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Prevalence and Correlates of Antipsychotic Polypharmacy: A Systematic Review and Meta-regression of Global and Regional Trends from the 1970s to 2009

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Abstract

Objective—To assess the prevalence and correlates of antipsychotic polypharmacy (APP) across decades and regions.

Methods—Electronic PubMed/Google Scholar search for studies reporting on APP, published from 1970–05/2009. Median rates and interquartile ranges (IQR) were calculated and compared using non-parametric tests. Demographic and clinical variables were tested as correlates of APP in bivariate and meta-regression analyses.

Results—Across 147 studies (1,418,163 participants, 82.9% diagnosed with schizophrenia [IQR=42–100%]), the median APP rate was 19.6% (IQR=12.9–35.0%). Most common combinations included first-generation antipsychotics (FGAs)+second-generation antipsychotics (SGAs) (42.4%, IQR=0.0–71.4%) followed by FGAs+FGAs (19.6%, IQR=0.0–100%) and SGAs+SGAs (1.8%, IQR=0.0–28%). APP rates were not different between decades (1970–1979:28.8%, IQR=7.5–44%; 1980–1989:17.6%, IQR=10.8–38.2; 1990–1999:22.0%, IQR=11–40; 2000–2009:19.2% IQR=14.4–29.9, $p=0.78$), but between regions, being higher in Asia and Europe than North America, and in Asia than Oceania ($p<0.001$). APP increased numerically by 34% in North America from the 1980s (12.7%) to 2000s (17.0%) ($p=0.94$) and decreased significantly by 65% from 1980 (55.5%) to 2000 (19.2%) in Asia ($p=0.03$), with non-significant changes in Europe. APP was associated with inpatient status ($p<0.001$), use of FGAs ($p<0.0001$) and anticholinergics (<0.001), schizophrenia ($p=0.01$), less antidepressant use ($p=0.02$), greater LAIs use ($p=0.04$),

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Conflicts of Interest

Dr.Gallego, Dr. Zhang and Dr. Bonetti have nothing to disclose.

Contributors

Dr. Gallego conducted the literature search, extracted the data, conducted the statistical analysis and wrote the first draft of the manuscript. Dr. Bonetti helped with literature search and data extraction and helped in editing the content of the manuscript. Dr. Zhang helped with data extraction, conducted the meta-regression analysis and helped editing the content of the manuscript. Dr. Kane helped reviewing the content of the manuscript. Dr. Correll designed the study, helped with data extraction and literature search, and helped editing the content of the manuscript. All authors contributed to and have approved the final manuscript.

shorter follow-up ($p=0.001$) and cross-sectional vs. longitudinal study design ($p=0.03$). In a meta-regression, inpatient status ($p<0.0001$), FGA use (0.046), and schizophrenia diagnosis ($p=0.004$) independently predicted APP ($N=66$, $R^2=0.44$, $p<0.0001$).

Conclusions—APP is common with different rates and time trends by region over the last four decades. APP is associated with greater anticholinergic requirement, shorter observation time, greater illness severity and lower antidepressant use.

Keywords

Combinations; Schizophrenia; Polypharmacy; Cotreatment; Meta-regression

1. Introduction

The use of two or more antipsychotic medications, also called “antipsychotic polypharmacy” (APP), is common (Faries et al., 2005), having been criticized due to the limited evidence supporting its use (Stahl, 1999a, b). Compared to antipsychotic monotherapy, APP has been associated with increased hospitalization rates and length of stay (Centorrino et al., 2004; Gilmer et al., 2007), adverse effects (Jerrell and McIntyre, 2008; McIntyre and Jerrell, 2008), antipsychotic doses (Bingefors et al., 2003; Elie et al., 2009; Hung and Cheung, 2008), treatment cost (Rupnow et al., 2007; Stahl and Grady, 2006), and mortality rates (Joukamaa et al., 2006; Waddington et al., 1998). However, not all studies have found negative effects of APP. A recent meta-analysis found superiority of APP compared to monotherapy regarding “study-defined” efficacy (Correll et al., 2009); however, most included studies were clozapine-augmentation studies. A second meta-analysis of antipsychotic augmentation studies of clozapine only found superiority of APP in open, but not in blinded studies (Barbui et al., 2009). In both meta-analyses, insufficient data on psychopathology and side effect rates precluded meaningful analyses. Moreover, few studies attempted to change patients from APP to monotherapy. In three such studies, 50–67% of patients on APP were able to tolerate conversion to monotherapy (Suzuki et al., 2004a; Suzuki et al., 2004b; Essock et al., 2011).

Despite the frequency and debated nature of APP, the prevalence and correlates of APP have not been systematically reviewed across geographic regions and decades. Prior reviews either did not systematically review all literature (Ananth et al., 2004) or focused only on restricted areas of interest, including SGAs (Pandurangi and Dalkilic, 2008), schizophrenia (Messer et al., 2006), bipolar disorder (Zarate and Quiroz, 2003), efficacy, and adverse effects (Tranulis et al., 2008).

2. Methods

2.1. Data sources

An electronic PubMed and Google scholar search without restrictions regarding language, diagnosis, antipsychotic type, treatment setting, or geographic region was conducted for articles published between 1970 and May 2009. For the search, the Boolean operator “AND” was used to connect the word “antipsychotics” with each of the following seven words: “polypharmacy”, “comedications”, “coprescription”, “concomitant”, “cotreatment”, “combination”, and “adjunctive”. Reference lists from retrieved articles were reviewed to identify additional studies.

2.2. Study Selection

Studies that reported on the frequency of APP, i.e., the concomitant use of 2 antipsychotics (excluding the combination of an LAI with the same oral antipsychotic), in patients aged

>18 years were included. Excluded were also: 1) intervention studies aimed at decreasing APP; 2) studies reporting on psychotropic polypharmacy, without specific information on APP. When studies reported in a single article more than one APP rate assessed at different times, we entered these APP rates as different observations or “time points”. Articles in different languages were translated by the investigators: JZ (Chinese), JG (Spanish and Italian), CC (German and French).

2.3. Data Extraction

Design, demographic, treatment, setting and illness variables were extracted independently by three investigators (JG, JB, CC). Although overlapping conceptually, the terms “mood stabilizers”, “anticonvulsants” and “lithium” were taken directly from the publications.

