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Antipsychotic Polypharmacy: A Survey Study of Prescriber Attitudes, Knowledge and Behavior

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Abstract

Objective—Although common in psychiatric practice, reasons for antipsychotic polypharmacy (APP) have remained unclear.

Methods—Single-site, semi-structured interview study of prescribers at a psychiatric teaching hospital inquiring about AAP attitudes and behaviors, including frequency, preferred combinations, rationale and concerns.

Results—Forty-four prescribers reported using AAP in 17.0±10.0% of antipsychotic-treated patients. Although clinicians themselves initiated APP in only 23.3±27.0% of cases, they did not attempt conversion to antipsychotic monotherapy in 40.9±37.7%, despite reported successful conversion in 28.0±30.8% of cases. The following reasons justified most APP (0–10): cross-titration (9.2±1.4), failed clozapine trial (8.2±2.2), randomized controlled evidence (8.0±2.0), and clozapine intolerance (7.7±2.6). Prescribers felt “moderately” (5.0±1.9) concerned about APP (0–10), mostly due to chronic side effects (7.6±2.0), lack of evidence (7.1±2.2), non-adherence risk (6.7±2.3) and mortality risk (6.7±3.2), while increased cost (4.9±2.5) and higher total

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antipsychotic dose (4.2±2.9) ranked lowest. Comparing high with low APP prescribers (>10% vs. ≤10% of patients; mean: 36.1±19.8 vs. 3.4±3.4, p<0.0001), no differences emerged on 25/26 ratings regarding APP justification and 9/9 ratings regarding concerns. In a multivariate analyses, only attending status (OR=10.3, p=0.0043) and endorsing a specific APP preference (OR=21.4, p=0.011) predicted APP use >10% (r^2:0.35, p<0.0001), yet no uniformly preferred APP strategy emerged.

Conclusions—High APP prescribers had more clinical experience, less concerns about APP and more likely a preferred APP choice, although no overall preferred strategy emerged. Otherwise, high and low APP prescribers shared attitudes toward APP. Both had inherited most of their APP cases and were reluctant to convert patients to antipsychotic monotherapy.

Keywords

Antipsychotics; Polypharmacy; Schizophrenia; Reasons; Prescriber; Attitudes

Schizophrenia and related disorders are associated with suboptimal response (Kane and Correll, 2010). This fact and the lack of successful non-antidopaminergic agents explain the use of antipsychotic polypharmacy in 7–50% of schizophrenia patients (Procyshyn et al., 2010; Zink et al., 2010; Pandurangi and Dalkilic, 2008), with some evidence of increasing rates (Ganguly et al., 2004; Gilmer et al., 2007; Mojtabai and Olfson, 2010; Nielsen et al., 2010).

Antipsychotic polypharmacy has been scrutinized mainly because of the disproportionate lack of evidence for its effectiveness and safety (Waddington et al., 1998; Stahl 1999; Stahl 2002a, 2002b; Miller and Craig., 2002; Centorrino et al., 2004; Joukamaa et al., 2006; Correll et al., 2007; Correll, 2008; Tranulis et al., 2008; Kessing et al., 2010) and cost (Rupnow et al. 2007; Valuck et al. 2007; Zhu et al. 2008). Two meta-analyses showed somewhat inconclusive results, in that superiority of antipsychotic polypharmacy might be mediated by potentially confounding factors, such as open treatment (Barbui et al., 2009), or by country in which the study was performed, therapeutic vs. low dose combinations, or cotreatment from the inception of antipsychotic treatment (Correll et al., 2009).

In the few studies examining motivations for antipsychotic polypharmacy, reasons have included residual positive symptoms (Biancosino et al., 2005), acute aggression, “getting stuck” in an aborted cross-titration (Tapp et al., 2003) or the attempt of reducing adverse events allowing for a decreased dose of the first antipsychotic (McCue et al., 2003). Even less data are available for clinician attitudes regarding antipsychotic polypharmacy (Sernyak et al., 2004; Tapp et al., 2003; Ito et al., 2005).

