Antipsychotic Dosing and Concurrent Psychotropic Treatments for Medicaid-Insured Individuals With Schizophrenia

by Susan dosReis, Julie Magno Zito, Robert W. Buchanan, and Anthony F. Lehman

Abstract

Antipsychotic medications have been first line treatment for schizophrenia for half a century, yet few studies have assessed outpatient maintenance treatment in large populations. This article describes oral antipsychotic dosing patterns and psychotropic treatments using computerized Medicaid claims data for individuals who were diagnosed with schizophrenia and received treatment on an outpatient basis during 1991. The findings show that the mean daily oral antipsychotic dose was 729 ± 586 chlorpromazine equivalents (CPZ-EQ) for high-potency agents and 304 ± 328 CPZ-EQ for low-potency agents. Males, younger individuals, and African-Americans received larger mean daily doses of high-potency agents, ranging from 747 to 800 CPZ-EQ. Antiparkinsonian agents were prescribed for over 90 percent of the outpatient antipsychotic treatment exposure. In summary, young adults, males, and African-Americans were given high-potency antipsychotic medications at outpatient maintenance doses that exceeded the maximum recommended levels, despite well-established evidence that high-dose antipsychotic treatment offers no additional benefit. Likewise, concurrent antiparkinsonian treatment exceeded the 1990 World Health Organization recommendations.

Keywords: Schizophrenia Patient Outcomes Research Team, pharmacoepidemiology, Medicaid, schizophrenia, antipsychotic dosage, concurrent pharmacotherapy.


Despite the long-term clinical use of antipsychotic medications for schizophrenia (Kane 1996), variability in antipsychotic dosing practices continues to raise questions about the quality of pharmacotherapy in typical practice settings. While minimizing total antipsychotic exposure and reducing side effects are important and well-established considerations for maintenance treatment of schizophrenia, the best strategy for implementing maintenance treatment has been debated (Buchanan and Carpenter 1996).

Randomized, double-blind controlled trials spanning more than three decades have consistently found that high-dose antipsychotic treatment does not provide additional therapeutic benefit over low-dose treatment; instead, it only increases the risk of undesirable and irreversible side effects. The studies, ranging in duration from 2 weeks to 1 year and involving individuals aged 16–70 years, provide strong evidence to support the use of low-dose antipsychotic treatment, in either inpatient (Quitkin et al. 1975; McEvoy et al. 1991; Rifkin et al. 1991; Volavka et al. 1992; Stone et al. 1995) or outpatient settings (Kane et al. 1983; Kane et al. 1985). Compared with high-dose antipsychotic treatment, low-dose antipsychotic treatment has not resulted in greater psychosocial dysfunction or a higher rate of relapse requiring hospitalization (Kane et al. 1983). Moreover, greater improvement on measures of global assessment and psychotic symptoms has been reported with low-dose treatment (Quitkin et al. 1975; McEvoy et al. 1991; Volavka et al. 1992; Stone et al. 1995). In a controlled study of 106 newly admitted individuals aged 18–57 years who met research criteria for schizophrenia or schizoaffective disorder, maximal therapeutic benefit was achieved at the lowest dose for which pharmacological activity was first apparent (McEvoy et al. 1991). Furthermore, use of more than 10 mg per day of haloperidol has not resulted in a clinically significant improvement (Rifkin et al. 1991).

Critical reviews of published randomized clinical trials have also concluded that maximal therapeutic benefit has been achieved with low-dose antipsychotic treatment (Gardos et al. 1973; Aubree and Lader 1980; Baldessarini et al. 1988; Bollini et al. 1994). In reviewing 12 dose-response studies published from 1968 to 1972, Gardos and colleagues reported four main findings (Gardos et al.
First, a majority of the studies involved treatment-resistant patients; thus, higher doses were required for this population. Second, a typical therapeutic dose is optimal given the increase in side effects at higher doses. Third, although a minority of individuals can be managed without medication, the majority of individuals with schizophrenia should be managed with a usual clinical dose. Finally, low doses may be more appropriate for individuals who are apathetic, depressed, or both (Gardos et al. 1973). Aubree and Lader reviewed 14 randomized, double-blind controlled trials and noted similar clinical improvement on high- and low-dose antipsychotic treatment in the majority of studies (55%) but a pronounced increase in extrapyramidal side effects at higher doses (Aubree and Lader 1980).

According to a review of 38 controlled studies, the maximal benefit of long-term antipsychotic treatment was achieved at doses not greater than 600 mg CPZ-EQ, and higher doses were associated with a 64 percent increase in side effects (Baldessarini et al. 1988). Long-term treatment with moderate doses approximating 50–150 mg CPZ-EQ per day prevented relapse in 50 percent of patients, suggesting that chronically ill schizophrenia patients could be successfully managed at lower doses (Baldessarini et al. 1988).

