National Trends in Psychotropic Medication Polypharmacy in Office-Based Psychiatry

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Context: Psychotropic medication polypharmacy is common in psychiatric outpatient settings and, in some patient groups, may have increased in recent years.

Objective: To examine patterns and recent trends in psychotropic polypharmacy among visits to office-based psychiatrists.

Design: Annual data from the 1996-2006 cross-sectional National Ambulatory Medical Care Surveys were analyzed to examine patterns and trends in psychotropic polypharmacy within nationally representative samples of 13,079 visits to office-based psychiatrists.

Setting: Office-based psychiatry practices in the United States.

Participants: Outpatients with mental disorder diagnoses visiting office-based psychiatrists.

Main Outcome Measure: Number of medications prescribed in each visit and specific medication combinations.

Results: There was an increase in the number of psychotropic medications prescribed across years; visits with 2 or more medications increased from 42.6% in 1996-1997 to 59.8% in 2005-2006; visits with 3 or more medications increased from 16.9% to 33.2% (both \( P < .001 \)).

Conclusions: There has been a recent significant increase in polypharmacy involving antidepressant and antipsychotic medications. While some of these combinations are supported by clinical trials, many are of unproven efficacy. These trends put patients at increased risk of drug-drug interactions with uncertain gains for quality of care and clinical outcomes.

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In many clinical situations, use of more than 1 psychotropic medication from the same or a different class is indicated.\(^1,2\) Depressed adults, for example, who partially respond to citalopram hydrobromide alone, significantly improve following addition of a second antidepressant (bupropion hydrochloride).\(^3\) Addition of antipsychotics to mood stabilizers for acute mania,\(^4\) short-term use of benzodiazepines in the early treatment course of major depression with antidepressants,\(^5\) and addition of antipsychotics to antidepressants for major depression with psychotic features\(^6\) represent other examples of empirically supported psychotropic polypharmacy. In routine psychiatric practice, however, patients often receive psychiatric medication combinations that are not well supported by controlled clinical trials.\(^7-16\) One increasingly common combination is treatment with 2 concurrent antipsychotic medications.\(^8,9,11-16\) Support for this practice is largely confined to case reports and open-label trials\(^11,17\) rather than double-blind trials.\(^16\) In 1 analysis of data from Medicaid enrollees diagnosed with schizophrenia, there was a 4-fold increase from 3.3% to 13.7% in the percentage of patients receiving antipsychotic polypharmacy between 1999 and 2005.\(^9\) Psychotropic polypharmacy is also common in mood disorders.\(^22-25\) In a study of patients with treatment-refractory mood disorders discharged from the US National Institute of Mental Health Biological Psychiatry Branch, the percentage taking 3 or more medications increased from 3.3% in 1974-1979 to 43.8% in 1990-1995.\(^22\)
Much remains to be learned regarding patterns of psychotropic polypharmacy in routine psychiatric practice. It is not known, for example, which combinations are most common in community practice, whether the likelihood of receiving these medication combinations has changed in recent years, and which patients are most likely to receive these medication combinations. Delineating within- and across-class psychotropic polypharmacy trends may inform evaluations of risk of adverse effects and drug-drug interactions and sources of the increasing share of mental health expenditures accounted for by medications. Identification of these emerging trends may also suggest candidate patient populations and medication combinations for clinical trials of drug efficacy and safety or for comparative effectiveness studies in real-world populations.

This report examines recent trends in psychotropic polypharmacy in a large and representative sample of visits to US office-based psychiatrists between the mid-1990s and mid-2000s. We explore trends in within- and between-class psychotropic polypharmacy focusing on some of the most common combinations of psychotropic medications in outpatient psychiatric practice. We further examine patterns of psychotropic polypharmacy according to patient sociodemographic and clinical characteristics. The analysis is limited to visits to psychiatrists because psychiatrists tend to treat the most severely ill mental health patients and have the most extensive training and experience prescribing psychotropic medications. To our knowledge, this is the first study to examine trends in psychotropic polypharmacy involving major medication classes in a nationally representative sample of visits to office-based psychiatrists.

