RESEARCH ARTICLE

Pharmacogenetics and Clinical Risk Factors for Risperidone-Related Weight Gain in Thai Autistic Spectrum Disorder Patients

Natchaya Vanwong[1,2], Sadeep Medhasi[2,3], Manat Pongchaidecha[4], Nattawat Ngamsamut[5], Apichaya Puangpetch[1,2], Montri Chamnanphon[1,2], Bhunnada Chamkrachchangpada[5], Teerarat Tan-kam[5], Yaowaluck Hongkaew[1,2], Penkhae Limsila[5], Chonlaphat Sukasem[1,2]

[1] *Division of Pharmacogenomics and Personalized Medicine, Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
[2] *Laboratory for Pharmacogenomics, Somdech Phra Debaratana Medical Center (SDMC), Ramathibodi Hospital, Bangkok, Thailand*
[3] *Department of Pharmacology, Faculty of Science, Mahidol University, Bangkok, Thailand*
[4] *Department of Pharmaceutics (Clinical Pharmacy), Faculty of Pharmacy, Silpakorn University, Sanamchandra Palace Campus, Nakhon Pathom, Thailand.*
[5] *Yuwaprasart Waithayopathum Child and Adolescent Psychiatric Hospital, Department of Mental Health Services, Ministry of Public Health, Thailand*

Abstract

Background: Risperidone produces marked adverse effects including weight gain which often causes patients to discontinue the treatment. However, if patients continue to receive further treatment, increasing weight gain was found to increase a risk of clinically significant obesity and several health problems. ***Objective****:* To investigate the factors associated with risperidone-related weight gain in Thai autistic spectrum disorder patients. ***Methods:*** We conducted a retrospective and observational study among Thai autistic patients treated with risperidone. The data collected included risperidone dose, sex, age, body weight and BMI baseline, concomitant drug therapy, duration of drug used, and phenotype/genotype of *CYP2D6* responsible for body weight gain during risperidone therapy. ***Results:*** Univariate analysis showed that factors affecting the body weight gain among risperidone-treated Thai autistic patients were duration of risperidone treatment (months) ($P<0.0001$), cumulative dose ($P<0.0001$), age ($P=0.001$) and BMI baseline ($P<0.01$). Multivariable analysis showed that factors affecting the body weight gain were duration of treatment (months) ($P=0.011$), baseline age ($P=0.002$) and age ($P<0.0001$). ***Conclusions:*** This study makes a preliminary contribution to provide opportunities for personalized medicine in the predictive assessment of weight gain and to minimize the risk for metabolic syndrome in risperidone-treated Thai patients.

Keywords: autistic spectrum disorder, risperidone, weight gain, Thai**,** *CYP2D6***,** SNP

Address correspondence and reprint request to: Chonlaphat Sukasem, Division of Pharmacogenetics and Personalized Medicine, Department of Pathology, Faculty of Medicine,Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. E-mail address: chonlaphat.suk@mahidol.ac.th

เภสัชพันธุศาสตร์และปัจจัยทางคลินิกที่ส่งผลต่อการเพิ่มน้ำหนักตัวในผู้ป่วยออทิสติกที่ใช้ยาริสเพอริโดน

ณัฐชยา แหวนวงศ์[1,2], Sadeep Medhasi[2,3], มนัส พงศ์ชัยเดชา[4], ณัฐวัฒน์ งามสมุทร[5], อภิชญา พวงเพ็ชร์[1,2], มนตรี ชำนาญพล[1,2], บุณณดา แจ่มกระจ่างภาดา[5], ธีรารัตน์ แทนขำ[5], เยาวลักษณ์ หงษ์แก้ว[1,2], เพ็ญแข ลิ่มศิลา[5], ชลภัทร สุขเกษม[1,2]

[1] *หน่วยงานเภสัชพันธุศาสตร์และการรักษาเฉพาะบุคคล ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล กรุงเทพมหานคร*

[2] *ห้องปฏิบัติการเภสัชพันธุศาสตร์ ศูนย์การแพทย์สมเด็จพระเทพรัตน์ โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล กรุงเทพมหานคร*

[3] *ภาควิชาเภสัชวิทยา คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล กรุงเทพมหานคร*

[4] *ภาควิชาเภสัชกรรม (เภสัชกรรมคลินิก) คณะเภสัชศาสตร์ มหาวิทยาลัยศิลปากร วิทยาเขตพระราชวังสนามจันทร์ นครปฐม*

