Exposure to Potentially Dangerous Drug-Drug Interactions Involving Antipsychotics

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Objective: **Antipsychotic drug therapy is the cornerstone of treatment of persons with schizophrenia. Because most antipsychotics are metabolized by the hepatic cytochrome P450 system, concomitant use of an antipsychotic and medications that are competitively metabolized by the same system may cause a potentially harmful drug-drug interaction. This study used a large state's Medicaid claims database to examine the proportion of patients exposed to such interactions and the risk factors associated with exposure.** ***Methods:*** **Claims from January 2000 through December 2003 for adult patients with a diagnosis of schizophrenia and at least one prescription for an antipsychotic (N=27,909) were examined for pairs of medications identified as potentially causing moderate or severe adverse drug effects. Logistic regression models were estimated to determine potential risk factors associated with exposure to the interaction pairs.** ***Results:*** **A total of 6,417 (23%) patients were exposed to 14,213 potentially harmful interactions; 4,725 patients had at least one exposure from the same pharmacy, and 4,032 patients were exposed by the same physician. The greatest number of exposures (N=1,353) to potentially harmful combinations involved olanzapine and haloperidol. Patients prescribed risperidone were most likely to be exposed to an interaction (13.1%), followed by patients prescribed olanzapine (10.3%), quetiapine (3.3%), and clozapine (3.2%). A higher risk of exposure was associated with being female (odds ratio [OR]=.94), being white (OR=1.43), having depression (OR=1.21), or having impulse-control disorder (OR=1.98).** ***Conclusions:*** **Interventions by physicians and pharmacies to reduce the prescribing and dispensing of potentially harmful pairs of medications to patients with schizophrenia are recommended. (*Psychiatric Services* 63:1080–1088, 2012; doi: 10.1176/appi.ps.201100443)**

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Drug-related morbidity and mortality are major medical issues with significant costs. Each year an estimated $177.4 billion is spent to address the treatment failures and new medical problems that are generated by adverse drug events (1,2). Such events occur in up to 40% of patients on five or more medications (3–5). It has been estimated that 6% to 10% of adverse events are drug-drug interactions and that 50% to 84% of adverse events are preventable through proper identification and surveillance (6,7).

The lifetime prevalence of schizophrenia, a serious and chronic psychotic disorder requiring medication, has been estimated at approximately 1% of the U.S. population (8), although the prevalence is higher in lower-income groups, such as the Medicaid population. In fact, Medicaid programs represent the nation's dominant payers for mental health services (9). In the United States, the treatment of schizophrenia consumes 2.5% of annual adult health care costs, or about $16 to $19 billion (10). The indirect costs of this disorder are far more substantial. Loss of productivity and family burden totaled $46 billion in 1995 (11). Unemployment rates for patients with schizophrenia reach 70% to 80% (12), and it is estimated that patients with schizophrenia constitute 10% of the totally and permanently disabled. Schizophrenia is also associated with an increased incidence of general medical illnesses and increased mortality,

especially from suicide. Up to 10% of patients with schizophrenia take their own lives (13).

Since conventional antipsychotics were introduced in the 1950s, antipsychotic drug therapy has been the cornerstone of treatment of persons with schizophrenia. These first-generation antipsychotics are effective in the management of the positive symptoms of psychosis, such as hallucinations and delusions (14). However, their use may cause debilitating side effects, such as extrapyramidal symptoms and tardive dyskinesia (15,16). The pharmacologic profiles of newer, second-generation antipsychotics have a lower risk of extrapyramidal symptoms and are somewhat more effective in the management of negative symptoms of schizophrenia, such as lack of emotion, flattened affect, and low energy (17–19).

Between 1989 and 2002, the U.S. Food and Drug Administration (FDA) approved six second-generation antipsychotics: clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. Adverse events associated specifically with second-generation antipsychotics include weight gain and metabolic-syndrome side effects (18,20–22). Adverse events associated with all antipsychotic use include seizures (23–26) and arrhythmias associated with QT prolongation and torsade de pointes (27,28).

