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Original article

Psychotropic drug-prescribing correlates of disorganized speech in Asians with schizophrenia: The REAP-AP study

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ABSTRACT

Background: Although disorganized speech is seen as one of the nuclear features of schizophrenia, there have been few reports of disorganized speech-associated psychotropic drug-prescribing patterns in large samples of schizophrenia patients.
Objective: We aimed to examine the prevalence of disorganized speech and its correlates in terms of psychotropic drug prescribing, using the data from the Research on Asian Psychotropic Patterns for Antipsychotics (REAP-AP) study.
Method: A total of 3744 patients with the ICD-10 diagnosis of schizophrenia were enrolled from 71 survey centers in 15 Asian countries/areas. An essential criterion of disorganized speech was that it was "severe enough to impair substantially effective communication" as defined in the DSM-5. A binary logistic model was fitted to identify the psychotropic drug-prescribing correlates of disorganized speech.
Results: After adjusting for the potential effects of confounding variables, the binary logistic regression model showed that the presence of disorganized speech was directly associated with adjunctive use of

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mood stabilizers ($P < 0.001$) and cumulative diazepam equivalent dose ($P < 0.0001$), and inversely associated with adjunctive use of anti-Parkinson drugs ($P < 0.0001$).
Conclusion: The association between disorganized speech and adjunctive use of mood stabilizers could perhaps be understood in the context of a relationship with impulsiveness/aggressiveness, or in terms of deconstructing the Kraepelinian dualism.

1. Introduction

Since formal thought disorder (FTD) is seen as one of the nuclear features of schizophrenia, and disorganized speech is conceptualized as the linguistic equivalent of FTD (Andreasen, 1988; Chen et al., 1996; Bowie et al., 2005; American Psychiatric Association, 2013), disorganized speech has been consistently used as one of the diagnostic criteria for psychosis. In terms of the prevalence and severity of disordered speech, it has been proposed that the gradient from normal to psychotic is exponential rather than linear (Roche et al., 2014). In the early era of modern psychiatry, Griesinger (1861), Kraepelin (1899) and Bleuler (1908) proposed "Inkohärenz" (incoherence: externally similar sound in word productions), "Zerfahrenheit" (derailment: loss of connection between idea chains), and "associative loosening", respectively, as the prototypical concepts of FTD. Thus, 'incoherence' or 'marked loosening of associations' was among the diagnostic criteria for schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) (American Psychiatric Association, 1980). Following criticism by Parnas (2012), the contemporary emphasis on empirical approaches in psychiatric nosology has led to the definition of schizophrenia being narrowed to a 'predominantly chronic delusional-hallucinatory syndrome.' Also, there has been a trend for the diagnostic construct of schizophrenia in the DSM to gradually ignore the phenomenological concepts of schizophrenia derived from European psychiatry (Andreasen, 2007). Consistent with this trend towards a neo-Kraepelinian approach to describing the FTD, 'incoherence' or 'loosening of association' in DSM-III was changed to 'disorganized speech' in both DSM-IV (American Psychiatric Association, 1994) and DSM-5 (American Psychiatric Association, 2013). Moreover, derailment or looseness of association, tangentiality and incoherence or word salads were noted as examples of disorganized speech in DSM-IV and DSM-5.

From the viewpoint of the evolution of psychiatry, disorganized speech has been more useful than Schneider's first rank symptoms for diagnosing schizophrenia (Cecherini-Nelli et al., 2007). Crow (2008) has proposed that language and psychosis share common biological underpinnings associated with a "big bang"-like genetic mechanism involving both the X and Y chromosomes, and that Schneider's first rank symptoms can be considered the extreme forms of language disorder. In addition, Crow (2010) has hypothesized that an extreme form of difficulty in distinguishing between speech production and speech perception in the sapiens-specific language circuit may be a central symptom of schizophrenia. Several studies have described the neural correlates of FTD and disorganized speech in patients with schizophrenia. An inverse association between FTD severity and the volume of the left superior temporal gyrus along with adjacent structures has been reported (Horn et al., 2009, 2010). In addition, increased fractional anisotropy in the left hemisphere pathways of the language system has been noted in schizophrenia-spectrum patients with negative FTD but not in those without negative FTD. Hence, it has been speculated that vulnerability to negative FTD may be accompanied by alterations in the relevant fiber tracts (Viher et al., 2016). Moreover, in a genome-wide association meta-analysis of 853 patients with FTD and 2694 controls *PKNOX2, MYH13, PHF2* and *GPC6* were identified as loci with potential roles in the pathogenesis of FTD and schizophrenia (Wang et al., 2012).

FTD has been proposed as a potential indicator of greater severity and poorer social functioning in patients with psychotic disorders (Roche et al., 2014). More specifically, a significant association between greater severity of FTD and current hospitalization was found in several studies (Lenz et al., 1986; Brier and Berg, 1999; Andreou et al., 2008). In addition, one study showed that verbal underproductivity predicted observer-rated social skills in patients with schizophrenia, and verbal dysconnectivity predicted social behaviors in role play situations (Bowie et al., 2011). Thus, we can speculate that FTD may be a measure of severity of schizophrenia.