[5] *โรงพยาบาลยุวประสาทไวทโยปถัมภ์ สมุทรปราการ*

บทคัดย่อ

หลักการและเหตุผล การใช้ยาริสเพอริโดนมีผลข้างเคียงให้เกิดการเพิ่มขึ้นของน้ำหนักตัว ซึ่งมักส่งผลให้ผู้ป่วยหยุดการรักษา และหากผู้ป่วยยังคงได้รับการรักษาต่อไปพบว่าจะเพิ่มปัจจัยเสี่ยงอย่างมีนัยสำคัญทางคลินิกโดยทำให้เกิดภาวะอ้วนและปัญหาโรคแทรกซ้อนต่าง ๆ ***วัตถุประสงค์*** เพื่อศึกษาปัจจัยที่มีความสัมพันธ์กับการเพิ่มขึ้นของน้ำหนักตัวในผู้ป่วยออทิสติกที่ใช้ยาริสเพอริโดน ***วิธีการศึกษา*** เป็นการศึกษาแบบรวบรวมข้อมูลย้อนหลังของผู้ป่วยออทิสติกทั้งหมด 86 รายที่ได้รับยาริสเพอริโดน โดยเก็บรวบรวมข้อมูลขนาดยา เพศ อายุ น้ำหนักตัวก่อนเริ่มใช้ยา ดัชนีมวลกาย (BMI) ก่อนเริ่มใช้ยา ยาร่วมที่ได้รับ ระยะเวลาการรักษา ฟีโนไทป์และจีโนไทป์ของยีน *CYP2D6* เพื่อใช้ในการวิเคราะห์หาปัจจัยที่มีผลต่อการเพิ่มขึ้นของน้ำหนักตัว ***ผลการศึกษา*** ผลจากการวิเคราะห์ปัจจัยเดี่ยว (univariate analysis) พบว่า ปัจจัยที่มีอิทธิพลต่อน้ำหนักตัวที่เพิ่มขึ้นในผู้ป่วยไทยที่ใช้ยาริสเพอริโดน ได้แก่ ระยะเวลาการรักษา ($P<0.0001$) ขนาดยาสะสม ($P<0.0001$) อายุ ($P=0.001$) และ BMI ก่อนรับยา ($P<0.01$) และผลจากการวิเคราะห์แบบหลายปัจจัย (multivariable analysis) พบว่าปัจจัยที่มีอิทธิพลต่อน้ำหนักตัวที่เพิ่มขึ้น ได้แก่ ระยะเวลาการรักษา ($P=0.011$) อายุก่อนเริ่มการรักษา ($P=0.002$) และอายุ ($P<0.0001$) ***สรุป*** การศึกษานี้เป็นการศึกษาเบื้องต้นในการหาปัจจัยที่ใช้ทำนายการเกิดภาวะน้ำหนักตัวเพิ่มจากการใช้ยาริสเพอริโดน เพื่อช่วยลดความเสี่ยงต่อการเกิดภาวะเมแทบอลิกซินโดรมในผู้ป่วยไทยที่ใช้ยาริสเพอริโดน

คำสำคัญ: ออทิสติก, ยาริสเพอริโดน, น้ำหนักตัวเพิ่ม

Introduction

Risperidone, a benzisoxazole derivative possessing both dopamine D2-receptor and serotonin 5-HT2-receptor antagonist properties, is classified as a second-generation or "atypical" antipsychotic and is approved as a mainline agent for both acute and maintenance treatment of schizophrenia.[1] In October 2006, the U.S. Food and Drug Administration (FDA) approved the use of risperidone in children and adolescents, who have symptoms of irritability associated with autism spectrum disorder (ASD).[2] Due to the lower risk of extrapyramidal side effects (EPS) compared to the first-generation drugs, atypical antipsychotics are used significantly in psychopharmacotherapy.[3-5] However, significant weight gain with the use of atypical antipsychotics has been of particular interest as an adverse event in the clinical settings.[6,7] Extreme weight gain, defined according to FDA criteria as $\geq$7% increase from baseline was the greatest in the olanzapine group (90.5% of olanzapine group), followed by risperidone (42.9% of risperidone group) and haloperidol (12.5% of haloperidol group).[8] Weight gain in risperidone-treated patients had been reported to be associated with increased risk of metabolic abnormalities like insulin resistance, dyslipidemia, and hypertension.[6,9-11] The exact mechanism for risperidone-related weight gain is still unclear.

Risperidone is mainly metabolized by the enzyme CYP2D6 to 9-hydroxy-risperidone.[12] CYP2D6 activity ranges from complete deficiency to ultrarapid metabolism, depending on the existence of a large number of allelic variants of the *CYP2D6* gene, causing either absent, decreased or increased enzyme activity in relation to the wild type allele.[13] Poor metabolizer (PM) subjects show higher concentrations of risperidone and very low concentrations of 9-hydroxyrisperidone (9-OH risperidone). On the contrary, extensive metabolizer (EM) and ultrarapid metabolizer (UM) subjects show low concentrations of risperidone and high concentrations of 9-OH risperidone.[14] The genetic variation of *CYP2D6* gene may be implicated in weight gain induced by risperidone in patients.