2.4. Statistical Analyses

Due to non-normally distributed data, non-parametric tests were used. Continuous variables were described using medians and interquartile ranges (IQR) and differences between groups were examined using Wilcoxon rank sum test or Kruskal-Wallis test. Post-hoc tests were conducted using a rank test corrected for multiple comparisons (Siegel and Castellan, 1988). Correlations were examined using the Spearman correlation coefficient and comparisons between categorical variables were analyzed using Fisher exact test. Analyses were conducted using STATA version 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP). Further details about methods regarding the analysis by geographic region (2.5.), decade (2.6.), illness severity proxy variables (2.7.), required APP duration (2.8.) and of the meta-regression analysis (2.9.) are reported in Supplemental File 1.

3. Results

3.1. Database

Of the 9,241 articles initially identified, only 147 were included in the final analyses (Figure 1; Supplemental file 1; Supplemental file 2).

3.2. Study characteristics

147 studies, reporting APP rates for 196 individual time points in a total of 1,418,163 patients (median=399 patients per study, IQR=157–1999, range=16–671,454), were analyzed (Table 1). 108 studies (73.5%) were cross-sectional and 39 (26.5%) were longitudinal, 31.9% were conducted in academic institutions, 60.4% were conducted only in urban areas, 80.3% gathered the clinical data from multiple sources (pharmacy claims, administrative claims, physician questionnaires, chart, etc) and 51.5% involved only inpatients. All but 20 studies (13.6%) used a cross-sectional definition of APP, measuring cotreatment only at a single time point. There were no significant differences in study characteristics across geographic regions. Overall, 82 (41.8 %) APP rates were reported in the 1990s, 67 (34.2%) in the 2000s, 35 (17.9%) in the 1980s and 12 (6.1%) in the 1970s. The number of APP rate reports was significantly different between regions in individual decades ($p<0.001$ for each decade) and for the number of assessment time points across regions in the 1970–1995 period vs. the 1996–2009 period ($p<0.001$) (Table 1).

3.3. Patient characteristics

The median patient age was 40.9 years (IQR=38.0–44.7). 55% (IQR=48–63.9) were male and 54% were white (IQR=39.0–76.0) with most patients (82.9% [IQR=42–100]) being diagnosed with schizophrenia. The proportion of patients with schizophrenia (lowest in Europe, $p=0.002$) and of Whites (highest in Europe, $p<0.001$) was significantly different

between geographic regions. Patients were followed up for longer periods of time in North America compared to the other regions ($p=0.004$). Only between 3 (1.5%) and 6 (3.1%) of assessment time points also reported on psychopathology measures, without significant group differences (Table 1).

3.4. Prescribing characteristics

The pooled median APP rate was 19.6% (IQR=12.9–35.0%) across all regions and decades. The most common combination included first-generation antipsychotics (FGAs)+SGAs (42.4%, IQR=0.0–71.4%) followed by FGAs+FGAs (19.6%, IQR=0.0–100%) and SGAs+SGAs (1.8%, IQR=0.0–28%). The majority of patients (68%, IQR=52.8–82.9%) in samples for which APP rates were reported were taking one antipsychotic, 17.8% (IQR=10.5–32.7%) were taking two and 0.2% (IQR=0.0–4.7%) were taking 3 antipsychotics (Table 2). Data on individual medication frequencies are reported in Table 2.

3.4.1. Prescribing characteristics by geographical region—Pooled APP rates were significantly lower in North America (16%, IQR=7.2–24.4%) compared to Asia (32%, IQR=19.2–53.0%) and Europe (23%, IQR=15.0–42.1%) ($p<0.001$). Similarly, the APP rate was significantly higher in Asia (32%, IQR=19.2–53%) than Oceania (16.4%, IQR=9.8–20.0) ($p<0.001$) (Table 2). The use of one antipsychotic ($p<0.001$), two SGAs ($p=0.007$), and concomitant anticonvulsants ($p=0.01$) was significantly higher in North America compared to Europe. The use of mood stabilizers was also significantly higher in North America compared to Asia ($p=0.007$). Asia had significantly higher rates of anticholinergic use (63.0%, IQR=47.0–67.2%) compared to North America (33.0%, IQR=20.0–41.9) and Europe (27.5%, IQR=19.0–41.3) ($p=0.001$). The use of FGAs was significantly higher in Asia and Europe compared to North America ($p=0.002$). Europe had significantly higher prescription rates of LAI preparations ($p=0.04$), two FGAs ($p=0.04$), and concomitant anxiolytics ($p=0.003$) than North America. The use of clozapine was significantly higher in Oceania compared to North America ($p=0.01$). The use of concomitant antidepressants was less common in Asia compared to Europe ($p=0.006$) (Table 2).

3.4.2. Prescribing characteristics by decade—There were no statistically significant differences in APP rates between decades ($p=0.78$) (Table 3). However, expectedly due to the wide introduction of SGAs only after 1990, the rate of individual antipsychotic class combinations was significantly different between decades, with the combination of two FGAs being more common in the 1970s and 1980s ($p<0.001$), and the combination of FGA+SGA and two SGAs being more common in 1990s and 2000s ($p<0.001$). Similarly, the use of FGAs was significantly higher in the 1970s, 1980s and 1990s ($p<0.001$), whereas the use of SGAs was significantly higher in the 1990s and 2000s ($p<0.001$). The use of one antipsychotic was significantly higher in the 2000s compared to the 1970s and 1980s ($p=0.001$), while the use of no antipsychotic was significantly higher in 1980s compared to the 2000 decade ($p<0.001$). The use of clozapine was significantly higher in the 1990s and 2000s compared to the 1970s and 1980s ($p<0.001$). The use of anticonvulsants was significantly higher in the 1990s compared to 1980s ($p=0.04$), and LAI use combined with other antipsychotics ($p=0.047$) was also significantly higher in the 1970s and 1980s compared to 1990s and the 2000 decade (Table 3).

LAI use combined with oral antipsychotics ($p=0.04$) and, expectedly, use of FGAs ($p<0.001$) and of two FGAs ($p<0.001$) was significantly higher in the period up to 1995. Conversely, the use of one antipsychotic ($p<0.001$), anticonvulsants ($p=0.02$), SGAs ($p<0.001$), clozapine ($p<0.001$), two SGAs ($p<0.001$) and FGA+SGA combinations ($p<0.001$) was significantly higher after 1995 (Table 3).

