# Persistent Antipsychotic Polypharmacy and Excessive Dosing in the Community Psychiatric Treatment Setting: A Review of Medication Profiles in 435 Canadian Outpatients

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***Objective:*** The present study aimed (1) to determine the proportion of patients treated with persistent antipsychotic polypharmacy in an outpatient population and (2) to determine if persistent antipsychotic polypharmacy is associated with excessive dosing.

***Method:*** Using a province-wide network that links all pharmacies in British Columbia, Canada, to a central set of data systems, we identified community mental health outpatients who had been treated with the same pharmacologic regimen for at least 90 days. Apart from antipsychotics, data collection included anticholinergics, antidepressants, mood stabilizers, benzodiazepines, lipid-lowering agents, and antidiabetic agents. Demographic data including sex, age, and diagnosis were obtained from the patient's chart. In order to compare dosages of the various antipsychotics we used a fixed unit of measurement based on dividing the prescribed daily dose (PDD) by the defined daily dose (DDD). A PDD/DDD ratio greater than 1.5 was defined as excessive dosing.

***Results:*** Four hundred thirty-five patients met the inclusion criteria and were included in the analysis. Overall, the prevalence of persistent antipsychotic polypharmacy was 25.7% for the entire cohort. The prevalence of persistent antipsychotic polypharmacy was highest for patients with schizoaffective disorder (33.7%), followed by schizophrenia (31.7%), psychosis not otherwise specified (20.0%), bipolar disorder (16.9%), and major depression (14.3%). The mean ± SD PDD/DDD ratio for all patients prescribed persistent antipsychotic polypharmacy was not only excessive, it was significantly greater compared to that of patients receiving antipsychotic monotherapy (1.94 ± 0.12 vs 0.94 ± 0.04, $P < .005$).

***Conclusions:*** Using a diagnostically heterogeneous outpatient population, this study is, we believe, the first to report that persistent antipsychotic polypharmacy is associated with excessive dosing, in and of itself as well as compared to antipsychotic monotherapy.

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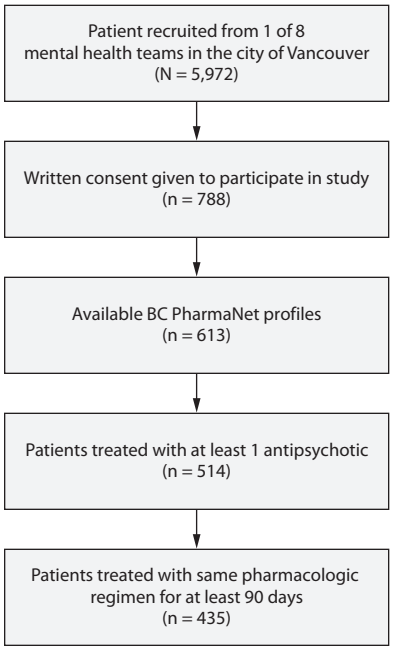
Despite lack of endorsement by clinical treatment guidelines, the practice of antipsychotic polypharmacy continues to increase.[1–10] A review of the literature finds that the overall point prevalence of antipsychotic polypharmacy ranges anywhere from 4.1% to 69%.[11–27] This wide range can be explained in part by differences in study design, patient population, diagnosis, coverage, and treatment setting. An increase in the prevalence over time has also been reported in the literature. In 2 studies that examined longitudinal prescribing trends in Medicaid recipients, antipsychotic polypharmacy increased from 5.7% in 1995 to 24.3% in 1999 (n = 836) and from 32% in 1998 to 41% in 2000 (n = 31,435).[11,28] We have also reported an increase in antipsychotic polypharmacy at a tertiary care facility in British Columbia; in this case, the practice increased from 27.5% to 44.7% between 1996 and 2000.[20,21]