Clinical factors governing weight change induced by antipsychotics have not been fully clarified. In clozapine treated patients, lower baseline body weight was related with maximum weight gain.[15-17] Younger age predicted larger weight gain in patients receiving clozapine or other antipsychotics, while gender did not influence clozapine-associated weight change.[17,18] Nevertheless, clozapine dosage and efficacy were associated with weight increase.[19,20] However, results from several studies were found inconsistent with respect to the effect of antipsychotics on weight gain.[16,18,21,22] Most of these studies were limited by small sample sizes. In olanzapine receivers, low baseline body mass index (BMI), younger age, and better clinical outcome were predictive of greater weight gain.[23-25] A previous study in risperidone-treated patients found lower initial body weight, younger age, undifferentiated subtype, higher dosage, and treatment response associated with body weight gain.[26] There are currently no studies about the pharmacogenetics of risperidone induced weight gain in Thai autistic spectrum disorder patients. The present study investigates the influence of *CYP2D6* polymorphism together with clinical factors on body weight of risperidone-treated patients.

Methods

Subjects

This retrospective and observational study was performed on a cohort of 322 autism patients receiving risperidone therapy. Written informed consent was obtained from each participant. This study was approved by the Ethics Committees at Ramathibodi Hospital, Bangkok. The subjects were recruited from Yuwaprasart Waithayopathum Child Psychiatric Hospital and Rajanakul Institute. Subjects treated with risperidone for at least 2 weeks were included in this study. Two hundred and thirty-six patients with incomplete data were excluded from the study. Two hundred and thirty-five of those patients had missing data for baseline body weight, current body weight or height and one patient had missing data for drug dose.

A total of 86 patients were included in this study. Data of all the patients regarding body weight (kg), height (cm), risperidone dose (mg/day), cumulative dose (mg), duration of treatment (months), age, gender, and concomitant medications affecting weight gain were recorded. However, only 79 patients had the data containing risperidone levels, *CYP2D6* genotypes and phenotypes. The endpoint of this study was weight gain, which defined as $\geq$7% increase from baseline, based on the FDA criteria.[8]

A five milliliter sample of venous blood was collected at steady state in an EDTA tube, before drug intake and was submitted to the Laboratory for Pharmacogenomics and Personalized Medicine, Ramathibodi Hospital, Mahidol University, for the *CYP2D6* genotyping. Samples were centrifuged at 3000 rpm for 15 minutes. The genomic DNA was isolated for genotyping. Steady-state plasma samples at 12 hours after dosing were stored at -20°C until risperidone levels analysis. The relationship between the plasma risperidone concentration and genetic polymorphism was also assessed in this study.

Genotyping of CYP2D6 and classification

Genotyping of *CYP2D6* was performed using the TaqMan genotyping assay (Applied Biosystems, CA, USA) to determine the *CYP2D6* alleles **4, *5,*41,* and **10* that are the most important null alleles and common alleles frequently found in Thai population.[27,28] We only identified patients with *CYP2D6*1,*4,*5,*41* and **10*. Then patients carrying *CYP2D6*1/*1*, **1/*10* and **1/*41* were classified as EM, and those carrying *CYP2D6 *1/*5, *4/*10, *5/*10, *10/*10, *10/*41* and **41/*41* were classified as IM. The allele-specific Taqman® MGB probe 5'nuclease chain reaction assay with real-time PCR Viia™ 7 system (Applied Biosystems, CA, USA) was performed with primers of *CYP2D6*4* (1846G>A, rs3892097) (assay ID: C_27102431_D0), *CYP2D6*10* (100C>T, rs1065852) (assay ID:C_ 11484460_40), *CYP2D6*41* (2988G>A, rs28371725) (assay ID: C_ C_34816116_20). One probe labeled with VIC fluorogenic dye detected the allele 1 sequence. The second probe labeled with FAM fluorogenic dye detected the allele 2 sequence. Each 20 µL PCR mixture contained 4 µL of genomic DNA (5 ng/µL), 10 µL of Taqman® Genotyping Mastermix, 1 µL of allele-specific Taqman® MGB probe and sequence-specific primer kit, and 5 µL of DNase-free H_2O. The thermal cycler program was set up as follows: at 95°C for 10 minutes, repeated 50 cycles at 92°C for 15 seconds and 60°C for 90 seconds. The Allelic Discrimination Plot was analyzed by Viia™ 7 software (Applied Biosystems, CA, USA).

