BMC Medicine

Association between CYP metabolizer phenotypes and selective serotonin reuptake inhibitors induced weight gain: a retrospective cohort study

Maria L. Ricardo-Silgado[1†], Sneha Singh[1†], Lizeth Cifuentes[1], Paul A. Decker[2], Daniel Gonzalez-Izundegui[1], Ann M. Moyer[3], Maria D. Hurtado[1,4], Michael Camilleri[1], Suzette J. Bielinski[2] and Andres Acosta[1*]

Abstract

Background: Prescription medications such as selective serotonin reuptake inhibitors (SSRIs), commonly used to treat depression, are associated with weight gain. The role of pharmacogenomics in predicting SSRI-induced weight gain is unclear.

Methods: In this retrospective cohort study from participants in the Mayo Clinic RIGHT study who were prescribed citalopram, paroxetine, sertraline, or fluoxetine, our aim was to evaluate the association of metabolizer phenotype and total body weight after 6 months of SSRIs initiation. We evaluated the metabolizer phenotypes (poor/intermediate, normal, and rapid/ultra-rapid) of the cytochromes P450 enzymes genes: *CYP2C9, CYP2C19,* and *CYP2D6* known to influence the metabolism of SSRI medications: *CYP2C19* for citalopram, *CYP2D6* for paroxetine, *CYP2D6* and *CYP2C19* for sertraline, and *CYP2D6* and *CYP2C9* fluoxetine. In addition, we assessed the association of metabolizer phenotype and total body weight change at six months following SSRI prescription using parametric analysis of covariance adjusted for baseline body weight and multivariate regression models.

Results: *CYP2C19* poor/intermediate metabolizers prescribed citalopram gained significantly more weight than normal or rapid/ultra-rapid metabolizers at 6 months (TBWG %: 2.6 [95% CI 1.3—4.1] vs. 0.4 [95% CI -0.5 – 1.3] vs. -0.1 [-95% CI -1.5—1.1]; $p = 0.001$). No significant differences in weight outcomes at six months of treatment with paroxetine, sertraline, or fluoxetine were observed by metabolizer status.

Conclusions: Weight gain observed with citalopram may be mediated by *CYP2C19* metabolizer status.

Keywords: Pharmacogenomics, Weight gain, CYP metabolizer phenotypes

†Maria L. Ricardo-Silgado and Sneha Singh contributed equally.

*Correspondence: acosta.andres@mayo.edu

¹ Precision Medicine for Obesity Program and Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN, USA
Full list of author information is available at the end of the article

Background

Obesity is a chronic and complex multifactorial disease associated with multiple metabolic comorbidities, such as type 2 diabetes mellitus, and psychiatric diagnoses such as major depressive and anxiety disorders. There is a bidirectional relation between depression and obesity; thus, patients with obesity have a 55% increased risk of being diagnosed with depression over time, and patients

Ricardo-Silgado *et al. BMC Medicine*   (2022) 20:261

Page 2 of 12

with depression have a 58% increased risk of developing obesity [1].

Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for depression. One side effect of their use is body weight gain during short- and long-term management. In fact, it is reported that patients prescribed an SSRI gain 4.2 kg more than non-users after a three-month treatment period [2], and that after 2.5 years of SSRI treatment, there is an increment of 2.5% of the initial body weight [3]. The risk factors associated with weight gain while receiving antidepressant medications are lower BMI at baseline, age under 65, and female gender [4]. However, the mechanisms of weight gain related to antidepressant use are not well known. Possible mechanisms include remission of major depression and increased neurotransmitters such as serotonin, which regulates feeding behaviors, energy expenditure [5, 6], and decreased brown adipose tissue thermogenesis [7].

Genetic variation is one of the factors that can alter a medication's efficacy by influencing its metabolism (i.e., pharmacokinetics), mechanism of action (i.e., pharmacodynamics), and even adverse side effects by gene-drug interactions. Because cytochrome P450 (CYP) enzymes contribute to phase I drug metabolism, CYP enzyme variation significantly impact treatment outcomes [8]. Pharmacogenomics offers the opportunity to optimize treatment considering these polymorphisms to develop a more personalized approach to antidepressant selection while reducing adverse drug events [9]. In 2013, the Clinical Pharmacogenetics Implementation Consortium (CPIC) developed dosing guidelines for paroxetine, citalopram, and sertraline based on their main metabolizer enzymes' phenotype status *CYP2C19* and/ or *CYP2D6*. Different CYP enzymes are involved in SSRI metabolism; however, each drug has a dominant metabolizer enzyme. Thus, citalopram is mainly metabolized by *CYP2C19*, paroxetine by *CYP2D6*, fluoxetine by *CYP2D6* and *CYP2C9,* and sertraline by *CYP2D6* and *CYP2C19* [10]. The guidelines recommend a 50% reduction in the starting dose of citalopram, paroxetine, and sertraline in individuals with *CYP2D6* or *CYP2C19* poor metabolizer phenotype. In addition, the Food and Drug Administration has made recommendations for a maximum dosage of SSRIs in patients with specific metabolizer phenotypes [11]. There are currently little data detailing how CYP2D6 phenotypic status impacts the total amount of fluoxetine; hence, no gene-based dosage recommendations for fluoxetine have been provided.

