Supplement 1.Supplementary method, figure and table

CONTENTS

Methods

1. Prospective Cohort Study

1.1 Setting

Patients in the Precision Medicine to Enhance Depression and Anxiety Outcome (PMEDA) study were recruited from seventeen hospitals in China, including the Peking University Sixth Hospital, the Fifth Hospital of Tangshan, Renmin Hospital of Wuhan University, Hebei Provincial Mental Health Center, the First Affiliated Hospital of Chongqing Medical University, Tianjin Anding Hospital, Weihai Mental Health Center, the Fourth People's Hospital of Ordos, Hefei Fourth People's Hospital, Fuzhou Neuropsychiatric Hospital, Hebei General Hospital, the First Affiliated Hospital of Jinan University, the First Affiliated Hospital of Anhui Medical University, Hangzhou Seventh People's Hospital, the First Affiliated Hospital of Air Force Medical University, the Affiliated Mental Health Center of Jiangnan University, and Tongde Hospital of Zhejiang Province. The recruitment period was between March 2021 and April 2023, and the follow-up and data collection was between March 2021 and June 2023.

1.2 Variables

In the PMEDA study, predictors were CYP2D6 metabolic phenotype and *CYP2D6* copy number variant. CYP2D6 metabolic phenotype was measured by numerical (activity score) and categorical (metabolizer status) variables. The primary outcome was paroxetine steady-state concentration in plasma, while secondary outcomes included treatment efficacy and adverse drug reaction of paroxetine. Covariates included demographic factors such as sex, age, smoking and drinking habits; clinical factors such as first-episode or not, current episode duration, receiving adjunctive medicine or not, and paroxetine daily dose.

1.3 Bias

In the PMEDA study, we took several measures to control potential sources of bias. Firstly, we conducted a multi-center study to control selection bias. By recruiting participants from multiple locations, we could reduce the impact of geographic bias and ensure that our sample was representative of the population. Secondly, we used standardized measurement methods to control measurement bias. By using the same measurement methods across all study sites, we ensured that our data was comparable and reliable. Thirdly, to control observative bias, personnel involved in collecting and evaluating efficacy and safety were blinded to the results of CYP2D6 phenotype and paroxetine concentration until all data were collected.

1.4 Power

To determine the post hoc power of the regression analysis, we utilized the pwr.f2.test() function from the pwr package in R (Champely, 2020), with log-transformed paroxetine concentration as the dependent variable and CYP2D6 metabolizer status as the independent variable. For the analysis, we assumed a effect size of $f^2 = 0.01$, a significance level of $\alpha = 0.05$ (two-sided), and a single predictor. The test yielded a power of 0.861 with a sample size of 921, indicating a high likelihood of detecting a significant effect if present.

1.5 Plasma Concentration Detection of Paroxetine

Blood samples were collected using EDTA anticoagulant tubes and centrifuged at 1700 g for 10 minutes at 4℃. The supernatant was used to prepare three dried blood spots, with each spot containing 25 μL of the sample. These dried blood

spots were air-dried at room temperature for 4-6 hours before being transported to a centralized testing laboratory for analysis.

Standard solutions of paroxetine (20, 100, 200, 400, 1000, and 2000 ng/mL) were prepared. Standard dried blood spots were prepared using these standard solutions. Dried blood spots were cut out from the test and standard dried blood spot cards, with a diameter of about 6 mm per piece. These were placed into 1.5 mL EP tubes. An internal standard solution (10 μl) and methanol (500 μl) were added to each EP tube. The tubes were vortexed at 1500 rpm for 10 minutes, followed by ultrasonic water bath treatment for 10 minutes and centrifugation at 13000 r/min for 5 minutes. A 400 μl of supernatant was transferred from each EP tube, and a 5 μl sample was taken for chromatographic analysis.

Plasma concentration detection of paroxetine was performed using LC-MS/MS (AB5500, AB Sciex). The analyte was separated using a Kinetex C18 chromatographic column (100×3 mm, 2.6 μm) maintained at 40℃. The mobile phase consisted of A: 0.1% V/V aqueous formic acid solution containing five mmol ammonium acetate and B: 0.1% V/V methanol solution containing five mmol ammonium acetate. The flow rate was set at 0.5 ml/min, with an injection volume of 5 μL and gradient elution. Mass spectrometry was performed using electrospray ionization (ESI) in positive ion mode, with an ion pair of m/z: 330.3→192.1. Internal standard quantification analysis of paroxetine was performed using a multipoint calibration curve.

1.6 Identification of Copy Number of CYP2D6 Gene

The copy number of *CYP2D6* was identified using the ΔΔCt relative quantitative method by CopyCaller V2.3.1 software (Thermo Fisher, Waltham, USA). To do this, first, normalize the CT value of the target (*CYP2D6* exon 9) for all test and calibration samples using the CT value of the internal reference (*RNase P*), as shown in equation (1).

$$\Delta\mathrm{CT}(\mathrm{test}) = \mathrm{CT}(\mathrm{target}, \mathrm{test}) - \mathrm{CT}(\mathrm{reference}, \mathrm{test}) \quad (1)$$

Next, normalize the ΔCT value of the test sample using the ΔCT value of the calibration sample, as shown in equation (2) and (3)

$$\Delta\mathrm{CT}(\mathrm{calibrator}) = \mathrm{CT}(\mathrm{target}, \mathrm{calibrator}) - \mathrm{CT}(\mathrm{reference}, \mathrm{calibrator}) \quad (2)$$

$$\Delta\Delta\mathrm{CT} = \Delta\mathrm{CT}(\mathrm{test}) - \Delta\mathrm{CT}(\mathrm{calibrator}) \quad (3)$$

Then, calculate the fold change using equation (4).

$$\mathrm{Fold\ Change} = 2^{-\Delta\Delta\mathrm{Ct}} \quad (4)$$

Finally, the copy number of *CYP2D6* can be determined by comparing the fold change to the threshold for each copy number. For example, if there is no signal for *CYP2D6* exon 9 but a signal for *Rnase-P*, and the curve is normal, the copy number is 0N (*CYP2D6* *5). If the fold change is less than 1.5, the copy number is 1N. If the fold change is between 1.5 and 2.8, the copy number is 2N. If the fold change is between 2.8 and 3.6, the copy number is 3N. If the fold change is between 3.6 and 4.6, the copy number is 4N, and so on.

1.7 Conversion from Genotype to Phenotype

Below, we provide the variants used to define each *CYP2D6* allele, its effect on enzyme activity and activity score.

***CYP2D6* Allele**	**Enzyme Activity**	**Activity Score**	**Recommend Tier**	**MAF in East Asian**
*CYP2D6*1*	Normal	1	NA	0.24531412
*CYP2D6*3*	Null	0	1	0.00005840
*CYP2D6*4*	Null	0	1	0.00537109
*CYP2D6*5* (*CYP2D6* copy number deletion)	Null	0	1	0.04863416
*CYP2D6*6*	Null	0	1	0.00016714
*CYP2D6*7*	Null	0	2	7.39125E-05
*CYP2D6*8*	Null	0	2	0
*CYP2D6*10*	Decreased	0.25	1	0.4356336
*CYP2D6*11*	Null	0	NA	0
*CYP2D6*12*	Null	0	2	0
*CYP2D6*14A(*114)*	Null	0	NA	0.0007862866
*CYP2D6*14B*	Decreased	0.5	2	0.002951926
*CYP2D6*15*	Null	0	2	9.10604E-05
*CYP2D6*17*	Decreased	0.5	1	0.000097891
*CYP2D6*41*	Decreased	0.5	1	0.022667762
x N (*CYP2D6* copy number duplication)	Increased	x N	1	0.009432879

MAF = minor allele frequency. The "None-wild-type cumulative frequency" was calculated by summing up the MAF of all tested alleles except *1, while the "Capacity to detect known none-wild-type variation" was obtained by dividing the "None-wild-type cumulative frequency" by (1- MAF of *1, which is equal to 0.75468588). Therefore, the none-wild-type cumulative frequency in our test equals 0.525966108, and the capacity to detect known none-wild-type variation equals 69.7%. Whereas the capacity of the Tier 1 variant suggested by the Association of Molecular Pathology[1] equals 86.1%.

2. Meta-Analysis

2.1 Search strategy and selection criteria

We systematically searched the databases of PubMed, Cochrane Library, Embase, and Web of Science using Medical Subject Headings (MeSH) such as "Cytochrome P-450 CYP2D6", "Paroxetine," and "Genotype/Phenotype" as well as relevant free-text words.

Two independent reviewers screened the retrieved articles based on their titles and abstracts. Those irrelevant to our research question were excluded. After full-text screening of the remaining articles, the articles meeting the following criteria were included for meta-analysis: P (participant): subjects are healthy volunteers or patients with mental illness; I (Intervention) : take paroxetine; E (Exposure) : CYP2D6 genotyping was performed, and metabolic phenotype could be inferred based on the activity scoring system which was mentioned above; O (Outcome) : Report the results of pharmacokinetic parameters such as Css, Cmax and AUC. To account for the influence of dose on paroxetine Css and to make results comparable between studies with different doses, we used the ratio of means (RoM) to perform a meta-analysis comparing different metabolizer statuses[2,3].

$$\text{RoM} = mean\ 1/mean\ 2$$

$$\log(\text{RoM}) = \ln(m1) - \ln(m2)$$

$$SElog(RoM) = SQRT(sd_1^2/m_1n_1^2 + sd_2^2/m_2n_2^2)$$

2.2 Method for Dose Adjustment Computation

Dose adjustments are provided for different CYP2D6 metabolizer statuses, including poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), and ultrarapid metabolizer (UM). Dose adjustments were based on differences in pharmacokinetic parameters, including peak concentration (Cmax), area under the concentration-time curve (AUC), and concentration at steady-state (Css) observed among different metabolizer statues.

Average dose recommendations (DAv) provided by manufacturers may be considered the pragmatic results of large-scale studies performed within genetically mixed populations. For example, DAv may be considered the weighted means from a Caucasian population with 10% genetically defined PMs, 40% IMs, and 50% EMs. We can calculate percent adjustment compared with the average dose DAv (100%) for EMs.