3.4.3. Distribution of APP by geographic region and decade—APP in North America increased numerically by 34% since 1980s (12.7%, IQR=4.5–46%) to 2000 (17%, IQR=9.1–23%) ($p=0.94$) (Figure 2). Oceania had an even a larger increase in APP from 2% (IQR=2–2) in the 1980s to 17.7% (IQR=14.6–20%) in the 2000s ($p=0.18$). Conversely, APP decreased in Asia by 65% from 1980 (55.5%) to 2000 (19.2%) ($p=0.03$) and increased in Europe in the 1990s, decreasing slightly in the 2000s. Specifically, except for Asia ($p=0.03$), there were no significant decade-specific APP differences in North America ($p=0.94$), Europe ($p=0.1$) and Oceania ($p=0.18$) across all four decades (overall $p=0.94$). However, there were significant regional differences within specific decades. In the 1970s, the APP was significantly higher in Europe (44.7%, IQR=44.0–56.0%) than in North America (26.0%, IQR=3.0–29.2%) ($p=0.04$). In the 1990s, the APP was significantly higher in Asia (44.7%, IQR=38.0–59.0%) than in North America (15.9%, IQR=7.0–24.1%), and Oceania (13.1%, IQR=7.2–19.2%) ($p<0.001$). In the same decade, the APP was also significantly higher in Europe compared to North America ($p<0.001$). There were no significant differences in APP rates between regions in the 1980s and 2000s.

3.5. Variables associated with use of antipsychotic polypharmacy

Continuous variables that were associated with APP in bivariate analyses were percent of patients with schizophrenia ($r=0.23$, $p=0.01$), length of patient follow up ($r=[-0.30]$, $p=0.001$), percent of FGA use ($r=0.31$, $p<0.001$), percent of LAI use ($r=0.26$, $p=0.04$), percent of concomitant antidepressant use ($r=[-0.23]$, $p=0.02$), and percent of concomitant anticholinergic use ($r=0.37$, $p<0.001$). In the analysis of categorical variables, inpatient treatment ($p<0.001$), cross-sectional design ($p=0.03$), study origin in Asia ($p=0.01$), Europe ($p=0.006$), and countries other than North America ($p<0.001$) were associated with APP (Table 4.)

3.6. Stratified analyses

Prescribing practices differed between the low use LAI <25% group vs. the LAI ≥25% group. The latter had significantly higher rates of use of 2 antipsychotics ($p=0.001$), APP ($p=0.04$), FGAs ($p=0.003$), anticholinergics ($p=0.004$), FGA+FGA ($p=0.03$), and LAIs plus other antipsychotics ($p=0.006$). Conversely, the LAI <25% group had significantly higher rates of use of SGAs ($p=0.03$), mood stabilizers ($p=0.03$), anticonvulsants ($p=0.007$), SGA+SGA ($p=0.02$) and FGA+SGA ($p=0.02$) (Table 5).

Analysis by decades and regions in the higher and lower LAI groups were not meaningful due to small sample sizes. There were no significant differences in the APP rate between the clozapine <5% group (16.3%, IQR=6.2–38.2) and the clozapine ≥5% group (23.5, IQR=15.0–36.6) ($p=0.24$) (data not shown).

3.7. Sensitivity analysis by APP duration

Only few studies using a longitudinal definition of APP were available for which region and time matched studies with a cross-sectional definition could be identified (4 days: $N=18$ vs. 39; 28 days: $N=13$ vs. 38; 42 days: $N=10$ vs. 38; and 60 days: $N=7$ vs. 28). Across these groups of studies, APP rates did not differ for any of the definitions requiring increasing APP durations ($p=0.42$ – 0.68).

3.8. Meta-regression analysis

Given the impact of LAI use on APP rates, meta-regression analyses were stratified and examined in the <25% and ≥25% LAI use group. After testing all four proposed models, the same three variables were independently associated with APP in the LAI <25% group in each of the models: schizophrenia ($p=0.004$), inpatient treatment ($p<0.0001$) and FGA

($p=0.046$). These three variables accounted for 44% of the variance of APP ($N=66$; $R^2=0.44$, $p<0.0001$) in all four models. These variables were not significantly associated with APP in the high use LAI group (data not shown).

4. Discussion

This largest study of APP prevalence rates and correlates confirms that APP is quite common and that it has been present for the last four decades in all geographic regions (De las Cuevas et al., 2005; Gilmer et al., 2007; Hung and Cheung, 2008; Linjakumpu et al., 2002). Although substantial variations exist between and within geographic locations, a global median of 19.5% of patients received APP. In addition, our study suggests that in North America APP has increased by 34% since the 1980s, although likely due to variations across studies, this finding was not significant. A similar trend in APP, but with larger differences, was observed in Medicaid claims data bases, showing an increase from 5.7% in 1995 to 24.3% in 1999 (Clark et al., 2002) and from 32% in 1998 to 41% in 2000 (Ganguly et al., 2004). Furthermore, a similar, but non-significant pattern was noted in Oceania, where APP increased from 2% to 17.7% over the past 3 decades with data. These increased trends could be partially explained by a wider availability of SGAs, which increase treatment options and may cause less extrapyramidal side effects when combined with other antipsychotics, potentially fostered by a more liberal health care system, particularly in North America. Moreover, the introduction of SGAs could have led to an increase in APP as more antipsychotic switches were attempted with a greater potential to not being completed, in addition to a general tendency to higher expectations regarding treatment outcomes in the recent decade. Furthermore, the more varied pharmacodynamic profiles of SGAs compared to FGAs on the one hand, and their less pronounced dopamine affinity compared to high-potency FGAs on the other hand, might have stimulated the belief that combining antipsychotics with more different profiles might yield better outcomes and be more justifiable, suggested by the highest cotreatment rate of SGAs+FGAs.

Conversely, the overall APP rates decreased in Asia over the last two decades and slightly decreased in Europe over the last decade. Reasons for these trends are unclear. While the introduction of SGAs could have led to a decrease in APP by replacing FGA APP with SGA monotherapy, because of expected or real improved efficacy, recent studies have refuted the earlier claims that SGAs had in general better efficacy than FGAs (Jones et al., 2006; Leucht et al., 2009; Lieberman et al., 2005), except for clozapine.

