



Heterogeneity in the association between CYP2D6 genotype and antipsychotic-induced extrapyramidal symptoms: A systematic review

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ABSTRACT

Introduction: Cytochrome-P450 2D6 (CYP2D6) activity modulates the biotransformation of many antipsychotics and neuroactive endobiotics. Functional polymorphisms yielding poor (PM), intermediate (IM), normal (NM) or ultrarapid (UM) metabolic phenotypes could therefore influence vulnerability to extrapyramidal symptoms (EPS). Aim of the present review was to critically summarize the evidence linking CYP2D6 genotype with antipsychotic-induced EPS.

Methods: A systematic search of PubMed, MEDLINE and EBSCO (1 January 1997 – 28 April 2025) identified studies that: (i) examined CYP2D6 genotype or phenotype in relation to antipsychotic exposure, (ii) quantitatively assessed EPS, and (iii) enrolled ≥ 10 participants.

Results: Eighteen studies (7 prospective cohorts, 10 cross-sectional studies, 1 randomized controlled trial; total n= 2037 participants) met inclusion criteria. Typical antipsychotics—particularly haloperidol and zuclopentixol-dominated the exposure profile (64 % of participants). Eleven studies reported a genotype-EPS association, consistently showing greater EPS prevalence or severity in PM and IM carriers. Reported odds ratios for EPS across included studies ranged ~2–5 for PM/IM vs EM/UM. Risperidone and haloperidol were the antipsychotics most frequently associated with EPS. Null findings were primarily reported by studies devoid of PM genotypes and enrolling adolescent cohorts receiving second-generation antipsychotics.

Conclusion: Some studies summarized in the present review supported the role of CYP2D6 genotype in the occurrence of EPS in patients treated with antipsychotics, particularly with high-potency D₂ antagonists. Prospective, genotype-stratified trials that incorporate concomitant inhibitors/inducers, polygenic scores and pharmacodynamic modifiers are still required before cost-effective implementation algorithms can be finalized.

Introduction

Extrapyramidal side effects (EPS) are among the most frequent iatrogenic movement disorders and the second most common cause of parkinsonism after idiopathic Parkinson's disease (PD).¹ Among users of antipsychotics, the prevalence of any extrapyramidal symptoms (EPS) has been reported to exceed 35%, including 20% for antipsychotic-induced parkinsonism, 11% for akathisia, and 7% for tardive dyskinesia (TD).² Although EPS may be related to a variety of different compounds, including antiemetics, cholinomimetics, antidepressants, and antiepileptic drugs, they have been consistently described as a possible side effect of antipsychotics.³ The antipsychotics more frequently related EPS are the first-generation antipsychotics, including

phenothiazines, butyrophenones, benzamides, due to their strong postsynaptic dopamine receptors antagonism.^{4,5}

Given the reported substantial negative impact of EPS on functioning and quality of life,⁶ identifying and characterizing risk factors that predispose individuals to EPS is essential to optimise treatment safety and outcomes. However, both real-world experience and previous studies indicate that predicting EPS remains challenging. Indeed, many patients may tolerate high doses of antipsychotics without developing EPS, whereas others experience severe EPS even at low doses, thus supporting the existence of a possible vulnerability.⁷ Age, female sex and genetic susceptibility are among the well-recognized risk factors associated with EPS.

Cytochrome P450 2D6 (CYP2D6) is a key drug-metabolizing enzyme,

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contributing to the biotransformation of approximately 20–25% of clinically used drugs, including haloperidol, risperidone, zuclopentixol and perphenazine, whereas others rely predominantly on alternative enzymes such as CYP1A2 (e.g., olanzapine, clozapine) or CYP3A4 (e.g., quetiapine, aripiprazole), underscoring why the clinical impact of CYP2D6 variation may differ across agents.⁸

The CYP2D6 gene is highly polymorphic; to date, ~170 alleles have been catalogued, leading to functional variability from loss of function to increased activity and to distinct metabolizer phenotypes—poor (PM), intermediate (IM), normal/extensive (NM/EM), and ultrarapid (UM). Non-functional alleles (e.g., *3, *4, *5, *6) result in little to no CYP2D6 activity and are typically associated with a PM phenotype. Reduced-function alleles (e.g., *10, *17, *41) decrease enzyme efficiency and, when present in combination with a normal or defective allele, often confer an IM phenotype. Individuals carrying two fully functional alleles (e.g., *1/*1, *1/*2) are classified as NN/EM. Conversely, duplication or multiplication of functional alleles (e.g., *1xN, *2xN) increases CYP2D6 expression and may lead to an UM phenotype.^{8,9}

In this context, CYP2D6 has been investigated as a genetic susceptibility factor for antipsychotic adverse effects.¹⁰

People with IM or PM CYP2D6 frequently present higher drug plasma level, thus increasing not only the drug efficacy but also the risk of side effects, treatment discontinuation, and non-adherence.^{11–13} For this reason, CYP2D6 pharmacogenetics should be considered in the design and implementation of tailored drug therapy to ensure drug efficacy and safety.

