

# 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.

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## Introduction

Benzodiazepines have hypnotic, anxiolytic, anticonvulsant, myorelaxant and amnesic properties that are useful for a wide range of conditions. Their main

clinical indications are for anxiety and sleep disorders (Ashton, 1994b), 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; Vormaa *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  $\chi^2$  (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  $\geq 10$  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  $\geq$  clonazepam  $\geq$  flunitrazepam  $\gg$  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.* 2003a; 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 ( <i>n</i> )	1524	308	181	1724	1138	491	1256	39	100	751
Men ( <i>n</i> , %)	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 $\pm$ s.d., yr	39.7 $\pm$ 13.7	42.8 $\pm$ 12.6	32.1 $\pm$ 10.8	52.3 $\pm$ 14.6	40.9 $\pm$ 10.8	44.5 $\pm$ 10.8	40.9 $\pm$ 11.1	37.7 $\pm$ 10.2	37.2 $\pm$ 10.7	43.6 $\pm$ 13.8 yr
BDZ use ( <i>n</i> , %)	592 (38.9)	92 (29.9)	83 (45.9)	1190 (69.0)	522 $\pm$ (45.9)	247 (50.3)	872 (69.4)	13 (33.3)	59 (59.0)	54.3 %
BDZ daily dose (DZPeq mg $\pm$ s.d.)	40.3 $\pm$ 42.6	20.2 $\pm$ 22.5	28.0 $\pm$ 26.7	28.5 $\pm$ 22.8	15.7 $\pm$ 24.3	10.6 $\pm$ 5.90	42.0 $\pm$ 40.6	42.3 $\pm$ 28.5	18.7 $\pm$ 14.1	30.3 $\pm$ 32.9 mg
BDZ (case $\pm$ s.d.)	1.07 $\pm$ 0.26	1.04 $\pm$ 0.21	1.04 $\pm$ 0.20	1.63 $\pm$ 0.81	1.06 $\pm$ 0.25	1.08 $\pm$ 0.26	1.23 $\pm$ 0.44	1.00 $\pm$ 0.00	1.00 $\pm$ 0.00	1.32 $\pm$ 0.61/case
APD daily dose (CPZeq mg $\pm$ s.d.)	476 $\pm$ 338	522 $\pm$ 528	482 $\pm$ 502	750 $\pm$ 712	685 $\pm$ 564	548 $\pm$ 482	493 $\pm$ 361	633 $\pm$ 332	374 $\pm$ 274	592 $\pm$ 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.

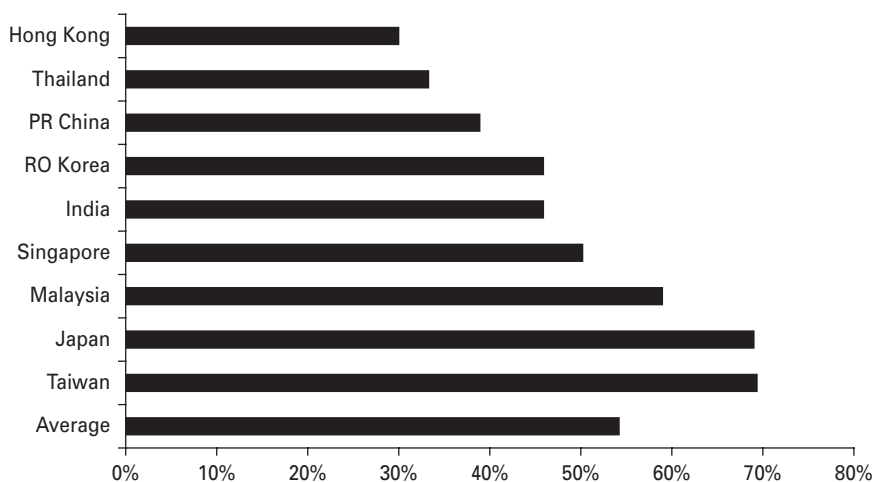
Means are averages weighted by *n*/country or region. Ranking of five most prescribed benzodiazepines is by total percentages of use.

