

Changes in Physician Antipsychotic Prescribing Preferences, 2002–2007

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Objective: Physician antipsychotic prescribing behavior may be influenced by comparative effectiveness evidence, regulatory warnings, and formulary and other restrictions on these drugs. This study measured changes in the degree to which physicians are able to customize treatment choices and changes in physician preferences for specific agents after these events. **Methods:** The study used 2002–2007 prescribing data from the IMS Health Xponent database and data on physician characteristics from the American Medical Association for a longitudinal cohort of 7,399 physicians. Descriptive and multivariable regression analyses were conducted of the concentration of prescribing (physician-level Herfindahl index) and preferences for and likelihood of prescribing two first-generation antipsychotics and six second-generation antipsychotics. Analyses adjusted for prescribing volume, specialty, demographic characteristics, practice setting, and education. **Results:** Antipsychotic prescribing was highly concentrated at the physician level, with a mean unadjusted Herfindahl index of .33 in 2002 and .29 in 2007. Psychiatrists reduced the concentration of their prescribing more over time than did other physicians. High-volume psychiatrists had a Herfindahl index that was half that of low-volume physicians in other specialties (.18 versus .36), a difference that remained significant ($p < .001$) after adjustment for physician characteristics. The share of physicians preferring olanzapine dropped from 29.9% in 2002 to 10.3% in 2007 ($p < .001$) while the share favoring quetiapine increased from 9.4% to 44.5% ($p < .001$). Few physicians (<5%) preferred a first-generation antipsychotic in 2002 or 2007. **Conclusions:** Preferences for specific antipsychotics changed dramatically during this period. Although physician prescribing remained heavily concentrated, the concentration decreased over time, particularly among psychiatrists. (*Psychiatric Services* 65:315–322, 2014; doi:10.1176/appi.ps.201200536)

Antipsychotics have been approved by the U.S. Food and Drug Administration (FDA) to treat schizophrenia, bipolar disorder, and major depression—disorders that impose an enormous morbidity and mortality burden (1,2). These medications are used off-label for many other indications (3). Physicians face a choice of more than 90 antipsychotic products (24 molecules and their reformulations). Six second-generation antipsychotics introduced between 1989 and 2002 rapidly became first-line treatments on the basis of claims that they were more effective and safer than first-generation antipsychotics. Second-generation antipsychotics continue to claim a majority of the market despite their higher costs (4).

However, comparative effectiveness research findings published ten to 15 years after second-generation antipsychotics were introduced indicate that these agents pose significant risks and that, with the exception of clozapine, they may be no more effective than first-generation antipsychotics. For example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), published in 2005, which compared four second-generation antipsychotics with one first-generation antipsychotic among patients with schizophrenia, found few differences among the drugs on all-cause discontinuation rates, the trial's primary endpoint. Notably, CATIE also found that the risk of adverse effects and reason for

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discontinuation differed widely across the five antipsychotics (5).

Although CATIE findings remain controversial (6,7), one might expect physicians to have changed their antipsychotic prescribing in response to these findings and those from other studies (8). Before the CATIE results were published, the FDA issued safety warnings in 2003 and 2005 (9,10) in response to evidence of risks (11), and consensus statements emphasized heterogeneous risk profiles across second-generation antipsychotics (12). Prescribing preferences are also shaped by formularies and utilization management tools (13,14), which were used by some payers during this period (15,16). Little is known about whether new evidence or changes in policy led clinicians to change their preferences for certain drugs or diversify their prescribing (17,18). Studies of prescribing for depression and bipolar disorder indicate that physicians rely heavily on preferred agents (19–24). One study examined the degree of concentration in antipsychotic prescribing, but results were reported at the facility level, not at the provider level, for a single year (25). We measured changes in physician antipsychotic prescribing behavior using data from a longitudinal cohort (2002–2007) of physicians from multiple specialties.

