

U.S. National Trends in the Use of Antipsychotics During Office Visits, 1998–2002

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Background. There is a paucity of studies on U.S. national trends in the use of antipsychotic medications in the 21st century. This study examined national trends in the prescribing of antipsychotic drugs in office-based physician practices.

Methods. National probability sample survey data from 1998–2002 National Ambulatory Medical Surveys were used to analyze the prescribing trends. The weighted visit estimates and percentages were compared across the years using z-test.

Results. The number of antipsychotic-related visits was found to increase significantly and nearly two-fold, from 4.6 million in 1998 to 8.6 million in 2002. During the same period, the number of visits for second-generation antipsychotic drugs nearly tripled. The proportion of visits for the second-generation agents, as a percentage of visits for all antipsychotic drugs, rose sharply from about 48% in 1998 to 84% in 2002. Correspondingly, the percentage of visits involving first-generation antipsychotic drugs declined. The growth in the number of visits involving antipsychotic drugs over the 5-year period was substantial (120%) in visits with non-psychiatrist physicians, but not in visits involving psychiatrists.

Conclusions. The trend of growth in prescription of antipsychotic drugs in office visits, accounted by increased use of second-generation antipsychotics, has persisted into the 21st century. Increased prescribing of these agents by non-psychiatrists is also apparently fueling this trend. This trend of shift from first-to-second generation antipsychotic agents, though not unambiguously supported by extant safety and efficacy data, is endorsed by guidelines based on expert-consensus and limited data. Given the high-level use of second-generation drugs, more practical studies of these drugs, focusing on effectiveness or long-term outcomes, are needed.

Keywords Antipsychotic, Trends, Office, Prescribing, Physicians

INTRODUCTION

Antipsychotic prescribing practices have changed remarkably with the introduction of second-generation antipsychotic medications. Two studies based on national U.S. data suggested that the overall prescription of antipsychotic medications in outpatient visits rose markedly in the 1990s, driven mainly by the use of second-generation antipsychotic medications (1,2). Analyzing 1989–1997 National Ambulatory Medical Care

Surveys (NAMCS), Hermann and associates found that antipsychotic prescribing rates increased significantly in the 1990s, after a nine-year decline (1). Using the combined 4-year (1997 to 2000) NAMCS and National Hospital Ambulatory Care Survey data, Van Brunt et al. reported that the use of antipsychotic drugs is substantial in outpatient settings; nearly 1% of all health-care visits involved antipsychotic drugs (2). Further, they noted that about 30% of these antipsychotic-related visits involved non-psychiatric physicians.

Hermann et al. reported that the total numbers of visits for first-generation drugs appeared relatively unchanged between 1989 and 1997 (1). However, these numbers significantly declined between 1997 and 2000 (2). Both studies found

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sizable increases in the proportions of visits in which second-generation antipsychotic drugs were prescribed. By 2000, the use of second-generation agents represented over two-thirds of outpatient visits involving antipsychotic agents (2). Risperidone and olanzapine were the most frequently prescribed antipsychotic drugs during physician visits in late 1990s. Although the use of second-generation antipsychotic agents is endorsed by guidelines based on expert-consensus and limited data (3,4), it is not unambiguously supported by extant safety and efficacy data (5). It remains unclear if these issues have affected the prescribing practices into the 21st century.

The theme of this special issue of the journal is the history of antipsychotic medications. This article contributes to this theme by providing pertinent nationally representative data for the 21st century. To our knowledge, data on the changes in the use of antipsychotic medications in the U.S. beyond 2000 have not been published. Based on the analysis of NAMCS surveys from 1998 to 2002, this paper extends the earlier studies on antipsychotic prescribing practices into the 21st century. Our objective is to determine whether the trends reported by the earlier studies have persisted beyond 2000. Specifically, four questions are addressed. First, is the overall number of office visits during which an antipsychotic drug is prescribed increasing? Second, is the proportion of visits for second-generation antipsychotic drugs (as a percentage of visits for all antipsychotic drugs) increasing? Third, is the proportion of visits for first-generation antipsychotic drugs decreasing? Fourth, is the proportion of visits involving prescription of antipsychotic drugs by non-psychiatric physicians increasing?

