International Journal of Neuropsychopharmacology (2011), **14**, 735–745. © CINP 2011
doi:10.1017/S146114571000163X

ARTICLE

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Adjunctive benzodiazepine treatment of hospitalized schizophrenia patients in Asia from 2001 to 2008

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Abstract

Benzodiazepines are commonly prescribed to patients with schizophrenia in many countries, but as little is known about such treatment in Asia, we evaluated their adjunctive use for 6761 in-patients diagnosed with schizophrenia in nine Asian countries using a cross-sectional study design in 2001, 2004 and 2008. Multivariate logistic regression and multivariate linear regression analyses were performed to assess predictors of benzodiazepine use and dose, respectively. Overall, 54% of the patients received adjunctive benzodiazepines at an average daily dose equivalent to 30.3 mg diazepam, with minor changes over the years sampled. Benzodiazepine use was highest in Taiwan and Japan, lowest in Thailand and China, and was associated with fewer years ill, presence of delusions (OR 1.24), hallucinations (OR 1.22), disorganized speech (OR 1.17), social or occupational dysfunction (OR 1.16), and use of mood stabilizers (OR 3.15), antiparkinsonian (OR 1.79) or antidepressant drugs (OR 1.33), and lower doses of antipsychotics (all $p=0.016$ to <0.001). Benzodiazepine doses were highest in Taiwan and China, lowest in Korea and Singapore; higher doses were associated with being young, male, physically aggressive, receiving mood stabilizers, and having electroconvulsive treatment (all $p=0.019$ to <0.001). Benzodiazepine use was associated with neurological and systemic adverse effects. In conclusion, benzodiazepine use was common in Asian patients with schizophrenia. Predictors of benzodiazepine use and dose differed in this population. Critical clinical guidelines should be developed specifically for Asian countries to address sound practices in regard to use of benzodiazepines for psychotic disorders.

Received 14 August 2010; Reviewed 9 November 2010; Revised 28 November 2010; Accepted 13 December 2010; First published online 4 February 2011

Key words: Adverse effects, antipsychotics, Asian, benzodiazepines, polytherapy, schizophrenia.

Introduction

Benzodiazepines have hypnotic, anxiolytic, anticonvulsant, myorelaxant and amnestic properties that are useful for a wide range of conditions. Their main clinical indications are for anxiety and sleep disorders (Ashton, 1994*b*), although they are also commonly used for rapid tranquillization in psychotic or manic agitation, as well as for some movement disorders (Gillies *et al*. 2005). Benzodiazepines may have limited antipsychotic and antimanic effects possibly through inhibition of pre-synaptic release of dopamine in the mesolimbic pathway (Gaillard *et al*. 2006) and they have been found to improve some prefrontal cerebral

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functions in schizophrenia patients (Lewis *et al*. 2008). However, benzodiazepines lack convincing evidence for exerting substantial long-term antipsychotic benefits (Bhoopathi & Soares-Weiser, 2006; Volz *et al*. 2007) in patients with schizophrenia. Benzodiazepine treatment is also associated with adverse effects including excessive sedation, cognitive impairment, dependence, discontinuation or withdrawal symptoms including increased anxiety (Chouinard, 2004). Adverse effects are more likely when high potency, short half-life benzodiazepines are prescribed in large and prolonged doses, perhaps particularly with clozapine (Gaillard *et al*. 2006). There is some inconsistent evidence that patients with schizophrenia may be at a lower risk of dependence (Brunette *et al*. 2003*b*; Wheeler *et al*. 2007).

Despite the apparently limited beneficial effects of benzodiazepines in patients with schizophrenia, their use in schizophrenia and other psychotic disorders appears to be common in many regions of the world, evidently mainly as non-specific, adjunctive sedatives to supplement the effects of antipsychotics. Estimates in the USA range from 43% (Brunette *et al*. 2003*a*, *b*) to 63% (Clark *et al*. 2004), while in Italy the estimate is 47% (Magliano *et al*. 2004). In China benzodiazepine use ranges from 29.9% to 34.8% (Xiang *et al*. 2007*a*). However, information on patterns of use, indications and optimal dosing of benzodiazepines for schizophrenia patients, and predictors of clinical response, beneficial and adverse effects are still limited (Barnas *et al*. 1993; Brunette *et al*. 2003*b*; Fang *et al*. 2009; Gorgels *et al*. 2006; Haw & Stubbs, 2007; Magliano *et al*. 2004; Neutel, 2005; Neutel *et al*. 2003; Nomura *et al*. 2006; Simon *et al*. 1996; van Hulten *et al*. 2003; Vorma *et al*. 2005; Voshaar *et al*. 2003; Wheeler *et al*. 2007; Xiang *et al*. 2007*a*). Moreover, studies of benzodiazepine do not usually assess predictors of use and dose together. Reports on adjunctive use of benzodiazepines among psychotic-disorder patients in Asian countries are particularly rare. Accordingly, we now report on findings from an international survey study of adjunctive use of benzodiazepines in patients diagnosed with schizophrenia in several Asian countries, and sampled in 2001, 2004, and 2008.