METHODS

SAMPLE

Data were drawn from 11 consecutive years of the National Ambulatory Medical Care Survey (NAMCS) from 1996 to 2006. NAMCS is a multistage probability survey of visits to office-based physicians. The survey response rate varied from 58.9% to 70.4% (median = 66.9%). A systematic random sample of visits to each physician was drawn during a randomly selected 1-week period (n = 284,638 visits). We further limited the sample to 13,079 visits to psychiatrists by adults (18 years or older) in which the patient actually saw the physician and was given a mental disorder diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification codes 290-319).

ASSESSMENTS

For each visit, the physician or a member of the physician’s staff provided information about patient sociodemographic and clinical characteristics as well as psychotropic medications prescribed, supplied, or administered at the visit. Psychotropic medications were ascertained based on generic names. Up to 6 medications were recorded in each visit in NAMCS 1996-2002. Starting from 2003, the maximum number of medications recorded was increased to 8. To make the years comparable for this study, we limited the maximum number of medications to 6 in all years. We focused on the 4 major classes of psychotropic medications for adults: antidepressants, antipsychotics, mood stabilizers, and sedative-hypnotics. Antidepressants included amitriptyline hydrochloride, amoxapine, bupropion, citalopram, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, duloxetine hydrochloride, escitalopram oxalate, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone hydrochloride, nor triptyline hydrochloride, paroxetine hydrochloride, phenelzine sulfate, protriptyline hydrochloride, sertraline hydrochloride, tranylcypromine sulfate, trazodone hydrochloride, trimipramine, and venlafaxine hydrochloride. Antipsychotics included aripiprazole, chlorpromazine hydrochloride, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone hydrochloride, olanzapine, perphenazine, pimozide, quetiapine fumarate, risperidone, thioridazine, thiothixene, trifluoperazine hydrochloride, and ziprasidone hydrochloride. Mood stabilizers included carbamazepine, lamotrigine, lithium, and valproate sodium/divalproex sodium. Sedative-hypnotics included alprazolam, butabarbital, chlor diazepoxide, chlorhydrate, clorazepate, clonazepam, diazepam, diphenhydramine, eszopiclone, estazolam, flurazepam hydrochloride, hydroxyzine, lorazepam, meperbamate, nitrazepam, oxazepam, pento barbital, secobarbital, temazepam, triazolam, zaleplon, and zolpidem tartrate.

We also assessed other psychotropic medications for calculation of the total number of prescribed medications. These included acamprosate calcium, amphetamine, atenolol, atomoxetine hydrochloride, benztrapine mesylate, buspironorphine hydrochloride, buspirone hydrochloride, clonid ine hydrochloride, dextromethaphan hydrochloride, dextroamphetamine, di sulfiram, donepezil hydrochloride, gabapentin, galantamine hydrobromide, guanfacine hydrochloride, methadone hydrochloride, methylphenidate hydrochloride, metoprolol, modafinil, naltrexone hydrochloride, naloxone hydrochloride, oxcarbazepine, pemoline, pregabalin, propranolol, rivastigmine tartrate, topiramate, and trihexyphenidyl hydrochloride.

We counted anticonvulsants (carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproate/divalproex, phenobarbi tal, gabapentin, and pregabalin) among psychotropic medications only if the patient did not have an additional seizure disorder diagnosis. Also, we counted guanfacine, clonidine, and β-blockers (atenolol, metoprolol, propranolol) among psychotropic medications only if the patient did not have an additional diagnosis of hypertension. Finally, selegiline, benztrapine, and trihexyphenidyl were counted among psychotropic medications only if the patient did not have an additional diagnosis of Parkinson disease.

Mental disorder diagnosis was recorded based on International Classification of Diseases, Ninth Revision, Clinical Modification codes. Up to 3 diagnoses were recorded for each visit. These diagnoses were given in 96.0% of all visits to psychiatrists during the study period. Specific diagnoses included major depression (codes 296.2 and 296.3), dysthymia (code 300.4), bipolar disorder (codes 296.0-296.1 and 296.4-296.8), other affective disorders (codes 296.9 and 311.0), generalized anxiety disorder (code 300.02), panic disorder with or without agoraphobia (codes 300.01 and 300.21), obsessive-compulsive disorder (code 300.3), posttraumatic stress disorder (code 300.8), social phobia (code 300.23), schizophrenia (code 295), and personality disorders (code 301). Because of the small number of sampled patient visits with each anxiety disorder, we combined these disorders into an “anxiety disorders” category. For the same reason, we combined dysthymia and other affective disorders. In addition, the total number of psychiatric diagnoses in each visit were dichotomized into 1 diagnosis vs more than 1 diagnosis.

