated later, possibly as second-line therapies (as indicated by higher proportions of patients receiving quetiapine or ziprasidone after switching from another antipsychotic). The study found that compliance with quetiapine may be significantly higher relative to olanzapine and risperidone as well as to other agents, and olanzapine and ziprasidone patients demonstrated significantly greater compliance than risperidone patients. Quetiapine and risperidone patients had significantly longer treatment duration than patients receiving olanzapine, ziprasidone, and the other agents.

Economic Outcomes Obtained From Trial-Based Economic Evaluations

Four of the eligible studies focusing on atypical antipsychotics were trial-based economic evaluations. Olanzapine was included as a comparator in all 4 of these studies, and no other atypical antipsychotics were included. The comparators for olanzapine were valproate in 2 studies and lithium in another. The fourth study was a before-and-after study of patients treated with olanzapine. Table 3 shows the total costs, total mental health costs, outpatient costs, inpatient costs, study drug costs, and other drug costs for each arm of these studies in which the data are available. Not all studies reported each of these costs.

Zhu et al.[28] (2005) used the resource use data collected from a 47-week clinical trial comparing olanzapine ($N = 77$) with valproate ($N = 70$) in patients with bipolar disorder experiencing an episode of acute mania. The trial randomly assigned 251 patients originally. There were no statistically significant differences between patients who did or did not enter the maintenance phase with respect to these baseline demographics and clinical characteristics. Costs collected included study medication, inpatient hospitalization, emergency room (ER) visits, partial hospitalization, and other (non-ER) outpatient services. Hospitalization costs during the first week were excluded from the cost calculations. The study found that although the cost of olanzapine was higher than the cost of valproate (olanzapine = $4662; valproate = $1755), the 2 treatments resulted in similar average per patient annual costs (olanzapine = $15,801; valproate = $14,967). The increased medication costs in the olanzapine group

Table 3. Costs for Atypical Antipsychotics Identified in Economic Trials

Study	Costing Method	Drug	Cost Type	Total Costs ($)[a]	Outpatient Costs ($)	Inpatient Costs ($)	Study Drug Costs ($)	Other Drug Costs ($)
Zhu et al[28]	Duration: annual	Olanzapine	Mental health	14,281	NR	NR	NR	NR
(2005)	Cost year: unspecified		Total	14,967	2,987	7,318	4,662	NR
		Valproate	Mental health	14,786	NR	NR	NR	NR
			Total	15,801	4,186	9,861	1,755	NR
Price et al[30]	Duration: annual	Olanzapine	Total	7,395[b,c]	NR	5,358[b]	1,637[b]	21[b]
(2004)	Cost year: unspecified	Lithium	Total	7,592[b,c]	NR	6,869[b]	191[b]	40[b]
Revicki et al[29]	Duration: 12 wk	Olanzapine	Total	15,180	1,080[d]	14,442	924	16
(2003)	Cost year: unspecified	Valproate	Total	13,703	541[d]	13,162	358	22
Namjoshi et al[31]	Duration: monthly	Olanzapine (49 wk)	Total	649	73	248	328	NR
(2002)	Cost year: 1995	52 wk prior	Total	1,533	354	1,179	NR	NR

[a]Total costs are not always the sum of the reported categories.
[b]Conversion rate: 1 USD = 1.263 AUD.
[c]Includes laboratory costs of $379 for olanzapine and $479 for lithium.
[d]Includes study drug costs and other drug costs; numbers do not add up for olanzapine arm in the published article.
Abbreviations: AUD = Australian dollar, NR = not reported, USD = United States dollar.

appeared to be offset by reduced resource utilization. Specifically, hospitalized patients had average lengths of stay of 24 days and 33 days for olanzapine- and valproate-treated patients, respectively. Also, 25% of olanzapine patients used ER services compared to 37% of valproate patients, but this difference did not reach statistical significance.

Revicki et al.[29] (2003) compared resource use between olanzapine and valproate in a 12-week, randomized, double-blind clinical trial of patients with a diagnosis of bipolar I disorder and hospitalization for an acute manic episode. Patients were hospitalized for 21 days. If, after 21 days, patients had not improved, they were discontinued from the study. Of the 120 patients randomly assigned initially, 52 provided data on resource use. (There was no difference in characteristics between those initially randomly assigned and the subgroup that provided resource use data). Costs collected included outpatient visits, physician and other professional visits, ER visits, other hospitalizations, study drugs, and other medications. The total mean 12-week medical costs were similar for olanzapine versus valproate patients ($15,180 vs. $13,703, respectively; p = .88). It should be noted that the costs in the Revicki et al. 12-week study were higher overall than the yearly costs from the Zhu et al. study, because the cost inclusion criteria used in the 2 studies were different.