Methods

We used monthly physician-level data from the Xponent database, maintained by IMS Health, on the number of prescriptions dispensed for all antipsychotics between January 2002 and December 2007. Xponent directly captures over 70% of all U.S. prescriptions filled in retail pharmacies and utilizes a patented proprietary projection methodology to represent 100% of prescriptions filled in these outlets. We linked prescribing data to information on physician characteristics from the American Medical Association (AMA) Masterfile (26). These data were available for a 10% nationally representative sample of physicians from ten specialties with the highest antipsychotic prescribing volume (internal medicine, general practice, family medicine, family practice,

pediatrics, psychiatry, geriatric psychiatry, child and adolescent psychiatry, neurology, and child neurology) (N=24,206). We limited the 10% sample to a longitudinal cohort of physicians who regularly prescribed antipsychotics (defined as ≥ 20 dispensed antipsychotic prescriptions or the equivalent of two patients filling prescriptions for ten months per year) both in 2002 and in 2007. Our rationale was that very-low-volume prescribers tell us little about the diversity of a physician's prescribing. For example, a physician who writes a single prescription is by definition 100% concentrated on that particular drug. Thus including observations for very-low-volume prescribers may yield unstable or misleading results. This reduced sample of 7,399 physicians accounted for 83% of all antipsychotic prescriptions among the 24,206 physicians in our sample in 2007. Sensitivity analyses that included the larger sample yielded qualitatively similar results.

We examined prescribing patterns for six orally administered second-generation antipsychotics (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole). Because aripiprazole was launched late in 2002 and was seldom used that year, we do not report its use separately in some analyses. We also examined prescribing of two oral first-generation antipsychotics: haloperidol, the most commonly prescribed first-generation antipsychotic, and perphenazine, because of its inclusion in CATIE. We combined other first-generation antipsychotics into a single group. Prescriptions for reformulations (for example, Zyprexa Zydis) were merged with the original ingredient (for example, olanzapine).

Dependent variables

We analyzed trends in three aspects of prescribing behavior. First, we measured the concentration of a physician's prescribing by constructing a Herfindahl index, a metric that characterizes the degree of competition in a market. Here we use it to describe the diversity of a physician's prescribing of antipsychotics to his or her patient population. The index is constructed as

$$H = \sum_{i=1}^N s_i^2$$

where s_i is the share of prescriptions for drug i in the antipsychotic market, and N is the number of drugs in the market. The smallest possible value of H is $1/N$ (prescribing each drug with the same frequency), and the largest is 1 (prescribing only one drug). Notably, H is dependent on the volume of a physician's prescribing (for example, $H=1$ by definition if the physician writes a single prescription), which is why we excluded very-low-volume prescribers. We hypothesized that physicians would reduce the concentration of their prescribing in response to evidence of differential side effects.

Second, we quantified changes in the specific drugs most preferred by physicians between 2002 and 2007. For each physician, we identified the drug with the most prescriptions filled in 2002 and then in 2007, yielding estimates of the proportion of physicians who demonstrated stable (or unstable) preferences over time. Third, we assessed changes in the proportion of physicians with any prescriptions for each drug in 2002 versus 2007. We hypothesized that physicians may have changed not only their preferences for but also their general use of specific agents on the basis of risk of metabolic effects, potentially reducing use of drugs with the highest risk (olanzapine and clozapine) and increasing use of drugs with intermediate risk (risperidone and quetiapine) and low risk (aripiprazole and ziprasidone) (12). We also examined whether physicians increased their use of lower-cost agents (first-generation antipsychotics) following evidence that these agents were cost-effective relative to second-generation antipsychotics (27).

Key explanatory variables

We examined whether changes in prescribing behavior differed by physician specialty and prescribing volume. We classified physicians based on specialty into two groups: psychiatry (general, child and adolescent, and geriatric) and "other," which included neurologists (general and child); pediatricians; and physicians

trained in internal medicine, family medicine, family practice, and general practice. Notably, general practitioners and other nonpsychiatrist specialists behaved similarly on the prescribing practices we observed. To assess prescribing volume, a potential proxy for a physician's experience prescribing antipsychotics, physicians were classified according to the total number of antipsychotic prescriptions their patients filled in 2001, one year before the study period. Physicians above the 50th percentile were considered high-volume prescribers. We included a dummy variable in the concentration analysis for the 1.8% of physicians whose patients did not fill any antipsychotic prescriptions in 2001.