Analysis of plasma concentrations of risperidone and 9-OH risperidone

Risperidone levels were measured using an early morning blood sample taken before the morning risperidone dose was given. Plasma concentrations of risperidone and 9-OH risperidone were measured using the validated liquid chromatography tandem mass spectrometric (LC/MS/MS) method. The chromatographic system consisted of an Agilent 1260 series HPLC system equipped with a binary pump, a system controller, and an autoinjector. The chromatographic system was connected to an API 3200 (AB SCIEX) with an internal diverter (Valco valve). Chromatographic separation was performed on a Waters Atlantis dC18 column (4.6 cm×50 mm; 1.8 um particle size), protected by an Atlantis dC18 4.6×12.5 mm guard column. Mobile phase A consisted of ammonium acetate (10mmol/l) containing 0.1% formic acid. Mobile phase B consisted of 100% acetonitrile. Risperidone and 9-OH risperidone were separated at a flow rate of 0.40 ml/min. Elutes were diverted for the first 2 minutes (to avoid contamination with perchloric acid) and introduced into the turbo-ion spray source thereafter. Ionization was achieved in the positive-ion mode with 5500 V ionization. The heater probe was set at 500°C. Sample analysis was performed in the multiple-reaction monitoring mode with the transitions m/z 411 to 191 for risperidone, m/z 428 to 207 for 9-OH risperidone derivative, and m/z 328 to 270 for clozapine. Collision energy was set at 40 V with nitrogen as the collision gas. Each sample was injected every 6 min. Integration of peak areas and determination of the concentrations were performed with Analyst 1.5.2 software (Applied Biosystems, CA, USA).Quadratic regression with 1/x weighted concentrations used. The accuracy of risperidone and 9-OH risperidone were 98-110% and 95-105%, respectively. The precisions (both inter- and intra-assay) were ≤9% for resperidone and ≤6% for 9-OH risperidone. Relationship between plasma risperidone concentrations and *CYP2D6* polymorphism was analyzed.

Statistical analysis

Data were analyzed using statistical software R (version 3.0.2). P-values <0.05 were considered to be statistically significant. For the continuous variable, data were expressed as mean±SD, while categorical data were expressed as percentage frequency (% frequency). Data under normal distribution were compared using ANOVA and t-test, while the data which did not show normal distribution were compared using a non-parametric test (Wilcoxon rank-sum test and Kruskal-Wallis test). Regression analyses (simple and multiple) were performed to determine the relationship between the weight or BMI change and the various factors, e.g., the duration of treatment, daily dose, cumulative dose, age, gender, risperidone levels, and *CYP2D6* genotype and phenotype.

Results

The clinical and demographic data of the subjects under risperidone therapy are summarized in Table 1. The average age of the cohorts was little more than 9 years old; 83.72% were male. The patients were classified according to the age group as babies (<3 years), preschoolers (3-5 years), young children (6-12 years), adolescents (13-18 years), and adults (>18 years). The mean duration of the risperidone therapy was 37.8 months (SD=20.28). Mean baseline body weight, baseline BMI, and risperidone dose differed significantly between Rajanakul Institute and Yuwaprasart Waithayopathum Child Psychiatry hospital (data not shown). However, the percentage changes in body weight and BMI after risperidone treatment for at least 1 year did not show any significant differences between these two clinical settings.

Table 1. Clinical and demographic data of patients enrolled in the study

Characteristics of patients (N = 86)	
Age (years, range)	4.3 – 18.6
Age (years, mean±SD)	9.4±3.6
Age distribution (n)	
Babies (<3 years)	0
Preschoolers (3-5 years)	8
Children (6-12 years)	59
Adolescents (13-18 years)	17
Adults (>18 years)	2
Male [n (%)]	72 (83.7)
Baseline body weight (kg, mean± SD)	26.5±13.1
Baseline BMI (kg/m^2, mean± SD)	18±3.7
Daily dose (mg/day, mean± SD)	0.9±0.8
Cumulative dose (mg, mean± SD)	1072.4±1186.9
Treatment duration (months, mean± SD)	37.8±20.3
Active drug level (ng/ml, mean± SD)	10.9±10.5
Concomitant drug affecting weight gain (n/total)	17/86
Patients with IM phenotype (n/total)	40/79

Abbreviations: BMI, Body Mass Index; IM, Intermediate Phenotype

Simple linear regression (univariate) analyses (Table 2) were performed to investigate the relationship between the covariates and change in body weight and BMI. A significant association was found between duration of risperidone treatment (months) (P<0.0001), duration of treatment within 2 years (P=0.046), cumulative dose (P<0.0001), baseline of preschooler age group (P<0.001), age (P=0.001), children age group (P<0.0001), and baseline BMI (P=0.003) and change in body weight (Table 2). However, the duration of risperidone treatment was the only covariate significantly associated with change in BMI (P=0.0253). There was a significant association of risperidone treatment duration and cumulative dose with % body weight change (P<0.001). However, none of the covariates were significantly associated with % BMI change.