METHODS

Data Source

The NAMCS conducted by the National Center for Health Statistics (NCHS) provides the most comprehensive data to monitor office-based practices in the United States. The study used data from the 1998–2002 NAMCS to examine antipsychotic prescribing trends in office-based settings. The survey data, available as public use data files, were downloaded from the NCHS website (6). The South Dakota State University Human Subjects Committee exempted the review of this project as it involves public use data files from the NCHS; these datasets are in public domain and do not contain individual identifiers. The NAMCS is a national probability cross-sectional sample survey of in-person visits to physician offices. The NCHS utilized a multistage probability design that involved probability samples of Primary Sampling Units, physician practices within each unit, and patient visits within those practices. The basic sampling unit was the physician-patient encounter or visit. Only office visits in the offices of non-federally employed physicians were included in the survey. More than 1000 physicians participated in the survey annually for an overall response rate around 65% of eligible physicians.

Data collection techniques and operational definitions for the 1998–2002 surveys were similar. The U.S. Bureau of Census Housing Survey Branch was responsible for data collection, and Constella Group, Inc. performed data processing and coding. Participating physicians or their staff collected data for a systematic random sample of office visits during a randomly assigned week using the Patient Record Form (PRF). This form included information on patient demographics, physician diagnoses, diagnostic services, drugs prescribed, and the disposition of the visit. With respect to medications, physicians were allowed to record up to six medications. This includes all new or continued medications ordered, supplied, or administered during each visit. The NCHS also collected data on physician characteristics prior to the survey implementation. Participating physicians collected over 20,000 PRFs annually.

Prescribed medications were coded for the products along with the generic ingredients according to a unique classification scheme developed at the NCHS, and drug classes were categorized based on National Drug Code numbers. During data coding and editing, detailed instructions were provided by the NCHS to concerned firms to manually review PRFs. The NCHS imputed missing values by randomly assigning a value from a PRF with similar characteristics such as diagnosis, physician specialty, and region. The medical and drug coding and keying operations also involved quality control procedures. In addition to a two-way 10-percent independent verification procedure, all PRFs with differences between coders or with illegible entries were reviewed and adjudicated at the NCHS. Further details concerning the data collection systems, sampling scheme, and definitions of the NAMCS can be found in other sources (7,8).

Coding of Antipsychotic Drugs

Antipsychotic medications selected for analyses included those that were examined in studies involving the NAMCS by Van Brunt et al. (2). These medications were updated and grouped using standard references (9). For the purpose of this study, the first-generation antipsychotics included chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, perphenazine, promazine, thioridazine, thiothixene, and trifluoperazine. The second-generation antipsychotics were aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone.

Data Analyses

SAS was used for data extraction and SUDAAN was used for descriptive analysis (10,11). The secondary data analyses involved the examination of antipsychotic medications prescribed by office-based physicians. Generically coded ingredients in single entity drugs and combination drugs were examined for the 17 antipsychotic medications. A total of

124,487 PRFs were analyzed, of which 1,640 contained anti-
psychotic medications during the five-year study period. The
PRFs involving antipsychotic medications were 223 for 1998,
273 for 1999, 341 for 2000, 352 for 2001, and 451 for 2002.
The national visit estimates were derived for these records
based on the inflation factor called patient sampling weight.
These weights were calculated for each visit by the NCHS
based on the physician and visit sampling rates and were
adjusted for nonresponse bias; the derived weighted estimates
allow for extrapolation to national patterns of practice.

The national estimates were also used to calculate the pro-
portions of visits that involved first-generation antipsychotic
drugs only, second-generation antipsychotic drugs only, and
both groups of antipsychotics, as the percentages of all antipsy-
chotic visits. Because the estimates presented in this study
were based on a sample rather than the entire universe of office
visits, they were subject to sampling variability. Therefore,
95% Confidence Intervals (CI) were calculated for the visit
estimates and proportions based on the standard error. Antipsy-
chotic prescribing trends were analyzed using z-test.

Analyses of the NAMCS data require special consideration
with regard to variance estimation and analysis due to the com-
plex sampling design that includes stratification, clustering,
multiple stages of selection and disproportionate sampling.
SUDAAN, a statistical design software, was used to describe
the national estimates and to analyze the trends using masked
design variables in the NAMCS (11,12). The analysis results in
more accurate standard error estimates than those derived from
the NCHS formula. Additional details regarding the use of
masked design variables in statistical analyses can be found
elsewhere (12).

RESULTS

The overall trends in the total number of antipsychotic-
related visits are presented in Figure 1. These visits nearly dou-
bled ($p < 0.01$), from 4.6 million (95% CI, 3.1 – 6.2 million) in
1998 to 8.6 million (95% CI, 6.2 – 11.0 million) in 2002. This
increase was also reflected in proportion of overall antipsychotic-
related visits. The proportion of antipsychotic-related visits, as
a percentage of all office visits, increased significantly
($p < 0.01$) from 0.6% in 1998 to 1.0% in 2002. During the
study period, the number of visits for second-generation anti-
psychotic drugs nearly tripled ($p < 0.01$) from 2.5 million
(95% CI, 1.7 to 3.3) in 1998 to 7.6 million (95% CI, 5.5 to 9.8)
in 2002.

