向精神薬によるQT延長

尾関祐二

獨協医科大学　精神神経医学講座

第105回東京精神医学会　　演者のCOI開示
演題発表に関連し、開示すべきCOI関係にある企業等はありません。

抗精神病薬、抗うつ薬と突然死

抗精神病薬を服用していると心臓突然死は増加する

● **Ray et al　N Engl J med　2009**

typical 44,218　atypical 46,089　control 186,600　虚血性心疾患のリスクを極力除外

typical　RR　**1.99**　(粗発生率　2.9/1,000人年)
atypical　RR　**2.26**　(粗発生率　2.8/1,000人年)

● **Murray-Thomas et al　Cardiovascular Psychiatry and Neurology 2013**

typical　115,491　atypical　67,901　control　544,726　non-user　193,920
年齢　性別　BMI　煙草　で補正

抗精神病薬使用者は健常人に比べて　RR　4.45　粗発生率　2.7/1,000　人年
non-userに比べて　RR　5.76

typical　粗発生率　3.8/1,000　人年
atypical　粗発生率　2.1/1,000　人年

突然死した統合失調症患者の剖検

●57人の突然死をした統合失調症患者　心筋梗塞52.9%、原因不明11.8%
（対象医療施設での統合失調症患者の0.79%；　一般人口の心臓突然死は0.1-0.2%）

51人で剖検　　55.9±9.4歳　男性　29名　　女性　22名

Cause of death	N (%)
Cardiovascular disorders	32 (62.8%)
Myocardial infarction	27 (52.9%)
Myocarditis	3 (5.9%)
Dilated cardiomyopathy	1 (2.0%)
Hemopericardium	1 (2.0%)
Respiratory disorders	11 (21.6%)
Pneumonia	6 (11.8%)
Airway obstruction	4 (7.8%)
Pulmonary embolus	1 (2.0%)
Neurological disorders	2 (3.9%)
Hemorrhagic stroke	1 (2.0%)
Brain tumor	1 (2.0%)
Unexplained	6 (11.8%)

心筋梗塞患者とそれ以外の患者で、年齢、性別、喫煙、喫煙、向精神薬量で差はない
(Ifeni P et al. Schizophrenia Research 2014)

●突然死し、剖検で死因が特定されず、向精神薬を服用していた患者10名(統合失調症9名)
missense polymorphysm　KCNQ1　8人
KCNH2　6人　　2遺伝子で7か所のpolymorphysmの例もあり
(Kamei S et al　Journal of Human Genetics 2014)

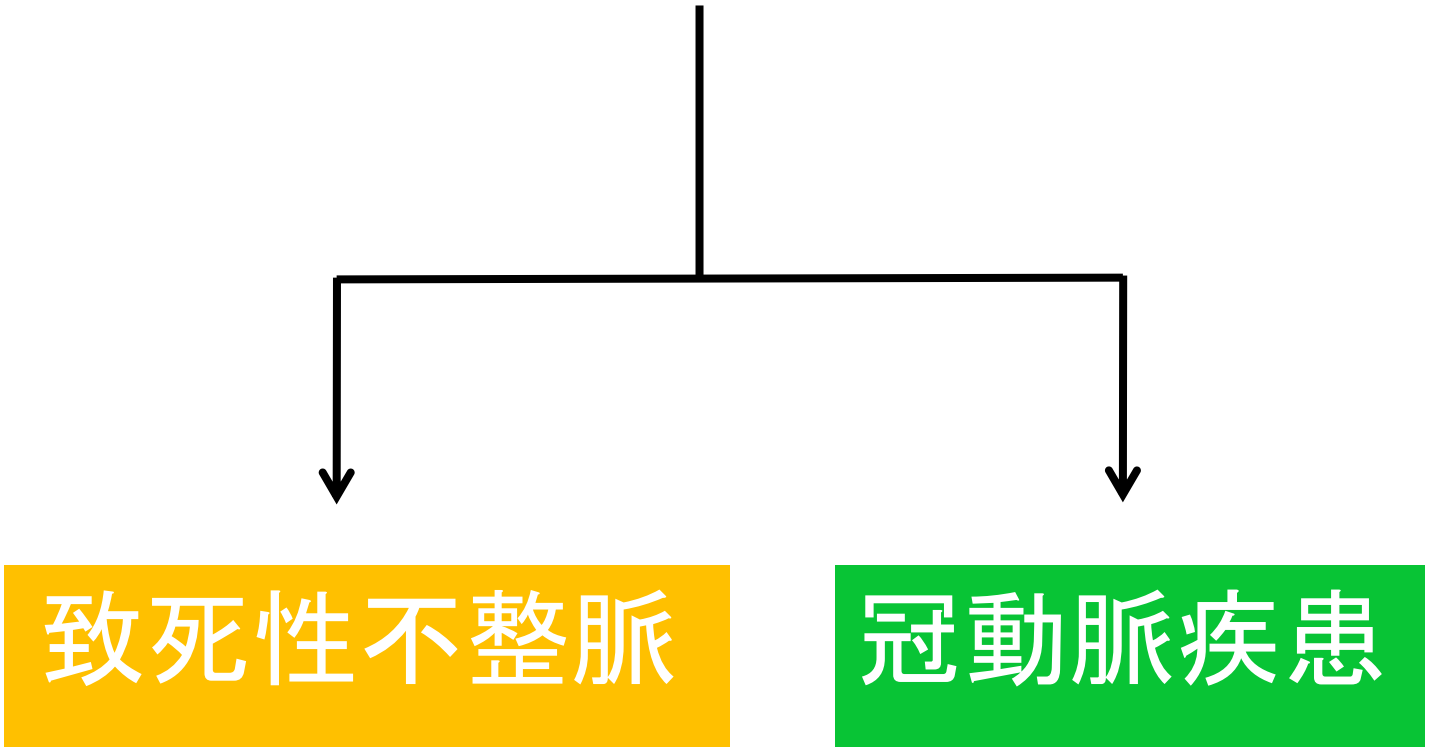
抗うつ薬と突然死

抗うつ薬は心室性不整脈の危険因子になる
(Vieweg WV et al Drugs Aging 2009)

30歳から50歳の女性看護師　75718人の調査
(Whang W et al J Am Coll Cardiol 2009)
（虚血性心疾患のリスクを極力除外）

抗うつ薬による心臓突然死	HR　3.34 (95% CI 2.03 to 5.50).
SSRI :	HR　5.07 (95% CI 1.73 to 14.8)
other antidepressant :	HR　3.19 (95% CI: 0.92 to 11.00)

心血管副作用としての突然死



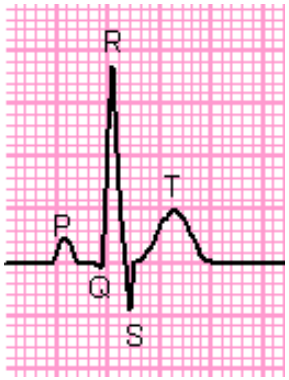
心室性不整脈による突然死は予測できるのか

心室性不整脈の危険因子

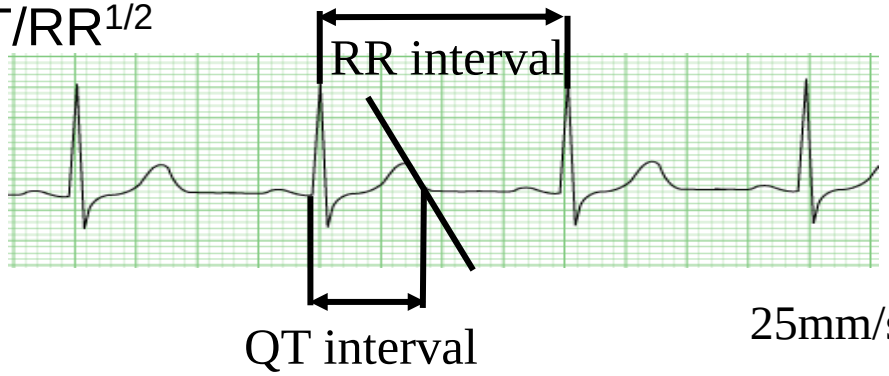
- 心臓における因子
  - QT延長症候群
  - 除脈
  - 虚血性心疾患
  - 心筋炎
  - 心筋梗塞
  - うっ血性心不全
- 代謝性因子
  - 低カリウム血症
  - 低マグネシウム血症
  - 低カルシウム血症
- その他の因子
  - 極端な身体運動
  - ストレスもしくはショック
  - 神経性無食欲症
  - 女性