Covariates

We included as covariates physician sex; age in 2002; and practice setting (solo practice; two-person; other, such as locum tenens, medical school, and inpatient attending only; or no classification available, with group practice as the reference category); whether the physician practiced in a hospital setting part- or full-time; attendance at a medical school ranked in the top 25 in 2010 by *U.S. News & World Report*; and whether the physician graduated from a foreign medical school. The final variable was included to explore any differences arising from training in other countries, where preferences for or availability of specific agents may have differed. As a potential proxy for less contact with the pharmaceutical industry, we included an indicator of whether the physician requested that the AMA withhold his or her information from pharmaceutical sales representatives. We included dummy variables for the state in which physicians practiced to account for time-invariant geographic variation in prescribing practices (28), including Medicaid program restrictions on some antipsychotics in some states (15).

Analyses

To examine the concentration of antipsychotic prescribing, we used generalized estimating equations (GEE) to account for repeated measurements made for the same physician each year.

Table 1

Characteristics of physicians prescribing antipsychotics in 2002^a

Characteristic	Total sample (N=7,399)		Psychiatrists (N=2,437)		Other physicians (N=4,962) ^b	
	N	%	N	%	N	%
Female	1,561	21.1	704	28.9	858	17.3
Age						
<30	777	10.5	168	6.9	610	12.3
30–39	2,375	32.1	675	27.7	1,702	34.3
40–49	2,841	38.4	909	37.3	1,935	39.0
≥50	1,398	18.9	685	28.1	715	14.4
Medical school						
U.S. top 25	829	11.2	346	14.2	481	9.7
Foreign	1,805	24.4	734	30.1	1,067	21.5
Practice type						
Solo	2,094	28.3	838	34.4	1,260	25.4
Two person	348	4.7	39	1.6	308	6.2
Group practice	3,130	42.3	534	21.9	2,595	52.3
No classification	784	10.6	380	15.6	407	8.2
Other	1,043	14.1	648	26.6	397	8.0
Any hospital practice	3,655	49.4	1,080	44.3	2,570	51.8
Requested AMA to withhold information from industry representatives	266	3.6	63	2.6	208	4.2
Antipsychotic prescriptions per year (M±SD)	272±591		649±893		86±156	
Annual prescribing volume quartile (N of antipsychotic prescriptions)						
1 (20–41)	1,872	25.3	158	6.5	1,717	34.6
2 (42–77)	1,857	25.1	222	9.1	1,632	32.9
3 (78–205)	1,820	24.6	519	21.3	1,305	26.3
4 (≥206)	1,850	25.0	1,540	63.2	308	6.2

^a Sources: IMS Xponent, January 2002–December 2007, IMS Health Inc. and American Medical Association (AMA) Masterfile, 2002–2007. Sample includes physicians with 20 or more antipsychotic prescriptions both in 2002 and in 2007.

^b Includes general practitioners (internal medicine, family practice, and primary care) and physicians from other specialties (neurology and pediatrics)

We used a gamma distribution with a log link function because of the skewed distribution of the Herfindahl index in our sample. We tested for differences in changes in the physician-level Herfindahl index over time by specialty or by volume by including three-way interaction terms between specialty, volume, and time (yearly indicators) and the three two-way interaction terms for these variables. In addition to these variables, the model adjusted for the other covariates listed above.

To explore the stability of preferences over time, we conducted a test of proportions comparing the proportion of physicians who preferred each drug in 2002 versus 2007.

Finally, we describe changes in the unadjusted rate of physicians' prescription of each drug to any of their patients in 2002 and in 2007.

Results

Characteristics of sample

Of the 7,399 physicians in our sample, 2,437 were psychiatrists and 4,962 were in other specialties (4,398 general practitioners and 564 neurologists or pediatricians) (Table 1). Psychiatrists were more likely than physicians in other specialties to be women, age 50 or older, and solo practitioners. Psychiatrists' mean annual antipsychotic prescribing volume was more than seven times that of other physicians.

Concentration of prescribing

Antipsychotic prescribing was highly concentrated in physicians' preferred agents. The unadjusted mean Herfindahl index for physicians was .33 in 2002 and .29 in 2007. Physicians in nonpsychiatric specialties below the median antipsychotic prescribing

Table 2

Analysis of variables as predictors of the concentration of physician prescribing of antipsychotics^a