Table 2. Univariate and multivariate analyses of genetic and non-genetic factors associated with risperidone-induced body weight gain

Clinical Characteristics	Univariate analysis				Multivariate analysis	
	Coefficient	Intersection	P-Value	R^2	Coefficient	Pr (|t|)
Gender	1.12	12.401	0.725	0.002		
Dose (mg/day)	2.389	10.428	0.121	0.028		
Duration of treatment (months)	0.298	1.304	<0.0001	0.314	0.163	0.011
Duration of treatment (range)	6.834	-1.323	<0.0001	0.296		
≥12, ≤ 24 months (n=26)	0.308	1.137	0.046	0.156		
>24, ≤48 months (n=35)	0.080	9.124	0.730	0.004		
>48, ≤ 72months (n=21)	0.385	-3.697	0.181	0.092		
>72, ≤ 96 months (n=4)	-0.496	66.698	0.816	0.034		
Cumulative Dose (mg)	0.004	8.522	<0.0001	0.173		
Baseline age (N=79)	0.07	11.616	0.848	0.001	-2.210	0.002
Preschoolers (n=34)	5.533	-11.502	<0.01	0.220		
Children (n=37)	0.472	12.388	0.709	0.004		
Adolescents (n=8)	-2.64	43.506	0.140	0.326		
Age (years) (N=86)	1.035	2.864	0.001	0.118	2.379	<0.0001
Preschoolers (n=8)	0.270	1.135	0.915	0.002		
Children (n=59)	3.403	-15.592	<0.0001	0.331		
Adolscents (n=17)	-2.9335	60.293	0.079	0.192		
Adults (n=17)	-30.00	576.00	-	1.00		
Group baseline age	1.360	8.425	0.454	0.007		
Group endpoint age	4.940	-2.983	0.010	0.076		
BMI Baseline (kg/m^2)	0.918	-3.945	0.003	0.099		
Drugs affecting weight gain	3.210	11.949	0.275	0.014		
***CYP2D6* gentype**	-0.051	12.237	0.939	<0.0001		
***CYP2D6* phenotype**	-0.698	13.108	0.768	0.001		

Constant = -2.168, Residual error= 8.044, R^2 = 0.427, F=18.59 and *P*<0.0001
Abbreviations: BMI, Body Mass Index

Multiple linear regression (multivariable) analyses found the duration of treatment, baseline age and age as a predictor of change in body weight (Table 2), with a regression equation: Y (Diff. BW) = -2.168 + (0.163×Duration of treatment (months)) – (2.210×Baseline age) + (2.379×Age endpoint). The results did not show any significant association of plasma risperidone levels and CYP2D6 metabolic phenotypes with the changes in body weight and BMI.

In the subgroup analysis, it was found that the patients treated with higher dose of risperidone (≥2mg/day) had significant effect on body weight change as compared to lower dose risperidone (<2mg/day) treated patients (Wilcoxon Rank-Sum test; P<0.05). Mean body weight change and % body weight change were significantly different among different age groups (Kruskal-Wallis test; P<0.001 and P<0.05, respectively). The factors which had no effect on change in body weight, % change in body weight, BMI change, and % change in BMI included gender differences, baseline BMI, concomitant drugs, and CYP2D6 metabolic phenotype. The relationship of *CYP2D6* genotypes and *CYP2D6* phenotypes to body weight gain and % of body weight gain are shown in Table 3.

Table 3. A multivariate analysis of independent factors associated with risperidone-induced body weight change

	Coefficient	Pr (|t|)	P-value	Multiple R-square	Residual error
Y-intercept	-26.0445	0.001735			
Gender	-0.1692	0.9480			
Dose (mg/day)	-0.6507	0.8228			
Duration of treatment (months)	0.1185	0.2170			
Cumulative Dose(mg)	0.0015	0.5026	3.383e-07	0.4323	8.549
Age (years)	1.7400	0.001735			
BW Baseline (kg)	-0.6736	0.007148			
BMI Baseline (kg/m^2)	1.9135	0.000945			
Drugs affecting weight gain	0.8549	0.7444			

The patients treated with high dose of risperidone and IM phenotype showed greater trend of change in body weight and BMI, although not significant, as compared to patients with EM phenotype. When the ratio of risperidone/9-OH risperidone was considered, patients with risperidone/9-OH risperidone ratio >1 demonstrated a trend towards higher changes in median body weight, median % of body weight, median BMI, and median % of BMI than patients with risperidone/9-OH risperidone ratio<1, although not statistically significant (Kruskal-Wallis test; P>0.05).