(Taylor DM et al　Acta Psychiatr Scand　2003)

QT間隔は心室性不整脈の予測因子



$QTc=QT/RR^{1/2}$

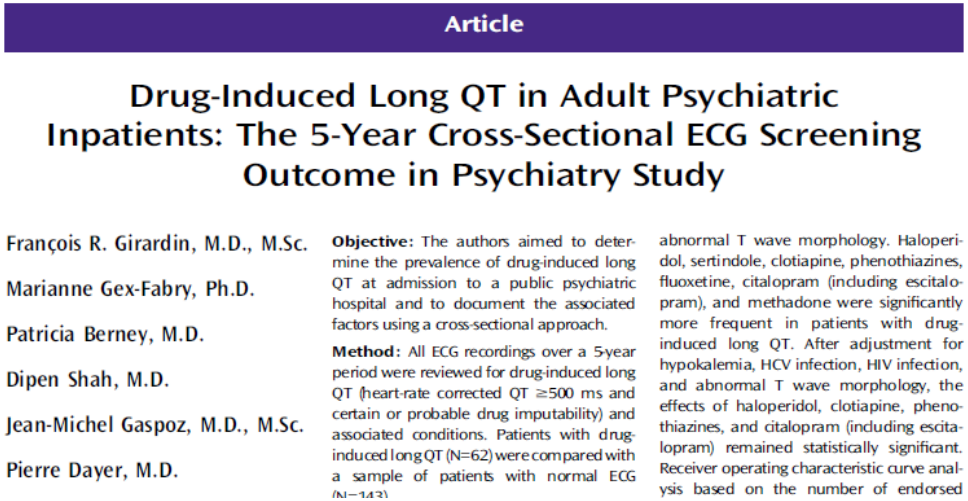


- QTの延長度は、催不整脈リスクの不完全なバイオマーカーの一つと認識されている（日米EU医薬品規制調和国際会議　ガイドラインE14　2005（以下ICH　E14））
- 心筋の脱分極から再分極までの時間を示していると考えられている
- 再分極までの時間が増加すれば、心室性不整脈の危険性が高まる
- 脈拍の影響を少なくするために、補正式が用いられる

Bazett:	$QTc = QT /(RR)^{1/2}$	(Bazett H, 1920)
Fridericia:	$QTc = QT /(RR)^{1/3}$	(Fridericia L, 1920)
Framingham:	$QTc= QT + 0.154 (1000 - RR)$	(Sagie A, 1992)
Hodges:	$QTc= QT + 105 (1/RR - 1)$	(Hodges MS, 1983)

QT間隔を延長させる危険因子 (ICH E14)

- 電解質異常の患者（例えば、低カリウム血症）
- うっ血性心不全の患者
- 薬物代謝能またはクリアランスに障害のある患者（例えば、腎臓または肝臓の障害、薬物相互作用が認められる場合）
- 女性の患者
- 年齢が16歳未満の患者及び65歳を超えた患者



Article

Drug-Induced Long QT in Adult Psychiatric Inpatients: The 5-Year Cross-Sectional ECG Screening Outcome in Psychiatry Study

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Objective: The authors aimed to determine the prevalence of drug-induced long QT at admission to a public psychiatric hospital and to document the associated factors using a cross-sectional approach.

Method: All ECG recordings over a 5-year period were reviewed for drug-induced long QT (heart-rate corrected QT ≥500 ms and certain or probable drug imputability) and associated conditions. Patients with drug-induced long QT (N=62) were compared with a sample of patients with normal ECG (N=143)

abnormal T wave morphology. Haloperidol, sertindole, clotiapine, phenothiazines, fluoxetine, citalopram (including escitalopram), and methadone were significantly more frequent in patients with drug-induced long QT. After adjustment for hypokalemia, HCV infection, HIV infection, and abnormal T wave morphology, the effects of haloperidol, clotiapine, phenothiazines, and citalopram (including escitalopram) remained statistically significant. Receiver operating characteristic curve analysis based on the number of endorsed

Girardin et al 2013 American Journal of Psychiatry

5年間6,790人の入院患者のうち、62人(0.91%）は薬剤性のQTc延長(QTc>500)をきたした

薬剤性のQT延長をきたした群とそうでない群で比較したとき、薬剤性のQTc延長をきたす下記因子が見いだされた

- 低カリウム
- HCV　感染症
- HIV　感染症
- Abnormal T wave morphology

（非対称　平坦、U波）

抗精神病薬、抗うつ薬とQT間隔

抗うつ薬とQT間隔

Original Paper

Pharmacotherapeutic Determinants for QTc Interval Prolongation in Japanese Patients with Mood Disorder

Authors

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Okayasu et al Psychopharmacology 2012

Distribution of medication and dosage

Administrated drugs	No. of patients n=729 (%)	Mean dose (SD), mg
Antidepressants (dose: Imipramine eq.)	502(68.9)	125.9(84.1)
TCA (dose: Imipramine eq.)	230(31.6)	105.0(63.6)
non TCA (dose: Imipramine eq.)	395(54.2)	98.9(61.9)
Paroxetine	129(17.7)	22.5(11.2)
Milnacipran	107(14.7)	84.7(37.0)
Mianserin	106(14.5)	25.9(23.3)
Amoxapine	94(12.9)	84.9(47.4)
Fluvoxamine	70(9.6)	105.4(49.3)
Clomipramine	60(8.2)	98.2(51.4)
Trazodone	56(7.7)	58.9(59.4)
Amitriptyline	43(5.9)	77.9(46.5)
Nortriptyline	28(3.8)	62.1(35.7)
Imipramine	22(3.0)	77.5(64.3)
Maprotiline	21(2.9)	61.3(30.6)
Sertraline	20(2.7)	53.8(26.0)
Mood stabilizers		
Carbamazepine	27(3.7)	369.0(208.8)
Sodium Valproate	69(9.5)	491.3(272.1)
Lithium	86(11.8)	516.3(252.0)
Antipsychotics (dose: chlorpromazine eq.)	280(38.4)	176.7(230.9)
Benzodiazepines (dose: diazepam eq.)	530(72.7)	15.3(26.9)
Antiparkinsonian drugs (dose: biperiden eq.)	59(8.1)	2.3(1.4)

eq: equivalent; TCA: tricyclic antidepressant

QTc prolongation effect of each neurotropic drug

	Forced entry model	Stepwise selection model
	Partial regression coefficient (95%CI)	Partial regression coefficient (95%CI)
age	0.23 (0.11-0.35)**	0.21 (0.09-0.33)**
sex	12.12 (8.13-16.10)**	12.09 (8.14-16.04)**
TCA (100mg)	5.23 (2.00-8.46)**	5.41 (2.21-8.61)**
non-TCA (100mg)	0.19 (-2.73-3.11)	
Chlorpromazine eq. (100mg)	1.39 (0.04-2.74)*	1.38 (0.22-2.54)*
Biperiden eq. (100mg)	0.09 (-2.91-3.08)	
Lithium(100mg)	0.15 (-1.01-1.31)	
Sodium Valproate (100mg)	0.63 (-0.57-1.82)	
Carbamazepine (100mg)	-1.28 (-3.76-1.20)	
Diazepam eq. (1mg)	0.06 (-0.03-0.14)	

**: p<0.01, *: p<0.05

TCA: tricyclic antidepressant, eq: equivalent dose

QTc prolongation effect of each antidepressant

	Foreced entry model	Stepwise selection model
	Partial regression coefficient (95%CI)	Partial regression coefficient (95%CI)
Age	0.19 (0.07-0.31)**	0.19 (0.07-0.31)**
Sex (risk of female)	11.9 (7.92-15.87)**	11.56 (7.64-15.48)**
Lithium(100mg)	0.61 (-0.45-1.66)	
Sodium Valproate (100mg)	0.79 (-0.40-1.98)	
Carbamazepine (100mg)	-1.10 (-3.53-1.33)	
Paroxetine (40mg)	1.05 (-6.97-9.07)	
Milnacipran (150mg)	7.20 (-1.55-15.94)	
Mianserin (60mg)	-5.38 (-14.68-3.92)	
Amoxapine (150mg)	-0.92 (-9.78-7.93)	
Fluvoxamine (150mg)	-6.55 (-15.01-1.90)	
Clomipramine (120mg)	18.43 (10.75-26.11)**	16.77 (9.27-24.27)**
Trazodone (300mg)	23.93 (-1.64-49.50)	
Amitriptyline (150mg)	18.28 (4.68-31.87)**	16.03 (2.65-29.41)*
Nortriptyline (150mg)	12.75 (-8.27-33.77)	
Imipramine (150mg)	-8.96 (-25.83-7.91)	
Maprotiline (150mg)	17.56 (-7.86-42.98)	
Sertraline (100mg)	-0.34 (-20.64-19.96)	