Methods

Study design and participants

The REAP study is a pharmacoepidemiological research project surveying clinical prescription practices pertaining to psychotropic drugs for hospitalized patients diagnosed with schizophrenia in collaborating Asian countries. The study began in 2001 in six Asian countries which participated again in 2004 and 2008, with the addition of three more countries in 2008. Methods of case-ascertainment, diagnosis, and assessment of treatments have been detailed previously (Chong *et al*. 2004; Sim *et al*. 2004) and are summarized below.

Over a 1-month period in each sampling year (2001, 2004, 2008), a random cross-sectional study was conducted to yield a total of 6761 in-patients (2399, 2136, 2226 in the respective years) with schizophrenia from the nine participating countries and regions (PR China, Hong Kong, Japan, RO Korea, Singapore and Taiwan in all 3 years, plus India, Thailand and Malaysia in 2008). Uniformity of case-identification and assessment was enhanced by regular consensus meetings among the participants. Patient-subjects fulfilled ICD-10 or DSM-IV diagnostic criteria for schizophrenia at study entry as assessed by experienced clinicians. Patients with clinically significant medical illnesses or psychotic symptoms considered secondary to substance-use disorders were excluded. We collected and recorded information on basic sociodemographic characteristics, clinical features, and the identity and doses of all psychotropic medications prescribed. Daily doses of antipsychotics, including long-acting injected preparations, were converted to approximate chlorpromazine-equivalents (CPZeq) using standard guidelines (APA, 1997; Gardner *et al*. 2010; Kane *et al*. 1998; Woods, 2003) and benzodiazepines similarly converted to diazepam equivalents (DZPeq) (Ashton, 2005; Inagaki *et al*. 1999). Ratios of prescribed *vs.* WHO-recommended daily doses of each antipsychotic drug were determined as the prescribed daily dose/daily defined dose (Tognoni, 1999; WHO, 2010). Ethical approval for the study was obtained by the Institutional Review Boards of all the participating centres.

Statistical analysis

Differences in sociodemographic and disease characteristics between countries were compared using χ^2 (for categorical data) or ANOVA (for continuous data). Participants were categorized into users ($n = 3671$) *vs.* non-users ($n = 3090$) of benzodiazepines and multiple logistic regression analysis was performed to assess the factors associated with benzodiazepine use by comparing the group of benzodiazepine users with non-users. Multiple linear regression with Bonferroni correction for multiple comparisons was performed to assess factors associated with diazepam equivalent doses in the group of participants who used

benzodiazepines ($n=3671$). Malaysia was chosen as the reference country in the multivariate analyses as it was representative of the average percentage use of benzodiazepines among the surveyed countries/regions. All analysis was performed using SPSS version 17 software (SPSS Inc., USA). Statistical significance was set at two tailed $p<0.05$.

Results

Sociodemographic and clinical features (*see Table 1*)

The mean age of the study population ($n=6761$) was 43.6 years (S.D. = 13.8) and the gender distribution was 58.0% ($n=3863$) male and 41.7% ($n=2779$) female. About two thirds (65.4%) of the population were diagnosed with schizophrenia for $\geqslant 10$ yr. An overall mean of 54.3% (weighted by subjects/country or region) of patients sampled received a benzodiazepine with antipsychotic drugs. The associated antipsychotic dose averaged 592 (S.D. = 534) mg/d CPZeq. In addition to use of benzodiazepines with antipsychotics, other adjunctive medication involved mood stabilizers (20.4%) and antidepressants (6.8%), in addition to prevalent use of antiparkinsonian agents (58.3%). Patients received an average of 1.32 (S.D. = 0.61) different benzodiazepines per person. Benzodiazepine dosing averaged 30.3 (S.D. = 32.9) mg/d DZPeq. The top five most commonly used benzodiazepines were lorazepam $\geqslant$ clonazepam $\geqslant$ flunitrazepam >> diazepam > estazolam. These findings are summarized in Table 1.

