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Research Article

The prescribing of potentially dangerous drug combinations involving antipsychotics within US physician offices

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ABSTRACT

Objective: Antipsychotic use has increased rapidly over the past decades. Because of the way in which most antipsychotics are metabolized, simultaneous use of antipsychotics with other medications that may interact negatively with the antipsychotic have the potential to cause serious harm. Using seven years of U.S. outpatient data for potentially dangerous prescribing patterns, this study updates and expands earlier research of nine combinations of potentially dangerous drug combinations.

Methods: 107 million physician office visits, where an antipsychotic was prescribed or continued, were analyzed from the 2006-2012 National Ambulatory Medical Care Survey (NAMCS) and used to calculate dangerous prescribing patterns and visit rates. Building on a prior list of potentially dangerous drug combinations involving nine antipsychotics: clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, haloperidol, perphenazine, and chlorpromazine, these drugs were classified into major, moderate, and major/moderate combinations of prescribing patterns based on their capability to cause permanent damage or harm.

Results: 10 percent of all U.S. physician office visits involving antipsychotics resulted in the patient being exposed to potentially dangerous drug combinations. The most prevalent combination involved risperidone and sertraline. Greater risks of exposure were associated with being between 15 and 40 years of age, being male, being covered by Medicaid or Medicare, and having schizophrenia or depression.

Conclusions: These findings point to the continued need for research and interventions that aim to identify appropriate drug dosage levels for potentially dangerous drug combinations and pragmatically inform physicians.

Introduction

Antipsychotic medications are increasingly being used to treat a widening range of psychiatric conditions [1-4]. Between 1995 and 2008, the number of outpatient visits involving antipsychotic prescriptions rose from 6.2 million to 14.3 million, an increase of 130 percent [4]. Originally intended to treat schizophrenia and bipolar disorder, today most antipsychotics are used "off label" to treat nonpsychotic conditions such as anxiety and attention deficit hyperactivity disorder (ADHD) in children [4-6].

While antipsychotics have proven enormously helpful in treating schizophrenia and bipolar disorder, there is little

evidence of their usefulness in treating many less severe nonpsychotic conditions despite their widespread use in treating those conditions [5,7-9]. Additionally, antipsychotics are known to have a high propensity to cause a range of neurological, metabolic, cardiovascular, gastrointestinal, hematological, genito-urinary, musculoskeletal, endocrine, and other side effects [5,7,9]. For example, antipsychotics have been associated with extrapyramidal symptoms, metabolic adverse effects, sedation, hypotension, cardiac arrhythmias, prolactin elevation and sexual dysfunction, in addition to central and peripheral anticholinergic side effects [7].

Patients using antipsychotics often use them in conjunction with additional medications, which increases the risks of side effects in some cases. Most patients with schizophrenia use an antipsychotic along with another medication for conditions such as hypertension, diabetes mellitus and depression [10]. Because of the way in which most antipsychotics are metabolized, simultaneous use of an antipsychotic and another medication that does not interact well with the antipsychotic can significantly increase the risk of adverse effects [11]. Yet prescribing physicians tend not to be well informed about potential drug interactions involving antipsychotics and regularly do not take those considerations into account when prescribing antipsychotics [12].

Despite these important concerns over the safety issue of our nation's increased use of antipsychotics, surprisingly few attempts have been made to quantify rates of exposure to potentially dangerous drug combinations involving antipsychotics. One study examining a large state's Medicaid claims data found that almost a quarter of patients using an antipsychotic for treatment of schizophrenia were exposed to a potentially dangerous drug combination and that nine percent were exposed to such a combination by the same prescriber and on the same day [11].

Our study seeks to update and expand our knowledge in this area by determining the national proportion of physician office visits involving antipsychotics that resulted in the patient being exposed to potentially dangerous drug combinations and the risk factors associated with exposure. To do so, we use a list of potentially dangerous drug combinations, first published in *Psychiatric Services* in 2012, to capture national trends in evolving ambulatory antipsychotic prescribing patterns.

Data and Methods

Data

We examined data from the National Ambulatory Medical Care Survey (NAMCS) for the period 2006-12. NAMCS, which provides nationally representative estimates of ambulatory care provided at physicians' offices and community health centers, is conducted annually by the National Center for Health Statistics and is a widely used data source within health policy research [13,14]. Randomly selected, NAMCS-participating providers complete a survey for approximately 30 visits that occurred during a randomly selected one-week period [13]. The survey collects an array of information on the patient and the provider in addition to the visit itself, including information on up to eight drug mentions [15]. These drug mentions include any prescription medications that the physician or community-health-center provider ordered or provided during the visit [16]. They also include any prescription medications that the physician or community-health-center provider ordered or provided prior to the visit and which the provider expects the patient to continue taking irrespective of whether a refill was provided at the visit.[16] Because these drug mentions are included in the survey, NAMCS has a long history of being used to examine issues related to the simultaneous use of multiple prescription drugs [17-22].

