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Antipsychotic polypharmacy: a Japanese survey of prescribers' attitudes and rationales

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Abstract

While combining antipsychotics is common in schizophrenia treatment, the literature on the reasons for antipsychotic polypharmacy (APP) is limited. We aimed to identify prescriber attitudes and rationales for APP in Japan where high APP utilization is reported. Two-hundred-seventeen psychiatrists participated in the survey, which assessed APP attitudes and behaviors. Prescribing APP to 47.7±24.7% (mean±SD) of their patients, psychiatrists reported that they were "moderately" concerned about APP. The most APP-justifiable factors were (1="not at all" to 5="extreme"): cross titration (4.50±0.67), randomized controlled evidence (3.67±0.83), and treatment of comorbid conditions (3.31±0.83). Conversely, APP-discouraging factors were: chronic side effects (4.14±0.64), difficulty determining cause and effect (4.07±0.74), and acute side effects (3.99±0.81). Comparing high to low APP prescribers (>50% vs. ≤50% of patients), no differences emerged regarding APP justification and concerns. In multivariate analyses, high APP use was associated with practice at a psychiatric hospital (OR: 2.70, 95%CI: 1.29-5.67, p=0.009), concern about potential drug-drug interactions (OR: 1.56, 95%CI: 1.04-2.35, p=0.031), and less reliance on case reports of APP showing efficacy (OR: 0.64, 95%CI: 0.44-0.92, p=0.017) (r^2=0.111, p=0.001). High and low APP prescribers shared a comparable degree of justifications and concerns. Future research should examine the impact of cultural determinants on APP.

Keywords

Antipsychotic combination therapy; polypharmacy; attitudes; concerns; schizophrenia; survey

1. Introduction

Antipsychotic polypharmacy (APP), i.e. the concurrent treatment with more than one antipsychotic, is common practice in schizophrenia. APP rates are relatively high, with reported prevalence of around 10% to 50% (Broekema et al., 2007; Brunot et al., 2002; Clark et al., 2002; Correll et al., 2007; Faries et al., 2005; Fourrier et al., 2000; Ganguly et al., 2004; Jaffe and Levine, 2003; Kreyenbuhl et al., 2006; Procyshyn et al., 2001; Sim et al., 2004; Tapp et al., 2003; Wang et al., 2000). The APP rate in Japan is reported to be even higher (Ito et al., 1999), with a more recent inpatient survey indicating that 66.2% of them were taking 2 or more antipsychotics (Yoshio et al., 2012). According to recent meta-analysis, APP prevalence and time trends differ by region. For example, APP was higher in Asia and Europe than in North America (p<0.001); moreover, APP has increased numerically in North America (1980s: 12.7% to 2000s: 17.0%, p=0.94), while there was a significant decrease in Asia (1980: 55.5% to 2000: 19.2%, p=0.03) (Gallego et al., 2012a). Given this diverse prevalence and time trends in countries or regions, patient-driven factors are unlikely to play any primary role in the choice of APP, but other factors, such as prescribing custom, adherence to treatment guidelines or understanding of the literature may be more relevant in this dicision making process.

The evidence for APP is relatively weak and controversial. A recent meta-analysis showed that APP was superior to monotherapy in some outcome measures, however, it was difficult to draw firm conclusions due to possible publication bias, strong heterogeneity of the results and lack of data on specific psychopathology ratings and adverse effects (Correll et al., 2009). Furthermore, APP has been associated with increased adverse events and higher cost (Baandrup et al., 2012; Gallego et al., 2012b; Joukamaa et al., 2006). Therefore, established treatment algorithms only recommend antipsychotic co-treatment with clozapine as a last stage strategy (Argo et al., 2008; Buchanan et al., 2010; Canadian Psychiatric Association,

2005; Falkai et al., 2005; McGorry et al., 2005; National Collaborating Centre for Mental Health, 2010).