According to the previous studies [4,5], the adjusted dose for the CYP2D6 EMs group DEM is given by:

$$DEM = \frac{100\%}{(0.1 * \frac{CssEM}{CssPM} + 0.4 * \frac{CssEM}{CssIM} + 0.5)}$$

Where CssPM, CssIM, CssEM are the Css for the respective metabolizer status, their coefficients reflect the phenotype frequency in the population. For every study, we extract the frequency of metabolizer statuses for the specific country from a previous study [6]. Dose adjustments for the intermediate and poor metabolizer groups (DIM and DPM) were calculated according to the below equations:

$$DIM = DEM * \frac{CssEM}{CssIM}$$

$$DPM = DEM * \frac{CssEM}{CssPM}$$

For the computation of dose adjustments in ultrarapid metabolizers (DUM), if PK data were available, the adjusted dose was calculated as follows:

$$DUM = DEM * \frac{CssEM}{CssUM}$$

If no data on the UMs group were available, the adjusted dose was computed based on extrapolated data:

$$DUM = 2 * DEM - DIM$$

If PK data were not available for PMs or IMs groups, they were extrapolated from available metabolizer statuses by assuming a linear gene-dose effect with CssIM laying in-between CssPM and CssEM as follows:

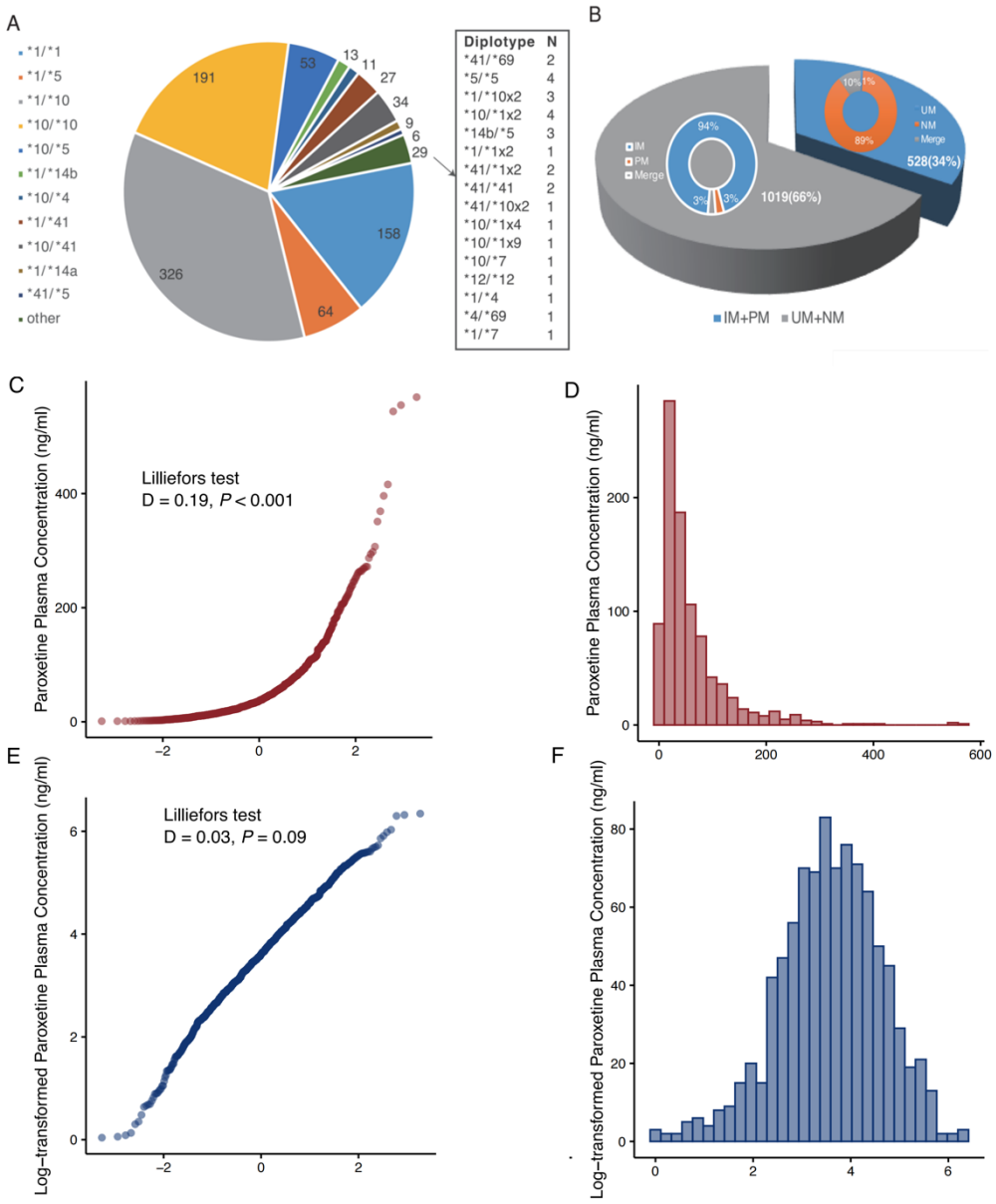
$$CssIM = \frac{CssEM + CssPM}{2}$$

$$CssPM = CssEM - 2 * (CssEM - CssIM)$$

In the following tables, dose adjustments were computed with these formulae for each study in meta-analytic literature. A final dose adjustment was computed by averaging these adjustments when more than one study was available. This final mean dose adjustment was used in Figure 4 of the main text and Supplemental Table S9-10.

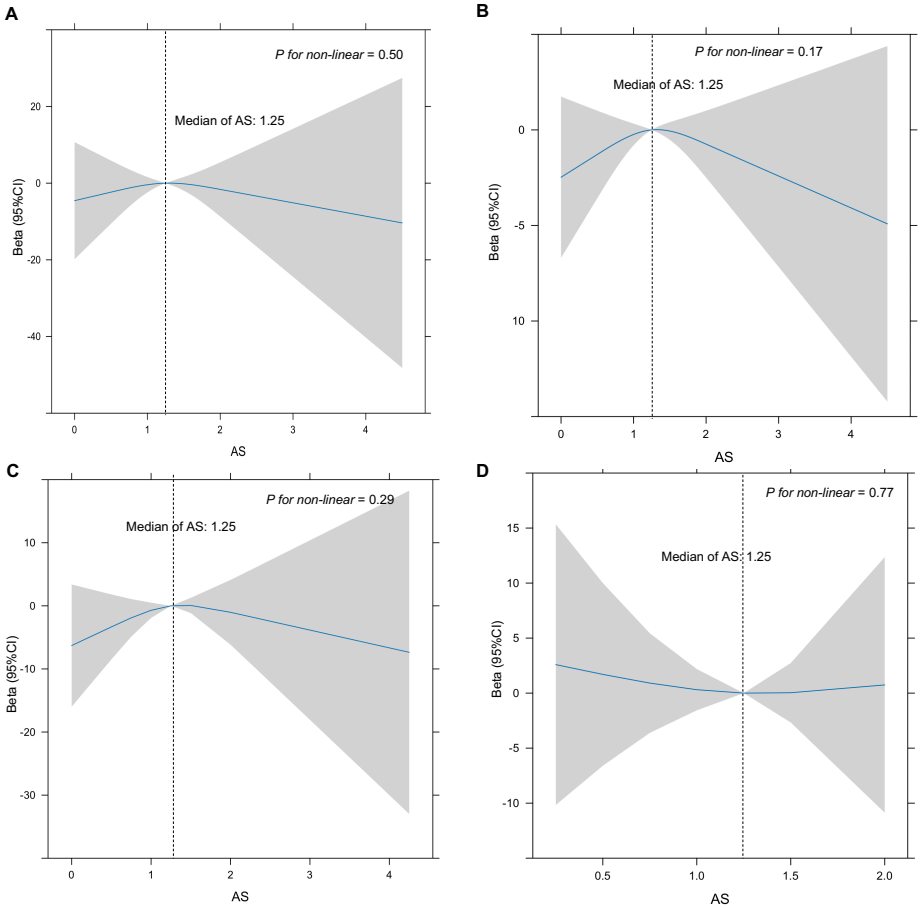
Figure and Table

Figure S1. Distribution of CYP2D6 Diplotype, CYP2D6 Metabolizer Status, and Paroxetine Steady-state Concentration.



UM=ultrarapid metabolizer, NM=normal metabolizer (extensive metabolizer), IM=intermediate metabolizer, PM=poor metabolizer. Note: Panel A shows the frequency of CYP2D6 diplotypes in the PMEDA study. Panel B illustrates the frequency of different CYP2D6 metabolizer statuses in 12 studies included in the meta-analysis. Panels shows histograms (C, E) and QQ plots (D, F), along with Lilliefors test results of raw and transformed paroxetine steady-state concentration.

Figure S2. Restricted Cubic Spline Analysis of CYP2D6 Activity Score.



Note: Restricted cubic spline (RCS) curves of CYP2D6 activity score and study outcomes, including steady-state concentration (Panel A), and the percentage improvements in HAMD, HAMA, and PDSS (Panels B, C, and D, respectively). Solid black lines represent crude Beta, with gray scales showing 95% confidence intervals derived from RCS regressions with three knots. The reference point (dashed lines) was set at the median value of the activity score, with three knots positioned at the 10th, 50th, and 90th percentiles.

Figure S3. Receiver Operating Characteristic (ROC) Curves of Paroxetine Steady-State Concentration (Css).