**: $p<0.01$, *: $p<0.05$

BMJ

BMJ 2013;346:f288 doi: 10.1136/bmj.f288 (Published 29 January 2013)

RESEARCH

QT interval and antidepressant use: a cross sectional study of electronic health records

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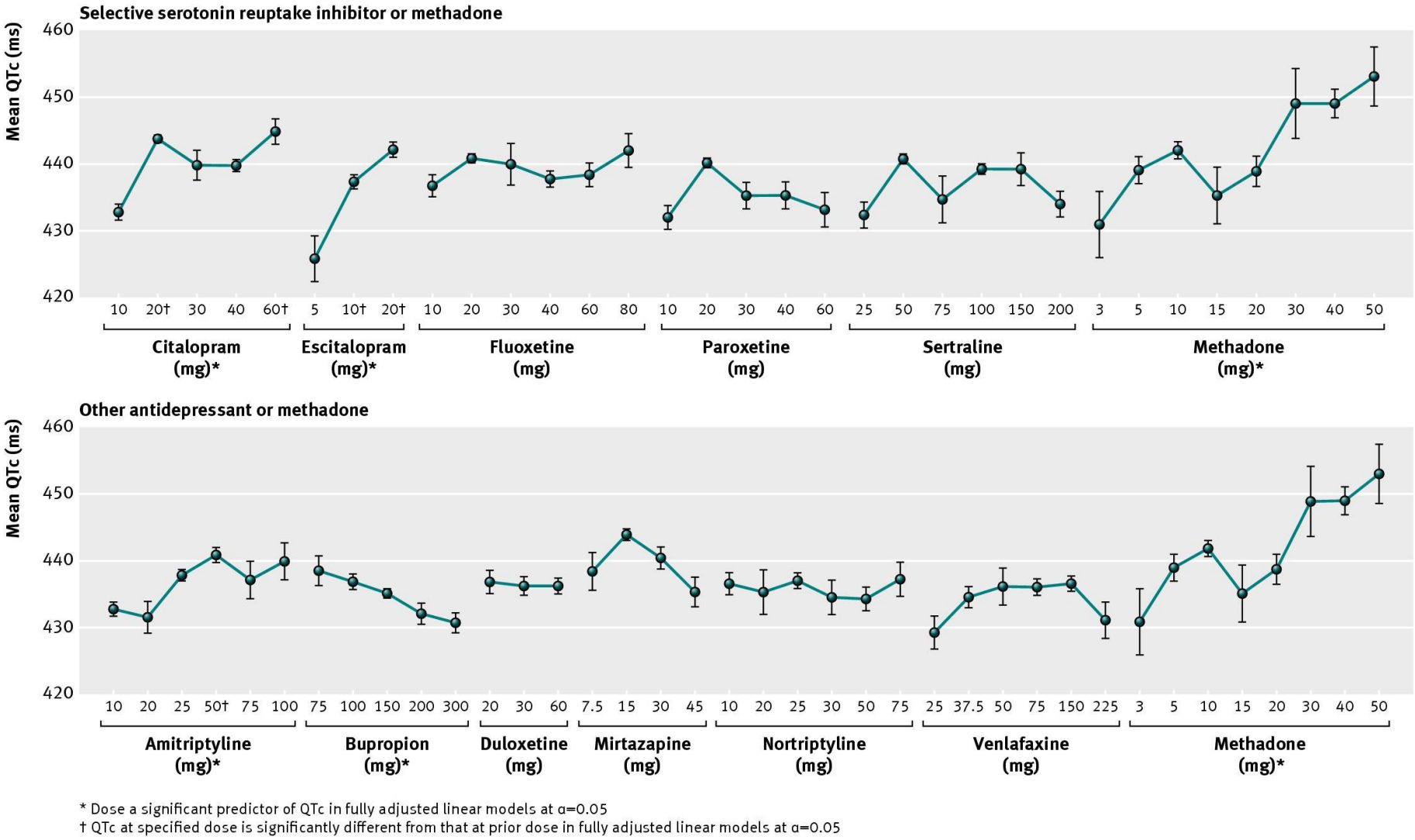
Table 2| **Overall effect of dose of antidepressant or methadone on corrected QT (QTc) interval 14–90 days after drug prescription in cohort of 38 397 adult patients. Results are beta values (SE) from linear regression analysis**

Drug	Unadjusted model	Adjusted model†
SSRIs:		
Citalopram	0.02 (0.04)	0.10 (0.04)**
Escitalopram	0.60 (0.15)***	0.58 (0.15)***
Fluoxetine	−0.01 (0.03)	0.07 (0.03)
Paroxetine	−0.07 (0.07)	0.03 (0.07)
Sertraline	−0.02 (0.01)	0.01 (0.01)
Other antidepressants:		
Amitriptyline	0.10 (0.03)***	0.11 (0.03)***
Bupropion	−0.03 (0.01)***	−0.02 (0.01)*
Duloxetine	−0.00 (0.05)	0.02 (0.05)
Mirtazapine	−0.22 (0.08)**	−0.13 (0.08)
Nortriptyline	−0.01 (0.04)	0.04 (0.04)
Venlafaxine	0.01 (0.01)	0.01 (0.01)

(Castro VM et al Bmj 2013)



* Dose a significant predictor of QTc in fully adjusted linear models at α=0.05
† QTc at specified dose is significantly different from that at prior dose in fully adjusted linear models at α=0.05

Mean (SD) corrected QT (QTc) interval recorded on electrocardiogram 14–90 days after prescription of antidepressant or methadone, by drug dose

(Castro VM et al Bmj 2013)

SSRIもQT間隔延長を引き起こす

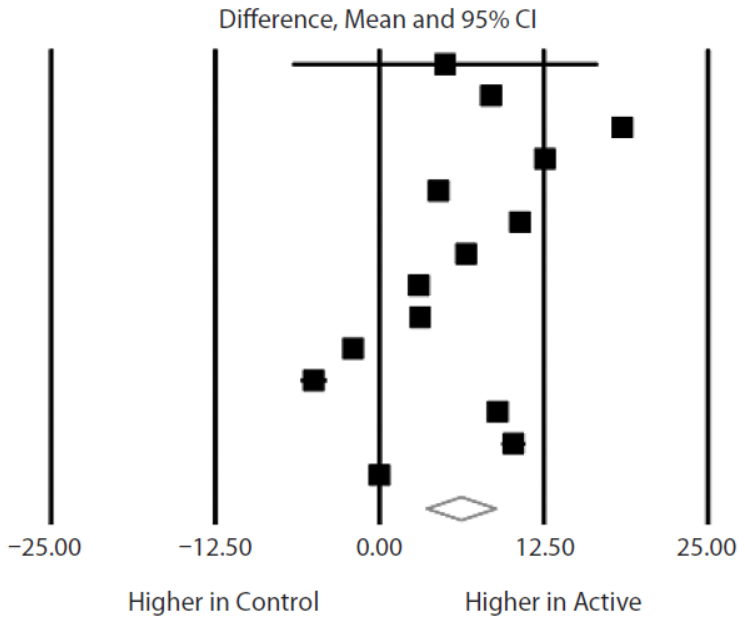
Beach SR et al J Clin Psychiatry 2014

14論文2,599人の患者を対象としたメタアナリシス： QTcへの影響 SSRI > placebo

11論文1,399人の患者を対象としたメタアナリシス： QTcへの影響 TCA > SSRI

Figure 2. Effects of Selective Serotonin Reuptake Inhibitors on QTc When Compared to Placebo

Study	N	Mean difference in QTc, ms	Standard Error	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Edwards et al[17]	20	5.00	5.96	−6.69	16.69	.4019
FDA-1[8]	120	8.50	0.09	8.33	8.67	< .001
FDA-2[8]	120	18.50	0.09	18.33	18.67	< .001
FDA-3 (modeled)[8]	120	12.60	0.09	12.43	12.77	< .001
FDA-4[26]	120	4.50	0.09	4.33	4.67	< .001
FDA-5[26]	120	10.70	0.09	10.53	10.87	< .001
FDA-6 (modeled)[26]	120	6.60	0.09	6.43	6.77	< .001
Glassman et al[23]	369	3.00	0.02	2.95	3.05	< .001
Lesperance et al[25]	284	3.10	0.02	3.06	3.14	< .001
Nelson et al[21]	1,466	−2.00	0.00	−2.00	−2.00	< .001
Robinson and Doogan[12]	27	−5.00	0.53	−6.05	−3.95	< .001
Roose et al[15]	87	9.00	0.38	8.26	9.74	< .001
Slavicek et al[24]	52	10.20	0.48	9.25	11.15	< .001
Strik et al[16]	54	0.00	0.31	−0.61	0.61	1.0000
Total	**3,079**	**6.10**	**1.34**	**3.47**	**8.73**	**< .001**