As shown before (Bitter et al., 2003; Chong et al., 2000a), APP rates in Asia and Europe have consistently been higher compared to North America and Oceania for the last four decades, although in our study, these differences only reached statistical significance in 1990s. Although reasons for higher APP rates in Asia are not entirely clear, this may be partially related to the belief in Oriental traditional medicine that a mixture of different medicinal compounds is superior to single compounds (Chong et al., 2000a). Our finding that Europe had higher APP rates than North America was previously shown by Bitter and colleagues (Bitter et al., 2003), finding higher rates of APP in Hungary (32.7% in first sample and 52% in another sample) compared to New York (16.9%). Reasons for a higher APP rate in Europe than North America are unclear, but could be due to the significantly higher use of LAI preparations in Europe or use of add-on low potency FGAs instead of adjunctive benzodiazepines. In Oceania, APP rates were generally lower than in other regions, which may be related to higher clozapine utilization. Nevertheless, despite cultural differences, APP rates generally converged over time across regions.

Regarding antipsychotic class combinations, FGAs were preferred as part of APP in Europe and Asia, while SGAs were used the most in North America and Oceania. Given the cost of

antipsychotics, it is not surprising that regions with a more “socialized” and cost conscious health care systems, like Asia and Europe, used FGAs preferentially, while countries like the US favored using SGAs.

Expectedly, the regional frequency of anticholinergic use paralleled that of APP. In fact, higher anticholinergic use has been associated with APP consistently (Carnahan et al., 2006; Centorrino et al., 2004). Anxiolytic and Hypnotic use was higher in Europe, which was associated with a higher use of FGAs, but not of anticholinergics, possibly because lower-potency antipsychotics are used that have less EPS potential (Leucht et al., 2003) or because benzodiazepines can reduce EPS (Lima et al., 2002).

The utilization of mood stabilizers and, specifically of anticonvulsants, was particularly higher in North America compared to Europe and Asia. Multiple factors could underlie these variations, including the use of different medications to address similar symptoms and side effects in different regions. Whereas Asian clinicians may use another antipsychotic to treat residual/acute symptoms, European clinicians may use benzodiazepines or low potency FGA, while North American clinicians tend to use more mood stabilizers to treat aggression and hostility (Volavka and Citrome 2008).

Strikingly, Asian clinicians did not use antidepressants as much as clinicians in all other regions, and the rate of antidepressant use was highest in Oceania where the APP rate was lower compared to Asia and Europe. This low use of antidepressants in Asia could also be explained by their potential use of a second antipsychotic to target depression, but under-recognition of depression in schizophrenia patients could also be a factor. However, the relationship between antidepressant and APP use requires further clarification.

Unfortunately, very few studies of APP reported psychopathology ratings or adverse effects, highlighting another under-researched area.

Consistent with prior reports (Biancosino et al., 2005; Brunot et al., 2002; Castberg and Spigset, 2008; Fourrier et al., 2000; Kreyenbuhl et al., 2007b; Lelliott et al., 2002; Millier et al., 2011; Morrato et al., 2007; Stroup et al., 2009; Tibaldi et al., 1997), APP was associated with variables that indicate patients had higher illness severity and, possibly refractoriness (Barbui et al., 2006b; Tomasi et al., 2006), including schizophrenia diagnosis, inpatient status, greater LAI use and shorter follow-up. Moreover, the fact that cross-sectional studies and those with shorter follow-up tended to have higher APP rates, suggests that at least some of the APP was either part of cross-titration or transient. The higher use of anticholinergics, found in multiple studies of APP (Chakos et al., 2006; Florez Menendez et al., 2004; Ganguly et al., 2004; Hong and Bishop, 2010; Kreyenbuhl et al., 2007b; Procyshyn et al., 2001; Sim et al., 2004), indicates that clinicians run the risk of inducing clinically relevant EPS in patients treated with APP. The association of peripherally measured anticholinergic medication load with impaired learning during cognitive remediation (Vinogradov et al., 2009) calls into question the benefits of treating patients with APP above the EPS threshold, followed by anticholinergic use. While the inverse correlation between antidepressant use and APP is interesting, it is currently unclear if there is any causal association. Nevertheless, prior studies have related APP to greater rates of depression (Kreyenbuhl et al., 2007a) and negative symptoms (Morrato et al., 2007). Thus antidepressant use may manage these symptom clusters that otherwise increase APP in a subgroup of patients. In contrast, in our meta-regression, only inpatient status, use of FGAs and schizophrenia diagnosis independently predicted APP. This discrepancy to the bivariate correlational analyses may have been a power issue, as information on these variables was not uniformly available across studies, highlighting the need for additional studies.

The results of our study need to be interpreted within its limitations, including the fact that many studies did not focus on APP or reported with too little specificity, reducing the amount of data for the meta-regression. Additionally, studies had heterogeneous design and population characteristics, and were conducted at different times across different health care systems and treatment cultures. Furthermore, differences pertaining to when and in whom LAIs are being prescribed make LAI use an imperfect proxy for illness chronicity. Moreover, there may be geographic differences in reimbursement structures that impact on APP rates or discourage high dose antipsychotic monotherapy, encouraging APP as a means of increasing dopamine blockade. Also, 86.4% of the studies used a cross-sectional APP definition, which does not allow us to accurately discriminate between cross-titration and relatively persistent polypharmacy. However, in our sensitivity analysis, we did not find significant differences between the APP rates of studies that used a cross-sectional definition or varying longitudinal definitions of APP. Nevertheless, only few studies required a defined duration of antipsychotic cotreatment. Therefore, future studies should provide rates for definitions of APP that require varying durations of antipsychotic overlap (e.g., 30, 60 and 90 days). Finally, APP rates were heterogeneous between and within geographic locations, so that one cannot generalize mean or median rates to a given practice location, country or continent.

In summary, this study shows that APP has been used for decades and across multiple regions, and disorders, being most common in patients with schizophrenia. APP seems to be prescribed for more severely ill and possibly more refractory patients, seemingly in lieu of clozapine use, and APP involving FGAs is associated with clinically relevant EPS requiring additional anticholinergic use. A better understanding of clinicians' rationale for using APP (Correll et al., 2011) and of the efficacy, tolerability (Gallego et al. in press) and effectiveness of this strategy is needed to guide clinicians and to inform the development of more evidence based treatment guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Quality of Research of Meta-analysis (QUORUM) flow chart.

Figure 2.

Antipsychotic polypharmacy rate by decade and geographic region

■p=0.04; ▲Omnibus (p=0.03). Regions were significantly different after post-hoc test using a rank test corrected for multiple comparisons. ^Number of time points included in the analysis. Time point definition: some studies reported in a single article two or more APP rates, examined at different points in time (e.g. 1999 and 2000), constituting two or more different individual samples or “time points” in our database. Total Number of studies: 147. Total number of time points: 196. Studies were classified based on time of data collection and not publication date.

