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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.

We surveyed hospital practices in the Boston area regarding use of antipsychotic drugs in 1984, 1989, and 1993 (1, 2). In contrast to earlier American practices, mean chlorpromazine-equivalent daily doses fell by the late 1980s, to accord with standard international practices, and conservative dosing was sustained into the early 1990s (2, 3). More recently, growing numbers of atypical antipsychotics have entered clinical use, along with other innovative treatments (4). It is our clinical impression, supported by recent research reports (5–8), that simultaneous use of multiple dissimilar antipsychotics is increasing. Accordingly, we completed a new survey of antipsychotic use to document current trends compared with our earlier findings over the past decade (1, 2).

Method

Consecutive patients admitted to McLean Hospital in March-May 1998 who were treated with antipsychotic medications were considered. Following review and approval for confidential and anonymous use of aggregate data by the hospital’s institutional review board, we reviewed clinical records to determine the patient’s sex, age, discharge DSM-IV diagnosis, and all medications given, with their doses and times.

Doses of antipsychotics were converted to chlorpromazine equivalents (mg/day) on the basis of potency ratios of approximate median recommended daily doses to chlorpromazine at 400 mg/day (4) (Table 1). For each patient, we compiled initial, maximum, and final (discharge) doses of primary antipsychotic agents (those used for the majority of inpatient days), as well as the total final dose when multiple antipsychotics were given. Comparisons were made of McLean patients treated in 1998 (N=349) with similar McLean inpatients in 1993 (N=299) and Boston area patients in 1989 (N=50) (2). Data on patients’ clinical improvement were obtained from hospital discharge records.

Averages are means and standard deviations. Continuous data were compared by using one-way analysis of variance, paired t tests, or unpaired t tests for unequal groups across years. Categorical data were compared by using contingency tables (chi-square). Correlations were based on Spearman nonparametric rank methods (r_s). Factors associated with contingency tables (chi-square). We used Statview-5 programs (SAS Corp., Cary, N.C.) for statistical analyses.
**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%) 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=376 mg/day, SD=342, t=4.19, df=765, 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).

### 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

<table>
<thead>
<tr>
<th>Group and Antipsychotic</th>
<th>Patients Given Antipsychotic</th>
<th>Potency Ratio</th>
<th>Dose (mg/day of chlorpromazine equivalents)b</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Total</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatients treated for 3 months in 1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>125</td>
<td>35.8</td>
<td>25.0</td>
<td>229 ± 151</td>
<td>321 ± 180</td>
<td>302 ± 186</td>
<td>376 ± 342</td>
<td>348</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>59</td>
<td>16.9</td>
<td>80.0</td>
<td>182 ± 173</td>
<td>267 ± 226</td>
<td>242 ± 221</td>
<td>265 ± 249</td>
<td>284</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>58</td>
<td>16.6</td>
<td>0.5</td>
<td>122 ± 133</td>
<td>266 ± 188</td>
<td>219 ± 157</td>
<td>296 ± 228</td>
<td>328</td>
<td></td>
</tr>
<tr>
<td>Perphenazine</td>
<td>34</td>
<td>9.7</td>
<td>14.0</td>
<td>330 ± 294</td>
<td>443 ± 342</td>
<td>422 ± 354</td>
<td>428 ± 349</td>
<td>435</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>21</td>
<td>6.0</td>
<td>50.0</td>
<td>220 ± 252</td>
<td>442 ± 275</td>
<td>388 ± 282</td>
<td>429 ± 336</td>
<td>353</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>21</td>
<td>6.0</td>
<td>50.0</td>
<td>280 ± 191</td>
<td>411 ± 244</td>
<td>379 ± 252</td>
<td>422 ± 473</td>
<td>405</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>12</td>
<td>3.4</td>
<td>1.0</td>
<td>117 ± 83</td>
<td>172 ± 103</td>
<td>165 ± 107</td>
<td>165 ± 107</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>9</td>
<td>2.6</td>
<td>40.0</td>
<td>920 ± 739</td>
<td>1,093 ± 627</td>
<td>951 ± 677</td>
<td>1,066 ± 687</td>
<td>1,066</td>
<td></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>10</td>
<td>2.9</td>
<td>1.0</td>
<td>117 ± 83</td>
<td>172 ± 103</td>
<td>165 ± 107</td>
<td>165 ± 107</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
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<td>411 ± 244</td>
<td>379 ± 252</td>
<td>422 ± 473</td>
<td>405</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>5</td>
<td>1.4</td>
<td>1.0</td>
<td>105 ± 110</td>
<td>150 ± 71</td>
<td>175 ± 117</td>
<td>195 ± 148</td>
<td>195</td>
<td></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>3</td>
<td>0.9</td>
<td>25.0</td>
<td>579 ± 469</td>
<td>1,068 ± 935</td>
<td>757 ± 502</td>
<td>924 ± 714</td>
<td>924</td>
<td></td>
</tr>
<tr>
<td>Loxapine</td>
<td>6</td>
<td>1.7</td>
<td>1.0</td>
<td>865 ± 752</td>
<td>931 ± 658</td>
<td>831 ± 799</td>
<td>1,098 ± 422</td>
<td>1,098</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>349</td>
<td>100.0</td>
<td></td>
<td>235 ± 256</td>
<td>351 ± 294</td>
<td>317 ± 279</td>
<td>371 ± 348</td>
<td>371</td>
<td></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 antipsychotics used at discharge.

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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.

Received Feb. 12, 2002; revision received May 7, 2002; accepted May 20, 2002. From the Department of Psychiatry and Neuroscience Program, Harvard Medical School, Boston; the Bipolar and Psychotic Disorders Program, McLean Hospital; the Department of Neuropsychiatry, Catholic University of Korea, College of Medicine, Seoul; and Bouvé College of Pharmacy and Allied Health Sciences, Northeastern University, Boston. Address reprint requests to Dr. Centorrino, Bipolar and Psychotic Disorders Clinic, North Belknap III, McLean Hospital, 115 Mill St., Belmont, MA 02478-9106; centorf@mcleanpo.mclean.org (e-mail).

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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 (χ²=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=−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=−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. Simulta-
Psychopharmacologic Treatment of Generalized Anxiety Disorder and the Risk of Major Depression

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Jack M. Gorman, M.D.

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.

5. Cox proportional hazards were used to determine the association between specific forms of treatment for generalized anxiety disorder and lower risk of depression.
6. 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.

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-