**Changes in the Proportion of Visits of First- and Second-
Generation Agents**

The changes in the proportion of visits for first- and second-
generation antipsychotic drugs alone and both (as a percentage
of all visits for antipsychotic drugs) are summarized in Table 1.

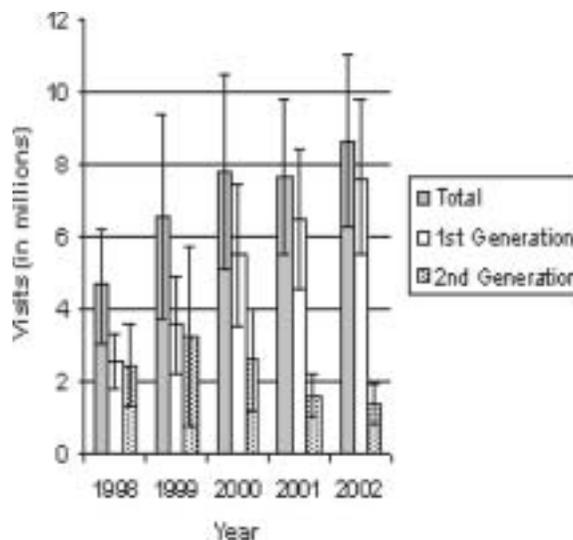


Figure 1 Visit trends involving antipsychotics in office settings, 1998–2002.

Table 1 Antipsychotic Prescribing Practices in Office Visits by Type, 1998–2002

Year		1998	1999	2000	2001	2002
Type						
Percentages* (95% confidence interval)						
1st Generation		45.5	45.3	29.4	15.5	11.7
only		(34.2-56.8)	(23.6-67.1)	(17.3-41.5)	(9.4-21.6)	(7.7-15.7)
2nd Generation		47.5	51.1	66.5	78.8	84.0
only		(36.2-58.8)	(29.4-72.8)	(54.3-78.7)	(72.4-85.1)	(79.2-88.9)
Both		7.0	3.6	4.1	5.7	4.2
		(1.8-12.2)	(1.6-5.5)	(1.1-7.1)	(1.5-9.9)	(2.0-6.4)

*Based on all visits involving antipsychotic drugs.

There was significant difference ($p \leq 0.05$) in these proportions
from 1998 to 2002. Office visits involving prescribing of first-
generation drugs alone declined significantly ($p < 0.01$) from
45.5% in 1998 to 11.7% in 2002. Haloperidol and thioridazine
were the most frequently prescribed first-generation antipsy-
chotic agent during the study period.

In 1998, four of six second-generation antipsychotic
agents were available and these agents alone were prescribed
in 47.5% (95% CI, 36.2 to 58.8) of visits involving antipsy-
chotic agents. All six second-generation antipsychotic agents
were prescribed in 2002 and these agents alone were pre-
scribed in 84.0% (95% CI, 79.2 to 88.9) of visits involving
antipsychotic agents. Olanzapine and risperidone were the
most frequently prescribed second-generation antipsychotic
agents during the study period. They accounted for 28.9%
(95% CI, 24.7% to 33.0%) and 27.4% (95% CI, 23.6% to
31.0%) of the visits involving antipsychotic agents, respec-
tively. The sample sizes on combination of first- and second-
generation agents were too small for a reliable determination
of the trends.

Changes by the Specialty: Psychiatrists vs. Non-Psychiatrists

Although proportion of antipsychotic-related visits involving non-psychiatrists slightly increased from 1998 to 2002, the trend was not statistically significant. Overall 67.8% (95% CI 61.9 to 73.7) of the antipsychotic-related visits involved psychiatrists during the study period. Psychiatrist visit estimates involving antipsychotic medications did not change significantly from 1998 to 2002. However, there was 120% increase ($p < 0.01$) in non-psychiatrist visits involving antipsychotic medications, from 1.5 million (95% CI, 0.8 to 1.8) in 1998 to 3.3 million (95% CI, 2.1 to 4.4) in 2002.

DISCUSSION

The results indicate that the trend of growth in prescription of antipsychotic drugs in office visits, driven by sizable increase in the use of second-generation antipsychotic drugs and increased prescribing of these agents by non-psychiatrists, persisted into the 21st century. Between 1989 and 1997, Herman et al. found approximately 2-fold increase in antipsychotic-related visits in their nine-year study (1). Using 1998–2002 NAMCS data, we also found nearly 2-fold increase, only in five years. This suggests that growth in antipsychotic-related visits was faster in recent years. Antipsychotics were prescribed in nearly 1% of office visits in 2002, indicating their increased use in office visits.

