RESEARCH

Utilization and Drug Cost Outcomes of a Step-Therapy Edit for Generic Antidepressants in an HMO in an Integrated Health System

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ABSTRACT

OBJECTIVE: Antidepressants do not differ significantly in their ability to treat depression. Excluding the tricyclic antidepressants (TCAs), these drugs also do not differ significantly in their incidence of adverse events. Therefore, the initial choice of antidepressant medication should be based, in part, on cost. The objective of this study was to evaluate the impact on utilization and costs of a generic step-therapy edit for antidepressant drugs excluding TCAs in a health maintenance organization (HMO) in an integrated health system (IHS).

METHODS: The pharmacy department of the 440,000-member HMO in an IHS collaborated with the Behavioral Health Clinical Program to design an intervention that required generic antidepressants as first-line pharmacotherapy. Under the GenericStart! Program, a brand-name antidepressant was covered only after trial with a generic antidepressant, excluding TCAs. A step-therapy edit was added to the pharmacy claims processing system on January 1, 2005. All new starts, defined as members with no claims history of antidepressant treatment within the preceding 6 months, were required to use a generic antidepressant. The member copayment was waived for the first prescription. All generic antidepressants were in tier 1 of the drug formulary, with an average copayment of $5 to $10. All brand-name antidepressants were in either tier 2 (preferred brand), with an average copayment of $20 to $25 or 25% coinsurance, or tier 3 (nonformulary brand), with an average copayment of $40 to $45 or 50% coinsurance. Pharmacy claims data from a national pharmacy benefit manager (PBM) without interventions for antidepressants in 2004 or 2005 were used for the comparison group.

RESULTS: The generic antidepressant dispensing rate increased by 20 points (32.5% to 52.5%) in the intervention group but only 7.4 points (24.9% to 32.3%) in the comparison group in 2005 compared with 2004. The principal measure of antidepressant drug cost per day of therapy in the intervention group decreased by 11.7% (from $2.40 to $2.12) in 2005 compared with 2004 versus a 2.7% decrease (from $2.60 to $2.53) in the comparison group (P <0.001). Days of antidepressant drug therapy per member per month (PMPM) dropped by 1.5% (from 1.74 to 1.71) in the intervention group versus a decrease of 5.0% (from 1.37 to 1.30) in the comparison group in 2005 compared with 2004. The combination of change in drug cost and utilization resulted in a 13.0% decrease in antidepressant drug cost, from $4.16 PMPM in 2004 to $3.62 in 2005, compared with a 7.6% decrease (from $3.57 to $3.30 PMPM) in the comparison group. The 9.0% difference in drug cost per day represents drug cost savings of approximately $0.36 PMPM or $1,880,562 in 2005 dollars for this HMO of approximately 440,000 members.

CONCLUSION: A step-therapy edit requiring HMO members to use a generic antidepressant, excluding tricyclics, prior to use of a brand-name antidepressant resulted in drug cost savings of 9.0% for the entire class of antidepressants, equal to $1,880,562 ($0.36 PMPM) in 2005 dollars in the first year of the intervention. A small (-1.5%) decrease in use of antidepressants occurred in the intervention group, which was less than the 5.0% decrease in utilization of antidepressants in the comparison group.

KEYWORDS: Antidepressant, Drug benefit design, Generic drug, Step therapy, Utilization management

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The direct cost of antidepressant drug therapy should be of interest to managed care organizations, such as health maintenance organizations (HMOs), for several reasons. First, the antidepressants, excluding the tricyclic antidepressants (TCAs), do not significantly differ in their ability to treat depression or in their incidence of adverse events (with some interpatient variability),[1-9] creating an opportunity for achieving similar or better clinical outcomes at lower cost. Second, active drug is not necessary to obtain a clinical response in many patients. In a meta-analysis of original data from 7 randomized controlled trials, Thase et al. found that 51% of outpatients with major depressive disorder responded to placebo, and 36% of the patients randomized to placebo experienced remission during follow-up.[10] Third, many managed care patients who receive antidepressant drugs may not have major depression. Theobald et al. found that only 7% of the medical charts for patients who had received antidepressant drug therapy had documentation of 5 of the 9 symptoms required to make a diagnosis of major depression, and 40% of the medical charts did not include a single symptom necessary to make a diagnosis of major depressive disorder.[11]

Given the lack of a significantly superior choice among the antidepressants, the initial choice of antidepressant medication should be made based, in part, on cost considerations.[12] The availability of multiple generic antidepressant medications creates the opportunity to improve the cost-effectiveness of treatment and lower the cost of treatment for patients as well as HMOs. Three of the selective serotonin reuptake inhibitors (SSRIs) currently on the market are available by generic name. Fluoxetine (Prozac) became available in generic form in August 2001.[13] The first abbreviated new drug application (ANDA) for