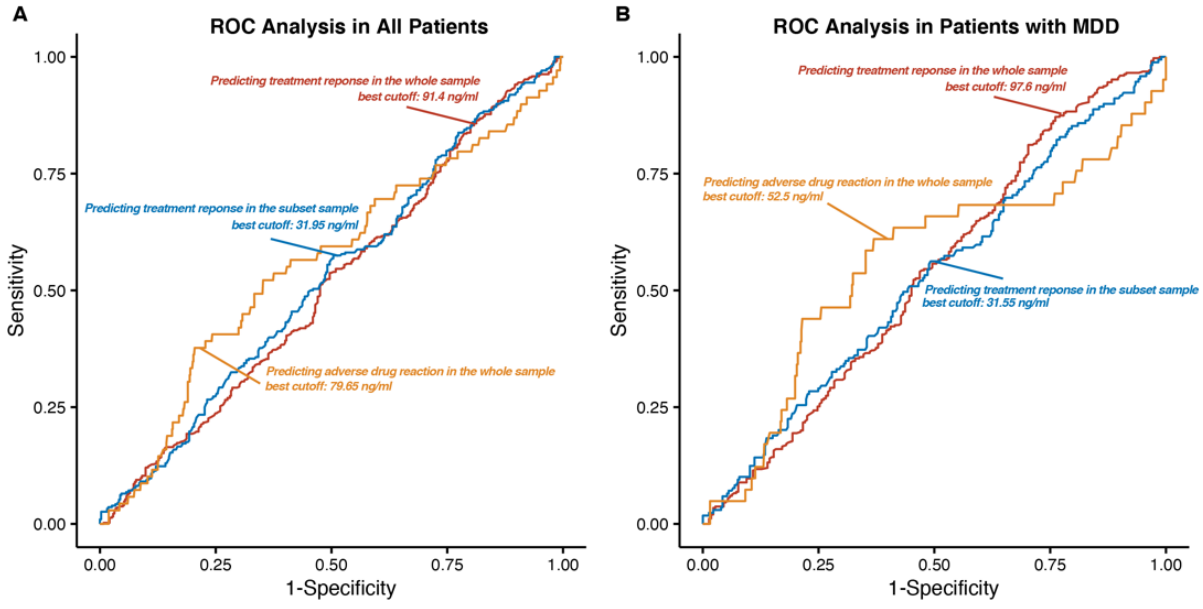
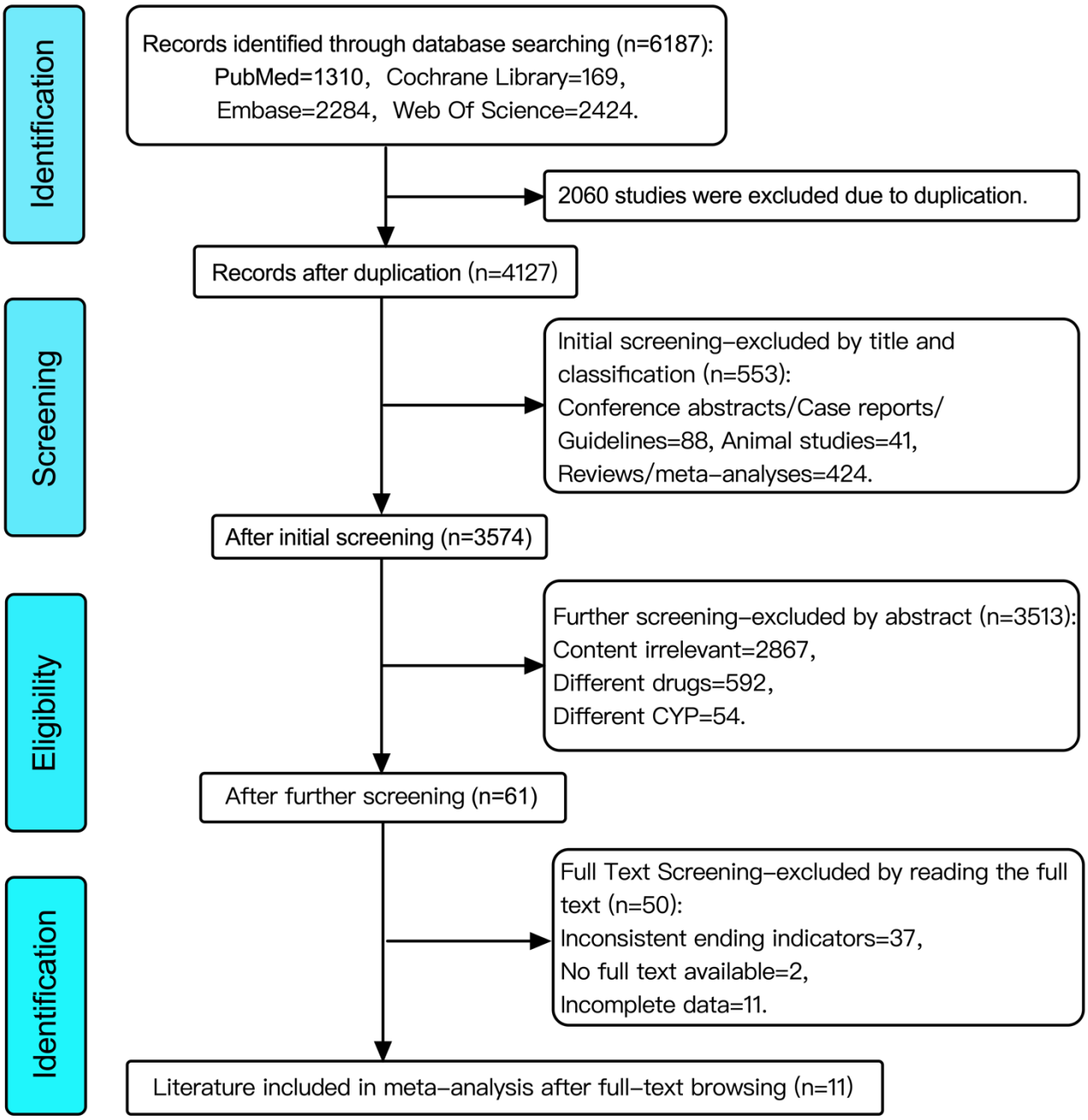
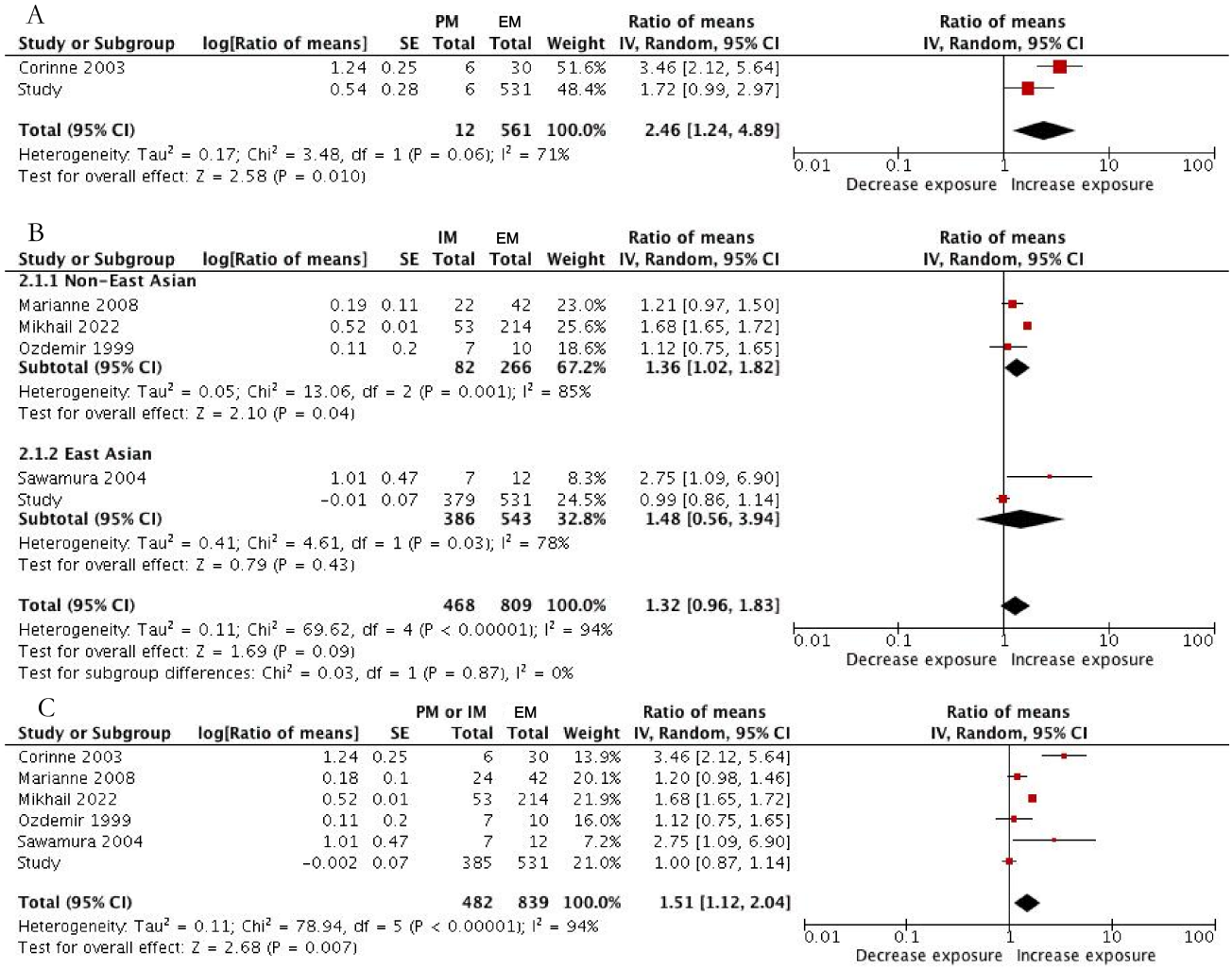


Figure S4. Literature Screening Flowchart.



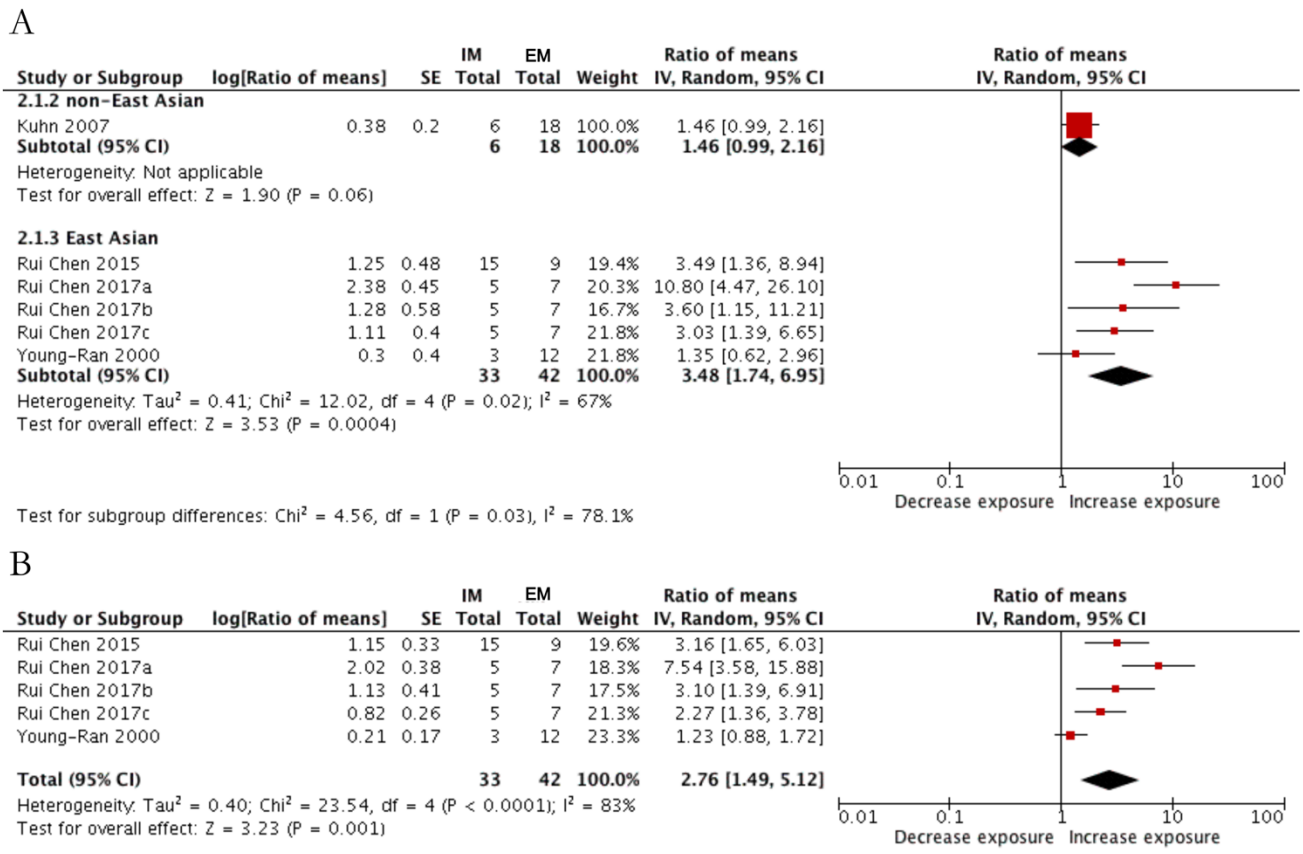
Note: The figure represents the literature excluded/included after each step.

Figure S5. Forest Plot for Paroxetine Steady-State Concentration.



Note: Panel A compares poor metabolizers (PMs) and extensive metabolizers (EMs). Panel B displays the comparison between intermediate metabolizers (IMs) and EMs. Panel C displays the comparison between PMs or IMs and EMs.