Finally, Bollini and colleagues performed a meta-analysis of randomized controlled trials published from 1964 through 1987 \( (n = 22) \) and noted two clinically relevant findings (1994). First, clinical effectiveness as measured by improvement on global assessment was similar for low \( (166–375 \text{ mg CPZ-EQ}) \), moderate \( (376–830 \text{ mg CPZ-EQ}) \), and high \( (> 830 \text{ mg CPZ-EQ}) \) doses. Second, significantly fewer side effects were reported at doses less than 375 mg CPZ-EQ compared with doses above 375 mg CPZ-EQ.

Nonetheless, a handful of studies conducted in community inpatient and outpatient settings suggest that low-dose antipsychotic practices have not been adopted in clinical practice (Baldessarini et al. 1984; Zito et al. 1987; Zito et al. 1988; Italian Collaborative Study Group 1999; Walkup et al. 2000). Consequently, the Schizophrenia Patient Outcomes Research Team (PORT) developed treatment recommendations based on the available scientific evidence in order to facilitate the translation of research into clinical practice (Lehman et al. 1998). These practice recommendations provide a benchmark from which to assess the standard of care. To our knowledge, only one other study, using an inpatient population with schizophrenia, has assessed antipsychotic dosing practices in relation to the Schizophrenia PORT recommendations (Walkup et al. 2000). This study found that African-American patients received higher doses than Caucasians (Walkup et al. 2000). Furthermore, two studies using an administrative claims data base characterized antipsychotic prescription patterns in an outpatient setting with respect to the duration of treatment and the extent of medication changes over the study year, but these patterns were not related to dose (McCombs et al. 1999; Williams et al. 1999). Notable findings from these studies were that antipsychotic use was lower among older patients than among younger patients (McCombs et al. 1999), one-fourth of individuals switched antipsychotics during the study year, and approximately 90 percent received concurrent psychotropic treatment (Williams et al. 1999).

The current study adds to the scientific knowledge of antipsychotic prescribing patterns in community outpatient settings for patients with schizophrenia and is unique in several ways. First, the study assessed antipsychotic dosing and concurrent pharmacotherapy for chronic treatment of schizophrenia in outpatient settings. Second, the relationship between daily dose and demographic characteristics, antipsychotic potency, and duration of treatment was examined. Third, the relationship between the duration of concurrent psychotropic medication and antipsychotic dose was assessed. We hypothesized that larger antipsychotic doses would be significantly associated with younger age, male gender, African-American race, high-potency agents, and concurrent psychotropic treatments, controlling for the duration of antipsychotic treatment.

**Methods**

**Study Cohort.** Calendar year 1991 was the index year for selecting the study population. Drawing from one large southern state, all Medicaid enrollees who had at least one claim associated with a physician-based diagnosis of schizophrenia (ICD–9 = 295) in an inpatient or outpatient setting were eligible \( (n = 10,101) \). Individuals were excluded \( (n = 1,411) \) if they were younger than 18 years of age, they were not continuously enrolled in the Medicaid program during 1991, or they had died before the end of 1991. Additionally, 153 individuals were excluded because they did not have a claim in 1991 associated with a diagnosis of schizophrenia (e.g., claim adjudicated in 1991 was for a service provided in the prior year). Individuals who were dually eligible for both Medicaid and Medicare benefits \( (n = 2,470) \) were excluded because the portion of their services covered by Medicare would not be available in the Medicaid data base. As a result, the study population consisted of 6,067 individuals diagnosed with schizophrenia in 1991.

**Data Source.** The Health Care Financing Administration (HCFA, now the Center for Medicare and Medicaid Services) provided Medicaid data from its
Tape-to-Tape Medicaid Project (formally called the Medicaid Analysis Project for States), which was funded through its Office of Research and Demonstrations. The contractor for the Tape-to-Tape Medicaid Project was the Research and Policy Division of the MEDSTAT Group. Applying the sampling criterion of a diagnosis of schizophrenia, HCFA selected out all paid claims contained in its uniform research files, which included outpatient and pharmacy service claims. HCFA also provided data from its enrollment and provider files. These data files were made accessible to the MEDSTAT Group. Through collaboration between Johns Hopkins University Schizophrenia PORT researchers and the MEDSTAT staff, file specifications that included the HCFA Tape-to-Tape and the Medicaid-specific coding standards and documentation were defined.