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generic Paxil (paroxetine) was approved on September 29, 2003, by the U.S. Food and Drug Administration (FDA),[14] and the FDA approved ANDAs from 5 manufacturers of generic citalopram (Celexa) on October 28, 2004.[15]

In addition to the 3 generic SSRIs, 2 other non-TCA antidepressants are available generically. An ANDA for bupropion SR (Wellbutrin SR), a weak inhibitor of norepinephrine and dopamine uptake, was approved by the FDA on March 22, 2004,[16] which was preceded by the ANDA for immediate-release bupropion that was issued by the FDA on April 17, 2000.[17] The first ANDA for mirtazapine (Remeron), a serotonin, alpha-adrenergic, and histamine antagonist, was approved by the FDA on January 24, 2003.[18] Some of the antidepressants have FDA-approved label indications for conditions other than treatment of depression. The vast majority of patients will both tolerate and respond to one of these 5 generic medications.

In light of multigeneric, multisource availability of the antidepressants, on January 1, 2005, IHC Health Plans and the IHC Behavioral Health Clinical Program introduced the GenericStart! Program. Patients new to antidepressant drug therapy (having no claims history of antidepressant treatment within the previous 6 months) were required to use a generic antidepressant medication (excluding TCAs) prior to coverage of a brand-name antidepressant.

The GenericStart! intervention in 2005 was preceded by the GenericSample program that had been in effect since 2003 for generic fluoxetine and was later expanded to include generic bupropion SR, generic citalopram, and generic paroxetine as these drugs became available generically. The GenericSample program waives the copayment or coinsurance for the first fill of the generic antidepressant when obtained at a participating community pharmacy.

Implementation of the GenericStart! Intervention in 2005 included a notice to all participating physicians. This notice included several key points: (a) generic antidepressants offer a dramatic improvement in cost-effectiveness over the brand-name equivalents because of their low expense with the same efficacy and safety profile as the higher-cost brand antidepressants; (b) generic antidepressants should be considered as the initial choice for a patient presenting with depression; (c) most patients respond within the first 4 to 6 weeks of drug treatment, but a substantial minority of patients may require 8 to 12 weeks of therapy with an antidepressant before response is observed; and (d) the possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs and, therefore, close supervision of high-risk patients should accompany drug therapy.

This research with administrative pharmacy claims was approved by the IHC Institutional Review Board and IHC Patient Privacy Board on February 17, 2006.

Methods

The drugs included in this study are shown in Table 1, which includes the copayment tier and formulary status of each drug. Generic drugs in this study are shown with the preface "generic" in Table 1 and include bupropion, citalopram, fluoxetine, mirtazapine, and paroxetine. Pharmacy claims with dates of service from January 1, 2004, through December 31, 2005, were included in the study if the National Drug Code (NDC) on the pharmacy claim was grouped under 1 of 4 Medispan Generic Product Indicators (GPIs): GPI starts with 5802 (mirtazapine), GPI starts with 5816 (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline), GPI starts with 5818 (duloxetine and venlafaxine), or GPI starts with 5830 (bupropion, maprotiline, and venlafaxine prior to the market introduction of duloxetine in August 2004).

The administrative claims data fields for this analysis were actual allowed drug (ingredient) cost, total days supply of antidepressant drug therapy, total pharmacy claims, total generic drug claims, and total eligible member-month counts. The principal outcome measures were generic dispensing ratio (GDR, the number of generic drug claims divided by the total number of drug claims), days of therapy per claim (prescription [Rx]), drug cost per claim, drug cost per day, and drug cost per member month (PMPM).

The study design involved a 12-month preperiod (calendar

TABLE 1 Formulary Status and Copayment Tiers of the Antidepressants in the Intervention Group*

Drug	Common Dosage Forms	Copayment Tier
Generic fluoxetine	10, 20, 40 mg cap	1
Fluoxetine (Prozac)	10, 20, 40 mg cap	3
Generic paroxetine	10, 20, 30, 40 mg tab	1
Paroxetine (Paxil)	10, 20, 30, 40 mg tab	3
Paroxetine (Paxil CR)	12.5, 25, 37.5 mg tab	2
Generic citalopram	10, 20, 40 mg tab	1
Citalopram (Celexa)	10, 20, 40 mg tab	3
Escitalopram (Lexapro)	10, 20 mg tab	3
Sertraline (Zoloft)†	25, 50, 100 mg tab	2
Generic bupropion	75, 100, 150 mg tab	1
Generic bupropion SR	100, 150 mg tab	1
Bupropion XL (Wellbutrin XL)	150, 300 mg tab	2
Generic mirtazapine	15, 30, 45 mg tab	1
Mirtazapine (Remeron)	15, 30, 45 mg tab	3
Venlafaxine (Effexor)	25, 37.5, 50, 75, 150 mg tab	2
Venlafaxine XR (Effexor XR)	37.5, 75, 150 mg cap	2
Duloxetine (Cymbalta)‡	20, 30, 60 mg cap	3