To the best of our knowledge, effective pharmacological treatments for FTD and disorganized speech have not been formally established. One mirror-image cohort design study reported that initial therapy with olanzapine was associated with favorable responses, particularly in the patients with thought disorders (Del Paqqio et al., 2002). Moreover, there have been few reports of psychotropic drug-prescribing patterns and adverse events associated with disorganized speech in large samples of schizophrenia patients. Using the data from the Research on Asian Psychotropic Patterns for Antipsychotics (REAP-AP) study (Park et al., 2018), which is the largest international collaborative project in the realm of psychiatry in Asia, our study aimed to investigate psychotropic drug-prescribing correlates of disorganized speech in schizophrenia patients, across Asian countries and areas.

2. Methodology

2.1. Study overview and subjects

As stated elsewhere study (Sim et al., 2004, 2009, 2011; Tor et al., 2011), the REAP-AP study aimed to survey psychotropic prescription patterns and their clinical correlates, and explore ways to improve prescription patterns in schizophrenia patients in Asian countries/areas. During the study period of March to June 2016, the 4th REAP-AP study enrolled 3744 consecutive patients with schizophrenia from 71 survey centers in 15 Asian countries and areas including Bangladesh, China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Myanmar, Pakistan, Singapore, Sri Lanka, Taiwan, Thailand and Viet Nam. Using the classification of the United Nations (UN), 15 Asian countries/areas were classified into three groups as follows: Eastern Asia (China, Hong Kong, Japan, Korea and Taiwan), Southern Asia (Bangladesh, India, Pakistan and Sri Lanka) and Southeastern Asia (Indonesia, Malaysia, Myanmar, Singapore, Thailand and Viet Nam) (Park et al., 2018). Using the World Bank list of economies, 15 Asian countries/areas were classified into three groups based on income as follows: high income (Hong Kong, Japan, Korea, Singapore and Taiwan), upper middle income (China, Malaysia, and Thailand) and lower middle income (Bangladesh, India, Indonesia, Myanmar, Pakistan, Sri Lanka and Vietnam) (Park et al., 2016b).

Informed consent was given by all study subjects prior to inclusion in the study, and the study protocol and informed consent

forms were approved by the institutional review boards of Tapei City Hospital, Tapei, Taiwan (receipt number: TCHIRB-10412128-E) and the other hospitals participating in the survey. Prior to initiation of the study a conference meeting was held to improve the consistency of data collection and diagnosis of schizophrenia among the survey centers. Trained study coordinators supervised by clinical psychiatrists at the survey centers collected demographic data and, clinical and treatment related details as per protocol. Data on the study subjects were collected using the predefined questionnaires as per protocol and stored on the REAP-AP study website.

In order to study patterns of prescribing in real clinical practice, based on the available resources of the participating countries/areas, a short and a long form were used. The inclusion criteria were (i) diagnosis of schizophrenia, based on DSM-5 (American Psychiatric Association, 2013), by clinical psychiatrists at the survey centers and (ii) medication with antipsychotics and/or other psychotropic drugs. The exclusion criteria were (i) presence of severe physical disease and (ii) inability to read or write.

2.2. Disorganized speech and other psychopathological characteristics

Following DSM-5 (American Psychiatric Association, 2013), disorganized speech was defined as "switching from one topic to another in terms of an individual's speech," "answers obliquely related or completely unrelated to questions," or "nearly incomprehensible speech, or speech resembling receptive aphasia in its linguistic disorganization" with the essential condition of being "severe enough to impair substantially effective communication." In addition in order to define the presence or absence of disorganized speech, additional usage was permitted, using the Scale for the Assessment of Thought, Language and Communication (TLC scale) (Andreasen, 1988) and Clinical Language Disorder Rating Scale (CLANG) (Chen et al., 1996). In addition, according to DSM-5 (American Psychiatric Association, 2013), delusions were defined as "beliefs not amenable to change in the light of conflicting evidence," hallucinations were defined as "perception-like experiences that occur without external stimulus," disorganized and catatonic behavior was defined as behavior "from childlike silliness to unpredictable agitation" and "marked decrease in reactivity to the environment," respectively. Negative symptoms were defined as "reductions in the expression of emotions in the face, eye contact, intonation of speech, and movements of the hand, head, and face that normally give an emotional emphasis to speech," "decrease in motivated self-initiated purposeful activities," "decreased ability to experience pleasure from positive stimuli, or degradation in the recollection of pleasure previously experienced," and "apparent lack of interest in social interactions." The existence or non-existence of disorganized speech and each of the other psychopathological characteristics was defined in accordance with the definitions of the corresponding domains in Clinician-Rated Dimensions of Psychosis Symptom Severity (Barch et al., 2013; Heckers et al., 2013). Aggression was defined as "hostile, injurious, or destructive behavior" (Siever, 2008), according to the significance of this behavior to patients in the month prior to the study enrollment.

