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Objective: Patterns of clinical use of antipsychotic agents have changed greatly in the past decade. The authors’ goal was to examine these patterns.

Method: They evaluated medication use in all McLean Hospital inpatients treated with antipsychotic drugs during 3 months in 1998 (N=349) and compared the results with McLean Hospital inpatients treated in 1993 (N=299) and Boston area inpatients in 1989 (N=50).

Results: The most commonly prescribed antipsychotics in 1998 were atypical agents; olanzapine was prescribed more often than risperidone or quetiapine, which were prescribed more often than other antipsychotics. Two or more antipsychotics were prescribed at some time during their hospitalization for 150 (43%) of the patients in 1998. The total discharge dose in chlorpromazine equivalents for the 349 patients for whom antipsychotics were prescribed at discharge was 371 mg/day, 29% higher than the total discharge dose for patients in 1993 and 46% greater than the dose in 1989. The dose of antipsychotics was greater for patients with psychotic illnesses than for those with affective illnesses. Higher doses were associated with greater clinical improvement, polypharmacotherapy, and younger patient age.

Conclusions: Emerging trends toward higher total antipsychotic doses and polypharmacotherapy require critical assessments of cost-benefit relationships.
TABLE 1. Daily Dose of Antipsychotic Agents During Hospitalization at McLean Hospital Among All Inpatients Treated With Antipsychotics During 3 Months in 1998 Compared With Earlier Groups of Inpatients a

<table>
<thead>
<tr>
<th>Group and Antipsychotic</th>
<th>Patients Given Antipsychotic N % Potency Ratio</th>
<th>Initial Dose (mg/day of chlorpromazine equivalents)b</th>
<th>Maximum Dose</th>
<th>Finalc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (Mean SD)</td>
<td></td>
<td>Dose (Mean SD)</td>
<td></td>
</tr>
<tr>
<td>Inpatients treated for 3 months in 1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>125 35.8</td>
<td>25.0</td>
<td>229 151</td>
<td>321 180</td>
</tr>
<tr>
<td>Risperidone</td>
<td>59 16.9</td>
<td>80.0</td>
<td>182 173</td>
<td>267 226</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>58 16.6</td>
<td>0.5</td>
<td>122 133</td>
<td>266 188</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>34 9.7</td>
<td>14.0</td>
<td>330 294</td>
<td>443 342</td>
</tr>
<tr>
<td>Clozapine</td>
<td>21 6.0</td>
<td>1.5</td>
<td>220 252</td>
<td>442 275</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>21 6.0</td>
<td>50.0</td>
<td>280 191</td>
<td>411 244</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>12 3.4</td>
<td>1.0</td>
<td>117 83</td>
<td>172 103</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>9 2.6</td>
<td>40.0</td>
<td>920 739</td>
<td>1,093 627</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>5 1.4</td>
<td>1.0</td>
<td>105 110</td>
<td>250 71</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>3 0.9</td>
<td>25.0</td>
<td>579 469</td>
<td>1,068 935</td>
</tr>
<tr>
<td>Loxapine</td>
<td>2 0.6</td>
<td>12.0</td>
<td>865 752</td>
<td>931 658</td>
</tr>
<tr>
<td>Total</td>
<td>349 100.0</td>
<td></td>
<td>235 256</td>
<td>351 294</td>
</tr>
<tr>
<td>Inpatients treated with antipsychotics in 1993</td>
<td>299 100.0</td>
<td></td>
<td>283 333</td>
<td>367 345</td>
</tr>
<tr>
<td>Inpatients treated with antipsychotics in 1989</td>
<td>50 100.0</td>
<td></td>
<td>238 270</td>
<td>269 321</td>
</tr>
</tbody>
</table>

a Twenty-eight of the 377 patients who were given antipsychotic medication during their hospitalization were discharged without antipsychotic medication and are not included in this table.
b Based on multiples of the proposed potency ratios (approximate median recommended daily doses to chlorpromazine at 400 mg/day).
c The final dose of the primary antipsychotic (used for a majority of days) was at hospital discharge; the final total dose includes all antipsychotics used at discharge.

Results

In the 3-month 1998 group, antipsychotics were prescribed for 377 (50%) of 754 psychiatric inpatients; antipsychotics were prescribed for 349 of these patients at the time of their hospital discharge. These 349 inpatients comprise the present study group of 211 women (60.0%) and 138 men (40.0%). The patients’ mean age was 45.7 years (SD=19.6, range=18–91), and they were hospitalized for a mean of 29.0 days (SD=26.2) (compared with a mean of 18.5 days in 1993 and 73.1 days in 1989). Their DSM-IV diagnoses were primary psychosis (N=136 [39.0%]), major depression (N=73 [20.9%]), bipolar disorder (N=78 [22.3%]), dementia (N=41 [11.7%]), substance use (N=8 [2.3%]), and miscellaneous disorders (N=13 [3.7%]). Average time from admission to first antipsychotic dose was 0.9 days (versus 1.5 in 1993 and 6.8 in 1989).