** Average tier-1 copayment of $5-$10; tier-2 copayment of $20-$25 or 25% coinsurance, and tier-3 copayment of $40-$45 or 50% coinsurance.*
† Zoloft (sertraline) moved from tier-2 to tier-3 copayment on April 1, 2005.
‡ Cymbalta (duloxetine) moved from tier-3 to tier-2 copayment on July 1, 2005.

TABLE 2A Utilization and Cost for Antidepressants*—Intervention Group

	2004				2005			
Intervention Group	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Rxs	67,435	66,922	66,861	67,028	62,689	62,726	65,124	66,098
Total days of therapy	2,222,985	2,210,707	2,207,740	2,289,231	2,181,231	2,178,170	2,264,819	2,362,329
Utilizing members	31,303	30,554	30,442	30,460	29,581	29,308	30,527	30,932
Ingredient cost†	$5,403,976	$5,354,397	$5,268,783	$5,371,476	$4,853,841	$4,701,993	$4,701,388	$4,757,358
Generic Rx ratio	28.51%	31.61%	32.44%	37.42%	45.69%	53.03%	54.35%	56.73%
Units per day	1.21	1.21	1.21	1.19	1.20	1.22	1.25	1.26
Days per Rx	32.96	33.03	33.02	34.15	34.79	34.73	34.78	35.74
Ingredient cost/Rx	$80.14	$80.01	$78.82	$80.14	$77.43	$74.96	$72.19	$71.97
Ingredient cost per utilizing member	$172.63	$175.24	$173.08	$176.35	$164.09	$160.43	$154.01	$153.80
Eligible members	427,79	426,671	426,597	432,674	429,964	431,312	440,214	449,218
Prevalence of use	7.3%	7.2%	7.1%	7.0%	6.9%	6.8%	6.9%	6.9%
Days PMPM	1.73	1.73	1.73	1.76	1.69	1.68	1.71	1.75
Rxs PMPM	0.0526	0.0523	0.0522	0.0516	0.0486	0.0485	0.0493	0.0490
Cost per day	$2.43	$2.42	$2.39	$2.35	$2.23	$2.16	$2.08	$2.01
Average cost PMPM	$4.22	$4.18	$4.12	$4.14	$3.76	3.63	3.56	3.53

** Antidepressants exclude tricyclic antidepressants and include the selective serotonin reuptake inhibitors (SSRIs, Medispan Generic Product Indicator [GPI] beginning with 5816), serotonin and norepinephrine reuptake inhibitors (SNRIs, GPI beginning with 5818), bupropion (GPI beginning with 5830), and mirtazapine (GPI beginning with 5803).*

† Ingredient cost is the actual allowed drug cost without dispense fees and before member cost-share.

PMPM = per member per month; Rx = prescription.

year 2004) and a 12-month postperiod (calendar year 2005). To control for change in new generic drug introduction (e.g., citalopram in November 2004)[15]; new label warnings for antidepressants regarding suicidality; and antidepressant market dynamics, including drug promotion to consumers and physicians and other factors, a comparison group of similar size (total membership) was identified from the pharmacy claims data for a national pharmacy benefit manager (PBM) without interventions for antidepressants during the 24-month study period. Approximately one third of members in the PBM data were subject to a 3-tier copay design (e.g., copayments of $5 for generic drugs, $15 for formulary brand drugs, and $30 for nonformulary brand drugs); the remaining two thirds of members in the PBM data were subject to a 2-tier copayment design (e.g., $10 generic, $20 brand).

For the intervention groups, all generic antidepressants had a tier-1 copayment, which was waived for the first fill for the 4 GenericSample drugs (generic bupropion, generic citalopram, generic fluoxetine, and generic paroxetine). Paxil CR (paroxetine), Wellbutrin XL (bupropion), and Effexor XR (venlafaxine) were in the second copayment tier in 2004 and 2005. Lexapro (escitalopram) was in the third copayment tier, and Zoloft (sertraline) moved from tier-2 to tier-3 copayment on April 1, 2005. Cymbalta (duloxetine) moved from tier-3 to tier-2 copayment on July 1, 2005 (Table 1).

The *t* test (MS Excel) was used to test the null hypothesis that the change in average drug cost per day of therapy in 2005 compared with 2004 was no different in the intervention group compared with the comparison group.