A shortcoming of studies that have reported prevalence rates of antipsychotic polypharmacy is that their operational definition of antipsychotic polypharmacy is limited by study design. Most studies that have examined antipsychotic polypharmacy have been cross-sectional and collected data from either 1 point in time or used a narrow time window, such as 1 month. In doing so, the accuracy of the resultant prevalence rates is jeopardized, as cross-sectional methods do not allow one to differentiate short-term from persistent antipsychotic polypharmacy. To illustrate this point, Kreyenbuhl et al[27] compared the prevalence rate of antipsychotic polypharmacy using a stringent criteria of greater than 90 days to rates using cross-sectional definitions. The cross-sectional definitions (including a prescription for a different antipsychotic within 7 days and discharge from hospital with more than 2 antipsychotics) failed to identify as many as 89% of patients receiving persistent polypharmacy. Similarly, these definitions were also associated with false positive rates as high as 50%. In the later case, this result

**Figure 1. Recruitment and Screening of Mentally Ill British Columbian Outpatients**




Abbreviation: BC = British Columbia.

would reflect patients who were receiving short-term overlapping antipsychotic medications either during periods of acute symptom exacerbation or during cross-titration; practices generally considered within the standard of care.[29]

To date, few studies have examined persistent antipsychotic polypharmacy in an entirely outpatient setting. What is more, no study has examined whether persistent antipsychotic polypharmacy, compared to monotherapy, is associated with excessive dosing. The present study used a diagnostically heterogeneous group of psychiatric outpatients, and its objectives are (1) to determine the proportion of patients treated with persistent antipsychotic polypharmacy in an outpatient population and (2) to determine if persistent antipsychotic polypharmacy is associated with excessive dosing.

## METHOD

Patients for this study were recruited from the 8 community mental health teams within the city of Vancouver, British Columbia between October 20, 2005 and October 6, 2006. These mental health teams provide individuals living in defined catchment areas with psychiatric assessment and comprehensive treatment including medication management, counseling, and rehabilitation. At the time of our study, the teams provided some form of service to 5,972 individuals, or approximately 1% of Vancouver's population, and thus offered an excellent opportunity for drawing a representative sample from the population of noninstitutionalized persons with severe and persistent mental illness.

To investigate persistent antipsychotic polypharmacy and excessive dosing, we screened a sample of 788 patients who gave written informed consent to have their medication profiles reviewed (Figure 1). Inclusion in the study at hand required (1) that the patient's comprehensive medication profile was available through British Columbia (BC) PharmaNet (a province-wide network that links all pharmacies in British Columbia, Canada, to a central set of data systems); (2) that the patient be treated with at least 1 antipsychotic; and (3) that the patient had been treated with the same pharmacologic regimen (same medications and dosages) for at least 90 days (Figure 1).

Data collected from BC PharmaNet included the following list of medications: antipsychotics, anticholinergics, antidepressants, mood stabilizers, benzodiazepines, lipid-lowering agents, and antidiabetic agents. This method did not include "as needed" *hora somni* medications; none of which were antipsychotics. Demographic data including sex, age, and diagnosis were obtained from the patient's medical chart. Diagnoses were based on clinical interviews performed by a psychiatrist. For a small minority of subjects (n = 27), medical charts were unavailable at community centers, and so diagnoses were obtained from PARIS, which is the Vancouver Coastal Health Authority integrated electronic database.

In order to compare dosages of the various oral antipsychotics, we have used a fixed unit of measurement based on dividing the prescribed daily dose (PDD) by the defined daily dose (DDD). The DDD is the international unit of drug utilization that has been approved by the World Health Organization for drug use studies.[30] *DDD* is defined as the "assumed average maintenance dose per day for a drug used in its main indication in adults."[30] It is a unit of measurement and does not necessarily reflect the recommended daily dose. Using DDD allows for a convenient method for comparing the cumulative dose of antipsychotics irrespective of whether they are used as a single agent or as part of a polypharmacy regimen. A PDD/DDD ratio equal to 1 would indicate that the PDD equals the DDD. Thus, a PDD/DDD that is greater than 1 would indicate that the PDD is higher than the standard dosage. To be consistent with previous investigators,[31,32] we have defined patients as being prescribed excessive doses if their PDD/DDD ratio is greater than 1.5. Although depot antipsychotics were included in the overall assessment of antipsychotic polypharmacy prevalence, they were excluded from the dosage analysis due to the inherent variability in their dosing intervals (ie, every 2–4 weeks). This variability prohibited us from calculating the PDD/DDD ratio, which stipulates a prescribed "daily" dose as the numerator.

