A. 研究目的

都道府県は，効率的で質の高い医療体制を構築するために，疾病・事業ごとに，公的統計や独自調査等により入手可能な臨床指標を活用して，現状を把握するよう求められている[1]。精神疾患は平成25年度以降の医療計画に記載すべき疾患となり，向精神薬の剤数や抗精神病薬の単剤処方割合などの現状を把握するよう推奨されている[2]。

先行研究により向精神薬の多剤処方の問題が認識され[3]，平成24年度の診療報酬改定により，抗不安又は睡眠薬が3剤以上処方されている場合に，精神科継続外来支援・指導料が20%減算されるようになった[4]。しかし，これまでの研究では，都道府県ごとの向精神薬の多剤処方の状況などは把握されてこなかった。また，被用者保険の加入者を対象とした研究が中心であり[3,5-7]，重複受診等による向精神薬の大量入手などの事案が発生している[8]，生活保護受給者に対する多剤処方の状況は検討されてこなかった。そこで，本研究では，医療扶助実態調査[9]をデータ源として，生活保護受給者の外来患者における，向精神薬の多剤処方の都道府県差を検討することを目的とした。

B. 研究方法

1. データ源

統計法第33条に基づき，医療扶助実態調査[9]に係る調査票情報の提供の申出を行い，その承諾通知を得た（社援発1216第4号)。本調査は，厚生労働省社会・援護局保護課が毎年実施している一般統計調査である。客体は，福祉事務所が保管している医療扶助レセプトのうち，支払基金6月審査分（4・5月診療分）の診療報酬明細書と調剤報酬明細書である。調査法は，2010年までは系統抽出法であったが，2011年からは悉皆調査に変更された。厚生労働省は，明細書の記入事項より，病院–診療所区分，都道府県–政令指定都市–中核市区分，性別，年齢，向精神薬の剤数，向精神薬の薬剤費などの情報を収集している。本研究では，2011年と2012年の調査票情報のうち，歯科を除いた調剤報酬明細書(調剤レセプト）を分析対象とした。

2. 評価項目

向精神薬が3剤以上処方されているか否かを主要評価項目とした。医療扶助実態調査では，調剤レセプトに記録されている医薬品の情報から，向精神薬の剤数が保存されている。なお，診療報酬明細書に記載されている医薬品の情報は保存されていない。つまり，医療扶助実態調査で把握できる向精神薬の剤数は，院外処方の場合に限られる。

ここで，医療扶助実態調査で採用されている向精神薬の定義は，「麻薬及び向精神薬取締法」(以下，法と略記する）で規制されている薬剤である[10]。表1に，法で規制される向精神薬の一般名と，通常診療として一般的な分類[11,12]との対応を示す。法で規制される向精神薬45種類のうち30種類は，一般的には抗不安・睡眠薬に分類される。精神刺激薬，抗てんかん薬，麻薬及び類似薬などに分類される薬剤の一部も含まれている。一方，一般的には抗不安・睡眠薬として分類される，bromovalerylurea，calcium bromide，chloral，etizolam，eszopiclone，flutazolam，flutoprazepam，mexazolam，ramelteon, rilmazafone, tandospirone citrate，triclofos，zopiclone の13種類は，向精神薬として規制されていない。加えて，大部分の抗精神病薬，抗うつ薬と気分安定薬は，向精神薬と

して規制されていない。

3. 観察項目

都道府県 47 地域と年齢区分（0–19 歳, 20–39 歳，40–59 歳，60 歳以上）を観察項目とした。

4. 統計解析

すべての統計解析には，データ解析環境 R version 3.0.1 を用いた。2011 年と 2012 年の調剤レセプトを合併し，年齢区分ごとに，47 の都道府県の向精神薬が 3 剤以上処方される標準化レセプト出現比（Standardized Claim Ratio: SCR）を経験的ベイズ推定により求めた[13-15]。SCR は標準化死亡比と類似の指標である。基準を 2 年間の日本全国の値とし，SCR が 100 よりも大きい場合に，当該地域において向精神薬が 3 剤以上処方されるリスクは全国平均よりも高いと解釈できる。これらの連続量の指標について可視化するため，階級数を 6 とした Fisher-Jenks の自然分類法により階級区分を行い，コロプレス図を描画した[15]。

C. 研究結果

調査対象の特性を表 2に示す。調剤レセプトの件数は，2 年間で 2,284,861 件であった。全レセプトのうち，診療所が 61%，女性が 54%，60 歳以上が 64%を占めていた。向精神薬が 1 剤以上処方されるレセプトは 21%であり，3 剤以上処方されるレセプトは 2%であった。

向精神薬の多剤処方の都道府県差を図 1に示す。0–19 歳の向精神薬 3 剤以上の処方割合は，愛媛県が突出しており，全国平均よりも 2 倍高かった。20–39 歳の向精神薬 3 剤以上の処方割合が全国平均よりも 32%以上高い地域は，岐阜県，大阪府，奈良県と和歌山県の 4 地域であった。40–59 歳の向精神薬 3 剤以上の処方割合は，和歌山県が突出しており，全国平均よりも 80%高かった。60 歳以上の向精神薬 3 剤以上の処方割合が全国平均よりも 42%以上高い地域は，北海道と滋賀県であった。