To address this knowledge gap, we conducted a clinician survey study, hypothesizing that clinicians prescribing antipsychotic polytherapy more liberally would be less concerned about antipsychotic polytherapy, see more justifications and endorse more specifically preferred combinations.

Methods

Setting and Procedures

All inpatient and outpatient prescribers at the Zucker Hillside Hospital were contacted to participate in this study. This included psychiatrists, nurse practitioners, and third- and fourth-year psychiatry residents. Prescribers were interviewed between December 2006 and April 2007, using a newly developed, semi-structured questionnaire, the Prescriber’s Reasons for Antipsychotic Combination Treatment Questionnaire (PRACT-Q, available

upon request from the first author). Prescribers unable to be interviewed in person could complete the survey independently with follow up by the interviewers as needed.

The PRACT-Q covers the following areas: 1) estimated percentage of patients on antipsychotic polypharmacy, inherited from a previous prescriber and self initiated; 2) preferred antipsychotic combination(s); 3) estimated percentage of patients in whom conversion to antipsychotic monotherapy was attempted and whether this was successful or unsuccessful; and 4) attitudes toward 26 areas of potential benefits/justifications and 9 areas of risks/concerns regarding antipsychotic polypharmacy. Clinicians were asked to rate on an 11-point ordinal scale how much they would feel justified (0=0% to 10=100%) prescribing more than one antipsychotic in 26 clinical situations and how concerned they were (0=none to 10=extreme) about nine areas.

The study was approved by the Institutional Review Board that requested prescribers to remain unidentifiable, preventing the association of reported behaviors with actual prescribing practices.

Data Analyses

In addition to descriptive statistics analyses of variance and chi-square tests were used to compare characteristics and attitudes of “high” vs. “low” antipsychotic polypharmacy prescribers. The median split of 10% of patients receiving antipsychotic polypharmacy was used to divide study participants into “high” antipsychotic polypharmacy prescribers (i.e., HP: >10% of patients) vs. “low” prescribers (i.e., LP: ≤ 10% of patients). To identify correlates of high vs. low antipsychotic polypharmacy use, we conducted stepwise backward elimination multivariate logistic regression analyses, entering into the model any characteristic that was different at a level of $p<0.1$ between the two groups (see table 1). All analyses were two-sided with alpha set at 0.05, using JMP 5.0.1, 1989–2003, SAS Institute Inc.

Results

Prescriber demographics

Forty-four prescribers (22 attending and 22 resident/fellow level clinicians) of 59 eligible clinicians (74.6%) participated in this study. Prescriber characteristics are summarized in table 1.

Antipsychotic Polypharmacy Prescribing

Among patients treated with antipsychotics, practitioners estimated that 17.0±10.0% of patients were receiving antipsychotic polypharmacy (table 1). Atypical antipsychotic combinations predominated 63.5±35.0%. Although clinicians estimated to have self-initiated antipsychotic polypharmacy in only 23.3±27.0% of cases, they reported not having attempted reducing the number of antipsychotics in 40.9±37.7%.

Among individual antipsychotics, quetiapine was the antipsychotic most combined (41.5%), followed by clozapine (39.6%) and the depot formulation of a either haloperidol or fluphenazine (24.5%) (data not shown). However, no consistent preferences regarding either antipsychotic combination classes or individual antipsychotic combinations emerged (table 1)

Clinician Attitudes

Clinicians were asked to rank on a scale from 0 (0% justified) to 10 (100% justified) how much certain clinical scenarios justified antipsychotic polypharmacy. Overall, prescribers

felt the following scenarios to justify antipsychotic polypharmacy the most: cross-titration (9.2±1.4), failed clozapine trial (8.2±2.2), randomized controlled evidence (8.0±2.0), and clozapine intolerance (7.7±2.6) (table 2).

On the other hand, prescribers felt "moderately" (5.0±1.9) concerned about APP (0–10). The most highly rated reasons included possibility for chronic side effects (7.6±2.0), lack of evidence base (7.1±2.2), and increased risk for non-adherence (6.7±2.3) and mortality (6.7±3.2). Interestingly, cost (4.9±2.5) and total antipsychotic dose (4.2±2.9) ranked lowest (table 3).