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

**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)	<i>p</i> value
<b>Region (reference is Malaysia)</b>		
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
<b>Duration of illness (reference is duration &gt; 20 yr)</b>		
5. <3 month	1.65 (1.00–2.70)	0.049
<b>Symptoms (reference is absence of variable)</b>		
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
<b>Adverse effects (reference is absence of variable)</b>		
10. Hypersalivation	0.78 (0.64–0.95)	0.014
11. QTc prolongation	1.83 (1.10–3.04)	0.019
<b>Other treatments (reference is absence of variable)</b>		
12. Mood stabilizer	3.15 (2.78–3.58)	<0.001
13. Antiparkinsonian	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
<b>Year of sampling</b>		
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 ( $\beta$ ) (95% CI)	<i>p</i> value
<b>Region (reference is Malaysia)</b>		
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
<b>Demographics</b>		
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
<b>Duration of illness (reference is duration &gt; 20 yr)</b>		
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
<b>Symptoms (reference is absence of variable)</b>		
9. Physical aggression	4.00 (0.65 to 7.36)	0.019
<b>Adverse effects (reference is absence of variable)</b>		
10. Dry mouth	3.07 (0.29 to 5.85)	0.031
11. Amenorrhoea, galactorrhoea	8.55 (2.33 to 14.8)	0.007
<b>Other treatments (reference is absence of variable)</b>		
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
<b>Year of sampling</b>		
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, 1994a; 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.* 2007b), 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.* 2007a) 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, 1994a; 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.

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### Statement of Interest

None.

### References

- An FR, Xiang YT, Wang CY, Zhang GP, *et al.* (2010). Change of psychotropic drug prescription for schizophrenia in a psychiatric institution in Beijing, China between 1999 and 2008. *International Journal of Clinical Pharmacology and Therapeutics* **48**, 270–274.
- APA (1997). *Practice Guidelines for the Treatment of Patients with Schizophrenia*. Washington, DC: American Psychiatric Press.
- Ashton H (1994a). Guidelines for the rational use of benzodiazepines. When and what to use. *Drugs* **48**, 25–40.
- Ashton H (1994b). The treatment of benzodiazepine dependence. *Addiction* **89**, 1535–1541.
- Ashton H (2005). The diagnosis and management of benzodiazepine dependence. *Current Opinion in Psychiatry* **18**, 249–255.
- Averill PM, Reas DL, Shack A, Shah NN, *et al.* (2004). Is schizoaffective disorder a stable diagnostic category: a retrospective examination. *Psychiatry Quarterly* **75**, 215–227.
- Baranchuk A, Simpson CS, Methot M, Gibson K, *et al.* (2008). Corrected QT interval prolongation after an overdose of escitalopram, morphine, oxycodone, zopiclone and benzodiazepines. *Canadian Journal of Cardiology* **24**, e38–e40.
- Barnas C, Whitworth AB, Fleischhacker WW (1993). Are patterns of benzodiazepine use predictable? A follow-up study of benzodiazepine users. *Psychopharmacology (Berlin)* **111**, 301–305.
- Basan A, Kissling W, Leucht S (2004). Valproate as an adjunct to antipsychotics for schizophrenia: a systematic review of randomized trials. *Schizophrenia Research* **70**, 33–37.
- Bhoopathi PS, Soares-Weiser K (2006). Benzodiazepines for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews*. Issue 3. Art. No. CD000205.
- Bitter I, Chou JC, Ungvari GS, Tang WK, *et al.* (2003). Prescribing for inpatients with schizophrenia: an international multi-center comparative study. *Pharmacopsychiatry* **36**, 143–149.
- Bobes J, Fillat O, Arango C (2009). Violence among schizophrenia out-patients compliant with medication: prevalence and associated factors. *Acta Psychiatrica Scandinavica* **119**, 218–225.