Price et al.[30] (2004 conference proceedings) conducted an economic substudy of an Australian 52-week, double-blind, randomized trial comparing olanzapine (N = 217) versus lithium (N = 214) in patients with bipolar disorder. The conference proceeding did not specify how patients lost to follow-up were analyzed. Resources considered were study drug, concomitant medication, hospitalizations, and laboratory tests. The study found that, although the acquisition cost of olanzapine was greater than that of lithium (olanzapine = $1637; lithium = $191), the fewer (82 vs. 88) and shorter hospitalizations (15 vs. 19.7 days) associated with olanzapine versus lithium led to overall costs being lower with olanzapine ($7395 vs. $7592, respectively). Another reason treatment with olanzapine was less expensive than treatment with lithium was that olanzapine does not require laboratory tests to monitor serum drug levels.

Finally, Namjoshi et al. (2002) performed a before-and-after analysis of health care costs of patients who participated in a clinical trial that included a 3-week acute phase (olanzapine vs. placebo) and a 49-week open-label extension.[31] Patients were included in the study if they had a diagnosis of bipolar I disorder with manic or mixed episodes. For 76 patients, 52-week costs prior to their entry into the clinical trial were tracked and compared to the 52-week costs after treatment with olanzapine (and/or placebo during the acute phase). Resource use collected included costs associated with hospitalizations, outpatient visits to mental health care providers, home health care costs, and costs of olanzapine for the open-label period. (Drug costs for the period prior to the trial were not available.) The study found that patients during the 49 weeks of olanzapine therapy had monthly costs of $649 compared to monthly costs of $1533 incurred in the previous 12 months of therapy. The cost savings were largely driven by reduced inpatient costs during the open-label extension ($248 vs. $1179 per month). While this study confirms the trend that olanzapine treatment may be associated with a reduction in other health care–related costs, the before-and-after design necessitates caution due to the possible confounding factors in these results. For example, of the 139 patients randomly assigned initially, only 113 entered the open-label extension, and only 76 provided sufficient data to report cost outcomes. Other factors, such as being part of a controlled study protocol, may explain the decrease in costs.

Relative Cost-Effectiveness of Atypical Antipsychotics

Three of the eligible studies used decision-analytic models to evaluate cost-effectiveness of treatments in

Table 4. Costs and Cost-Effectiveness of Atypical Antipsychotics

Study	3-Week Costs (UK, NHS Perspective)	ICER (3-week) (UK, NHS Perspective)	24-Week Costs	Lifetime Costs	ICER (Lifetime)
Bridle et al[32] (2004)[a,b]					
Olanzapine	£3,161 ($6,174)	£7,179 ($14,021) per additional responder (compared to haloperidol)	NR	NR	NR
Quetiapine	£3,165 ($6,182)	Dominated	NR	NR	NR
Haloperidol	£3,047 ($5,951)	NA	NR	NR	NR
Lithium	£3,162 ($6,176)	Dominated	NR	NR	NR
Valproate	£3,139 ($6,131)	Dominated	NR	NR	NR
McGarry et al[34] (2004)[b,c]					
Olanzapine	NR	NR	£3,697 ($7,221)	£17,555 ($34,287)	Dominated
Risperidone	NR	NR	£3,401 ($6,643)	£17,260 ($33,711)	Dominates olanzapine and haloperidol
Haloperidol	NR	NR	£3,531 ($6,896)	£17,388 ($33,961)	Dominated
McGarry et al[33] (2003)[b,c]					
Olanzapine + MS[d]	NR	NR		Range, $32,000 to $32,500[e]	$8,700/QALY (compared to haloperidol + MS)
Risperidone + MS[d]	NR	NR		Range, $31,500 to $32,500[e]	$3,300/QALY (compared to haloperidol + MS)
Haloperidol + MS[d]	NR	NR		Range, $31,500 to $32,500[e]	NA
Lithium monotherapy	NR	NR		Range, $32,500 to $32,500[e]	Dominated
Valproate monotherapy	NR	NR		Range, $32,500 to $32,500[e]	Dominated