However, both regulatory and scientific consortia and working groups still report conflicting indications. Indeed, both the U.S. Food and Drug Administration and the European Medicines Agency include only brief, non-binding references to CYP genotyping in their product labeling for antipsychotic–CYP2D6 interactions. In line with this, the PharmGKB database currently reports a low and inconsistent level of evidence for such interactions.¹⁴ However, the Dutch Pharmacogenetics Working Group (DPWG) recently recommended the normal dose reduction of several antipsychotics (i.e. aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopentixol) for CYP2D6-predicted PMs and the Clinical Pharmacogenetics Implementation Consortium is still finalizing its guideline on CYP2D6 guided dosing for antipsychotics.^{15,16} Therefore, as a result, pharmacogenetic testing is rarely incorporated into everyday psychiatric prescribing, and clinicians continue to base dose titration primarily on clinical response or therapeutic drug monitoring rather than genotype data.

Recent systematic reviews explored the association between CYP2D6 genotype and adverse side effects in order to evaluate the potentially beneficial role of pharmacogenetic testing in patients treated with antipsychotics in influencing clinical or economic outcomes. However, these reviews considered side effects as a whole, without focusing on EPS or were limited by the evaluation of only some second-generation antipsychotics such as risperidone, aripiprazole and quetiapine without including other antipsychotics agents.^{17–20}

The aim of the present review was to summarize literature data concerning the association between CYP2D6 genotype and EPS in people treated with antipsychotics and to better understand whether implementing CYP2D6 genotyping in clinical setting may be useful to optimize therapy through personalized approaches.

Methods

Search strategy

This review was structured following the PRISMA checklist items. Studies published from 1st January 1997 to 28th April 2025 were considered. The following databases were interviewed: PubMed, Medline via Ovid and EBSCO (PsycINFO and CINAHL) and the following terms searched: "CYP2D6" OR "cytochrome P450 2D6" OR "CYP2D6

polymorphism" OR "CYP2D6 genotype" OR "CYP2D6 metabolism" AND "extrapyramidal symptoms" OR "extrapyramidal side effects" OR "extrapyramidal disorders" OR parkinsonism OR "drug-induced parkinsonism" OR "parkinsonian symptoms" OR "extrapyramidal motor symptoms" OR "parkinsonism secondary to antipsychotics" OR "parkinsonism secondary to antipsychotics" OR "antipsychotic agents" OR "neuroleptics" OR "antipsychotic-induced side effects". Both narrative and systematic reviews were included to ensure comprehensive coverage of the evidence.

Eligibility criteria

Inclusion criteria: (1) human studies involving antipsychotics-exposed participants with psychiatric disorders; (2) CYP2D6 genotyping or phenotyping; (3) quantitative EPS assessment with validated instruments (4) sample size ≥10 participants.

Exclusion criteria: (1) healthy volunteers study; (2) cohorts with movement disorders unrelated to antipsychotics (3) combined treatment with antidepressants metabolized by CYP2D6 unless outcome could be disaggregated; (4) non-English articles.

Study selection and data extraction

The number of articles screened after removal of duplicates was recorded. Papers were selected based on their titles and abstracts. The full text of the items matching the field of interest of the review were read by two reviewers independently (A.L. and A.S.). For each included study, the reported association between CYP2D6 and EPS was extracted and summarized according to the interpretation presented in the original paper. In doing so, we considered the statistical significance of the reported results, the direction of the association, and the analytical context (e.g., covariates included, subgroup analyses, and specific EPS outcomes assessed). The overall risk of bias for each study was determined using the relevant Joanna Briggs Institute (JBI) critical appraisal checklists for cross-sectional studies, cohort studies, and randomized controlled trials.²¹ In accordance with JBI guidance, no summary score was calculated; instead, predefined qualitative criteria were applied. A study was rated as having low risk of bias when all or nearly all items were marked as "Yes", with no critical domains rated as "No". Moderate risk was assigned when some items were marked as "No" or "Unclear", provided that critical domains were not affected. High risk of bias was assigned when one or more critical items were rated as "No". For cohort studies, critical domains were considered to include the measurement of exposure, absence of outcome at baseline, control for confounding, and completeness of follow-up. In cross-sectional studies, the definition of the population, the validity and reliability of exposure and outcome measurements, and control for confounding were considered critical. For randomized controlled trials, critical items included randomization, allocation concealment, blinding of participants and personnel, and analysis according to the intention-to-treat principle. CYP2D6 phenotypes were harmonized to PM+IM vs EM+UM and summarized study-level odds ratios descriptively.^{22,23} The inter-rater agreement was assessed using Cohen's kappa statistic.