Moreover, the risk of these events occurring from the use of antipsychotics may be heightened by concomitant drug therapy and exposure to potentially harmful drug-drug-interactions of medication pairs. Patients with schizophrenia commonly receive multiple medications. Chwastiak and others (29) reported that 53% of patients with schizophrenia who used antipsychotic medication also received drug therapy for a comorbid chronic condition, such as hypertension, diabetes mellitus, coronary artery disease, depression, infections, asthma, congestive heart failure, and chronic obstructive pulmonary disease (COPD) (29).

Potentially harmful drug-drug interactions are often listed on labels for antipsychotic medications. For example, given the potential for QT prolongation, ziprasidone is contraindicated for concomitant use with haloperidol, bupropion, and antiarrhythmics (30,31). Risperidone may interact with a 5-HT6 antagonist, leading to an increase of electroencephalogram alpha and beta bands (32). An interaction between quetiapine and atazanavir or ritonavir may lead to rapid, severe weight gain and increased sedation and mental confusion (33). Substantially reduced serum concentrations of quetiapine occur after lamotrigine exposure (34). Additional evidence of potentially harmful interactions was reported in the recent literature (35–37).

Most antipsychotics are metabolized by the hepatic cytochrome P450 (CYP450) system. CYP450 enzymes CYP1A2, CYP2D6, and CYP3A4 are of particular importance to the metabolism of antipsychotics (38). Concomitant use of an antipsychotic and another drug may competitively inhibit an enzyme that metabolizes the antipsychotic or, alternatively, may induce the action of that enzyme. The result of metabolic inhibition may be a higher plasma level of an antipsychotic, which may result in the adverse events discussed above (38–41). Inducing the enzyme action may result in these or other adverse events, although scant evidence of this possibility has been gathered to date.

Documentation and quantification of exposure of patients with schizophrenia to potentially harmful drug-drug interactions are very limited. This study attempted to identify the proportion of patients with schizophrenia who concomitantly received antipsychotics and other medications that are metabolized by the liver and to estimate the effect of various risk factors on exposure to a potentially harmful interaction. Investigating relationships between such exposures and adverse events was beyond the scope of this study.

Methods

Study design and cohort selection

A retrospective, population-based cohort design was used. The study period was January 2000 to December 2003 (four calendar years). Adult patients aged 18 or older with a diagnosis of schizophrenia who had received at least one prescription for an antipsychotic were selected from a large state's Medicaid claims database. The database includes medical, institutional, and pharmacy claims along with a patient enrollment file. A diagnosis of schizophrenia was indicated by *ICD-9* codes 295.xx. Diagnoses were found in either institutional or medical claims. The use of claims databases to identify potentially harmful drug-drug-interaction pairs and adverse events in populations has been well documented (42–46).

A total of 33,567 patients were identified. We excluded 458 patients with ≤90 days of continuous enrollment and 5,200 patients who were aged 65 or older. The final cohort included 27,909 patients. [A figure depicting the selection of study patients is available in an online appendix to this report at ps.psychiatryonline.org.]

To protect patient confidentiality, names, addresses, Medicaid-recipient identification numbers, and other patient identifiers were deleted from the database. A randomized patient number was used as the unique identification. All research data were stored in a stand-alone server with password protection. Only the principal investigator, the data analysis programmer, and the statistician for the project were able to access the patient-level data sets. The research protocol was approved by the University of Cincinnati Medical Center Institutional Review Board.

Drug-drug interaction pairs

Using information from *Facts and Comparisons 4.0*, we developed systematically a list of clinically significant, potentially harmful pairs of antipsychotics and other medications (47). Because we found in a previous study that second-generation antipsychotics account for a majority of prescriptions for antipsychotics in the Medicaid system (48), we focused on interaction pairs that involved a second-generation drug. However, we considered as well three widely used first-generation antipsychotics: haloperidol, perphenazine, and chlorpromazine (48). Drug-drug interactions can be further categorized by their effects on CYP450 enzymes

CYP1A2, CYP2D6, and CYP3A4 and by the type of interaction (enzyme inducers versus enzyme inhibitors) (48).