Correlates of use of benzodiazepine as adjunctive therapy

Taiwan and Japan had the highest rates of using adjunctive benzodiazepine treatment, and Thailand and China had the least (See Fig. 1). In the multivariate analysis, only four countries and regions (China, Hong Kong, India, Korea) remained significantly associated with lower benzodiazepine use.

There was a significant trend towards more use of benzodiazepines as adjunctive therapy in 2008 compared to 2004. Benzodiazepine use was greater among patients with fewer years of illness and with current delusions, hallucinations, disorganized speech and social or occupational dysfunction, and was associated with simultaneous treatment with mood stabilizers, antiparkinsonian and antidepressant drugs, as well as somewhat lower doses of antipsychotics. Among adverse effects, there was less hypersalivation and somewhat greater risk of QTc prolongation in the electrocardiogram. Table 2 summarizes the findings from the multivariate logistic regression analysis for use of benzodiazepines among Asian patients with schizophrenia.

Correlates of doses among benzodiazepines users

Patients in Thailand, Taiwan and China received the highest total daily DZPeq doses of benzodiazepines, and in Singapore and Korea, the lowest, with a significant trend towards lower doses in 2008 than in earlier years, even among the six countries sampled in all 3 years. By multivariate modelling, only Taiwan, China and India were associated with higher doses and Singapore with lower doses (Table 3). Being young, male, physically aggressive, receiving a mood stabilizer, and having electroconvulsive therapy (ECT) all were associated with higher doses of benzodiazepines. Lower doses of benzodiazepines also were associated with antipsychotic doses within WHO-recommended limits. Relatively high doses of benzodiazepines were associated with higher risks of dry mouth as well as amenorrhoea and galactorrhoea; these effects may have been due to an association of higher doses of benzodiazepines with higher doses of antipsychotics as well as exposure to other psychotropic drugs (polytherapy). Table 3 summarizes the findings from the multivariate linear regression analysis for dose of benzodiazepines among Asian patients with schizophrenia.

Discussion

A main finding from this study is that adjunctive benzodiazepine treatment of in-patients diagnosed with DSM-IV or ICD-10 schizophrenia has been prevalent in Asia over the past decade, averaging 54% of over 6700 schizophrenia patients sampled at 12 centres in nine countries. The most commonly used benzodiazepines were the potent agents lorazepam and clonazepam. Use of adjunctive benzodiazepines was associated with prominent positive psychotic symptoms (delusions and hallucinations), aggressive behaviour, and occupational or social dysfunction. Moreover, benzodiazepines also were associated with use of other drugs, notably mood stabilizers and antidepressants, in addition to common use of antiparkinsonian agents. The present findings thus add to the impression that use of benzodiazepines as an adjunct to antipsychotic drugs for the treatment of psychotic-disorder patients has been about as prevalent in Asia as it is in many other countries (Brunette *et al*. 2003*a*; Clark *et al*. 2004; Haw & Stubbs, 2007; Magliano *et al*. 2004; Mauri *et al*. 2005).

Recent guidelines for benzodiazepine use emphasize their indication for the treatment of anxiety or

Table 1. Characteristics of 6761 in-patients in Asian countries with schizophrenia in REAP study 2001–2008