Sample

To create samples of sufficient size capable of generating antipsychotic-specific estimates, we aggregated surveys from 2006-12. During this time period, there were 119 million physician office visits where antipsychotics were prescribed or continued. Of these visits, 12 million were excluded from our study because the antipsychotics prescribed at the visit could not be analyzed due to a lack of clinical literature on their potentially dangerous pairing with other drugs. Our sample therefore included the remaining 107 million (90%) of visits involving prescriptions for antipsychotics.

Exposure

We defined exposure to potentially dangerous drug combinations based on information from *Facts and Comparisons* [23]. A drug reference tool produced by Wolters Kluwer Health, *Facts and Comparisons* classifies potentially harmful drug combinations into five levels ranging from minor to severe harm. Paralleling a previous study, we focused on drug combinations classified as having the potential to cause: (a) severe or life-threatening harm or (b) less severe but still clinically significant harm [11]. We therefore defined visits resulting in "potentially dangerous drug combinations" as visits where an antipsychotic was prescribed or continued along with another medication that, when used with the antipsychotic, could cause life-threatening or clinically significant harm to the patient. All other visits were defined as not having potentially dangerous drug combinations prescribed.

Our study includes an analysis of the severity levels of potentially dangerous drug combinations. Using classifications in *Facts and Comparisons*, "Major" refers to potentially severe or life-threatening combinations capable of causing permanent damage. "Moderate" refers to combinations that are not life-threatening but may cause deterioration in a patient's clinical status possibly requiring additional treatment, hospitalization or an extended hospital stay. Lastly, "Major/Moderate" refers to combinations capable of resulting in *both* types of harm to the patient.

Guided by the earlier list, we examined potentially dangerous drug combinations involving nine antipsychotics: clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, haloperidol, perphenazine, and chlorpromazine. Again, physician office visits involving these nine specific antipsychotics in our investigation accounted for 90 percent of all visits involving antipsychotics over our seven-year study period.

Analyses

Table 1 presents demographic and clinical characteristics of physician office visits involving any antipsychotic prescriptions. Table 2 lists the 10 most common potentially dangerous drug combinations at such visits. Table 3 shows risk factors associated with exposure to potentially dangerous drug combinations. The risk factors were estimated using a logistic regression model generating odds ratios for various demographic and clinical characteristics of the patients and providers at each visit.

Table 1. Characteristics of physician office visits involving antipsychotics, overall and by visits in which the patient was exposed to potentially dangerous drug combinations involving the antipsychotic, averaged over 2006-2012.

Characteristic	Total % N = 15,243,000 visits per year	Exposed % N = 1,603,000 visits per year
Total	100.0	10.5
Age		
<15	7.2	9.6
15-40	28.8	12.4
41-64	48.1	11.0
65+	15.9	6.1
Sex		
Women	55.3	10.1
Men	44.7	11.1
Location		
Urban	86.7	10.8
Rural	13.3	8.6
Race		
White	74.9	10.9
Black	11.7	10.6
Other	13.4	8.4
Payer		
Private	33.7	11.1
Medicare	30.6	9.9
Medicaid/CHIP	21.2	12.6
Other/unknown	14.5	7.5
Setting		
Psychiatrist	51.6	11.3
Primary care physician	30.5	9.1
Other specialty	17.9	10.7
Psychiatric		
Yes	79.1	11.0
No	20.9	8.7
Condition		
Depression	54.3	12.0
Schizophrenia	11.6	15.5
Anxiety disorders	13.4	10.9
Antipsychotic		
Quetiapine	36.3	5.2
Aripiprazole	21.8	11.0
Risperidone	21.5	20.2
Olanzapine	12.8	14.5
Ziprasidone	7.3	6.3
Haloperidol	4.6	13.0
Clozapine	2.1	21.2
Chlorpromazine	1.6	14.9
Perphenazine	1.2	9.6[a]

The characteristics of each visit include the patient's age, sex, geographic residential location, race, diagnosis, and expected payer source, the visit's setting, and the antipsychotic prescribed or continued at the visit. To classify demographic characteristic variables, we followed the conventions used by the Ambulatory and Hospital Care Statistics Branch.[16] For example, we classified patients with multiple expected payer sources based on the following hierarchy: Medicaid/Children's Health Insurance Program (CHIP), Medicare, private insurance, worker's compensation, self-pay, no charge, and other. Due to sample size restraints, we grouped "worker's compensation, "self-pay," and "no charge" with "other."