On the basis of *Facts and Comparisons 4.0*, potentially harmful interactions are classified into five levels of significance: 1, major; 2, moderate; 3, minor; 4, major or moderate; and 5, minor or any. For the purposes of this study, we examined only major (potentially severe or life threatening) and moderate (less severe but still clinically significant) interactions (significance levels 1, 2, and 4). Focusing on severe and moderate interactions only makes sense given the problem of "alert fatigue" during medication prescribing and dispensing (43,49,50). Some drugs, such as cisapride and troglitazone, were excluded from the study because they were withdrawn from the market prior to the study period. [Potentially harmful interaction pairs investigated are listed in an online appendix to this report.]

Concomitant prescriptions for antipsychotic medications and contraindicated medications were identified from computerized Medicaid pharmacy claims files. All prescriptions (as opposed to only new prescriptions) for these medications were included. Concomitant exposure was defined as an overlap of one or more days in the days of supply of an antipsychotic prescription and a contraindicated medication (47). For example, if a patient had a 20-day prescription for ziprasidone starting on October 29, 2002, and a 30-day prescription for ketoconazole starting on November 18, 2002, one overlap was counted. We decided on the one-day overlap after determining that results and conclusions were not substantially altered with a five- or ten-day overlap requirement. A one-day overlap is consistent with the literature on drug-drug interactions involving hepatic metabolism (43,44). Interaction exposures were further stratified by significance level (severe or moderate), interaction type (inhibitor or inducer), and enzyme type (CYP2D6, CYP1A2, or CYP3A4).

Covariates and confounding factors

The Medicaid recipient eligibility file provided information about the patient's age, age upon first receiving an antipsychotic medication included in the study, race, and sex. Race was identified as Caucasian, African American, Hispanic, or other. Sex was defined by a dichotomous variable (male=1 and female=0). The file also provided information about other potentially important confounding factors that have gained a lot of interest in recent years (20,51–57). These included alcohol use disorder (*ICD-9* code 303.xx), substance use disorders (304.xx), anxiety disorders (300.xx), impulse-control disorders (312.xx), personality disorders (301.xx), and eating disorders (307.5x). Key medical comorbidities included cerebrovascular diseases (433.xx–438.xx), ischemic heart diseases (411.xx–414.xx), neoplasm or cancer (140.xx–208.xx, except 173.xx, 211.5x, 230.xx, 235.xx, and 239.0x), arthritis (711.xx–716.xx), obesity (278.xx), diabetes mellitus (250.xx), hypertension (401.xx), and COPD (496.xx).

Statistical data analysis

All statistical analyses were conducted with SAS for Windows, version 9.1. Descriptive statistics for the study cohort were produced. We calculated the cumulative frequency of clinically significant, potentially harmful interaction pairs among the cohort patients during the study period. Two logistic regression models to determine the potential risk factors associated with exposure to the drug-drug interaction pairs were estimated. The first model included only psychiatric comorbidities, and the second model included psychiatric as well as medical comorbidities.

Results

A total of 6,417 (23%) patients were exposed to potentially harmful interaction pairs (Table 1). (A total of 5,949 and 5,021 patients were exposed if overlaps of five and ten days, respectively, were imposed). The average age of patients who were and were not exposed was 42.5 and 42.2 years, respectively. Compared with patients who were not exposed to potentially harmful interaction pairs, patients who were exposed had significantly higher rates of depression, anxiety disorder, hypertension, obesity, and hyperlipidemia. The proportion of white patients was higher among individuals exposed to potentially harmful interactions than among individuals with no interaction exposure.

There were 14,213 interaction exposures among the 6,417 exposed patients (Table 2). The most common pair was the combination of the antipsychotics olanzapine and haloperidol (N=1,353, 9.5%). The next most common combinations were risperidone and sertraline, fluoxetine, paroxetine, and carbamazepine. The combination of quetiapine and ritonavir was not among the top 50 interaction pairs, but ritonavir was prescribed with risperidone or olanzapine. The vast majority of the interactions were of the inhibitor type. The top five interactions involved the enzyme type CYP2D6.

Most patients who were exposed to potentially harmful drug-drug interactions were not exposed through multiple physicians and pharmacies. In fact, 4,725 patients had at least one exposure from the same pharmacy, and 4,032 patients were exposed by the same physician (Table 3). Same-day exposures were not uncommon. Again, 2,645 patients were exposed by the same pharmacy on the same day, and 2,447 patients were exposed by the same prescriber on the same day.