Primary source of payment was classified as private insurance, Medicaid, Medicare, self-pay, or “other types.”
Other variables used in the multivariate analyses included patient's age, sex, race/ethnicity (white, minority), office setting (freestanding private solo practice, freestanding private group practice, other settings), visit order (established vs first-time or new patient), and region of the country (Northeast, South, West, Southwest).

**ANALYTIC APPROACH**

Analyses were conducted in 2 stages. In the first stage, we examined time trends in the number of psychotropic medications prescribed using bivariate and multivariate binary logistic models. Survey year was transformed by subtracting 1996 from the year and dividing the results by 10. Thus, the transformed value was 0 for 1996 and 1 for 2006. The odds ratios (ORs) associated with this transformed variable of survey year represent a change in odds of psychotropic polypharmacy during the entire study period (ie, 1996-2006).

The multivariate model adjusted for and examined the effects of age, sex, race/ethnicity, psychiatric diagnosis, number of psychiatric diagnoses, insurance, visit order, office setting, and region. To assess variation in associations of patient and visit characteristics across years, interaction terms with survey year were introduced into the model and tested one by one. Significant interaction terms suggest variations in time trends across groups.

In the second stage, these bivariate and multivariate analyses were repeated for each specific combination of the 4 medication classes. The same variables described earlier were entered into the multivariate models.

Analyses were conducted using the Stata 10 software. All analyses were adjusted for visit weights, clustering, and stratification of data using design elements provided by the National Center for Health Statistics. When adjusted for these design elements, NAMCS data represent annual visits to office-based physicians in the United States. Because of the large sample size, a P value of <.01 was used to assess statistical significance.

**RESULTS**

**OVERALL TRENDS**

Between 1996-1997 and 2005-2006, the percentage of visits in which any psychotropic medications were prescribed increased from 73.1% to 86.2% (OR, 2.40; 99% confidence interval [CI], 1.36-4.24; P < .001). Similarly, the percentage of visits with 2 or more psychotropic medications increased from 42.6% to 59.8% (OR, 2.10; 99% CI, 1.41-3.15; P < .001) and those with 3 or more psychotropic medications increased from 16.9% to 33.2% (OR, 2.60; 99% CI, 1.61-4.22; P < .001) (Figure). The median number of medications prescribed per visit doubled from 1 in 1996-1997 to 2 in 2005-2006. The mean number increased by 40.1% from 1.42 in 1996-1997 to 1.99 in 2005-2006.

The time trend persisted in a multivariate model adjusting for demographic and clinical characteristics of visits (Table 1). Furthermore, the time trend was similar across most demographic and clinical characteristics as indicated by the statistically nonsignificant tests for all interaction terms except for the anxiety disorders (F1,601 = 6.95; P = .009). The percentage of visits in which 2 or more psychotropic medications were prescribed increased more slowly among visits with an anxiety disorder diagnosis (52.8% in 1996-1997 to 61.2% in 2005-2006) than among visits with other diagnoses (40.7% to 59.4%, respectively).

Visits were more likely to involve prescription of 2 or more psychotropic medications if they were made by patients aged 45 to 64 years compared with patients aged 18 to 44 years; patients with major depression, bipolar disorder, anxiety disorders, or schizophrenia compared with other diagnoses; patients with comorbid disorders compared with those with a single diagnosis; and those covered by public or “other” types of insurance compared with private insurance. In contrast, visits were less likely to involve 2 or more medications if they were made by men compared with women, self-paying patients compared with those covered by private insurance, and new patients compared with returning patients (Table 1).

**ANALYSES OF SPECIFIC MEDICATION COMBINATIONS**

The top section of Table 2 presents numbers and percentages of visits to psychiatrists in which each major medication class and combination were prescribed. During the study period, antidepressants (61.7%) were the most commonly prescribed class of medications followed by sedative-hypnotics (31.5%), antipsychotics (22.4%), and mood stabilizers (12.4%). Combinations of antidepressants with sedative-hypnotics (23.1%), antipsychotics (12.9%), and other antidepressants (12.6%) were the first, second, and third most commonly prescribed psychotropic medication combinations overall and maintained these relative rankings across survey years (Table 2, middle section).