Despite this disconnect between the frequent APP use in clinical practice and treatment guidelines and clinical trial evidence discouraging APP, only few studies examined clinician perspectives toward APP. The reasons for APP reported by previous studies include skepticism towards the use of algorithms, nurses' request (Ito et al., 2005), discontinued switching (Tapp et al., 2003), and aiming to reduce positive symptoms (Sernyak and Rosenheck, 2004; Tapp et al., 2003). Our recent survey, which targeted prescribers at a psychiatric teaching hospital in the US reported that high APP prescribers had more clinical experience, less concerns about APP and more likely a preferred APP choice (Correll et al. 2011). However, these studies mentioned above included relatively small sample sizes (12 to 78 prescribers), therefore the information is still limited.

In addition, there was a specific therapeutic difference in Japan due to lack of access to clozapine until 2010. Since APP trials have mostly examined clozapine in combination with another antipsychotic, guidelines only recommend APP after clozapine treatment has been unsuccessful. Therefore, the use of APP by Japanese psychiatrists and their attitudes toward APP may be different from that of US. As far as we know, this is the largest survey so far which directly targeted psychiatrists' attitudes regarding APP.

2. Methods

2.1. Setting and Procedures

The survey was conducted between June 2009 and April 2010. Psychiatrists prescribing antipsychotics to psychiatric patients were invited to participate in the survey. A total of 40 facilities across 8 prefectures, including universities, psychiatric hospitals, and clinics participated. Since the survey did not require any patient information, the study was exempted from ethics review. This was not a random sample of clinicians/institutions, but rather an attempt was made to identify local physicians who could assist in facilitating high response rates to the surveys in a variety of representative clinical centers. The "Prescriber's Reasons for Antipsychotic Combination Treatment Questionnaire: PRACT-Q" (Correll et al., 2011) (original version written in English) was translated into Japanese by the first author of this manuscript. The Japanese version of the survey (PRACT-Q-J) was back translated by a third person into English and it was validated by two English speakers, including the author of the original version. However, during the process of translation, some modifications were made in order to fit Japanese treatment settings or simplify the survey procedure (e.g. demographic characteristics, range of Likert scale). Moreover, although we included the clozapine-related items in the questionnaire, we made them optional questions, taking into consideration that many doctors did not have enough knowledge about clozapine. The PRACT-Q-J covers the following areas: 1) estimated percentage of patients on antipsychotic polypharmacy; 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; 4) how much prescribers feel that APP is problematic (using a 7-point Likert scale: 1= "not at all" to 7= "extreme"); 5) attitudes toward 24 areas of potential benefits/justifications as well as 9 areas of risks/concerns regarding APP (using a 5-point Likert scale assessing how much prescribers felt APP was justified: 1= "not at all" to 5= "extreme") in each of the 24 clinical situations, and assessing how concerned prescribers were (1= "not at all" to 5= "extreme") about nine potentially problematic areas associated with APP. PRACT-Q-J was distributed in a form of a written questionnaire or excel file via email. No reimbursement for participants was offered.

2.2. Data Analyses

Descriptive statistics were used to describe the study sample and prescriber responses. We compared characteristics and attitudes of "high" vs. "low" APP prescribers. The median split of 50% of patients receiving more than one antipsychotic was used to divide study participants into "high" APP prescribers (i.e. >50% of patients) vs. "low" prescribers (i.e. ≤50% of patients). In addition to the median split, we also conducted *a priori* defined sensitivity analysis, where we used >10% vs. ≤10% of patients receiving APP as a cutoff in order to be consistent with the median split grouping used in the US survey (Correll et al., 2011). Distributions of all variables were inspected using histograms, q-q plots and Shapiro-Wilks tests before conducting statistical analyses. Differences in patient characteristics between groups were examined using chi-square analysis for categorical variables and ANOVA or Wilcoxon rank sum test for continuous variables. In order to avoid type I errors due to multiple comparisons, we applied Bonferroni correction within each of the subcategories of the comparisons. Furthermore, to identify significant predictors for high APP use, we conducted stepwise backward elimination multivariate logistic regression analyses, entering into the model any characteristic that was different at a level of $p<0.10$ between high and low APP prescribers. All analyses were two-sided with alpha was set at 0.05. Data were analyzed using JMP 5.0.1, SAS Institute Inc and SPSS 11.5.1, IBM Inc.