[a]Includes costs for initial hospitalization, drug acquisition, and laboratory and diagnostic tests for monitoring. Does not include costs of adverse events.
[b]Conversion rate: 1 USD = 0.512 GBP.
[c]Includes costs for drugs, hospitalizations, and outpatient care. Adverse events (tardive dyskinesia and weight gain) included only in McGarry et al.[33]
[d]MS = mood stabilizer (either lithium or valproate).
[e]Based on graph.
Abbreviations: GBP = British pound, ICER = incremental cost-effectiveness ratio, MS = mood stabilizer, NA = not applicable, NHS = National Health Service, NR = not reported, QALY = quality-adjusted life-year, UK = United Kingdom, USD = United States dollar.

bipolar disorder.[32–34] One high-quality health technology assessment report for the United Kingdom and 2 conference proceedings from ISPOR were identified. Additional data were provided by the authors of one of the conference proceedings upon request.[34] Results of these cost-effectiveness analyses are presented in Table 4.

One model examined a 3-week time frame for treatment of an acute manic episode in the United Kingdom from the perspective of the NHS.[32] The study treatments included olanzapine, quetiapine, valproate semisodium, haloperidol, and lithium. Costs included costs of initial hospitalization, drug acquisition, and laboratory and diagnostic tests required for monitoring. Costs of adverse events were not included. The model estimated the cost per additional responder using the Young Mania Rating Scale response rate of > 50% as the response measure. Results indicated that quetiapine, valproate, and lithium were dominated interventions, i.e., they were less effective and more costly than olanzapine and haloperidol. The cost per additional responder for olanzapine compared to haloperidol was £7179 ($14,021), making olanzapine potentially cost-effective for the treatment of an acute manic episode requiring hospitalization.

Two studies by McGarry and colleagues[33,34] (conference proceedings) used a Markov model to evaluate the cost-effectiveness of monotherapy with atypical antipsychotics and combination therapy of atypical antipsychotics + mood stabilizers (MS) in the treatment of acute mania and as maintenance therapy. Both models present 24-week and lifetime results, costs, quality-adjusted life-years (QALYs), and cost per QALY gained. The monotherapy model was developed for the United Kingdom NHS and included costs of initial hospitalization, drug acquisition, and laboratory and diagnostic tests for monitoring but did not include costs of adverse events. The results of the cost-effectiveness model (U.S. payer perspective) for combination therapy showed that therapy with atypicals + MS was more cost-effective in treating acute mania when compared to haloperidol + MS, and it dominated monotherapy with lithium or valproate.[33] Though haloperidol + MS was the least costly therapy option, risperidone + MS was the most effective. Risperidone + MS cost an additional $3300, and olanzapine + MS an additional $8700 per QALY, compared to haloperidol + MS.

The combination-therapy model used a United States payer perspective.[34] Costs in this model included 2003 costs for drugs, hospitalizations, outpatient care, and adverse events (tardive dyskinesia and weight gain). Results showed that the 24-week and lifetime costs of treating acute mania were lowest with risperidone monotherapy

($6643 and $33,711, respectively) compared to haloperidol ($6896 and $33,961, respectively) and olanzapine ($7221 and $34,287, respectively). Risperidone monotherapy was dominant relative to both olanzapine and haloperidol monotherapy by being both less costly and more effective in the treatment of acute mania from the perspective of the NHS in the United Kingdom.

DISCUSSION

We identified 14 relevant studies in this systematic review of the literature. However, these did not yield sufficient information to provide any ranking of interventions in terms of least to most costly in overall resource consumption or in terms of their relative cost-effectiveness. In claims data, results from the 3 studies reporting costs were inconsistent, and overall costs between olanzapine, quetiapine, risperidone, and ziprasidone could not be differentiated. The 4 additional claims studies providing hospitalization and adherence rates need further extrapolation to assess the impact on overall costs. The trend apparent in the 4 trial-based economic evaluations was that, despite higher drug acquisition costs, olanzapine had overall costs similar to valproate and lower than lithium. No other atypical antipsychotic was the subject of a trial-based economic evaluation. Each of the cost-effectiveness models identified used different perspectives and/or time horizons and was therefore not directly comparable. Unsurprisingly, their results were inconsistent.