Parametric analysis was conducted on continuous variables using the Student *t* test, assuming equal variances.

**Table 1. Demographic and Clinical Characteristics of Mentally Ill British Columbian Outpatients (N = 435) Treated With the Same Pharmacologic Regimen for at Least 90 Days**

| Characteristic | Monotherapy, n = 323 (74.3%) | Polypharmacy, n = 112 (25.7%) | *P* Value |
|---|---|---|---|
| Sex, n (%)[a] | | | |
| Male | 162 (50.2) | 61 (54.5) | |
| Female | 154 (47.7) | 51 (45.5) | .56 |
| Age, mean (SD), y | 47.5 (12.1) | 46.1 (12.1) | .33 |
| Diagnosis, n | | | |
| Schizophrenia | 112 | 52 | – |
| Schizoaffective disorder | 55 | 28 | – |
| Major depression | 42 | 7 | – |
| Bipolar disorder | 64 | 13 | – |
| Psychosis NOS | 24 | 6 | – |
| No diagnosis noted | 26 | 6 | – |
| Treatment, n | | | |
| Quetiapine | 78 | 61 | – |
| Olanzapine | 109 | 50 | – |
| Risperidone | 69 | 41 | – |
| Clozapine | 24 | 9 | – |
| Typical antipsychotics (oral) | 29 | 35 | – |
| Typical antipsychotics (IM) | 14 | 15 | – |
| Anticholinergics, n (%) | 43 (13.3) | 33 (29.5) | < .001 |
| Antidepressants, n (%) | 158 (48.9) | 45 (40.2) | .11 |
| Mood stabilizers, n (%) | 114 (35.3) | 38 (33.9) | .79 |
| Benzodiazepines, n (%) | 122 (37.8) | 51 (45.5) | .15 |
| Lipid-lowering agents, n (%) | 48 (14.9) | 17 (15.2) | .94 |
| Antidiabetics, n (%) | 29 (9.0) | 12 (10.7) | .59 |

[a]Sex was determined by self-report. Seven subjects in the monotherapy group identified themselves as *transgender* or *other*.
Abbreviations: IM = intramuscular, NOS = not otherwise specified.

To test categorical variables for independence, the $\chi^2$ or Fisher exact test was performed. The study protocol was approved by the University of British Columbia Research Ethics Board. The study was conducted in accordance with the principles of Good Clinical Practices and the Declaration of Helsinki.

## RESULTS

Four hundred thirty-five patients met the inclusion criteria of having received at least 90 days of stabilized (unchanging) pharmacotherapy. Among these patients were 164 diagnosed with schizophrenia, 83 with schizoaffective disorder, 49 with major depression, 77 with bipolar disorder, and 30 with psychosis not otherwise specified (NOS) (Table 1). No diagnoses were available for 32 of our patients. Overall, the prevalence of persistent antipsychotic polypharmacy was 25.7% for the entire cohort. When diagnoses were considered, significant differences in the prevalence of persistent antipsychotic polypharmacy were observed ($\chi^2_4 = 12.63$, $P = .013$; Figure 2A). The prevalence was highest for patients with schizoaffective disorder (33.7%), followed by patients with schizophrenia (31.7%), psychosis NOS (20.0%), bipolar disorder (16.9%), and major depression (14.3%).

Significant differences were also noted between antipsychotics in terms of how they were utilized in polypharmacy combinations ($\chi^2_5 = 13.61$, $P = .018$; Figure 2B). In this respect, a higher proportion of oral conventional antipsychotics was used as part of a polypharmacy regimen, with a rate of 54.7%. For the atypical agents, quetiapine was used proportionately more often as part of a polypharmacy regimen (43.9%) followed by risperidone (37.3%), olanzapine (31.4%), and clozapine (27.7%).