Variable	PR China	Hong Kong	India	Japan	RO Korea	Singapore	Taiwan	Thailand	Malaysia	Means
Cases (*n*)	1524	308	181	1724	1138	491	1256	39	100	751
Men (*n*, %)	854 (56.0)	114 (58.4)	84 (46.4)	984 (57.1)	656 (57.6)	275 (56.0)	797 (63.5)	27 (69.2)	72 (72.0)	57.1%
Age ± S.D., yr	39.7 ± 13.7	42.8 ± 12.6	32.1 ± 10.8	52.3 ± 14.6	40.9 ± 10.8	44.5 ± 10.8	40.9 ± 11.1	37.7 ± 10.2	37.2 ± 10.7	43.6 ± 13.8 yr
BDZ use (*n*, %)	592 (38.9)	92 (29.9)	83 (45.9)	1190 (69.0)	522 ± (45.9)	247 (50.3)	872 (69.4)	13 (33.3)	59 (59.0)	54.3%
BDZ daily dose (DZPeq mg ± S.D.)	40.3 ± 42.6	20.2 ± 22.5	28.0 ± 26.7	28.5 ± 22.8	15.7 ± 24.3	10.6 ± 5.90	42.0 ± 40.6	42.3 ± 28.5	18.7 ± 14.1	30.3 ± 32.9 mg
BDZ (case ± S.D.)	1.07 ± 0.26	1.04 ± 0.21	1.04 ± 0.20	1.63 ± 0.81	1.06 ± 0.25	1.08 ± 0.26	1.23 ± 0.44	1.00 ± 0.00	1.00 ± 0.00	1.32 ± 0.61/case
APD daily dose (CPZeq mg ± S.D.)	476 ± 338	522 ± 528	482 ± 502	750 ± 712	685 ± 564	548 ± 482	493 ± 361	633 ± 332	374 ± 274	592 ± 533 mg
Years ill (%)										
< 1.0	10.7	1.40	23.9	3.13	3.60	2.85	1.60	6.70	10.0	5.30
1–5	21.6	12.0	32.2	6.67	11.8	9.55	10.1	20.0	19.0	12.9
5–10	14.7	16.4	22.2	8.60	23.4	23.1	18.2	20.0	32.0	16.4
> 10	53.0	70.2	21.7	81.6	61.2	64.5	70.1	53.3	39.0	65.4
BDZ selections (%)	Clonazepam (20.9)	Diazepam (11.7)	Lorazepam (30.9)	Flunitrazepam (37.6)	Lorazepam (21.2)	Diazepam (44.2)	Estazolam (26.9)	Clonazepam (25.6)	Lorazepam (49.0)	Lorazepam (12.3)
	Alprazolam (10.4)	Clonazepam (10.7)	Clonazepam (18.2)	Nitrazepam (15.6)	Diazepam (17.5)	Lorazepam (7.54)	Clonazepam (21.7)	Diazepam (5.13)	Clonazepam (7.00)	Clonazepam (12.0)
	Lorazepam (4.66)	Lorazepam (8.44)	Nitrazepam (2.21)	Brotizolam (10.8)	Clonazepam (4.22)	Lormetazepam (0.41)	Lorazepam (17.1)	Lorazepam (2.56)	Diazepam (3.00)	Flunitrazepam (11.4)
	Estazolam (2.56)	Flurazepam (0.32)	–	Lorazepam (7.02)	Alprazolam (3.43)	Clonazepam (0.20)	Flunitrazepam (7.88)	–	–	Diazepam (8.9)
	Diazepam (0.79)	–	–	Etizolam (5.63)	Flurazepam (1.14)	–	Flurazepam (5.81)	–	–	Estazolam (7.4)

APD, Antipsychotic drug; BDZ, benzodiazepine; CPZeq, chlorpromazine-equivalent; DZPeq, diazepam-equivalent.

Means are averages weighted by *n*/country or region. Ranking of five most prescribed benzodiazepines is by total percentages of use.

All differences between countries were highly significant ($p < 0.001$) by ANOVA or χ^2.

Table 2. Significant variables associated with use of benzodiazepines in Asian patients with schizophrenia from multivariate logistic analysis

Independent variable		Use of benzodiazepines	
		OR (95% CI)	*p* value
Region (reference is Malaysia)			
1.	PR China	0.49 (0.31–0.80)	0.004
2.	Hong Kong	0.55 (0.32–0.97)	0.040
3.	India	0.50 (0.29–0.87)	0.014
4.	RO Korea	0.59 (0.37–0.95)	0.028
Duration of illness (reference is duration >20 yr)			
5.	<3 month	1.65 (1.00–2.70)	0.049
Symptoms (reference is absence of variable)			
6.	Delusions	1.24 (1.10–1.40)	0.001
7.	Hallucinations	1.22 (1.08–1.37)	0.001
8.	Disorganized speech	1.17 (1.03–1.34)	0.015
9.	Social/Occupational dysfunction	1.16 (1.03–1.31)	0.016
Adverse effects (reference is absence of variable)			
10.	Hypersalivation	0.78 (0.64–0.95)	0.014
11.	QTc prolongation	1.83 (1.10–3.04)	0.019
Other treatments (reference is absence of variable)			
12.	Mood stabilizer	3.15 (2.78–3.58)	<0.001
13.	Antiparkisonian	1.79 (1.58–2.01)	<0.001
14.	Antidepressant	1.33 (1.07–1.67)	0.011
15.	Total chlorpromazine equivalent dosage (units in 100 mg)	0.98 (0.97–1.00)	0.010
Year of sampling			
16.	2001	0.85 (0.72–1.00)	0.043
17.	2004	0.79 (0.68–0.92)	0.002
18.	2008	Reference	

OR, Odds ratio; CI, confidence interval.