Results

The intervention group was similar to the comparison group in the number of total eligible members, the number of utilizing members (patients), and total antidepressant drug costs (Tables 2a and 2b). For the principal measure of drug (ingredient) cost per day of therapy, the comparison group experienced a small dip in average cost, from $2.60 per day in the first quarter (Q1) of 2004 to $2.53 per day in 2005 Q4 (Figure 1). The intervention group experienced a cost per day nearly parallel to the comparison group until the first quarter of the intervention (2005 Q1), and the reduction in drug cost became increasingly evident over the 4 calendar quarters of the 12-month intervention period.

The source of the drug cost savings is found in the generic dispensing ratio (Figure 2). The slope of the GDR was similar for the intervention and comparison groups until 2004 Q4, and the GDR became increasingly divergent throughout the 12-month intervention period, ending in a GDR of 52.5% for

TABLE 2B Utilization and Cost for Antidepressants*—Comparison Group

	2004				2005			
Comparison Group†	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Rxs	59,982	57,325	55,590	55,050	53,122	53,180	49,700	49,124
Total days of therapy	2,099,305	2,024,803	1,978,274	1,962,688	1,882,799	1,892,078	1,771,615	1,746,636
Utilizing members	30,942	29,413	29,274	28,245	27,843	27,487	26,036	25,083
Ingredient cost‡	$5,528,569	$5,309,003	$5,116,906	$5,052,124	$4,806,113	$4,819,268	$4,438,808	$4,424,389
Generic Rx ratio	21.98%	25.62%%	25.48%	26.86%	29.59%	34.19%	33.26%	32.31%
Units per day	1.22	1.22	1.21	1.20	1.20	1.20	1.20	1.20
Days per Rx	35.00	35.32	35.59	35.65	35.44	35.58	35.65	35.56
Ingredient cost/Rx	$92.17	$92.61	$92.05	$91.77	$90.47	$90.62	$89.31	$90.07
Ingredient cost per utilizing member	$178.68	$180.50	$174.79	$178.87	$172.61	$175.33	$170.49	$176.39
Eligible members	509,044	495,930	489,086	465,057	483,444	470,330	462,699	448,696
Prevalence of use	6.1%	5.9%	6.0%	6.1%	5.8%	5.8%	5.6%	5.6%
Days PMPM	1.37	1.36	1.35	1.41	1.30	1.34	1.28	1.30
Rxs PMPM	0.039	0.039	0.038	0.039	0.037	0.038	0.036	0.036
Cost per day	$2.63	$2.62	$2.59	$2.57	$2.55	$2.55	$2.51	$2.53
Average cost PMPM	$3.62	$3.57	$3.49	$3.62	$3.31	$3.42	$3.20	$3.29

** Antidepressants exclude tricyclic antidepressants and include the selective serotonin reuptake inhibitors (SSRIs, Medispan Generic Product Indicator [GPI] beginning with 5816), serotonin and norepinephrine reuptake inhibitors (SNRIs, GPI beginning with 5818), bupropion (GPI beginning with 5830), and mirtazapine (GPI beginning with 5803).*

† The comparison group comprises approximately 500,000 beneficiaries who were not subject to interventions involving antidepressant drug therapy in either 2004 or 2005. Approximately 36% of these beneficiaries were enrolled in 3-tier copayment plans in 2004 and about 30% in 2005, and the remainder was enrolled primarily in 2-tier copayment plans. The common copayments were $5-$10 for tier 1 for community pharmacy drugs, $15-$25 for tier-2 drugs, and $30-$45 for tier-3 drugs. Mail-service copayments were generally 2 times the community pharmacy copayment amounts.

‡ Ingredient cost is the actual allowed drug cost without dispense fees and before member cost-share.

PMPM=per member per month; Rx=prescription.

antidepressant drugs for the intervention group in 2005 Q4 versus 32.3% for the comparison group.

Utilization of antidepressant drugs as measured by the days of drug therapy PMPM changed very little during the 8 calendar quarters of observation (Figure 3). For the intervention group, the days of drug therapy PMPM was 1.73 in 2004 Q1 and 1.75 days PMPM in 2005 Q4. The days of antidepressant drug therapy PMPM was lower for the comparison group, 1.37 PMPM in 2004 Q1 and 1.30 in 2005 Q4, but the slope of the lines showing this utilization measure were similar throughout the 8 calendar quarters of observation.

The combination of drug cost (per day of therapy) and utilization (days PMPM) are shown in Figure 4 for the 8 calendar quarters. The average drug cost PMPM for antidepressant drugs was parallel for the 2 groups in the preperiod in 2004 and converged during the intervention period in 2005.