Table 4 shows patients exposed to interactions stratified by the antipsychotic taken, the significance of the interaction, the interaction type (inhibitor or inducer), and the enzyme type. Patients taking risperidone were the most likely to be exposed to an interaction—13.1% of the cohort was exposed to a potentially harmful medication pair involving risperidone. The next most common combinations involved olanzapine (10.3% of patients), quetiapine (3.3%), and clozapine (3.2%). The percentage of patients exposed to interaction pairs was highest for category 4 (major or moderate) interactions and lowest for category 2 (moderate) interactions. The percentage of patients exposed to enzyme type CYP2D6 (14.7%) was higher than the percentage exposed to either CYP3A4 (5.4%) or CYP1A2 (5.2%).

The results of a logistic regression that predicted exposure to a potentially harmful interaction pair are shown in

Table 1

Demographic and clinical characteristics of patients who were or were not exposed to potentially dangerous drug-drug interactions[a]

Characteristic	Not exposed (N=21,492)		Exposed (N=6,417)	
	N	%	N	%
Age (M±SD years)[b]	42.2±11.2		42.5±11.1	
Female[b]	10,356	48.2	3,233	50.4
White	13,792	64.2	4,635	72.2
Age group[b]				
18–34	4,989	23.2	1,461	22.8
35–49	10,523	49.0	3,089	48.1
50–65	5,980	27.8	1,867	29.1
Deceased[b]	649	3.0	256	4.0
Any medication treatment > 12 months[b]	15,805	73.5	4,662	72.6
Second-generation antipsychotic				
Clozapine	20	.01	662	10.3
Olanzapine	24	.01	2,009	33.3
Quetiapine	13	.01	614	9.6
Risperidone	34	.02	2,543	39.6
Ziprasidone	0	—	25	.4
Aripiprazole	1	.00	39	.6
Key comorbidity[c]				
Psychiatric				
Depression[b]	2,619	12.2	971	15.1
Substance use disorder[b]	5,057	23.5	1,457	22.7
Anxiety disorder[b]	2,485	11.6	866	13.5
Impulse-control disorder[b]	181	.8	114	1.8
Personality disorder[b]	1,686	7.8	566	8.8
Eating disorder[b]	26	.12	18	.3
Attention-deficit hyperactivity disorder	49	.23	17	.3
Medical				
Diabetes mellitus	2,212	16.0	755	11.8
Hypertension[b]	3,446	16.0	1,134	17.7
Chronic obstructive pulmonary disease	1,168	5.4	462	7.2
Cerebral vascular disease[b]	243	1.1	93	1.5
Ischemic heart disease[b]	553	2.6	184	2.9
Arthritis[b]	698	3.2	233	3.6
Obesity[b]	1,108	5.2	372	5.8
Neoplasm[b]	213	1.0	83	1.3
Hyperlipidemia[b]	1,163	5.4	401	6.2
Kidney disease	304	1.4	101	1.6
Liver disease[b]	204	1.0	67	1.0

[a] Chi square tests were used to compare patients who were and were not exposed to a potentially dangerous drug-drug interaction for all variables except age and length of treatment, which were compared with Student's t tests.

[b] $p<.001$, except for $p<.05$ for comparison of anxiety disorder

[c] A patient may have more than one comorbidity.

Table 5. A higher risk of exposure was associated with being female (odds ratio [OR]=.94), being white (OR=1.43), having depression (OR=1.21), having impulse-control disorder (OR=1.99), or having an eating disorder (OR=2.16). COPD was the only medical comorbidity estimated to have a statistically significant effect on exposure (OR=1.20).

Discussion

This study was a longitudinal, retrospective analysis of a large state's Medicaid claims database that quantified the proportion of patients with schizophrenia exposed to potentially harmful drug-drug interactions involving antipsychotic medication. Nearly one-quarter of patients (N=6,417) with schizophrenia were exposed to clinically significant interaction pairs with a risk of adverse events such as seizures or QT prolongation. A majority of patients who were exposed to a potentially harmful drug-drug interaction were prescribed the drugs by the same physician (N=4,032) or the same pharmacy (N=4,725). This finding is consistent with the findings of a similar study conducted by Howe and colleagues (58) with a PHARMetrics database. Frois and others (59) reported that only 9.2% of psychiatrists considered themselves well-informed about antipsychotic drug-drug interactions, and only 19.8% tracked antipsychotic-related drug-drug interactions in their practices.