Pharmacogenomics is a tool to personalize management in multiple areas, such as psychiatry and weight management [9, 12]. Multiple mood disorder studies have evaluated SSRI responsiveness for depression and lithium therapy in bipolar illness in GWAS studies and polygenic risk scores analysis [13–15]. These studies have found the link between genetic variants of obesity and SSRIs treatment response in depression [16]. However, a study investigating pharmacogenomics and weight gain in mood disorders is required. We hypothesized that patients with decreased metabolism of SSRIs by these cytochrome enzymes would be more likely to experience weight gain as a side effect. The study assesses the association between metabolizer phenotype and weight gain six months following SSRI prescription.
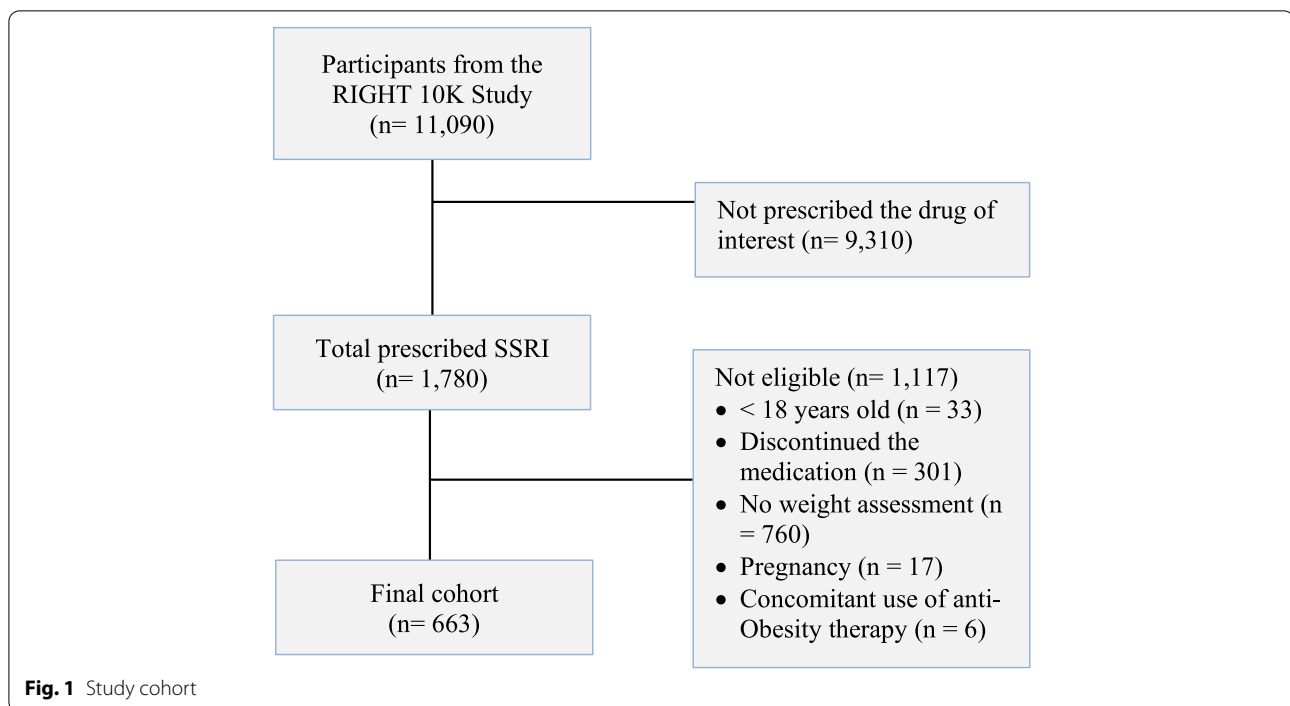
Methods

Study design

This retrospective cohort study approved by the Mayo Clinic Institutional Review Board (IRB 19–001,222) included participants from the Right Drug, Right Dose, Right Time (RIGHT) Study who underwent genetic sequencing of pharmacogenomic genes [17]. The RIGHT study included 11,090 participants, of which 60% were female and 97% were White. For the analyses, we considered participants from the RIGHT Study who had been prescribed citalopram, paroxetine, sertraline, or fluoxetine between 2004–2018. From those, we only included patients with a stable weight in the 6 months before starting the SSRI ($n = 1,780$). Of these, we exclude those who were < 18 years old, patients who did not have at least 6 months of treatment, did not have weight assessed during follow-up, had a history of bariatric surgery, were pregnant, or had a history of anti-obesity therapy ($n = 1,117$). The final analytic sample included 663 participants (Fig. 1). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (Additional file 2: Table S1).

Data collection

Three physicians exhaustively reviewed the electronic medical record (EMR) to confirm inclusion and exclusion criteria. For the 663 participants included in the analysis, medication list, height, and body weight were extracted from the EMR, and comorbidities were extracted with ICD-9 and ICD-10 codes. Race was self-reported by study participants in the EMR, and race categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White) were defined based on the US Office of Management and Budget's Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity. Body weight was extracted in kilograms at the time of prescription (± 2 weeks), three (± 2 weeks), and six (± 2 weeks) months of the initial prescription. Body mass index (BMI) was calculated with the formula weight in kilograms divided by height in meters squared.

Fig. 1 Study cohort

Exposure

As part of the RIGHT cohort, the Clinical Laboratory Improvement Amendments (CLIA)-certified and College of American Pathologists (CAP)-accredited Baylor College of Medicine's Human Genome Sequencing Center Clinical Laboratory sequenced 77 genes using version 3 (v.3.) of the PGRN-Seq assay (now termed PGx-seq) [18]. *CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DPYD, SLCO1B1, TPMT, UGT1A1, VKORC1, HLA-A,* and *HLA-B* were interpreted and reported by the Personalized Genomics Laboratory[17]. Genes studied are those pertinent to the enzymatic metabolism of the SSRI medications. The cytochrome P450 enzyme genes were *CYP2C19* for citalopram; *CYP2D6* for paroxetine; *CYP2D6* and *CYP2C9* for fluoxetine, and *CYP2C19* and *CYP2D6* sertraline [10]. Genotypes, including both rare and common variants, were translated into diplotypes using star allele nomenclature, when applicable, as described in PharmVar (www.pharmvar.org, last accessed 1/29/2022). Diplotypes were assigned a predicted metabolic phenotype (metabolizer status) using standard clinical laboratory processes, which rely on the assignment of the function of each allele present relative to a normal function (or "wild-type") allele (Additional file 2: Table S2). Details of the genetic analysis have been previously reported [19]. Metabolizer status was classified as: poor/intermediate, normal (extensive), and rapid/ultra-rapid metabolizer [20]. We evaluate the concomitant use of inducers and inhibitors for P450-mediated metabolism (Additional file 2: Tables S3 and S4)[21].

Outcome measurements

The outcome was calculated using the following formula:

$$TBWG\% = \frac{Body\,weight\,at\,6\,months - Baseline\,body\,weight}{Baseline\,body\,weight} \times 100$$

Statistical analysis

Baseline anthropometric and demographics were not normally distributed according to the Shapiro-Wilks test and are summarized as median and interquartile range (IQR). Categorical data are presented as frequency and percentages. Categorical data were analyzed using Pearson's chi-squared test. ANCOVA models were used to assess the difference in total body weight change (%) with metabolizer status and BMI as a covariate. Multiple linear regression was calculated to evaluate the effect of metabolizer status and total body weight change (%) with normal metabolizer as a reference group and in three models, and parameter estimates with standard error (SE) were calculated for poor/intermediate metabolizer and rapid/ultra-rapid metabolizer. Model one included BMI; model two included BMI and age, and model three included BMI, sex, and age. The analysis also excluded patients with concomitant strong and moderate inducers and

Ricardo-Silgado *et al. BMC Medicine*   (2022) 20:261

Page 4 of 12

inhibitors for P450-mediated metabolism. To investigate whether the weight gain varies between BMI groups according to the World Health Organization classification (i.e., underweight and normal weight, overweight, and obesity), we stratified the analysis by normal weight, overweight, and obesity groups. ANCOVA models were used to assess the difference in total body weight change (%) with metabolizer status within these groups with BMI as a covariate, data are presented as mean and 95% confidence intervals (CI). Plots and statistical analyses were performed in SAS 9.2 (SAS Institute Inc., Cary, NC). *P*-values ≤ 0.05 were considered statistically significant.