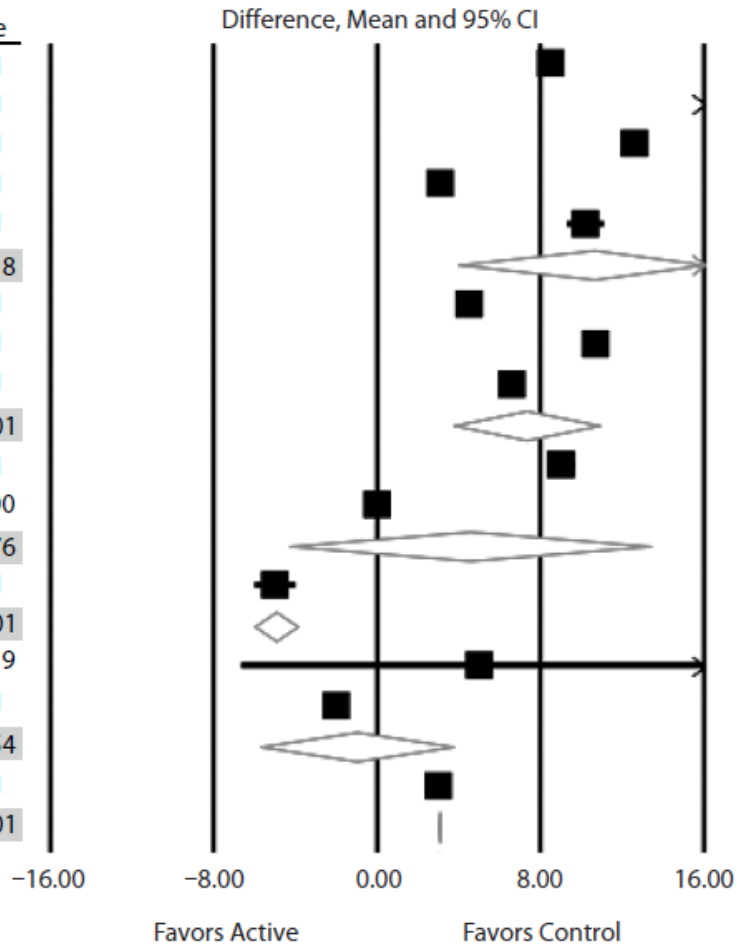
Abbreviations: FDA = US Food and Drug Administration, QTc = corrected QT interval.

Citalopramが最もQT間隔への影響が大きい

Beach SR et al J Clin Psychiatry 2014

Figure 4. Effects of Individual Selective Serotonin Reuptake Inhibitors (SSRIs) on QTc When Compared to Placebo

SSRI	Study	N	Mean Difference in QTc, ms	Standard Error	95% CI Lower Limit	95% CI Upper Limit	*P* Value
Citalopram	FDA-1[8]	120	8.50	0.09	8.33	8.67	< .001
Citalopram	FDA-2[8]	120	18.50	0.09	18.33	18.67	< .001
Citalopram	FDA-3 (modeled)[8]	120	12.60	0.09	12.43	12.77	< .001
Citalopram	Lesperance et al[25]	284	3.10	0.02	3.06	3.14	< .001
Citalopram	Slavicek et al[24]	52	10.20	0.48	9.25	11.15	< .001
Citalopram		696	10.58	3.39	3.93	17.23	.0018
Escitalopram	FDA-4[26]	120	4.50	0.09	4.33	4.67	< .001
Escitalopram	FDA-5[26]	120	10.70	0.09	10.53	10.83	< .001
Escitalopram	FDA-6 (modeled)[26]	120	6.60	0.09	6.43	9.74	< .001
Escitalopram		360	7.27	1.82	3.78	10.83	< .0001
Fluoxetine	Roose et al[19]	81	9.00	0.38	8.26	13.32	< .001
Fluoxetine	Strik et al[16]	54	0.00	0.31	−0.61	−3.95	1.0000
Fluoxetine		135	4.50	4.50	−4.32	13.32	.3176
Fluvoxamine	Robinson ad Doogan[12]	27	−5.00	0.53	−6.05	16.69	< .001
Fluvoxamine		27	−5.00	0.53	−6.05	−3.95	< .0001
Paroxetine	Edwards et al[17]	20	5.00	5.96	−6.69	3.68	.4019
Paroxetine	Nelson et al[21]	1,466	−2.00	0.00	−2.00	3.05	< .001
Paroxetine		1,486	−1.04	2.41	−5.76	3.68	.6654
Sertraline	Glassman et al[23]	369	3.00	0.02	2.95		< .001
Sertraline		369	3.00	0.02	2.95	3.05	< .0001



Abbreviations: FDA = US Food and Drug Administration, QTc = corrected QT interval.

抗精神病薬とQT間隔

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QTc prolongation and antipsychotic medications in a sample of 1017 patients with schizophrenia

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Medication and rate of QTc prolongation in 1017 schizophrenic patients

administrated drugs	No. of Patients n= 1017(100 %)	Mean Dose (SD), mg	prevalence of QTc prolongation (male: > 470 ms, female > 480 ms)
Equivalent dose			
CP eq.	875(86)	963.0 (879.0)	23 (2.6)
Diazepam eq.	672(66)	14.6 (14.6)	18 (2.7)
Biperiden eq.	645(63)	3.8 (2.2)	19 (2.9)
Mood stabilizer			
CBZ	74(7)	478.9 (201.8)	3 (4.1)
VPA	54(5)	650.0 (334.1)	1 (1.9)
Lithium	47(5)	587.2 (199.6)	4 (8.5)
Antipsychotics			
HPD	375(37)	15.9 (12.6)	16 (4.3)
CP	299(29)	190.5 (198.7)	9 (3.0)
LP	258(25)	91.9 (94.5)	14 (5.4)
Risperidone	248(24)	5.6 (3.7)	4 (1.6)
Zotepine	116(11)	179.9 (124.9)	3 (2.6)
Olanzapine	104(10)	15.6 (6.4)	0 (0.0)
Quetiapine	60(6)	375.5 (258.5)	0 (0.0)
Bromperidol	49(5)	10.7 (8.6)	0 (0.0)
Sultopride	49(5)	1032.9 (810.2)	10 (20.4)
HPD iv	47(5)	16.0 (10.5)	8 (17.0)

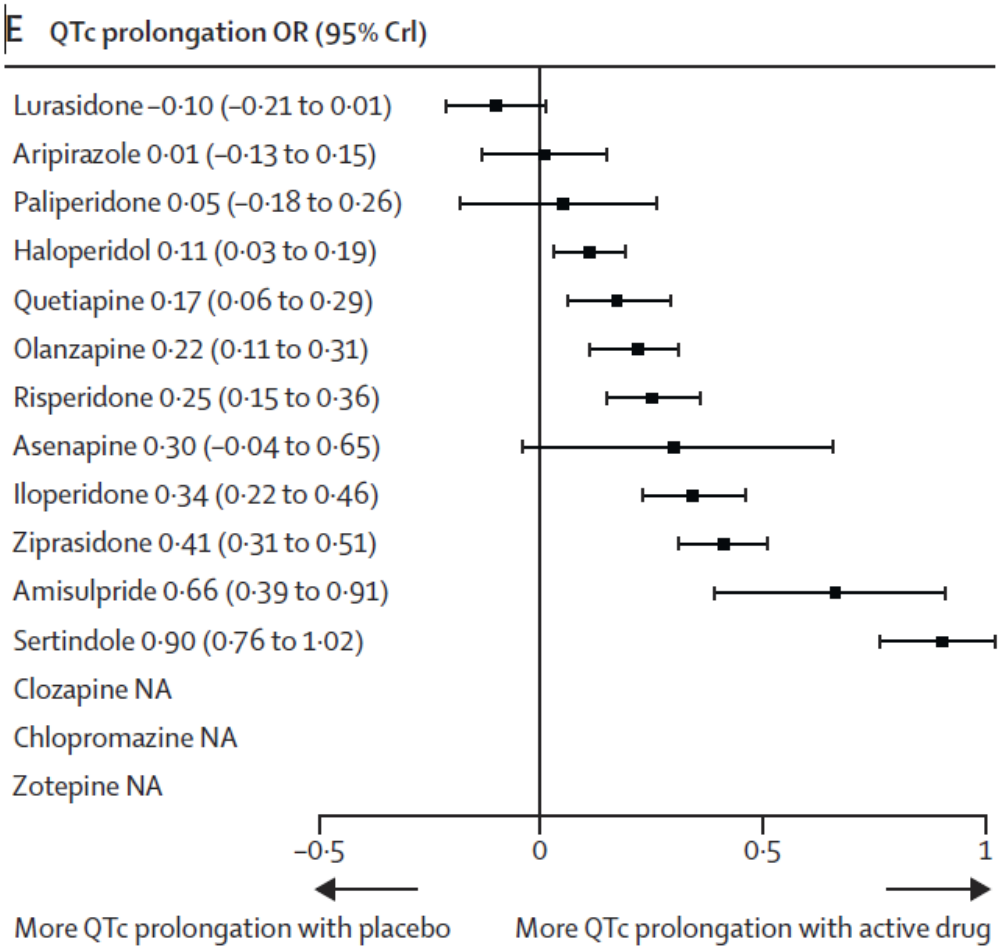
QTc prolongation effect of each antipsychotic by linear regression model