Interestingly, the results of this study were similar to those of a study by Jones and others (43) of cisapride and contraindicated medications metabolized by enzyme type CPY3A4. Of all the potentially harmful interaction

Table 2

Potentially dangerous drug-drug interactions (N=14,213) encountered by patients using an antipsychotic, by frequency of exposure

Frequency	N	%	Antipsychotic	Interacting drug	Significance[a]	Interaction type	Enzyme type
1	1,353	9.5	Olanzapine	Haloperidol	4	Inhibitor	2D6
2	1,217	8.6	Risperidone	Sertraline	1	Inhibitor	2D6
3	1,160	8.2	Risperidone	Fluoxetine	1	Inhibitor	2D6
4	1,046	7.4	Risperidone	Paroxetine	1	Inhibitor	2D6
5	928	6.5	Risperidone E	Carbamazepine	4	Inducer	2D6
6	921	6.5	Olanzapine	Fluoxetine	4	Inhibitor	1A2
7	817	5.8	Clozapine	Sertraline	1	Inhibitor	2D6
8	795	5.6	Olanzapine	Carbamazepine	4	Inducer	1A2
9	674	4.7	Clozapine	Fluoxetine	1	Inhibitor	2D6
10	534	3.8	Clozapine	Citalopram	1	Inhibitor	2D6
11	424	3.0	Risperidone	Ketoconazole	2	Inhibitor	3A4
12	416	2.9	Quetiapine	Carbamazepine	4	Inducer	3A4
13	396	2.8	Haloperidol	Carbamazepine	2	Inducer	3A4
14	311	2.2	Olanzapine	Fluvoxamine	4	Inhibitor	1A2
15	311	2.2	Quetiapine	Phenytoin	2	Inducer	3A4
16	295	2.1	Clozapine	Phenytoin	4	Inhibitor	3A4
17	267	1.9	Olanzapine	Ciprofloxacin	4	Inhibitor	1A2
18	226	1.6	Clozapine	Ciprofloxacin	4	Inhibitor	1A2
19	219	1.5	Risperidone	Thioridazine	4	Inhibitor	2D6
20	179	1.3	Quetiapine	Fluvoxamine	4	Inhibitor	3A4
21	158	1.1	Quetiapine	Ketoconazole	2	Inhibitor	3A4
22	126	.9	Quetiapine	Erythromycin	4	Inhibitor	3A4
23	109	.8	Clozapine	Fluvoxamine	1	Inhibitor	3A4
24	98	.7	Quetiapine	Clarithromycin	4	Inhibitor	3A4
25	83	.6	Haloperidol	Ketoconazole	2	Inhibitor	3A4
26	70	.5	Perphenazine	Paroxetine	2	Inhibitor	2D6
27	69	.5	Clozapine	Carbamazepine	4	Inducer	3A4
28	67	.5	Risperidone	Fluconazole	2	Inhibitor	3A4
29	67	.5	Chlorpromazine	Trazodone	4	Inhibitor	2D6
30	57	.4	Olanzapine	Clomipramine	4	Inhibitor	2D6
31	56	.4	Quetiapine	Fluconazole	2	Inhibitor	3A4
32	50	.4	Olanzapine	Ritonavir	2	Inhibitor	1A2
33	49	.4	Perphenazine	Phenytoin	4	Inducer	3A4
34	48	.4	Haloperidol	Fluphenazine	4	Inhibitor	2D6
35	47	.3	Chlorpromazine	Phenytoin	4	Inhibitor	3A4
36	42	.3	Aripiprazole	Fluoxetine	4	Inhibitor	2D6
37	38	.3	Chlorpromazine	Fluoxetine	1	Inhibitor	2D6
38	36	.3	Chlorpromazine	Haloperidol	4	Inhibitor	2D6
39	35	.3	Risperidone	Itraconazole	2	Inhibitor	3A4
40	34	.2	Aripiprazole	Carbamazepine	2	Inducer	3A4
41	34	.2	Haloperidol	Thioridazine	4	Inhibitor	2D6
42	34	.2	Haloperidol	Fluvoxamine	4	Inhibitor	1A2
43	31	.2	Chlorpromazine	Paroxetine	2	Inhibitor	2D6
44	29	.2	Risperidone	Nelfinavir	4	Inhibitor	3A4
45	28	.2	Clozapine	Cimetidine	4	Inhibitor	1A2
46	22	.2	Ziprasidone	Carbamazepine	2	Inducer	3A4
47	21	.2	Chlorpromazine	Propranolol	1	Inhibitor	1A2
48	19	.1	Risperidone	Ritonavir	4	Inhibitor	3A4
49	17	.1	Clozapine	Phenobarbital	2	Inducer	3A4
50	16	.1	Perphenazine	Haloperidol	4	Inhibitor	2D6
Other	134	.9					