Results

The final cohort included 663 participants (age 61 [46 – 72] years, 76% females, and 94% white). The median BMI was 27.8 (24.0 – 32.9) kg/m^2, 62% of our cohort had normal weight or overweight, and 38% had obesity (Table 1). The prevalence of the different metabolizer status phenotypes for *CYP2C19, CYP2D6,* and *CYP2C9* by SSRI is described in Table 2 and Additional file 3: Figure S1. The normal metabolizer phenotype was the most frequent in all cytochrome enzymes, except for *CYP2D6,* where the poor/intermediate metabolizer was the most predominant. The rapid/ultrarapid metabolizer phenotype was the least frequent. There were no significant differences

Table 1 Participant characteristics in all participants and by drug. Data are shown as mean ± standard deviation or percentage

	Total $N=663$	Citalopram $N=202$	Fluoxetine $N=191$	Paroxetine $N=107$	Sertraline $N=163$	*p*-value[*]
Demographics						
Age, years	61 (46 – 72)	51 (40 – 66)	65 (53 – 76)	59 (48 – 69)	64 (46 – 77)	< 0.001
Gender, females	507 (76%)	158 (78%)	151 (79%)	80 (75%)	118 (72%)	0.44
Race, White	621 (94%)	190 (94%)	181 (95%)	100 (93%)	150 (92%)	0.79
Anthropometrics						
Weight, kg	78.0 (65.3 – 94)	76.2 (64.3 – 91.1)	82.0 (69.7 – 97)	74.2 (62 – 92.7)	76.7 (65 – 93.7)	0.03
BMI, kg/m^2	27.8 (24.0 – 32.9)	27.2 (23.6 – 32.1)	30.0 (25.1 – 34.4)	26.3 (23.8 – 32.5)	27.7 (23.7 – 32.5)	0.009
BMI Class						
Class, underweight or normal weight	211 (32%)	61(30%)	46 (24%)	45 (35%)	59 (36%)	
Class, overweight	202 (30%)	79 (39%)	48 (25%)	25 (23%)	50 (31%)	
Class, obesity	250 (38%)	62 (31%)	97 (51%)	37 (42%)	52 (33%)	

Continuous data are summarized as median (IQR). Categorical data are presented as frequencies and percentages

Abbreviations used: *BMI* Body mass index

[*] *p*-value: calculated with ANOVA

Table 2 Distribution of phenotypes of cytochromes enzymes involved in the metabolism of citalopram, paroxetine, fluoxetine, and sertraline among the participants

	Total $N=663$	Citalopram $N=202$	Fluoxetine $N=191$	Paroxetine $N=107$	Sertraline $N=163$
CYP2C19					
Poor/intermediate metabolizer, n	196 (30%)	58 (29%)			46 (28%)
Normal metabolizer, n	268 (40%)	83 (41%)			66 (41%)
Rapid/ultrarapid metabolizer, n	199 (30%)	61 (30%)			51 (31%)
CYP2D6					
Poor/intermediate metabolizer, n	462 (70%)		136 (71%)	70 (65%)	127 (78%)
Normal metabolizer, n	191 (29%)		53 (28.9%)	34 (32%)	31 (19%)
Rapid/ultrarapid metabolizer, n	10 (1%)		2 (0.1%)	3 (3%)	5 (3%)
CYP2C9					
Poor/intermediate metabolizer, n	234 (35%)		70 (37%)		
Normal metabolizer, n	429 (65%)		121 (63%)		

Categorical data are presented as frequencies and percentages

Ricardo-Silgado *et al. BMC Medicine*   (2022) 20:261

Page 5 of 12

in comorbidities among metabolizer phenotype (Additional file 2: Table S5).

The detail medications used which inhibit or induce the CYP 450 enzymes by SSRI can be found in Additional file 2: Tables S3 and S4. From patients taking citalopram, 1 (0.5%) was concomitantly prescribed rifampin, a strong inducer for *CYP2C19*, and 3 (1.5%) were prescribed fluconazole or fluvoxamine, strong inhibitors for *CYP2C19*. From patients taking fluoxetine, 1 (0.05%) was concomitantly prescribed terbinafine, a strong inhibitor for *CYP2D6*, and 11 (5.7%) were prescribed a moderate inhibitor for *CYP2C9* or *CYP2D6* (i.e., fluconazole [$n=8$], and duloxetine [$n=3$]). From the patients taking paroxetine, 1 (1%) was prescribed duloxetine, a moderate inhibitor of *CYP2D6*. From patients taking sertraline, 1 (1%) was concomitantly prescribed phenytoin, a moderate inducer for *CYP2C19*, and 2 (1%) were prescribed fluconazole a strong inhibitor for *CYP2C19*.

Total body weight gain % by metabolizer status

The total body weight gain percentage (TBWG %) at six months for the patients prescribed any SSRIs was 0.7% (-1.4 – 2.9). When analyzed by medication prescribed, TBWG % at six months for citalopram was 1.1% (-1.3 – 3.1), paroxetine 0.9% (-1.2 – 3.3), sertraline 1.1% (-1.0 – 2.9), and fluoxetine 0.1% (-1.9 – 2.6). For patients on citalopram, patients who were poor/intermediate *CYP2C19* metabolizers gained significantly more weight than normal and rapid/ultrarapid metabolizers (TBWG %: 2.6 [95% CI 1.3—4.1] vs. 0.4 [95% CI -0.5 – 1.3] vs. -0.1 [-95% CI -1.5—1.1], respectively; $p=0.001$) (Fig. 2). After excluding 3 patients with an inducer or inhibitor of the CYP 450, patients who were poor/intermediate

CYP2C19 metabolizers gained significantly more weight than normal and rapid metabolizers (TBWG %: 2.2 [95% CI 1.1—4.0] vs. 0.4 [95% CI -0.5 – 1.5] vs. -0.2 [95% CI -1.3—1.4], respectively; $p=0.003$). No significant difference was found in TBWG percentage at three or six months according to the *CYP2D6* phenotype for paroxetine, fluoxetine, and sertraline, *CYP2C9* for fluoxetine *CYP2C19* for fluoxetine and sertraline (Table 3).

Total body weight gain % by metabolizer status among BMI groups

Table 4 details the effect of metabolizer status and TBWG % after six months for each medication by BMI group. Patients in the overweight group that were prescribed citalopram who were poor/intermediate *CYP2C19* metabolizers gained significantly more weight than normal and rapid metabolizers (TBWG %: 3.0 [95% CI -0.3 – 6.4] vs. -0.3 [95% CI -2.1 – 1.5] vs. 1.3 [95% CI -3.6 – 1.1], respectively; p = 0.02). We did not observe any significant difference in TBWG % between metabolizer status among patients in the underweight, normal weight, or obesity group taking citalopram, fluoxetine, sertraline, or paroxetine (Table 5).