2.3. Classification of psychotropic drugs and adverse events

In the Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization, 2016), psychotropic drugs are classified in the following categories: antipsychotics (N05A), mood stabilizers (antiepileptics and lithium; N03A and N05AN), antidepressants (N06A), anxiolytics and hypnotics (N05B and N05C) and antiparkinson drugs (N04). In the classification of Tandon et al., (2010), antipsychotics are dichotomously classified into first- and second-generation medications. High-dose antipsychotic medication was defined as a cumulative dose of $\geq$1000 mg/-day chlorpromazine equivalent or a ratio of prescribed daily dose (PDD) to defined daily dose (DDD) $\geq$ 1.5 (Sim et al., 2004; Tihonen et al., 2016). In addition, the cumulative daily doses of antipsychotics, antidepressants, anxiolytics, sedatives and hypnotics and antiparkinson drugs were calculated as chlorpromazine, imipramine, diazepam and levodopa equivalents, respectively.

The following adverse effects of antipsychotics and other psychotropic drugs were evaluated from the subjects' self-reports and psychiatrists' interviews/observations: movement disturbance (rigidity, akinesia, tremor, akathisia and dystonia), autonomic disturbance (constipation, excessive salivation, dry mouth, postural hypotension, urinating difficulty and blurred vision), endocrine disturbance (sexual dysfunction and galactorrhea or amenorrhea), metabolic disturbance (impaired glucose tolerance, hypercholesterolemia and weigh gain) and other (QTc prolongation and oversedation).

2.4. Statistical analyses

The baseline and clinical characteristics of schizophrenia patients with and without disorganized speech were compared by χ^2 tests for discrete variables and independent *t*-tests for continuous variables. In addition, psychotropic drug prescribing patterns and adverse events in the two groups were compared by binary logistic analysis for discrete variables and analysis of covariance (ANCOVA) after adjusting the effects of confounding variables, a binary logistic regression model was fitted to identify psychotropic drug-prescribing correlates of disorganized speech with adjusting for the effects of confounding variables. Standard methods that control for interaction and multi-collinearity were used to select and validate the final model. Using Bonferroni correction, statistical significance was set at $P < 0.00102$ (0.05/49; two-tailed) for all tests, in an effort to reduce family-wise errors due to multiple comparisons. All statistical calculations were carried out with the statistics software SPSS 21 for Windows (SPSS Inc., Chicago, Il, USA).

3. Results

3.1. Baseline and psychopathological characteristics of schizophrenia patients with and without disorganized speech

As shown in Table 1, the overall prevalence of disorganized speech was 29.7% (n = 1110) and the prevalence rates among Eastern Asians, Southeastern Asians and Southern Asians were 21.4%, 29.0% and 39.1%, respectively ($\chi^2 = 73.617$, $P < 0.0001$). The prevalence among high income, upper middle income and lower middle-income groups was 20.0%, 12.3% and 35.7%, respectively ($\chi^2 = 138.878$, $P < 0.0001$). More of the subjects with disorganized speech than of those without disorganized speech were inpatients ($\chi^2 = 329.461$, $P < 0.0001$) and suffered from delusions ($\chi^2 = 178.361$, $P < 0.0001$), hallucinations ($\chi^2 = 132.527$, $P < 0.0001$), disorganized behaviors ($\chi^2 = 330.289$, $P < 0.0001$), social or occupational dysfunction ($\chi^2 = 219.382$, $P < 0.0001$), verbal aggression ($\chi^2 = 259.333$, $P < 0.0001$), physical aggression ($\chi^2 = 302.456$, $P < 0.0001$) and significant affective symptoms ($\chi^2 = 11.321$, $P = 0.001$). Although the difference was not statistically significant, those with disorganized speech had a tendency to be younger ($t = -2.477$, $P = 0.013$) and present with higher negative symptoms ($\chi^2 = 8.958$, $P = 0.003$) than those without disorganized speech. There were no significant differences in gender ($\chi^2 = 0.567$, $P = 0.451$) and duration of illness ($\chi^2 = 9.214$, $P = 0.162$) between the two groups.

Table 1
Baseline and psychopathological characteristics of schizophrenia patients with and without disorganized speech.