[a] Potentially harmful drug-drug interactions are classified by *Facts and Comparisons 4.0* (47) into five levels of significance: 1, major; 2, moderate; 3, minor, 4, major or moderate; and 5, minor or any; interactions classified as level 1, 2, or 4 are the subject of this study.

pairs, 50% were found to be prescribed by the same physician for the same patient, 89% were dispensed by the same pharmacy for the same patient, and 17% were dispensed on the same day for the same patient (43,44).

Our study suggests that both prescribing and pharmacy-based dispensing may represent important intervention points for preventing potentially harmful interactions. Moreover, much intervention may be accomplished without involving complicated communications among different physicians or pharmacies. The results from this study indicate that certain comorbidities, such as depression and COPD, are associated with a higher risk of a potentially harmful interaction. Prescribers need

to be aware of these higher risks and monitor their prescribing habits for patients suffering from multiple diseases.

The literature suggests that although most pharmacies have computer-based warning systems, these systems do not consistently prevent the dispensing of contraindicated drugs. Possible reasons for such inconsistent prevention include pharmacy-based drug information systems that embed contraindications in a large volume of other material, making them difficult to find; warning systems that do not present current information in a rationally prioritized layout; and pharmacists' concerns about questioning the prescribing physicians' decisions (21,43).

Regardless of potentially harmful drug-drug interactions, choosing a specific antipsychotic is nontrivial. Recent studies have associated metabolic effects, such as weight gain, diabetes mellitus, and dyslipidemia, with some of the second-generation antipsychotics, such as olanzapine and risperidone (46,60). First-generation antipsychotic drugs carry high risks of parkinsonism and tardive dyskinesia (48). Risks and benefits of the various pharmacologic treatments available must be carefully analyzed.

Jing and colleagues (48) reported that utilization of antipsychotic medication in state Medicaid programs increased dramatically in recent years because second-generation antipsychotic agents are now used to manage conditions other than schizophrenia. These drugs, except for clozapine, have been approved for use by the U.S. Food and Drug Administration (FDA) for bipolar disorder and are often prescribed for that condition. They are also often prescribed, off label, for obsessive-compulsive disorder, borderline personality disorder, and autism. A black box warning by the FDA in 2005 slowed their use by elderly patients for treatment of behavioral and psychological symptoms of dementia (61). Identification and quantification of potentially harmful drug-drug interactions are clearly important for these additional populations and will require further study.

Of course, finding that patients with comorbidities are at a greater risk of potentially harmful drug-drug interactions is not particularly surprising. After all, taking more prescription medications automatically puts patients at greater risk. However, not all comorbidities were associated with a higher risk, so this explanation is not generally satisfying. White patients and female patients experienced a significantly higher risk of a potentially harmful interaction. The use of antidepressants to treat major depressive disorder, impulse-control disorder, and eating disorders and the relationship between the incidence of these comorbidities with gender and race may involve a complicated interaction that increases the risk among a certain group of patients. In fact, estimates of a statistically significant association between death and potentially harmful interactions do not indicate the direction of causation. Although it is possible that the interaction led to the patient's death, it is also possible, given our study design, that sicker patients were both more likely to die as well as to experience a drug-drug interaction (Table 5).