Table 1

Prescribing characteristics by geographic region

Study and Patient Characteristics	All regions	North America	Asia	Europe	Oceania	P value
<i>Fisher's exact test</i>						
Study Characteristics						
Total Number of studies, n (%)	147 (100)	52 (35.4)	13 (8.8)	74 (50.3)	8 (5.4)	
<i>Data Source, n (%)</i>						
From patient interview	132(100)					
Other sources	26 (19.7)	7 (14.9)	4 (30.8)	13 (19.7)	2 (33.3)	0.4
<i>Location, n (%)</i>						
Urban	106 (80.3)	40 (85.1)	9 (69.2)	53 (80.3)	4 (66.7)	
Mixed (urban and rural)	91(100)					
University-teaching	55 (60.4)	13 (46.4)	10 (90.9)	29 (60.4)	3 (75.0)	0.06
Mixed	36 (39.6)	15 (53.6)	1 (9.1)	19 (39.6)	1 (25.0)	
<i>Institution type, n (%)</i>						
University-teaching	91(100)					
Mixed	29 (31.9)	10 (27.0)	4 (40.0)	14 (36.8)	1 (16.7)	0.7
<i>Study design, n (%)</i>						
Cross sectional	62 (68.1)	27 (73.0)	6 (60.0)	24 (63.2)	5 (83.3)	
Longitudinal	147(100)					
Setting, n (%)	108 (73.5)	34 (65.4)	12 (92.3)	55 (74.3)	7 (87.5)	0.2
Inpatient	39(26.5)	18 (34.6)	1 (7.7)	19 (25.7)	1 (12.5)	
Outpatient	132(100)					
Mixed	68 (51.5)	16 (36.4)	7 (58.3)	43 (63.2)	2 (25.0)	0.051
Patient Characteristics						
<i>Demographics</i>						
Total number of time points *, n (%)	196(100)	65(33.2)	17(8.7)	103(52.6)	11(5.6)	
Number of patients (total)	1,418.136	586,788	17,147	796,614	17,587	
Number of patients (Median, IQR)[*]	399.0(157.0–1999)[196]	741.0(282.0–3184.0)[65]	491.0(139.0–957.0)[17]	293.0(121.0–811.0)[103]	2057.0(364.0–2418.0)[11]	0.004
Age yrs	40.9(38.0–44.7)[124]	42.2 (39.0–46.0)[n=34]	41.3(30.1–43.6) [n=17]	40.0(38.0–45.7) [n=64]	39.0(38.0–40.0) [n=9]	0.23
White %	54.0(39.0–76.0)[33]	52.0 (43.0–70.5) [n=20]	0.0(0.0–0.0) [n=4]	84.0(60.0–99.0)[n=9]	- [n=0]	<0.001
Male %	55.0(48.0–63.9)[155]	55.0(49.0–65.0) [n=42]	59.0(54.0–61.8)[n=17]	54.0(45.0–62.3) [n=85]	63.8(59.0–67.1)[n=11]	0.1
Schizophrenia diagnosis %	82.9(42.0–100)[130]	96.0(52.7–100) [n=40]	100(100–100) [n=12]	59.4(40.0–100) [n=69]	86.0(83.7–100)[n=9]	0.002
Illness duration yrs	14.0(9.5–16.4)[37]	18.2(14.7–20.4)[n=4]	13.2(0.5–15.8)[n=12]	13.2(9.8–16.7) [n=20]	15.0(15.0–15.0) [n=1]	0.27

Kruskal-Wallis

Study and Patient Characteristics		All regions	North America	Asia	Europe	Oceania	P value
Psychopathology							
CGI severity score (Median, IQR) [°]		5.5(5.0–5.8) [6]	5.5(5.2–5.7) [4]	- [0]	5.1(3.8–6.4) [2]	- [n=0]	>0.9
PANSS total score		87.5(63.1–89.0)[5]	76.5(57.2–95.8) [n=2]	63.1(63.1–63.1)[n=1]	88.3(87.5–89.0) [n=2]	- [n=0]	0.74
PANSS positive score		18.9(15.3–21.1)[4]	13.8(13.8–13.8) [n=1]	- [n=0]	21.0(16.8–21.2) [n=3]	- [n=0]	0.18
PANSS negative score		20.6(18.1–22.6)[4]	17.0(17.0–17.0)[n=1]	- [n=0]	22.1(19.1–23.0)[n=3]	- [n=0]	0.18
BPRS total score		39.9(25.3–46.0)[6]	34.2(25.3–47.0)[n=3]	- [n=0]	45.5(24.4–46.0) [n=3]	- [n=0]	0.83
BPRS psychosis score		13.9(8.1–35.0)[3]	- [n=0]	- [n=0]	13.9(8.1–35.0) [n=3]	- [n=0]	N/A
GAF score		55.1(43.5–59.2)[4]	50.9(50.9–50.9)[n=1]	59.2(59.2–59.2)[n=1]	47.6(36.0–59.2) [n=2]	- [n=0]	0.66
Time points by Decade[^]		196	65	17	103	11	<i>Kruskal-Wallis</i>
1970–1979 n, (% per decade)		12 (100%)	7 (58.3)	0 (0.0)	5 (41.7)	0 (0.0)	<0.001
1980–1989		35 (100%)	3 (8.6)	2 (5.7)	29 (82.9)	1 (2.9)	<0.001
1990–1999		82 (100%)	30 (36.6)	6 (7.3)	42 (51.2)	4 (4.9)	<0.001
2000–2009		67 (100%)	25 (37.3)	9 (13.4)	27 (40.3)	6 (9.0)	<0.001
1970–1995		73 (100%)	14 (19.2)	3 (4.1)	54 (74.0)	2 (2.7)	<0.001
1996–2009		127 (100%)	51 (41.5)	14 (11.4)	49 (39.8)	9 (7.3)	<0.001

^{*} Number of time points: some studies reported in a single article two or more APP rates examined in different points in time (e.g. 1999 and 2000), constituting two or more different individual samples in our database.

^b Due to missing information in some reports, the percentages describing the study and patient characteristics in each geographic region may be based on a lower number of studies than the total number of studies per region.