Discussion

In our study population of Thai autistic patients, we examined the association of genetic and non-genetic factors related to weight change and BMI. The notable factors associated with change in body weight, including duration of treatment (months), baseline age and age of patient, were considered as a predictor for change in body weight in multivariate analysis.

The difference in body weight change was found to be 45% in patients with BMI <23 and 36.41% in patients with BMI ≥23. Although the % weight changes in two groups are different, but not statistically significant. However, a previous study among the schizophrenic inpatients treated with risperidone, the patients with BMI <25 increased in weight significantly more than patients with BMI ≥25 (P<0.001) in the first month as well as the second month (P<0.001).[29] Although our result did not find significant difference of % weight change, we found that the patients with BMI <23 (normal weight) had body weight change more than the group of patients with BMI ≥23 (obese) after treatment with risperidone. There are conflicting results which showed the greater increase in body weight in patients with low baseline BMI as compared to those with high baseline BMI.[30,31] A study found the patients with long term treatment (8 years), low baseline BMI, and high baseline BMI had comparable body weight change, although not significant.[32] These findings show the increase of body weight change in patients with low baseline BMI in short-term risperidone treatment.

In our study, the patients were divided into four age groups; preschoolers (3-5 years), young children (6-12 years), adolescents (13 -18 years) and adults (>18 years). The result found that the age range have significant effect on the difference of weight change. The children had weight change more than another age. That discordance with the findings in previous study which found that adolescents had weight change and BMI change more than young children and adults.[33]

Gender was not considered as a significant predictor of change in body weight and BMI among the patients treated with risperidone. However, females showed the trend of greater change in body weight as compared to male, which has also been reported in earlier studies.[29,34] The physiological mechanism of lower metabolism rate and higher accumulation of fat in women than men might explain the greater change in body weight in women as compared to men.

Concomitant drugs may promote increased change in body weight as mentioned in earlier study where drug combination of valproic acid and risperidone significantly increased weight more than risperidone alone.[35] There was a significant weight gain (>5 kg) among the valproic acid treated patients.[36] The mechanism involving valproic acid-induced weight gain may be explained by the capability of valproic acid to induce the expression of the adipokine genes in the pituitary gland, which controls neuropeptides associated with the central energy metabolism, such as resistin (RSTN) and fasting-induced adipose factor (FIAF), leading to increased leptin and insulin resistance.[37] Our findings did not find the association of concomitant drug, valproic acid, with change in body weight. It is possible that the influence of drug combination may affect the neuropeptides in the brain only in the early stages of treatment. Our study was also based on a long term treatment, while previous study was done in short term duration, resulting in different conclusion. As reported in previous study, there were significant differences in body weight change and BMI change at 3rd month, while no significant difference was observed at 12th month.[38] This study is in concordance with our findings, suggesting the lack of long term risperidone treatment effect on difference in body weight change and BMI change.

As for the *CYP2D6* polymorphisms, we did not find a significant difference in median body weight between extensive metabolizers and intermediate metabolizers in our samples of patients (Table 3). Although intermediate metabolizers showed greater change in % body weight than extensive metabolizers, there was greater changes in BMI and % BMI among the extensive metabolizers than intermediate metabolizers. *CYP2D6* genotype groups did not exhibit any significant differences in change in body weight as well. The *CYP2D6* genotype and phenotype status would be helpful to determine dose at therapeutic level and avoid possible adverse events in the clinical practice.

This study has some limitations that should be taken into consideration when interpreting the results and should be addressed in the future studies. First, most of the patients recruited in this study were children and adolescents; they are characterized by rapid physical growth. The physical growth (height and weight) may affect to weight gain. Thus, it is unable to know the real cause of weight gain, which caused by physical growth or medication. Healthy children and adolescents should be recruited as controls in further studies. Second, the number of patients in this study is small. Therefore the generalization and comparison of the results to

other studies must be done with caution. Future studies should include a larger sample population of risperidone-treated patients with autism. Third, the sample numbers of patients various in different age groups. In the future study, the same sample number in different age groups should be recruited. Finally, due to the retrospective design, the data on patients' height and weight were recorded during wide range of duration of risperidone treatment.

Conclusions

In conclusion, our study has identified, for the first time, genetic and non-genetic factors implicated in risperidone-induced body weight gain in risperidone-treated Thai autistic patients. The patients receiving risperidone treatment usually require a long-term therapy, so initial diagnosis and management is important to reduce the morbidity and mortality associated with obesity.

