Psychiatry Research 209 (2013) 406–411

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

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

Taishiro Kishimoto [a,b,c,d,*], Koichiro Watanabe [a,e], Hiroyuki Uchida [a,f], Masaru Mimura [a], John M. Kane [b,c,d,g], Christoph U. Correll [b,c,d,g]

[a] Keio University School of Medicine, Department of Neuropsychiatry, Shinjuku, Tokyo, Japan
[b] The Zucker Hillside Hospital, Psychiatry Research, North Shore-Long Island Jewish Health System, Glen Oaks, NY, USA
[c] Hofstra North Shore LIJ School of Medicine, Hempstead, NY, USA
[d] The Feinstein Institute for Medical Research, Manhasset, NY, USA
[e] Kyorin University School of Medicine, Department of Neuropsychiatry, Mitaka, Tokyo, Japan
[f] Centre for Addiction and Mental Health, Geriatric Mental Health Program, Toronto, Canada
[g] Albert Einstein College of Medicine, Bronx, NY, USA

ARTICLE INFO

Article history:
Received 19 November 2012
Received in revised form
13 February 2013
Accepted 18 March 2013

Keywords:
Antipsychotic combination therapy
Polypharmacy
Attitudes
Concerns
Schizophrenia
Survey

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 and seventeen psychiatrists participated in the survey, which assessed APP attitudes and behaviors. Prescribing APP to 47.7 ± 24.7% (mean ± S.D.) 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.

1. Introduction

Antipsychotic polypharmacy (APP), i.e. the concurrent treatment with more than one antipsychotic, is a common practice in schizophrenia. APP rates are relatively high, with reported prevalence of around 10–50% (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 two 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 decision 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.,

* Corresponding author at: The Zucker Hillside Hospital, Psychiatry Research, North Shore-Long Island Jewish Health System, Glen Oaks, NY, USA.
Tel.: +1 718 470 8386; fax: +1 718 343 1659.
E-mail addresses: taishiro-k@mti.biglobe.ne.jp, tkishimoto@nshs.edu (T. Kishimoto).

0165-1781/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psychres.2013.03.014

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 toward 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 USA, 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 (12–78 prescribers), and 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 eight 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"); and (5) attitudes toward 24 areas of potential benefits/justifications as well as nine 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 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 eight prefectures and 40 facilities. Of these, 217 (38.1%) (190 attendings, 27 residents) participated in the survey. Demographic characteristics are summarized in Table 1.

Table 1
Clinician and antipsychotic treatment characteristics in high vs. low Antipsychotic Polypharmacy Prescribers (APP). Values in bold indicate statistical significance ($p < 0.05$).

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 ± S.D.)	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 (% ± S.D.)							
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 (% ± S.D.)							
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

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

* Became insignificant after Bonferroni correction.