There are some interesting trends within the average utilization of antidepressants in the intervention. The increase in market share of generic citalopram at the end of 2004 and throughout 2005 is approximately equal to the sum of the decline in brand citalopram plus the decline in the chemically similar escitalopram (Table 3). The Rx market share of both bupropion XL and venlafaxine XR dipped in 2005 compared with the end of the preintervention period in 2004, while the large decline in Rx market share of bupropion SR was balanced closely by a corresponding increase in the Rx market share of generic bupropion SR.

Generic fluoxetine maintained its position as the most commonly dispensed non-TCA antidepressant, accounting for about 22% of all non-TCA antidepressant pharmacy claims at the end of the observation period in 2005 Q4 (Table 3). The Rx market share for generic citalopram rose dramatically to more than 15% in 2005 Q4, at the apparent expense of branded sertraline (Zoloft), which dropped in Rx market share from 16% in the 4 quarters of 2004 to 12% in 2005 Q4.

The intervention group experienced a relative 61.5% increase in the generic utilization ratio, from 32.5% of all non-TCA antidepressants in 2004 to 52.5% in 2005, versus a 29.7% relative increase in the comparison group, from 24.9% in 2004 to 32.3% in 2005 (Table 4). For the principal measure of average drug (ingredient) cost per day of therapy, the intervention group experienced a relative decrease of 11.7%, from $2.40 in 2004 to $2.12 in 2005, versus a 2.7% relative decrease in the comparison

FIGURE 1 Average Ingredient Cost of Antidepressants per Day of Therapy

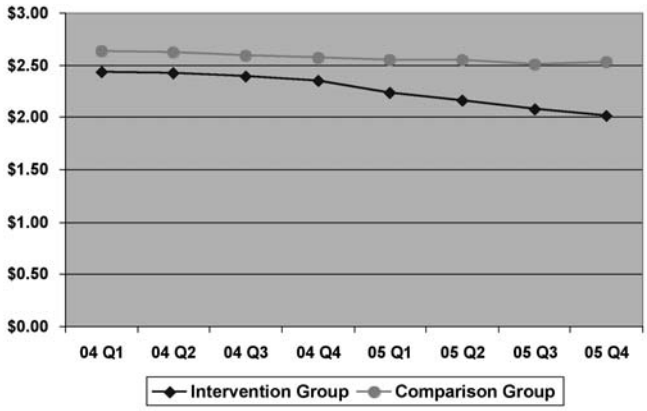
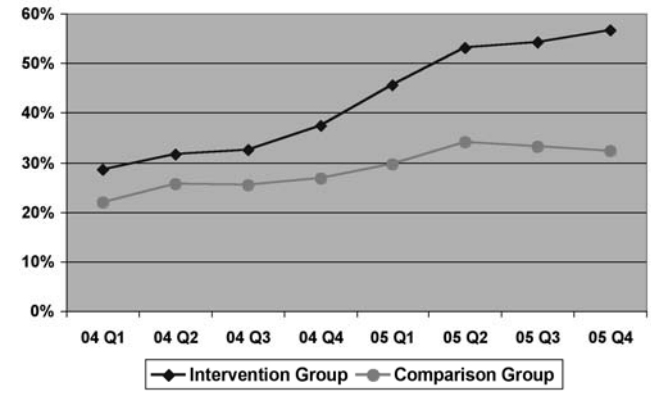


FIGURE 2 Average Ratio of Generic Claims for Antidepressants



group, from $2.60 per day in 2004 to $2.53 in 2005 (*t* value 23.78, *P* <0.001). The 9.0% relative savings in actual drug cost translates into total savings of $1,880,562 in 2005 (actual drug ingredient cost of $19,014,580 versus projected drug cost of $20,895,142 absent the intervention).

Discussion

The principal measure in this study was the drug cost per day of drug therapy. This step-therapy intervention requiring first-line therapy with a generic antidepressant was not expected to adversely affect utilization of antidepressant drugs. Implementation of a generics-first, step-therapy protocol for antidepressant drug therapy in this HMO with approximately 440,000 members reduced the average drug cost per day of therapy by 9.0%. The utilization of antidepressant drugs, as measured by either the prevalence of use of antidepressants or the days of drug therapy PMPM, was not adversely affected.