[^] Studies were classified based on time of data collection as opposed of publication date. CGI: Clinical Global Impressions Scale; PANSS: Positive and Negative Syndrome Scale; BPRS: Brief Psychiatric Rating Scale; GAF: Global Assessment of Functioning Scale. IQR: Interquartile range (percentile 25–75).

Table 2

Psychotropic medication prescribing practices by geographic region

Treatment Characteristics	No. of time points ^a	All regions	North America (NA)	Asia (AS)	Europe (E)	Oceania (O)	P value [*]	Post-Hoc ^{**}
Antipsychotics								
0 Antipsychotic % (Median, IQR)	158	0.0(0.0–10.0)	0.0(0.0–1.2)	1.0(0.0–3.2)	0.0(0.0–16.3)	0.0(0.0–0.0)	0.18	
1 Antipsychotic	158	68.0(52.8–82.9)	80.1(63.4–85.3)	63.4(40.0–77.3)	60.0(46.2–73.0)	81.7(78.0–85.4)	<0.001	NA>E
2 Antipsychotics	90	17.8(10.5–32.7)	13.9(6.6–26.0)	26.7(22.3–40.4)	19.8(10.5–35.0)	14.9(13.4–17.1)	0.06	
3 or more Antipsychotics	90	0.2(0.0–4.7)	0.0(0.0–2.0)	1.9(0.0–15.7)	0.0(0.0–6.0)	0.6(0.0–0.9)	0.40	
APP (>= 2 Antipsychotics) ^a	196	19.6(12.9–35.0)	16.0(7.23–24.4)	32.1(19.2–53.0)	23.0(15.0–42.1)	16.4(9.8–20.0)	<0.001	AS, E>NA; AS>O
First-generation antipsychotics	139	51.0(33.0–86.4)	44.0(23.6–54.9)	73.1(67.0–97.0)	54.6(40.0–90.0)	40.5(26.0–56.0)	0.002	AS, E>NA.
Second-generation antipsychotics	131	53.0(13.6–86.6)	59.0(27.0–89.6)	28.0(13.6–61.9)	46.0(3.5–94.5)	68.7(58.9–82.0)	0.32	
Clozapine	97	7.0(0.0–19.6)	2.0(0.0–10.5)	14.8(0.6–17.0)	8.5(0.0–23.0)	21.0(15.5–35.0)	0.01	O>NA
Long-acting injectable preparations	65	23.2(14.6–41.8)	13.0(0.0–23.0)	33.2(22.1–46.2)	24.0(16.0–54.0)	24.8(23.3–26.0)	0.04	E>NA
Comedications								
Mood stabilizers ^b	40	17.7(7.5–27.9)	27.7(14.2–30)	4.3(1.0–7.0)	17.7(10.5–26.0)	27.3(22.6–32.0)	0.007	NA>AS
Lithium ^b	49	5.5(3.0–10.8)	6.9(1.0–12.8)	3.1(1.9–4.0)	6.1(4.0–10.0)	15.0(13.0–17.0)	0.09	
Anticonvulsants ^b	40	7.0(3.3–13.1)	24.6(10.7–44.0)	6.3(4.3–9.0)	5.7(1.0–8.9)	8.0(3.0–13.0)	0.01	NA>E
Anxiolytics/hypnotics	94	33.8(19.6–53.0)	23.1(13.1–34.0)	24.3(8.6–30.0)	38.4(28.6–65.9)	23.5(8.0–39.0)	0.003	E>NA
Antidepressants	98	19.1(10.0–30.6)	19.3(7.0–29.0)	7.0(5.9–11.3)	24.0(11.0–35.6)	24.7(18.0–47.0)	0.006	E>AS
Anticholinergics	94	30.9(20.0–46.8)	33.0(20.0–41.9)	63.0(47.0–67.2)	27.5(19.0–41.3)	3.0(3.0–3.0)	0.001	AS>NA,E
APP (>= 2 Antipsychotics)								
FGA + FGA	98	19.6(0.0–100)	0.0(0.0–23.2)	42.2(0.0–58)	66.8(0.0–100)	55.4(37.0–100)	0.04	E>NA
SGA + SGA	94	1.8(0.0–28)	21.0(0.0–55.5)	2.1(0.0–7.3)	0.0(0.0–7.2)	2.3(0.0–2.3)	0.007	NA>E
FGA + SGA	106	42.4(0.0–71.4)	52.6(0.0–74.1)	36.5(8.2–79.7)	36.4(0.0–84.4)	42.2(4.5–53.7)	0.8	
Long-acting injectable preparations	29	57.2(13.6–100)	0.0(0.0–25.0)	57.2(57.2–57.2)	80.0(25.0–100)	54.2(8.4–100)	0.09	

^a Number of time points: some studies reported in a single article two or more APP rates, examined at different points in time (e.g. 1999 and 2000), constituting two or more different individual samples in our database. Total Number of studies: 147. Total number of time points: 196.

^{*} Kruskal Wallis test.

^{**} Using a rank test corrected for multiple comparisons at p<0.05. APP: Antipsychotic Polypharmacy. FGA: First-Generation Antipsychotic. SGA: Second-Generation Antipsychotic. IQR: Interquartile range (percentile 25–75).

^aThe APP rate is not identical to the sum of patients taking 2 or ≥ 3 antipsychotics, as not all studies reporting on APP specified the exact number of antipsychotics prescribed;

^bAlthough overlapping conceptually, the terms “mood stabilizers”, “anticonvulsants” and “lithium” are taken directly from the publications.