This study highlights a number of issues that can inform future research in this area. While some limitations, which have been discussed elsewhere,[35,36] may be associated with the type of economic study design itself, we also identified limitations that were specific to the 14 studies identified in the review.

First, the choice of comparators in these studies may be a significant issue. In most studies, the number of comparators is restricted, and the rationale for excluding other interventions is not always explicit. In the trial-based economic evaluations, olanzapine was used in all 4 studies, but no other atypical antipsychotics have been studied in trials. It should be noted that no economic study included aripiprazole. Comparators should probably not be limited to atypical antipsychotics but, where relevant, should include typical antipsychotics and combination therapy with mood stabilizers. The recently published results of the cost-effectiveness of the Clinical Antipsychotic Trials of Intervention Effectiveness in schizophrenia showed that a typical antipsychotic, perphenazine, may be less costly than olanzapine, quetiapine, risperidone, or ziprasidone for similar effectiveness.[37] It remains to be shown whether similar results would hold in a population of bipolar patients, but these results do highlight the need to include all relevant comparators in economic studies.

Second, the comparability of results appeared to be limited due to the variety of approaches used in the studies. In claims data, studies used different inclusion and exclusion criteria when selecting patient populations, as well as different time lines (monthly or annual) and different treatment comparators. In trial-based economic evaluations, the studies used different time lines and included different cost categories in their calculation of overall costs. In cost-effectiveness studies, the difficulty of generalizing and comparing results is well known.[38] This certainly holds true for the 2 United Kingdom cost-effectiveness models that investigated different interventions, used different time horizons, and included different types of costs. Unsurprisingly, the results of these studies were inconsistent.

Finally, the dearth of data reported was an issue not only because of the limited number of studies that we identified overall but also because of the number of studies published as conference proceedings rather than in peer-reviewed publications. In fact, the majority of the studies included were conference proceedings (8 out of 14). It should be noted that trial-based economic evaluations were more likely to be published in peer-reviewed journals (3 out of 4) than the other 2 types of study designs. When reviewing conference proceedings, it is difficult to assess the validity of the methods, results, and limitations of the study, because this information tends not to be comprehensively reported. However, in cost-effectiveness models, for example, it is particularly important to provide an explicit statement of the methods, because often assumptions must underlie different choices of parameters. Because 2 of the 3 cost-effectiveness models identified were conference proceedings, the data available on the cost-effectiveness of atypical antipsychotics in bipolar disorder are severely limited.

While no robust conclusions can be drawn on the relative costs and cost-effectiveness of atypical antipsychotics, this study does highlight a number of important issues in this area of research. Overall, these limitations in the current studies highlight the need for the development of a reference case for economic studies in this area. Such reference cases have been developed in other disease areas—for example, in rheumatoid arthritis and osteoporosis—and they provide researchers with a common framework on which to develop their analyses.[39,40] These reference cases both make reporting explicit and also improve the comparability of results from different studies. They provide guidelines for how to incorporate issues of effectiveness, safety, adherence, quality of life, and resource use. Issues such as the choice of comparators and the treatment of adverse events can be dealt with explicitly.

To our knowledge, this is the first systematic review of economic studies of atypical antipsychotics in the area of bipolar disorder. A nonsystematic review by Fleurence et al.[41] identified only 6 studies (conference proceedings

were not included) and concluded that, based on limited available studies, no significant difference in health care resource use between olanzapine, quetiapine, risperidone, and valproate could be identified.

There are some limitations to this systematic review. Conference abstracts were included in order to present a complete set of studies; however, as previously discussed, it is difficult to judge the quality of a study based on this reporting method alone. As a rule, conference proceedings provided less information than published articles, and the quality of this gray literature has been questioned.[42,43] Our study, therefore, had to balance the goal of completeness with the need to include quality studies. To address this issue, we contacted authors of conference proceedings to obtain further information, such as posters or presentations. We also indicate throughout the text which studies are conference proceedings. A second limitation to our study is that our inclusion criteria restricted the selected studies to atypical antipsychotic interventions. We did not include studies that investigated typical antipsychotics or mood stabilizers alone. This focus may have limited the breadth of data reported.

In conclusion, there is a scarcity of economic studies in this field. A reference case outlining how to address the complex interplay between effectiveness, safety, adherence, quality of life, and their impact on resource use and costs is needed to contribute to improving the treatment of patients with bipolar disorder while making the best use of scarce health resources.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), divalproex (Depakote), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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