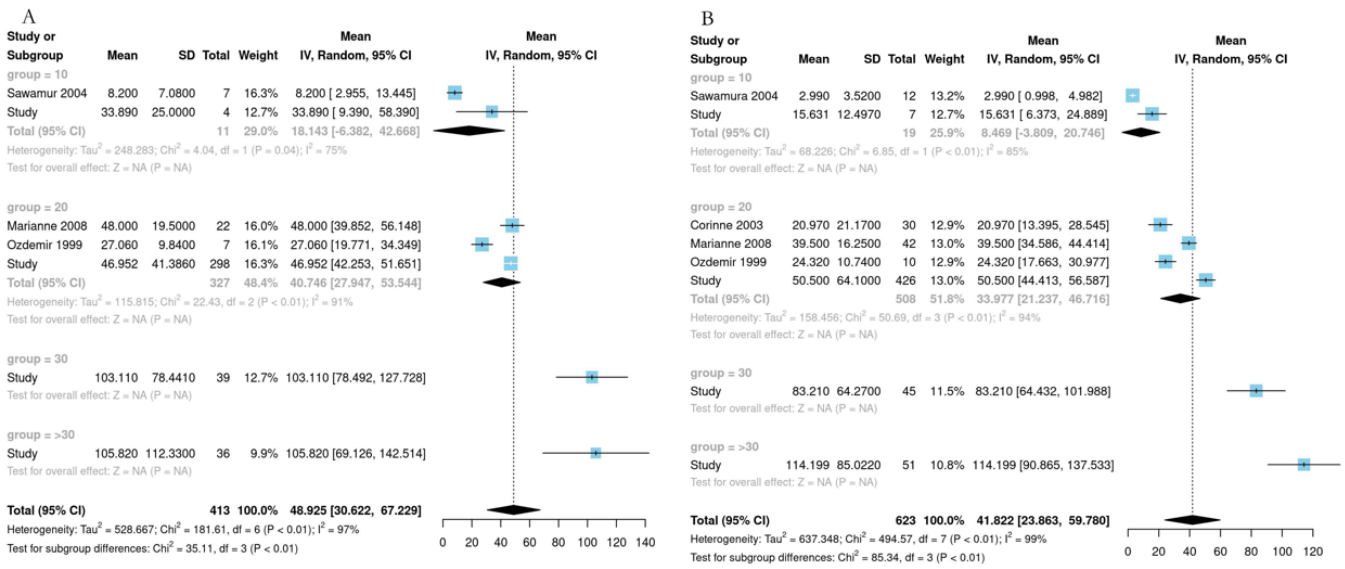
Figure S6. Forest Plot for Area Under Curve and Peak Concentration.



Note: Panel A: Forest plot of Area Under the Curve (AUC) for intermediate metabolizers (IMs) vs. extensive metabolizers (Ems). Rui Chen et al., 2017 reported the AUC data at three different doses, so it was divided into three arms, a, b, and c, representing 12.5 mg/d, 25 mg/d, and 37.5 mg/d, respectively.

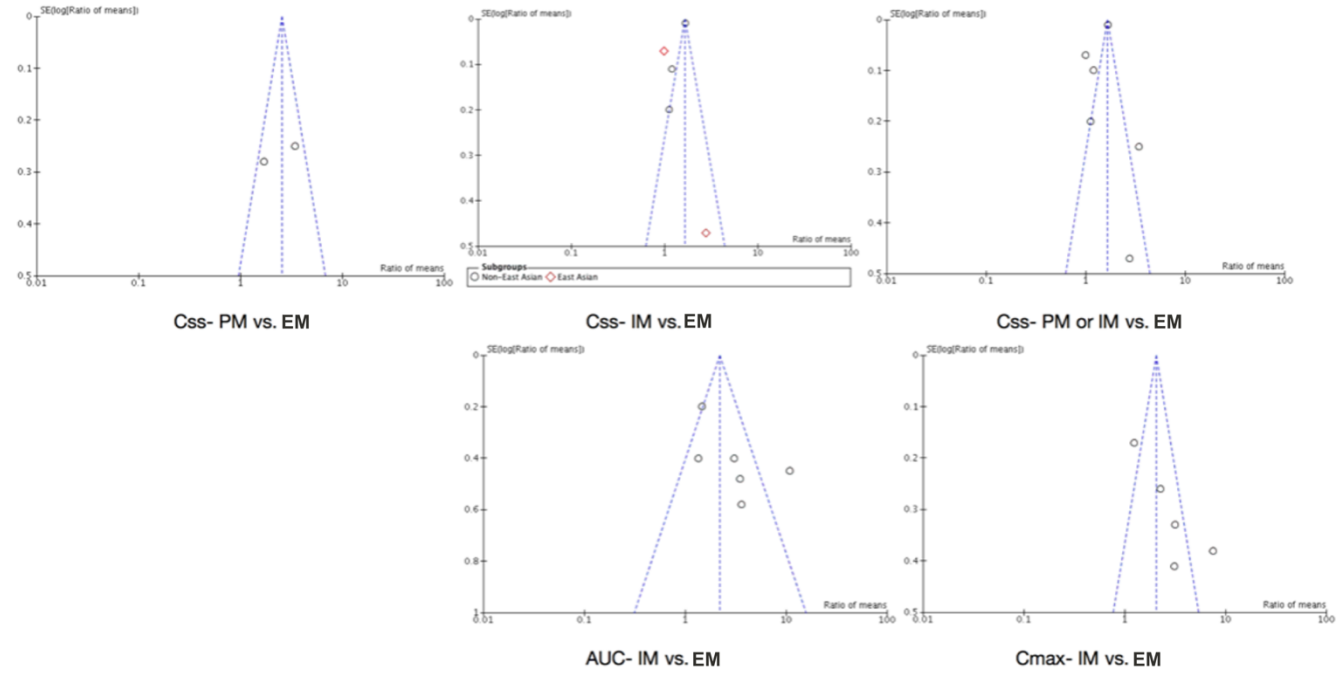
Panel B: Forest plot of Peak Concentration (Cmax) for IMs vs. EMs. Rui Chen et al., 2017 reported Cmax data at three different doses and therefore split into three arms, a, b, and c, representing 12.5mg/d, 25mg/d, and 37.5mg/d, respectively.

Figure S7. Forest Plot Based on Dose Subgroups



Note: Panel A: Intermediate metabolizers (IMs) subgroup forest plot; Panel B: Extensive metabolizers (EMs) subgroup forest plot.

Figure S8. Funnel Plots.



Abbreviation: Css=Steady-State Concentration, AUC= Area Under the Concentration-time Curve, Cmax=Peak Concentration, UM=ultrarapid metabolizer, EM=extensive metabolizer, IM=intermediate metabolizer, PM=poor metabolizer.

Table S1. A Search Strategy.

MeSH (Controlled Terms)	Free Text
Cytochrome P-450 CYP2D6	CYP2D6, Cytochrome P-450; Cytochrome P 450 CYP2D6; P-450 CYP2D6, Cytochrome; Sparteine Monooxygenase; Monooxygenase, Sparteine; Cytochrome P450 2D6; P450 2D6, Cytochrome; Debrisoquine 4-Monooxygenase; 4-Monooxygenase, Debrisoquine; Debrisoquine 4 Monooxygenase; Imipramine 2-Hydroxylase; 2-Hydroxylase, Imipramine; Imipramine 2 Hydroxylase; CYP2D6; CYP 2D6; Debrisoquine 4-Hydroxylase; 4-Hydroxylase, Debrisoquine; Debrisoquine 4 Hydroxylase; Debrisoquine Hydroxylase; Hydroxylase, Debrisoquine.
Paroxetine	Aropax; BRL-29060; BRL 29060; BRL29060; FG-7051; FG 7051; FG7051; Paroxetine Acetate; Seroxat; Paroxetine Hydrochloride Anhydrous; Paroxetine Maleate; Paroxetine, cis-(+)-Isome; Paroxetine, cis-(-)-Isomer; Paroxetine, trans-(+)-Isomer; Paxil; Paroxetine Hydrochloride Hemihydrate; Paroxetine Hydrochloride, Hemihydrate; Paroxetine Hydrochloride; polymorphism.
Genotype Phenotype Polymorphism, Genetic	Genotypes; Genogroup; Genogroups; Phenotypes; Polymorphisms, Genetic; Genetic Polymorphism; Genetic Polymorphisms; Gene Polymorphism; Gene Polymorphisms; Polymorphism, Gene; Polymorphisms, Gene; Polymorphism (Genetics); Polymorphisms (Genetics).

Note: Consists of Medical Subject Headings (MeSH) in PubMed with its corresponding Free Text.

Table S1. B Search History in PubMed

Search number	Query	Search Details	Results
1	"Phenotype"[Mesh]	"Phenotype"[MeSH Terms]	341,440
2	"Genotype"[Mesh]	"Genotype"[MeSH Terms]	456,734
3	(((Phenotypes[Title/Abstract]) OR (Genogroups[Title/Abstract])) OR (Genogroup[Title/Abstract])) OR (Genotypes[Title/Abstract])	"Phenotypes"[Title/Abstract] OR "Genogroups"[Title/Abstract] OR "Genogroup"[Title/Abstract] OR "Genotypes"[Title/Abstract]	330,142
4	(("Phenotype"[Mesh]) OR ("Genotype"[Mesh])) OR ((((Phenotypes[Title/Abstract]) OR (Genogroups[Title/Abstract])) OR (Genogroup[Title/Abstract])) OR (Genotypes[Title/Abstract]))	"Phenotype"[MeSH Terms] OR "Genotype"[MeSH Terms] OR "Phenotypes"[Title/Abstract] OR "Genogroups"[Title/Abstract] OR "Genogroup"[Title/Abstract] OR "Genotypes"[Title/Abstract]	894,787
5	"Polymorphism, Genetic"[Mesh]	"polymorphism, genetic"[MeSH Terms]	301,957
6	(((((((Polymorphisms, Genetic[Title/Abstract]) OR (Genetic Polymorphism[Title/Abstract])) OR (Genetic Polymorphisms[Title/Abstract])) OR (Gene Polymorphism[Title/Abstract])) OR (Gene Polymorphisms[Title/Abstract])) OR (Polymorphism, Gene[Title/Abstract])) OR (Polymorphisms, Gene[Title/Abstract])) OR (Polymorphism (Genetics[Title/Abstract]))) OR (Polymorphisms (Genetics[Title/Abstract]))	"polymorphisms genetic"[Title/Abstract] OR "genetic polymorphism"[Title/Abstract] OR "genetic polymorphisms"[Title/Abstract] OR "gene polymorphism"[Title/Abstract] OR "gene polymorphisms"[Title/Abstract] OR "polymorphism gene"[Title/Abstract] OR "polymorphisms gene"[Title/Abstract] OR (("polymorphic"[All Fields] OR "polymorphics"[All Fields] OR "polymorphism s"[All Fields] OR "polymorphism, genetic"[MeSH Terms] OR ("Polymorphism"[All Fields] AND "Genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "Polymorphism"[All Fields] OR "Polymorphisms"[All Fields]) AND "Genetics"[Title/Abstract]) OR (("polymorphic"[All Fields] OR "polymorphics"[All Fields] OR "polymorphism s"[All Fields] OR "polymorphism, genetic"[MeSH Terms] OR ("Polymorphism"[All Fields] AND "Genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "Polymorphism"[All Fields] OR "Polymorphisms"[All Fields]) AND "Genetics"[Title/Abstract])	80,949