3. Results

3.1. Prescriber demographics

A total of 569 questionnaires were distributed throughout the country across 8 prefectures and 40 facilities. Of these, 217 (38.1%) (190 attendings, 27 residents) participated in the survey. Demographic characteristics are summarized in Table 1.

3.2. Prescriber practice

Psychiatrists estimated that as many as 47.7±24.7% (mean±SD) of their patients were prescribed APP. For the patients who received APP, psychiatrists did not attempt to switch to monotherapy in 35.2±27.4% of the cases, successfully switched to monotherapy in 28.3±19.1%, and tried to switch to monotherapy, but failed, in 37.0±21.8% of cases. Second-generation antipsychotic combination was most frequently prescribed form of APP (47.9±25.3%), followed by second- plus first-generation antipsychotics (35.4±28.4%). Regarding specific combinations, risperidone+levomepromazine was the most frequently prescribed antipsychotic co-treatment (14.9%), followed by risperidone+quetiapine (12.2%), risperidone+olanzapine (9.0%), risperidone+chlorpromazine (6.4%) and olanzapine +levomepromazine (4.9%). Among individual medications, risperidone was the antipsychotic most used as part of APP (54.5%), followed by levomepromazine (31.3%) and quetiapine (24.8%).

3.3. Attitudes towards antipsychotic polypharmacy

Overall, psychiatrists felt "moderately" concerned about APP (3.87±0.96). The most justified scenarios for APP were: cross-titration, randomized controlled evidence treatment of comorbid conditions and different route of administration (Table 2). Augmentation after failed clozapine, and augmentation due to intolerance to clozapine were ranked high as a justification (ranked 8^{th} and 9^{th} out of 24 respectively), but only 23% (50/217) of the participants answered these questions. On the other hand, the most highly rated reasons discouraging psychiatrists from APP use included the possibility for chronic side effects, difficulty determining cause and effect, acute side effects, potential for higher mortality, and potential drug-drug interactions (Table 3).

3.4. Predictor for higher use of antipsychotic polypharmacy

Using a median split of reported APP prescribing (i.e., "high": >50%, "low": ≤50%), high APP prescribing clinicians were more likely to have a practice at a psychiatric hospital [85.6% vs. 68.5%; χ^2(df)=8.30(1); p=0.004]. Moreover, high APP utilizing psychiatrists reported more often no preference regarding specific antipsychotic class combinations compared to low APP psychiatrists [25.3% vs. 14.5%; χ^2(df)=3.86(1); p=0.049] (Table 1). There was no difference between high and low APP utilizing psychiatrists regarding their beliefs, which justified (23/24 items) or discouraged (9/9 items) APP. High APP prescribing psychiatrists differed from low APP prescribing psychiatrists in less reliance on single case reports as a justification for APP [2.65±0.82 vs.2.91±0.79, F(df1, df2)=5.37(1,213), p=0.021] however, these difference became insignificant after Bonferroni correction (Table 2). In multivariate analyses, practice at a psychiatric hospital (OR: 2.70, 95%CI: 1.29-5.67, p=0.009), concern about potential drug-drug interactions (OR: 1.56, 95%CI: 1.04-2.35, p=0.031), and less reliance on case reports showing APP efficacy (OR: 0.64, 95%CI: 0.44-0.92, p=0.017) were associated with high APP use (r^2=0.111, p=0.001).

When we used >10% vs. ≤10% as cutoff to divide psychiatrists, very low APP prescribers were less likely to be attending clinicians [89.1% vs. 75.0%; χ^2(df)=3.91(1); p=0.048]; i.e., more likely to be residents (10.9% vs. 25.0%). There was no difference between the two groups regarding factors justifying (23/24) or discouraging APP (9/9). The only difference was that very low APP prescribing psychiatrists were less concerned about higher total dosage than high APP prescribing psychiatrists [3.83±0.74 vs. 3.46±0.88; F(df1, df2)=5.01(1,213); p=0.026] which became insignificant after Bonferroni correction (Table 3). In multivariate analyses, concern about higher total dosage (OR: 2.07, 1.18-3.64, p=0.011), and less concern about difficulty determining cause and effect (OR: 0.43, 95%CI: 0.22-0.84, p=0.014) were associated with high APP use (r^2=0.87 p=0.008).