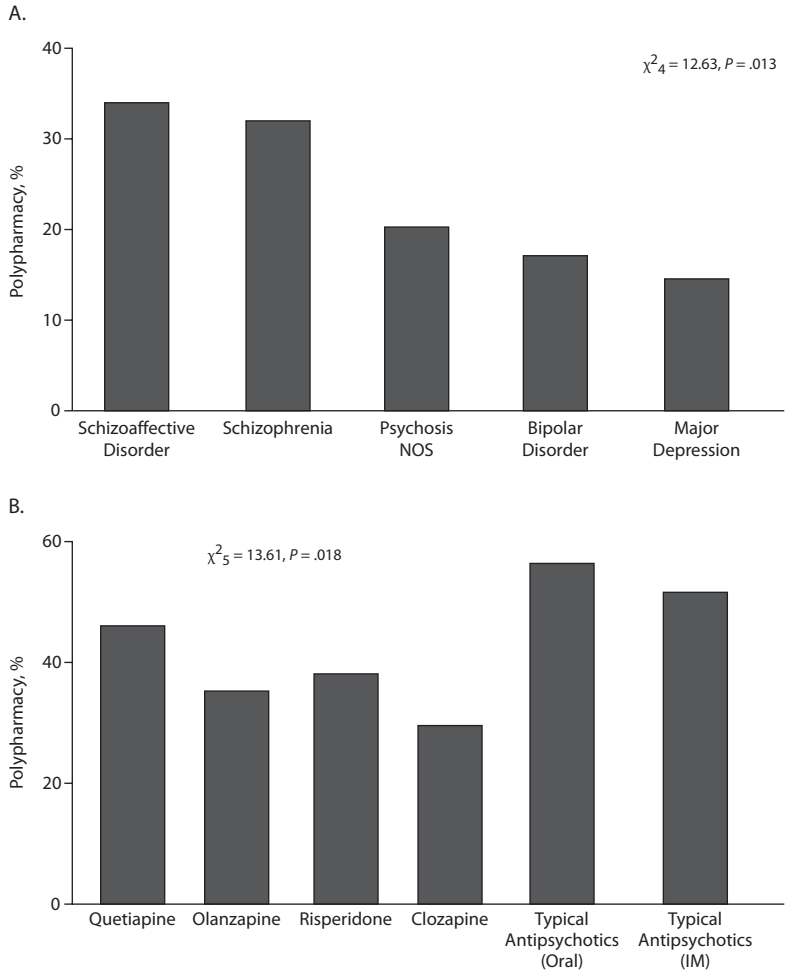
Mean ± SD values of PDD/DDD ratios and the proportion of patients prescribed excessive doses (ie, PDD/DDD > 1.5) are depicted in Figure 3A and B. The mean ± SD PDD/DDD ratio for all patients prescribed persistent antipsychotic polypharmacy was not only excessive, it was significantly greater compared to patients prescribed antipsychotic monotherapy (1.94 ± 0.12 vs 0.94 ± 0.04, $P < .005$; Figure 3A). Without exception, the mean ± SD PDD/DDD ratios across all diagnoses were significantly greater for patients prescribed persistent antipsychotic polypharmacy compared to patients prescribed antipsychotic monotherapy (Figure 3A). Examining only those patients prescribed excessive doses, our data found that excessive dosing was significantly associated with persistent antipsychotic polypharmacy, compared to monotherapy, irrespective of diagnoses ($P < .005$, Figure 3B). Furthermore, the mean PDD/DDD for each of the atypical antipsychotics increased whenever it was prescribed as part of a polypharmacy regimen (Figure 4).

Overall, significantly more individuals treated with a persistent antipsychotic polypharmacy regimen were also treated with an anticholinergic agent compared with those individuals prescribed only 1 antipsychotic (29.5% vs 13.3%, respectively, $\chi^2_1 = 15.05$, $P < .001$, Table 1). However, a post hoc analysis revealed that the significant finding was limited to schizophrenia patients ($\chi^2 = 5.51$, $P = .02$). Persistent antipsychotic polypharmacy was not found to be associated with a significantly increased utilization of other concomitant medications, including antidepressants, mood stabilizers, benzodiazepines, lipid-lowering agents, or antidiabetic agents (Table 1).