- Bond WS** (1991). Ethnicity and psychotropic drugs. *Clinical Pharmacology* **10**, 467–470.
- Bondolfi G, Rubin C, Bryois C, Eap CB** (1997). Galactorrhoea induced by a pharmacodynamic interaction between citalopram, alprazolam and tramadol: a case report. *Therapie* **52**, 76–77.
- Brunette M, Noordsy D, Xie H, Drake R** (2003a). Benzodiazepine use and abuse among patients with severe mental illness and co-occurring substance use disorders. *Psychiatric Services* **54**, 1395.
- Brunette MF, Noordsy DL, Xie H, Drake RE** (2003b). Benzodiazepine use and abuse among patients with severe mental illness and co-occurring substance use disorders. *Psychiatric Services* **54**, 1395–1401.
- Centorrino F, Ventriglio A, Vincenti A, Talamo A, et al.** (2010). Changes in medication practices for hospitalized psychiatric patients: 2009 vs. 2004. *Human Psychopharmacology* **25**, 179–186.
- Chen ML** (2006). Ethnic or racial differences revisited: impact of dosage regimen and dosage form on pharmacokinetics and pharmacodynamics. *Clinical Pharmacokinetics* **45**, 957–964.
- Chen YR, Swann AC, Johnson BA** (1998). Stability of diagnosis in bipolar disorder. *Journal of Nervous and Mental Disorders* **186**, 17–23.
- Chong MY, Tan CH, Fujii S, Yang SY, et al.** (2004). Antipsychotic drug prescription for schizophrenia in East Asia: rationale for change. *Psychiatry and Clinical Neurosciences* **58**, 61–67.
- Chouinard G** (2004). Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. *Journal of Clinical Psychiatry* **65** (Suppl. 5), 7–12.
- Citrome L** (2009). Adjunctive lithium and anticonvulsants for the treatment of schizophrenia: what is the evidence? *Expert Review of Neurotherapies* **9**, 55–71.
- Clark RE, Xie H, Brunette MF** (2004). Benzodiazepine prescription practices and substance abuse in persons with severe mental illness. *Journal of Clinical Psychiatry* **65**, 151–155.
- Crockford D** (2005). Re: Lorazepam-induced prolongation of the QT interval in a patient with schizoaffective disorder and complete AV block. *Canadian Journal of Psychiatry* **50**, 184–185; author reply 185.
- Dunbar GC, Perera MH, Jenner FA** (1989). Patterns of benzodiazepine use in Great Britain as measured by a general population survey. *British Journal of Psychiatry* **155**, 836–841.
- Ekedahl A, Lidbeck J, Lithman T, Noreen D, et al.** (1993). Benzodiazepine prescribing patterns in a high-prescribing Scandinavian community. *European Journal of Clinical Pharmacology* **44**, 141–146.
- Fang SY, Chen CY, Chang IS, Wu EC, et al.** (2009). Predictors of the incidence and discontinuation of long-term use of benzodiazepines: a population-based study. *Drug and Alcohol Dependence* **104**, 140–146.
- FDA (Taiwan)** (2009). Guidelines for benzodiazepine usage in sedation and hypnosis. Food and Drug Administration, Taiwan.
- Gaillard R, Ouanas A, Spadone C, Llorca PM, et al.** (2006). Benzodiazepines and schizophrenia, a review of the literature. *Encephale* **32**, 1003–1010.
- Gardner DM, Murphy AL, O'Donnell H, Centorrino F, et al.** (2010). International consensus study of antipsychotic dosing. *American Journal of Psychiatry* **167**, 686–693.
- Gillies D, Beck A, McCloud A, Rathbone J** (2005). Benzodiazepines alone or in combination with antipsychotic drugs for acute psychosis. *Cochrane Database of Systematic Reviews*. Issue 19(4). Art. No. CD003079.
- Goodnick PJ, Jerry J, Parra F** (2002). Psychotropic drugs and the ECG: focus on the QTc interval. *Expert Opinion in Pharmacotherapies* **3**, 479–498.
- Gorgels WJ, Oude Voshaar RC, Mol AJ, van de Lisdonk EH, et al.** (2006). Predictors of discontinuation of benzodiazepine prescription after sending a letter to long-term benzodiazepine users in family practice. *Family Practice* **23**, 65–72.
- Haw C, Stubbs J** (2007). Benzodiazepines – a necessary evil? A survey of prescribing at a specialist UK psychiatric hospital. *Journal of Psychopharmacology* **21**, 645–649.
- Hermos JA, Young MM, Lawler EV, Stedman MR, et al.** (2005). Characterizations of long-term anxiolytic benzodiazepine prescriptions in veteran patients. *Journal of Clinical Psychopharmacology* **25**, 600–604.
- Hussain MZ, Harinath M, Murphy J** (1972). Tranquillizer-induced galactorrhea. *Canadian Medical Association Journal* **106**, 1107–1108.
- Inagaki A, Inada T, Fujii Y** (1999). *Equivalent Dose of Psychotropics*. Tokyo: Seiwa Shoten.
- Isacson D** (1997). Long-term benzodiazepine use: factors of importance and the development of individual use patterns over time – a 13-year follow-up in a Swedish community. *Social Sciences and Medicine* **44**, 1871–1880.
- Joyal CC, Gendron C, Cote G** (2008). Nature and frequency of aggressive behaviours among long-term inpatients with schizophrenia: a 6-month report using the modified overt aggression scale. *Canadian Journal of Psychiatry* **53**, 478–481.
- Kane JM, Aguglia E, Altamura AC, Ayuso Gutierrez JL, et al.** (1998). Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology Consensus Conference in Siena, Italy. *European Neuropsychopharmacology* **8**, 55–66.
- Kato R, Watanabe R, Miki H, Ijiri Y, et al.** (2009). Does the sedative agent, JM-1232(–) cause QT prolongation with subsequent torsades de pointes? *Life Sciences* **85**, 737–741.
- Kopecek M, Bares M, Horacek J, Mohr P** (2006). Low-dose risperidone augmentation of antidepressants or anxiolytics is associated with hyperprolactinemia. *Neuroendocrinology Letters* **27**, 803–806.
- Lai HY, Hwang SJ, Chen YC, Chen TJ, et al.** (2009). Prevalence of the prescribing of potentially inappropriate medications at ambulatory care visits by elderly patients covered by the Taiwanese national health insurance program. *Clinical Therapeutics* **31**, 1859–1870.
- Lewis DA, Cho RY, Carter CS, Eklund K, et al.** (2008). Subunit-selective modulation of GABA type A receptor