D. 考察

本研究の結果，向精神薬の多剤処方の地域差は明瞭に存在することが明らかになった。年齢区分により，向精神薬の多剤処方が多い地域は明らかに異なっていた。

本研究は生活保護受給者における向精神薬の処方状況を検討した初めての研究であるが，限界として，以下の点がある。第 1 に，本研究における「向精神薬 3 剤以上処方」を，「抗不安・睡眠薬の 3 剤以上処方」と読み替えられる程度が不確かである。先に述べたように，法で規制される向精神薬と，通常診療として一般的な向精神薬の分類との対応は取れていないため解釈が困難である。第 2 に，本研究で把握している情報は，生活保護受給者の院外処方の情報に限られ，院内処方の状況は把握できていない。医療扶助実態調査において，①院内処方の情報を加えること，②医薬品コードの粒度でデータを保存すること，の 2 点に関して，調査設計の変更がなされることが望まれる。この 2 つの変更により，実情に即した向精神薬の多剤処方の地域差を，定期的にモニタリングできるようになる。第 3 に，多剤処方の地域差の規定要因と，多剤処方の 2011 年と 2012 年の地域別変化を検討できていない。この点は，次年度の以降に検討することを計画している。

E. 結論

向精神薬の多剤処方の地域差は明瞭に存在し，年齢区分により多剤処方の多い地域は異なっていた。向精神薬の多剤処方の状況を定期的にモニタリングするための体制を構築し，地域の実

情に応じた対策を進めることが望まれる。

謝辞

本研究の実施にあたり，データの提供を承諾頂きました，厚生労働省社会・援護局の関係者に感謝します。

引用文献

1) 厚生労働省医政局指導課長．疾病・事業及び在宅医療に係る医療体制について [http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryou/iryou_keikaku/dl/tsuuchi_iryou_taisei1.pdf (accessed 2013-3-5)].

2) 厚生労働省医政局指導課長．疾病・事業及び在宅医療に係る医療体制について：別表 [http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryou/iryou_keikaku/dl/tsuuchi_iryou_taisei2.pdf (accessed 2013-3-5)].

3) 中川敦夫：向精神薬の処方実態に関する国内外の比較研究 平成22年度 統括・分担研究報告書．厚生労働科学研究費補助金厚生労働科学特別研究事業，東京，2011.

4) 厚生労働省．医療計画（精神疾患）について（平成２４年４月２７日説明会資料） [http://www.ncnp.go.jp/nimh/syakai/file/20120426_file01.pdf (accessed 2014-1-27)].

5) Onishi, Y., Hinotsu, S., Furukawa, T. A. et al: Psychotropic prescription patterns among patients diagnosed with depressive disorder based on claims database in Japan. Clin Drug Investig 33: 597-605, 2013.

6) Furukawa, T. A., Onishi, Y., Hinotsu, S. et al: Prescription patterns following first-line new generation antidepressants for depression in Japan: a naturalistic cohort study based on a large claims database. J Affect Disord 150: 916-922, 2013.

7) Abe, S., Enomoto, M., Kitamura, S. et al: Prescription hypnotics and associated background factors in a large-scale Japanese database. Sleep and Biological Rhythms 10: 319-327, 2012.

8) 厚生労働省社会・援護局保護課．向精神薬大量入手事案を受けた生活保護の緊急サンプル調査結果 （二次調査）について [http://www.mhlw.go.jp/stf/houdou/2r9852000000orgt.html (accessed 2014-1-28)].

9) 厚生労働省．医療扶助実態調査 [http://www.mhlw.go.jp/toukei/list/67-16.html (accessed 2013-5-24)].

10) 電子政府の総合窓口イーカブ．麻薬及び向精神薬取締法（昭和二十八年三月十七日法律第十四号) [http://law.e-gov.go.jp/htmldata/S28/S28HO014.html (accessed 2013-11-12)].

11) 浦部晶夫，島田和幸，川合眞一：今日の治療薬(2011年版)：解説と便覧．南江堂，東京，2011.

12) 浦部晶夫，島田和幸，川合眞一：今日の治療薬(2012年版)：解説と便覧．南江堂，東京，2012.

13) 藤森研司，松田晋哉．精神疾患の医療計画作成のための National Database の活用の実際．*精神医学*. 2012: 54: 983-995.

14) 松田晋哉，村松圭司，林田賢史，藤森研司，石川ベンジャミン光一，伏見清秀．National Database(NDB)からみる都道府県の医療提供体制　NDBから作成された公開指標の概要とそれを用いた基本診療関連医療行為の分析．*社会保険旬報*. 2013: 18-26.

15) 谷村晋：地理空間データ分析．共立出版，東京，2010.

F. 研究発表

1. 論文発表

なし

2. 学会発表

なし

G. 知的財産権の出願・登録状況

なし

表 1　麻薬及び向精神薬取締法による向精神薬の定義

分類/一般名
抗精神病薬
chlorpromazine-promethazine-phenobarbital combined
抗不安・睡眠薬
alprazolam
amobarbital
barbital
bromazepam
brotizolam
chlordiazepoxide
clorazepate dipotassium
clotiazepam
cloxazolam
diazepam
estazolam
ethyl loflazepate
fludiazepam
flunitrazepam
flurazepam
haloxazolam
lorazepam
lormetazepam
medazepam
nimetazepam
nitrazepam
oxazolam
pentobarbital calcium
phenobarbital
phenobarbital sodium
prazepam*
quazepam
secobarbital sodium
triazolam
zolpidem
精神刺激薬
methylphenidate
modafinil
pemoline
抗てんかん薬
clobazam
clonazepam
diazepam (DZP)
phenytoin-phenobarbital
phenytoin-phenobarbital-caffeine and sodium benzoate
麻薬及び類似薬
buprenorphine
pentazocine
その他
midazolam
mazindol
mepenzolate bromide− phenobarbital
proxyphylline-ephedrine hydrochloride-phenobarbital