Over time, the percentages of visits in which combinations of antidepressants and antipsychotics or combinations of 2 or more antipsychotics or 2 or more antidepressants were prescribed significantly increased (Table 2, middle and lower sections). In contrast, combinations of mood stabilizers and sedative-hypnotics with each other and with other medication groups did not appreciably change (Table 2, middle and lower sections).
MULTIVARIATE ANALYSES OF WITHIN–PSYCHOTROPIC MEDICATION CLASS COMBINATIONS

The results of multivariate analyses of within–psychotropic medication class combinations were generally consistent with the bivariate analyses (Table 3). The time trend for 2 or more sedative-hypnotics, which was not statistically significant in bivariate analyses, became significant in the multivariate model (Table 3).

Specific psychotropic medication combinations were significantly more commonly prescribed for some patient groups than others (Table 3). Combinations of 2 or more antidepressants, for example, were significantly more common in visits by patients aged 45 to 64 years compared with visits by patients aged 18 to 44 years, women compared with men, and patients with mood and anxiety disorders compared with other diagnoses (Table 3).

A combination of 2 or more antipsychotics was significantly more common in visits with a diagnosis of schizophrenia compared with other diagnoses and in visits paid for with public compared with private insurance (Table 3). This medication combination was less common in visits with a diagnosis of other depressive disorders. The interaction term for diagnosis of major depression with survey year was statistically significant ($F_{1,601}=11.43; P<.001$). Over time, the prevalence of visits with 2 or more antipsychotics modestly decreased in the treatment of major depression (1.5% in 1996–1997 to 0.9% in 2005–2006), whereas this combination became more common in visits with other diagnoses (1.2% to 5.6%, respectively).

The prevalence of visits with 2 or more mood stabilizers did not change across survey years. However, such visits were many times more common in the treatment of bipolar disorder compared with other diagnoses (5.9% in 1996–1997 vs 0.3% in 2005–2006) (Table 3).

Two or more sedative-hypnotics were more commonly prescribed in visits by women than by men, visits with a diagnosis of anxiety disorder than other diagnoses, visits with more than 1 psychiatric diagnosis than those with 1 diagnosis, and visits covered by Medicare than other payers. Furthermore, interaction terms of survey year with the 65 years and older age group, diagnosis of schizophrenia, and Medicare insurance coverage were statistically significant, indicating that time trends were significantly different across these groups. Over time, multiple sedative-hypnotics became more commonly prescribed in visits by patients younger than 65 years (3.2% to 7.9%), though less common in visits by older patients (7.4% to 2.5%) ($F_{1,601}=15.05; P<.001$). This medication combination also became more common in visits by patients with diagnoses other than schizophrenia (3.1% to 7.6%), but less common in visits by patients with schizophrenia (9.6% to 0.3%) ($F_{1,601}=7.89; P=.005$). The combination of 2 or more sedative-hypnotics also became less commonly prescribed in Medicare-insured visits (7.3% in 1996–1997 to 6.6% in 2005–2006), but more common in visits covered by other payers (3.3% to 7.4%) ($F_{1,601}=7.36; P=.007$) (Table 3).

### Table 1. Multivariate Analyses of Trends and Patterns in Psychotropic Medication Polypharmacy (≥2 Medications) in Visits to Office-Based Psychiatrists Between 1996 and 2006

<table>
<thead>
<tr>
<th>Source of payment</th>
<th>AOR (99% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private insurance</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Medicaid</td>
<td>1.77 (1.30-2.39)</td>
<td>&lt;.001 $^b$</td>
</tr>
<tr>
<td>Medicare</td>
<td>1.73 (1.32-2.26)</td>
<td>&lt;.001 $^b$</td>
</tr>
<tr>
<td>Self-pay</td>
<td>0.74 (0.58-0.94)</td>
<td>.001 $^b$</td>
</tr>
<tr>
<td>Other</td>
<td>1.61 (1.11-2.33)</td>
<td>.001 $^b$</td>
</tr>
<tr>
<td>Visit sequence</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>New patient</td>
<td>0.59 (0.45-0.77)</td>
<td>&lt;.001 $^b$</td>
</tr>
<tr>
<td>Practice type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solo</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Group</td>
<td>1.30 (0.99-1.70)</td>
<td>.01</td>
</tr>
<tr>
<td>Other type of practice</td>
<td>1.38 (0.96-1.97)</td>
<td>.02</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Midwest</td>
<td>1.01 (0.73-1.40)</td>
<td>.92</td>
</tr>
<tr>
<td>South</td>
<td>1.12 (0.84-1.49)</td>
<td>.30</td>
</tr>
<tr>
<td>West</td>
<td>0.94 (0.69-1.29)</td>
<td>.62</td>
</tr>
</tbody>
</table>