Clinical Significance

This study makes a preliminary contribution to provide opportunities for personalized medicine in the predictive assessment of weight gain and to minimize the risk for metabolic syndrome in risperidone-treated Thai patients. Patients who develop signs of metabolic syndrome, clinicians must choose between switching to an antipsychotic with fewer metabolic adverse effects or continuing risperidone therapy with monitoring and management of the metabolic effects.

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References

1. Kane JM. Schizophrenia. N Engl J Med. 1996 Jan 4;334(1):34-41.
2. Scott L, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. Paediatr Drugs. 2007;9(5):343-54.

3. Jones P, Barnes T, Davies L, Dunn G, Lloyd H, Hayhurst K, et al. Randomized controlled trial of the effect on Quality of Life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006 Oct;63(10):1079-87.
4. Malone R, Sheikh R, Zito J. Novel antipsychotic medications in the treatment of children and adolescents. Psychiatr Serv. 1999 Feb;50(2):171-4.
5. Aman M, Binder C, Turqay A. Risperidone effects in the presence/absence of psychostimulant medicine in children with ADHD, other disruptive behavior disorders, and subaverage IQ. J Child Adolesc Psychopharmacol. 2004 Summer; 14(2):243-54.
6. Calarge C, Acion L, Kuperman S, Tansey M, Schlechte J. Weight gain and metabolic abnormalities during extended risperidone treatment in children and adolescents. J Child Adolesc Psychopharmacol. 2009 Apr;19(2):101-9.
7. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA. 2009 Oct 28;302(16):1765-73.
8. Bishop JR, Pavuluri MN. Review of risperidone for the treatment of pediatric and adolescent bipolar disorder and schizophrenia. Neuropsychiatr Dis Treat. 2008 Feb;4(1):55-68.
9. Reaven G. Insulin resistance: the link between obesity and cardiovascular disease. Endocrinol Metab Clin North Am. 2008 Sep;37(3):581-601.
10. Lane HY, Liu YC, Huang CL, Chang YC, Wu PL, Lu CT, et al. Risperidone-related weight gain: genetic and nongenetic predictors. Journal of clinical psychopharmacology. 2006 Apr;26(2):128-34.
11. Monteleone P, Martiadis V, Maj M. Management of schizophrenia with obesity, metabolic, and endocrinological disorders. Psychiatr Clin North Am. 2009 Dec;32(4):775-94.
12. Scordo M, Spina E, Facciola G, Avenoso A, Johansson I, Dahl M. Cytochrome P450 2D6 genotype and steady state plasma levels of risperidone and 9-hydroxyrisperidone. Psychopharmacology (Berl). 1999 Dec;147(3):300-5.
13. Sachse C, Brockmoller J, Bauer S, Roots I. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. Am J Hum Genet. 1997 Feb;60(2):284-95.
14. Novalbos J, Lopez-Rodriguez R, Roman M, Gallego-Sandin S, Ochoa D, Abad-Santos F. Effects of CYP2D6 genotype on the pharmacokinetics, pharmacodynamics, and safety of risperidone in healthy volunteers. J Clin Psychopharmacol. 2010 Oct;30(5):504-11.
15. Hong CJ, Lin CH, Yu YW, Yang KH, Tsai SJ. Genetic variants of the serotonin system and weight change during clozapine treatment. Pharmacogenetics. 2001 Apr;11(3):265-8.

16. Umbricht DS, Pollack S, Kane JM. Clozapine and weight gain. J Clin Psychiatry. 1994 Sep;55 Suppl B:157-60.

17. Wetterling T, Mussigbrodt HE. Weight gain: side effect of atypical neuroleptics? J Clin Psychopharmacol. 1999 Aug;19(4):316-21.

18. Hummer M, Kemmler G, Kurz M, Kurzthaler I, Oberbauer H, Fleischhacker WW. Weight gain induced by clozapine. Eur Neuropsychopharmacol. 1995 Dec;5(4):437-40.

19. Frankenburg FR, Zanarini MC, Kando J, Centorrino F. Clozapine and body mass change. Biol Psychiatry. 1998 Apr 1;43(7):520-4.

20. Leadbetter R, Shutty M, Pavalonis D, Vieweg V, Higgins P, Downs M. Clozapine-induced weight gain: prevalence and clinical relevance. Am J Psychiatry. 1992 Jan;149(1):68-72.

21. Bustillo JR, Buchanan RW, Irish D, Breier A. Differential effect of clozapine on weight: a controlled study. Am J Psychiatry. 1996 Jun;153(6):817-9.