* 2012 年 3 月販売中止

表 2　調査対象の特性

特性	全体 (N = 2,284,861) n	%	2011 年 (n = 1,100,217) n	%	2012 年 (n = 1,184,644) n	%
病院–診療所区分						
病院	885,468	38.8	431,699	39.2	453,769	38.3
診療所	1,399,393	61.2	668,518	60.8	730,875	61.7
性別						
男性	1,034,002	45.3	497,500	45.2	536,502	45.3
女性	1,251,104	54.8	602,717	54.8	648,387	54.7
年齢区分						
< 20	159,963	7.0	77,816	7.1	82,147	6.9
20– 29	40,842	1.8	19,748	1.8	21,094	1.8
30– 39	110,493	4.8	54,335	4.9	56,158	4.7
40– 49	209,562	9.2	99,503	9.0	110,059	9.3
50– 59	300,915	13.2	147,137	13.4	153,778	13.0
60– 74	896,694	39.2	433,057	39.4	463,637	39.1
≥ 75	566,637	24.8	268,621	24.4	298,016	25.2
向精神薬の剤数						
0	1,806,859	79.1	866,848	78.8	940,011	79.3
1	330,903	14.5	160,472	14.6	170,431	14.4
2	100,218	4.4	49,110	4.5	51,108	4.3
≥ 3	47,126	2.1	23,787	2.2	23,339	2.0

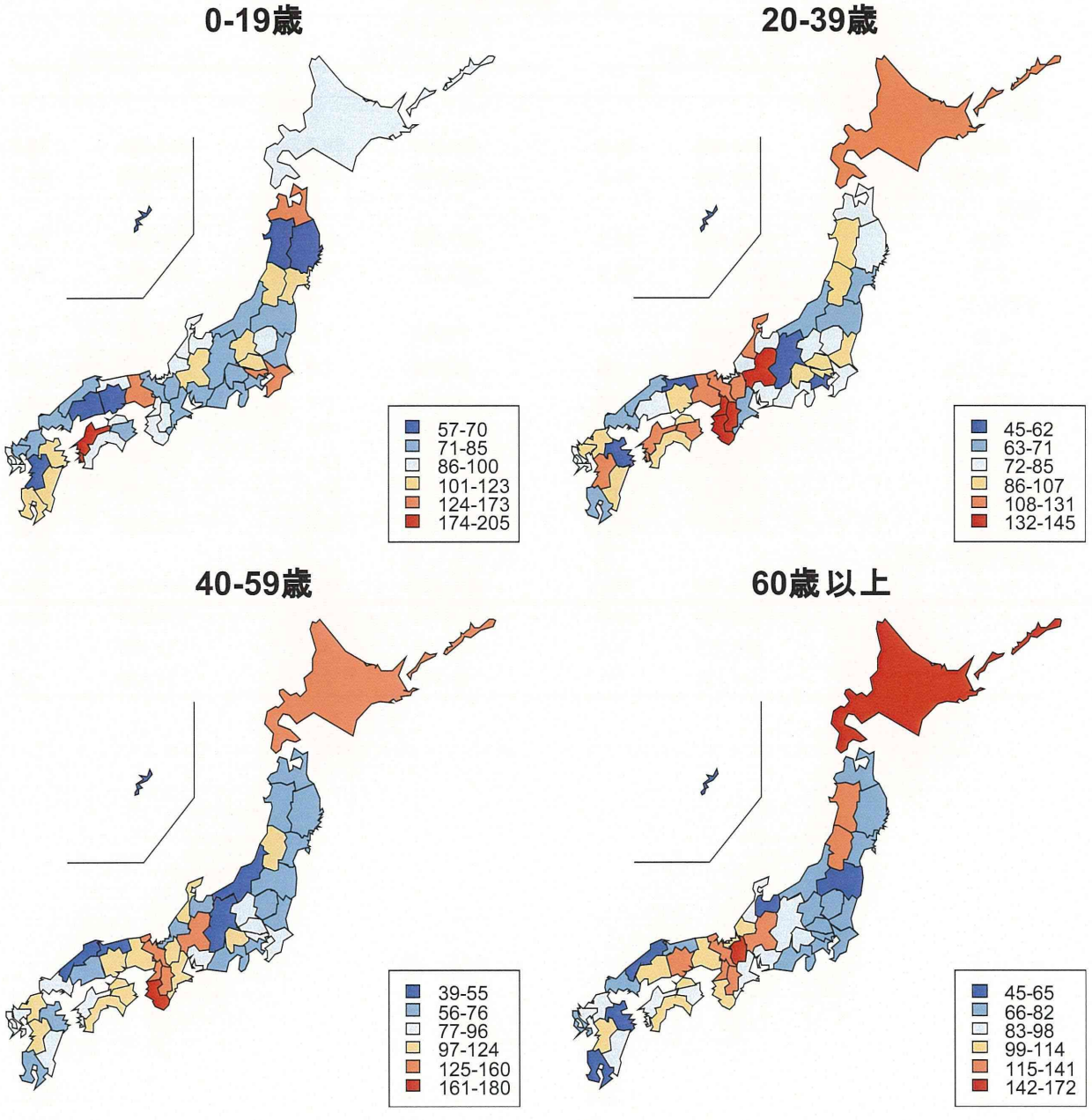

図 1　向精神薬の多剤処方の標準化レセプト出現比

厚生労働科学研究費補助金（障害者対策総合研究事業）
研究協力報告書

統合失調症患者への抗精神病薬処方の併用パターンと QTc 間隔延長

研究協力者　福内友子　国立精神・神経医療研究センター 精神保健研究所
社会精神保健研究部

研究要旨：抗精神病薬は統合失調症患者の QTc を延長する可能性がある。抗精神病薬の併用パターンと QTc 延長との関連を分析した。***研究方法***：対象は、2004 年 4 月から 2005 年 5 月に退院した統合失調症患者（n = 508）である。入院中の臨床検査値、(≥440 ms)および退院時処方の関連を分析した。***結果***：高齢（>60 歳）、女性は QTc 間隔延長が高い傾向があった。QTc 間隔と抗精神病薬の単剤・多剤または処方量（クロールプロジン換算値）とは有意な関連はなかった。しかし bromperidol または zotepine を処方されている患者の QTc 間隔が延長していた ($p < 0.05$). 一般に Zotepine は他の抗精神病薬と併用されていた (58/60, 96.7%)。最も多いパターンである Zotepine とハロペリドールとの併用の場合、QTc が延長する傾向があった。***まとめ***：統合失調症患者への抗精神病薬の処方パターンの中には、QTc が延長する可能性がある場合があることを、本分析は示唆している。