The current study used the pharmacy claims file to identify all psychotropic medications dispensed during the year for the 6,067 individuals who met the study criteria. Pharmacy claims data represent reimbursement claims for medications dispensed from community outpatient pharmacies. The variables available in the pharmacy claims file that were used for this study include the recipient identification number, the prescription dispensing date, the quantity dispensed, and the National Drug Code (NDC), which is a unique identifier for each manufacturer's version of a medication. The medication name, strength, and American Hospital Formulary System (AHFS) therapeutic classification code were not in the Medicaid prescription record data but were obtained from a computerized medication dictionary. The dictionary was created using data files from the Food and Drug Administration (FDA), Medispan®, and First Databank®. Psychotropic medications were grouped by AHFS class as antipsychotics, antidepressants, anticonvulsants, antiparkinsonians, sedative/hypnotics, benzodiazepines, and miscellaneous anxiolytics as well as lithium. The enrollment file was used to gather information on age, gender, race, and continuous enrollment. Race was not recorded for approximately 631 (10%) individuals.

**Characterization of Antipsychotic Treatment**

**Antipsychotic exposure.** The duration of antipsychotic exposure was derived from the pharmacy claims data. Because the daily dose could not be established for depot formulations, only oral formulations were included in this analysis. To establish antipsychotic exposure during the study year, consecutive refills for the same medication were linked using the NDC. Because multiple manufacturers produce the same generic version of a medication, multiple NDCs could represent one medication (i.e., chlorpromazine); thus, linkage also occurred across different NDCs corresponding to the same medication.

The duration of antipsychotic exposure was based on the time interval between prescription refills. A gap of not more than 14 days between the end of one prescription and the start of the next prescription was considered continuous treatment. This criterion was adopted because research has shown that individuals do not always obtain prescription refills on time (Schulz and Gagnon 1982), averaging 4-19 days late (Ascione et al. 1985), and because medication changes often require titration over a period of 7-14 days. The overall duration of continuous antipsychotic exposure was calculated as the number of days between the dispensing date of the original prescription and the dispensing date of the last prescription plus an additional 30 days, which was an estimate of the days' supply for the last dispensed prescription. This estimation was based on the state's Medicaid policy, which allowed a maximum of 30 days' supply per dispensing. The current study focuses on maintenance treatment, and so only those individuals with 30 days or more of antipsychotic exposure were included in the daily dose analysis.

Several validation steps were undertaken to carefully inspect the data prior to linking prescription refills. First, the chronological sequence of prescription refills was examined to identify the pattern of use and highlight inconsistencies. Adjustment claims for a previously dispensed medication (i.e., duplicate claims) mainly were responsible for inconsistencies in the refill pattern; thus, duplicate claims were deleted. Second, the estimated number of doses per day was calculated to determine whether the dose exposure within a time interval was reasonable. For example, a 90-day exposure that included 270 tablets of chlorpromazine 100 mg was estimated to be three tablets per day, which was reasonable. Doses per day that appeared to be too low (e.g., < half of a tablet per day) or too high (e.g., > 8 tablets per day) were reexamined.

**Antipsychotic daily dose.** The average daily dose (ADD) was established for each antipsychotic medication and was converted at a relative potency equivalent to 100 mg of chlorpromazine (i.e., CPZ-EQ) based on information published in the literature (Davis 1976; Zito 1994; Kane 1996). Although we do acknowledge the limitations of this conversion method at higher doses, CPZ-EQ is the standard measure for making comparisons with published reports and with treatment recommendations such as those developed by the Schizophrenia PORT investigators (Lehman et al. 1998).

The ADD for antipsychotic treatment was calculated as the product of the quantity dispensed and the strength of the medication (in mg) divided by the length (in days) of the
analyses between antipsychotic doses and demographic characteristics, antipsychotic potency, and concurrent psychotropic treatment were assessed using analysis of variance for associations among categorical and continuous variables and Pearson correlation for associations among continuous variables.

Linear regression was used to assess the association between antipsychotic dose (CPZ-EQ) and demographic variables, antipsychotic potency, and duration of concurrent treatment, controlling for duration of antipsychotic exposure. According to the univariate test of normality (Kolmogorov-Smirnov test statistic; D = 0.179681; p < 0.01), the dependent variable, antipsychotic dose, was not normally distributed. Because normality is a critical assumption for linear regression, a log transformation was used to obtain a normal distribution of antipsychotic dose. The multivariable analysis included only Caucasian and African-American racial groups, for ease of interpretation. Statistical significance was set at 0.05 for all analyses, and a Bonferroni correction was used to account for multiple comparisons.

Results

Psychotropic-Treated Cohort. Among the 6,067 individuals who received a diagnosis of schizophrenia in 1991 and met the study criteria, 5,880 (97%) had at least one claim for a psychotropic medication. The 187 (3%) who did not have a psychotropic claim during the study year were more likely to be male ($\chi^2 = 88.7; p < 0.0001$), less than 50 years old ($\chi^2 = 24.7; p < 0.0001$), and African-American ($\chi^2 = 10.4; p < 0.01$) compared with those who had a psychotropic claim. The 5,880 individuals had 104,788 psychotropic prescription claims. Based on the prescription refill pattern, the daily supply of medication, and the estimated number of doses per day, 219 (4%) individuals and 308 (0.3%) claims were deleted because of questionable accuracy. This change resulted in 5,661 individuals with 104,480 psychotropic prescription claims.