	Forced Entry Model	Stepwise Selection Model
	Coefficient (95% CI)	Coefficient (95% CI)
Age	0.19 (0.10 - 0.28)*	0.20 (0.11 - 0.29)*
Sex (risk of female)	3.22 (- 0.01 - 6.44)	
HPD (2mg)	0.42 (0.09 - 0.76)	
CP (100mg)	3.91 (2.69 - 5.13)*	3.82 (2.62 - 5.02)*
LP (100mg)	4.87 (2.14 - 7.60)*	4.65 (1.94 - 7.37)*
Risperidone (1mg)	0.07 (- 0.47 - 0.61)	
Zotepine (66mg)	- 0.36 (- 1.91 - 1.20)	
Olanzapine (2.5mg)	0.30 (- 0.47 - 1.08)	
Quetiapine (66mg)	0.11 (- 0.87 - 1.09)	
Bromperidol (2mg)	0.08 (- 1.00 - 1.16)	
Sultopride (200mg)	3.65 (2.48 - 4.82)*	3.56 (2.41 - 4.72)*
HPD iv (2mg)	3.16 (2.36 - 3.96)*	3.13 (2.34 - 3.93)*

*p < 0.001

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis



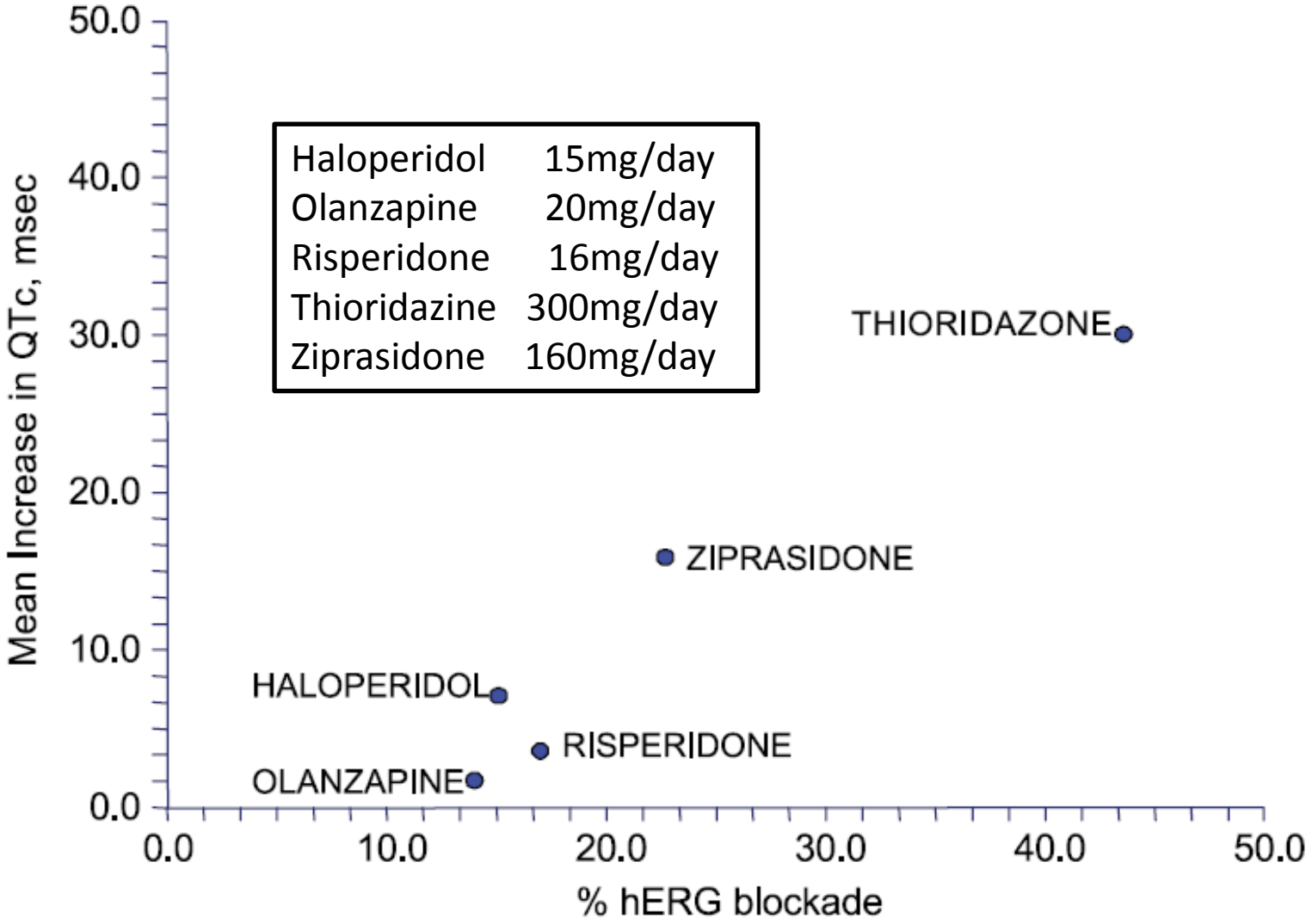
(Leucht S et al Lancet 2013)

QTc延長への寄与率

因子	寄与率 (%)
年齢	6.2
HPD iv	4.9
Chlorpromazine	4.1
Sultopride	3.7
Levomepromazine	1.9
Haloperidol	1.4
	16.5

なぜQT間隔は延長するのか

hERG (KCNH2)チャネルの阻害とQTc間隔



William et al Pharmaceutical Research 2006

KCNH2(hERG)遺伝子は統合失調症と関連する

Hashimoto R et al	World J Biol Psychiatry 2013
Apud JA et al	Am J Psychiatry 2012
Atalar F et al	Behav Brain Funct 2010
Huffaker SJ et al	Nat Med 2009

統合失調症患者は内服前から軽度QT間隔が延長している？

OPEN ACCESS Freely available online

PLOS ONE

QT Is Longer in Drug-Free Patients with Schizophrenia Compared with Age-Matched Healthy Subjects

Kumiko Fujii[1], Yuji Ozeki[1,2]*, Hiroaki Okayasu[1], Yumiko Takano[1], Takahiro Shinozaki[1], Hiroaki Hori[2], Masami Orui[3], Minoru Horie[4], Hiroshi Kunugi[2], Kazutaka Shimoda[1]

1 Department of Psychiatry, Dokkyo Medical University School of Medicine, Tochigi, Japan, **2** Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan, **3** Department of Health Care, Dokkyo Medical University School of Medicine, Tochigi, Japan, **4** Department of Cardiovascular and Respiratory Medicine, Shiga University School of Medical Science, Shiga, Japan

Abstract

The potassium voltage-gated channel KCNH2 is a well-known gene in which mutations induce familial QT interval prolongation. KCNH2 is suggested to be a risk gene for schizophrenia. Additionally, the disturbance of autonomic control, which affects the QT interval, is known in schizophrenia. Therefore, we speculate that schizophrenic patients have characteristic features in terms of the QT interval in addition to the effect of antipsychotic medication. The QT interval of patients with schizophrenia not receiving antipsychotics (n = 85) was compared with that of patients with schizophrenia receiving relatively large doses of antipsychotics (n = 85) and healthy volunteers (n = 85). The QT interval was corrected using four methods (Bazett, Fridericia, Framingham or Hodges method). In ANCOVA with age and heart rate as covariates, patients not receiving antipsychotic treatment had longer QT intervals than did the healthy volunteers, but antipsychotics prolonged the QT interval regardless of the correction method used ($P<0.01$). Schizophrenic patients with and without medication had a significantly higher mean heart rate than did the healthy volunteers, with no obvious sex-related differences in the QT interval. The QT interval prolongation may be manifestation of a certain biological feature of schizophrenia.