High Use of Antipsychotic Polypharmacy

HP clinicians were more likely to be attendings than trainees (76.2%vs. 26.1%, p=0.0009), have been practicing for longer (20.8 vs. 9.5 years, p=0.0046), see more patients per week (27.0±15.6 vs. 21.1±17.9, p=0.0025), and have a preferred antipsychotic polypharmacy treatment (95.2% vs. 53.2%, p=0.014) (table 1). HP clinicians were also more likely to follow a previous clinicians' advice to continue antipsychotic polypharmacy (5.1±2.4 vs. 3.6±2.7, p=0.046) (table 2) and regarded polypharmacy as less problematic (4.3±2.0 vs. 5.7±1.7, p=0.021) (table 3). However, there were no differences on 25/26 justifications for antipsychotic polypharmacy (table 2) and 9/9 concerns of antipsychotic polypharmacy (table 3). In multivariate analyses, only attending status (OR:10.3, 95%CI:2.3–60.7, p=0.0043) and greater likelihood to have a specific antipsychotic polypharmacy preference (OR:21.4, 95%CI:2.8–473.4, p=0.011) remained significant (r^2:0.35, p<0.0001).

Discussion

This study found that most prescribers provided appropriate justifications for antipsychotic polypharmacy, and that 75% of their cases of polypharmacy had been inherited. Furthermore, clinicians were reluctant to reduce the number of antipsychotics in more than 40% of cases, although they reported this was successful in 28% of cases. Similarly, a prior co-treatment with antipsychotic polytherapy was reported being a strong predictor of future polypharmacy (Biancosino et al., 2005).

Although no specific antipsychotic combination emerged as a clear choice, consistent with prior reports, quetiapine and clozapine were most often part of antipsychotic polypharmacy (Correll et al., 2007; Jaffee and Levine, 2003; Faries et al., 2005; Ganguly et al., 2004; Stahl et al., 2004). This may be due to the fact that quetiapine does not seem to increase the extrapyramidal side effect burden when combined with other antidopmaninergic agents and because it often seems to be combined at a lower dose for sleep induction, anxiety and agitation. Using another antipsychotic with clozapine is arguably most justified, as there are no other options for clozapine resistant patients and/or those intolerant of higher doses. Moreover, the best evidence involves clozapine combinations (Correll et al., 2009; Barbui et al., 2009; Paton et al., 2007; Chang et al., 2008; Fleischhacker et al 2010). The fact that no specific combination emerged among all prescribers points to a lack of specific theoretical, evidence-based or pragmatic guidelines for antipsychotic polypharmacy.

Prescribers treating >10% of patients with antipsychotic polypharmacy were more likely attendings, see more patients, follow the advice of prior prescribers to continue antipsychotic polypharmacy, and have less general concerns about antipsychotic polypharmacy. Furthermore, when initiating antipsychotic polypharmacy, they tended to have more specific combination preferences. Besides these characteristics, however, high vs. low antipsychotic polypharmacy prescribers differed on none of the other rating scales, and only attending physician status and having a preferred antipsychotic combination choice remained significant in a multivariate regression analysis. These results could point to a

greater familiarity with the effectiveness of (specific) antipsychotic combinations, or to the fact that these more experienced physicians treat more chronic and severely ill patients. However, future research needs to address characteristics that differentiate high from low antipsychotic polypharmacy prescribers further.

Several limitations of this study require consideration, including the relatively small sample size, lack of additional sites, and lack of questioning of antipsychotic coprescribing practices relative to more detailed patient characteristics. Finally, clinicians' reported behaviors could not be compared against actual behaviors. Despite these caveats, this is the first study to our knowledge that investigated systematically attitudes and self-reported behaviors in clinicians regarding antipsychotic polypharmacy prescribed as part of usual clinical practice.