Effect of metabolizer status on total body weight gain %

Multiple linear regression was calculated to evaluate the effect of metabolizer status and TBWG % after six months for each medication. For citalopram, when adjusting for BMI, poor/intermediate *CYP2C19* metabolizer status resulted in a weight gain of 1.7% (Standard Error [SE] 0.5; $p=0.001$), while rapid/ultrarapid metabolizer status resulted in a decrease of 1.2% (SE 0.5; $p=0.01$). This effect remained significant after adjusting for BMI and
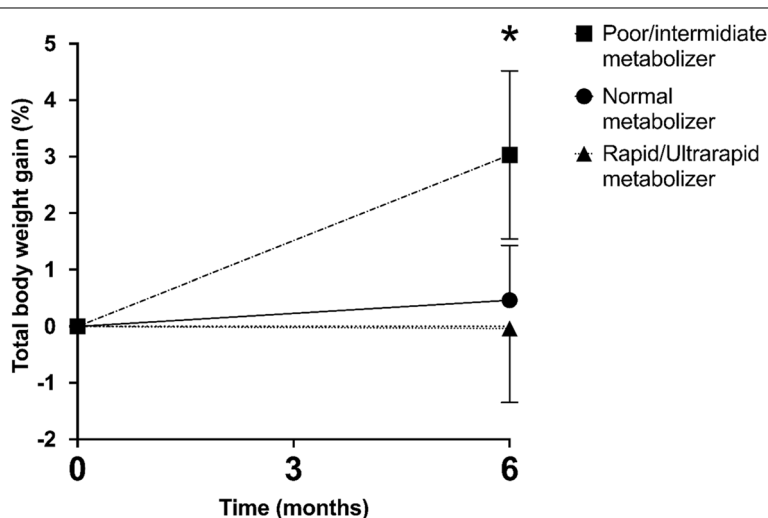

Fig. 2 Effect of citalopram on total body weight by CYP2C19 phenotype. *$p=0.001$

Ricardo-Silgado *et al. BMC Medicine*   (2022) 20:261

Page 6 of 12

Table 3 Total body weight gain percentage by CYP phenotype in participants prescribed with citalopram, paroxetine, fluoxetine, and sertraline

	Poor/intermediate metabolizer	Normal metabolizer	Rapid/ultra-rapid metabolizer	*p*- value
CYP2C19				
Citalopram				
TBWG 6 months, %	2.6 (95% CI 1.3 – 4.1)	0.4 (95% CI -0.5 – 1.3)	-0.1 (95% CI -1.5 – 1.1)	**0.001**
Sertraline				
TBWG 6 months, %	0.9 (95% CI -0.09 – 2.1)	0.4 (95% CI -0.6 – 1.5)	1.7 (95% CI 0.7 – 2.9)	0.13
CYP2D6				
Paroxetine				
TBWG 6 months, %	0.7 (95% CI -0.1 – 1.5)	1.6 (95% CI 0.2 – 2.9)	0.7 (95% CI -4.8 – 6.1)	0.50
Sertraline				
TBWG 6 months, %	1.1 (95% CI 0.4 – 1.9)	0.8 (95% CI -0.3 – 1.8)	0.9 (95% CI -9.0 – 10.9)	0.98
Fluoxetine				
TBWG 6 months, %	0 (95% CI -0.7 – 0.7)	0.2 (95% CI -1.2 – 1.5)	1.3 (95% CI -3 – 3)	0.84
CYP2C9				
Fluoxetine				
TBWG 6 months, %	0.5 (95% CI -0.5 – 1.6)	-0.1 (95% CI -1.1 – 0.6)		0.33

Continuous data are summarized as mean and 95% confidence interval (CI)

Abbreviations used: *TBWG* Total Body Weight Gain

p-value: calculated with ANCOVA with metabolizer status and BMI as covariates

age where poor/intermediate *CYP2C19* metabolizer status resulted in a weight gain of 1.7% (Standard Error [SE] 0.6; $p = 0.001$), while rapid/ultrarapid metabolizer status resulted in a decrease of 1.2% (SE 0.5; $p = 0.02$). This trend was also seen after adjusting for BMI, sex, and age where poor/intermediate *CYP2C19* metabolizer status resulted in a weight gain of 1.7% (Standard Error [SE] 0.5; $p = 0.001$), while rapid/ultrarapid metabolizer status resulted in a decrease of 1.2% (SE 0.5; $p = 0.02$). No significant effect was found for *CYP2D6* phenotype for paroxetine, fluoxetine, and sertraline, *CYP2C9* for fluoxetine, *CYP2C19* for fluoxetine, and sertraline when adjusting for BMI, BMI and age, or BMI, age, and sex.

Discussion

The current study identified that poor/intermediate metabolizer status for *CYP2C19* is associated with a 1.7% more weight gain after 6 months than normal metabolizers in patients taking citalopram. This study shows that this remains significant among patients with overweight, where patients with poor/intermediate metabolizer status for *CYP2C19* and taking citalopram had a TBWG of 3.0%. There were no disparities in comorbidities across individuals with various metabolizer statuses, and the difference in weight change remained after excluding patients who were using a CYP 450 inducer or inhibitor concurrently, highlighting the importance of the metabolizer status. Our results are generally consistent with previous studies showing the effect of citalopram on body weight [4, 22]. Aldrich et al. conducted a retrospective study using an electronic medical record of 263 youth with anxiety and depression prescribed citalopram. They showed a significant association between poor *CYP2C19* metabolizer phenotype and earlier weight gain after 45 days of treatment [23]. The weight changes related to other antidepressants were not connected with the other pharmacogenomic genes of interest.

Our findings are also consistent with previous studies in which fluoxetine and sertraline have shown minimal effects on weight gain [24]. Conversely, paroxetine has demonstrated a greater risk of weight gain. Serretti et al. reported that the mean weight difference during 8 months of treatment was 2.73 kg for paroxetine [25]. These findings were not replicated in our cohort treated with paroxetine; this discrepancy might be explained by the different intervals of the observations in the two studies.

A number of reasons complicate weight changes in individuals receiving depression medication; they may indicate an improvement in those who have lost weight due to their depression, but they can also be a side effect of the treatment. In our study, weight gain was seen in overweight patients on citalopram with poor/intermediate *CYP2C19* metabolizer status. Previous research has found that participants who considered their weight status as overweight were more likely to gain weight in the future [26]. We found that weight increase in patients treated with citalopram was significant even after

Ricardo-Silgado *et al. BMC Medicine*   (2022) 20:261

Page 7 of 12

Table 4 Total body weight gain by obesity class and CYP phenotype in participants prescribed with citalopram, paroxetine, fluoxetine, and sertraline