Variable	Estimated outcome ratio	95% CI	p
Intercept	.44	.43–.46	<.001
Female (reference: male)	1.04	1.03–1.05	<.001
Age	1.00	1.00–1.00	<.001
Medical school (reference: ranked ≥ 26)			
U.S. top 25	1.02	1.01–1.04	<.001
Foreign	.97	.96–.98	<.001
Practice type (reference: group practice and other)			
Solo practice	1.02	1.01–1.03	<.001
Two person	.99	.97–1.00	.119
No classification	1.00	.99–1.01	.898
Any hospital practice (reference: none)	.99	.97–1.00	.067
Requested AMA to withhold information from industry representatives (reference: no request) ^b	.99	.97–1.01	.227
Specialty and prescribing volume			
Psychiatrist (reference: general practitioner and other specialists)	.95	.94–.97	<.001
High-volume prescriber (reference: low volume)	1.17	1.16–1.18	<.001
Psychiatrist $\times$ high volume	.68	.67–.70	<.001
Missing volume information in 2001	1.03	1.02–1.03	<.001
Year (reference: 2002)			
2003	.93	.92–.95	<.001
2004	.87	.85–.88	<.001
2005	.86	.84–.87	<.001
2006	.86	.84–.88	<.001
2007	.88	.87–.90	<.001
Time trend by specialty			
2003 $\times$ psychiatrist	.96	.95–.97	<.001
2004 $\times$ psychiatrist	.94	.92–.95	<.001
2005 $\times$ psychiatrist	.95	.93–.96	<.001
2006 $\times$ psychiatrist	.94	.93–.96	<.001
2007 $\times$ psychiatrist	.94	.93–.96	<.001

^a Fixed effects for U.S. state were included in the analysis.

^b AMA, American Medical Association

volume had the most concentrated prescribing, with an unadjusted Herfindahl index of .36, compared with a Herfindahl index of .18 for psychiatrists prescribing a high volume of antipsychotics.

Our initial model included the three-way interaction between specialty, volume, and time and the three two-way interactions involving the same variables. Because the third-order interaction explained almost no variation in the data, we removed it and refit the model with the two-way interactions. We found two interactions—one between specialty and time and one between specialty and volume—that were highly significant.

Table 2 presents results from the GEE model examining the effects of provider characteristics on prescribing concentration.

The coefficients comprising the specialty by time interaction revealed that the concentration of prescribing among psychiatrists decreased over time and in a manner consistent across high- and low-volume prescribers. Specifically, the Herfindahl index decreased (that is, prescribing was less concentrated) across time for psychiatrists compared with nonpsychiatrists. For example, in 2002 the concentration of prescribing by psychiatrists was 4.9% lower than that of nonpsychiatrists who had the same volume, and

in 2007 the concentration of psychiatrists was 10.5% lower than that of nonpsychiatrists who had the same volume ($p < .001$). The interaction between specialty and volume indicated that antipsychotic prescribing volume was also strongly associated with concentration after the analysis controlled for other factors and that its effect depended on specialty. Specifically, in the same year, high-volume psychiatrists had a Herfindahl index that was 44.7% lower than that of low-volume physicians in other specialties ($p < .001$), and low-volume psychiatrists had a Herfindahl index only 4.9% lower than that of low-volume prescribers in other specialties (both cases $p < .001$).

Changes in preferred antipsychotics

Figure 1 shows the dramatic changes in physicians' preferred agents between 2002 and 2007. In 2002, few physicians favored a first-generation antipsychotic, with only 3.7% preferring haloperidol, .6% perphenazine, and 23.8% one of the other first-generation antipsychotics. Among second-generation antipsychotics in 2002, more than two-thirds of physicians favored the three agents—risperidone (30.2%), olanzapine (29.9%), and quetiapine (9.5%)—whereas only 1.8% preferred clozapine, and .5% ziprasidone.

By 2007, a vast majority of physicians had shifted preferences to a different drug (all $p < .001$) (Figure 1). Among the first-generation antipsychotics, even a smaller proportion of physicians favored haloperidol (2%) or perphenazine (.5%) in 2007 than in 2002. For half of the second-generation antipsychotics, substantial reductions were noted in the share of physicians preferring them. Olanzapine had the largest decline in the share of physicians preferring it (from 29.9% in 2002 to 10.3% in 2007), and only 16.4% of physicians preferred it in 2002. A decline in physician preference for risperidone was noted—from 30.2% of physicians in 2002 to 23.1% in 2007.

The largest increase in the share of physicians preferring a drug was for quetiapine—the fifth of the second-generation antipsychotics to be introduced. Preference for quetiapine

increased more than fourfold (from 9.4% to 44.5% of physicians). Increases in the share of physicians preferring ziprasidone and aripiprazole were also noted, although the absolute share was low.