## DISCUSSION

The primary finding of this study was that 25.7% of our outpatient sample was treated with persistent antipsychotic polypharmacy. When diagnosis was considered, those with schizoaffective disorder and schizophrenia had the highest prevalence rates at 33.7% and 31.7% respectively. Meaningful comparison of these findings to those of others is limited due to differences in (1) study design, (2) the year in which the study was conducted, (3) diagnoses of the sample population, and (4) the operational definition of antipsychotic polypharmacy. With these constraints in mind, we limited our comparison to studies that reported prevalence rates of persistent antipsychotic polypharmacy of more then 60 continuous days in an entirely outpatient population. Sixty days was chosen as a cutoff, since expert consensus guidelines[33] have suggested that short-term

Figure 2. Prevalence of Persistent Antipsychotic Polypharmacy Across (A) Diagnoses and (B) Antipsychotics




Abbreviations: IM = intramuscular, NOS = not otherwise specified.

antipsychotic polypharmacy, defined as less than 60 days, may be warranted for some patients. The majority of studies were conducted using Medicaid claims databases and the reported prevalence rates of persistent antipsychotic polypharmacy ranged from 4.1% to 47.1% (Table 2). In the study that identified patients with schizophrenia, bipolar disorder, and depression, the rates of antipsychotic polypharmacy were 12.9%, 7.3%, and 5.2%, respectively.[35] Furthermore, in one study the rate of persistent antipsychotic polypharmacy was very likely conservative, as the definition was limited to 2 atypical antipsychotics.[34]

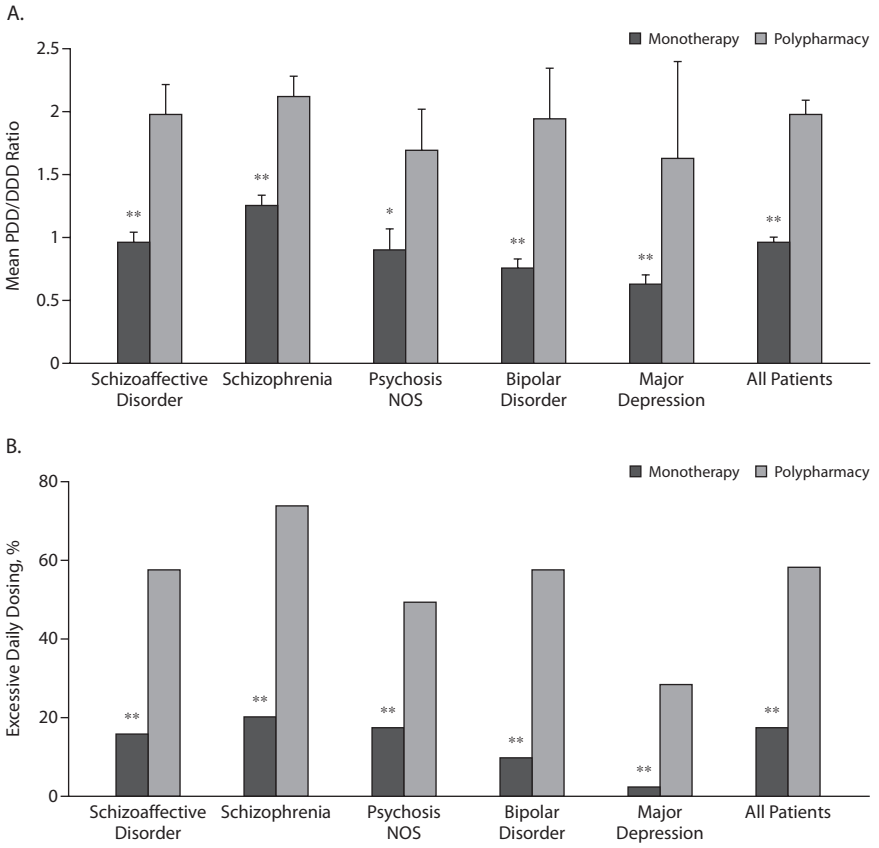
Our second main finding was that persistent antipsychotic polypharmacy was associated with excessive dosing according to the definition that we and others have used (ie, PDD/DDD > 1.5).[31,32] Not only was the mean PDD/DDD ratio for all patients across all diagnoses prescribed persistent antipsychotic polypharmacy excessive, it was also significantly greater compared to that of patients prescribed antipsychotic monotherapy (Figure 3A). Of particular note is the fact that the mean PDD/DDD for the individual atypical antipsychotics actually increased when prescribed as part of an polypharmacy regimen (Figure 4). Not surprisingly, the cumulative mean PDD/DDD of the resulting polypharmacy combinations are greater than 1.5 in every case. Taken together, these findings fail to support a previously proposed rationale for antipsychotic polypharmacy; that using lower dosages of 2 agents with different receptor and side effect profiles may achieve efficacy while mitigating side effects that would have occurred at a higher dosage of a single agent.[38] Also, the suggestion that practitioners may be prescribing small doses of a second antipsychotic to treat auxiliary symptoms such as sleep or anxiety is not substantiated by these data.