		Poor/intermediate metabolizer	Normal metabolizer	Rapid/ultra-rapid metabolizer	p-value
Normal and Underweight Group					
CYP2C19					
Citalopram	TBWG 6 mths, %	n=17 4.4 (95% CI 1.9 – 6.8)	n=26 1.5 (95% CI -0.3 – 3.4)	n=18 1.5 (95% CI -0.6 – 3.5)	0.11
Sertraline	TBWG 6 mths, %	n=12 2.6 (95% CI 0.9 – 4.5)	n=28 1.2 (95% CI -0.8 – 3.1)	n=19 2.7 (95% CI 1.1 – 4.3)	0.32
CYP2D6					*p*-value
Paroxetine	TBWG 6 mths, %	n=33 0.6 (95% CI -0.7 – 1.9)	n=11 0.4 (95% CI -2.7 – 3.6)	n=1 3.0	0.65
Sertraline	TBWG 6 mths, %	n=49 1.8 (95% CI 0.6 – 3.1)	n=8 1.4 (95% CI -0.5 – 3.4)	n=2 6.7 (95% CI -55.1 – 69.6)	0.16
Fluoxetine	TBWG 6 mths, %	n=32 1.2 (95% CI -0.3 – 2.7)	n=14 0.9 (95% CI -1.8 – 3.6)		0.88
CYP2C9					*p*-value
Fluoxetine	TBWG 6 mths, %	n=26 1.9 (95% CI -0.3 – 4.1)	n=20 0.5 (95% CI -1.1 – 2.1)		0.60
Overweight Group					
CYP2C19					*p*-value
Citalopram	TBWG 6 mths, %	n=21 3.0 (95% CI -0.3 – 6.4)	n=34 -0.3 (95% CI -2.1 – 1.5)	n=24 1.3 (95% CI -3.6 – 1.1)	**0.02**
Sertraline	TBWG 6 mths, %	n=19 1.5 (95% CI -0.2 – 3.1)	n=17 0.7 (95% CI -0.7 – 2.1)	n=14 2.3 (95% CI 0.6 – 4.1)	0.44
CYP2D6					*p*-value
Paroxetine	TBWG 6 mths, %	n=12 1.6 (95% CI -0.8 – 3.9)	n=12 3.5 (95% CI 1.4 – 5.6)	n=1 1.3	0.13
Sertraline	TBWG 6 mths, %	n=40 1.3 (95% CI 0.3 – 2.3)	n=8 2.3 (95% CI -0.5 – 3.4)	n=2 0.9 (95% CI -25.0 – 26.8)	0.69
Fluoxetine	TBWG 6 mths, %	n=28 1.2 (95% CI -2.9 – 0.4)	n=20 0.5 (95% CI -2.2 – 3.2)		0.21
CYP2C9					*p*-value
Fluoxetine	TBWG 6 mths, %	n=16 0.6 (95% CI -3.3 – 2.1)	n=32 0.5 (95% CI -2.3 – 1.3)		0.91
Obesity Group					
CYP2C19					*p*-value
Citalopram	TBWG 6 mths, %	n=20 0.8 (95% CI -0.5 – 1.9)	n=23 0.4 (95% CI -0.8 – 1.7)	n=19 -0.3 (95% CI -2.7 – 2.2)	0.18
Sertraline	TBWG 6 mths, %	n=15 -0.9 (95% CI -3.1 – 1.2)	n=21 -0.7 (95% CI -2.6 – 1.2)	n=18 0.6 (95% CI -1.7 – 2.9)	0.52
CYP2D6					*p*-value
Paroxetine	TBWG 6 mths, %	n=11 0.4 (95% CI -0.8 – 1.6)	n=25 0.7 (95% CI -1.3 – 2.6)	n=1 0.4	0.98
Sertraline	TBWG 6 mths, %	n=38 0.1 (95% CI -1.6 – 1.3)	n=15 0.3 (95% CI -1.8 – 1.2)	n=1 -10.6	0.26
Fluoxetine	TBWG 6 mths, %	n=19 0.1 (95% CI -0.9 – 1.0)	n=76 -0.9 (95% CI -3.1 – 1.2)	n=2 1.3 (95% CI -33.0 – 35.6)	0.79
CYP2C9					*p*-value
Fluoxetine	TBWG 6 mths, %	n=34 0.2 (95% CI -1.1 – 1.5)	n=63 -0.3 (95% CI -1.5 – 0.8)		0.30

Continuous data are summarized as mean (95% CI)

Abbreviations used: *CI* confidence interval, *TBWG* Total Body Weight Gain

p-value: calculated with ANCOVA with metabolizer status and BMI as covariate

Table 5 Multiple regression variate analysis. Total body weight gain by obesity class and CYP phenotype in participants prescribed with citalopram, paroxetine, fluoxetine, and sertraline

CYP2C19

		Model 1 Poor/intermediate metabolizer PE	p-value*	Model 1 Rapid/ultra-rapid metabolizer PE	p-value*	Model 2 Poor/intermediate metabolizer PE	p-value+	Model 2 Rapid/ultra-rapid metabolizer PE	p-value+	Model 3 Poor/intermediate metabolizer PE	p-value++	Model 3 Rapid/ultra-rapid metabolizer PE	p-value++
Citalopram	TBWG 6 mths, %	1.7 (0.5)	**0.001**	-1.2 (0.5)	**0.01**	1.7 (0.6)	**0.001**	-1.2 (0.5)	**0.02**	1.7 (0.5)	**0.001**	-1.2 (0.5)	**0.02**
Sertraline	TBWG 6 mths %	-0.03 (0.4)	0.94	0.7 (0.4)	0.08	0.01 (0.4)	0.99	0.7 (0.4)	0.10	0.01 (0.4)	0.99	0.7 (0.4)	0.11

CYP2D6

		Model 1 Poor/intermediate metabolizer PE	p-value*	Model 1 Rapid/ultra-rapid metabolizer PE	p-value*	Model 2 Poor/intermediate metabolizer PE	p-value+	Model 2 Rapid/ultra-rapid metabolizer PE	p-value+	Model 3 Poor/intermediate metabolizer PE	p-value++	Model 3 Rapid/ultra-rapid metabolizer PE	p-value++
Paroxetine	TBWG 6 mths, %	-0.3 (1.4)	0.82	-0.3 (0.7)	0.71	-0.4 (0.7)	0.61	-0.1 (1.4)	0.96	0.4 (0.7)	0.61	-0.1 (1.4)	0.96
Sertraline	TBWG 6 mths %	0.1 (0.6)	0.76	-0.3 (1.2)	0.80	0.1 (0.6)	0.89	-0.3 (1.2)	0.77	0.1 (0.6)	0.91	0.3 (1.2)	0.77
Fluoxetine	TBWG 6 mths %	-0.6 (1.1)	0.58	1.2 (2.2)	0.57	-0.6 (1.1)	0.57	1.3 (2.2)	0.50	-0.6 (1.1)	0.60	1.2 (2.2)	0.57

CYP2C9

		Model 1 Poor/intermediate metabolizer PE	p-value*	Model 1 Rapid/ultra-rapid metabolizer PE	Model 2 Poor/intermediate metabolizer PE	p-value+	Model 2 Rapid/ultra-rapid metabolizer PE	Model 3 Poor/intermediate metabolizer PE	p-value++	Model 3 Rapid/ultra-rapid metabolizer PE
Fluoxetine	TBWG 6 mths %	0.3 (0.3)	0.33		0.3 (0.6)	0.33		0.3 (0.3)	0.39	

p-value: multivariate linear regression with normal metabolizer as reference group

* model including BMI

\+ model including BMI and age

\++ model including BMI, age and sex

Abbreviations used: *BMI* body mass index; *PE* parameter estimates; *TBWG* Total Body Weight Gain

controlling for BMI, indicating the importance of metabolizer status. As a result, it is critical to identify individuals who are prone to weight gain and risk factors that may contribute to it. It is crucial to underline that a decision tool such as pharmacogenomics may be more effective in these individuals as an ad hoc instrument.