Individuals were characterized according to their exposure to antipsychotic and other psychotropic medications (table 1). For example, an individual with claims for haloperidol and chlorpromazine but no other psychotropic claims would be classified as receiving only antipsychotic medications. Of the 5,661 individuals with at least one psychotropic claim, 782 (14%) had claims for only antipsychotic medications, 4,051 (71%) had claims for antipsychotic medications as well as other psychotropic agents, and 828 (15%) did not receive antipsychotic medication but had claims for other psychotropic medications.

The psychotropic-treated population was largely female, African-American, and less than 50 years old. Psy-
Table 1. Demographic and clinical characteristics of the sample according to psychotropic medication use (n = 5,661)

<table>
<thead>
<tr>
<th>Demographic and clinical variables</th>
<th>Antipsychotic only (n = 782), n (%)</th>
<th>Antipsychotic and other psychotropic (n = 4,051), n (%)</th>
<th>Other psychotropic only (n = 828), n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>289 (37)</td>
<td>1,424 (35)</td>
<td>286 (35)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>493 (63)</td>
<td>2,627 (65)</td>
<td>542 (65)</td>
</tr>
<tr>
<td>Age</td>
<td>18–34</td>
<td>225 (29)</td>
<td>1,445 (36)</td>
<td>293 (36)</td>
</tr>
<tr>
<td></td>
<td>35–49</td>
<td>268 (34)</td>
<td>1,614 (40)</td>
<td>326 (39)</td>
</tr>
<tr>
<td></td>
<td>50–64</td>
<td>259 (33)</td>
<td>942 (23)</td>
<td>194 (23)</td>
</tr>
<tr>
<td></td>
<td>65+</td>
<td>30 (4)</td>
<td>50 (1)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian</td>
<td>217 (28)</td>
<td>1,256 (31)</td>
<td>254 (31)</td>
</tr>
<tr>
<td></td>
<td>African-American</td>
<td>478 (61)</td>
<td>2,340 (58)</td>
<td>485 (58)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>87 (11)</td>
<td>455 (11)</td>
<td>89 (11)</td>
</tr>
<tr>
<td>Other mental disorders</td>
<td>Affective</td>
<td>14 (2)</td>
<td>380 (9)</td>
<td>90 (11)</td>
</tr>
<tr>
<td></td>
<td>Alcohol abuse</td>
<td>7 (0.9)</td>
<td>135 (3)</td>
<td>29 (4)</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>28 (4)</td>
<td>581 (14)</td>
<td>119 (14)</td>
</tr>
<tr>
<td></td>
<td>Bipolar</td>
<td>5 (0.6)</td>
<td>189 (5)</td>
<td>39 (5)</td>
</tr>
<tr>
<td></td>
<td>Drug abuse</td>
<td>16 (2)</td>
<td>94 (2)</td>
<td>27 (3)</td>
</tr>
<tr>
<td></td>
<td>Other psychotic disorders</td>
<td>25 (3)</td>
<td>349 (9)</td>
<td>38 (5)</td>
</tr>
<tr>
<td></td>
<td>Other psychiatric disorders</td>
<td>61 (8)</td>
<td>515 (13)</td>
<td>114 (14)</td>
</tr>
<tr>
<td></td>
<td>Personality disorders</td>
<td>3 (0.4)</td>
<td>54 (1)</td>
<td>8 (1)</td>
</tr>
<tr>
<td></td>
<td>Mental retardation</td>
<td>31 (4)</td>
<td>125 (3)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Psychotropic medications¹</td>
<td>Anticonvulsants</td>
<td>—</td>
<td>516 (13)</td>
<td>102 (12)</td>
</tr>
<tr>
<td></td>
<td>Antidepressants</td>
<td>—</td>
<td>1,287 (32)</td>
<td>302 (36)</td>
</tr>
<tr>
<td></td>
<td>Antiparkinsonian agents</td>
<td>—</td>
<td>2,984 (74)</td>
<td>383 (46)</td>
</tr>
<tr>
<td></td>
<td>Sedatives/hypnotics</td>
<td>—</td>
<td>80 (2)</td>
<td>28 (3)</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines</td>
<td>—</td>
<td>835 (21)</td>
<td>198 (24)</td>
</tr>
<tr>
<td></td>
<td>Lithium</td>
<td>—</td>
<td>503 (12)</td>
<td>83 (10)</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous anxiolytics</td>
<td>—</td>
<td>688 (17)</td>
<td>176 (21)</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>782 (100)</td>
<td>3,939 (97)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Fixed combinations²</td>
<td>—</td>
<td>279 (7)</td>
<td>7 (0.8)</td>
</tr>
</tbody>
</table>

¹ Chi-square analyses for nonantipsychotic psychotropic medications among antipsychotic plus other psychotropic versus other psychotropic-only groups.