Results

Literature search

A total of 329 records were identified through database research. A preliminary screening excluded 13 duplicate records, 278 articles based on title review, and 18 non-original articles (reviews, case-reports, case series). Abstract screening was conducted on 20 articles, resulting in the exclusion of 291 papers. Full-text analysis was performed on 19 studies, with 1 excluded for not meeting inclusion criteria. Among the identified studies, after full-text analysis, 18 studies fulfilled the inclusion criteria and were included in the final review (Fig. 1). Inter-rater agreement for

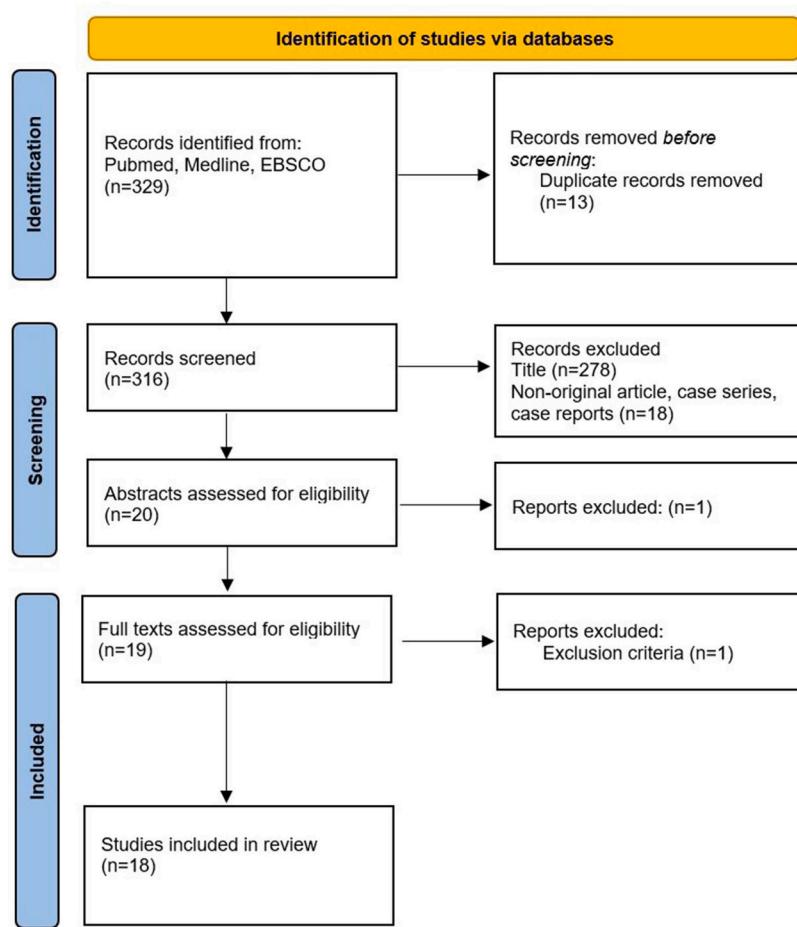


Fig. 1. Flowchart of the selection process for the studies included in the review using PRISMA guidelines.

inclusion decisions was complete ($\kappa = 1.0$).

Study characteristics

The 18 studies encompassed $n=2037$ participants. Seven studies had a prospective design,^{24–30} 10 studies had a cross-sectional design,^{31–40} and one study was a randomized controlled trial (RCT).⁴¹ All but one study enrolled participants with schizophrenia or schizophrenia spectrum disorders.³⁰ Only the RCT enrolled adolescents with first-episode psychosis.⁴¹ Eleven out of the 18 included studies reported an association between EPS and CYP2D6 genotype. The role of CYP2D6 on TD was assessed by 5 studies^{24,27,35–37} of which only one³⁶ explored sex-related differences (Table 1). The overall risk of bias of the included studies according to the JBI checklist is shown in Tables 2 and 3.

Association between CYP2D6 and EPS

Eleven studies supported the presence of an association, although not always statistically significant, between CYP2D6 and EPS.^{24–27,30,31,33,34,36,39,40} Qualitatively summarized, studies comparing PM/IM with EM/UM reported odds ratios for EPS ranging approximately from 2 to 5, consistent in direction across studies, but with heterogeneity precluding meta-analysis. In four haloperidol cohorts, 40–80% of PM developed clinically relevant EPS compared with 12–30% of EM.^{25,30,39,40}

Studies predominantly involving second-generation antipsychotics (risperidone)

Studies on risperidone have shown a higher risk of parkinsonism

among individuals with the PM genotype^{24,31} although this association did not always reach statistical significance.³¹ Findings regarding TD were equivocal: two prospective studies suggested a modest risk elevation in PM.^{24,27,35}