Multiple drugs with indications for chronic weight management have been authorized with improved safety profiles [27]. However, in a patient-centered care model, it is important to recognize barriers that may decrease to less effective and efficient weight management and that negatively impact weight loss outcomes. One of these barriers is weight gain as a medications' side effect, i.e. obesogenic drugs [28]. According to the findings of a patient survey, the most common reason for discontinuing antidepressant medication is a lack of effectiveness. However, up to 27% of patients who reported noncompliance discontinued the drug due to weight increase [29]. Previous research has looked at the link between metabolizer status and medicine discontinuation; however, no convincing relationship has been identified due to study design and sample collection [30]. More research is needed to determine the true impact of metabolizer status on drug discontinuation, particularly in individuals who are overweight and using SSRIs.

Despite their widespread usage of antidepressant medicine, initial drug selection success might be lower. According to the findings of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, only one-third of the patients achieved remission within the first treatment level [31]. Previous studies have found the clinical benefits of using pharmacogenomics to tailor the therapeutic approach in patients with major depressive disorder and anxiety [32–37]. Poor metabolizers taking escitalopram resulted in a greater rate of therapeutic failure, indicating the potential clinical value of *CYP2C19* genotyping for individualization of escitalopram [38]. However, there has not been any difference in adverse drug events reported between pharmacogenomic tailored treatment compared with controls [8, 9, 32].

Previous studies have retrospectively assessed side effects and metabolizer status with antidepressants such as tricyclic antidepressants (TCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and SSRIs [39, 40]. In terms of side effects and *CYP2C19* and citalopram/escitalopram, a meta-analysis of 2037 patients found that, compared to normal metabolizers, *CYP2C19* poor metabolizers had a greater risk of gastrointestinal, neurological, and sexual adverse effects [41]. The Patient Rated Inventory of Side Effects (PRISE), which includes weight gain among other items and covers 9 categories and 32 items, is a typical measure used to evaluate side effects in most pharmacogenomics studies. Most

research, however, focuses on side effects associated with a specific organ or system, which may restrict the relationship between pharmacogenomic studies with weight gain. Another study has looked at variations in the genes *CYP2D6*, *CYP2C19*, and *CYP2C9* in patients taking SSRIs and tolerability and did not find a clear pharmacogenetic explanation for side effects [30]. In a recent study of 9500 participants, poor metabolizers were at higher risk of side effects adding to the evidence for a link between *CYP2C19* metabolism and SSRI tolerability [42]. However, tolerability and side effects were evaluated by a survey using a qualitative assessment considering weight gain. The relationship between poor *CYP2C19* metabolizer status and early weight gain documented in the medical record in children using escitalopram or citalopram has been described, adding to the data connecting metabolizer status and weight increase [43]. This is the first study to objectively evaluate one of the common side effects of SSRIs, regardless of the response to treatment in adults.

Although studies on the association between citalopram blood concentrations and pharmaceutical effectiveness and tolerability are lacking, it is usually assumed that a 50% difference in blood concentration will have a clinical impact [10, 44]. Because of the increase in concentration for *CYP2C19* poor metabolizers compared to normal metabolizers, there is an implied risk of adverse outcomes, and the recommendation is to reduce the citalopram dose by 50% [10]. Further studies are needed to evaluate drug blood concentrations and weight gain according to metabolizer status.

Our study has some limitations. First, the low prevalence of some CYP enzyme phenotypes (*CYP2D6* rapid/ultrarapid metabolizer) and the small sample size might cause a type II error in assessing our primary outcome. This limits the ability to detect a difference in TBWG % with other enzyme phenotypes. Importantly, given the nature of the study, we could not include all patients prescribed an SSRI because a few had no follow up at our institution. Second, the generalizability of the data is limited by the retrospective nature of our study and does not establish a causal link between CYP enzyme phenotypes and weight gain. Third, it is difficult to investigate characteristics such as drug compliance since medical record data varies so much between health care providers, and the influence of polypharmacy on patient outcomes was not evaluated. This is an important aspect to consider in future research. Previously, tricyclic antidepressants, which have a more profound effect on bodyweight, weight gain, have been a clear limitation of compliance to the medication. Weight gain in our cohort may have resulted in noncompliance, concealing the differences in weight in our cohort among drugs that have previously

been associated with higher weight gain. Fourth, there are ascertainment biases inherent to a study conducted in tertiary care centers with a study population that is predominately White. Fifth, the mood response to the SSRI was not formally recorded with validated questionnaires, and this outcome was unclear from retrospective chart review during data gathering. Thus, response to treatment of depression could confound weight gain or weight loss.

In addition to the CYP genes, other genes related to the serotonin and norepinephrine signaling have been implicated with the therapeutic responses to SSRI. Previous studies have evaluated the effect of genetic variants on change in depressive symptoms and found significant associations with several variants in the serotonin receptor gene (*HTR2A*) and the response to escitalopram, the norepinephrine transporter gene (*SLC6A2*) and the response to nortriptyline, and the glucocorticoid receptor gene (*NR3C1*) and the response to both nortriptyline and escitalopram [45]. Here, we did not evaluate the effect of genetic variants that may affect the response to drugs with different mechanisms of action. Studies have also examined genes related to weight gain and SSRIs, such as catechol-O-methyltransferase (*COMT*), tryptophan hydroxylase 1 (*TPH1*), *HTR2C*, and serotonin transporter gene *(SLC6A4)*. The evidence shows that GG *COMT* and AA *TPH1* genotypes have more weight gain outcomes than *HTR2C* and *SLC6A4* polymorphism[9, 16, 37]. Our research did not cover the effect of other genes involved in the SSRI metabolisms; therefore, further research focusing on other enzymes involved in the SSRI metabolism is needed to understand the variability in weight gain response to this class of medication. The study's strengths include a high level of detail regarding CYP genotypes polymorphisms and weight loss outcomes and complications after bariatric surgery. It is, to our knowledge, the largest research evaluating weight change outcomes, combining the administration of CYP inducers and inhibitors at the same time.

Conclusions

In conclusion, we have performed a retrospective pharmacogenomics study to understand the SSRIs' common weight gain side effects. We showed that the *CYP2C19* genotype might explain weight gain in citalopram patients, and it might become a projection tool for preventing weight gain and obesity, particularly in patients who are overweight. Further studies are needed to validate this observation in prospective trials.