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

$^a$Odds ratios associated with the transformed survey year variable: (survey year−1996)/10.

$^b$Regression coefficients different than 1 at a statistically significant level ($P<.01$).

$^c$Statistically significant interaction with survey year ($F_{1,601}=6.95; P=.009$).

### MULTIVARIATE ANALYSES OF BETWEEN–MEDICATION CLASS COMBINATIONS

The association of survey year with prescription of antidepressant-antipsychotic combinations persisted in multivariate analysis (Table 4). Antidepressant-antipsychotic combinations were also more commonly prescribed in visits by women than men; visits with diagnoses of major depression, bipolar disorder, and schizophrenia than other diagnoses; visits with more than 1 psychiatric diagnosis; and visits covered by public insurance or payment arrangements other than private insurance or self-pay, but less commonly in visits by the 65 years and older age group than younger patients (Table 4). An-
Antidepressant–mood stabilizer combinations were more common in visits with a bipolar or schizophrenia diagnosis than with those other diagnoses and by new compared with returning patients (Table 4). Antidepressant and sedative-hypnotic combinations occurred disproportionately in visits by patients aged 45 to 64 years, visits with a diagnosis of major depression or anxiety disorder, and visits covered by Medicare. This combination was less commonly prescribed in visits by men, minorities, and self-paying patients (Table 4).

Antipsychotic–mood stabilizer combinations were significantly more common in visits with a bipolar disorder or schizophrenia diagnosis compared with other diagnoses. This combination was also more common in publicly insured visits and visits with “other” payment arrangements than in privately insured visits. By contrast, this combination was less commonly prescribed among visits by older patients compared with younger patients and among those with depressive disorders, anxiety disorders, and new patients as compared with returning patients (Table 5).

Antipsychotic and sedative-hypnotic combinations were significantly more common in visits by patients aged 45 to 64 years than the younger age group, visits with a diagnosis of bipolar disorder or schizophrenia, visits with more than 1 diagnosis, and visits with public insurance than other payment sources. This combination was less commonly prescribed for visits by older adults than younger adults, men than women, and new than returning patients (Table 5). Finally, mood stabilizer–sedative-hypnotic combinations were more commonly prescribed in visits by patients aged 45 to 64 years compared with younger adults and visits with a bipolar or schizophrenia diagnosis compared with other diagnoses (Table 5).

The results of this study should be interpreted in the context of several limitations. First, this is an observational study and although the multivariate analyses adjust for a number of patient and visit characteristics, the range of variables is limited and multivariate methods cannot rule out residual confounding due to unmeasured differences among patient groups across survey years. Thus, results should be interpreted with caution. Second, the analyses were limited to office-based psychiatric practices. The trends and patterns in psychotropic polypharmacy may not generalize to other treatment settings. However, psychotropic polypharmacy (ie, prescription of ≥2 psychotropic medications) also increased among outpa-
Fifth, despite the relatively large sample sizes, the limited number of visits within certain patient groups and specific medication combinations forced us to combine some patient groups (e.g., anxiety disorders, racial/ethnic minorities). Furthermore, results for the less common medication combinations, such as combinations of 2 or more mood stabilizers, should be interpreted with caution. Sixth, diagnoses might not be exactly comparable across time. For example, patients given a diagnosis of bipolar disorder in 1996 might be somewhat different from those given this diagnosis in 2006. Without expert validation or structured interviews, it is not possible to examine these variations. Finally, because NAMCS records visits rather than...
Table 4. Multivariate Analyses of Trends and Patterns in Medication Combinations Involving Antidepressants in Visits to Office-Based Psychiatrists Between 1996 and 2006.a