Visits were characterized by diagnosis; those with a primary, secondary or tertiary *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9)* code between 290 and 316 or equal to 780 were considered to be visits involving a psychiatric illness. Visits where the survey indicated that the patient had depression were also considered to be visits involving a psychiatric illness. Visits by patients with schizophrenia were defined as visits with an ICD-9 code of 295, visits by patients with anxiety disorders were defined as visits with an ICD-9 code of 300, and visits by patients with depression were defined as visits where the survey indicated the patient had depression.

The National Center for Health Statistics considers an estimate using NAMCS data to be reliable if: (1) it is based on a sample of 30 or more office visits and (2) the standard error is no more than 30 percent of the estimate.[24] All estimates reported in this study meet these criteria unless otherwise noted. Our research does not meet the definition of human subject research and is deemed exempt from IRB review.

Results

Characteristics of Visits

An antipsychotic was prescribed or continued at a total of 15,243,000 physician office visits annually over the period 2006-12 (Table 1). For each of these over 15 million visits we examine the presence and type of prescriptions for *other* antipsychotic drugs and hence, examine prescriptions of potentially dangerous combinations by the same physician.

Patients ages 15 or above accounted for the vast majority of these visits, with patients between ages 41 and 64 accounting for almost half of these visits. Women accounted for a greater share of these visits than men (55% vs. 45%). White patients accounted for three quarters of these visits, with blacks accounting for 12 percent and patients of other or multiple races comprising the remaining 13 percent. Privately insured patients accounted for a third of these visits, followed by Medicare beneficiaries accounting for 31 percent, Medicaid/CHIP beneficiaries accounting for 21 percent, and all other patients accounting for the remaining 15 percent.

The setting and specialty of most visits was psychiatrists' offices (52%), followed by primary care physicians' offices (31%) and other medical specialty offices (18%). Patients who

Table 2. The 10 most common prescriptions of potentially dangerous drug combinations involving antipsychotics within physician office visits, averaged over 2006-2012.

Rank	N (per year)	%	Antipsychotic	Other drug	Severity
1	266,000	15.5	Risperidone	Sertraline	Major
2	220,000	12.8	Aripiprazole	Fluoxetine	Major/Moderate
3	162,000	9.5	Olanzapine	Fluoxetine	Major/Moderate
4	157,000	9.2	Risperidone	Fluoxetine	Major
5	148,000	8.6	Risperidone	Paroxetine	Major
6	98,000	5.7	Aripiprazole	Paroxetine	Major/Moderate
7	90,000	5.2	Risperidone	Carbamazepine	Major/Moderate
8	86,000	5.0	Quetiapine	Carbamazepine	Major/Moderate
9	57,000[a]	3.3	Quetiapine	Fluvoxamine	Major/Moderate
10	49,000[a]	2.9	Ziprasidone	Carbamazepine	Moderate
Sum	1,334,000	77.8			
Total	1,715,000[b]	100.0			

SOURCE: Authors' analysis and estimates of data from the National Ambulatory Medical Care Survey (NAMCS). NOTES Unweighted cell sample sizes are greater than 30 visits and standard errors are less than 30 percent of the estimate except as noted with the symbol "[a]". The reader will notice that the total estimate (with the symbol "[b]" to the right of it) is greater than 1,603,000 (the annual number of visits resulting in exposure each year). This simply means that some patients had visits in which they were exposed more than once. Severity categories come from *Facts and Comparisons*. "Major" refers to potentially severe or life-threatening combinations capable of causing permanent damage. "Moderate" refers to combinations that may cause deterioration in a patient's clinical status possibly requiring additional treatment, hospitalization or an extended hospital stay. "Major/Moderate" refers to combinations capable of resulting in both types of harm to the patient.

Table 3. Risk factors of exposure to potentially dangerous drug combinations involving antipsychotics within physician office visits, averaged over 2006-2012.