4. Discussion

Results from our survey showed high reported APP use in Japan. Moreover, faced with APP, psychiatrists were reluctant to convert to monotherapy in over one-third of the cases, while this was successful in 28% of the cases when attempted. Dividing psychiatrists into high vs. low APP prescribers, using the median split of 50% of their patients receiving APP as the cutoff, very few differences emerged. Practice at a psychiatric hospital was related to high reported APP utilization, which is intuitive considering the Japanese psychiatric system since more severely ill patients are seen in psychiatric hospitals compared to psychiatric units that are part of general medical hospitals. Even using 10% as a cutoff in order to be comparable with the previous US survey (Correll et al., 2011), no specific differences were seen between the groups, except that high APP prescribers were more likely to be attending clinicians, rather than residents. This is consistent with the US survey, which found that high reported APP use was associated with being an attending (76.5% vs. 26.1%, p=0.0009) and having a longer practice in psychiatry (20.8+/−13.8 years vs. 9.5+/−11.3 years, p=0.0046) (Correll et al., 2011). One potential explanation may be that attending clinicians treat more severely ill patients, or that they are more likely to have inherited patients from the time of rapid neuroleptization in the 1970s when even more APP was used in Asia (Gallego et al., 2012a).

One question raised by this survey study is why the APP rate is this high in Japan. It was surprising that high and low APP prescribers shared similar levels of concern and justification toward APP, in that such attitudes did not have a significant impact on their APP prescribing behavior. Similar results were found in the US-based study (Correll et al., 2011). Moreover, despite a considerably lower reported APP rate in the US compared to that of Japan (17.0±27.0% vs. 47.7±24.7%, respectively), the psychiatrists' general attitude

toward APP was not that different between the two countries. For example, psychiatrists in both countries were “moderately” concerned about APP. Although conversion to monotherapy was successful in 28% in both countries, prescribers did not attempt conversion in 41% of cases in US and in 35% of cases in Japan. Moreover the ranking of justifications for and concerns about APP were similar, except that “lack of evidence” ranked lower in Japan as a concern about APP. It is not easy to explain considerably different reported APP rates despite such similarity. However, APP prescribing habits may reflect direct and indirect influences of current and local standard of care as well as training, and may be less determined by concepts and attitudes of the prescriber regarding APP.

Another question is whether inaccessibility to clozapine has anything to do with the high utilization of APP in Japan. Clozapine is the only antipsychotic, which has consistent evidence for efficacy in the treatment of refractory patients (Chakos et al., 2001; Kane et al., 1988), hence it is potentially understandable that APP is high in a country where clozapine is not available. However, even in settings where clozapine is available, prescribers have reported a preference toward combining antipsychotics, rather than using clozapine (Nielsen et al., 2010), and combining antipsychotics as one way of attempting to address treatment refractoriness is common practice (Correll and Gallego, in press). We attempted to examine the impact of inaccessibility to clozapine on APP among Japanese psychiatrists. In fact, failure or intolerance to clozapine treatment ranked high for justification of APP (which was a hypothetical and, thus, optional question at that time for Japanese psychiatrists). However, due to the low response rate (23%), these findings are difficult to interpret. The best way to study the potential APP-increasing effect of inaccessibility of clozapine would be to evaluate changes in APP prescription patterns a few years after the introduction of clozapine in Japan. As a side note, clozapine was only introduced in Japan in 2010, which was after the survey was conducted, and since then the initiation has still been limited to certain inpatient settings.