The ranking of antipsychotic use for the 349 patients was as follows: olanzapine 36%, risperidone 17%, quetiapine 17%, perphenazine 10%, clozapine 6%, and haloperidol for 6%; other typical neuroleptics were used for 3% or less of the patients (Table 1). An atypical agent was the initial treatment for 254 (72.8%) of the patients; women started with atypical agents nonsignificantly more often than men (N=107 [77.5%] compared with N=145 [69.7%]) (χ²=2.61, df=1, p=0.11). Frequency of atypical primary agents among all antipsychotics was similar across diagnostic groups: psychotic (N=101 [74.3%]), affective (N=108 [71.5%]), and other disorders (N=50 [80.6%]).

Atypical agents were used in lower initial chlorpromazine-equivalent doses than typical neuroleptics (mean=190 mg/day, SD=164, versus mean=318 mg/day, SD=384) (F=20.5, df=1, 375, p<0.0001) as well as in lower discharge doses (mean=277 mg/day, SD=202, versus mean=438 mg/day, SD=415) (F=22.9, df=1, 347, p<0.0001). Maximum and total final doses of chlorpromazine and thioridazine were the most conservative, and the doses of fluphenazine, loxapine, and thiothixene were the highest (Table 1).

At discharge, two or more antipsychotics were prescribed for 55 (15.8%) of the patients (37 [17.5%] of the women and 18 [13.0%] of the men). By diagnosis, discharge polypharmacotherapy ranked as follows: psychotic (N=34 [25.0%]), affective (N=16 [10.6%]), and other (N=5 [8.1%]) disorders (χ²=14.5, df=2, p=0.0007). However, this practice included 133 (38.1%) of patients at some time during hospitalization and accounted for 20.0% of inpatient days in 1998, compared with 5.7% of inpatient days in 1993 and 1.7% in 1989 (1, 2). Typical neuroleptics were added only to primary atypical antipsychotics, but atypical agents were combined with both typical (217 patients [62.2%]) and other atypical (132 patients [37.8%]) primary antipsychotics.

The chlorpromazine-equivalent mean dose at discharge was 317 mg/day (SD=279) for primary agents but 371 mg/day (SD=348) with combinations included (Table 1) (t=5.92, df=348, p<0.0001). Discharge doses were also higher than initial doses (t=18.3, df=348, p<0.0001) but not significantly different from final doses in 1993 (t=1.85, df=646, p=0.08), although 24.8% greater than in 1989 (t=6.03, df=387, p<0.0001) (Table 1). However, the final total dose in 1998 was 29.3% greater than in 1993 (t=3.48, df=646, p=0.001) and 46.1% greater than in 1989 (t=2.56, df=397, p=0.02).

Discharge total doses were also 24.9% greater in men than women (mean=422 mg/day, SD=379, versus mean=357 mg/day, SD=342, t=2.61, df=754, p=0.01). The chlorpromazine-equivalent mean dose for the 349 patients was 317 mg/day (SD=279) for typical agents but 371 mg/day (SD=348) for combinations (Table 1) (t=5.92, df=348, p<0.0001). Discharge doses were also higher than initial doses (t=18.3, df=348, p<0.0001) but not significantly different from final doses in 1993 (t=1.85, df=646, p=0.08), although 24.8% greater than in 1989 (t=6.03, df=387, p<0.0001) (Table 1). However, the final total dose in 1998 was 29.3% greater than in 1993 (t=3.48, df=646, p=0.001) and 46.1% greater than in 1989 (t=2.56, df=397, p=0.02).
338 mg/day, SD=323) (F=4.90, df=1, 347, p=0.03). However, 65 (47.1%) of the men were psychotic, whereas 101 (47.9%) of the women were affectively ill ($\chi^2=6.64$, df=1, p=0.04).

By diagnosis, final total doses were ranked as follows: primary psychosis (mean=547 mg/day, SD=418), major affective disorder (mean=286 mg/day, SD=240), and other disorders (mean=194 mg/day, SD=209) (overall F=35.8, df=2, 346, p<0.0001). The final total dose fell somewhat with increasing age ($r_s=-0.22$, N=349, p<0.001) and was higher in patients with ratings of moderate or major than in those with ratings of minor or no improvement (mean=423 mg/kg, SD=397, versus mean=329 mg/kg, SD=371) (F=2.95, df=1, 193, p=0.09) but was unrelated to longer hospitalization ($r_s=-0.08$, N=349, p<0.14).

Since some factors may covary, multivariate analysis was applied. Four factors were associated with higher total discharge chlorpromazine-equivalent antipsychotic dose: psychotic versus major affective diagnosis (risk ratio=6.80, 95% CI=3.22–14.3), greater clinical improvement (risk ratio=3.36, 95% CI=1.65–6.84), use of two or more antipsychotics (risk ratio=1.94, 95% CI=1.14–3.22), and younger age (risk ratio=1.03, 95% CI=1.01–1.05). Discharge dose was no longer associated with sex, number of days in the hospital, primary agent typical versus atypical, use of depot neuroleptic, or use of a supplemental sedative.