Risk Factor	Odds Ratio	95% Confidence Interval	P value
Age			
<15 years (reference)	1.00	-	-
15-40 years	1.14	1.14 - 1.14	< .001
41-64 years	.97	.97 - 0.98	< .001
65+ years	.52	.52 - 0.52	< .001
Sex			
Women (reference)	1.00	-	-
Men	1.11	1.11 - 1.11	< .001
Location			
Urban (reference)	1.00	-	-
Rural	.74	.74 - .74	< .001
Race			
White (reference)	1.00	-	-
Black	.88	.88 - .88	< .001
Other	.70	.70 - .70	< .001
Payer			
Private (reference)	1.00	-	-
Medicare	1.11	1.11 - 1.12	< .001
Medicaid/CHIP	1.20	1.20 - 1.21	< .001
Other/unknown	.65	.65 - .65	< .001
Setting			
Other specialty (reference)	1.00	-	-
Psychiatrist	.77	.77 - .77	< .001
Primary care physician	.75	.75 - .75	< .001
Condition			
None of the below (reference)	1.00	-	-
Schizophrenia	1.82	1.82 - 1.82	< .001
Anxiety disorders	1.07	1.06 - 1.07	< .001
Depression	1.57	1.57 - 1.57	< .001

SOURCE Authors' analysis of data from the National Ambulatory Medical Care Survey (NAMCS).

had depression accounted for a majority of these visits (54%), whereas patients with schizophrenia and anxiety disorders accounted for much smaller percentages (12% and 13%, respectively). Quetiapine was prescribed or continued at over a third of these visits, followed by aripiprazole and risperidone each at 22 percent, olanzapine at 13 percent, ziprasidone at 7 percent, haloperidol at 5 percent, and clozapine, chlorpromazine and perphenazine together comprising the remaining 5 percent.

Exposure to drug combinations

Of these office visits involving antipsychotics, there were a total of 1,603,000 visits annually resulting in patients being

exposed to potentially dangerous drug combinations by the same physician (Table 1). This translates to 10.5 percent of all visits involving antipsychotics. Visits involving the most commonly prescribed or continued antipsychotic, quetiapine, were least likely to result in exposure to potentially dangerous drug combinations (5.2% of such visits resulted in exposure). Reciprocally, visits involving one of the least commonly prescribed or continued antipsychotics, clozapine, were most likely to result in exposure to a potentially dangerous drug combination (21% of such visits resulted in exposure). Visits involving risperidone, the third most common antipsychotic, resulted in a dangerous exposure 20 percent of the time.

The most prevalent potentially dangerous drug combinations involved risperidone and sertraline (16% of such combinations), followed by aripiprazole and fluoxetine (13%), olanzapine and fluoxetine (10%), risperidone and fluoxetine (9%), and risperidone and paroxetine (also 9%) (Table 2). Together, the 10 most common potentially dangerous drug combinations involving antipsychotics prescribed or continued at physician office visits accounted for over three quarters of the potentially dangerous combinations involving antipsychotics. Each of nine most common combinations had severity levels of either "Major" or "Major/Moderate" and therefore were potentially severe or life-threatening combinations capable of causing permanent damage.

Our logistic regression analysis shows that certain patients were at increased risk of exposure to potentially dangerous drug combinations involving antipsychotics at physician office visits (Table 3). Compared to young patients under age 15, patients between ages 15 and 40 were more likely to be exposed (OR=1.14) whereas patients above age 40 were less likely to be exposed (OR=.97 and .52 for patients between ages 41 and 64 and ages 65 or older, respectively). Men were more likely than women to be exposed (OR=1.11). Patients from urban areas were more likely than patients in rural areas to be exposed (OR=.74 for rural patients). Whites were more likely than blacks and patients of other or multiple races to be exposed (OR=.88 and .70 for blacks and patients of other or multiple races, respectively). Medicaid/CHIP and Medicare beneficiaries were more likely than privately insured patients to be exposed (OR=1.20 and 1.11, respectively). Patients seen in settings other than psychiatrists' offices and primary care physicians' offices were more likely to be exposed (OR=.77 and .75 for patients seen in psychiatrists' offices and primary care physicians' offices, respectively). And patients with depression, schizophrenia, and (to a lesser degree) anxiety disorder were more likely than patients without those diagnoses to be exposed (OR=1.57, 1.82, and 1.07, respectively).

Discussion

Our study used NAMCS data averaged over the seven most recent years, 2006-2012, to quantify the share of physician office visits involving antipsychotics that resulted in exposure to potentially dangerous drug combinations that increased the risk of adverse events such as seizures or QT prolongation [11].

Nationally, one out of every ten physician office visits involving antipsychotics resulted in such exposure. This finding is consistent with the findings from a similar study using a large state's Medicaid claims data, which found that nine percent of Medicaid patients using antipsychotics for treatment of schizophrenia in the state were exposed to potentially dangerous drug combinations by the same prescriber and on the same day[11] and suggests that this problem appears to persist nationally and across payers. Our finding is also consistent with the findings that only nine percent of the physicians considered themselves well-informed about drug interactions involving antipsychotics and only 20 percent monitored such interactions in their practices [12].