<table>
<thead>
<tr>
<th>Stabilizer Combination</th>
<th>Survey yearb</th>
<th>Age, y</th>
<th>Sex</th>
<th>Race/ethnicity</th>
<th>Psychiatric diagnosis</th>
<th>No. of psychiatric diagnoses</th>
<th>Source of payment</th>
<th>Visit sequence</th>
<th>Practice type</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AOR (99% CI)</td>
<td>P Value</td>
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<td></td>
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<tr>
<td>Antidepressant + Mood</td>
<td>1.96 (1.30-2.96)</td>
<td>&lt;.001c</td>
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<tr>
<td>Antipsychotic Combination</td>
<td>0.95 (0.60-1.51)</td>
<td>.78</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant + Sedative-Hypnotic Combination</td>
<td>1.17 (0.74-1.85)</td>
<td>.36</td>
<td></td>
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</tr>
<tr>
<td>Antidepressant + Antipsychotic Combination</td>
<td>1.07 (0.83-1.38)</td>
<td>.51</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Antidepressant + Mood Stabilizer Combination</td>
<td>0.63 (0.36-0.93)</td>
<td>.03</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant + Sedative-Hypnotic Combination</td>
<td>1.00 (0.75-1.33)</td>
<td>.97</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

See “Methods” section for description of medications in each class.

Odds ratios associated with the transformed survey year variable: (survey year−1996)/10.

Regression coefficients different than 1 at a statistically significant level (P<.01).

Patients, some patient duplication may have occurred during the 1-week sampling period.

Despite these limitations, this report represents the first national study of psychotropic polypharmacy trends in office-based psychiatric practice to our knowledge. Between 1996 and 2006, there was a substantial increase in the proportion of patient visits in which 2 or more psychotropic medications were prescribed. During this period, the proportion of visits in which 3 or more psychotropic medications were prescribed increased from fewer than 1 in 5 to nearly 1 in 3.

Significant time trends appeared to be mainly limited to concomitant prescription of 2 or more antidepressants or antipsychotics as well as combinations of antipsychotics and antidepressants. With the exception of combinations of 2 or more sedative-hypnotics, none of the other combinations involving mood stabilizers or sedative-hypnotics showed a significant increase across time in multivariate analysis. This finding is consistent with other reports indicating an increase in the use of antidepressant and antipsychotic medications in recent years.37,39

Much of the available literature on psychotropic polypharmacy has focused on antipsychotic polypharmacy.* Frequently, antipsychotic polypharmacy represents an attempt by the physician to achieve a greater or a faster therapeutic response.11 Many patients in routine care settings continue to experience significant symptoms while following usual treatment regimens.42 In other cases, antipsychotic polypharmacy may be the result of “getting stuck” in switching from 1 antipsychotic medi-

*References 8, 9, 11, 12, 17, 21, 26, 40, 41.
The evidence for combining antidepressants from different classes is somewhat stronger than other medications in each class. For example, a double-blind controlled study of risperidone added to clozapine in refractory schizophrenia found no evidence for improved outcome in the combined-treatment group compared with the clozapine-alone group but did find a significantly greater increase in fasting blood glucose level in the combined-treatment group.36 Similarly, a small study of combined olanzapine-risperidone therapy in patients with schizophrenia who had not responded to sequential monotherapy with olanzapine, quetiapine, and risperidone found a significant increase in body weight, prolactin level, and total cholesterol level after an average of 10 weeks of concomitant treatment.43 These data call for more careful monitoring of metabolic parameters in patients taking multiple antipsychotic medications. Concerns have been voiced about increased risk of QT prolongation in concomitant use of ziprasidone with low-potency conventional antipsychotic medications (eg, thioridazine),44 as well as worsening of psychosis due to displacement of antipsychotic medications from the D2 receptor when aripiprazole is added as a concomitant treatment.44,45

Table 5. Multivariate Analyses of Trends and Patterns in Combinations of Antipsychotics and Mood Stabilizers, Antipsychotics and Sedative-Hypnotics, and Mood Stabilizers and Sedative-Hypnotics in Visits to Office-Based Psychiatrists Between 1996 and 2006