On June 30, 2005, the FDA released a public health advisory regarding the risk of suicidality in adult patients treated with antidepressants and, specifically, all of the drugs in the present study.[19] This announcement drew increased attention from the public as well as health care professionals to the potential risk associated with a class of drugs formerly thought to be virtually risk free.[20] In October 2004, the FDA requested new "black box" labeling on 32 antidepressants, warning of increased risk of suicidality when used in children.[21] This was followed by a request for all manufacturers to include notice of the new risk warning in direct-to-consumer advertisements on or before February 11, 2005.[22]

The attention to possible threats to safety in the use of antidepressants during the study period would be expected to have a downward influence on the utilization of these drugs. Market data from Verispan for 54,000 community pharmacies in 2005 showed that SSRI utilization declined in 2005, with volume in prescriptions down 4.1% compared with 2004 and sales down 13.9% in dollars.[23] This market-wide influence may be reflected in the days of antidepressant drug therapy PMPM, particularly in 2005 Q1 (Figure 3). The prevalence of use of antidepressants, excluding TCAs, dipped slightly by a relative 5.4% in 2005 (10.5%) compared with 2004 (11.1%) in the intervention group and by nearly the same relative decline (-6.7%) in the comparison group, from 10.5% in 2004 to 9.8% in 2005.

Over the entire 24-month study period, the average days of antidepressant drug therapy PMPM declined by only 1.5% in the intervention group, from 1.74 in 2004 to 1.71 in 2005, and by 5.0% in the comparison group, from 1.37 days PMPM in 2004 to 1.30 days PMPM in 2005 (Table 4). This slightly deeper decline in utilization in the comparison group contributed to the 7.6% drop in antidepressant drug cost PMPM, from $3.57 in 2004 to $3.30 in 2005, versus a 13.0% drop in antidepressant drug cost PMPM in the intervention group, from $4.16 in 2004 to $3.62 in 2005.

The 9.0% savings in cost per day of non-TCA antidepressant drug therapy compares favorably with other managed care interventions. In a study of the cost and utilization outcomes following the implementation of prescriber profiles (report cards) with academic detailing, Yokoyama et al. found 7.4% cost savings per day of SSRI therapy, from $2.43 per day in 1998 to $2.25 in 1999, and 4.0% additional savings, to $2.16 per day in 2000.[24] These savings translated into $0.07 PMPM in the first year and $0.04 PMPM in the second year, compared with $0.36 PMPM in drug cost savings in the present study.

The step-therapy intervention implemented in this HMO did not permit prior authorization (PA) or medical exception. In a study of 3 step-therapy programs for one Midwest employer of approximately 20,000 beneficiaries, Motheral et al. found savings in PMPM drug costs for the proton pump inhibitors (for heartburn) and for the nonsteroidal anti-inflammatory drugs

but not for the SSRIs.[1] One of the major differences in the intervention described by Motheral et al. and the present study was the opportunity for exceptions and the outcome that 23% of affected members reported receiving a medical exception to the first-line therapy.

Review of the medical literature through a PubMed/MEDLINE search conducted in March 2006 using the keywords "step therapy and depression" revealed only 20 published studies. None of these 20 studies addressed directly the subject of using generic antidepressants as first-line therapy in major depressive disorder. One study did report that drug switching is an important strategy in the treatment of depression since half of all treated depressed patients fail to respond adequately to the first prescribed antidepressant.[25]

Fleck and Horwath concluded, from a MEDLINE review for the years 1999 to 2004, that antidepressant clinical trials are typically inadequate in the stratification of patients by disease severity to better manage difficult to treat depression.[26] A 2-step approach is necessary to achieve better outcomes in pharmacologic treatment of major depression. Factors such as comorbid medical and psychiatric conditions are considered first in evaluation of patients nonresponsive to pharmacotherapy. The second step involves 4 strategies for enhancing the efficacy of antidepressant therapy: optimization of dose, augmentation, combination, and drug switching. Given the high rate of drug switching in the effective pharmacological management of depression, first-line treatment with a generic non-TCA agent seems particularly cost effective.

Utilization of antidepressants is an important consideration in clinical outcomes of patients with major depressive disorder, but the issue is far from simple.[27] In the ARTIST (A Randomized Trial Investigating SSRI Treatment) study, 46% of patients (n = 256) with major depressive disorder treated with an SSRI were nonresponders at 6 months, and 53% of the patients (n = 222) who received SSRI therapy for at least 6 months did not achieve remission.[28] While a minimum of 6 to 8 weeks of antidepressant drug therapy is considered to be necessary to determine if antidepressant drug therapy will be effective,[29] 30% to 50% of patients have substantial residual symptoms after adequate first-line therapy,[30] and the absence of improvement after 4 weeks of treatment with an adequate dose of a given antidepressant predicts an ultimate inadequate response.[31]