Importantly, and perhaps disturbingly, nearly two-thirds of the office visits treated with antipsychotics were for two non-psychotic diagnoses - depression (54%) and anxiety disorders (13%). Schizophrenia, was the third highest visit condition (12%) but had the largest share of patients (15.5%) exposed to these potentially dangerous drug combinations.

Our study suggests that interventions aimed at reducing exposure to potentially dangerous drug combinations are needed and that physician offices need to be targets of such interventions. Given our data source, it was beyond the scope of our study to determine the extent to which exposure to potentially dangerous drug combinations involving antipsychotics is the result of prescriptions from multiple physicians or pharmacies. Other studies suggest that exposure to potentially dangerous drug combinations arising from multiple physicians and pharmacies does happen, but that exposure to potentially dangerous drug combinations through the same physician or pharmacy in fact happens more often [11]. This suggests that much better health outcomes might be accomplished with relatively simple interventions aimed at making individual physicians aware of the possible adverse consequences of their prescribing practices and/or interventions that in some way incentivize more careful prescribing practices.

Physicians should also be made aware of the risk factors associated with exposure to potentially dangerous drug combinations. Our study found that 20 percent of all visits involving risperidone resulted in exposure to a potentially dangerous drug combination. The most common combination pair involved risperidone and sertraline, while the next four most common involved aripiprazole and fluoxetine, olanzapine and fluoxetine, risperidone and fluoxetine, and risperidone and paroxetine.

Our study also found that certain kinds of patients were at increased risk of exposure, including patients between ages 15 and 40, men, patients from urban areas, whites, patients covered by Medicaid/CHIP or Medicare, patients seen in settings other than psychiatrists' offices and primary care physicians' offices, and patients with depression or schizophrenia. The Medicaid/CHIP and Medicare programs have the capacity to disseminate information, monitor and perhaps provider financial incentives through their managed care contracts, provider manuals or payment systems that could better inform large numbers of physicians regarding these risks. Physicians need to be more aware of these risk factors and monitor their prescribing patterns

accordingly.

Our study has several limitations. First, given the limitations of our data source, we could not distinguish between office physician visits where the physician was unaware of the potential risks of simultaneous use of the drug pair and office visits where the physician was aware but decided to prescribe or continue the drug pair anyway because he/she concluded the benefits of prescribing the drug pair would outweigh the costs. It may have been that for some patients, especially those with severe conditions or multiple chronic conditions, the physician knew the risk of certain drug combinations but chose to prescribe the drugs anyway because he/she thought it was still in the best interest of the patient.

Second, we could not determine the dosage of drugs given or prescribed to patients. Some might argue that low dosages of some drugs and drug combinations might pose less significant risk. For example, quetiapine is often an 'add on' drug used in lower dose for anxiety and sedation and it is used liberally in these regards. In our findings, quetiapine was prescribed or continued in over a third of the visits. This raises the important question of dosage and the relationship between dose levels and dangerous which is not always clear.

In contrast to quetiapine, for clozapine, an antipsychotic used much less than others, we find a relatively high rate of dangerous drug combinations. There may be a clinical explanation for this - clozapine is used in the treatment of patients with more severe conditions, like treatment resistant schizophrenia, where there is a greater tendency for polypharmacy. While this doesn't assuage the concern about dangerous drug combinations, it does put it in the context of current clinical practice.

Even more pertinent to the discussion of 'dose and dangerous' is a drug combination like fluoxetine and olanzapine which is now FDA approved. While our methodology builds on a list of dangerous drugs published just five years ago, it underscores the evolution, or perhaps, revolution of clinical practice and the critical need for a more clear-cut and widespread understanding of the relationship between dosage level and danger [11].

Third, we would note that over 50% of the patient visits are in psychiatrists' offices which might lead one to expect higher levels of these drug combinations per visit.

Finally, our analyses focused on exposure caused by the same physician, even though exposure owing to multiple physicians or pharmacies is equally as concerning.

Conclusion

Each year 1.6 million physician office visits result in patients being exposed to potentially dangerous drug combinations involving antipsychotics. This represents one in ten physician office visits involving antipsychotics nationwide. Since these exposures were caused by the same physician, and not by poor communication across multiple physicians and pharmacies, simple interventions aiming to make physicians more aware of potentially dangerous drug combinations and to incentivize more careful prescribing practices are recommended. Although exposure does not always mean harmful or lacking patient benefits, given the scarcity of data on dosage levels and danger for many of these antipsychotic drug combinations more research is critical.

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