<table>
<thead>
<tr>
<th>Location</th>
<th>Antipsychotic + Mood Stabilizer Combination</th>
<th>Antipsychotic + Sedative-Hypnotic Combination</th>
<th>Mood Stabilizer + Sedative-Hypnotic Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AOR (99% CI)</td>
<td>P Value</td>
<td>AOR (99% CI)</td>
</tr>
<tr>
<td>Northeast</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Midwest</td>
<td>0.77 (0.55-1.08)</td>
<td>.16</td>
<td>1 (0.99-1.09)</td>
</tr>
<tr>
<td>South</td>
<td>0.88 (0.69-1.16)</td>
<td>.26</td>
<td>1.04 (0.92-1.17)</td>
</tr>
<tr>
<td>West</td>
<td>1.01 (0.85-1.20)</td>
<td>.99</td>
<td>1.09 (0.96-1.23)</td>
</tr>
</tbody>
</table>

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

a See “Methods” section for description of medications in each class.

b Odds ratios associated with the transformed survey year variable: (survey year−1996)/10.

c Regression coefficients different than 1 at a statistically significant level (P<.05).

d Other depressive disorders 0.50 (0.30-0.84) .001c 1.00 (0.71-1.40) .98 1.05 (0.66-1.68) .79

While the evidence for added benefit of antipsychotic polypharmacy is limited, there is growing evidence regarding the increased adverse effects associated with such combinations. For example, a double-blind controlled study of risperidone added to clozapine in refractory schizophrenia found no evidence for improved outcome in the combined-treatment group compared with the clozapine-alone group but did find a significantly greater increase in fasting blood glucose level in the combined-treatment group.36 Similarly, a small study of combined olanzapine-risperidone therapy in patients with schizophrenia who had not responded to sequential monotherapy with olanzapine, quetiapine, and risperidone found a significant increase in body weight, prolactin level, and total cholesterol level after an average of 10 weeks of concomitant treatment.43 These data call for more careful monitoring of metabolic parameters in patients taking more than 1 antipsychotic medication.
Antidepressant combinations also carry increased risks for adverse effects. The risks of serotonin syndrome and hypertensive crisis when combining monoamine oxidase inhibitors with other antidepressants are well known. In addition, some antidepressants inhibit cytochrome P450 enzymes and thus impact the metabolism of other psychotropic medications, including other antidepressants. Fluoxetine, sertraline, and paroxetine are potent inhibitors of cytochrome P450 2D6 and could potentially lead to marked elevations in concentration of desipramine and nortriptyline. Thus, coadministration of antidepressant medications calls for careful consideration of these drug-drug interactions and may require monitoring of serum levels of these medications. A further potential complication associated with overuse of antidepressant medications is the risk of emerging manic symptoms in susceptible depressed patients and acceleration of mood cycles in patients with bipolar disorder. However, it is not clear whether antidepressant polypharmacy is associated with additional risk of these outcomes.

The use of antidepressant-antipsychotic medication combinations in selected patient groups is also supported by some evidence. The fluoxetine-olanzapine combination for treatment of bipolar depression was one of the first psychotropic medication combinations to receive Food and Drug Administration approval for treatment of a mood disorder. Nevertheless, there are concerns about overprescription of antipsychotic medications in patients with major depression and overprescription of antidepressants in patients with schizophrenia. In an observational study of schizophrenic outpatients stabilized with antipsychotics and antidepressants, no change was noted over 3 months in Clinical Global Impressions—Improvement ratings in 82% of antipsychotic tapers; improvement occurred in 14% of tapers; and worsening, in only 5%. In another study, discontinuation of conventional antipsychotic use in a small sample of patients with major depression led to significant improvement in clinical status. Furthermore, antidepressant-antipsychotic combinations are especially prone to adverse drug-drug interactions mainly because of the effects of antidepressants on the cytochrome P450 system. For example, both fluoxetine and fluvoxamine significantly increase the serum level of concomitantly used clozapine. Similar drug-drug interactions among other antidepressants and antipsychotics have also been reported. These interactions call for added caution when prescribing these medication combinations and, in some cases, careful monitoring of serum levels.