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8	((("Phenotype"[Mesh]) OR ("Genotype"[Mesh])) OR ((((Phenotypes[Title/Abstract]) OR (Genogroups[Title/Abstract])) OR (Genogroup[Title/Abstract])) OR (Genotypes[Title/Abstract]))) OR (("Polymorphism, Genetic"[Mesh]) OR (((((((((Polymorphisms, Genetic[Title/Abstract]) OR (Genetic Polymorphism[Title/Abstract])) OR (Genetic Polymorphisms[Title/Abstract])) OR (Gene Polymorphism[Title/Abstract])) OR (Gene Polymorphisms[Title/Abstract])) OR (Polymorphism, Gene[Title/Abstract])) OR (Polymorphisms, Gene[Title/Abstract])) OR (Polymorphism (Genetics[Title/Abstract]))) OR (Polymorphisms (Genetics[Title/Abstract]))))	"Phenotype"[MeSH Terms] OR "Genotype"[MeSH Terms] OR ("Phenotypes"[Title/Abstract] OR "Genogroups"[Title/Abstract] OR "Genogroup"[Title/Abstract] OR "Genotypes"[Title/Abstract]) OR ("polymorphism, genetic"[MeSH Terms] OR ("polymorphisms genetic"[Title/Abstract] OR "genetic polymorphism"[Title/Abstract] OR "genetic polymorphisms"[Title/Abstract] OR "gene polymorphism"[Title/Abstract] OR "gene polymorphisms"[Title/Abstract] OR "polymorphism gene"[Title/Abstract] OR "polymorphisms gene"[Title/Abstract] OR (("polymorphic"[All Fields] OR "polymorphics"[All Fields] OR "polymorphism s"[All Fields] OR "polymorphism, genetic"[MeSH Terms] OR ("Polymorphism"[All Fields] AND "Genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR	1,027,553

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9	"Paroxetine"[Mesh]	"Paroxetine"[MeSH Terms]	4,166
10	((((((((((((((((Aropax[Title/Abstract]) OR (BRL-29060[Title/Abstract])) OR (BRL 29060[Title/Abstract])) OR (BRL29060[Title/Abstract])) OR (FG-7051[Title/Abstract])) OR (FG 7051[Title/Abstract])) OR (FG7051[Title/Abstract])) OR (Paroxetine Acetate[Title/Abstract])) OR (Seroxat[Title/Abstract])) OR (Paroxetine Hydrochloride Anhydrous[Title/Abstract])) OR (Paroxetine Maleate[Title/Abstract])) OR (Paroxetine, cis-(+)-Isomer[Title/Abstract])) OR (Paroxetine, cis-(-)-Isomer[Title/Abstract])) OR (Paroxetine, trans-(+)-Isomer[Title/Abstract])) OR (Paxil[Title/Abstract])) OR (Paroxetine Hydrochloride Hemihydrate[Title/Abstract])) OR (Paroxetine Hydrochloride, Hemihydrate[Title/Abstract])) OR (Paroxetine Hydrochloride[Title/Abstract])) OR (polymorphism[Title/Abstract])	"Aropax"[Title/Abstract] OR "BRL-29060"[Title/Abstract] OR "BRL-29060"[Title/Abstract] OR "FG-7051"[Title/Abstract] OR "FG-7051"[Title/Abstract] OR (("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "Acetate"[Title/Abstract]) OR "Seroxat"[Title/Abstract] OR (("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "hydrochloride anhydrous"[Title/Abstract]) OR (("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "Maleate"[Title/Abstract]) OR ((("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "cis"[All Fields]) AND "isomer"[Title/Abstract]) OR ((("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "cis"[All Fields]) AND "isomer"[Title/Abstract]) OR ((("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "trans"[All Fields]) AND "isomer"[Title/Abstract]) OR "Paxil"[Title/Abstract] OR "paroxetine hydrochloride hemihydrate"[Title/Abstract] OR "paroxetine	198,826

		hydrochloride hemihydrate"[Title/Abstract] OR "paroxetine hydrochloride"[Title/Abstract] OR "polymorphism"[Title/Abstract]	
11	("Paroxetine"[Mesh]) OR ((((((((((((((((((Aropax[Title/Abstract]) OR (BRL-29060[Title/Abstract])) OR (BRL 29060[Title/Abstract])) OR (BRL29060[Title/Abstract])) OR (FG-7051[Title/Abstract])) OR (FG 7051[Title/Abstract])) OR (FG7051[Title/Abstract])) OR (Paroxetine Acetate[Title/Abstract])) OR (Seroxat[Title/Abstract])) OR (Paroxetine Hydrochloride Anhydrous[Title/Abstract])) OR (Paroxetine Maleate[Title/Abstract])) OR (Paroxetine, cis-(+)-Isomer[Title/Abstract])) OR (Paroxetine, cis-(-)-Isomer[Title/Abstract])) OR (Paroxetine, trans-(+)-Isomer[Title/Abstract])) OR (Paxil[Title/Abstract])) OR (Paroxetine Hydrochloride Hemihydrate[Title/Abstract])) OR (Paroxetine Hydrochloride, Hemihydrate[Title/Abstract])) OR (Paroxetine Hydrochloride[Title/Abstract])) OR (polymorphism[Title/Abstract]))	"Paroxetine"[MeSH Terms] OR ("Aropax"[Title/Abstract] OR "BRL-29060"[Title/Abstract] OR "BRL-29060"[Title/Abstract] OR "FG-7051"[Title/Abstract] OR "FG-7051"[Title/Abstract] OR (("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "Acetate"[Title/Abstract]) OR "Seroxat"[Title/Abstract] OR (("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "hydrochloride anhydrous"[Title/Abstract]) OR (("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "Maleate"[Title/Abstract]) OR ((("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "cis"[All Fields]) AND "isomer"[Title/Abstract]) OR ((("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "cis"[All Fields]) AND "isomer"[Title/Abstract]) OR ((("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "trans"[All Fields]) AND "isomer"[Title/Abstract]) OR "Paxil"[Title/Abstract] OR "paroxetine hydrochloride hemihydrate"[Title/Abstract] OR "paroxetine hydrochloride hemihydrate"[Title/Abstract] OR "paroxetine hydrochloride"[Title/Abstract] OR "polymorphism"[Title/Abstract])	202,769
12	"Cytochrome P-450 CYP2D6"[Mesh]	"Cytochrome P-450 CYP2D6"[MeSH Terms]	4,783
13	((((((((((((((((((CYP2D6, Cytochrome P-450[Title/Abstract]) OR (Cytochrome P 450 CYP2D6[Title/Abstract])) OR (P-450 CYP2D6, Cytochrome[Title/Abstract])) OR (Sparteine Monooxygenase[Title/Abstract])) OR (Monooxygenase,	(("cytochrome p 450 cyp2d6"[MeSH Terms] OR ("Cytochrome"[All Fields] AND "P-450"[All Fields] AND "CYP2D6"[All Fields]) OR "cytochrome p 450 cyp2d6"[All Fields] OR "CYP2D6"[All Fields]) AND "cytochrome p	7,940

	Sparteine[Title/Abstract])) OR (Cytochrome P450 2D6[Title/Abstract])) OR (P450 2D6, Cytochrome[Title/Abstract])) OR (Debrisoquine 4-Monooxygenase[Title/Abstract])) OR (4-Monooxygenase, Debrisoquine[Title/Abstract])) OR (Debrisoquine 4 Monooxygenase[Title/Abstract])) OR (Imipramine 2-Hydroxylase[Title/Abstract])) OR (2-Hydroxylase, Imipramine[Title/Abstract])) OR (Imipramine 2 Hydroxylase[Title/Abstract])) OR (CYP2D6[Title/Abstract])) OR (CYP 2D6[Title/Abstract])) OR (Debrisoquine 4-Hydroxylase[Title/Abstract])) OR (4-Hydroxylase, Debrisoquine[Title/Abstract])) OR (Debrisoquine 4 Hydroxylase[Title/Abstract])) OR (Debrisoquine Hydroxylase[Title/Abstract])) OR (Hydroxylase, Debrisoquine[Title/Abstract])	450"[Title/Abstract]) OR "cytochrome p 450 cyp2d6"[Title/Abstract] OR ("P-450"[All Fields] AND "cyp2d6 cytochrome"[Title/Abstract]) OR "sparteine monooxygenase"[Title/Abstract] OR (("mixed function oxygenases"[MeSH Terms] OR ("mixed"[All Fields] AND "function"[All Fields] AND "oxygenases"[All Fields]) OR "mixed function oxygenases"[All Fields] OR "Monooxygenase"[All Fields] OR "monooxygenases"[All Fields]) AND "Sparteine"[Title/Abstract]) OR "cytochrome p450 2d6"[Title/Abstract] OR "p450 2d6 cytochrome"[Title/Abstract] OR "debrisoquine 4 monooxygenase"[Title/Abstract] OR ("4-Monooxygenase"[All Fields] AND "Debrisoquine"[Title/Abstract]) OR "debrisoquine 4 monooxygenase"[Title/Abstract] OR "imipramine 2 hydroxylase"[Title/Abstract] OR ("2-Hydroxylase"[All Fields] AND "Imipramine"[Title/Abstract]) OR "imipramine 2 hydroxylase"[Title/Abstract] OR "CYP2D6"[Title/Abstract] OR "cyp 2d6"[Title/Abstract] OR "debrisoquine 4 hydroxylase"[Title/Abstract] OR ("4-Hydroxylase"[All Fields] AND "Debrisoquine"[Title/Abstract]) OR "debrisoquine 4 hydroxylase"[Title/Abstract] OR "debrisoquine hydroxylase"[Title/Abstract] OR "hydroxylase debrisoquine"[Title/Abstract]	
14	("Cytochrome P-450 CYP2D6"[Mesh]) OR ((((((((((((((((((CYP2D6, Cytochrome P-450[Title/Abstract]) OR (Cytochrome P 450 CYP2D6[Title/Abstract])) OR (P-450 CYP2D6, Cytochrome[Title/Abstract])) OR (Sparteine Monooxygenase[Title/Abstract])) OR (Monooxygenase, Sparteine[Title/Abstract])) OR (Cytochrome P450 2D6[Title/Abstract])) OR (P450 2D6, Cytochrome[Title/Abstract])) OR (Debrisoquine 4-Monooxygenase[Title/Abstract])) OR (4-Monooxygenase, Debrisoquine[Title/Abstract])) OR (Debrisoquine 4 Monooxygenase[Title/Abstract])) OR (Imipramine 2-	"Cytochrome P-450 CYP2D6"[MeSH Terms] OR (("Cytochrome P-450 CYP2D6"[MeSH Terms] OR ("Cytochrome"[All Fields] AND "P-450"[All Fields] AND "CYP2D6"[All Fields]) OR "Cytochrome P-450 CYP2D6"[All Fields] OR "CYP2D6"[All Fields]) AND "cytochrome p 450"[Title/Abstract]) OR "Cytochrome P-450 CYP2D6"[Title/Abstract] OR ("P-450"[All Fields] AND "cyp2d6 cytochrome"[Title/Abstract]) OR "sparteine monooxygenase"[Title/Abstract] OR (("mixed function oxygenases"[MeSH Terms] OR ("mixed"[All Fields] AND "function"[All Fields] AND "oxygenases"[All Fields]) OR "mixed function	8,680