Future studies need to correlate prescriber perceptions and reports with actual behaviors. A recent survey study found that settings with lower use of antipsychotic polypharmacy were characterized by higher awareness of local/national guidelines, more participation in local educational activities and research among doctors, and a lower perception of an overwhelming work load and time pressures among nurses (Baandrup et al., 2010), providing initial leads for the potential to reduce unnecessarily high rates of antipsychotic coprescribing. In addition to testing initiatives to reduce antipsychotic polypharmacy, more controlled research of antipsychotic combinations is needed to inform clinical practice.

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Table 1

Clinician and Antipsychotic Treatment Characteristics in High vs. Low Antipsychotic Polypharmacy Prescribers (APP).

Characteristic	Total (N=44)	High APP (>10%) (N=21)	Low APP (≤ 10%) (N=23)	F / chi2 Statistic	P-value
Prescriber Demographics					
Attending clinician (N, %)	22 (50.0)	16 (76.2)	6 (26.1)	χ2:11.02	**0.0009**
Years of practice (years±SD)	14.9±12.6	20.8±13.8	9.5±11.3	F: 8.98	**0.0046**
Treatment Setting (N, %)				χ2:0.86	0.36
Inpatient	8 (18.2)	5 (23.8)	3 (13.02)		
Outpatient	36 (81.8)	16 (76.2)	20 (87.0)		
Number of Patients/week	23.1±15.6	27.0±15.6	21.1±17.9	F: 10.35	**0.0025**
Antipsychotic Cotreatment Frequency (%±SD)					
Any antipsychotic polytherapy	17.0±10.0	31.9±14.0	3.4±3.4	F: 89.50	**<0.0001**
SGA+SGA	63.5±35.0	62.6±27.1	64.7±42.8	F: 0.035	0.85
SGA+FGA	35.4±34.7	35.5±26.5	35.3±42.8	F: 0.0003	0.99
FGA+FGA	1.1±3.6	1.9±5.8	0.0±0.0	F: 2.74	0.11
Antipsychotic Cotreatment History (%±SD)					
Patients initiated on polytherapy by current provider	23.3±27.0	31.5±24.0	15.8±29.5	F: 3.70	0.061
Patients successfully switched to monotherapy	28.0±30.8	22.8±13.5	32.8±40.4	F: 1.12	0.30
Patients unsuccessful switch to monotherapy	24.8±30.2	26.8±21.5	23.0±36.3	F: 0.17	0.68
Patients currently undergoing switch to monotherapy	3.9±30.2	3.8±12.4	4.1±16.8	F: 0.0038	0.95
Switch to monotherapy not attempted	40.9±37.7	46.9±29.8	35.4±43.7	F: 0.98	0.33
Preferred Antipsychotic Combinations (N, %)					
None	12 (27.3)	1 (4.8)	11 (47.8)	χ^2: 10.26	**0.014**
SGA+SGA	15 (34.1)	10 (47.6)	5 (21.7)	χ^2: 3.27	0.070
SGA+FGA	17 (38.6)	10 (47.6)	7 (30.4)	χ^2: 1.37	0.24

FGA= first-generation antipsychotic; SGA= second-generation antipsychotic

Table 2

Prescribers' Level of Justification for Antipsychotic Polypharmacy (Rating 0–10).