Table 3

Psychotropic medication prescribing practices over time

Treatment Characteristics	No. of TP*	1970–1979 (1)	1980–1989 (2)	1990–1999 (3)	2000–2009 (4)	P value [†]	Post-Hoc ^{††}	<1996	1996	P value [^]
Antipsychotics										
0 Antipsychotic (median, IQR)	158	13.8(0.0–42.5)	6.0(0.0–39.0)	0.0(0.0–4.3)	0.0(0.0–0.0)	0.003	2>4	6.0(0.0–23.9)	0.0(0.0–1.2)	<0.001
1 Antipsychotic	158	44.0(41.0–51.3)	56.2(40.0–67.4)	70.8(54.5–82.4)	77.7(60.7–84.1)	<0.001	4,3>1; 4>2	56.2(41.8–70)	75.0(59.0–84.0)	<0.001
2 Antipsychotics	90	26.0(6.2–41.0)	14.7(4.5–31.0)	19.3(12.8–32.2)	17.1(12.4–34)	0.62	-	16.5(5.5–34.3)	18.7(12.8–31.7)	0.33
3 or more Antipsychotics	90	2.0(0.0–13.0)	0.0(0.0–4.7)	2.7(0.0–8.3)	0.0(0.0–1.2)	0.15	-	0.0(0.0–5.0)	0.2(0.0–4.2)	0.90
APP (2 Antipsychotics) ^a	196	28.8(7.5–44.4)	17.6(10.8–38.2)	22.0(11.0–40.0)	19.2(14.4–29.9)	0.78	-	19.0(10.8–40.0)	19.8(14.1–34.0)	0.90
First-generation antipsychotics	139	88.4(56.0–100)	86.8(55.9–100)	53.0(38.5–88.0)	40.5(21.7–51.0)	<0.001	1,2,3>4	88.2(56.0–100)	44.0(28.0–53.0)	<0.001
Second-generation antipsychotics	131	0.0(0.0–0.0)	0.0(0.0–1.0)	56.0(24–100)	67.9(46–86.6)	<0.001	4,3>1,2	0.0(0.0–23.4)	67.6(45.0–89.6)	<0.001
Clozapine	97	0.0(0.0–0.0)	0.0(0.0–6.5)	11.9(6.2–23.3)	13.6(3.3–19.6)	<0.001	4,3>1,2	0.0(0.0–11.7)	13.5(5.8–21.0)	<0.001
Long-acting injectable preparation	65	62.1(13.4–100)	25.4(11.0–58.0)	23.3(18.0–35.0)	19.4(8.7–22.9)	0.24	-	25.2(11.0–54.0)	22.7(17–26.9)	0.47
Comedications										
Mood stabilizers ^b	40	None	5.0(3.0–17.7)	20.3(10.9–27.7)	16.7(7.0–31.1)	0.24	-	6.5(5.0–17.7)	20.0(10.5–30.0)	0.07
Lithium ^b	49	3.7(0.8–8.0)	9.0(3.7–12.3)	5.2(3.2–11.8)	4.2(3.0–6.1)	0.32	-	8.0(3.7–12.3)	4.7(2.9–7.7)	0.13
Anticonvulsants ^b	40	7.0(0.0–10.7)	3.5(0.0–8.0)	10.1(6.3–20.7)	10.0(5.7–13.1)	0.04	3>2	5.6(2.0–9.0)	10.0(6.9–23.0)	0.02
Anxiolytics/hypnotics	94	15.0(8.2–71.0)	31.2(16.0–38.8)	39.5(21.8–51.8)	35.1(24.8–62.1)	0.38	-	33.1(15.0–51.1)	36.2(23.6–57.3)	0.30
Antidepressants	98	9.0(5.3–21.5)	14.1(9.8–30.7)	21.4(10.6–27.3)	28.8(12.5–38.1)	0.08	-	15.5(9.0–28.0)	22.2(11.3–33.3)	0.14
Anticholinergics	94	38.7(23.0–72.1)	37.0(26.9–48.3)	30.0(21.3–41.9)	23.9(15.5–44.6)	0.36	-	37.0(21.6–51.0)	27.5(17.9–41.9)	0.06
APP (>=2 Antipsychotics)										
FGA + FGA	98	100(100–100)	100(100–100)	0.0(0.0–55.4)	0.0(0.0–12.0)	<0.001	1,2>3,4	100(100–100)	0.0(0.0–17.2)	<0.001
SGA + SGA	94	0.0(0.0–0.0)	0.0(0.0–0.0)	4.1(0.0–23.5)	28.5(8.3–55.5)	<0.001	3,4>1,2	0.0(0.0–0.0)	16.6(2.0–42.5)	<0.001
FGA + SGA	106	0.0(0.0–0.0)	0.0(0.0–0.5)	50.0(10.0–85.7)	57.5(39.5–69.9)	<0.001	3,4>1,2	0.0(0.0–0.0)	57.5(39.0–79.0)	<0.001
Long-acting injectable preparation	29	100(100–100)	80.0(13.6–100)	25.0(8.4–81.0)	25.0(16.4–31.8)	0.047	1,2>3,4	81.0(13.6–100)	25.0(12.0–40.7)	0.04

* Number of time points: some studies reported in a single article two or more APP rates, examined at different points in time (e.g. 1999 and 2000), constituting two or more different individual samples in our database. Total Number of studies: 147. Total number of time points: 196.

[†] Kruskal Wallis test.

^{††} Using a rank test corrected for multiple comparisons at p<0.05.

¹ Mann-Whitney test. APP: Antipsychotic Polypharmacy. FGA: First-Generation Antipsychotic. SGA: Second-Generation Antipsychotic. IQR: Interquartile range (percentile 25–75).

^a The APP rate is not identical to the sum of patients taking 2 or 3 antipsychotics, as not all studies reporting on APP specified the exact number of antipsychotics prescribed;

^b Although overlapping conceptually, the terms “mood stabilizers”, “anticonvulsants” and “lithium” are taken directly from the publication

Table 4

Categorical and continuous variables associated with Antipsychotic Polypharmacy

Continuous variables	Time Points [^]	r (Spearman's Rho)		P -value
Age (yrs)	124	-0.09		0.31
% White	33	-0.23		0.20
% Male	155	0.16		0.05
% Schizophrenia	130	0.23		0.01
Patient f/u (months)	117	-0.30		0.001
Baseline CGI (severity)	6	0.54		0.27
Total PANSS score	5	0.10		0.87
Positive PANSS score	4	-0.60		0.40
Negative PANSS score	4	-0.80		0.20
Total BPRS score	6	0.03		0.96
GAF score	4	0.74		0.26
% FGA	139	0.31		<0.001
% SGA	131	0.09		0.30
% Clozapine	97	0.05		0.60
% Long-acting injectable preparations	65	0.26		0.04
% Mood stabilizers	40	0.19		0.23
% Lithium	49	-0.06		0.71
% Anticonvulsants	40	-0.13		0.44
% Anxiolytics/hypnotics	94	0.11		0.29
% Antidepressants	98	-0.23		0.02
% Anticholinergics	94	0.37		<0.001
% Long-acting injectable preparations (APP sample)	29	0.36		0.05
% FGA + FGA	98	0.03		0.73
% SGA + SGA	94	-0.02		0.86
% FGA + SGA	106	0.05		0.58
Categorical variables		1st group	2nd group	P- value ⁺
From patient interview vs. other sources	176	18.9(4.8–29.9)	21.0(13.0–38.0)	0.19
Urban vs. mixed (urban and rural)	125	22.0(13.0–38.0)	18.5(9.5–29.5)	0.34
Academic institutions vs. others	122	22.7(10.5–34.0)	18.9(13.0–37.3)	0.99
Cross-sectional vs. longitudinal	196	22.0(14.7–39.5)	17.0(9.9–27.5)	0.03
Other vs. Inpatient	175	17.0(9.8–24.1)	27.5(16.1–46.0)	<0.001
Schizophrenia <70% vs. ≥70% [*]	130	20.0(7.0–27.0)	20.0(14.7–43.4)	0.06
Other decades vs. 1970–1979	196	19.1(13.0–34.5)	28–8(7.5–44.4)	0.47
Other decades vs. 1980–1989	196	21.0(14.1–34.0)	17.6(10.8–38.2)	0.49
Other decades vs. 1990–1999	196	19.0(13.0–34.0)	22.0(11.0–40.0)	0.63
Other decades vs. 2000–2009	196	20.0(10.8–39.0)	19.2(14.4–29.9)	0.76
<1996 vs. ≥1996	196	19.0(10.8–40.0)	19.8(14.1–34.0)	0.90
Other vs. North America	196	23.0(15.0–42.1)	16.0(7.2–24.4)	<0.001