Abbreviations
BMI: Body mass index; CPIC: Clinical Pharmacogenetics Implementation Consortium; CYP: Cytochrome P450; EMR: Electronic medical record; IQR: Interquartile range; PE: Parameter estimates; RIGHT: Right Drug, Right Dose, Right Time; SSRIs: Selective serotonin reuptake inhibitors; TBWG: Total Body Weight Gain.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12916-022-02433-x.

> **Additional file 1:**
>
> **Additional file 2: Table S1.** STROBE reporting check list. T**able S2.** Variants/star alleles considered in this study. **Table S3.** Clinical inducers and inhibitors for P450-mediated metabolism considered. [46]. **Table S4.** Distribution of concomitant use of clinical inducers and inhibitors for P450-mediated metabolism by antidepressant. **Table S5.** Distribution of comorbidities by metabolizer status. CYP2C9>
>
> **Additional file 3: Figure S1.** Distribution of phenotypes of cytochromes enzymes involved in the metabolism of citalopram, paroxetine, fluoxetine, and sertraline among the participants.

Declarations

Ethics approval and consent to participate
All participants provided written informed consent for genotyping analysis and further utilization of their data as part of the Mayo Clinic Biobank and the RIGHT Study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Mayo Clinic Institutional Review Board (IRB 19–001222), formal consent was waived due to minimal risk.

Consent for publication
Not applicable.

Competing interests
Dr. Andres Acosta is a stockholder in Gila Therapeutics and Phenomix Sciences; he serves as a consultant for Rhythm Pharmaceuticals, General Mills. Dr. Camilleri is a stockholder in Phenomix Sciences and Enterin and serves as a consultant to Takeda, Allergan, Kallyope, and Arena with compensation to his employer, Mayo Clinic. Drs. Sneha Singh, Maria L Ricardo-Silgado, Lizeth Cifuentes, Daniel Gonzalez-Izundegui, Maria Daniela Hurtado, Ann Moyer, and Suzette Bielinski have no disclosures.

Author details
[1]Precision Medicine for Obesity Program and Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MN, USA. [2]Division of Epidemiology, Department of Quantitative Health Research, Mayo Clinic, Rochester, MN, USA. [3]Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine and Science, Mayo Clinic, Rochester, MN, USA. [4]Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Medicine, Mayo Clinic Health System, La Crosse, WI, USA.

Ricardo-Silgado *et al. BMC Medicine*　　(2022) 20:261

Page 11 of 12

References

1. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, Obesity, and Depression: A Systematic Review and Meta-analysis of Longitudinal Studies. Arch Gen Psychiatry. 2010;67(3):220–9. https://doi.org/10.1001/archgenpsychiatry.2010.2.
2. Noordam R, Aarts N, Tiemeier H, Hofman A, Stricker BH, Visser LE. Sex-specific association between antidepressant use and body weight in a population-based study in older adults. J Clin Psychiatry. 2015;76(6):e745–51. Epub 2015/07/02. doi: https://doi.org/10.4088/JCP.13m08896. PubMed PMID: 26132681.
3. Demyttenaere K, Jaspers L. Review: Bupropion and SSRI-induced side effects. J Psychopharmacol. 2008;22(7):792–804. Epub 2008/03/01. doi: https://doi.org/10.1177/0269881107083798. PubMed PMID: 18308785.
4. Uguz F, Sahingoz M, Gungor B, Aksoy F, Askin R. Weight gain and associated factors in patients using newer antidepressant drugs. Gen Hosp Psychiatry. 2015;37(1):46–8.
5. De Long NE, Stepita RA, Taylor VH, Holloway AC. Major depressive disorder and diabetes: does serotonin bridge the gap? Curr Diabetes Rev. 2015;11(2):71–8.
6. Gill H, Gill B, El-Halabi S, Chen-Li D, Lipsitz O, Rosenblat JD, et al. Antidepressant Medications and Weight Change: A Narrative Review. Obesity (Silver Spring). 2020. Epub 2020/10/07. doi: https://doi.org/10.1002/oby.22969. PubMed PMID: 33022115.
7. Young RL, Lumsden AL, Keating DJ. Gut serotonin is a regulator of obesity and metabolism. Gastroenterology. 2015;149(1):253–5.
8. Brethauer SA, Kim J, el Chaar M, Papasavas P, Eisenberg D, Rogers A, et al. Standardized outcomes reporting in metabolic and bariatric surgery. Surg Obes Relat Dis. 2015;11(3):489–506. Epub 2015/06/22. doi: https://doi.org/10.1016/j.soard.2015.02.003. PubMed PMID: 26093765.
9. Singh S, Ricardo-Silgado ML, Bielinski SJ, Acosta A. Pharmacogenomics of Medication Induced Weight Gain and Antiobesity Medications. Obesity. 2021;29(2):265–73.
10. Hicks JK, Bishop JR, Sangkuhl K, Müller DJ, Ji Y, Leckband SG, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015;98(2):127–34.
11. Conrado DJ, Rogers HL, Zineh I, Pacanowski MA. Consistency of drug-drug and gene-drug interaction information in US FDA-approved drug labels. Pharmacogenomics. 2013;14(2):215–23. Epub 2013/01/19. doi: https://doi.org/10.2217/pgs.12.203. PubMed PMID: 23327581.
12. Amare AT, Schubert KO, Baune BT. Pharmacogenomics in the treatment of mood disorders: strategies and opportunities for personalized psychiatry. EPMA Journal. 2017;8(3):211–27.
13. McMahon FJ, Buervenich S, Charney D, Lipsky R, Rush AJ, Wilson AF, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. Am J Hum Genet. 2006;78(5):804–14. Epub 2006/04/28. doi: https://doi.org/10.1086/503820. PubMed PMID: 16642436; PubMed Central PMCID: PMCPMC1474035.
14. Ising M, Lucae S, Binder EB, Bettecken T, Uhr M, Ripke S, et al. A genome-ewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. Arch Gen Psychiatry. 2009;66(9):966–75. Epub 2009/09/09. doi: https://doi.org/10.1001/archgenpsychiatry.2009.95. PubMed PMID: 19736353; PubMed Central PMCID: PMCPMC4465570.
15. Amare AT, Schubert KO, Tekola-Ayele F, Hsu Y-H, Sangkuhl K, Jenkins G, et al. Association of the polygenic scores for personality traits and response to selective serotonin reuptake inhibitors in patients with major depressive disorder. Front Psych. 2018;9:65.
16. Amare AT, Schubert KO, Tekola-Ayele F, Hsu Y-H, Sangkuhl K, Jenkins G, et al. The association of obesity and coronary artery disease genes with response to SSRIs treatment in major depression. J Neural Transm. 2019;126(1):35–45. https://doi.org/10.1007/s00702-018-01966-x.
17. Bielinski SJ, St Sauver JL, Olson JE, Larson NB, Black JL, Scherer SE, et al. Cohort Profile: The Right Drug, Right Dose, Right Time: Using Genomic Data to Individualize Treatment Protocol (RIGHT Protocol). Int J Epidemiol. 2020;49(1):23–4k. Epub 2019/08/06. doi: https://doi.org/10.1093/ije/dyz123. PubMed PMID: 31378813; PubMed Central PMCID: PMCPMC7124480.
18. Gordon AS, Fulton RS, Qin X, Mardis ER, Nickerson DA, Scherer S. PGRNseq: a targeted capture sequencing panel for pharmacogenetic research and implementation. Pharmacogenet Genomics. 2016;26(4):161–8. Epub 2016/01/07. doi: https://doi.org/10.1097/fpc.0000000000000202. PubMed PMID: 26736087; PubMed Central PMCID: PMCPMC4935646.
19. Lopes JL, Harris K, Karow MB, Peterson SE, Kluge ML, Kotzer KE, et al. Targeted Genotyping in Clinical Pharmacogenomics: What Is Missing? J Mol Diagn. 2022. Epub 2022/01/19. doi: https://doi.org/10.1016/j.jmoldx.2021.11.008. PubMed PMID: 35041929.
20. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138(1):103–41.
21. Verbeurgt P, Mamiya T, Oesterheld J. How common are drug and gene interactions? Prevalence in a sample of 1143 patients with CYP2C9, CYP2C19 and CYP2D6 genotyping. Pharmacogenomics. 2014;15(5):655–65.
22. Blumenthal SR, Castro VM, Clements CC, Rosenfield HR, Murphy SN, Fava M, et al. An electronic health records study of long-term weight gain following antidepressant use. JAMA Psychiat. 2014;71(8):889–96.
23. Aldrich SL, Poweleit EA, Prows CA, Martin LJ, Strawn JR, Ramsey LB. Influence of CYP2C19 metabolizer status on escitalopram/citalopram tolerability and response in youth with anxiety and depressive disorders. Front Pharmacol. 2019;10:99.
24. Dent R, Blackmore A, Peterson J, Habib R, Kay GP, Gervais A, et al. Changes in body weight and psychotropic drugs: a systematic synthesis of the literature. PLoS ONE. 2012;7(6): e36889.
25. Serretti A, Mandelli L, Laura M. Antidepressants and body weight: a comprehensive review and meta-analysis. The Journal of clinical psychiatry. 2010;71(10):0-.
26. Robinson E, Hunger J, Daly M. Perceived weight status and risk of weight gain across life in US and UK adults. Int J Obes. 2015;39(12):1721–6.
27. Fujioka K. Safety and tolerability of medications approved for chronic weight management. Obesity. 2015;23:S7.
28. Fastenau J, Kolotkin RL, Fujioka K, Alba M, Canovatchel W, Traina S. A call to action to inform patient-centred approaches to obesity management: Development of a disease-illness model. Clinical obesity. 2019;9(3): e12309.
29. Ashton AK, Jamerson BD, Weinstein WL, Wagoner C. Antidepressant-related adverse effects impacting treatment compliance: results of a patient survey. Curr Ther Res. 2005;66(2):96–106.
30. Maggo S, Kennedy MA, Barczyk ZA, Miller AL, Rucklidge JJ, Mulder RT, et al. Common CYP2D6, CYP2C9, and CYP2C19 gene variants, health anxiety, and neuroticism are not associated with self-reported antidepressant side effects. Frontiers in Genetics. 2019:1199.
31. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR* D: implications for clinical practice. Am J Psychiatry. 2006;163(1):28–40.
32. Bradley P, Shiekh M, Mehra V, Vrbicky K, Layle S, Olson MC, et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility. J Psychiatr Res. 2018;96:100–7. https://doi.org/10.1016/j.jpsychires.2017.09.024.
33. Winner JG, Carhart JM, Altar CA, Goldfarb S, Allen JD, Lavezzari G, et al. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. Curr Med Res Opin. 2015;31(9):1633–43.
34. Winner J, Allen J, Altar CA, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl Psychiatry. 2013;3(3):e242-e.
35. Winner JG, Carhart JM, Altar A, Allen JD, Dechairo BM. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov Med. 2013;16(89):219–27.
36. Hall-Flavin D, Winner J, Allen J, Jordan J, Nesheim R, Snyder K, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. 2012;2(10):e172-e.