Justification for Antipsychotic Polypharmacy	Total (N=44)	High APP (>10%) (N=21)	Low APP (≤ 10%) (N=23)	F-Value	P-value
Antipsychotic Treatment/History					
Cross titration	9.2±1.4	9.6±0.9	8.9±1.7	3.25	0.078
Augmentation after failed CLZ	8.2±2.2	8.6±1.6	7.9±2.6	1.14	0.29
Augmentation due to intolerance to CLZ	7.7±2.6	7.8±2.3	7.7±2.8	0.042	0.84
Augmentation after 3 failed AP trial	6.3±3.1	7.0±2.7	5.6±3.4	2.13	0.15
Aborted cross titration	5.3±2.8	5.9±2.5	4.7±3.1	1.91	0.17
Different route of administration	5.1±3.3	5.5±2.8	4.7±3.7	0.61	0.44
Reached upper dose limit of 1st AP	4.5±3.1	4.9±2.9	4.1±3.3	0.72	0.40
Augmentation after 2 failed AP trial	4.4±3.1	5.1±3.1	3.7±3.1	2.04	0.16
One AP believed insufficient for relapse	3.9±3.3	4.1±3.6	3.8±3.1	0.072	0.79
Augmentation after 1 failed AP trial	3.0±3.0	3.1±2.7	2.9±3.3	0.062	0.80
Improving Outcomes					
Treatment of comorbid condition	5.3±2.8	6.0±2.1	4.6±3.3	2.92	0.095
Enhance effect	5.1±2.9	5.7±3.1	4.6±2.8	1.56	0.22
Minimize adverse events	4.5±3.3	5.1±3.2	3.9±3.4	1.62	0.21
Different target symptoms	4.4±2.6	5.0±2.6	3.9±2.5	2.13	0.15
Reduce dose of 1st AP	3.7±2.8	4.3±3.1	3.1±2.5	2.05	0.16
Reduce number of non-AP medications	3.0±2.5	3.3±2.4	2.7±2.5	0.61	0.44
Speed up effect	2.5±2.3	3.0±2.5	2.4±2.1	1.87	0.18
Level of Evidence for efficacy of APP					
Double blind placebo controlled trials	8.0±2.0	7.7±1.8	8.3±2.1	1.13	0.29
Open label trials	4.7±1.9	5.0±2.0	4.3±1.9	1.63	0.12
Case report	3.7±2.4	4.0±2.4	3.5±2.5	0.42	0.52
Other					
Different Pharmacology	5.1±3.0	5.3±2.8	4.9±3.2	0.21	0.65
Family/patient choice	4.2±2.6	4.9±2.7	3.4±2.5	3.75	0.07
Recommended by prior treating clinician	4.3±2.5	5.1±2.4	3.6±2.7	4.21	**0.046**
Prescriber habit	2.9±2.7	2.9±2.5	2.9±2.9	0.0094	0.92

Justification for Antipsychotic Polypharmacy	Total (N=44)	High APP (>10%) (N=21)	Low APP (≤ 10%) (N=23)	F-Value	P-value
Poor communication between services	2.1±2.7	2.8±3.4	1.5±2.1	2.20	0.14
Marketing pressures	1.2±1,8	1.3±2.0	1.2±1.6	0.042	0.84

AP: antipsychotic; APP: Antipsychotic Polypharmacy Prescriber; CLZ: clozapine

Table 3

Prescribers' Level of Concern about Antipsychotic Polypharmacy (Rating 0–10).

Degree to which Scenario Discourages Antipsychotic Polypharmacy (0–10)	Total (N=44)	High APP (>10%) (N=21	Low APP (≤ 10%) (N=23)	F-Value	P-value
General Concern					
How problematic is antipsychotic polypharmacy	5.0±1.9	4.3±2.0	5.7±1.7	5.73	**0.021**
Clinical scenario					
Potential for higher chronic adverse events	7.6±2.0	7.2±2.1	7.9±1.8	1.06	0.31
Lack of evidence base	7.1±2.2	6.7±1.9	7.3±2.5	0.76	0.39
Increased risk of non-adherence	6.7±2.3	6.0±2.5	7.3±2.1	3.17	0.082
Potential for higher mortality	6.7±3.2	6.3±3.4	7.1±3.0	0.57	0.45
Potential drug-drug interactions	6.6±2.7	6.6±2.5	6.5±2.8	0.027	0.87
Potential for higher acute adverse events	6.5±2.4	6.4±2.7	6.6±2.1	0.17	0.68
Difficulty determining cause and effect	6.4±2.4	5.9±2.2	6.8±2.5	1.42	0.24
Increased cost	4.9±2.5	5.1±2.3	4.8±2.6	0.23	0.63
Higher total dosage of AP	4.2±2.9	4.0±2.7	4.3±3.1	0.056	0.81

APP: Antipsychotic Polypharmacy Prescriber