	Total sample (n = 3744)	Disorganized speech		Statistical coefficient	*P*-value
		Present (n = 1110)	Absent (n = 2634)		
Age, mean (SD) years	39.5 (13.1)	38.6 (12.7)	39.9 (13.3)	t = −2.653	0.008
Men, n (%)	2199 (58.7)	641 (57.7)	1558 (59.1)	χ^2 = 0.633	0.426
Country/area				χ^2 = 532.723	<0.0001
Bangladesh, n (%)	99 (2.6)	77 (6.9)	22 (0.8)		
China, n (%)	160 (4.3)	29 (2.6)	131 (5.0)		
Hong Kong, n (%)	31 (0.8)	9 (0.8)	22 (0.8)		
India, n (%)	479 (12.8)	97 (8.7)	382 (14.5)		
Indonesia, n (%)	581 (15.5)	143 (12.9)	438 (16.6)		
Japan, n (%)	229 (6.1)	67 (6.0)	162 (6.2)		
Korea, n (%)	131 (3.5)	16 (1.4)	115 (4.4)		
Malaysia, n (%)	305 (8.1)	62 (5.6)	243 (9.2)		
Myanmar, n (%)	164 (4.4)	67 (6.0)	97 (3.7)		
Pakistan, n (%)	298 (8.0)	191 (17.2)	107 (4.1)		
Singapore, n (%)	171 (4.6)	48 (4.3)	123 (4.7)		
Sri Lanka, n (%)	97 (2.6)	15 (1.4)	82 (3.1)		
Taiwan, n (%)	403 (10.8)	82 (7.4)	321 (12.2)		
Thailand, n (%)	322 (8.6)	46 (4.1)	276 (10.5)		
Viet Nam, n (%)	274 (7.3)	161 (14.5)	113 (4.3)		
Regional classification[†]				χ^2 = 73.674	<0.0001
Eastern Asia, n (%)	954 (25.5)	203 (18.3)	751 (28.5)		
Southeastern Asia, n (%)	1817 (48.5)	527 (47.5)	1290 (49.0)		
Southern Asia, n (%)	973 (26.0)	380 (34.2)	593 (22.5)		
Income group[‡]				χ^2 = 138.878	<0.0001
High income, n (%)	965 (25.8)	222 (20.0)	743 (28.2)		
Upper middle income, n (%)	787 (21.0)	137 (12.3)	650 (24.7)		
Lower middle income, n (%)	1992 (53.2)	751 (35.7)	1241 (47.1)		
Inpatient, n (%)	1951 (52.1)	832 (75.0)	1119 (42.5)	χ^2 = 329.956	<0.0001
Duration of illness				χ^2 = 9.157	0.165
<3 month, n (%)	161 (4.3)	34 (3.1)	127 (4.8)		
3–6 months, n (%)	125 (3.3)	34 (3.1)	91 (3.5)		
6 months–1 year, n (%)	199 (5.3)	65 (5.8)	134 (5.1)		
1–5 years, n (%)	794 (21.2)	249 (22.4)	545 (20.7)		
5–10 years, n (%)	729 (19.5)	213 (19.2)	516 (19.6)		
10–20 years, n (%)	971 (25.9)	278 (25.0)	693 (26.3)		
>20 years, n (%)	765 (20.4)	237 (21.4)	528 (20.0)		
Psychopathological characteristic					
Delusions, n (%)	1599 (42.7)	658 (59.3)	941 (35.7)	χ^2 = 177.065	<0.0001
Hallucinations, n (%)	1752 (46.8)	680 (61.3)	1072 (40.7)	χ^2 = 132.621	<0.0001
Disorganized behaviors, n (%)	666 (17.8)	392 (35.3)	274 (10.4)	χ^2 = 331.421	<0.0001
Negative symptoms, n (%)	1313 (35.1)	429 (38.6)	884 (33.6)	χ^2 = 8.876	0.003
Social or occupational dysfunction, n (%)	1693 (45.2)	708 (63.8)	985 (37.4)	χ^2 = 219.518	<0.0001
Verbal aggression, n (%)	942 (25.2)	475 (42.8)	467 (17.7)	χ^2 = 260.511	<0.0001
Physical aggression, n (%)	780 (20.8)	429 (38.6)	351 (13.3)	χ^2 = 303.619	<0.0001
Significant affective symptoms, n (%)	425 (11.4)	156 (14.1)	269 (10.2)	χ^2 = 11.452	0.001

[†] According to the United Nations classification: Eastern Asia (China, Hong Kong, Japan, Korea and Taiwan), Southern Asia (Bangladesh, India, Pakistan and Sri Lanka) and Southeastern Asia (Indonesia, Malaysia, Myanmar, Singapore, Thailand and Viet Nam).
[‡] According to the World Bank list of economies: high income (Hong Kong, Japan, Korea, Singapore and Taiwan), upper middle income (China, Malaysia, and Thailand) and Lower middle income (Bangladesh, India, Indonesia, Myanmar, Pakistan, Sri Lanka and Viet Nam).

3.2. Psychotropic drug-prescribing patterns for schizophrenia patients with and without disorganized speech

As shown in Table 2, after adjusting potential effects of age, regional classification, income group, inpatient status, delusions, hallucinations, disorganized behaviors, negative symptoms, social or occupational dysfunction, verbal aggression, physical aggression and significant affective symptoms, the subjects with disorganized speech were characterized by a significantly lower prescription rate of antiparkinson drugs (adjusted odds ratio [aOR] = 0.728, $P < 0.0001$), a higher prescription rate of mood stabilizers (aOR = 1.665, $P < 0.0001$) and a higher chlorpromazine (F = 11.986, $P = 0.001$) and diazepam equivalent dose (F = 16.219, $P < 0.0001$) than those without disorganized speech. However, there were no significant differences between the two groups in terms of prescriptions of antipsychotic polypharmacy (aOR = 1.259, $P = 0.006$), long-acting injectable antipsychotics (aOR = 1.114, $P = 0.351$), high-dose antipsychotic medication (aOR = 1.186, $P = 0.126$), first-generation antipsychotics (aOR = 1.194, $P = 0.043$), second-generation antipsychotics (aOR = 0.864, $P = 0.194$), olanzapine (aOR = 0.837, $P = 0.079$), clozapine (aOR = 1.005, $P = 0.964$), antidepressants (aOR = 0.735, $P = 0.037$), anxiolytics, sedatives and hypnotics (aOR = 1.236, $P = 0.023$) and electroconvulsive therapy (aOR = 0.891, $P = 0.560$). There were also no significant differences in relation to imipramine (F = 0.677, $P = 0.411$) and levodopa (F = 0.003, $P = 0.956$) equivalent doses.