² Fixed combinations were amitriptyline/chlordiazepoxide and amitriptyline/perphenazine; fixed combination use under "other psychotropic only" was exclusively amitriptyline/chlordiazepoxide, the statistical significance of which is due to the fact that this group did not receive the combination with perphenazine.

Antipsychotic treatment regimens differed significantly with age (χ² = 67.4; p < 0.0001), such that individuals aged 50 years or older were more likely to have received only an antipsychotic medication, whereas younger individuals were more likely to have received an antipsychotic and another psychotropic treatment. The proportion of individuals who received a psychotropic medication and also had at least one claim associated with an outpatient diagnosis of affective (χ² = 54.9; p < 0.0001), alcohol abuse (χ² = 14.0; p < 0.001), anxiety (χ² = 69.6; p < 0.0001), bipolar (χ² = 27.7; p < 0.0001), other psychiatric disorder (χ² = 38.8; p < 0.0001), or other psychiatric disorder (χ² =
16.9; p < 0.001) during the study year was significantly lower among those who received only an antipsychotic compared with the other two groups.

**Antipsychotic daily dose.** Antipsychotic dosing and concurrent treatment analyses were based on the 4,833 (85%) individuals who received an oral antipsychotic medication (i.e., those in columns 1 and 2 in table 1). Of this group, 933 (19%) were excluded from further analyses because they (1) had only one antipsychotic claim during the year, which was not indicative of maintenance treatment, or (2) had a claim for only an antipsychotic depot or fixed combination formulation (i.e., amitriptyline and perphenazine combination in one tablet). Individuals were not excluded entirely if they had an oral antipsychotic exposure; only the depot or fixed combination claims were excluded. Individuals who received chlorprothixene or pimozide (n = 3; 0.1%) and who were 65 years or older (n = 68; 1.4%) also were excluded because of small numbers that would not permit subgroup comparisons. Furthermore, to exclude possible acute treatment episodes, the 372 (8%) individuals with less than 30 days of antipsychotic exposure and the 392 (8%) individuals with 2 or more separate periods of antipsychotic exposure during 1991 were also removed from further analyses. This resulted in 61,785 psychotropic prescription claims for 3,065 individuals who had 1 period of antipsychotic exposure of at least 30 days during the study year from which daily doses and concurrent psychotropic treatment could be established. The 3,065 individuals did not differ in age, gender, and race compared with the 4,833 who received any antipsychotic medication.

The average duration of antipsychotic exposure was 128 (± 100) days, which did not differ by gender. Ranges in the duration of antipsychotic exposure were as follows: 132 (± 104) days for high potency and 122 (± 93) days for low/moderate potency; 111 (± 90) days for 18–34 year olds, 129 (± 102) days for 35–49 year olds, and 147 (± 105) days for 50–64 year olds; and 142 (± 103) days for Caucasians and 120 (± 97) days for African-Americans.

Bivariate analyses revealed significant associations (table 2). Higher antipsychotic daily doses were associated with higher potency agents (F = 662.62; df = 1,3063; p < 0.0001) and male gender (F = 49.06; df = 1,3063; p < 0.0001). There was a trend toward higher doses among African-American individuals. The correlation between antipsychotic daily dose and age was -0.13 (p < 0.0001), indicating a decrease in dose with increasing age. However, this explains less than 2 percent of the variance, which may not be clinically significant.

Because higher CPZ-EQ antipsychotic doses were observed among individuals receiving high-potency antipsychotic medications (of which 63 percent was haloperidol), daily dosing patterns were further explored for this subgroup of individuals. Table 2 also displays the mean daily dose among high-potency users (n = 1,177) according to age, gender, and race. Doses were significantly higher among males (F = 11.8; df = 1,1177; p < 0.001) and younger individuals (r = -0.10; p < 0.01).

<table>
<thead>
<tr>
<th>Table 2. Variation in the average daily dose in CPZ-EQ according to sample characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Characteristics</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Potency</td>
</tr>
<tr>
<td>Low/moderate</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>35–49</td>
</tr>
<tr>
<td>50–64</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>African-American</td>
</tr>
<tr>
<td>Other/unknown</td>
</tr>
</tbody>
</table>

Note.—CPZ-EQ = chlorpromazine equivalents; SD = standard deviation.

*p < 0.001; **p < 0.01; *** p < 0.01
However, the statistical significance of the correlation with age is likely to be due to the sample size and may not be clinically meaningful.