With regard to specific antipsychotic combinations, risperidone+levomepromazine was the most frequently prescribed co-treatment, followed by risperidone+quetiapine, and risperidone+olanzapine. It seemed that the high potency risperidone served as the main antipsychotics, whereas the lower potency antipsychotics, levomepromazine and quetiapine, served as secondary antipsychotics. This strategy is somewhat similar to the findings in the US survey and to other reports where quetiapine and clozapine were most often part of APP (Correll and Gallego, in press; Correll et al., 2007; Correll et al., 2011). Presumably, these secondary antipsychotics are used in an attempt to reduce extrapyramidal side effects (Faries et al., 2005; Ganguly et al., 2004; Jaffe and Levine, 2003; Stahl and Grady, 2004), for sleep induction, or to reduce anxiety and agitation (Chue et al., 2001; Correll et al., 2011; Potkin et al., 2002). However, again, the biggest difference to results in other countries is the lack of clozapine availability in Japan at the time of our study, and it is difficult to determine how much this influenced the individual APP prescription pattern in Japan.

The results of the study need to be interpreted in the context of limitations. First we asked psychiatrists to base their answer on their clinical practice. However, it is most likely impossible to be perfectly accurate or candid when answering the questions, such as the frequency of APP or the justifications for APP. Respondents may have underestimated the use of APP since it is discouraged in the literature, or they might have chosen some ideal reasons for justifying APP, which does not necessarily reflect their everyday decision making. Second, although we included teaching hospitals as well as non-academic, psychiatric hospitals and clinics, psychiatrists were not randomly selected. Most of the facilities that participated in the survey were located in Tokyo or other prefectures nearby. Hence, the results of the survey were not necessarily reflective of all of the regions in Japan. In addition, psychiatrists who participated in the survey are likely to be more interested in

this issue, or familiar with the literature. The low return rate (40%) could have further increased this selection bias. This is an inherent difficulty of any survey, however, the large sample size (217 psychiatrists) may have somewhat minimized this bias. Lastly, some clinical characteristics, such as agitation or aggression, can have a big impact on APP, however, we did not cover these areas which can limit the interpretation of the results.

Given inconsistent efficacy results of APP and the potential for increased side effects and cost, APP should remain a last-resort treatment option after monotherapy, switching and non-antipsychotic combinations have failed (Essock et al., 2011; Fleischhacker and Uchida, 2012; Gallego et al., 2012b). There are studies that examined the impact of interventions to convert APP to antipsychotic monotherapy; from educational interventions (Baandrup et al., 2010) to more aggressive ones including active prescription monitoring and direct feedback (Hazra et al., 2011; Laska et al., 1980; Thompson et al., 2008). As passive interventions have shown to have limited efficacy, while more active interventions have a larger effect on decreasing APP (Fleischhacker and Uchida, 2012; Tani et al., in press), the results of this study are potentially helpful in informing more specific approaches, such as identifying specific target doctor populations, concerns that are underestimated, or justifications that are overestimated.

As the survey indicated that prescribing habits may be less determined by concepts and attitudes of the prescriber than might be expected, further research needs to be done to examine the impact of regulations or cultural determinants on APP. Moreover, since inaccessibility to clozapine might have contributed the high reported APP rate in Japan, APP utilization studies should be conducted that compare APP before and after clozapine introduction, and the survey should be repeated after clozapine has been widely available in a few years in order to assess potential changes in attitudes toward APP.