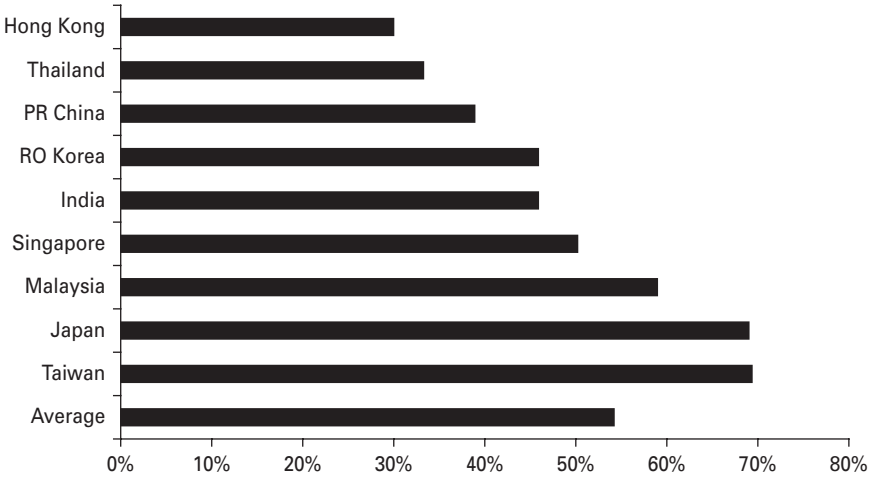

Fig. 1. Rate (%) of use of benzodiazepines adjunctively with antipsychotic drugs in the treatment of hospitalized patients diagnosed with schizophrenia in nine Asian countries, with a weighted (by *n*/country or region) average of 54.3%.

Table 3. Significant variables associated with dose of benzodiazepines in Asian patients with schizophrenia from multivariate linear regression analysis

Independent variable		Dose of benzodiazepines	
		Slope (β) (95% CI)	p value
Region (reference is Malaysia)			
1.	PR China	15.3 (6.53 to 24.0)	0.001
2.	India	10.4 (0.04 to 20.8)	0.049
3.	Singapore	−11.5 (−20.4 to −2.5)	0.012
4.	Taiwan	18.8 (10.4 to 27.2)	<0.001
Demographics			
5.	Age (yr)	−0.11 (−0.213 to −0.002)	0.046
6.	Male (Reference is female)	3.07 (1.00 to 5.12)	0.004
Duration of illness (reference is duration >20 yr)			
7.	6–12 month	−8.63 (−15.8 to −1.47)	0.018
8.	5–10 years	−3.91 (−7.34 to −0.48)	0.025
Symptoms (reference is absence of variable)			
9.	Physical aggression	4.00 (0.65 to 7.36)	0.019
Adverse effects (reference is absence of variable)			
10.	Dry mouth	3.07 (0.29 to 5.85)	0.031
11.	Amenorrhoea, galactorrhoea	8.55 (2.33 to 14.8)	0.007
Other treatments (reference is absence of variable)			
12.	Mood stabilizer	17.4 (15.3 to 19.5)	<0.001
13.	ECT	10.4 (4.35 to 16.4)	0.001
14.	Meets WHO APD dosing guidelines (reference is exceeding guidelines)	−5.48 (−9.59 to −1.36)	0.009
Year of sampling			
15.	2001	3.50 (0.69 to 6.25)	0.015
16.	2004	2.72 (0.07 to 5.36)	0.044
17.	2008	Reference	

CI, Confidence interval.
p value of statistical significance with Bonferroni correction.

insomnia, as well as for rapid sedation in acute phases of schizophrenia or other psychotic disorders or mania [APA, 1997; Ashton, 1994*a*; FDA (Taiwan), 2009; RACGP, 2000; RANZCP, 1999; Taylor *et al*. 2009]. Most guidelines do not include use of benzodiazepines for chronic psychotic disorders and generally encourage use of low doses for short periods of time, possibly as a reflection of concern for potential abuse and dependence of this class of central depressants (Taylor *et al*. 2009).