The results of this study may not be generalizable to other managed-care populations or to other diseases because the study population was limited to a state's Medicaid patients with schizophrenia. The design of the study limits the ability to infer the impact of potentially harmful drug pairs on resource use and cost. Further

Table 3

Exposures to a potentially dangerous drug-drug interaction by the same prescriber or the same pharmacy among patients (N=27,909) who were or were not exposed on the same day

	Any exposure		Same-day exposure	
Variable	N	%	N	%
Same prescriber	4,032	14.4	2,447	8.8
Same pharmacy	4,725	16.9	2,645	9.5

Table 4

Exposures to a potentially dangerous drug-drug interaction among patients (N=27,909) who were or were not exposed on the same day[a]

	Any exposure		Same-day exposure	
Variable	N	%	N	%
Significance[b]				
1	2,582	9.3	1,566	5.6
2	963	3.5	251	.9
4	3,505	12.6	1,715	6.2
Enzyme for metabolism				
1A2	1,465	5.2	742	2.7
2D6	4,108	14.7	2,369	8.5
3A4	1,496	5.4	411	1.5
Antipsychotic				
Aripiprazole	76	.3	32	.1
Clozapine	899	3.2	262	.9
Olanzapine	2,882	10.3	1,453	5.2
Quetiapine	931	3.3	273	1.0
Risperidone	3,651	13.1	2,074	7.4
Ziprasidone	32	.1	13	.1
Chlorpromazine	211	.8	94	.3
Haloperidol	430	1.5	135	.5
Perphenazine	119	.4	50	.2

[a] Patients may be exposed to more than one potentially dangerous drug-drug interaction.

[b] Potentially harmful drug-drug interactions are classified by *Facts and Comparisons 4.0* (47) into five levels of significance: 1, major; 2, moderate; 3, minor; 4, major or moderate; and 5, minor or any; interactions classified as level 1, 2, or 4 are the subject of this study.

Table 5

Exposure to potentially harmful drug-drug interactions among patients with schizophrenia (N=27,909), by patient characteristic[a]

Characteristic	Model 1		Model 2	
	OR	95% CI	OR	95% CI
Sex (reference: female)	.929	.877–.984	.935	.882–.991
Race (reference: other)	1.425	1.339–1.517	1.430	1.343–1.523
Age	1.001	.999–1.004	.999	.997–1.002
Deceased (reference: not deceased)	1.295	1.114–1.505	1.246	1.069–1.453
Any medication treatment >12 months (reference: <12 months)	.965	.905–1.030	.946	.886–1.010
Key comorbidity (reference: not present)				
Psychiatric				
Depression	1.236	1.134–1.346	1.206	1.106–1.315
Substance use disorder	.958	.892–1.029	.936	.870–1.006
Anxiety disorder	1.096	1.002–1.200	1.076	.983–1.178
Impulse-control disorder	2.014	1.586–2.557	1.986	1.564–2.522
Personality disorder	1.013	.911–1.126	.994	.893–1.105
Eating disorder	2.089	1.139–3.834	2.158	1.176–3.958
Attention-deficit hyperactivity disorder	1.087	.624–1.894	1.091	.626–1.901
General medical				
Diabetes mellitus	—	—	1.095	.996–1.204
Hypertension	—	—	1.083	.996–1.177
Chronic obstructive pulmonary disease	—	—	1.201	1.066–1.353
Cerebrovascular disease	—	—	1.138	.889–1.456
Ischemic heart disease	—	—	.953	.798–1.138
Arthritis	—	—	1.011	.865–1.182
Obesity	—	—	1.035	.912–1.176
Cancer or tumor	—	—	1.120	.862–1.456
Hyperlipidemia	—	—	1.062	.940–1.200
Kidney disease	—	—	1.073	.851–1.352
Liver disease	—	—	1.076	.813–1.425

[a] Goodness of fit for both models was significant (χ^2=245.37, −2 log likelihood=29,851, p<.001, model 1, and χ^2=273.45, −2 log likelihood=29,823, p<.001, model 2).

research with a prospective design is needed to explore these relationships. There were limited clinical data to validate exposure to potentially harmful interactions.