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Table 1

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

Characteristic	**(N=217)**	**>50% APP (n=90)**	**≤50% APP (n=127)**	**P-value**	**>10% (N=193)**	**≤10% (N=24)**	**P-value**
Prescriber Demographics							
Attending clinician (N, %)	190 (87.6)	82 (91.1)	108 (85.0)	0.18	172 (89.1)	18 (75.0)	**0.048**
Years of practice (years±SD)	10.5±8.6	11.7±10.6	9.7±6.9	0.11	10.7±8.8	8.8±6.1	0.31
Practice at psychiatric hospital	164 (75.6)	77 (85.6)	87 (68.5)	**0.004**	149 (77.2)	15 (62.5)	0.11
Antipsychotic Cotreatment Frequency (% ± SD)							
Any combination	48.3±13.6	72.4±9.8	31.2±15.8	<**0.001**	53.4±20.9	7.2±3.4	<**0.001**
SGA+SGA	47.9±25.3	48.9±24.2	47.2±26.1	0.63	48.1±25.7	46.0±22.7	0.71
SGA+FGA	35.4±28.4	33.5±28.0	36.7±28.6	0.43	35.0±2.1	38.5±5.8	0.56
FGA+FGA	17.2±18.1	18.1±18.2	16.5±18.0	0.52	17.4±18.4	15.4±15.4	0.61
Antipsychotic Cotreatment History (% ± SD)							
Patients successfully switched to monotherapy	28.3±19.1	28.4±19.2	28.3±18.9	0.97	28.1±19.6	29.8±14.1	0.69
Patients unsuccessful switch to monotherapy	37.0±21.8	38.4±20.5	35.9±22.7	0.41	37.7±22.4	31.0±15.7	0.16
Switch to monotherapy not attempted	35.2±27.4	33.3±27.2	36.6±27.6	0.39	34.7±28.1	39.2±21.5	0.45
Preferred Antipsychotic Class Combinations (N, %)							
No preference	40 (19.0)	22 (25.3)	18(14.5)	**0.032***	37 (37.0)	3 (21.4)	0.16
SGA + FGA	102 (53.7)	40 (53.3)	62 (53.9)	0.92	55 (32.7)	11 (50.0)	0.27
SGA + SGA	69 (36.3)	23 (30.7)	46 (40.0)	0.47	89 (53.0)	13 (59.1)	0.86
*Became insignificant after Bonferroni correction							

Chi^2 or ANOVA/Wilcoxon rank sum test were used to detect differences between groups.

Table 2

Prescribers' Level of Justification for Antipsychotic Polypharmacy

Justification for Antipsychotic Polypharmacy (Rating 1-5)	**Total (N=217)**	**(>50%) (N=90)**	**(≤50%) (N=127)**	**P-value**	**(>10%) (N=193)**	**(≤10%) (N=24)**	**P-value**
Antipsychotic Treatment/History							
Cross titration	4.50±0.67	4.53±0.69	4.48±0.65	0.67	4.50±0.67	4.54±0.66	0.77
Different route of administration	3.28±0.94	3.34±0.99	3.25±0.89	0.49	3.29±0.96	3.29±0.69	0.99
*Augmentation after failed clozapine	3.10±1.06	3.00±1.09 (n=26)	3.21±1.02 (n=24)	0.49	3.10±1.08 (n=48)	3.00±0.00 (n=2)	0.89
*Augmentation due to intolerance to clozapine	3.02±1.12	3.00±1.23 (n=26)	3.04±0.98 (n=23)	0.89	3.02± 1.13 (n=47)	3.00± 0.00 (n=2)	0.98
Augmentation after 3 failed AP trial	3.01±1.13	3.06±1.16	2.98±1.11	0.65	3.06±1.16	2.67±0.82	0.11
Aborted cross titration as pt improved	2.96±0.82	3.01±0.86	2.92±0.79	0.43	2.96±0.83	2.96±0.75	1.00
One AP believed insufficient for relapse prevention	2.95±0.98	2.92±0.98	2.97±0.99	0.69	2.96±0.99	2.92±0.93	0.85
Reached upper dose limit of 1st AP	2.92±0.94	2.91±0.97	2.92±0.92	0.94	2.93±0.95	2.79±0.83	0.49
Augmentation after 2 failed AP trial	2.89±1.15	2.94±1.18	2.85±1.13	0.55	2.92±1.14	2.63±1.24	0.24
Augmentation after 1 failed AP trial	2.86±0.98	2.92±1.04	2.81±0.95	0.42	2.90±0.995	2.50±0.89	0.061
Recommended by prior treating clinician	2.37±0.84	2.37±0.86	2.37±0.82	0.97	2.38±0.62	2.33±0.17	0.81
Improving Outcomes							
Treatment of comorbid condition	3.31±0.83	3.4±0.79	3.2±0.85	0.10	3.29±0.85	3.42±0.65	0.49
Different target symptoms	3.16±0.89	3.27±0.89	3.08±0.89	0.14	3.19±0.90	2.92±0.78	0.15
Enhance effect	2.89±0.84	2.94±0.86	2.87±0.82	0.50	2.91±0.86	2.79±0.59	0.51