An interesting finding from this study is that there were distinct covariates associated with use of benzodiazepines and with their doses. The decision to use benzodiazepines as an adjunctive treatment was associated with positive psychotic symptoms (delusions, hallucinations, disorganized speech), aggressive behaviour, and relatively recent onset of psychotic illness, with sufficiently severe illness as to interfere with daily social and occupational functions. Benzodiazepine use also was associated with psychotropic polytherapy, especially involving mood stabilizers, and sometimes antidepressants and ECT, and higher doses were more common among aggressive, young, male patients. These associations, taken together, suggest that benzodiazepines were being used for additional sedative effects among particularly difficult to treat psychotic patients.

We propose that more specific guidelines for adjunctive use of benzodiazepines in schizophrenia be developed, including considerations that may be specific to particular Asian countries, which varied substantially in the use and doses of benzodiazepines. The multivariate analysis showed that use of benzodiazepines was lower in PR China and Hong Kong, possibly because of strict governmental regulation and accounting of benzodiazepines and public education

of the their potential adverse effects in that country. The lower use of benzodiazepines in PR China and Hong Kong could also be related to the relatively high use of clozapine (62% and 34%, respectively) in patients with schizophrenia (Chong *et al*. 2004) and long duration of illness (53% and 70%, respectively of patients ill for >10 yr) that decreases the need for additional sedation. The lower doses of benzodiazepines in Singapore could be related to the adoption of guidelines for recommended drug doses within the psychiatric hospital and their strict government enforcement. Similarly, governmental regulation could also account for the higher doses of benzodiazepines in Taiwan as in recent years there has been a national database to track benzodiazepine use and prevent 'doctor shopping' by patients and over-prescription of benzodiazepines. The prescription of any psychotropic medication is ultimately a result of a myriad of interactional factors including patient, prescriber and practice setting factors (Shinfuku & Tan, 2008; Tan *et al*. 2008; Xiang *et al*. 2007*b*), that change rapidly over time (An *et al*. 2010; Mojtabai & Olfson, 2010) and are unlikely to be attributable to any single aspect. Further studies are needed to elucidate prescriber attitudes towards the administration of specific medications including benzodiazepines and relevant pharmacoeconomic issues which can affect prescription patterns. Dosing of benzodiazepines in many countries, including in Asia, has often followed guidelines from the USA (APA, 1997) or Europe (Taylor *et al*. 2009), as specific guidelines for the use of psychotropic drugs for Asian populations remain rare [FDA (Taiwan), 2009]. Although the proportion of schizophrenia patients given adjunctive benzodiazepines in the present Asian samples is similar to that reported in Western countries (Clark *et al*. 2004; Magliano *et al*. 2004; Neutel, 2005), there is some indication that the metabolic clearance of benzodiazepines may be less rapid among Asians than Caucasians, with correspondingly higher peak plasma concentrations per dose (Bond, 1991; Chen, 2006). Nevertheless, it is likely that regional variance in the adjunctive use of benzodiazepines and their dosing reflects the influence of local prescribing practices in Asia (Bitter *et al*. 2003; Lai *et al*. 2009; Nakao *et al*. 2007; Xiang *et al*. 2007*a*) as in other parts of the world (Dunbar *et al*. 1989; Ekedahl *et al*. 1993; Hermos *et al*. 2005; Isacson, 1997; Neutel, 2005; Petitjean *et al*. 2007; Ruiz *et al*. 1993; Valenstein *et al*. 2004).

A major predictor for both increased use and higher doses of benzodiazepines is the simultaneous use of mood stabilizers along with antipsychotic drugs (polytherapy). There is little evidence that Asian patients diagnosed with schizophrenia have unusually prominent mood disturbances, although misdiagnosis of schizoaffective disorders, psychotic mood disorders, or bipolar disorder, or the presence of comorbid anxiety disorders, can occur in chronically psychotic patients (Averill *et al*. 2004; Chen *et al*. 1998; Salvatore *et al*. 2009; Smith *et al*. 1992; Subramaniam *et al*. 2007). Diagnoses of most psychotic disorders by either DSM-IV or ICD-10 criteria (Salvatore *et al*. 2009, in press) may not be stable over time. Such factors, as well as the irritability and aggressive behaviour found in association with adjunctive treatment in this study, may contribute to use of mood stabilizers as well as benzodiazepines with antipsychotic drugs (Bobes *et al*. 2009; Centorrino *et al*. 2010; Joyal *et al*. 2008; Magliano *et al*. 2004; Swanson *et al*. 2006). In general, it seems especially likely that benzodiazepines were used largely in a non-specific manner, as relatively well-tolerated central depressants and sedatives, to address unsatisfactory responses or lack of tolerance of standard antipsychotic drug therapy (Basan *et al*. 2004; Citrome, 2009).