Within this overall increase in antipsychotic-related visits, the visits involving second-generation antipsychotic drugs grew substantially both in absolute terms and as a proportion. Consistent with the findings of earlier NAMCS based analyses (1,2), this study found a 3-fold increase in the number of visits involving these newer drugs, from 2.5 million in 1998 to 7.6 million in 2002. The proportion of antipsychotic visits involving second-generation drugs also increased markedly, from nearly one in two antipsychotic-related visits in 1998 to five out of six antipsychotic-related visits in 2002. Either olanzapine or risperidone was prescribed in nearly one-fourth of visits during the study period. Overall, more than 80% of prescriptions for antipsychotics involved second-generation antipsychotic drugs, making them the “de facto” drugs of choice. These findings imply that the growth in the use of antipsychotic drugs can be completely accounted by increased prescribing of second-generation agents.

In this study, the percentage of visits for first generation drugs declined significantly, from 46% in 1998 to 12% in 2002. This is in contrast to the findings of no change in rate of use of first generation drugs by Herman et al. using the same data source prior to 1998 (1). Combined with the findings of Van Brunt et al. (2), this study suggests that the use of first generation drugs is decreasing in recent years after being relatively stable prior to 1998, possibly due to increased use of second-generation drugs and greater availability of new second-generation drugs. Two new second-generation drugs, namely aripiprazole and ziprasidone, were introduced during this study period.

Our findings suggest that non-psychiatric physicians are to some extent responsible for this growth in the use of antipsychotic agents. Antipsychotic-related visits to non-psychiatrists grew significantly (120%) in the 5-year period; however, there was no significant change in proportion of non-psychiatrist visits as a percentage of all antipsychotic visits. By contrast, antipsychotic-related visits involving psychiatrists were relatively unchanged both in absolute terms and as a proportion. Our findings suggest that second-generation antipsychotic drugs are being used with increasing frequency and substantially outside of the psychiatric specialty. The adoption of these newer drugs by non-psychiatrists may be related to the perception that they are relatively safe compared to the first generation agents. It is also conceivable that psychiatrists (as specialists) were early adopters of newer antipsychotic drugs, and now other physicians are catching up. However, nearly two-thirds of all antipsychotic prescriptions are still written by psychiatrists, indicating the predominant role of the specialty sector. The growing use of second-generation agents might also be an effect of targeted promotion by pharmaceutical companies, and the extensive off-label use of these agents.

Off-Label Use of Antipsychotic Drugs

The literature suggests that clinicians often use second-generation agents for indications not approved by the Food and Drug Administration (13–16). For example, a study in veterans found that although a majority (57%) of patients ($n = 73,981$) were prescribed antipsychotic drugs for schizophrenia in a 4-month period, nearly 43% had diagnoses other than schizophrenia (13). An Italian study revealed that 52% of patients receiving antipsychotic drugs received off-label prescriptions of second-generation agents (14). Thus substantial off-label use of these medications, particularly in mood and anxiety disorders, can partially account for the observed growth in second-generation antipsychotic prescription.

A systematic review on off-label indications of these medications has recently been published (15). The review revealed that data on the off-label usefulness of newer second-generation antipsychotic drugs were limited. However, the available data provided positive cues for the off-label use of these agents in a broad spectrum of psychiatric disorders, underlining the need for “hard” research data. Although such off-label use may frequently not be evidence-based, it can be supported by guidelines based on expert consensus. For example, in geriatric psychiatry, an expert consensus (16) appears to be emerging that antipsychotic drugs are usually indicated in disorders with psychotic symptoms, such as schizophrenia, mania with psychosis, dementia with agitation and delusions, psychotic depression, and delusional disorder. These drugs may also be sometimes indicated in non-psychotic disorders, including mania without psychosis, delirium, dementia with agitation but no delusions, and agitated non-psychotic major depression (16).