**Concurrent psychotropic treatment.** Sixty-five percent \( (n = 1,998) \) received an antiparkinsonian agent, and 16 percent \( (n = 484) \) received a TCA concurrently with an antipsychotic medication. Antiparkinsonian and TCA medications were used concurrently for 93 percent and 89 percent of the antipsychotic treatment exposure, respectively. The duration of concurrent antiparkinsonian treatment (in days) was associated with race \( (F = 7.6; df = 2,1985; p < 0.001) \) and age \( (r = 0.14; p < 0.0001) \) but not gender, antipsychotic potency, or antipsychotic daily dose. Although the duration of concurrent TCA treatment (in days) was significantly associated with antipsychotic dose \( (r = 0.12; p < 0.01) \), this explains less than 2 percent of the variance and is unlikely to be clinically significant. Concurrent TCA treatment was not significantly associated with age, gender, race, or antipsychotic potency. There were 257 individuals \( (8\%) \) treated simultaneously with an antipsychotic, an antiparkinsonian agent, and a TCA for at least 14 days.

**Multivariate analysis.** Significant main effects of age, gender, and potency \( (table\ 3;\ model\ 1) \) did not change when the duration of antipsychotic exposure was added to the model \( (model\ 2) \). Because several bivariate analyses revealed significant associations among potency, age, race, and gender, the interactions between race and potency, age and potency, gender and potency, and gender and race, and age and race on antipsychotic dose were assessed in a multivariate model. The model that included these interaction terms explained 26 percent of the variance in daily dose, and only the interaction of antipsychotic potency with race was significant \( (p < 0.001) \). A more parsimonious model, after removing the nonsignificant interactions, also explained 26 percent of the variance in daily dose \( (model\ 3) \). After including the interaction between race and potency \( (model\ 3) \), the main effect of race was significant, and the incremental change in the explained variance from model 2 to model 3 was significant \( (F = 11.28; df = 1,2707; p < 0.01) \). Concurrent TCA pharmacotherapy was not significantly associated with antipsychotic dose.

Although a log transformation was used to obtain a normal distribution of antipsychotic daily dose, the overall qualitative interpretation of the estimate does not change; that is, positive values indicate that as the predictor increases, the outcome \( (log \text{ antipsychotic dose}) \) tends to increase as well. One caveat is that the degree of average change in the original dependent variable is not proportional to the degree of average change in the log of the dependent variable. Moreover, averages are not preserved in the back translation from log dose to mg CPZ-EQ, but medians are preserved. To interpret changes in the predictor in relation to changes in real units of the median antipsychotic dose, we exponentiated mean log doses \( (\text{which equal the median}) \) and compared the resulting mg CPZ-EQ doses across categories of gender, race, age, and potency. Because space limitations preclude the display of all translations, we decided to highlight those predictors that demonstrated the strongest effect in our final multivariate model \( (model\ 3) \). Table 4 demonstrates the effect of African-American and Caucasian males receiving high-potency agents, per decade of age. For this example, the duration of the antipsychotic exposure was fixed at the median of 91 days. These data show that the average difference in the dose of high-potency antipsychotics between 20-year-old African-American males (709 CPZ-EQ) and Caucasian males (624 CPZ-EQ) was 85 mg CPZ-EQ. By comparison, among 50-year-old males, the average difference between African-Americans (535 CPZ-EQ) and Caucasians (471 CPZ-EQ) was 64 mg CPZ-EQ.

### Table 3. Linear regression of antipsychotic daily dose on age, gender, race, and antipsychotic potency \( (n = 2,714) \)

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>( \beta )</th>
<th>( p )</th>
<th>( \beta )</th>
<th>( p )</th>
<th>( \beta )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>5.642</td>
<td>&lt; 0.0001</td>
<td>5.586</td>
<td>&lt; 0.0001</td>
<td>5.631</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>High potency</td>
<td>0.989</td>
<td>&lt; 0.0001</td>
<td>0.992</td>
<td>&lt; 0.0001</td>
<td>0.808</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.136</td>
<td>&lt; 0.001</td>
<td>0.132</td>
<td>&lt; 0.001</td>
<td>0.129</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>African-American race</td>
<td>-0.063</td>
<td>0.0814</td>
<td>-0.052</td>
<td>0.1549</td>
<td>-0.140</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td>-0.009</td>
<td>&lt; 0.0001</td>
<td>-0.009</td>
<td>&lt; 0.0001</td>
<td>-0.0094</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>African-American high-potency</td>
<td></td>
<td></td>
<td>0.269</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic exposure (days)</td>
<td></td>
<td></td>
<td>0.001</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Adjusted ( R^2 )</td>
<td>0.250</td>
<td></td>
<td>0.253</td>
<td></td>
<td>0.256</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* \( \beta = \text{[natural log (chlorpromazine dose)]} \). Reference groups were low/moderate potency, female gender, and Caucasian.
Table 4. Translation of log-transformed linear regression estimates for African-American and Caucasian males receiving high-potency agents