Introduction

Patients with schizophrenia have a 2- to 3-fold higher risk of premature death than the general population [1]. This increased mortality has been attributed to a combination of lifestyle factors (smoking, substance abuse, and homelessness), high suicide rates (especially in young male patients soon after diagnosis), premature development of cardiovascular disease and a higher prevalence of metabolic syndromes. In addition, patients with schizophrenia exhibit higher rates of sudden unexpected death [2-5]. One likely factor contributing to early unexpected death is cardiac arrhythmia [6]. Patients with schizophrenia are at a higher risk of developing cardiovascular diseases, possible because long-term use of certain antipsychotics may trigger adverse cardiovascular events such as QTc interval prolongation (or long QTc syndrome). Together, these risk factors may lead to torsades de pointes (TdP) or sudden cardiac death.

Warner et al. [7] reported QTc prolongation (>420 ms) in 23% of patients with chronic schizophrenia compared with only 2% of age-matched, drug-free controls. Reilly et al. [8] reported that 8% of 495 psychiatric patients, the majority on antipsychotics, had QTc

prolongation. Currently available antipsychotics have widely varying effects on the QTc interval [9-18]. Long-term treatment with typical antipsychotics (TAPs) involves a greater risk of QTc interval prolongation than atypical antipsychotics (AAPs) [19, 20]. The association between AAPs with QTc prolongation and with sudden death has become a more conflictive subject after an article published in 2009 [21]. However, a more recent cross-sectional study in a large clinical sample from Japan found an association between long QTc and chlorpromazine, intravenous haloperidol and sultopride therapy, whereas the second-generation antipsychotic drugs (olanzapine, quetiapine, risperidone and zotepine) did not prolong the QTc interval [22,23]. In light of these inconsistencies, the effects of TAPs and APPs on QTc prolongation requires more rigorous study.

Other notable risk factors include female gender, which confers a 2-fold increase in risk and age >65 years [18,24]. Furthermore, the prevalence varies according to many patient-specific factors, including concurrent electrolyte disturbances (specifically, potassium, magnesium, and calcium), and genetic susceptibility (polymorphisms that increase long QTc risk) [25].

The present study aimed to further identify risk factors, both patient-specific and drug-induced, for QTc prolongation in schizophrenic outpatients on long-term antipsychotic drug therapy. Apart from older age, female gender and smoking habit, we identified polypharmacy with zotepine, particularly in combination with haloperidol, as a possible risk factor for prolonged QT in patients with schizophrenia.

Methods

Study Population

Patient data were collected as part of a larger study funded by the Japanese Association of Psychiatric Hospitals (JAPH) on the effectiveness of outpatient day care activities and antipsychotics for schizophrenia. The details of this project have been provided elsewhere [26, 27]. In brief, we conducted a retrospective open cohort study of 1216 member hospitals of JAPH in 2007. Our study population comprised all patients with schizophrenia discharged between April 2004 and March 2005 and who continued to receive outpatient treatment from JAPH member hospitals. A systematic sampling technique was used to select every 5th schizophrenic patient from the medical records. Our study protocol was approved by the ethics committees of the JAPH and the National Center of Neurology and Psychiatry.

Assessment

A record administrator from each hospital retrospectively reviewed patient medical charts. We collected information as follows: (1) demographic characteristics of the participants (gender and age), (2) clinical test results acquired during hospitalization, including results for liver function (GOT, GTP and γGTP), glucose and lipid metabolism, systolic blood pressure, diastolic blood pressure and electrocardiography, (3) cardiovascular disease

history (including arrhythmia, ischemic or valvular heart disease and hypertension), diabetes history and presence of other chronic metabolic diseases and (4) drug prescriptions for schizophrenia at hospital discharge. Antipsychotic doses were converted to chlorpromazine equivalents (CPZEq). Clinical test results were acquired within one month after the start of hospitalization, within one month after hospital discharge and the intermediate period. In addition, the main prescription drug and their daily dose were recorded both discharge medication and outpatient treatment medication. In this study, we used the prescription data at hospital discharge and the clinical test result which were measured within one month before hospital discharge. The exclusion criteria were (1) age <19 or >100 years and (2) the absence of information on gender, incomplete clinical test results during hospitalization or uncertainty on antipsychotic prescriptions issued at hospital discharge.

Definition of prolonged QTc interval

The QT interval was measured from the beginning of the QRS complex to the return of the T wave to the isoelectric line. When the T wave was interrupted by the U wave, the end of the T wave was defined as the nadir between T and U waves. Intervals were measured in two consecutive beats from each chest lead except from leads where the T wave was isoelectric. All patients had normal sinus rhythm. Heart rate correction was performed using Bazett's formula, and each patient's QTc interval was the mean duration of all QTc measurements. This measurement method is similar to that used in previous studies [28]. A long QTc was defined as a QTc interval ≥440 ms [29].

Definition of Antipsychotic Prescription Patterns

We classified antipsychotics as TAPs and AAPs. TAPs included bromperidol, carpipramine, chlorpromazine, clocapramine, fluphenazine, haloperidol, levomepromazine, moperone, mosapramine, nemonapride, oxypertine, perphenazine, pimozide, pipamperone, prochlorperazine, propericiazine, spiperone, sulpiride, sultopride, thioridazine, tiapride, timiperone, trifluoperazine, zotepine, fluphenazine decanoate and haloperidol decanoate. AAPs included olanzapine, perospirone, quetiapine and risperidone.