	Hydroxylase[Title/Abstract])) OR (2-Hydroxylase, Imipramine[Title/Abstract])) OR (Imipramine 2 Hydroxylase[Title/Abstract])) OR (CYP2D6[Title/Abstract])) OR (CYP 2D6[Title/Abstract])) OR (Debrisoquine 4-Hydroxylase[Title/Abstract])) OR (4-Hydroxylase, Debrisoquine[Title/Abstract])) OR (Debrisoquine 4 Hydroxylase[Title/Abstract])) OR (Debrisoquine Hydroxylase[Title/Abstract])) OR (Hydroxylase, Debrisoquine[Title/Abstract]))	oxygenases"[All Fields] OR "Monooxygenase"[All Fields] OR "monooxygenases"[All Fields]) AND "Sparteine"[Title/Abstract]) OR "cytochrome p450 2d6"[Title/Abstract] OR "p450 2d6 cytochrome"[Title/Abstract] OR "debrisoquine 4 monooxygenase"[Title/Abstract] OR ("4-Monooxygenase"[All Fields] AND "Debrisoquine"[Title/Abstract]) OR "debrisoquine 4 monooxygenase"[Title/Abstract] OR "imipramine 2 hydroxylase"[Title/Abstract] OR ("2-Hydroxylase"[All Fields] AND "Imipramine"[Title/Abstract]) OR "imipramine 2 hydroxylase"[Title/Abstract] OR "CYP2D6"[Title/Abstract] OR "cyp 2d6"[Title/Abstract] OR "debrisoquine 4 hydroxylase"[Title/Abstract] OR ("4-Hydroxylase"[All Fields] AND "Debrisoquine"[Title/Abstract]) OR "debrisoquine 4 hydroxylase"[Title/Abstract] OR "debrisoquine hydroxylase"[Title/Abstract] OR "hydroxylase debrisoquine"[Title/Abstract])	
15	(((((("Phenotype"[Mesh]) OR ("Genotype"[Mesh])) OR ((((Phenotypes[Title/Abstract]) OR (Genogroups[Title/Abstract])) OR (Genogroup[Title/Abstract])) OR (Genotypes[Title/Abstract]))) OR (("Polymorphism, Genetic"[Mesh]) OR (((((((((Polymorphisms, Genetic[Title/Abstract]) OR (Genetic Polymorphism[Title/Abstract])) OR (Genetic Polymorphisms[Title/Abstract])) OR (Gene Polymorphism[Title/Abstract])) OR (Gene Polymorphisms[Title/Abstract])) OR (Polymorphism, Gene[Title/Abstract])) OR (Polymorphisms, Gene[Title/Abstract])) OR (Polymorphism (Genetics[Title/Abstract]))) OR (Polymorphisms (Genetics[Title/Abstract])))))) AND (("Cytochrome P-450 CYP2D6"[Mesh]) OR ((((((((((((((((((((CYP2D6, Cytochrome P-450[Title/Abstract]) OR (Cytochrome P 450 CYP2D6[Title/Abstract])) OR (P-450 CYP2D6, Cytochrome[Title/Abstract])) OR (Sparteine	("Phenotype"[MeSH Terms] OR "Genotype"[MeSH Terms] OR ("Phenotypes"[Title/Abstract] OR "Genogroups"[Title/Abstract] OR "Genogroup"[Title/Abstract] OR "Genotypes"[Title/Abstract]) OR ("polymorphism, genetic"[MeSH Terms] OR ("polymorphisms genetic"[Title/Abstract] OR "genetic polymorphism"[Title/Abstract] OR "genetic polymorphisms"[Title/Abstract] OR "gene polymorphism"[Title/Abstract] OR "gene polymorphisms"[Title/Abstract] OR "polymorphism gene"[Title/Abstract] OR "polymorphisms gene"[Title/Abstract] OR (("polymorphic"[All Fields] OR "polymorphics"[All Fields] OR "polymorphism s"[All Fields] OR "polymorphism, genetic"[MeSH Terms] OR ("Polymorphism"[All Fields] AND "Genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "Polymorphism"[All Fields] OR "Polymorphisms"[All Fields]) AND	1,310

	Monooxygenase[Title/Abstract])) OR (Monooxygenase, Sparteine[Title/Abstract])) OR (Cytochrome P450 2D6[Title/Abstract])) OR (P450 2D6, Cytochrome[Title/Abstract])) OR (Debrisoquine 4-Monooxygenase[Title/Abstract])) OR (4-Monooxygenase, Debrisoquine[Title/Abstract])) OR (Debrisoquine 4 Monooxygenase[Title/Abstract])) OR (Imipramine 2-Hydroxylase[Title/Abstract])) OR (2-Hydroxylase, Imipramine[Title/Abstract])) OR (Imipramine 2 Hydroxylase[Title/Abstract])) OR (CYP2D6[Title/Abstract])) OR (CYP 2D6[Title/Abstract])) OR (Debrisoquine 4-Hydroxylase[Title/Abstract])) OR (4-Hydroxylase, Debrisoquine[Title/Abstract])) OR (Debrisoquine 4 Hydroxylase[Title/Abstract])) OR (Debrisoquine Hydroxylase[Title/Abstract])) OR (Hydroxylase, Debrisoquine[Title/Abstract]))))) AND (("Paroxetine"[Mesh]) OR ((((((((((((((((((Aropax[Title/Abstract]) OR (BRL-29060[Title/Abstract])) OR (BRL 29060[Title/Abstract])) OR (BRL29060[Title/Abstract])) OR (FG-7051[Title/Abstract])) OR (FG 7051[Title/Abstract])) OR (FG7051[Title/Abstract])) OR (Paroxetine Acetate[Title/Abstract])) OR (Seroxat[Title/Abstract])) OR (Paroxetine Hydrochloride Anhydrous[Title/Abstract])) OR (Paroxetine Maleate[Title/Abstract])) OR (Paroxetine, cis-(+)-Isomer[Title/Abstract])) OR (Paroxetine, cis-(-)-Isomer[Title/Abstract])) OR (Paroxetine, trans-(+)-Isomer[Title/Abstract])) OR (Paxil[Title/Abstract])) OR (Paroxetine Hydrochloride Hemihydrate[Title/Abstract])) OR (Paroxetine Hydrochloride, Hemihydrate[Title/Abstract])) OR (Paroxetine Hydrochloride[Title/Abstract])) OR (polymorphism[Title/Abstract]))))	"Genetics"[Title/Abstract]) OR (("polymorphic"[All Fields] OR "polymorphics"[All Fields] OR "polymorphism s"[All Fields] OR "polymorphism, genetic"[MeSH Terms] OR ("Polymorphism"[All Fields] AND "Genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "Polymorphism"[All Fields] OR "Polymorphisms"[All Fields]) AND "Genetics"[Title/Abstract])))) AND ("Cytochrome P-450 CYP2D6"[MeSH Terms] OR ((("Cytochrome P-450 CYP2D6"[MeSH Terms] OR ("Cytochrome"[All Fields] AND "P-450"[All Fields] AND "CYP2D6"[All Fields]) OR "Cytochrome P-450 CYP2D6"[All Fields] OR "CYP2D6"[All Fields]) AND "cytochrome p 450"[Title/Abstract]) OR "Cytochrome P-450 CYP2D6"[Title/Abstract] OR ("P-450"[All Fields] AND "cyp2d6 cytochrome"[Title/Abstract]) OR "sparteine monooxygenase"[Title/Abstract] OR (("mixed function oxygenases"[MeSH Terms] OR ("mixed"[All Fields] AND "function"[All Fields] AND "oxygenases"[All Fields]) OR "mixed function oxygenases"[All Fields] OR "Monooxygenase"[All Fields] OR "monooxygenases"[All Fields]) AND "Sparteine"[Title/Abstract]) OR "cytochrome p450 2d6"[Title/Abstract] OR "p450 2d6 cytochrome"[Title/Abstract] OR "debrisoquine 4 monooxygenase"[Title/Abstract] OR ("4-Monooxygenase"[All Fields] AND "Debrisoquine"[Title/Abstract]) OR "debrisoquine 4 monooxygenase"[Title/Abstract] OR "imipramine 2 hydroxylase"[Title/Abstract] OR ("2-Hydroxylase"[All Fields] AND "Imipramine"[Title/Abstract]) OR "imipramine 2 hydroxylase"[Title/Abstract] OR "CYP2D6"[Title/Abstract] OR "cyp 2d6"[Title/Abstract] OR "debrisoquine 4 hydroxylase"[Title/Abstract] OR ("4-Hydroxylase"[All Fields] AND "Debrisoquine"[Title/Abstract]) OR "debrisoquine 4 hydroxylase"[Title/Abstract] OR "debrisoquine hydroxylase"[Title/Abstract] OR "hydroxylase debrisoquine"[Title/Abstract])) AND ("Paroxetine"[MeSH Terms] OR	

		("Aropax"[Title/Abstract] OR "BRL-29060"[Title/Abstract] OR "BRL-29060"[Title/Abstract] OR "FG-7051"[Title/Abstract] OR "FG-7051"[Title/Abstract] OR (("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "Acetate"[Title/Abstract]) OR "Seroxat"[Title/Abstract] OR (("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "hydrochloride anhydrous"[Title/Abstract]) OR (("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "Maleate"[Title/Abstract]) OR ((("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "cis"[All Fields]) AND "isomer"[Title/Abstract]) OR ((("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "cis"[All Fields]) AND "isomer"[Title/Abstract]) OR ((("paroxetin"[All Fields] OR "Paroxetine"[MeSH Terms] OR "Paroxetine"[All Fields] OR "paroxetine s"[All Fields]) AND "trans"[All Fields]) AND "isomer"[Title/Abstract]) OR "Paxil"[Title/Abstract] OR "paroxetine hydrochloride hemihydrate"[Title/Abstract] OR "paroxetine hydrochloride hemihydrate"[Title/Abstract] OR "paroxetine hydrochloride"[Title/Abstract] OR "Polymorphism"[Title/Abstract]))	

Table S2. A The Effect of CYP2D6 Metabolizer Status on Paroxetine Efficacy in Single Disease Group