- neurotransmission and cognition in schizophrenia. *American Journal of Psychiatry* **165**, 1585–1593.
- Magliano L, Fiorillo A, Guarneri M, Marasco C, et al.** (2004). Prescription of psychotropic drugs to patients with schizophrenia: an Italian national survey. *European Journal of Clinical Pharmacology* **60**, 513–522.
- Mauri MC, Regispani F, Beraldo S, Volonteri LS, et al.** (2005). Patterns of clinical use of antipsychotics in hospitalized psychiatric patients. *Progress in Neuropsychopharmacology and Biological Psychiatry* **29**, 957–963.
- Mojtabai R, Olfson M** (2010). National trends in psychotropic medication polypharmacy in office-based psychiatry. *Archives of General Psychiatry* **67**, 26–36.
- Nakao M, Takeuchi T, Yano E** (2007). Prescription of benzodiazepines and antidepressants to outpatients attending a Japanese university hospital. *International Journal of Clinical Pharmacological Therapies* **45**, 30–35.
- Neutel CI** (2005). The epidemiology of long-term benzodiazepine use. *International Review of Psychiatry* **17**, 189–197.
- Neutel CI, Walop W, Patten SB** (2003). Can continuing benzodiazepine use be predicted? *Canadian Journal of Clinical Pharmacology* **10**, 202–206.
- Nomura K, Nakao M, Sato M, Yano E** (2006). Regular prescriptions for benzodiazepines: a cross-sectional study of outpatients at a university hospital. *Internal Medicine* **45**, 1279–1283.
- Petitjean S, Ladewig D, Meier CR, Amrein R, et al.** (2007). Benzodiazepine prescribing to the Swiss adult population: results from a national survey of community pharmacies. *International Clinical Psychopharmacology* **22**, 292–298.
- RACGP** (2000). Guidelines: Benzodiazepines. The Royal Australian College of General Practitioners.
- RANZCP** (1999). College guidelines for use of benzodiazepines. Practice Guideline no. 5. Psychotropic Drugs Committee, The Royal Australian and New Zealand College of Psychiatrists.
- Ruiz I, Offermanns J, Lancot KL, Busto U** (1993). Comparative study on benzodiazepine use in Canada and Chile. *Journal of Clinical Pharmacology* **33**, 124–129.
- Salvatore P, Baldessarini RJ, Tohen M, Khalsa HM, et al.** (2009). McLean-Harvard International First-Episode Project: two-year stability of DSM-IV diagnoses in 500 first-episode psychotic disorder patients. *Journal of Clinical Psychiatry* **70**, 458–466.
- Salvatore P, Baldessarini RJ, Tohen M, Khalsa HM, et al.** (in press). McLean-Harvard International First-Episode Project: two-year stability of ICD-10 diagnosis in 500 first-episode psychotic disorder patients. *Journal of Clinical Psychiatry*.
- Shinfuku N, Tan CH** (2008). Pharmacotherapy for schizophrenic inpatients in East Asia – changes and challenges. *International Review of Psychiatry* **20**, 460–468.
- Shioiri T, Kita N, Takahashi S** (1996). Two cases of alprazolam-induced hyperprolactinemia in patients with panic disorder. *International Clinical Psychopharmacology* **11**, 149–152.
- Sim K, Su A, Leong JY, Yip K, et al.** (2004). High dose antipsychotic use in schizophrenia: findings of the REAP (research on east Asia psychotropic prescriptions) study. *Pharmacopsychiatry* **37**, 175–179.
- Simon GE, VonKorff M, Barlow W, Pabiniak C, et al.** (1996). Predictors of chronic benzodiazepine use in a health maintenance organization sample. *Journal of Clinical Epidemiology* **49**, 1067–1073.
- Smith GN, MacEwan GW, Ancill RJ, Honer WG, et al.** (1992). Diagnostic confusion in treatment-refractory psychotic patients. *Journal of Clinical Psychiatry* **53**, 197–200.
- Subramaniam M, Pek E, Verma S, Chan YH, et al.** (2007). Diagnostic stability 2 years after treatment initiation in the early psychosis intervention programme in Singapore. *Australia and New Zealand Journal of Psychiatry* **41**, 495–500.
- Swanson JW, Swartz MS, Van Dorn RA, Elbogen EB, et al.** (2006). A national study of violent behavior in persons with schizophrenia. *Archives of General Psychiatry* **63**, 490–499.
- Tan CH, Shinfuku N, Sim K** (2008). Psychotropic prescription practices in east Asia: looking back and peering ahead. *Current Opinion in Psychiatry* **21**, 645–650.
- Taylor D, Paton C, Kapur S** (2009). *The Maudsley Prescribing Guidelines 10th Edition*. Informa Healthcare.
- Tkachenko NM, Bogdanova EA, Moroz MG, Afonina LI** (1984). Use of tranquilizers in the diagnosis of causes of secondary amenorrhea in girls. *Akushertvo i ginekologiya* **11**, 69–71.
- Tognoni G** (1999). Pharmacoepidemiology of psychotropic drugs in patients with severe mental disorders in Italy. *European Journal of Clinical Pharmacology* **55**, 685–690.
- Valenstein M, Taylor KK, Austin K, Kales HC, et al.** (2004). Benzodiazepine use among depressed patients treated in mental health settings. *American Journal of Psychiatry* **161**, 654–661.
- van Hulten R, Teeuw KB, Bakker A, Leufkens HG** (2003). Initial 3-month usage characteristics predict long-term use of benzodiazepines: an 8-year follow-up. *European Journal of Clinical Pharmacology* **58**, 689–694.
- Volz A, Khorsand V, Gillies D, Leucht S** (2007). Benzodiazepines for schizophrenia. *Cochrane Database of Systematic Reviews*. Issue 24(1). Art No. CD006391.
- Vorma H, Naukkarinen HH, Sarna SJ, Kuoppasalmi KI** (2005). Predictors of benzodiazepine discontinuation in subjects manifesting complicated dependence. *Substance Use and Misuse* **40**, 499–510.
- Voshaar RO, Gorgels W, Mol A, van Balkom A, et al.** (2003). Predictors of relapse after discontinuation of long-term benzodiazepine use by minimal intervention: a 2-year follow-up study. *Family Practice* **20**, 370–372.
- Weizman A, Tyano S, Wijsenbeek H, Ben David M** (1984). High dose diazepam treatment and its effect on prolactin secretion in adolescent schizophrenic patients. *Psychopharmacology (Berlin)* **82**, 382–385.