Statistical Analyses

Continuous variables were compared using Student's t-test, and categorical variables were compared using Fisher's exact test. The proportions of female patients, patients aged >60 years, patients with indices of liver dysfunction or hypertension, smokers, patients with a history of specific systemic or neurological illnesses and patients with a long QTc interval (≥440 ms) were compared using the chi-square test. Statistical analyses were performed using the SPSS 18 software package. $p < 0.05$ was considered statistically significant. The study was approved by the local bioethical committee, and all patients gave their informed consent.

Results

Figure 1 illustrates the patient selection process

used for this multi-centre retrospective study. Between April 2004 and March 2005, 21,396 patients with schizophrenia were discharged and continued to receive outpatient treatment from 526 JAPH member hospitals. A total of 4176 patients were selected using a systematic sampling technique. We excluded 3117 patients using the exclusion criteria described above. In total, 508 patients were examined by various clinical tests including electrocardiography (ECG) for the measurement of the QTc interval within 1 month before discharge. Mean age of the study population was 46.2 ± 14.8 years, and 238 patients (46.9%) were female. Mean QTc was 411.3 ± 25.4 ms. Seventy-four patients (14.6%) had a prolonged QTc interval (≥440 ms).

The mean QTc interval was longer in females (417.7 ± 26.4 ms vs. 405.6 ± 23.1 ms, $p < 0.001$) and in patients aged >60 years (418.0 ± 28.1 ms vs. 409.4 ± 24.3 ms; $p < 0.001$). Smoking led to a mean decrease in QTc of approximately 8.6 ms ($p < 0.001$). In contrast, patients with a history of cardiovascular or metabolic diseases had mean QTc intervals that were not significantly different from those with no history of these diseases (Table 1).

Several antipsychotic drugs have been linked to prolonged ventricular repolarization, which is reflected by a longer QT interval on ECG. This effect is likely more pronounced at higher doses or when antipsychotic drugs are used in multi-drug regimens. We assessed the effect of dosage, specific antipsychotics and combinations of antipsychotics on the QTc interval (Table 2 and 3). The mean QTc interval of patients receiving an antipsychotic dosage ≥1000 mg/day in CPZEq was not significantly different from the mean QTc interval of patients receiving lower dosages (412.3 ± 29.5 ms, n = 138 vs. 410.9 ± 23.7 ms, n = 370) (Table 2). Moreover, the proportion of patients with QTc ≥440 ms was not significantly different between high- and lose-dose groups (15.2% vs.14.3%, $p > 0.05$). Almost twice as many patients in this sample were taking two or more antipsychotic drugs (n = 334, 65.7%) than a single drug (n = 174, 34.3%). In the monotherapy group, more patients were taking a single AAP (n = 138, 27.1%) than a single TAP (n = 36, 7.1%). No significant difference was observed in the mean QTc interval between AAP and TAP monotherapy patients or among the TAP+TAP, TAP+AAP or AAP+AAP polypharmacy groups.

While patient groups defined by monotherapy vs. polypharmacy or AAP vs. TAP exhibited no differences in the mean QTc interval, significant differences in mean QTc intervals were observed among patient subgroups taking specific drug combinations (Table 3). The most frequently prescribed antipsychotics were risperidone (n = 209), haloperidol (n = 132), levomepromazine (n = 132) and olanzapine (n = 124). Bromperidol- and zotepine-treated patients using polypharmacy had significantly longer mean QTc intervals than patients taking these particular drugs in monotherapy (bromperidol QTc= 9.3 ms; zotepine QTc= 10.5 ms; $p < 0.05$

for both drugs).

Certain subgroups of patients taking specific drug combinations also exhibited longer mean QTc intervals (Table 4). Levomepromazine plus haloperidol was by far the most common polypharmacy, but 52 other combinations were identified. The proportion of patients with long QTc was actually lower in the levomepromazine plus haloperidol subgroup compared to the mean of all polypharmacy patients (9.6% vs. 14.7%), while the proportion of patients with long QTc was higher in the subgroup treated with zotepine plus haloperidol (26%, n = 23) than in any of the other 10 most common polypharmacy combinations that included zotepine. Similarly, subgroups taking zotepine or haloperidol with AAPs, such as olanzapine, perospirone or quetiapine, and subgroups taking two AAPs, such as risperidone plus perospirone, quetiapine plus olanzapine or perospirone plus quetiapine, had significantly higher proportions of patients with long QTc intervals.

Discussion

Many non-congenital factors may predispose to QT prolongation and higher risk of TdP, including older age, female gender, pre-existing cardiovascular diseases, bradycardia and electrolyte disturbances [18, 24]. Furthermore, a number of clinically useful drugs may cause QTc prolongation by blocking K^+ currents [30] or by increasing serum levels of other K^+ channel blockers by reducing cytochrome P450 (CYP) metabolic activity [31, 32]. Higher doses and renal failure may also result in higher serum levels of these drugs and consequently in QTc prolongation [33]. This study aimed to determine the prevalence of a prolonged QTc interval in a relatively large population of patients with schizophrenia and to identify specific relationships between QTc and patient demographic variables, clinical characteristics and drug treatment regimens. In this patient cohort, QTc prolongation (≥440 ms) was found in 14.6% of patients. Female patients had a higher prevalence of QTc prolongation and a longer mean QTc interval than male patients, consistent with previous studies [34, 35]. We found a significant increase in the QTc interval in patients aged >60 years but not in patients ≥65 years. Cardiovascular disease is a major cause of QTc prolongation and arrhythmia, but this is not likely to be a significant factor for QTc prolongation in the present study. It is commonly believed that higher doses and multiple antipsychotic drug regimens can increase the QT interval compared with low-dose treatment or monotherapy [7, 8, 21, 36]. However, we found no significant increase in the mean QTc interval in patients receiving high dosage treatment (>1000 mg/day CPZEq) or the polypharmacy subgroup.