3.3. Adverse effects of psychotropic drugs in schizophrenia patients with and without disorganized speech

As shown in Table 3, after adjusting potential effects of the confounding variables mentioned earlier, the subjects with disorganized speech had significantly greater rate of excessive salivation (aOR = 1.614, $P < 0.0001$) than those without disorganized speech. There were no significant differences between the two groups in terms of rigidity (aOR = 1.141, $P = 0.302$), akinesia (aOR = 1.128,

Table 2
Psychotropic drug prescribing patterns for schizophrenia patients with and without disorganized speech.

	Total sample (n = 3744)	Disorganized speech		Statistical coefficient	Unadjusted *P*-value	Adjusted *P*-value[†]
		Present (n = 1110)	Absent (n = 2634)			
Antipsychotic polypharmacy, n (%)	1597 (42.6)	556 (50.1)	1041 (39.5)	$\chi^2 = 35.658$	<0.0001	0.006
Long-acting injectable antipsychotics, n (%)	659 (17.6)	200 (18.0)	459 (17.4)	$\chi^2 = 0.189$	0.664	0.351
High-dose antipsychotic medication, n (%)	734 (19.6)	250 (22.5)	484 (18.4)	$\chi^2 = 8.523$	0.004	0.126
First-generation antipsychotics, n (%)	1428 (38.1)	481 (43.3)	947 (36.0)	$\chi^2 = 18.029$	<0.0001	0.043
Second-generation antipsychotics, n (%)	3126 (83.4)	922 (83.1)	2204 (83.7)	$\chi^2 = 0.212$	0.645	0.194
Olanzapine, n (%)	761 (20.3)	236 (21.3)	525 (19.9)	$\chi^2 = 0.852$	0.356	0.079
Clozapine, n (%)	691 (18.5)	201 (18.1)	490 (18.6)	$\chi^2 = 0.127$	0.722	0.964
Antiparkinson drugs, n (%)	1400 (37.4)	322 (29.9)	1068 (40.5)	$\chi^2 = 37.741$	<0.0001	<0.0001
Mood stabilizers, n (%)	526 (14.0)	217 (19.5)	309 (11.7)	$\chi^2 = 39.530$	<0.0001	<0.0001
Antidepressants, n (%)	384 (10.3)	86 (7.7)	298 (11.3)	$\chi^2 = 10.788$	0.001	0.037
Anxiolytics and hypnotics, n (%)	1185 (31.7)	398 (35.9)	787 (29.9)	$\chi^2 = 12.897$	<0.0001	0.023
Chlorpromazine equivalent, mean (SD) mg	570.2 (567.6)	685.8 (725.9)	521.5 (477.5)	t = 6.933	<0.0001	0.001
Imipramine equivalent, mean (SD) mg	14.5 (89.6)	20.5 (122.9)	11.9 (70.9)	t = 2.173	0.030	0.441
Diazepam equivalent, mean (SD) mg	8.5 (43.4)	14.7 (71.3)	5.9 (22.6)	t = 4.010	<0.0001	<0.0001
Levodopa equivalent, mean (SD) mg	45.2 (83.8)	38.2 (94.3)	48.2 (78.8)	t = −3.103	0.002	0.956
Electroconvulsive therapy, n (%)	165 (4.4)	50 (4.5)	115 (4.4)	$\chi^2 = 0.036$	0.850	0.560

[†] Adjusted for the effects of age, regional classification, income group, inpatient status, delusions, hallucinations, disorganized behaviors, negative symptoms, social or occupational dysfunction, verbal aggression, physical aggression and significant affective symptoms.

Table 3
Adverse events in response to psychotropic drug in schizophrenia patients with and without disorganized speech.