Citation: Fujii K, Ozeki Y, Okayasu H, Takano Y, Shinozaki T, et al. (2014) QT Is Longer in Drug-Free Patients with Schizophrenia Compared with Age-Matched Healthy Subjects. PLoS ONE 9(6): e98555. doi:10.1371/journal.pone.0098555

Editor: Peter John McKenna, Benito Menni Complejo Asistencial en Salud Mental, Spain

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Table 3. Demographic data of participants whose heart rate is less than 90 beats per minutes.

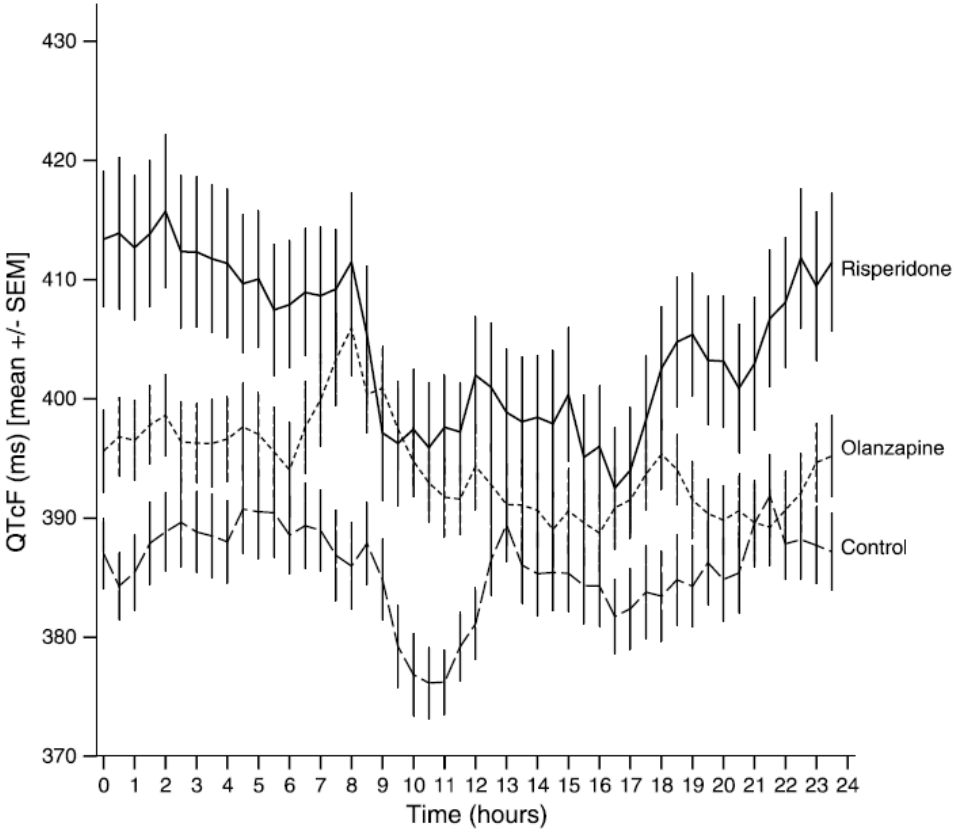
	Normal control	Schizophrenia (drug free)	Schizophrenia (medication)
N	83	55	65
Chlorpromazine equivalent daily dose (SD):mg/day	_	0	1654.2(1313.7)
Male(n, %)	37(45)	24(44)	31(48)
Age, years (SD)	42.4(5.5)	40.4(14.2)	40.3(14.3)
Smoking (n, %)*	19(45)	23(42)	28(43)
Pulse, beat per minute (SD)**	63.3(7.8)	68.9(11.9)	73.4(11.0)
QTcB (SD)$^{+}$:msec	390.5(21.3)	408.8(25.2)	427.1(28.9)
QTcFri (SD)$^{+}$:msec	387.5(18.5)	400.6(26.5)	414.0(29.8)
QTcFra (SD)$^{+}$:msec	387.5(18.8)	401.4(24.7)	414.7(27.5)
QTcH (SD)$^{+}$:msec	387.5(18.0)	401.4(26.1)	413.2(28.1)

Pulse$<$90.
Statistically Significant *p$<$.05; **p$<$.01 by one-way ANOVA
Statistically Significant $^{+}$p$<$.01 by ANCOVA.
doi:10.1371/journal.pone.0098555.t003

QT間隔は　突然死予測因子として理想的か？

QT間隔はよい予測因子なのか？

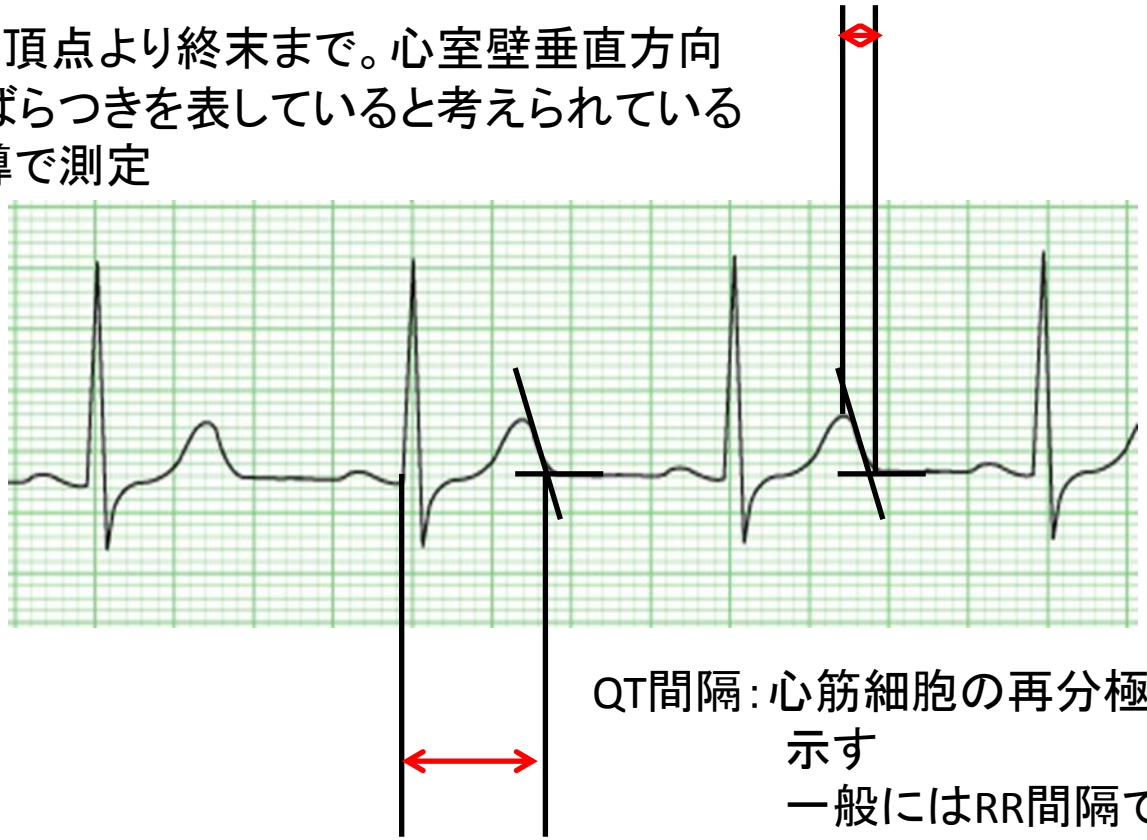
心拍数に影響を受ける
測定時間に影響を受ける
QTの絶対値とQTcのどちらが重要か結論は出ていない



Watanabe J Journal of Clinical Psychopharmacology 2011

心室性不整脈を予測する因子

Tp-e： T波の頂点より終末まで。心室壁垂直方向の再分極のばらつきを表していると考えられている
今回はV_5誘導で測定



QT間隔：心筋細胞の再分極のばらつきを示す
一般にはRR間隔で補正して評価し、補正方法としては
Bazett（$QT/RR^{1/2}$）などが
用いられる　原法はII誘導で測定