On the other hand, significant differences were observed in the QTc interval among specific drug regimen subgroups. Zotepine-treated patients in combination had a longer mean QTc interval compared with patients treated with other antipsychotics or in monotherapy. Zotepine has been in use in Germany since 1990, in Japan since 1982, but it

is not approved for use in the United States. It has both dopaminergic (D2/D3 > D1/D4) and serotonergic (5-HT2A and 5-HT2C) receptor blocking activity. Ozeki Y *et.al.* reported that the second-generation antipsychotic drugs olanzapine, quetiapine, risperidone and zotepine did not prolong the QTc interval, and therefore may be more appropriate for patients with pre-existing cardiovascular diseases or other risk factors for TdP [22]. Many studies have investigated the effects and risks associated with single QTc-prolonging drugs, but few have compared the effects of different multi-drug regimens on the QTc interval. In our cohort, zotepine was almost always used with another antipsychotic drug (96.7%), such as risperidone or haloperidol. Although no difference was observed in the QTc interval between the total monotherapy and polypharmacy groups, certain drug combinations, including zotepine plus haloperidol, bromperidol, olanzapine or perospirone may increase the risk of QTc prolongation.

In humans, the QTc interval is strongly dependent on the rapid component of the delayed rectifier K^+ current (I_{Kr}) [37]; therefore, blockade of the channel mediating this current will delay ventricular repolarization and prolong the QTc interval. The pore-forming subunit of the delayed rectifier K^+ channel is encoded by the ether-a-go-go-related gene hERG. Many drugs associated with QT interval prolongation have been found to block hERG-containing channels [10, 16, 38, 39]. Drug characteristics determining the degree of QT prolongation are the (1) potency of the drug for the hERG channel blockade, (2) plasma concentration reached and (3) drug–drug interactions that influence the plasma concentration of the higher potency I_{Kr} antagonist. In case of zotepine, the half maximal (50%) inhibitory concentration for hERG is 207 nM, as high as other antipsychotics, while the value of hERG IC50/Cmax-free is lower than others (Table 5). Furthermore, zotepine is metabolized mainly by CYP 3A4 [40], the same liver isozyme responsible for haloperidol, quetiapine and bromperidol metabolism [41]. Thus, these specific combinations may reach higher plasma concentrations when administered together than when administered separately, leading to greater I_{Kr} blockade and QTc prolongation (Table 4 and 5). This applies to haloperidol as well. Thus, we considered that there was probable cause to the high prevalence rate of long QTc in the several combination descriptions, such as zotepine plus haloperidol or quetiapine (Table 4).

The study shares the limitations of all retrospective open cohort studies. In addition, QTc was obtained within one month before hospital discharge, while the antipsychotics regimen was discharge medication. Thus, additional case-control clinical and animal-based pharmacokinetic studies are required to establish causal relationships between long QTc and specific antipsychotic drug combinations and to determine the pathogenic mechanisms.

In conclusion, we demonstrate that female gender (OR, 1.6) and age >60 years (OR,

1.7) are significant risk factors for QTc prolongation in schizophrenic outpatients on antipsychotic therapy. In addition, certain antipsychotic regimens were associated with longer QTc. Specifically, polypharmacy that included zotepine was associated with increased risk of QTc prolongation compared with other mono- or polypharmacies. These data may be useful for selecting the safest antipsychotic regimen for individual patients with schizophrenia.

Acknowledgment

All supports for administrating the study came from the project cost of the Health-Economics Committee of Japanese Association of Psychiatric Hospitals. Funding for writing this article was supported by a Health Labour Scientific Research (Research on Regulatory Science of Pharmaceuticals and Medical Devices) from the Ministry of Health, Labour and Welfare of Japan.

References

1. Joukamaa M, Heliovaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Mental disorders and cause-specific mortality. *Br. J. Psychiatry* 2001; 179: 498-502.
2. Auquier P, Lancon C, Rouillon F, Lader M, Holmes C. Mortality in schizophrenia. *Pharmacoepidemiol. Drug Saf.* 2006; 15: 873-9.
3. Bobes J, Garcia-Portilla MP, Bascaran MT, Saiz PA, Bousono M. Quality of life in patients with schizophrenia. *Dialogues Clin. Neurosci.* 2007; 9: 215-26.
4. Bobes J, Arango C, Aranda P, Carmena R, Garcia-Garcia M, Rejas J. Cardiovascular and metabolic risk in outpatients with schizoaffective disorder treated with antipsychotics: results from the CLAMORS study. *Eur. Psychiatry.* 2010; 27: 267-74.
5. Ruschena D, Mullen PE, Burgess P, Cordner SM, Barry-Walsh J, Drummer OH, Palmer S, Browne C, Wallace C. Sudden death in psychiatric patients. *Br. J Psychiatry.* 1998; 172: 331-6.
6. Koponen H, Alaraisanen A, Saari K, Pelkonen O, Huikuri H, Raatikainen MJ, Savolainen M, Isohanni M. Schizophrenia and sudden cardiac death: a review. *Nord. J Psychiatry.* 2008; 62: 342-5.
7. Warner JP, Barnes TR, Henry JA. Electrocardiographic changes in patients receiving neuroleptic medication. *Acta Psychiatr. Scand.* 1996; 93: 311-3.
8. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; 355: 1048-52.
9. Glassman AH. Schizophrenia, antipsychotic drugs, and cardiovascular disease. *J Clin. Psychiatry* 2005; 66 Suppl 6: 5-10.
10. Drolet B, Yang T, Daleau P, Roden DM, Turgeon J. Risperidone prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current. *J Cardiovasc. Pharmacol.* 2003; 41: 934-7.
11. Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The association between the length of the QT interval and mortality in

the Cardiovascular Health Study. *Am. J Med.* 2003; 115: 689-94.