Figure 2 highlights the particularly dramatic shift in physicians' observed preferences among the 2,215 physicians who favored olanzapine above other antipsychotics in 2002. Over half (52.8%) of all prescriptions filled by patients of these physicians were for olanzapine in 2002. However, beginning in the second quarter of 2003 (before CATIE was published or the FDA warning was issued), these physicians reduced their use of olanzapine such that by 2007, it accounted for only 17.8% of their prescriptions. Most of the shift was to prescriptions for quetiapine and risperidone.

Changes in any prescribing of specific antipsychotics

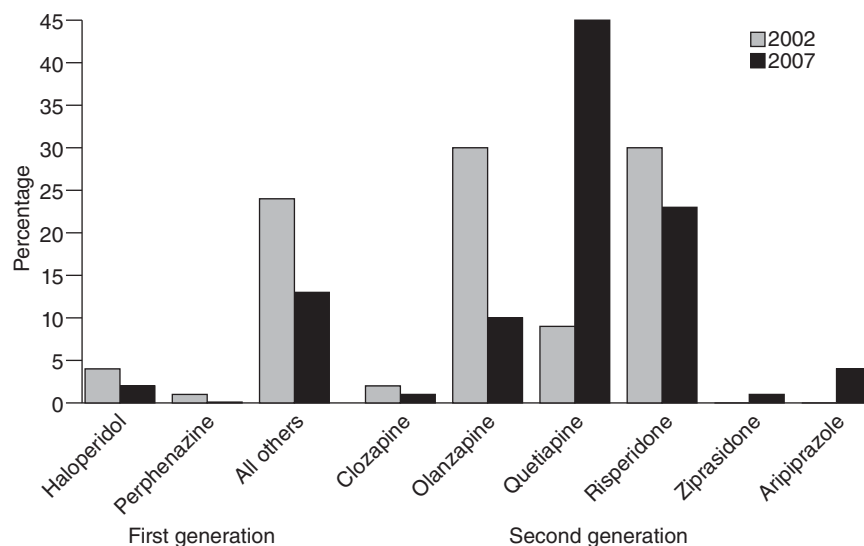
From 2002 to 2007, the share of physicians with any prescribing of the two first-generation antipsychotics in their practice dropped slightly from 56% to 49% for haloperidol and from 20% to 19% for perphenazine (Figure 3). Among the second-generation antipsychotics, the share of physicians prescribing olanzapine to any of their patients decreased (from 87% to 76%), and a decrease was also noted for risperidone (from 88% to 86%). The share of physicians prescribing any quetiapine, ziprasidone, and clozapine increased; the largest increase was for quetiapine (from 66% to 92% of physicians). All of these changes were statistically significant ($p < .001$).

Discussion

We report three key findings. First, physicians' reliance on a preferred antipsychotic agent, as measured by the concentration of their prescribing, declined between 2002 and 2007, particularly among psychiatrists. Second, clear differences were found by specialty and prescribing volume in the concentration of a physician's antipsychotic prescribing. Third, substantial changes were noted in the antipsychotic agent most preferred by physicians. These findings have a number of implications for clinicians, researchers, and policy makers.

Figure 1

Changes in preferred antipsychotic medication among 7,399 physicians between 2002 and 2007^a



^a Source: IMS Xponent, January 2002–December 2007, IMS Health Inc. The preferred medication is the product for which the physician's patients filled the most prescriptions in a given year.