QT dispersion（QTD）： 心電図におけるすべての誘導のうち最大値と最小値の差
単純なQT間隔より再分極のばらつきをより評価できる

QT dispersion

QT 間隔は脱分極から再分極を表すのに対してQT dispersionは心室の再分極のばらつきを見るものでありQT延長症候群以外に
うっ血性心不全などでも心室性不整脈の予測因子となる。
(Pan KL et al Int Heart J 2011)

Tp-e (T peak to end)

心筋の垂直方向の再分極のばらつきを見ることができ、QT間隔では予測ができないような突然死を予測することができる(Brugada Syndromeやhypertrophic cardiomyopathyで報告あり)
(Barbhaiy C et al Pacing and Clinical Electrophysiology 2013)

Tp-e/QT

Tp-eは心拍数に影響を受けるので、心拍数に影響を受けにくいTp-e/QTがより正確に心室性不整脈を予測できる指摘する報告もある
(Zhao X Clin. Cardiol. 2012)

QT間隔以外の
心室性不整脈による突然死予測因子

-Brugada型の心電図-

統合失調症患者ではBrugada型の心電図が多く認められる

Blom et al ***Circ Arrhythm Electrophysiol*. 2014**

Original Article

Brugada Syndrome ECG Is Highly Prevalent in Schizophrenia

Marieke T. Blom, MA, MSE; Dan Cohen, MD, PhD; Adrie Seldenrijk, MSc, PhD; Brenda W.J.H. Penninx, MSc, PhD; Giel Nijpels, MD, PhD; Coen D.A. Stehouwer, MD, PhD; Jacqueline M. Dekker, MSc, PhD; Hanno L. Tan, MD, PhD

Background—The causes of increased risk of sudden cardiac death in schizophrenia are not resolved. We aimed to establish (1) whether ECG markers of sudden cardiac death risk, in particular Brugada-ECG pattern, are more prevalent among patients with schizophrenia, and (2) whether increased prevalence of these ECG markers in schizophrenia is explained by confounding factors, notably sodium channel–blocking medication.

Methods and Results—In a cross-sectional study, we analyzed ECGs of a cohort of 275 patients with schizophrenia, along with medication use. We determined whether Brugada-ECG was present and assessed standard ECG measures (heart rate, PQ-, QRS-, and QT-intervals). We compared the findings with nonschizophrenic individuals of comparable age (the Netherlands Study of Depression and Anxiety [NESDA] cohort; N=179) and, to account for assumed increased aging rate in schizophrenia, with individuals 20 years older (Hoorn cohort; n=1168), using multivariate regression models. Brugada-ECG was significantly more prevalent in the schizophrenia cohort (11.6%) compared with NESDA controls (1.1%) or Hoorn controls (2.4%). Moreover, patients with schizophrenia had longer QT-intervals (410.9 versus 393.1 and 401.9 ms; both $P<0.05$), increased proportion of mild or severe QTc prolongation (13.1% and 5.8% versus 3.4% and 0.0% [NESDA], versus 5.1 and 2.8% [Hoorn]), and higher heart rates (80.8 versus 61.7 and 68.0 beats per minute; both $P<0.05$). The prevalence of Brugada-ECG was still increased (9.6%) when patients with schizophrenia without sodium channel–blocking medication were compared with either of the control cohorts.

Conclusions—Brugada-ECG has increased prevalence among patients with schizophrenia. This association is not explained by the use of sodium channel–blocking medication. (***Circ Arrhythm Electrophysiol*. 2014;7:384-391.**)

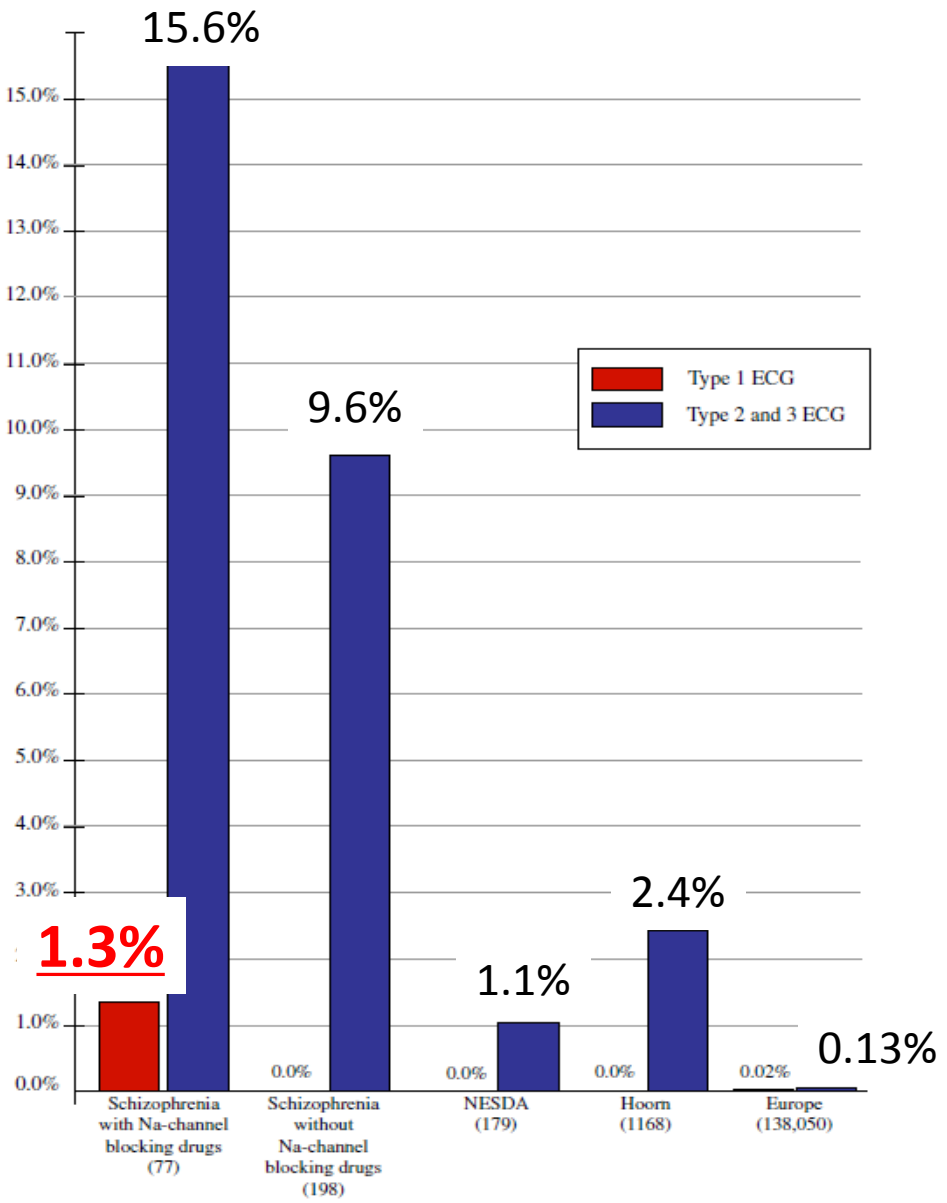
Key Words: Brugada Syndrome ■ electrocardiography ■ schizophrenia

Patients with severe mental illness have 14 to 32 years reduced life expectancy.[1] Schizophrenia is associated with increased standardized mortality ratios for all-cause death,[2] cardiovascular death,[3] and sudden cardiac death (SCD).[4] The causes for SCD risk in schizophrenia are unresolved.[5] SCD is mostly caused by lethal cardiac arrhythmias resulting from disrupted cardiac electrophysiology (depolarization

individuals.[3] The possibility that inherited factors are also relevant has so far received less recognition.