We found no increase across the survey years in the prevalence of visits in which 2 or more mood stabilizers or any combinations of mood stabilizers with other psychotropic medications were prescribed. The decline in the use of lithium—once the most commonly prescribed mood stabilizer—and the parallel growth in the use of antipsychotic medications as mood stabilizers in outpatient settings in recent years may be, at least partly, responsible for this finding. Between the years 1992-1995 and 1996-1999, the prevalence of psychiatric outpatient visits with a diagnosis of bipolar disorder in which lithium was prescribed decreased from 50.9% to 30.1%, while visits in which atypical antipsychotic medications were prescribed increased from 1.2% to 17.0%. While there is evidence supporting the efficacy of some antipsychotic medications in the treatment of acute manic episodes, the evidence regarding the efficacy of these medications in maintenance treatment of bipolar disorder is much less well developed. Furthermore, there are relatively few large head-to-head comparisons of antipsychotics and mood stabilizers for the treatment of bipolar disorder.

The reasons for the recent increase in antidepressant and antipsychotic polypharmacy remain unclear. Changes in characteristics of patients, including increasing severity of illnesses, encountered in psychiatric practices and greater prevalence or recognition of psychiatric comorbidities offer possible explanations. Previous research suggests an association between severity of symptoms and antipsychotic polypharmacy. Furthermore, psychiatric comorbidities among outpatients are increasingly recognized, and an association between psychiatric comorbidities and psychotropic polypharmacy has been previously noted. We also found an association between comorbidities and prescription of antidepressant-antipsychotic combinations as well as antipsychotic-sedative-hypnotic combinations. However, time trends for antidepressant and antipsychotic polypharmacy remained significant even after adjusting for psychiatric diagnosis and comorbidity. Furthermore, we did not observe a significant change in the number of patients referred from general medical providers to psychiatrists—an indicator of greater clinical severity or complexity of disorders—over the study period (data not shown). Thus, there is little indication that changes in patient illness severity or comorbidity account for the observed trends in psychotropic polypharmacy.

A change in the style of psychiatric practice may have contributed to the increase in antidepressant-antipsychotic polypharmacy. Some psychiatrists may be placing greater emphasis on symptom reduction while lowering their concerns over the number of medications required to achieve this clinical goal. Another common practice is the off-label prescription of adjunctive atypical antipsychotic medications as sedatives. Growth in off-label prescription of antidepressant and antipsychotic medications has raised concerns. Consistent with this broad trend, most interaction terms of antidepressant and antipsychotic polypharmacy remain unclear. Changes in characteristics of patients, including increasing severity of illnesses, encountered in psychiatric practices and greater prevalence or recognition of psychiatric comorbidities offer possible explanations. Previous research suggests an association between severity of symptoms and antipsychotic polypharmacy. Furthermore, psychiatric comorbidities among outpatients are increasingly recognized, and an association between psychiatric comorbidities and psychotropic polypharmacy has been previously noted. We also found an association between comorbidities and prescription of antidepressant-antipsychotic combinations as well as antipsychotic-sedative-hypnotic combinations. However, time trends for antidepressant and antipsychotic polypharmacy remained significant even after adjusting for psychiatric diagnosis and comorbidity. Furthermore, we did not observe a significant change in the number of patients referred from general medical providers to psychiatrists—an indicator of greater clinical severity or complexity of disorders—over the study period (data not shown). Thus, there is little indication that changes in patient illness severity or comorbidity account for the observed trends in psychotropic polypharmacy.

In response to these concerns, there have been recent attempts to curtail psychotropic polypharmacy through quality improvement initiatives and physician training programs and by delineating explicit criteria for rational psychotropic polypharmacy regi-
Despite these efforts, the present analysis suggests that the rate of antidepressant and antipsychotic polypharmacy in outpatient psychiatric practice has increased in recent years. Continued unabated, the cost increases associated with increased use of these medications may bring on administrative mandates and restrictions in coverage to limit this practice. Because scant data exist to support the efficacy of some of the most common medication combinations, such as antipsychotic combinations or combinations of antidepressants and antipsychotics, prudence suggests that renewed clinical efforts should be made to limit the use of these combinations to clearly justifiable circumstances. At the same time, a new generation of research is needed to assess the efficacy, effectiveness, and safety of common concomitant medication regimens, especially in patients with multiple disorders or monotherapy-refractory conditions.

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REFERENCES