Practice versus Evidence

Given the sizable prescription of second-generation antipsychotic drugs, it is pertinent to examine the reasons why guidelines based on expert-consensus and limited data have endorsed these newer drugs as first-line therapy for schizophrenia (3,4). The main reason for preferring second-generation agents over the older antipsychotic drugs is that the former are better tolerated, equal in treating positive symptoms, and equal or better in treating negative symptoms (3,5). A growing body of evidence suggests that the second-generation antipsychotic drugs are less likely to cause tardive dyskinesia than first-generation drugs (3). Additionally, there is evidence that second-generation agents are more likely to be accepted (as shown by trial drop-out rates) by individuals with schizophrenia than the first-generation agents (5). Also, a growing number of U.S. as well as Italian psychiatrists apparently believe that the extant scientific evidence clearly supports the use of second-generation agents as first-line therapy (14,17). Hence, second-generation agents are an emerging standard of care in treating schizophrenia. The main disadvantages of using second-line drugs are: (i) their higher cost, and (ii) metabolic side effects associated with several newer antipsychotic drugs.

The sharp rise in the prescribing of second-generation antipsychotic drugs has not been matched by an equivalent growth in safety and efficacy data, resulting in a mismatch between practice and knowledge. A recent systematic review of second-generation antipsychotic drugs revealed that the evidence for effectiveness of these drugs, in general, was of poor quality (5). This evidence consisted mostly of short-term efficacy trials, whose findings were difficult to generalize to the whole population of patients with schizophrenia. Although the poor quality of trial data precludes any firm conclusions, this systematic review of these data cautiously suggested that many second-generation drugs were more effective in relieving overall symptoms of schizophrenia. With the exception of clozapine, which was more efficacious in treatment-resistant schizophrenia, the second-generation drugs are similar in efficacy. Overall, the review on second-generation agents revealed a paucity of useful effectiveness data and long-term studies. In the absence of definitive data on the relative efficacy, safety, and cost-effectiveness of antipsychotic drugs, the use of second-generation agents is supported by guidelines based on expert consensus and limited data. Given this high-level use of second-generation drugs, long-term and more useful (effectiveness) trials of these drugs are needed.

LIMITATIONS

Limitations of this study pertained to the definitions and the data source used in the study. The research findings will be affected by both sampling error and sources of non-sampling error in the NAMCS, which include nonresponse bias, respondent reporting and processing errors, and incomplete response.

The annual visit estimates reported in this study are reliable and stable according to the NCHS due to sample size and standard error considerations. Extrapolation of national visits from the sub-samples could create potential problems regarding the reliability and confidence level of smaller estimates. Consequently, these smaller estimates such as combination of first- and second-generation agents were not analyzed. The inherent disadvantages of using secondary data, such as dependency in the variables collected by the NCHS, difficulty in evaluating accuracy in data collection and reporting, and use of imputed data may also be limitations of the study.

A potential threat to the validity of findings is the reliance of NAMCS surveys on physician-reported data, which may be subject to inherent inaccuracies. Although the NAMCS data are generalizable to the frequency of drug use per office visit ("encounter"), community estimates of how frequently a medication is being used per patient (prevalence) cannot be obtained (18). Consequently, these results should be interpreted with caution because of the limitations of the NAMCS database.

This database does not provide information from physicians who practice outside of nonfederal, office-based ambulatory practice settings. Thus it excludes treatment settings in which many individuals with chronic psychotic illnesses receive care, such as correctional facilities, Department of Veterans Affairs outpatient clinics, and hospital outpatient departments. Hence, it is unclear if the trends reported here are generalizable to physician practices in these settings. Because NAMCS does not account for non-compliance, drug usage may be overestimated (19). Nevertheless, this NAMCS analysis is valuable because it allows for comparisons with previously reported NAMCS data on antipsychotic use (1). Moreover, given the paucity of national data on the use of antipsychotic drugs in the 21st century, our data are nevertheless informative of the national trends in the use of these drugs. Despite the limitations noted above, NAMCS is the most comprehensive national survey of office-based U.S. practices (1).

CONCLUSIONS

This article reports four important national trends in the use of antipsychotic drugs in the 21st century that suggest a widespread impact of introduction of second-generation antipsychotic drugs. First, the overall use of antipsychotics in office-based practices has substantially increased. Second, this increase is entirely accounted by growth in prescription of second-generation antipsychotic drugs. Third, the use of first-generation antipsychotic drugs is declining. Fourth, non-psychiatric physicians are now playing an increasingly important role in prescription of antipsychotic drugs. Indeed, they may be now fueling the growing use of antipsychotic drugs. Overall, our data suggest that a vast majority (>80%) of prescriptions Overall, antipsychotics involved second-generation

antipsychotic drugs, making them the “de facto” drugs of choice. This trend of shift from first-to-second generation antipsychotic agents, though not unambiguously supported by extant safety and efficacy data, is endorsed by guidelines based on expert-consensus and limited data. Given this high-level use of second-generation drugs, long-term and more useful (effectiveness) trials of these drugs are needed.

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