The excessive doses associated with antipsychotic polypharmacy raise concerns about the potential for increased adverse events. Although it is well known that, when these agents are used as monotherapy they can cause potentially serious adverse events that include an increase in blood glucose, body weight, serum triglycerides, and QTc interval,[39,40] virtually no information is available regarding the prevalence and severity of these and other adverse events that may be associated with persistent antipsychotic polypharmacy in and of itself or when combined with excessive dosing. In this regard, Waddington et al[41] reported, in a cohort of patients with schizophrenia followed prospectively over a 10-year period, that antipsychotic polypharmacy was associated with reduced survival (relative risk = 2.46, 95% CI, 1.10–5.47; $P = .03$). At the least, when physicians initiate a polypharmacy regimen they should assess the benefit-to-risk ratio.

The overall rate of excessive dosing (monotherapy and persistent antipsychotic polypharmacy) in our study was 30.0%, which is consistent with another study that used the same definition (ie, PDD/DDD > 1.5). In this 1-year European study[31] that examined in- and outpatients with schizophrenia (N = 375), it was reported that 28% of all patients, irrespective of polypharmacy, were treated with persistently high doses of antipsychotics. Baseline use of a conventional plus an atypical antipsychotic, as well as high antipsychotic doses at baseline, was found to be a predictor of excessive dosing, whereas psychopathology was not.

**Figure 3. Comparisons of Persistent Antipsychotic Polypharmacy to Monotherapy Considering (A) Mean PDD/DDD Ratios and (B) Prevalence of Excessive Dosing**




*$P < .05$.
**$P < .005$.
Abbreviations: DDD = defined daily dose, NOS = not otherwise specified, PDD = prescribed daily dose.

In another prospective study[32] (N = 402) that examined a more diagnostically heterogeneous group of psychiatric inpatients, the overall rate of excessive dosing was 15.4%. In this study, the strongest predictor of persistence with excessive doses of antipsychotics was antipsychotic polypharmacy on admission, followed by the male sex and positive symptoms. Negative symptoms were found to be negatively associated with high doses of antipsychotics. In both studies, the investigators did not compare the prevalence rate of excessive dosing associated with antipsychotic polypharmacy to monotherapy.