		Visit 1									Visit 2								
		Crude Model			Adj Model One*			Adj Model Two§			Crude Model			Adj Model One*			Adj Model Two§		
		β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*
MDD																			
	EM	Ref	-	-	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
	PM	-0.81	0.58	0.17	-0.77	0.58	0.18	-0.67	0.58	0.25	-0.57	0.58	0.33	-0.48	0.57	0.40	-0.32	0.56	0.57
	IM	-0.04	0.09	0.68	-0.03	0.09	0.74	-0.04	0.09	0.66	-0.02	0.09	0.85	0.01	0.09	0.93	0.02	0.09	0.85
	UM	-0.98	0.50	**0.05**	-0.93	0.50	0.07	-0.98	0.50	**0.049**	-0.66	0.50	0.19	-0.54	0.50	0.28	-0.55	0.49	0.26
GAD																			
	EM	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
	PM	-0.60	0.59	0.31	-0.64	0.59	0.28	-0.73	0.60	0.23	0.35	0.59	0.55	0.43	0.58	0.46	0.53	0.59	0.37
	IM	-0.01	0.14	0.93	0.001	0.15	0.99	0.02	0.15	0.91	0.17	0.15	0.25	0.17	0.15	0.26	0.18	0.15	0.23
PD																			
	EM	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
	IM	0.25	0.24	0.32	0.22	0.26	0.40	0.25	0.27	0.36	-0.07	0.25	0.79	-0.11	0.27	0.70	-0.01	0.28	0.96

Table S2. B The Effect of CYP2D6 Activity Score on Paroxetine Efficacy in Single Disease Group

	Visit 1									Visit 2								
	Crude Model			Adj Model One*			Adj Model Two§			Crude Model			Adj Model One*			Adj Model Two§		
	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*
MDD	0.001	0.06	0.99	-0.003	0.06	0.96	-0.01	0.06	0.90	-0.003	0.07	0.97	-0.02	0.06	0.80	-0.03	0.06	0.62
GAD	0.18	0.12	0.14	0.18	0.12	0.15	0.17	0.13	0.18	-0.09	0.13	0.50	-0.09	0.12	0.50	-0.08	0.13	0.51
PD	-0.06	0.22	0.78	-0.02	0.23	0.93	-0.01	0.23	0.96	-0.02	0.22	0.92	-0.01	0.24	0.98	-0.07	0.24	0.78

Table S2. C The Effect of *CYP2D6* CNV on Paroxetine Efficacy in Single Disease Group

		Visit 1									Visit 2								
		Crude Model			Adj Model One*			Adj Model Two§			Crude Model			Adj Model One*			Adj Model Two§		
		β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*	β_{std}	*SE*	*P*
MDD																			
	NON	Ref	-	-	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
	DEL	-0.06	0.12	0.64	-0.05	0.12	0.68	-0.05	0.12	0.69	0.12	0.12	0.34	0.13	0.12	0.28	0.15	0.12	0.20
	DUP	-0.05	0.31	0.86	-0.04	0.31	0.89	-0.04	0.30	0.89	-0.12	0.32	0.70	-0.09	0.31	0.78	-0.08	0.31	0.80
GAD																			
	NON	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
	DEL	0.11	0.22	0.61	0.13	0.22	0.56	0.16	0.23	0.49	0.30	0.21	0.16	0.27	0.21	0.21	0.32	0.22	0.15
	DUP	0.25	1.01	0.80	0.25	1.01	0.81	0.19	1.02	0.86	0.05	1.00	0.96	-0.09	1.00	0.93	-0.17	1.00	0.87
PD																			
	NON	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–	Ref	–	–
	DEL	0.65	0.35	0.07	0.63	0.38	0.10	0.73	0.38	0.06	0.33	0.38	0.39	0.34	0.41	0.40	0.42	0.41	0.32

*Sex and age were used as covariates. § Sex, age, current episode duration, baseline symptom severity, paroxetine daily dose, and adjunctive medication status were used as covariates. β_{std} = Standardized coefficient, UM=ultrarapid metabolizer, EM=extensive metabolizer, IM=intermediate metabolizer, PM=poor metabolizer, NON=CNV non-carrier, DEL=CNV deletion carrier, DUP=CNV duplication carrier. Note: Visit 1 took place following a 4-week treatment period with paroxetine, while Visit 2 occurred after an 8-week treatment period.

Table S3. The Effects of CYP2D6 Metabolic Phenotype and *CYP2D6* CNV on Paroxetine Efficacy in Pooled-Analysis

		Visit 1					Visit 2				
		β_{std} (95% CI)	*P*	*Q*	P_Q	I^2	β_{std} (95% CI)	*P*	*Q*	P_Q	I^2
Metabolizer											
	EM	Reference	–	–	–	–	Reference	–	–	–	–
	PM	-0.68 (-1.57, 0.21)	0.13	0.01	0.94	<0.01	-0.10 (-1.01, 0.81)	0.83	1.09	0.30	8.37
	IM	-0.001 (-0.14, 0.14)	0.98	1.04	0.60	<0.01	0.05 (-0.09, 0.20)	0.46	0.98	0.61	<0.01
AS		0.04 (-0.08, 0.14)	0.54	1.63	0.44	<0.01	-0.05 (-0.16, 0.06)	0.41	0.15	0.93	<0.01
CNV											
	NON	Reference	–	–	–	–	Reference	–	–	–	–
	DEL	0.06 (-0.31, 0.44)	0.74	4.05	0.13	50.59	0.21 (0.01, 0.41)	**0.04**	0.75	0.69	<0.01
	DUP	0.02 (-0.67, 0.70)	0.96	0.05	0.83	<0.01	-0.10 (-0.78, 0.58)	0.77	0.01	0.93	<0.01

β_{std} = Standardized coefficient, *P*=*P* for pooled-analysis unsing random effect meta-analysis, P_Q=*P* for hetergenetity, UM=ultrarapid metabolizer, EM=extensive metabolizer, IM=intermediate metabolizer, PM=poor metabolizer, AS=activity score, NON=CNV non-carrier, DEL=CNV deletion carrier, DUP=CNV duplication carrier.

Note: Sex, age, current episode duration, baseline symptom severity, paroxetine daily dose, and adjunctive medication status were used as covariates. Visit 1 took place following a 4-week treatment period with paroxetine, while Visit 2 occurred after an 8-week treatment period.

Table S4. The Effects of CYP2D6 Metabolic Phenotype and *CYP2D6* CNV on Paroxetine ADR

		Crude Model		Adj Model One*		Adj Model Two§	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Metabolizer							
	EM	Reference	–	Reference	–	Reference	–
	PM	2.64 (0.3, 23.22)	0.38	2.57 (0.28, 23.71)	0.41	2.61 (0.28, 24.05)	0.40
	IM	1.57 (0.96, 2.59)	0.07	1.55 (0.94, 2.57)	0.09	1.55 (0.94, 2.57))	0.09
	UM	–	0.98	–	0.98	–	0.98
AS		0.62 (0.40, 0.98)	**0.04**	0.62 (0.39, 0.97)	**0.04**	0.62 (0.40, 0.98)	**0.04**
CNV							
	NON	Reference	–	Reference	–	Reference	–
	DEL	1.63 (0.87, 3.04)	0.13	1.60 (0.85, 3.02)	0.14	1.59 (0.84, 2.99)	0.15
	DUP	1.06 (0.13, 8.33)	0.96	0.99 (0.12, 7.96)	1.00	0.95 (0.12, 7.64)	0.96

*Sex and age were used as covariates. § Sex, age, first-episode or not, and paroxetine daily dose were used as covariates.

UM=ultrarapid metabolizer, EM=extensive metabolizer, IM=intermediate metabolizer, PM=poor metabolizer, AS=activity score, NON=CNV non-carrier, DEL=CNV deletion carrier, DUP=CNV duplication carrier.

Note: Large estimate and standard error for CYP2D6 UM (beta=-13.0 in all models), interpret with caution.

Table S5. The Effects of *CYP2D6* CNV on Paroxetine Log-transformed Steady-State Concentration.

		Crude Model		Adj Model One*		Adj Model Two§	
		Exponentiated β (95% CI)	*P*	Exponentiated β (95% CI)	*P*	Exponentiated β (95% CI)	*P*
Whole Sample							
	NON	Reference	−	Reference	−	Reference	−
	DEL	1.54 (1.27, 1.87)	**<0.001**	1.53 (1.26, 1.85)	**<0.001**	1.50 (1.25, 1.80)	**<0.001**
	DUP	0.65 (0.37, 1.15)	0.13	0.64 (0.36, 1.12)	0.12	0.72 (0.42, 1.23)	0.22
Female	NON	Reference	−	Reference	−	Reference	−
	DEL	1.56 (1.24, 1.95)	**<0.001**	1.52 (1.21, 1.92)	**<0.001**	1.51 (1.22, 1.87)	**<0.001**
	DUP	0.52 (0.27, 0.98)	**0.04**	0.53 (0.28, 0.999)	0.05	0.61 (0.34, 1.12)	0.11
Male							
	NON	Reference	−	Reference	−	Reference	−
	DEL	1.49 (1.04, 2.13)	**0.03**	1.47 (1.03, 2.09)	**0.04**	1.45 (1.03, 2.03)	**0.04**
	DUP	1.22 (0.36, 4.06)	0.75	1.31 (0.39, 4.40)	0.66	1.43 (0.45, 4.59)	0.55

* Sex, age, body mass index, smoking and drinking habit were used as covariates. § Sex, age, body mass index, smoking and drinking habit, and paroxetine daily dose were used as covariates. NON=CNV non-carrier, DEL=CNV deletion carrier, DUP=CNV duplication carrier.

Table S6. A Quality Assessment Based on Strengthening the Reporting of Genetic Association Studies.

Study	Credible genetic testing method	Replicability of statistical methods	Assessment of Hardy Weinberg equilibrium	Sufficient descriptive demographic data	Clear report of dropouts and reasons	Statement of genotype frequencies and outcome data
Corinne 2003	+	+	-	+	-	+
Rui Chen 2017	+	+	-	+	-	+
Rui Chen 2015	+	+	-	+	-	+
Marianne 2008	+	+	-	+	-	+
Kuhn 2007	+	+	-	+	+	+
Murphy 2003	-	+	-	+	-	+
Sawamura 2004	+	+	-	-	+	+
Segura 2003	-	+	-	+	+	+
Özdemir 1999	-	+	-	-	+	+
Young-Ran 2000	+	+	-	-	+	+
Mikhail 2022	-	+	-	+	+	+

Note: " + " detailed description; " − " no description.

Table S6. B Quality Assessment Based on Risk of Bias Assessment-the Cochrane's Risk of Bias Tool

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Corinne 2003	M	L	L	L	L	L	M	M
Rui Chen 2017	M	L	M	L	L	L	M	M
Rui Chen 2015	M	L	M	L	L	L	M	M
Marianne 2008	M	L	M	L	L	L	NI	M
Kuhn 2007	M	L	L	L	L	L	M	M
Murphy 2003	M	L	L	NI	L	L	M	M
Sawamura 2004	M	NI	L	NI	L	L	S	S
Segura 2003	M	L	L	L	L	L	NI	M
Özdemir 1999	M	L	L	NI	L	L	M	M
Young-Ran 2000	M	L	L	L	L	L	M	M
Mikhail 2022	M	L	L	L	L	L	M	M

Note:

D1 – Bias due to confounding

D2 – Bias in selection of participant into study

D3 – Bias in measurement classification of intervention

D4 – Bias due to deviations from intended intervention

D5 – Bias due to missing data

D6 – Bias in measurement of outcomes

D7 – Bias in selection of the reported results

Reaching risk of bias judgement on a domain-level within the study:

Low risk of bias (L) – The study is comparable to a well performed randomized trial with regard to the domain

Moderate risk of bias (M) - The study is sound for a nonrandomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial

Serious risk of bias (S) - The study has some important problems in this domain

Critical risk of bias (C) – The study is too problematic in this domain to provide any useful evidence on the effects of intervention

No Information (NI) – No information on which to base a judgement about risk of bias for this domain

Table S7. Characteristics of Included Studies in Meta-Analysis.