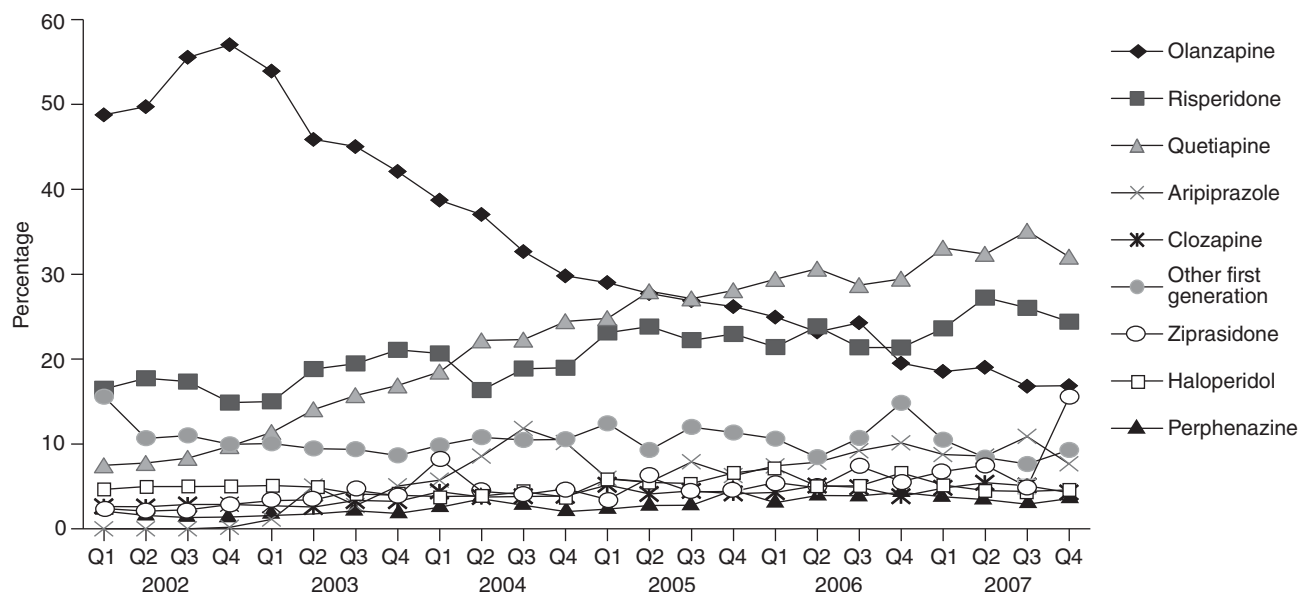
We measured changes in the concentration of prescribing in the wake of high-profile FDA safety warnings, consensus statements issued from professional societies, a landmark comparative effectiveness study, expanded approval of new indications and off-label use, highly publicized litigation against second-generation antipsychotic manufacturers (29), and policy changes regarding coverage of these drugs. We hypothesized that evidence of substantial heterogeneity in risk profiles might have induced physicians to diversify their choice of agent, and we found evidence of this effect, particularly among psychiatrists. The rise in antipsychotic polypharmacy during this period may have increased the diversity of agents prescribed (30). We found a mean Herfindahl index of .27 to .33 depending on the year, which is slightly higher than that reported for antidepressants, suggesting greater concentration in antipsychotic prescribing (22,24). Customizing drug treatment to individual patients requires more time and communication with patients and can impose a significant burden on physicians (19). To reduce this burden, physicians often rely heavily on a few drugs per class (19–21,23,24,31), an

approach often reinforced in clinical pharmacology education (32). However, heavy reliance by physicians on a few antipsychotics could be problematic for patients because of heterogeneity in their side effects.

Our finding that psychiatrists were so much less concentrated (more diversified) in their choice of antipsychotic than physicians in other specialties suggests that the capacity to customize treatment may vary by the degree of specialization, by experience, or with the severity of patient illness (33,34). Psychiatrists generally focus their prescribing on a few therapeutic categories, whereas psychiatric medication makes up a smaller (if growing) part of primary care physicians' prescribing (35). Variability in concentration may also be related to interspecialty differences in the clinical indications for use or in patient severity. Notably, the effects of specialty remained strong even after adjustment for volume differences. Given the dramatic expansion in antipsychotic prescribing in primary care settings, it is important to better understand these specialty differences (36,37) and their implications for the quality of pharmacotherapy for mental disorders (38–40).

Figure 2

Quarterly share (percentage) of prescriptions written for antipsychotics among 2,215 physicians who favored olanzapine above other antipsychotics in 2002^a



^a Source: IMS Xponent, January 2002–December 2007, IMS Health Inc.