When we examined adjunctive medications, schizophrenia patients treated with persistent antipsychotic polypharmacy, compared to those treated with monotherapy, were more likely to be prescribed an anticholinergic agent. Using data from Medicaid claims (California and Georgia, N = 10,584) of individuals with schizophrenia, regression analysis confirmed that exposure to "Parkinson disease drugs" was associated with long-term (ie, greater than 60 days) antipsychotic polypharmacy (adjusted odds ratio = 2.84; 95% CI, 2.50–3.23, $P < .0001$).[11] Similarly, using data from the Veteran Affairs National Psychosis Registry (1999–2001, N = 45,571), Kreyenbuhl et al[42] reported an increase in the overall utilization of anticholinergic agents in schizophrenia and schizoaffective patients receiving persistent antipsychotic polypharmacy compared to monotherapy (50% vs 36%, respectively; $P < .001$). Finally, rates of anticholinergic utilization were also reported in a study[37] that assessed the use of psychiatric services and prescriptions in outpatients with long-term psychiatric disorders. In this case, anticholinergics were prescribed in 56.3% of patients treated with antipsychotic polypharmacy (ie, one conventional agent plus one atypical agent), in 44.8% of patients treated with a single conventional antipsychotic, and in 8.1% of patients treated with a single atypical antipsychotic ($\chi^2_2 = 17.1$, $P < .01$).

This study exposes a relatively high prevalence of persistent antipsychotic polypharmacy in an outpatient population with severe and persistent mental illness. However, this study is unable to report the reasons clinicians prescribe a persistent antipsychotic polypharmacy regimen. We can only speculate that there may be many reasons,



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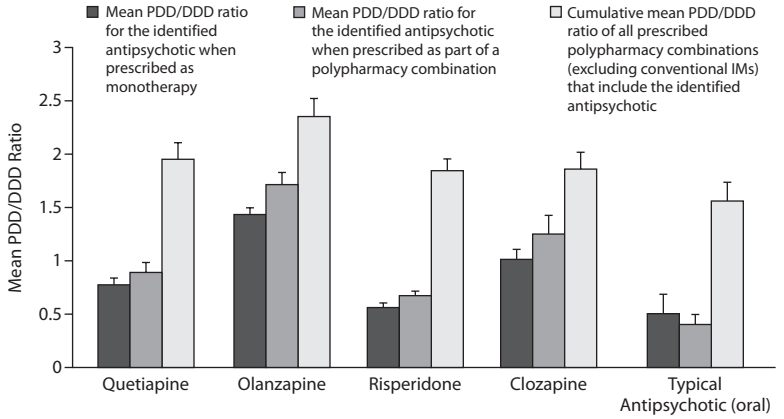
**Figure 4. Comparison of Mean PDD/DDD Ratios by Drug**




Abbreviations: DDD = defined daily dose, IM = intramuscular, PDD = prescribed daily dose.

**Table 2. Prevalence of Persistent Antipsychotic Polypharmacy in the Outpatient Setting**

| Study | N | Prevalence Rate | Denominator | Data Collection Period | Source of Data | Diagnoses Included |
|---|---|---|---|---|---|---|
| Gilmer et al,[34] 2007 | 15,962 | 36.4%[a] | 4–11 mo | 1999 | Medicaid claims database: San Diego County, California | Schizophrenia |
| | | 47.1%[a] | 4–11 mo | 2004 | | |
| | | 5.1%[a] | 1 y | 1999 | | |
| | | 14.4%[a] | 1 y | 2004 | | |
| Morrato et al,[35] 2007 | 55,481 | 6.4% | >60 d | 1998–2003 | Medicaid claims database: California, Nebraska, Oregon, Utah, Wyoming | Schizophrenia, bipolar disorder, depression |
| Stahl and Grady,[36] 2006 | 116,114 | 4.1% | >60 d | 1999–2000 | Medicaid claims database: California | Not specified |
| Kogut et al,[24] 2005 | 8,616 | 10.1% | >90 d | 2003 | Medicaid claims database: Rhode Island | Not specified |
| Ganguly et al,[11] 2004 | 31,435 | 23% | >2 mo | 1998–2000 | Medicaid claims database: California, Georgia | Schizophrenia |
| Tempier and Pawliuk,[37] 2003 | 83 | 19.3% | 2 y | 1997–2000 | Patient charts: Montreal, Canada | Schizophrenia, schizoaffective disorder, depressive disorder, psychosis NOS |

[a]Limited to polypharmacy with 2 atypical antipsychotics.
Abbreviation: NOS = not otherwise specified.