No.	Study	Age	Female（%）	Country	Sample size	Type of participants	Dosage	Phenotypic classification	Genotyping method	Phenotype	Genotype	AS	Number of subjects	Outcomes
1	Corinne 2003 [7]	43.2± 12.7	0	Belgium	37	Patient-depression	20mg/d	Genetic tests	PCR	UM	*2/*2x2	3	1	Css
										EM	Unclear	NA	30	
										PM	*4/*4, *4/*3, *4/*5	0	6	
2	Rui Chen 2017 [8]	24.6± 3.9	67	China	12	Healthy volunteer	12.5-37.5mg/d	Genetic tests	PCR	EM	*1/*1, *1/*2, *1/*10, *2/*10	2, 1.25	7	Cmax, AUC
										IM	*5/*10，*10/*10，*10/*14B	0.25, 0.5, 0.75	5	
3	Rui Chen 2015 [9]	25.6± 5.5	42	China	24	Healthy volunteer	25mg/d	Genetic tests	PCR	EM	*1/*1, *1/*2, *1/*10, *1/*41, *2/*10, *2/*14B	2, 1.25, 1.5	9	Cmax, AUC
										IM	*1/*5,*5/*10,*10/*10,*10/*14B,*10/*41	1, 0.25, 0.5, 0.75	15	
4	Marianne 2008 [10]	19-62	54	Switzerland	71	Patient-depression	20mg/d	Genetic tests	PCR	Undefined	*1/*xN	NA	4	Css
										EM	*1/*1	2	42	
										IM	*1/*4, *1/*5, *1/*6	1	22	
										PM	*4/*6, *4/*4	0	2	
5	Kuhn 2007 [11]	25.1 ± 3.3	0	Germany	25	Healthy volunteer	30mg/d	Genetic tests	PCR	EM	Wt/Wt, Wt/*41	2, 1.5	18	AUC
										IM	Wt/*3, Wt/*4, Wt/*5, Wt/*6, *41/*4	1, 0.5	6	
										PM	*4/*4	0	1	

6	Murphy 2003 [11]	20.8 ± 10.9	53	USA	120	Patient-depression	20-40mg/d	Genetic tests	NA	UM+EM	Wt/Wt, Wt/WtxN	2, >2	105	Css
										IM+PM	Null/Null, Null/Red, Red/Red	0, 0.25, 0.5, 0.75, 1	15	
7	Sawamura 2004 [12]	39.9± 15.4	0	Japan	51	Patient	10mg/d	Genetic tests	PCR	EM	*1/*1	2	12	Css
										IM	*10/*10	0.5	7	
8	Segura 2003 [13]	23.1± 2.0	0	Spanish	9	Healthy volunteer	20mg/d	Dextromethorphan dextrorphan ratio	NA	EM	Dextromethorphan dextrorphan ratio	NA	9	Cmax, AUC
9	Özdemir 1999 [14]	21-49	0	Canada	17	Healthy volunteer	20 mg/d	Genetic tests	NA	EM	*1/*1	2	10	Css
										IM	*1/*3, *1/*4, *1/*5	1	7	
10	Young-Ran 2000 [15]	22.4± 1.4	0	Korean	16	Healthy volunteer	40mg/d	Genetic tests	PCR	EM	*1/*1,*1/*10	2, 1.25	12	Cmax, AUC
										IM	*10/*10	0.5	3	
										PM	log_{10}MR(Metabolic ratio) greater than 1.1 (or MR >12.6)	0	1	
11	Mikhail 2022 [16]	40.25 ±14.34	0	USA	267	Patient-depression	25.1±9.5mg/d	Genetic tests	NA	EM	*1/*1	2	214	Css
										IM	*1/*4	1	53	

Note: Dextromethorphan dextrorphan ratio: Dextromethorphan was used as a drug probe, and the dextromethorphan/dextrorphan urinary metabolic ratio was used to classify subjects as normal or poor metabolizers. PCR: A 20 μL PCR reaction was performed to detect *CYP2D6* genotypes. Primers were designed using Primer3 software. PCR amplification was performed using SolGent™ f-Taq DNA Polymerase.

Abbreviation: AS=Activity Score, Css=Steady-State Concentration, AUC=Area Under the Concentration-time Curve, Cmax=Peak Concentration, UM=ultrarapid metabolizer, EM=extensive metabolizer, IM=intermediate metabolizer, PM=poor metabolizer, NA=ot Available, Wt=Wild type alleles with normal function, Red=Alleles that result in reduced function of CYP2D6 enzyme, Null=Alleles that result in no function of CYP2D6 enzyme.

Table S8. Results of the Cross-ethnic Meta-Analysis.

Outcome	Group	Included studies（N）	Sample size of CYP2D6 metabolizer		*P*-value	RoM (95% CI)	Heterogeneity	
			PM/IM/PM+IM	EM			I^2 (%)	Model
Css	PM vs. EM RoM	2	12	561	**0.01**	2.46 (1.24, 4.89)	71	Random
	IM vs. EM RoM	5	468	809	0.09	1.32 (0.96, 1.83)	94	Random
	PM+IM vs. EM RoM	6	482	839	**0.007**	1.51 (1.12, 2.04)	94	Random
AUC	IM vs. EM RoM	4	39	60	**0.001**	2.89 (1.54, 5.44)	76	Random
Cmax	IM vs. EM RoM	3	33	42	**0.001**	2.76 (1.49, 5.12)	83	Random
Css Subgroup-IM vs. EM RoM	Non-East-Asian	3	82	266	**0.04**	1.36 (1.02, 1.82)	85	Random
	East Asian	2	386	543	0.43	1.48 (0.56, 3.94)	78	Random
AUC Subgroup-IM vs. EM RoM	Non-East-Asian	1	6	18	0.06	1.46 (0.99, 2.16)	-	Random
	East Asian	3	33	42	**0.0004**	3.48 (1.74, 6.95)	67	Random

Abbreviation: RoM=Ratio of Mean, Css=Steady-State Concentration, AUC=Area Under the Concentration-time Curve, Cmax=Peak Concentration, EM=extensive metabolizer, IM=intermediate metabolizer, PM=poor metabolizer.

Note: CYP2D6 EM was set as a reference to calculate the RoM.

Table S9. Dose Adjustments Based on Difference in Pharmacokinetic Parameters of Paroxetine across CYP2D6 Metabolizer Statuses in the East Asian Population.

Study conditions and parameters measured				Sample Size				Extrapolated dose adjustments				References
Country	PK	Dose (mg)	Participants	PM	IM	EM	UM	PM (%)	IM (%)	EM (%)	UM (%)	
Japan	Css	10mg/d	Patient	0	7	12	0	#27	(44	121)	#198	Sawamura et al. 2004
China	Css	10-60mg/d	MDD or AD	6	379	531	5	59	(103	101)	364	Study*
China	Cmax	25mg/d	Volunteer	0	15	9	0	#27	46	144	#243	RuiChen et al. 2015
China	Cmax	12.5 mg/d	Volunteer	0	5	7	0	#12	21	163	#304	RuiChen et al. 2017
China	Cmax	25 mg/d	Volunteer	0	5	7	0	#28	46	144	#241	RuiChen et al. 2017
China	Cmax	37.5 mg/d	Volunteer	0	5	7	0	#38	59	134	#209	RuiChen et al. 2017
Korean	Cmax	40mg/d	Volunteer	0	3	12	0	#74	(88	109)	#130	Young-Ran et al. 2000
China	AUC	25mg/d	Volunteer	0	15	9	0	#25	42	147	#252	RuiChen et al. 2015
China	AUC	12.5 mg/d	Volunteer	0	5	7	0	#8	15	167	#319	RuiChen et al. 2017
China	AUC	25 mg/d	Volunteer	0	5	7	0	#24	41	148	#255	RuiChen et al. 2017
China	AUC	37.5 mg/d	Volunteer	0	5	7	0	#28	47	143	#240	RuiChen et al. 2017
Korean	AUC	40mg/d	Volunteer	0	3	12	0	#66	(83	112)	#142	Young-Ran et al. 2000
								35	**40**	**143**	**241**	**Pool estimate**

#: Data were extrapolated, * refer to as the PMEDA study.

Note: The column "Dose" represents the doses administered in clinical studies, shown as a range of multiple doses given. The column "Participants" represents healthy volunteers or patients participating in the study. The column "Sample Size" represents the participants for each metabolizer status. The column "Extrapolated dose adjustments" represents dose adjustment from an average 'common' dose for each metabolizer status and study, calculated as described in the text. Results in parentheses indicate non-statistically significant PK differences and no dose adjustments are recommended based on these studies, the percentages are given solely for the completeness of this quantitative meta-analysis.

Abbreviation: PK=Pharmacokinetic Parameter, Cmax=Peak Concentration, AUC=Area Under the Concentration-time Curve, Css=Steady-State Concentration, MDD=Major Depressive Disorder; AD=Anxiety Disorder.

Table S10. Dose Adjustments Based on Difference in Pharmacokinetic Parameters of Paroxetine across CYP2D6 Metabolizer Statuses in the Non-East-Asian population.

Study conditions and parameters measured				Numbers				Extrapolated dose adjustments				References
Country	PK	Dose (mg）	Participants	PM	IM	EM	UM	PM (%)	IM (%)	EM (%)	UM (%)	
Germany	AUC	30 mg/d	Volunteer	0	6	18	0	#64	(84	122)	#161	Kuhn et al. 2007
Belgium	Css	20mg/d	MDD	6	0	30	0	40	#62	137	#213	Corinne et al. 2003
Switzerland	Css	20mg/d	MDD	2	22	42	0	(150	87	106	#125)	Marianne et al. 2008
USA	Css	25.1±9.5mg/d	MDD	0	53	214	0	#52	73	124	#174	Mikhail et al. 2022
Canada	Css	20 mg/d	Volunteer	0	7	10	0	#91	(100	111)	#123	Ozdemir et al. 1999
								62	**68**	**131**	**159**	**Pool estimate**

#:Data were extrapolated.

Note: The column "Dose" represents the doses administered in clinical studies, shown as a range of multiple doses given. The column "Participants" represents healthy volunteers or patients participating in the study. The column "Sample Size" represents the participants for each metabolizer status. The column "Extrapolated dose adjustments" represents dose adjustment from an average 'common' dose for each metabolizer status and study, calculated as described in the text. Results in parentheses indicate non-statistically significant PK differences and no dose adjustments are recommended based on these studies, the percentages are given solely for the completeness of this quantitative meta-analysis.

Abbreviation: PK=Pharmacokinetic Parameter, Cmax=Peak Concentration, AUC=Area Under the Concentration-time Curve, Css=Steady-State Concentration, MDD=Major Depressive Disorder; AD=Anxiety Disorder.

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