12. Straus SM, Bleumink GS, Dieleman JP, van der Lei J, t Jong GW, Kingma JH, Sturkenboom MC, Stricker BH. Antipsychotics and the risk of sudden cardiac death. *Arch. Intern. Med.* 2004; 164: 1293-7.
13. Zarate CA, Jr., Patel J. Sudden cardiac death and antipsychotic drugs: do we know enough? *Arch. Gen. Psychiatry* 2001; 58: 1168-71.
14. De Ponti F, Poluzzi E, Montanaro N. QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience. *Eur. J Clin. Pharmacol.* 2000; 56: 1-18.
15. De Ponti F, Poluzzi E, Montanaro N, Ferguson J. QTc and psychotropic drugs. *Lancet* 2000; 356: 75-6.
16. Witchel HJ, Hancox JC, Nutt DJ, Wilson S. Antipsychotics, HERG and sudden death. *Br. J Psychiatry* 2003; 182: 171-2.
17. Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs* 2002; 62: 1649-71.
18. Isbister GK, Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. *Br. J Clin. Pharmacol.* 2012; 20:.
19. Vieweg WV. New Generation Antipsychotic Drugs and QTc Interval Prolongation. Prim Care Companion. *J Clin. Psychiatry* 2003; 5: 205-15.
20. Zemrak WR, Kenna GA. Association of antipsychotic and antidepressant drugs with Q-T interval prolongation. *Am. J Health Syst. Pharm.* 2008; 65: 1029-38.
21. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N. Engl. J Med.* 2009; 360: 225-35.
22. Ozeki Y, Fujii K, Kurimoto N, Yamada N, Okawa M, Aoki T, Takahashi J, Ishida N, Horie M, Kunugi H. QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2010; 34: 401-5.
23. Sadanaga T, Sadanaga F, Yao H, Fujishima M. Abnormal QT prolongation and psychotropic drug therapy in psychiatric patients: significance of bradycardia-dependent QT prolongation. *J Electrocardiol.* 2004; 37: 267-73.
24. Li EC, Esterly JS, Pohl S, Scott SD, McBride BF. Drug-induced QT-interval prolongation: considerations for clinicians. *Pharmacotherapy* 2010; 30: 684-701.
25. Chiang CE, Roden DM. The long QT syndromes: genetic basis and clinical implications. *J Am. Coll. Cardiol.* 2000; 36: 1-12.
26. Okumura Y, Ito H, Kobayashi M, Mayahara K, Matsumoto Y, Hirakawa J. Prevalence of diabetes and antipsychotic prescription patterns in patients with schizophrenia: a nationwide retrospective cohort study. *Schizophr. Res.* 2010; 119: 145-52.

27. Kobayashi M, Ito H, Okumura Y, Mayahara K, Matsumoto Y, Hirakawa J. Hospital readmission in first-time admitted patients with schizophrenia: smoking patients had higher hospital readmission rate than non-smoking patients. *Int. J Psychiatry Med* 2010; 40: 247-57.
28. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart* 2003; 89: 1363-72.
29. Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. *Circulation* 2011; 124: 2181-4.
30. Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am. Heart J* 2007; 153: 891-9.
31. Letsas KP, Efremidis M, Filippatos GS, Sideris AM. Drug-induced long QT syndrome. *Hellenic J Cardiol*. 2007; 48: 296-9.
32. Roden DM. Drug-induced prolongation of the QT interval. *N. Engl. J Med.* 2004; 350: 1013-22.
33. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA 2003; 289: 2120-7.
34. Seeman MV. Schizophrenia: women bear a disproportionate toll of antipsychotic side effects. *J Am. Psychiatr. Nurses. Assoc.* 2010; 16: 21-9.
35. Rettenbacher MA, Eder-Ischia U, Bader A, Edlinger M, Hofer A, Hummer M, Kemmler G, Weiss EM, Hochleitner M, Fleischhacker WW. QTc variability in schizophrenia patients treated with antipsychotics and healthy controls. *J Clin. Psychopharmacol.* 2005; 25: 206-10.
36. Harrigan EP, Miceli JJ, Anziano R, Watsky E, Reeves KR, Cutler NR, Sramek J, Shiovitz T, Middle M. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin. Psychopharmacol*. 2004; 24: 62-9.
37. Michelsen JW, Meyer JM. Cardiovascular effects of antipsychotics. *Expert Rev. Neurother.* 2007; 7: 829-39.
38. Witchel HJ, Hancox JC, Nutt DJ. Psychotropic drugs, cardiac arrhythmia, and sudden death. *J Clin. Psychopharmacol.* 2003; 23: 58-77.
39. De Ponti F, Poluzzi E, Cavalli A, Recanatini M, Montanaro N. Safety of non-antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: an overview. *Drug Saf.* 2002; 25: 263-86.
40. Kondo T, Tanaka O, Otani K, Mihara K, Tokinaga N, Kaneko S, Chiba K, Ishizaki T. Possible inhibitory effect of diazepam on the metabolism of zotepine, an antipsychotic drug. *Psychopharmacology (Berl)* 1996; 127: 311-4.
41. Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: a review of last decade of research. *Mol. Psychiatry* 2007; 12: 707-47.
42. Silvestre JS, Prous JR. Comparative evaluation of hERG potassium channel

blockade by antipsychotics. *Methods Find Exp. Clin. Pharmacol.* 2007; 29: 457-65.

43. Ekins S, Crumb WJ, Sarazan RD, Wikel JH, Wrighton SA. Three-dimensional quantitative structure-activity relationship for inhibition of human ether-a-go-go-related gene potassium channel. *J Pharmacol. Exp. Ther.* 2002; 301: 427-34.
44. Kongsamut S, Kang J, Chen XL, Roehr J, Rampe D. A comparison of the receptor binding and HERG channel affinities for a series of antipsychotic drugs. *Eur. J Pharmacol.* 2002; 450: 37-41.