<table>
<thead>
<tr>
<th>Race</th>
<th>Age Decade</th>
<th>Log Scale Median</th>
<th>Original Mg CPZ-EQ Median</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>20 years old</td>
<td>6.564 (^2)</td>
<td>709.4</td>
<td>650.7 – 773.4</td>
</tr>
<tr>
<td></td>
<td>30 years old</td>
<td>6.471</td>
<td>645.9</td>
<td>598.8 – 696.7</td>
</tr>
<tr>
<td></td>
<td>40 years old</td>
<td>6.377</td>
<td>588.0</td>
<td>544.9 – 634.6</td>
</tr>
<tr>
<td></td>
<td>50 years old</td>
<td>6.283</td>
<td>535.4</td>
<td>490.4 – 584.5</td>
</tr>
<tr>
<td></td>
<td>60 years old</td>
<td>6.189</td>
<td>487.4</td>
<td>438.1 – 542.3</td>
</tr>
<tr>
<td>Caucasian</td>
<td>20 years old</td>
<td>6.436</td>
<td>624.0</td>
<td>550.8 – 706.9</td>
</tr>
<tr>
<td></td>
<td>30 years old</td>
<td>6.342</td>
<td>568.1</td>
<td>506.1 – 637.8</td>
</tr>
<tr>
<td></td>
<td>40 years old</td>
<td>6.249</td>
<td>517.2</td>
<td>461.5 – 579.7</td>
</tr>
<tr>
<td></td>
<td>50 years old</td>
<td>6.155</td>
<td>470.9</td>
<td>417.6 – 531.0</td>
</tr>
<tr>
<td></td>
<td>60 years old</td>
<td>6.061</td>
<td>428.7</td>
<td>375.4 – 489.7</td>
</tr>
</tbody>
</table>

Note.—CPZ-EQ = chlorpromazine equivalents. Duration of antipsychotic exposure was fixed at the median of 91 days.

1 Computation of the 95% confidence interval = \( e^{\text{log base estimate} \times 1.96 \times \text{log base standard error}} \).

2 Using the log scale estimates in table 3, the dose for 20-year-old African-American males is calculated as follows: 5.631 + 0.8076 + 0.1293 + (-0.1403) + (20 * -0.00938) + (91 * 0.000612) + 0.2686 = 6.564 \([e^{6.564} = 709.4]\).

Thus, the disparity in dosing was greater among younger individuals than among older individuals.

Discussion

The main finding of this analysis of antipsychotic outpatient maintenance treatment for adults with schizophrenia was that mean daily doses of high-potency agents were 22 percent above the maximum recommended daily dose of 600 mg CPZ-EQ (Lehman et al. 1998). Significantly larger daily doses were associated with male gender, younger age (18–34 years), and high-potency antipsychotic medications. Furthermore, significantly higher daily doses were observed among African-Americans who received high-potency antipsychotics.

Several findings carry potentially important implications for clinical practice and future research in schizophrenia. First, the higher dose level associated with high-potency antipsychotic agents that was reported in this study is consistent with previously published findings. Two studies conducted in inpatient settings reported that high-potency agents such as haloperidol (1,237–1,450 mg CPZ-EQ) and fluphenazine (1,170–1,200 mg CPZ-EQ) were prescribed at doses that were 2–2.5 times higher than those of low-potency agents such as chlorpromazine (597–727 mg CPZ-EQ) and thioridazine (308 mg CPZ-EQ) (Baldessarini et al. 1984; Zito et al. 1987). Notably, although the high-potency doses reported in the current study exceeded the Schizophrenia PORT recommendations, they were considerably lower than inpatient doses reported in studies conducted during the 1980s. This underscores the importance of studies (such as the one presented in this article) that evaluate community patterns of psychopharmacologic treatment for schizophrenia.

Second, prior research has not indicated that African-American patients require higher antipsychotic doses than Caucasian patients, yet they were more likely to receive higher doses of high-potency antipsychotics. There is limited evidence regarding pharmacokinetics and virtually no pharmacodynamic studies to clarify whether biological characteristics might explain why African-Americans receive higher doses (Strickland et al. 1991; Jeste et al. 1996). It has been reported that African-American patients are viewed as less compliant and more difficult to manage, thereby resulting in higher antipsychotic dosing (Strickland et al. 1991). An important focus for future research in schizophrenia should be to identify whether biological characteristics or perceptual differences explain the relatively higher doses, particularly of high-potency agents, among this population.