The apparently increased risk of certain adverse effects associated with adjunctive benzodiazepine treatment is noteworthy, as detailed above. There were unexpected associations with higher risk of QTc prolongation, as well as more dry mouth, amenorrhoea and galactorrhoea, but less hypersalivation during benzodiazepine treatment, especially at higher doses. Many of these adverse effects are associated with antipsychotic drugs, and are less likely to be attributable to benzodiazepines (Taylor *et al*. 2009). There is some evidence that benzodiazepines use, especially with other drugs, can increase risk of slowed cardiac repolarization (QTc prolongation) (Baranchuk *et al*. 2008; Kato *et al*. 2009; Yamagiwa *et al*. 2010; Ziegenbein & Kropp, 2004) although this association is not unequivocal (Crockford, 2005; Goodnick *et al*. 2002). However the evidence that benzodiazepines can contribute to amenorrhoea and galactorrhoea (presumably via hyperprolactinaemia) is more robust (Hussain *et al*. 1972; Shioiri *et al*. 1996; Tkachenko *et al*. 1984), especially for higher doses of benzodiazepine (Weizman *et al*. 1984) and in combination with antipsychotics (Bondolfi *et al*. 1997; Kopecek *et al*. 2006). It seems prudent to warn patients of these uncommon side-effects of benzodiazepines, especially when they are given in high doses and with other psychotropic medicines for patients with schizophrenia.

There was a curious pattern of simultaneous increasing use and decreasing dose of benzodiazepines in second and third waves of the REAP study. Benzodiazepines are indicated for the treatment of

anxiety, insomnia and for rapid tranquillization in schizophrenia [APA, 1997; Ashton, 1994*a*; FDA (Taiwan), 2009; RACGP, 2000; RANZCP, 1999; Taylor *et al*. 2009]. Their use adjunctively with antipsychotic drugs to treat chronically psychotic patients without a great deal of backing from research or practice guidelines may have encouraged clinicians to be cautious in their dosing of benzodiazepines in such circumstances, but to select them to counter such symptoms as anxiety, insomnia, agitation, or aggression, as well as to limit doses of antipsychotics.

Study limitations

This study involved only 1-month samples from 3 yr of the past decade, small numbers of patients in some sites, lack of control of potential sources of heterogeneity across sites, and was limited to hospitalized patients diagnosed with schizophrenia by one of two standard international diagnostic systems, and to single assessments. Moreover, as a cross-sectional survey study, it was limited in its ability to explore associations among benzodiazepine use and dose with beneficial or adverse effects over time, and relationships to sociodemographic variables and both current and past clinical details. The interpretation of some statistically significant associations should therefore be made with caution, and conservatively applied with Bonferroni corrections.

Conclusion

Adjunctive benzodiazepine treatment of Asian patients diagnosed with schizophrenia was common over the past decade, and use of such treatment and doses varied substantially between countries. Adjunctive benzodiazepine treatment was more prevalent among patients with positive psychotic symptoms or aggressive behaviours, and was often encountered with use of polytherapy. These associations suggest that this and perhaps use of other adjuncts to antipsychotic drugs reflects the relative severity of psychotic illnesses that do not respond adequately to standard antipsychotic treatment alone, or when antipsychotics are not well tolerated, especially in high doses. Finally, we recommend that critical clinical guidelines be developed specifically for Asian countries to address sound practices in regard to use of benzodiazepines for psychotic disorders, as well as for other aspects of treatment with psychotropic drugs.

Acknowledgements

This study was supported by research funds from the Department of Research, Institute of Mental Health, Singapore (to K.H.Y., K.S.); International Centre for Medical Research, Japan (to N.S.); Bureau of National Health Insurance, Taiwan (to M.Y.C., S.Y.Y.); a grant from the Bruce J. Anderson Foundation and the McLean Private Donors Psychopharmacology Research Fund (to R.J.B.).

Statement of Interest

None.

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