**Discussion**

Over the past decade, atypical agents have emerged as the dominant choice among antipsychotics. At our hospital in 1993 (2), atypical agents accounted for only 12% of antipsychotics prescribed, compared with 72% in 1998 (Table 1). The most commonly used agents in 1998 were olanzapine, risperidone, and quetiapine (olanzapine was used more than risperidone, which was used as much as quetiapine), and atypical agents were used at similar rates across diagnostic groups. By multivariate analysis, total chlorpromazine-equivalent discharge doses were significantly higher for patients with psychotic diagnoses than those with major affective diagnoses, for those with greater clinical improvement during hospitalization (despite clinically individualized dosing), those prescribed multiple antipsychotics, and younger patients. Discharge doses were not significantly related to sex, hospital stay, typical/atypical antipsychotic type, or addition of sedatives. Total discharge chlorpromazine-equivalent antipsychotic doses increased by approximately 46% over the past decade.

It seems unlikely that increasing total doses of antipsychotics reflect major changes in admission policies or the impact of managed care. The length of stay did not decrease between 1993 and 1998 (range=19–29 days). Instead, increasing antipsychotic dosing appears to reflect use of moderate doses of individual agents but a rising cumulative total because of polypharmacotherapy. Simultaneous use of two or more antipsychotics was found in 55 (15.8%) of the patients in the 1998 study group at discharge, but in 133 (38.1%) at some time during hospitalization. The most frequent combinations involved typical antipsychotics added to atypical primary agents. This tendency may reflect incomplete confidence in monotherapy with atypical antipsychotic agents in inpatient practice. Additional combinations of several psychotropic agents also were common in 1998 (69 [19.8%] of the patients received four or more agents).

Polypharmacotherapy in major psychiatric disorders is a growing international phenomenon, despite lack of research evidence of superior effectiveness without compromising safety or acceptable financial cost (5–12). We conclude that upward trends in total antipsychotic dosing and growing use of different forms of polypharmacotherapy require additional empirical study with modern antipsychotic agents to evaluate critically their risks, benefits, and costs.

References

8. Procynshyn RM, Kennedy NB, Tse G, Thompson B: Antipsychotic polypharmacy: a survey of discharge prescriptions from a ter-
Psychopharmacologic Treatment of Generalized Anxiety Disorder and the Risk of Major Depression

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Objective: The authors sought to determine the association between treatment for generalized anxiety disorder and the risk of major depression among adults in the community.

Method: Data were drawn from the National Comorbidity Survey (N=8,098), a representative sample of the United States population age 15–54. Cox proportional hazards were used to determine the association between specific forms of treatment for generalized anxiety disorder and the risk of major depression.

Results: Psychopharmacologic treatment of generalized anxiety disorder was associated with a significantly lower risk of major depression. There was no significant association between either having seen a mental health professional for generalized anxiety disorder or having been prescribed a medication for generalized anxiety disorder and the risk of depression.

Conclusions: These results suggest an association between treatment for generalized anxiety disorder and lower risk of depression, which appears specific to pharmacologic treatment. Future research that leads to a more precise delineation of the underlying mechanism of the observed association is needed to identify and develop effective strategies to prevent onset of depression.


The majority of data from epidemiology and clinical studies suggest that generalized anxiety disorder and major depression co-occur more frequently than would be expected by chance (1–3). The co-occurrence of these two disorders is associated with significantly greater psychiatric comorbidity, social and occupational impairment, and suicidal ideation and suicide behavior compared with either disorder without the other (4–7). Previous evidence suggests that the onset of generalized anxiety disorder occurs before the onset of major depression in the majority of cases (8–10) and that in some cases, generalized anxiety disorder may be a precursor to the onset of major depression (1, 2, 4–6, 8).

Despite the well-documented finding that most people with one mental disorder will develop at least one other disorder in their lifetime, there remain relatively few data on the feasibility of the prevention of secondary comorbidity and even less that describe effects associated with specific types of treatment. The goal of the current study was to determine the association between the treatment of generalized anxiety disorder and the risk of depression among adults in the community.

Method

The National Comorbidity Survey is based on a national probability sample of individuals 15–54 years of age in the noninstitutionalized population (11). Fieldwork was carried out between September 1990 and February 1992. There was an 82.4% response rate. The total sample includes 8,098 interviewed respondents. The data were weighted for differential probabilities of selection and nonresponse. Weights are described in detail elsewhere (11, 12).

The group under study consisted of respondents with diagnoses of generalized anxiety disorder (lifetime prevalence) (N=219), either with depression (with onset occurring after onset of generalized anxiety disorder) or without depression. Diagnoses were generated from a modified version of the World Health Organization (WHO) Composite International Diagnostic Interview, a structured interview designed for use by lay interviewers (13). WHO field trials and National Comorbidity Survey clinical reappraisal studies have documented acceptable reliability and validity for these diagnoses (13–15).

For the diagnostic sections that assessed symptoms of generalized anxiety disorder, respondents were asked whether they had ever seen a mental health specialist (defined as a psychiatrist, psychologist, or social worker) regarding these symptoms, been prescribed a medication for treatment of the symptoms, and whether they had taken medication for the symptoms at least four times or more. Psychopharmacologic treatment was defined as respondents who endorsed having taken psychotro-