including physician's comfort with antipsychotics that may result in trials of new combinations, pressure from patients and family for better treatment outcomes, marketing from the pharmaceutical industry, and inadequate treatment response to clozapine monotherapy.[35,43] We do not believe that the latter point is a likely explanation, as we would have expected to see a much greater proportion of patients receiving polypharmacy combinations with clozapine. As it is, our data show that clozapine is the agent least likely to be coprescribed with another antipsychotic. In fact, its underutilization (overall prevalence = 7.6%) is cause for concern, and we must question, as did Taylor et al,[44] whether polypharmacy is contributing to reluctance and the delay in prescribing clozapine. Whatever the rationale may be for prescribing a polypharmacy regimen, it is very likely influenced by subjective clinical impressions rather than by scientific evidence.

In a recent review, Tranulis et al[45] concluded that antipsychotic polypharmacy was not supported by the evidence-based literature. Weaknesses identified included small sample sizes, lack of control of confounding variables, and short duration of follow-up. The reality is that the majority of the evidence for this questionable practice comes from uncontrolled open-label trials, case series, and case reports (see Tranulis et al[45] for review). In fact, to date there have only been 4 randomized controlled trials that have evaluated the efficacy of antipsychotic polypharmacy; more specifically clozapine augmentation with risperidone[46–48] and sulpiride.[49] In the first controlled antipsychotic polypharmacy trial ever conducted (N = 28), investigators randomly

assigned clozapine partial responders to receive either sulpiride 600 mg/d or placebo.[49] After 10 weeks of treatment, the sulpiride/clozapine group was found to exhibit significant improvements in positive and negative symptoms compared to the placebo/clozapine group. Similarly, in another trial (N = 40), clozapine partial or nonresponders were randomly assigned to have their clozapine augmented with either risperidone (up to 6 mg/d) or placebo for 12 weeks.[47] From baseline to week 6 and 12, positive and negative symptom improvement was significantly greater in the risperidone augmentation group compared to the placebo augmentation group. This positive finding for augmenting clozapine with risperidone was not confirmed by 2 other studies. In one study[46] (N = 30), patients with schizophrenia showing only partial response to clozapine were randomized to risperidone up to 6 mg/d or placebo. After 6 weeks, no benefit was found in psychopathology or quality of life in patients in the risperidone/clozapine group. In fact, greater improvement in positive symptoms was found in the placebo/clozapine group. Finally, our group also conducted a trial in a group of patients with schizophrenia and poor response to treatment with clozapine (N = 68).[48] After the 8-week blinded phase (and 18-week open-label phase of risperidone augmentation), no statistically significant difference in symptomatic benefit was noted between the 2 groups. The latter studies failed to show efficacy but, apart from that result, they also reported significant increases in prolactin[46] and blood glucose,[48] thus raising concerns about the safety of this combination.

The results of this study need to be interpreted within the context of the limitations imposed by its cross-sectional design. First, the cross-sectional design is limited to the observation of a defined population at a single point in time. As investigators, we did not actively manipulate the experimental variables in this design but rather looked for relationships among variables. As such, cross-sectional studies are useful for establishing associations between variables, but they in themselves do not establish causation. This study design also precludes our determining the reasons physicians prescribe an antipsychotic polypharmacy regimen or the therapeutic outcomes it produces. Furthermore, we are unable to comment on aspects of the chronological treatment course, such as severity of illness, previous pharmacologic trials (including clozapine), or number of psychiatrically related hospitalizations, that led to a persistent antipsychotic polypharmacy regimen.

Using a diagnostically heterogeneous outpatient population, this study is, we believe, the first to report that persistent antipsychotic polypharmacy is associated with excessive dosing, in and of itself as well as compared to antipsychotic monotherapy. Given that persistent antipsychotic polypharmacy very likely increases costs[28] and the risk of adverse effects,[50] drug interactions, decreased treatment adherence, and perhaps mortality,[41,51] more research is needed to determine the actual effectiveness and safety of persistent antipsychotic polypharmacy in the treatment of individuals with severe and persistent mental disorders.

***Drug names:*** clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).
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