	Total sample (n = 3744)	Disorganized speech		Statistical coefficient	Unadjusted *P*-value	Adjusted *P*-value[†]
		Present (n = 1110)	Absent (n = 2634)			
Rigidity, n (%)	400 (11.1)	162 (15.1)	238 (9.4)	$\chi^2 = 25.118$	<0.0001	0.302
Akinesia, n (%)	220 (6.1)	102 (9.5)	118 (4.7)	$\chi^2 = 30.468$	<0.0001	0.460
Tremor, n (%)	666 (18.4)	275 (25.5)	391 (15.4)	$\chi^2 = 51.256$	<0.0001	0.004
Akathisia, n (%)	240 (6.7)	113 (10.5)	127 (5.0)	$\chi^2 = 36.206$	<0.0001	0.003
Dystonia, n (%)	80 (2.2)	31 (2.9)	49 (1.9)	$\chi^2 = 3.097$	0.078	0.831
Constipation, n (%)	794 (22.1)	280 (26.1)	513 (20.4)	$\chi^2 = 14.406$	<0.0001	0.203
Excessive salivation, n (%)	445 (12.3)	188 (17.5)	257 (10.2)	$\chi^2 = 37.278$	<0.0001	<0.0001
Dry mouth, n (%)	561 (15.5)	196 (18.2)	365 (14.4)	$\chi^2 = 8.210$	0.004	0.161
Postural hypotension, n (%)	162 (4.5)	68 (6.3)	94 (3.7)	$\chi^2 = 11.827$	0.001	0.176
Urinating difficulty, n (%)	93 (2.6)	51 (4.8)	42 (1.7)	$\chi^2 = 28.611$	<0.0001	0.035
Blurred vision, n (%)	196 (5.5)	72 (6.8)	124 (4.9)	$\chi^2 = 4.801$	0.028	0.972
Sexual dysfunction, n (%)	204 (6.4)	80 (8.7)	124 (5.4)	$\chi^2 = 11.785$	0.001	0.075
Galactorrhea, n (%)	116 (3.4)	40 (4.0)	76 (3.2)	$\chi^2 = 1.516$	0.218	0.152
Impaired glucose tolerance, n (%)	188 (6.2)	53 (5.6)	135 (6.4)	$\chi^2 = 0.671$	0.413	0.875
Hypercholesterolemia, n (%)	252 (8.5)	65 (7.2)	187 (9.1)	$\chi^2 = 2.801$	0.094	0.320
Weight gain, n (%)	444 (13.2)	101 (10.5)	343 (14.3)	$\chi^2 = 8.581$	0.003	0.945
QTc prolongation,[‡] n (%)	27 (1.1)	4 (0.5)	23 (1.3)	$\chi^2 = 3.806$	0.051	0.048
Oversedation, n (%)	369 (10.3)	159 (14.9)	210 (8.4)	$\chi^2 = 34.083$	<0.0001	0.035

[†] Adjusted for the effects of age, regional classification, income group, inpatient status, delusions, hallucinations, disorganized behaviors, negative symptoms, social or occupational dysfunction, verbal aggression, physical aggression and significant affective symptoms.
[‡] n = 2555.

P = 0.460), tremor (aOR = 0.349, *P* = 0.004), akathisia (aOR = 1.597, *P* = 0.003) dystonia (aOR = 0.945, *P* = 0.831), constipation (aOR = 1.140, *P* = 0.203), dry mouth (aOR = 1.173, *P* = 0.161), postural hypotension (aOR = 1.294, *P* = 0.176), urinating difficulty (aOR = 1.682, *P* = 0.035), blurred vision (aOR = 1.006, *P* = 0.972), sexual dysfunction (aOR = 1.363, *P* = 0.075), galactorrhea (aOR = 1.406, *P* = 0.152), impaired glucose tolerance (aOR = 1.030, *P* = 0.875), hypercholesterolemia (aOR = 0.844, *P* = 0.320), weight gain (aOR = 0.990, *P* = 0.945), QTc prolongation (aOR = 0.114, *P* = 0.048) and oversedation (aOR = 1.328, *P* = 0.035).

3.4. Binary logistic regression model for detecting psychotropic drug-prescribing patterns and adverse effects associated with disorganized speech

As shown in Table 4, after adjusting potential effects of the confounding variables mentioned earlier, a binary logistic regression model was fitted to detect psychotropic drug-prescribing correlates of disorganized speech. The Hosmer-Lemeshow goodness-of-fit test ($\chi^2 = 17.620$, *df* = 8, *P* = 0.230) confirmed the acceptability of the binary logistic regression model. The final model accounted for 32.6% (Nagelkerke R^2) of the variability of disorganized speech and showed that antiparkinson drugs (aOR = 0.676, *P* < 0.0001), mood stabilizers (aOR = 1.570, *P* < 0.0001) and diazepam equivalent dose (aOR = 1.007, *P* < 0.0001) were independently associated with increased likelihood of disorganized speech.

4. Discussion

Overall about one third of the 3744 Asians with schizophrenia displayed disorganized speech. After adjusting the effects of the confounding variables, a binary logistic regression model showed that more use of mood stabilizers, less use of antiparkinson drugs,

Table 4
Binary logistic model for assessing psychotropic drug prescribing patterns and adverse events associated with disorganized speech.

	B	Standard error	Wald	Adjusted *P*-value[†]	Adjusted odds ratio[†]	95% confidence interval
Antiparkinson drugs	−0.391	0.093	17.658	<0.0001	0.676	0.564–0.812
Mood stabilizers	0.451	0.120	14.073	<0.0001	1.570	1.240–1.986
Diazepam equivalent dose	0.007	0.002	21.229	<0.0001	1.007	1.004–1.010

[†] Adjusted for the effects of age, regional classification, income group, inpatient status, delusions, hallucinations, disorganized or catatonic behavior, negative symptoms, social or occupational dysfunction, verbal aggression, physical aggression and significant affective symptoms.

cumulative dose of anxiolytics and hypnotics were significant psychotropic drug- prescribing correlates of disorganized speech.