Ricardo-Silgado *et al. BMC Medicine*   (2022) 20:261

Page 12 of 12

37. Singh AB. Improved antidepressant remission in major depression via a pharmacokinetic pathway polygene pharmacogenetic report. Clinical Psychopharmacology and Neuroscience. 2015;13(2):150.

38. Jukić MM, Haslemo T, Molden E, Ingelman-Sundberg M. Impact of CYP2C19 genotype on escitalopram exposure and therapeutic failure: a retrospective study based on 2,087 patients. Am J Psychiatry. 2018;175(5):463–70.

39. Steimer W, Zopf K, von Amelunxen S, Pfeiffer H, Bachofer J, Popp J, et al. Amitriptyline or not, that is the question: pharmacogenetic testing of CYP2D6 and CYP2C19 identifies patients with low or high risk for side effects in amitriptyline therapy. Clin Chem. 2005;51(2):376–85.

40. Müller DJ, Kekin I, Kao AC, Brandl EJ. Towards the implementation of CYP2D6 and CYP2C19 genotypes in clinical practice: update and report from a pharmacogenetic service clinic. Int Rev Psychiatry. 2013;25(5):554–71.

41. Fabbri C, Tansey KE, Perlis RH, Hauser J, Henigsberg N, Maier W, et al. Effect of cytochrome CYP2C19 metabolizing activity on antidepressant response and side effects: Meta-analysis of data from genome-wide association studies. Eur Neuropsychopharmacol. 2018;28(8):945–54.

42. Campos AI, Byrne EM, Mitchell BL, Wray NR, Lind PA, Licinio J, et al. Impact of CYP2C19 metaboliser status on SSRI response: a retrospective study of 9500 participants of the Australian Genetics of Depression Study. The Pharmacogenomics Journal. 2022:1–6.

43. Aldrich SL, Poweleit EA, Prows CA, Martin LJ, Strawn JR, Ramsey LB. Influence of CYP2C19 metabolizer status on escitalopram/citalopram tolerability and response in youth with anxiety and depressive disorders. Frontiers in Pharmacology. 2019:99.

44. Funk KA, Bostwick JR. A comparison of the risk of QT prolongation among SSRIs. Ann Pharmacother. 2013;47(10):1330–41.

45. Uher R, Huezo-Diaz P, Perroud N, Smith R, Rietschel M, Mors O, et al. Genetic predictors of response to antidepressants in the GENDEP project. Pharmacogenomics J. 2009;9(4):225–33. https://doi.org/10.1038/tpj.2009.12.

46. FDA. Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers FDA03/10/2020. Available from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3.