Even after the analyses controlled for specialty, antipsychotic prescribing volume was negatively associated with concentration, suggesting that physicians' ability to diversify medication choice may increase with experience, perhaps because the burden of customization decreases. Although a volume-quality relationship is well documented in other areas of health

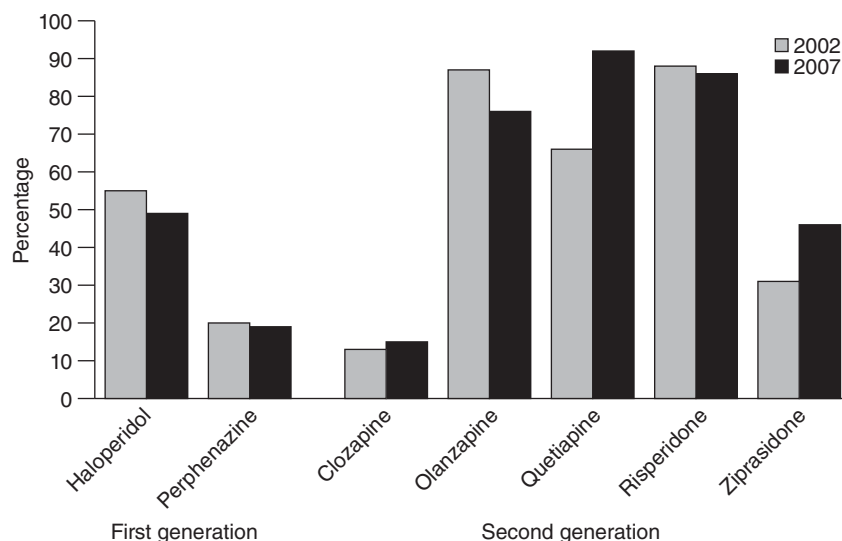
care, we are unaware of evidence of such a relationship for prescribing (31).

Preferences for specific drugs changed dramatically. The antipsychotic for which the greatest decline was noted was olanzapine, and the share of physicians who prescribed any of the two first-generation antipsychotics we studied (haloperidol and perphenazine) also fell. In terms

of physician preference, quetiapine showed the greatest increase. How does one explain these shifts? We were unable to tease out the effects on prescribing behavior of any single event, because all physicians were equally "exposed," and we lacked a comparison group. However, four important factors warrant discussion. First, although metabolic effects are arguably one of the most salient issues influencing antipsychotic prescribing, the shifts in observed physician preferences cannot be entirely explained by differences in metabolic effects. Physicians increased use of one drug with intermediate risk (quetiapine) but not the other (risperidone), and a reduction in prescribing was noted for a drug with low metabolic risk (ziprasidone). Second, some shifts in preferences may have been driven by off-label use (for example, quetiapine for sleep disturbances) (3,41). Third, the reduction in use of first-generation antipsychotics and clozapine suggests that physicians either were unaware of or not influenced by evidence of the cost-effectiveness of first-generation antipsychotics (27) and the greater effectiveness of clozapine for patients with treatment-resistant illness (42). Fourth, antipsychotics are heavily promoted by the pharmaceutical

Figure 3

Percentage of 7,399 physicians prescribing antipsychotics^a



^a Source: IMS Xponent, January 2002–December 2007, IMS Health Inc.

industry through sales representatives, sponsorship of professional meetings, and other means (43), which have significant effects on physician prescribing preferences (44–46). Unfortunately, data on the exposure of individual physicians to promotion are not available. Notably, aripiprazole has also been advertised to consumers (43).

Our study had several limitations. First, we lacked patient-level information and therefore could not determine the reason for antipsychotic use or the severity of illness or distinguish between new treatment starts and ongoing treatment episodes. Second, although we selected our time period to coincide with key events, such as FDA warnings and the CATIE trial, other underlying factors may have had an effect on prescribing behavior, and we cannot infer a causal relationship between the release of studies or warnings and prescribing decisions. Third, our data were for prescriptions filled through retail outlets (that is, no data were included from mail order programs or long-term care facilities), and we thus could not observe changes in these settings. Furthermore, to the extent that we had data only for filled prescriptions (not for all those written), our results were confounded by factors affecting patient decisions to fill prescriptions. However, it is not likely that discrepancies between prescriptions written and filled differed systematically by drug. Finally, we were unable to adjust for some important influences on prescribing behavior, such as manufacturers' promotional efforts. Such factors may vary by specialty, by health systems in which physicians practice, and by payers, which may shape physician preferences through formularies and utilization management tools (15,16).

Conclusions

Physician preferences for specific antipsychotics changed dramatically from 2002 to 2007. Some physicians remained heavily concentrated in their antipsychotic prescribing, whereas others diversified their choice of agent, with striking differences by specialty.

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