Since the prevalence rate of disorganized speech in psychosis has ranged from 5% to 91% in previous studies (Roche et al., 2014), the narrowness of the definition for disorganized speech is thought to have the most influence on its prevalence rate (Jampala et al., 1989; Taylor et al., 1994). Brier and Berg (1999) found that the prevalence rate of FTD in 1665 patients with schizophrenia was 50.4% using the score on the disorganization item on the Positive and Negative Symptom Scale (PANSS), whereas Howard et al. (1993) reported a rate of 27.4% among 336 hospitalized patients with schizophrenia-spectrum disorders using the condition of being "severe enough to substantially impair effective communication" in DSM-5. The prevalence rate of disorganized speech in our study was 29.7% partly consistent with the findings of Howard et al. (1993), and we also defined disorganized speech in accordance with DSM-5. Although the relative severity of the symptoms rather than their simple presence or absence has been emphasized in the diagnostic conceptualization of FTD (Wahlberg et al., 2000; Roche et al., 2014), disorganized speech was not dichotomized into positive and negative FTD symptoms in our study. However, based on the previous findings that the presence of disorganized speech is indicated by a total score of $\geq$8 on the TLC scale (Park et al., 2015) or total score $\geq$7 on the CLANG (Park et al., 2016a), we may assume that the disorganization of speech in our study was severe.

Moreover, the prevalence of disorganized speech differed significantly between areas in our study. To the best of our knowledge, regional differences in the prevalence rates of disorganized speech have been rarely examined in previous studies. Reported prevalence rates in different countries/areas have ranged from 12.2% (n = 131; Korea) to 77.8% (n = 99; Bangladesh). With regards to UN geographical classification, they range from 21.4% (n = 955; Eastern Asia) to 39.1% (n = 974; Southern Asia), and, in terms of the World Bank list of economies, have ranged from 12.3% (n = 127; upper middle income group) to 35.7% (n = 751; lower middle income group). These regional differences can be explained as follows: First, the contribution of ethnic and cultural factors to the prevalence rate of disorganized speech may be linked not only with genetic or neurodevelopmental intervening factors but, also direct pathoplastic features. Indeed, according to 'language determinism,' it has been suggested that among patients with schizophrenia, flexibility and variability in lexicon usage can be different across cultures and languages (Adewuya and Adewuya, 2008). Second, the evaluation of disorganized speech using a single questionnaire can be hindered by major difficulties, including the ignorance of the cultural context of the studied population. Hence, further studies for regional differences in disorganized speech should be conducted with more reliable tools and methodologies, taking into account culture and the incorporation of cultural variables and qualitative data into epidemiological surveys (Kohn and Bhui, 2007). Third, as mentioned above, Schneider's first rank symptoms have been proposed as extreme forms of language disorder (Crow, 2008). Since Schneider's 'first rank symptoms' has not been clearly defined from the viewpoint of operational diagnostic systems, debate surrounding their empirical psychopathological value continues. However, in the phenomenological sense, the diagnostic value of Schneider's first rank symptoms can be reconfirmed (Nordgaard et al., 2008). Although it is known that the prevalence of FTD may be associated with breadth of FTD definition (Jampala et al., 1989; Taylor et al., 1994), the psychopathological significance of disorganized speech can be confirmed from the viewpoint not of operational definition, but phenomenological approach. Fourth, because the REAP-AP study was not designed as an epidemiological survey, a meta-analysis on the prevalence rates of disorganized speech might be limited. In addition, the clinical significance of the statistical interregional differences in the prevalence of disorganized speech might be small. Broad inclusion criteria can contribute to the considerable heterogeneity of the patients studied, suggesting confounding factors may influence some of our findings. However, it can be speculated that the demographic and clinical characteristics of the subjects, and individual peculiarities of the 15-countries/areas are partly associated with the potential regional variations in rates of disorganized speech.

Our binary logistic regression model showed that the presence of disorganized speech in patients with schizophrenia was directly associated with the adjunctive use of mood stabilizers and cumulative dose of benzodiazepine, and inversely associated with the adjunctive use of antiparkinson drugs. In terms of the temporal relationship between disorganized speech and several psychotropic drugs, causality cannot be definitely established. However, considering several studies, it has been reproducibly shown that FTD or disorganized speech has a tendency to persistent in the longitudinal course of schizophrenia rather than nonpsychotic disorders (Bowie et al., 2005; Jampala et al., 1989; Parnas et al., 1988). Hence, despite the temporal relationship between disorganized speech and several psychotropic drugs, reverse causality might be limited in our findings. Remarkably a significant direct association between disorganized speech and adjunctive use of mood stabilizers (OR = 1.50, $P < 0.001$) was also seen in the 6441 schizophrenia inpatients in the 1st, 2nd and 3rd REAP-AP studies (Sim et al., 2011). These findings cannot be easily explained. However, despite the limited evidence for their efficacy, mood stabilizers are usually prescribed to control impulsiveness and aggressiveness in patients with schizophrenia (Citrome et al., 2000; Chen et al., 2007; Pickar et al., 2008; Glick et al., 2009). Since disorganized speech was significantly associated with verbal and physical aggression in our study, we may speculate that disorganized speech is associated with the overall severity of impulsiveness/aggressiveness in patients with schizophrenia. This would suggest that it may not be desirable to escalate the antipsychotic dose precipitously in these patients, and is consistent with the finding that there was no significant difference in rate of high dose prescription in our study. In addition, the findings may be understood in relation to the hypothesis that disordered thought is a distinct disease entity corresponding to the current diagnosis of bipolar disorder. Lake (2008) has hypothesized that distractibility reflects a core defect of selective attention and the severity of mania. However, Cuesta and Peralta (2011) found that distractibility was not specific to mania-related attentional impairment among 667 in-patients with schizophrenia-spectrum disorders.