Because this study was based on claims from pharmacies and medical offices, we were unable to determine how often physicians chose to avoid or pharmacists chose not to dispense contraindicated medication pairs or how often pharmacists called physicians to question the prescriptions. We also could not determine how often pharmacists dispensed overlapping prescriptions for an antipsychotic and a contraindicated medication but instructed the patient to discontinue one of the medications while taking the other.

Moreover, regardless of whether physicians are well aware of the literature on potentially harmful effects of combining some drugs, the perceived benefit of the treatment regimen may outweigh the risks, especially for some patients with severe mental illness. The physicians may be cautious and carefully monitor patient response in order to minimize the risk of an adverse event. Unfortunately, this type of detail cannot be captured by a study of such a large database.

Conclusions

One-fourth of patients with schizophrenia were exposed to potentially harmful drug-drug interactions. Because many of these patients were exposed by the same prescriber or the same pharmacy, and even on the same day, simple interventions by both physicians and pharmacies are recommended. Practitioners should be aware of the possible clinical consequences stemming from certain pairs of antipsychotics and other drugs. Meanwhile, pharmacies need good systems in place to catch prescriptions for two contraindicated medications.

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Dr. Wu was employed by Johnson & Johnson at the time of this research . Dr. Jing, a graduate student at the time of this research, is an employee of Bristol-Myers Squibb and owns stock in the company. Dr. Keck is a paid consultant to the advisory board of Bristol-Myers Squibb and to Pamlab and is a coinventor (U.S. patent 6,387,956) of a method of tramadol administration for treatment of obsessive-compulsive spectrum disorder. He has received no financial gain from this patent. Dr. Patel receives grant support or is under contract to AstraZeneca, Janssen Scientific Affairs, and Pfizer, Inc. The other authors report no competing interests.

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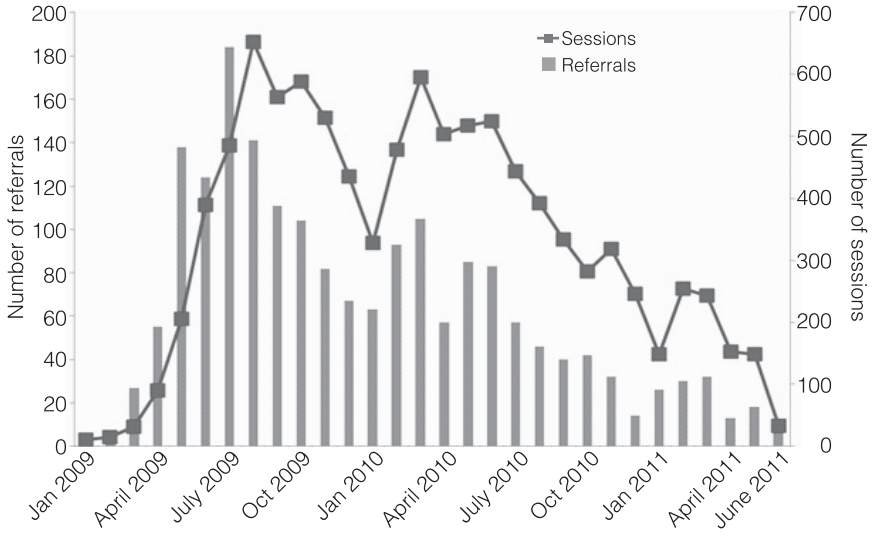
Correction to Bassilios et al., 2012

In the article "Enhanced Primary Mental Health Services in Response to Disaster," by Bridget Bassilios, D.Psych., Lennart Reifels, Dipl.-Psych., and Jane Pirkis, Ph.D. (September 2012 issue, pp. 868–874), the legend of Figure 1, on page 870, is incorrect. The key should indicate that the curve represents sessions and the bars represent referrals. A corrected figure appears below.

Figure 1

Monthly referrals for mental health care through Australia's Access to Allied Psychological Services program after the 2009 bushfires, January 2009 to June 2011[a]



[a] An additional five referrals and ten sessions were recorded as having taken place pre-January 2009, but the dates are likely to be data entry errors.