Figure 1. Flow diagram

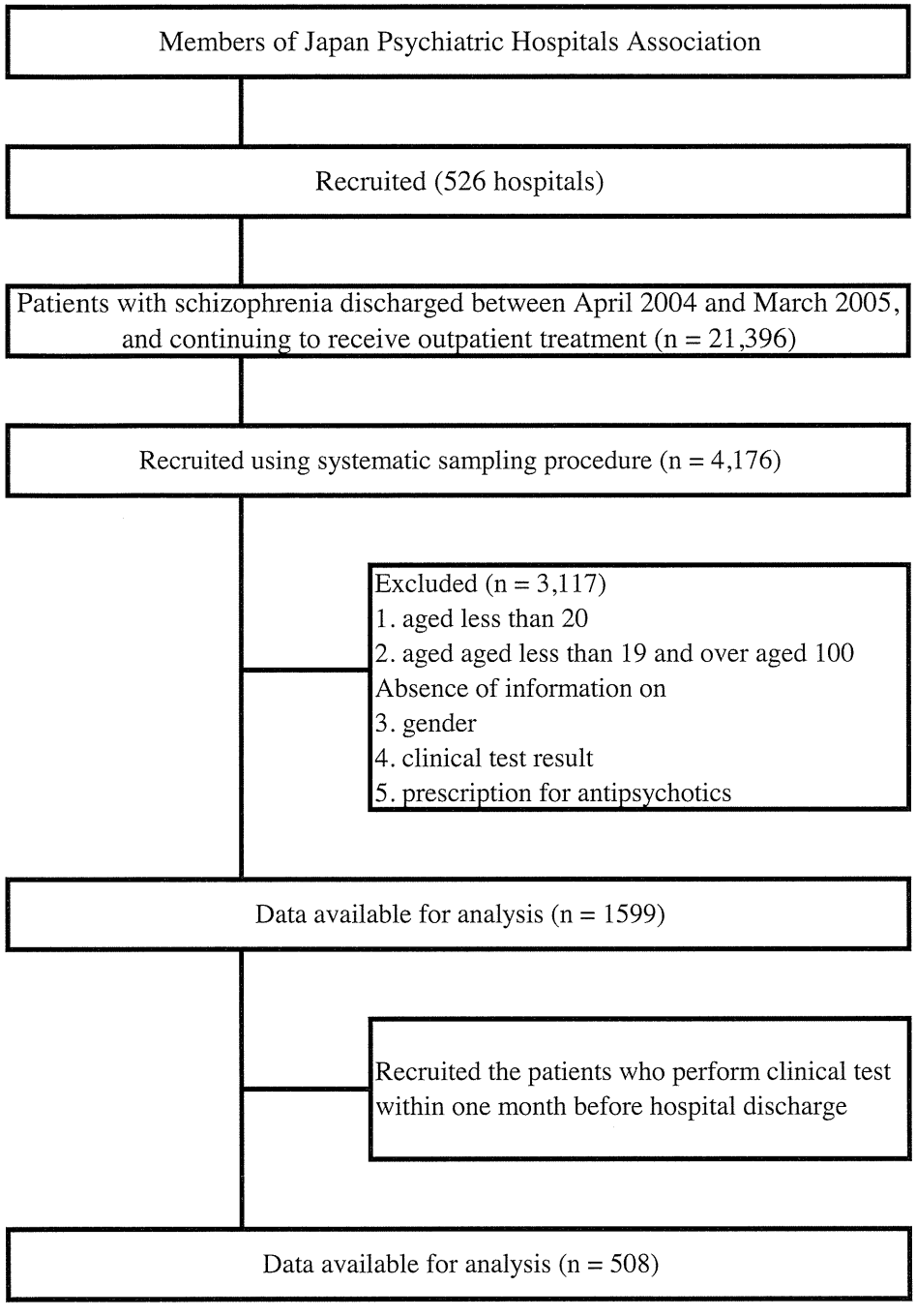

Table 1. Patient's demographics and clinical characteristics

Characteristic		Patient (n=508)	Average QTc(msec)	S.D.	*p*
Age					
	below the age of 60 years old	398	409.4	24.3	0.00
	over-60 years old	110	418.0	28.1	
Gender					
	Male	270	405.6	23.1	0.00
	Female	238	417.7	26.4	
History of cardiovascular disease					
	Yes	14	406.7	28.2	0.58
	No	494	411.4	25.3	
History of other physical illness					
	Yes	137	412.4	25.2	0.55
	No	371	410.9	25.5	
History of seen in other departments					
	Yes	440	411.7	25.6	0.38
	No	68	408.8	23.8	
Diabetes					
	Diabetes	50	408.1	25.8	0.35
	normal	458	411.6	25.3	
Smorking					
	Yes	239	406.8	22.7	0.00
	No	269	415.3	27.0	

Table 2. The number or dose of drug prescriptions by QTc

	Patients (n=508)	Rate of prescription (%)	Normal QTc	Long QTc	Rate of Long QTc(%)	95%CI	*p*
Dose prescribing (CPZEq)							
<1000mg CPZeq	370	72.8	317	53	14.3	0.621 to 1.857	0.80
1000mg CPZeq and over	138	27.2	117	21	15.2		
Number of antipsychotics							
Monotherapy	174	34.3	149	25	14.4	0.609 to 1.725	0.93
Polypharmacy	334	65.7	285	49	14.7		
Monotherapy							
TAP	36	7.1	34	2	5.6	0.763 to 15.157	0.09
AAP	119	27.0	99	20	16.8		
Polypharmacy							
TAP+TAP	107	21.1	90	17	15.9		
AAP+TAP	202	39.8	172	30	14.9		
AAP+AAP	25	4.9	23	2	8.0		