Despite the findings, we may speculate that disorganized speech or FTD is associated with a psychopathological or neurobiological overlap between schizophrenia and severe mood disorders (Andreasen and Grove, 1986; Keller et al., 2007). We also noted a significant association between disorganized speech and affective symptoms. In accordance with these findings, a binary logistic regression model presented that disorganized speech was independently associated with conceptual disorganization, uncooperativeness and excitement items of the Brief Psychiatric Rating Scale (BPRS) in another analysis of the REAP-AP study. Hence, we may suppose that the association between disorganized speech and adjunctive use of mood stabilizers partly reflects a relationship between FTD and mania. Further study may be needed to reveal the efficacy of adjunctive use of mood stabilizers for treating disorganized speech in patients with schizophrenia.

In addition, there was a significant direct association between disorganized speech and the adjunctive use of benzodiazepine (OR = 1.17, $P = 0.015$) among 6761 schizophrenia inpatients in the 1st, 2nd and 3rd REAP-AP studies (Tor et al., 2011). As shown in Table 2, the subjects with disorganized speech were more likely to use anxiolytics and hypnotics than those without disorganized speech, although the difference was not significant. However, we cannot exclude the possibility that higher cumulative doses of anxiolytics and hypnotics contributed to the reduced adjunctive use of antiparkinson drugs. Equally the higher doses of benzodiazepine may have been prescribed for disorganized speech as a form of off-label use.

A significant inverse association between disorganized speech and use of low-dose antipsychotics (OR = 0.73, $P = 0.002$) was reported among 2,136 schizophrenia inpatients in the 2nd REAP-AP study (Sim et al., 2009). As shown in Table 2, the higher level of prescription of high-dose antipsychotic medications and a greater cumulative dose of antipsychotics in our subjects with disorganized speech was not observed after adjusting the potential effects of confounding variables. This may suggest that delusions, hallucinations and other psychopathological factors are more closely associated than disorganized speech with the use of high-dose antipsychotic medications and high cumulative dose of antipsychotics. A possible explanation for the lower use of adjunctive antiparkinson drugs is that significant FTD may also reduce effective communication between the patients and clinicians, and so lower reporting of side effects in routine clinical practice. Hence, patients may receive less use of adjunctive antiparkinson drugs.

There are several limitations to our study. First, since the REAP-AP study cannot be considered an epidemiological survey as discussed previously, generalization and extrapolation of our findings should be limited. Second, although executive function has been proposed as a predictor of thought disorder in patients with first-episode schizophrenia (Xu et al., 2014; Park et al., 2018), cognitive domains were not evaluated in our study. Third, disorganized speech was evaluated in terms of simple presence or absence rather than differential levels of positive and negative FTDs. Fourth, although there was a consensus meeting before the start of our study, inter-rater reliability for assessing disorganized speech and other psychopathological characteristics and adverse events due to psychotropic drugs was not measured. Fifth, since data on educational status, employment, religion, economic status and other demographic characteristics were not collected, the potential effects of these variables on our findings could not be adjusted. Sixthly, although non-biological factors including insurance regulations and psychiatrists' or patients' preferences may have influenced psychotropic drug prescription, these variables were not controlled. Finally, we did not adjust for the potential effects of psychiatric or physical comorbidities. Despite these limitations, our work has the virtue of pioneering the study of prevalence rates and the psychotropic drug-prescribing correlates of disorganized speech in Asian patients with schizophrenia.

5. Conclusion

In conclusion, we have shown that a third of 3744 Asian patients with schizophrenia had disorganized speech when the essential condition of being "severe enough to impair substantially effective communication" was used when defining FTD. After adjusting the potential effects of confounding variables, we found a direct association between disorganized speech and the adjunctive use of mood stabilizers, cumulative dose of anxiolytics and hypnotics, and an inverse association with the adjunctive use of antiparkinson drugs. Since disorganized speech can be regarded as a nuclear symptom of schizophrenia, the prevalence rates and psychotropic drug-prescribing correlates of disorganized speech in our study were assessed from the perspective of a continuum from disorganized speech to self-disturbance. The association between disorganized speech and adjunctive use of mood stabilizers may be explained in terms of the relationship between FTD and impulsiveness/aggressiveness or between FTD and mania. Hence, our findings suggest the speculation that disorganized speech or FTD reflects the overall severity of psychopathology in patients with schizophrenia, or that it plays a role in the realm of deconstructing the Kraepelinian dualism.

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