FIGURE 3 *Utilization of Antidepressants in Days per Member per Month*

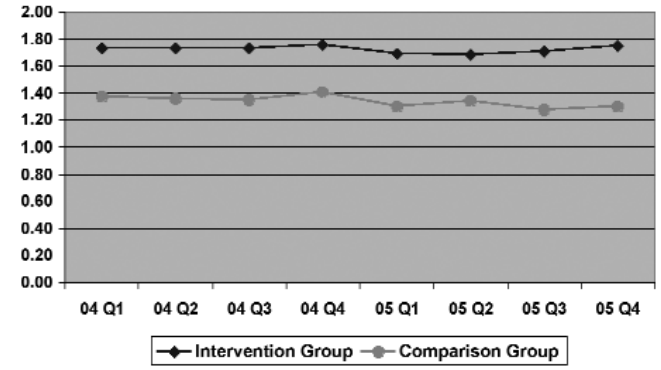
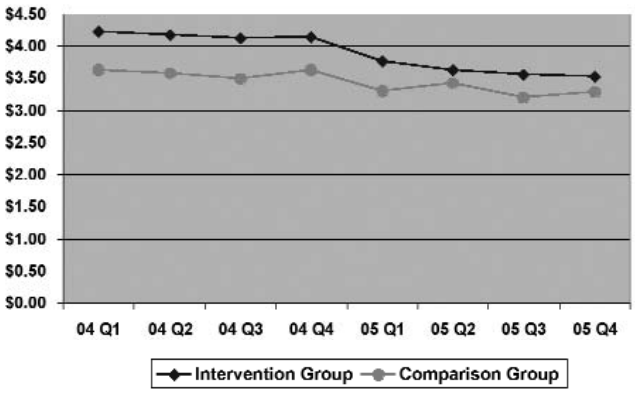


FIGURE 4 *Average Ingredient Cost of Antidepressants per Member per Month*



Limitations

This study examined only the effects of a managed care protocol on direct drug costs. While there is no expectation that the use of generic SSRIs as first-line therapy in depression would have an influence on medical or other health system costs, these other costs were not measured in the present study. The only study specific to this issue of total medical costs associated with an SSRI generic step-therapy program was published in a sponsored supplement that may or may not have received adequate peer review.[32] Second, any managed care intervention is likely to have an effect on humanistic outcomes, including patient satisfaction, and these outcomes were not measured in the present study.

The savings in cost per day in the present study was probably influenced, in part, by the implementation in mid-2005 of a dose-optimization intervention for generic fluoxetine. At the time, the maximum allowable cost (MAC) for fluoxetine 40 mg capsules was $1.59, and the MAC for fluoxetine 20 mg capsules was $0.15. HMO members who were using 40 mg per day of fluoxetine were switched by community pharmacists from one 40 mg capsule to two 20-mg capsules. This fluoxetine dose-optimization intervention did not affect utilization, but undoubtedly had some influence on the average cost per day of drug therapy in 2005 compared with 2004 even though it was in effect for only half of 2005. Another consideration in the

TABLE 3 Market Share* (%) of the Commonly Used Antidepressants in the Intervention Group

	2004				2005			
Drug	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Generic fluoxetine	20.59	20.25	20.59	20.47	21.34	21.59	21.56	21.78
Fluoxetine (Prozac)	0.94	0.89	0.83	0.71	0.52	0.52	0.40	0.42
Generic paroxetine	5.89	6.01	6.08	6.21	6.72	9.74	9.29	8.88
Paroxetine (Paxil)	0.98	0.71	0.53	0.42	0.34	0.31	0.18	0.09
Paroxetine (Paxil) CR	5.07	4.86	4.44	4.19	3.21	0.31	0.75	0.99
Generic citalopram	NA	NA	NA	4.52	10.47	12.25	13.46	15.38
Citalopram(Celexa)	10.49	9.91	9.67	4.82	0.48	0.35	0.30	0.26
Escitalopram (Lexapro)	11.06	11.25	11.48	12.02	10.37	9.31	8.79	7.41
Sertraline (Zoloft)	16.19	16.12	16.20	15.91	15.79	14.22	13.09	12.39
Generic bupropion	0.47	0.48	0.48	0.47	0.50	0.45	0.52	0.54
Bupropion (Wellbutrin)	0.01	0.02	0.01	0.02	0.01	0.01	0.02	0.01
Generic bupropion SR	0.35	4.04	4.39	4.79	5.75	8.12	8.56	9.31
Bupropion (Wellbutrin) SR	7.68	2.37	1.32	0.95	0.45	0.26	0.20	0.14
Bupropion (Wellbutrin) XL	5.70	7.37	8.03	8.33	7.48	7.15	6.82	6.48
Generic mirtazapine	0.78	0.83	0.90	0.96	0.91	0.88	0.96	0.84
Mirtazapine (Remeron)	0.26	0.14	0.11	0.07	0.06	0.05	0.05	0.03
Venlafaxine (Effexor)	0.44	0.46	0.41	0.41	0.37	0.44	0.44	0.39
Venlafaxine (Effexor XR)	12.67	12.92	12.86	12.79	12.03	11.72	11.53	11.01
Duloxetine (Cymbalta)	NA	NA	0.03	0.33	1.28	1.94	2.71	3.30
Total generic	28.08	31.61	32.44	37.42	45.69	53.03	54.35	56.73
Total brand	71.49	67.02	65.92	60.97	52.39	46.59	45.28	42.92
Other	0.43	1.37	1.64	1.61	1.92	0.37	0.37	0.35
Total	100	100	100	100	100	100	100	100