- Wheeler A, Kairuz T, Sheridan J, McPhee E** (2007). Sedative-hypnotic treatment in an acute psychiatric setting; comparison with best practice guidance. *Pharmacology World Sciences* **29**, 603–610.
- WHO** (2010). ATC/DDD Index 2010. World Health Organization.
- Woods SW** (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *Journal of Clinical Psychiatry* **64**, 663–667.
- Xiang YT, Weng YZ, Leung CM, Tang WK, et al.** (2007a). Clinical and social determinants of long-term use of benzodiazepines and its impact on quality of life of Chinese schizophrenia patients. *Pharmacopsychiatry* **40**, 269–274.
- Xiang YT, Weng YZ, Leung CM, Tang WK, et al.** (2007b). Clinical and social determinants of psychotropic drug prescription for schizophrenia outpatients in China. *Progress in Neuropsychopharmacology and Biological Psychiatry* **31**, 756–760.
- Yamagiwa T, Amino M, Morita S, Yamamoto R, et al.** (2010). A case of torsades de pointes induced by severe QT prolongation after an overdose of eperisone and triazolam in a patient receiving nifedipine. *Clinical Toxicology (Philadelphia)* **48**, 149–152.
- Ziegenbein M, Kropp S** (2004). Lorazepam-induced prolongation of the QT interval in a patient with schizoaffective disorder and complete AV block. *Canadian Journal of Psychiatry* **49**, 414.