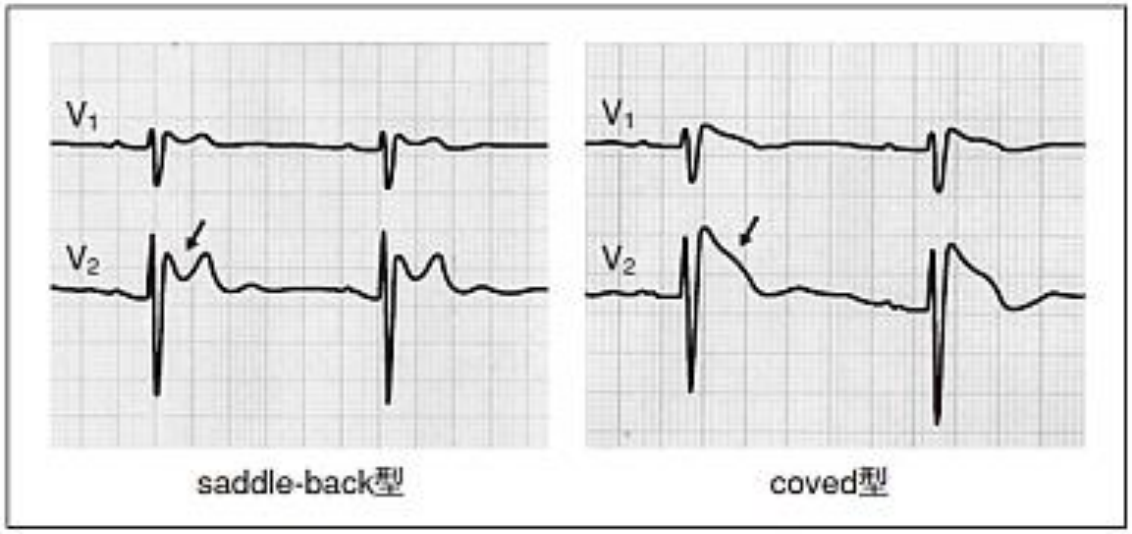
Editorial see p 365
Clinical Perspective on p 391

These considerations prompted us to conduct the present study. We systematically compared ECGs of a cohort of patients with schizophrenia to ECGs of 2 cohorts of non-



ブルガダ症候群

Brugada 症候群は心電図で右脚ブロック様波形と，V1～V3 誘導における特徴的なST 上昇を呈し，**主に夜間に心室細動で突然死する疾患**



Brugada症候群における特徴的ST上昇

西崎光弘： Brugada症候群の診断基準　心電図診断と負荷試験　医学の歩み　2008年

ブルガダ症候群

- 男性に多い
- 有病率　0.15%　　罹患率　0.014%
- SCN5A　チャネル（Naチャネル）異常が一部に確認されている
- 重篤な心事故を発症；　心室細動の既往例　17%/年
  失神の既往例　6%/年　無症候性では0.5-4%/年
- 植え込み型除細動器（ICD:　Implantable Cardioverter Defibrillator ）で治療
- 危険性：　coved型＞saddle back型
- 三環系抗うつ薬はリスクのひとつ

Brugada型心電図患者の治療方針（鎌倉氏）

Brugada型心電図	既往		心電図自然Type1	家族歴	年間心事故発生率	治療	備考
	心室細動	失神					
○	○				10.3%	ICD	
○	(-)	○	○	○	4.5%	ICD	
○	(-)	○	○	(-)	0.0%	経過観察	要検討
○	(-)	○	Type1以外		0.5%	経過観察	要検討
○	(-)	(-)	○	○	3.4%	ICD	
○	(-)	(-)	○	(-)	0.3%	経過観察	
○	(-)	(-)	Type1以外		0.1%	経過観察	

日経メディカル2007.8

向精神薬による心室性不整脈予測の今後

- 抗精神病薬や抗うつ薬による突然死を
  より正確に予測する因子はあるのか

- 遺伝的な要因からリスクを予測する

- QT以外にも注意すべき点がある

日本精神神経学会向精神薬の副作用診断・治療対応マニュアル タスクフォース

向精神薬の副作用モニタリング・対応マニュアル

【薬物性QT延長症候群】

内田裕之
齊尾武郎、鈴木映二、鈴木雄太郎、高橋啓介、中川敦夫、三國雅彦、山田和男

1. QTC値が440ms以上の場合に、QT延長症候群と診断される。

2. とくにQTCが500 msを超える場合，重篤な不整脈を誘発するリスクは高くなる。

3. 様々な向精神薬がQT延長を引き起こしうることを念頭におくべきである。

4. QTc値が440ms以上（男性）もしくは470ms以上（女性）の場合は、減量あるいは他の薬への変更、循環器科医への相談が望ましい。

5. QTc値が500ms以上の場合は、原因薬の中止または他の薬への変更を行い、速やかに循環器科医へ相談する。

現時点で考えられる　致死的不整脈の回避

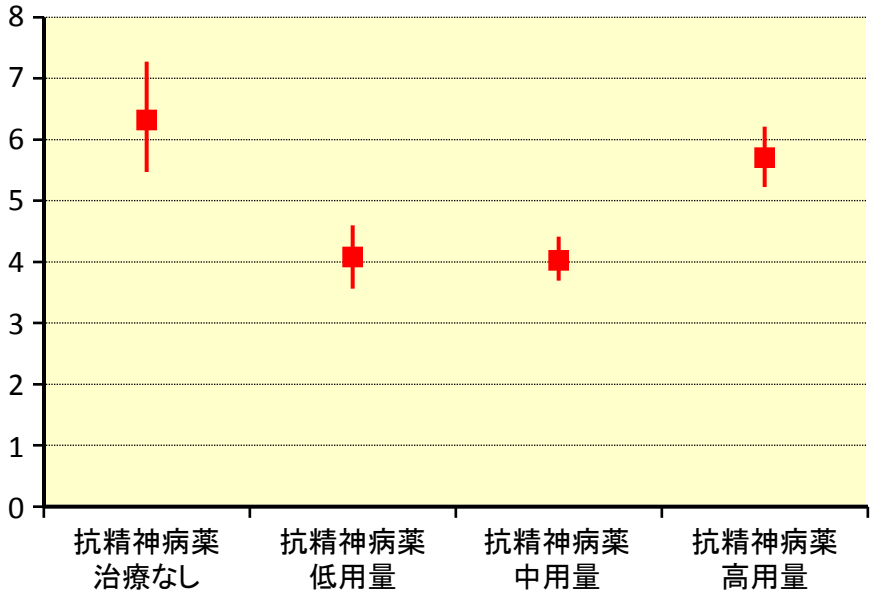
- 失神の既往と突然死の家族歴聴取

- 身体リスク変動時の評価　内服のリスクを踏まえて使用
  経時的心電図
  低カリウムなど電解質異常への注意
  虚血性心疾患、うっ血性心不全　など心疾患に注意
  薬物代謝の変化　（腎機能や肝機能の変化、
  多剤併用は問題を複雑にする）
  加齢への配慮

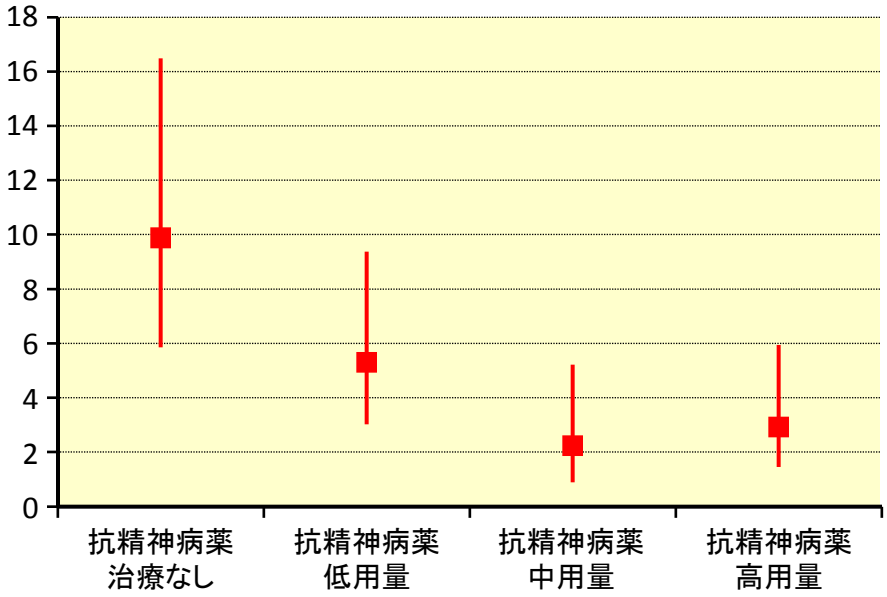
抗精神病薬は　どの程度危険なのか？

抗精神病薬と死亡リスク

慢性統合失調症患者（N=21,492）
の死亡ハザード比



初発統合失調症患者（N=1,230）
の死亡ハザード比



スウェーデンでの大規模コホート研究（N=7,040,632）
2006～2010年に抗精神病薬治療を受けた統合失調症患者の死亡リスクを集計
死亡ハザード比は一般人口を対照とし算出
DDD；1日規定用量（成人の仮想維持用量）
低用量；0DDD～0.5DDD/日、中用量；0.5DDD～1.5DDD/日、高用量；1.5DDD/日を超える

Torniainen M, et al. Schizophr Bull. 2014