Justification for Antipsychotic Polypharmacy (Rating 1-5)	**Total (N=217)**	**(>50%) (N=90)**	**(≤50%) (N=127)**	**P-value**	**(>10%) (N=193)**	**(≤10%) (N=24)**	**P-value**
Minimize adverse events	2.61±0.97	2.56±0.98	2.65±0.97	0.53	2.63±0.99	2.50±0.83	0.55
Speed up effect	2.54±0.93	2.54±0.95	2.55±0.91	0.93	2.55±0.94	2.50±0.83	0.80
Reduce number of non-AP medications	2.59±0.94	2.49±0.95	2.65±0.92	0.23	2.58±0.95	2.66±0.87	0.66
Reduce dose of 1st AP	2.49±0.96	2.43±0.90	2.56±1.01	0.16	2.44±0.97	2.83±0.87	0.062
Level of Evidence for APP efficacy							
Double blind placebo controlled trials	3.67±0.83	3.61±0.86	3.70±0.80	0.42	3.66±0.85	3.75±0.61	0.61
Open label trials	3.19±0.80	3.11±0.88	3.25±0.74	0.24	3.20±0.82	3.13±0.91	0.67
Case report	2.80±0.81	2.65±0.82	2.91±0.79	**0.021** **	2.83±0.81	2.58±0.83	0.17
Other							
Different pharmacological mechanism	3.19±0.89	3.2±0.92	3.2±0.88	0.94	3.20±0.899	3.08±0.83	0.55
Family/patient choice	2.77±0.88	2.8±0.87	2.7±0.88	0.70	2.88±0.877	2.63±0.88	0.40
Clinical wisdom	2.55±0.88	2.5±0.92	2.6±0.85	0.96	2.56±0.886	2.46±0.83	0.59

Chi^2 or ANOVA/Wilcoxon rank sum test were used to detect differences between groups.

* The response was voluntary.

** Became insignificant after Bonferroni correction

Table 3

Prescribers' Level of Concern about Antipsychotic Polypharmacy

Degree to which Scenario Discourages Antipsychotic Polypharmacy	**Total (N=217)**	**High APP (>50%) (N=90)**	**Low APP (≤50%) (N=127)**	**P-value**	**(>10%) (N=193)**	**(≤10%) (N=24)**	**P-value**
General Concern							
How problematic is antipsychotic polypharmacy (Rating 1-7)	3.87±0.96	3.93±1.02	3.84±0.91	0.49	3.87±0.97	3.9±0.90	0.84
Clinical scenario (Rating 1-5)							
Potential for higher chronic adverse events	4.14±0.64	4.10±0.61	4.16±0.66	0.53	4.12±0.64	4.25±0.61	0.35
Difficulty determining cause and effect	4.07±0.74	4.09±0.67	4.05±0.79	0.67	4.03±0.75	4.33±0.64	0.059
Potential for higher acute adverse events	3.99±0.81	3.94±0.76	4.02±0.83	0.47	4.01±0.78	3.83±1.01	0.31
Potential for higher mortality	3.91±0.87	4.00±0.84	3.84±0.87	0.18	3.91±0.87	3.91±0.85	0.97
Potential drug-drug interactions	3.91±0.75	4.01±0.62	3.83±0.82	0.087	3.91±0.76	3.88±0.68	0.83
Higher total dosage of AP	3.79±0.76	3.81±0.75	3.76±0.78	0.61	3.83±0.74	3.46±0.88	**0.026** *
Increased risk of non-adherence	3.65±0.80	3.74±0.72	3.58±0.84	0.16	3.63±0.80	3.75±0.79	0.50
Lack of evidence base	3.54±0.91	3.63±0.99	3.48±0.86	0.24	3.57±0.93	3.29±0.75	0.16
Increased cost	3.13±0.92	3.20±1.00	3.08±0.85	0.35	3.12±0.92	3.29±0.86	0.37

Chi^2 or ANOVA/Wilcoxon rank sum test were used to detect differences between groups.

* Became insignificant after Bonferroni correction