Continuous variables	Time Points [^]	r (Spearman's Rho)		P -value
Other vs. Asia	196	19.0(11.0–34.0)	32.0(19.2–53.0)	0.01
Other vs. Europe	196	17.1(9.1–28.3)	23.0(15.0–42.1)	0.006
Other vs. Oceania	196	20.0(13.0–37.3)	16.4(9.8–20.0)	0.09
Clozapine <5% vs. ≥ 5% [*]	93	16.3(6.2–38.2)	23.5(15.0–36.6)	0.24
Long-acting injectable <25% vs. ≥25% [*]	65	22.0(15.2–35.0)	35.7(18.5–46.0)	0.04
Mood stabilizers <5% vs. ≥ 5% [*]	40	20.9(11.9–23.9)	22.0(15.9–29.5)	0.46
Lithium <5% vs. ≥ 5% [*]	48	18.9(10.5–37.8)	16.9(11.9–35.0)	0.77
Anticonvulsants <5% vs. ≥ 5% [*]	40	28.5(16.2–51.5)	25.6(14.4–41.7)	0.52
Anxiolytics/hypnotics <5% vs. ≥ 5% [*]	94	13.7(7.9–36.4)	20.2(10.5–34.0)	0.52
Antidepressants <5% vs. ≥ 5% [*]	98	17.5(8.8–45.0)	20.2(9.4–34.0)	0.89
Antidepressants <5% vs. ≥ 5% [*]	94	8.8(2.0–39.0)	24.3(15.2–40.0)	0.32

^{*} Continuous variables were dichotomized based on described values.

[^] Number of time points: some studies reported in a single article two or more APP rates, examined at different points in time (e.g. 1999 and 2000), constituting two or more different individual samples in our database. Total Number of studies: 147. Total number of time points: 196. APP: antipsychotic polypharmacy; CGI: Clinical Global Impressions Scale; PANSS: Positive and Negative Syndrome Scale; BPRS: Brief Psychiatric Rating Scale; GAF: Global Assessment of Functioning Scale; FGA: First-Generation Antipsychotic. SGA: Second-Generation Antipsychotic.

⁺ Mann-Whitney test.

Table 5

Psychotropic medication prescribing practices after stratifying based on 25% use of long acting injectable

Treatment Characteristics	LAI <25%	LAI ≥25%	<i>P</i> value*
Antipsychotics			
0 Antipsychotic, Median % (IQR)[[^]]	4.2(0.0–19.0)[26]	0.0(0.0–6.0)[26]	0.10
1 Antipsychotic	61.7(44.5–73.0)[26]	56.1(42.0–76.0)[26]	0.60
2 Antipsychotics	14.1(8.4–23.6)[20]	34.6(20.7–42.9)[20]	0.001
3 or more Antipsychotics	1.8(0.0–5.8)[20]	4.8(0.0–11.8)[20]	0.20
APP (≥2 Antipsychotics) ^a	22.0(15.2–35.0)[37]	35.7(18.5–46.0)[28]	0.04
First-generation antipsychotics	55.0(45.0–90.1)[34]	90.5(74.0–100)[24]	0.003
Second-generation antipsychotics	44.1(6.0–59.9)[26]	1.1(0.0–24.0)[19]	0.03
Clozapine	7.8(0.0–14.2)[26]	0.0(0.0–9.5)[16]	0.18
Long-acting injectable preparations	16.0(8.7–21.8)[37]	47.1(30.5–66.2)[28]	<0.0001
Comedications			
Mood stabilizers ^b	19.9(14.2–22.7)[10]	6.5(4.0–11.1)[4]	0.03
Lithium ^b	4.3(1.9–10.0)[14]	4.7(3.0–7.2)[10]	0.95
Anticonvulsants ^b	7.3(4.0–10.7)[10]	1.0(0.0–5.7)[12]	0.007
Anxiolytics/hypnotics	32.0(15.7–40.0)[25]	33.1(15.0–39.0)[18]	0.94
Antidepressants	14.1(7.8–24.7)[27]	10.0(6.2–24.2)[17]	0.45
Anticholinergics	35.1(26.9–46.8)[27]	48.0(37.1–67.2)[17]	0.004
APP (≥2 Antipsychotics)			
FGA + FGA	52.0(0.0–100)[23]	100(99.0–100)[15]	0.03
SGA + SGA	1.5(0.0–15.6)[21]	0.0(0.0–0.0)[15]	0.02
FGA + SGA	26.5(0.0–56.5)[24]	0.0(0.0–5.15)[16]	0.02
Long-acting injectable preparations	11.4(0.0–31.8)[10]	81.0(55.1–100)[16]	0.006

* Mann-Whitney test.

[^] Number of time points. IQR: Interquantile range (percentile 25–75). APP: Antipsychotic Polypharmacy. FGA: First-Generation Antipsychotic. SGA: Second-Generation Antipsychotic.

^a The APP rate is not identical to the sum of patients taking 2 or ≥3 antipsychotics, as not all studies reporting on APP specified the exact number of antipsychotics prescribed;

^b Although overlapping conceptually, the terms “mood stabilizers”, “anticonvulsants” and “lithium” are taken directly from the publications.