22. Ganguli R. Weight gain associated with antipsychotic drugs. J Clin Psychiatry. 1999;60 Suppl 21:20-4.

23. Basson BR, Kinon BJ, Taylor CC, Szymanski KA, Gilmore JA, Tollefson GD. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. J Clin Psychiatry. 2001 Apr;62(4): 231-8.

24. Jones B, Basson BR, Walker DJ, Crawford AM, Kinon BJ. Weight change and atypical antipsychotic treatment in patients with schizophrenia. J Clin Psychiatry. 2001;62 Suppl 2:41-4.

25. Kinon B, Kaiser C, Ahmed S, Rotelli M, Kollack-Walker S. Association between early and rapid weight gain and change in weight over one year of olanzapine therapy in patients with schizophrenia and related disorders. J Clin Psychopharmacol. 2005 Jun;25(3):255-8.

26. Lane HY, Chang YC, Cheng YC, Liu GC, Lin XR, Chang WH. Effects of patient demographics, risperidone dosage, and clinical outcome on body weight in acutely exacerbated schizophrenia. J Clin Psychiatry. 2003 Mar;64(3):316-20.

27. Sukasem C, Sirachainan E, Chamnanphon M, Pechatanan K, Sirisinha T, Ativitavas T, et al. Impact of *CYP2D6* polymorphisms on tamoxifen responses of women with breast cancer: a microarray-based study in Thailand. Asian Pac J Cancer Prev. 2012;13(9):4549-53.

28. Sirachainan E, Jaruhathai S, Trachu N, Panvichian R, Sirisinha T, Ativitavas T, et al. *CYP2D6* polymorphisms influence the efficacy of adjuvant tamoxifen in Thai breast cancer patients. Pharmgenomics Pers Med. 2012;5:149-53.

29. Lee SY, Park MH, Patkar AA, Pae CU. A retrospective comparison of BMI changes and the potential risk factors among schizophrenic inpatients treated with aripiprazole, olanzapine, quetiapine or risperidone. Prog Neuropsychopharmacol Biol Psychiatry. 2011 Mar 30;35(2):490-6.

30. Saddichha S, Ameen S, Akhtar S. Predictors of antipsychotic-induced weight gain in first-episode psychosis: conclusions from a randomized, double-blind, controlled prospective study of olanzapine, risperidone, and haloperidol. J Clin Psychopharmacol. 2008 Feb;28(1):27-31.

31. Boden R, Haenni A, Lindstrom L, Sundstrom J. Biochemical risk factors for development of obesity in first-episode schizophrenia. Schizophr Res. 2009 Dec;115(2-3):141-5.

32. Bai YM, Chen JY, Chen TT, Lin CY, Chou P, Su TP, et al. Weight gain with clozapine: 8-year cohort naturalistic study among hospitalized Chinese schizophrenia patients. Schizophr Res. 2009 Mar;108(1-3):122-6.

33. Hellings JA, Zarcone JR, Crandall K, Wallace D, Schroeder SR. Weight gain in a controlled study of risperidone in children, adolescents and adults with mental retardation and autism. J Child Adol Psychop. 2001 Fall;11(3):229-38.

34. Bobes J, Rejas J, Garcia-Garcia M, Rico-Villademoros F, Garcia-Portilla MP, Fernandez I, et al. Weight gain in patients with schizophrenia treated with risperidone, olanzapine, quetiapine or haloperidol: results of the EIRE study. Schizophr Res. 2003 Jul 1;62(1-2):77-88.

35. Meltzer HY, Bonaccorso S, Bobo WV, Chen Y, Jayathilake K. A 12-month randomized, open-label study of the metabolic effects of olanzapine and risperidone in psychotic patients: influence of valproic acid augmentation. J Clin Psychiatry. 2011 Dec;72(12):1602-10.

36. Verrotti A, D'Egidio C, Mohn A, Coppola G, Chiarelli F. Weight gain following treatment with valproic acid: pathogenetic mechanisms and clinical implications. Obes Rev. 2011 May;12(5):e32-43.

37. Brown R, Imran SA, Ur E, Wilkinson M. Valproic acid and CEBPalpha-mediated regulation of adipokine gene expression in hypothalamic neurons and 3T3-L1 adipocytes. Neuroendocrinology. 2008;88(1):25-34.

38. Perez-Iglesias R, Vazquez-Barquero JL, Amado JA, Berja A, Garcia-Unzueta MT, Pelayo-Teran JM, et al. Effect of antipsychotics on peptides involved in energy balance in drug-naive psychotic patients after 1 year of treatment. J Clin Psychopharmacol. 2008 Jun;28(3):289-95.