Third, nearly half (48%) of the 187 individuals diagnosed with schizophrenia who did not receive a psychotropic treatment in an outpatient setting were young African-American males. Those who did not receive a psychotropic medication may represent a subgroup that is less likely to be maintained in an outpatient setting, such as those who are institutionalized or intolerant to medication, refuse treatment, or have more severe problems. Other researchers have found that African-Americans were more likely to utilize inpatient and residential services than outpatient mental health services (Cheung and Snowden 1990). Using 1990 data, others have found that African-Americans comprised 30 percent of the involuntarily committed inpatient population and only 18 percent of the outpatient population in community mental health
centers (Lawson et al. 1994). On the other hand, much of
the literature on medication refusal has involved inpatient
psychiatric populations. A 1-year survey of all adult psy-
chiatric and forensic institutions in the state of New York
reported a 1 percent medication refusal rate (Zito et al.
1991). Higher rates of refusal (35%) have been reported
among individuals involuntarily committed to forensic
hospitals (Rodenhauser et al. 1987), and psychotic disor-
ders, particularly schizophrenia, are more common among
individuals who refuse treatment (Rodenhauser et al.
1987; Williams et al. 1988). Unfortunately, information
on treatment refusal or institutionalization was not avail-
able in the data, so we could not determine the extent to
which this explained why 3 percent of the sample did not
receive psychotropic treatments in an outpatient setting.
Additional studies should examine whether distrust of the
mental health system or culturally insensitive services
explain why young African-American males are less
likely to receive psychopharmacologic treatment in an
outpatient setting.

Fourth, the finding that antiparkinsonian agents were
prescribed for 93 percent of the antipsychotic exposure is
not consistent with the 1990 World Health Organization
(UNESCO) consensus statement on the use of anticholinergic
agents (i.e., antiparkinsonian agents) to lessen the risk of
extrapyramidal side effects (WHO 1990). This statement,
published 1 year prior to the year that this article's data
were gathered, supports the use of antiparkinsonian agents
when parkinsonian symptoms develop secondary to
antipsychotic treatment. However, discontinuation of
antiparkinsonian agents is recommended after 3 months to
assess the need for continued treatment (WHO 1990).
Despite the fact that WHO does not advocate prophylactic
anticholinergic use during maintenance antipsychotic
treatment (WHO 1990), 65 percent of the 3,065 individu-
als in this study received antiparkinsonian agents as well
as antipsychotics for approximately 4 months. The extent
to which antiparkinsonian agents continue to be pre-
scribed simultaneously with antipsychotic medication,
and the appropriateness of this combined regimen, are
important areas for future research.

The reader should keep in mind the inherent limita-
tions of this study when interpreting the results. First, the
treatment patterns apply to one state's Medicaid popula-
tion and may not generalize to Medicaid populations in
other states. Second, the dosing patterns reflect only those
individuals who were successfully maintained in an out-
patient setting. Antipsychotic dosing and the use of
adjunctive pharmacotherapy among institutionalized indi-
viduals are likely to be different given a presumably more
severe level of impairment. Also, individuals who experi-
enced adverse events or discontinued medications (i.e.,
stopped getting them filled at the pharmacy) were not
identifiable in this sample. Third, the data do not contain
information on illness severity, and so the extent to which
larger doses were prescribed for the most severely
impaired patients could not be determined. Fourth, dosage
patterns for depot antipsychotic medications could not be
assessed, and thus the daily dose estimate may be under-
estimated. Fifth, the findings do not generalize to individ-
uals with shorter (< 30 days) acute episodes or with mul-
iple treatment episodes within 1 calendar year. Multiple
antipsychotic treatment episodes may be associated with
treatment failure, and the dosing patterns for these indi-
viduals may be different than for those included in our
analyses. Finally, with the exception of clozapine, these
data did not include dosing patterns among individuals
treated with the newer, atypical antipsychotic agents.
Despite these limitations, the Medicaid claims data
afforded the opportunity to examine antipsychotic dosing
patterns for a large cohort of patients with schizophrenia
who were receiving treatment in an outpatient setting.

This study has important policy implications for the
use of antipsychotics in schizophrenia treatment in clini-
cal practice settings. Scientific evidence for optimal
antipsychotic dosing to maximize therapeutic benefit has
not been translated successfully into practice. It is possi-
ble that clinicians in outpatient practices do not feel that
the samples in randomized controlled trials, largely inpa-
tient or treatment-resistant patients, are representative of
their patients. It is also likely that older patients are more
compliant with treatment and can be successfully main-
tained on lower doses and in an outpatient setting.
Furthermore, males and younger individuals may display
more aggressive behavior or be more difficult to manage,
thereby requiring larger daily doses.

The variability in outpatient dosing patterns is partic-
ularly relevant to the newer generation of antipsychotic
medications. Additional investigation is needed to deter-
mine the impact of newer antipsychotics on the patterns of
psychotropic treatment for schizophrenia. The goal for
future research on psychopharmacologic treatment of
schizophrenia is to identify the mediating factors that
impede the translation of optimal dosing reported in effi-
cacy studies into clinical practice.

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