** Market share in pharmacy claims (prescriptions).*
NA = not available.

present study was the temporary market unavailability of Paxil CR, which is evident in the Rx share data in Table 3 beginning in 2005 Q2. However, the comparison group was similarly affected.

The present study was designed to assess aggregate drug cost and drug utilization outcomes associated with a step-therapy requirement for HMO members to use a generic SSRI as first-line therapy prior to coverage of a brand-name antidepressant. No attempt was made to determine how many HMO members were affected or how much of the observed reduction in aggregate SSRI drug cost was due to first-time SSRI users who were affected directly or indirectly by the SSRI step-therapy edit. Also left to future research is the subject of adherence and persistence with SSRI therapy. McManus et al. found that 38% of "new users" of SSRIs were still receiving SSRIs 6 to 8 months later, but this research was conducted among patients eligible for social security entitlements in Australia and did not address generic versus brand-name SSRIs.[33]

The present study was conducted in an HMO that is part of an integrated health system that has been ranked consistently as #1 or #2 in the top 100 health systems in the United States by the measure of degree of integration.[34-36] However, the results of this study should be generalizable to other populations since the intervention involved primarily an administrative change in pharmacy benefits, an intervention that did not necessarily involve either physician or pharmacy provider cooperation and support.

There are administrative costs associated with step-therapy interventions, and these costs were not measured in this study. The step-therapy intervention employed in the present study used pharmacy claims history to identify prior antidepressant drug use and thereby avoided some of the administrative burden for pharmacists, members, and prescribers that would have otherwise been incurred by a simple PA requirement for brand-name SSRIs.[37] Nevertheless, community pharmacists undoubtedly did incur some administrative costs associated

TABLE 4 *Primary Outcomes for the Intervention Group Versus the Comparison Group for Antidepressants*

	Intervention Group			Comparison Group		
	2004	2005	% Change	2004	2005	% Change
Generic Rx ratio	32.5%	52.5%	61.5	24.9%	32.3%	29.7
Days per Rx	33.3	35.0	5.2	35.4	35.6	0.5
Drug cost per Rx	$79.77	$74.09	-7.1	$92.15	$90.10	-2.2
Days PMPM	1.74	1.71	-1.5	1.37	1.30	-5.0
Rxs PMPM	0.0522	0.0489	-6.4	0.0388	0.0367	-5.5
Drug cost PMPM	$4.16	$3.62	-13.0	$3.57	$3.30	-7.6
Drug cost per day [SD]	$2.40* [1.32]	$2.12* [1.38]	-11.7	$2.60* [2.07]	$2.53* [2.07]	-2.7
Patients	47,542	46,097		51,546	45,817	
Mean age [SD]	39.3 [14.4]	39.1 [14.4]		42.9 [12.9]	43.6 [12.8]	
% female	67.9%	68.6%	1.0	70.4%	70.8%	0.5
Average membership	428,280	437,677		489,779	466,292	
Prevalence of use	11.1%	10.5%	-5.4	10.5%	9.8%	-6.7
Days/patient	187.8	194.9	3.8	156.5	159.2	1.7
Drug cost/patient	452.68	414.44	-8.4	$407.53	$403.53	-1.0

** P <0.001 for the t test comparison of means.*
PMPM=per member per month; Rx=prescription.

with contacting prescribers to obtain first-line antidepressant prescriptions and in counseling patients about the administrative edit and therapeutic interchange,

Conclusion

This HMO of approximately 440,000 members implemented a step-therapy protocol for members new to antidepressant drug therapy, excluding tricyclic antidepressants, in which the use of a generic antidepressant was required prior to coverage of a brand-name antidepressant. First-year savings in 2005 were $1,880,562, equivalent to $0.36 PMPM. The generic utilization ratio for antidepressants increased from 32.5% in 2004 to 52.5% in 2005, and the average actual drug cost per day of antidepressant therapy declined by 11.7% or a relative 9.0% compared with the comparison group. Antidepressant drug utilization PMPM did not appear to be affected by the intervention.

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