Discussion

EPS are common and sometimes serious side effects of many medications used in psychiatric settings including antipsychotics, antidepressants, mood stabilizers and benzodiazepines.^{17,42} However, the strongest association between EPS and drugs has been reported for antipsychotics, especially first-generation antipsychotics,^{43,44} being more recent ones better tolerated.^{45–48} In the present review, eleven studies^{24–27,30,31,33,34,36,39,40} supported the hypothesis that reduced CYP2D6 function (PM or IM status, or carriage of loss-of-function alleles such as *4 allele, *6 allele and 1846G>A genotype) predisposes patients to EPS, although sometimes with only a trend of association. In particular, in the study performed by Parkhomenko et al.³⁰ EPS were not significantly more frequent in patients with PM genotypes than in those with other genotypes. However, it is worth noting that only six out of 131 patients enrolled in the study were classified as PM. Of these six, one had TD and one had parkinsonism. Therefore, the low representation of PM individuals in the sample may have resulted in a lack of statistical significance.

Moreover, it has been reported that PM patients treated with haloperidol, risperidone or zuclopentixol consistently showed higher dose-corrected plasma concentrations of drugs and a significantly greater scores at the motor scales assessing EPS (e.g., Simpson-Angus Scale-SAS; Barnes Akathisia Rating Scale-BARS; Drug-Induced Extrapyramidal

Table 1

Summary of the studies included in the review.

Study	Design	Treatment	Alleles genotyped	Phenocopying control	Subjects	Findings
Andreassen et al 1997 ²⁴	Prospective	Thioridazine, sulpiride, risperidone, fluphenazine decanoate, flupenthixol decanoate, haloperidol decanoate	*1,*3, *4, *5, *6, *7	Not reported	100 participants with schizophrenia	PM genotype was more frequent but not significantly among TD and parkinsonism (OR 3.92, 95 % CI 0.67–27.10, p= 0.076).
Ohmori et al 1999 ³⁷	Cross-sectional	Haloperidol equivalent dosage reported	*2 (primarily), *10 (in regression model)	Not reported	99 participants with schizophrenia	No association between CYP2D6*2 and TD. No PM participants.
Scordo et al 2000 ³⁹	Cross-sectional	Haloperidol	*3,*4,*5,*6	Not reported	119 participants with schizophrenia	EPS and acute dystonic reaction were more frequent among PM
Lam et al 2001 ³⁶	Cross-sectional	Haloperidol	*4,*10	Implicitly controlled	70 participants with schizophrenia	Females with TD were more frequently PM (n=13, 81%) than females without TD (n=5, 31%, p=0.004).
Jaanson et al 2002 ²⁷	Prospective	Zuclopentixol decanoate	*3,*4	Not reported	52 participants with schizophrenia	PM and IM had more frequently parkinsonism (OR 2.3, 95% CI 0.7–6.9) and TD 1.7 (95% CI 0.5–4.9).
Brockmöller et al 2002 ²⁵	Prospective	Haloperidol	*1,*15,*17+ duplication of *1 and *2	Explicitly controlled	175 participants with psychosis	EPS were significantly more frequent in PM (80%) vs other genotypes (20%, p= 0.02).
Inada et al 2003 ³³	Cross-sectional	Antipsychotics	*2,*3,*4,*10, *12	Not reported	320 participants with schizophrenia	CYP2D6*2 polymorphism was significantly more frequent in EPS (30.3%) vs no-EPS (14.6 %; p=0.018).
Kakihara et al 2005 ²⁸	Prospective	Risperidone	*5,*10	Implicitly controlled	136 participants with schizophrenia	No association between CYP2D6 genotypes and EPS was found.
Plesničar et al 2006 ³⁸	Cross-sectional	Haloperidol, fluphenazine, zuclopentixol or risperidone	*2, *3, *4, *5, *6, *8, *9, *10, *11, *12, *14, *15 + duplication analysis	Explicitly controlled	131 participants with SSD	No EPS difference according to CYP2D6 genotype.
Crescenti et al 2008 ²⁶	Prospective	Amisulpride, long-acting injectable risperidone, risperidone, haloperidol, clozapine, olanzapine, zuclopentixol, ziprasidone, quetiapine, trifluoperazine.	*3,*4,*5,*6	Not reported	267 participants with schizophrenia related disorders	EPS was associated with the homozygous genotype for the CYP2D6*4 polymorphism (OR 4.1, 95% CI 1.0–16.0, p= 0.01) and the heterozygous genotype for the CYP2D6*6 polymorphism (OR 5.4, 95% CI 1.1–18.0, p= 0.003). A trend towards an association between EPS and PM status was observed (OR 2.9; P = 0.07).
Koola et al 2014 ³⁵	Cross-sectional	Haloperidol decanoate, flupentixol decanoate, fluphenazine decanoate, thioridazine, chlorpromazine, zuclopentixol decanoate, pimozide, fluphenazine, sulpiride	*3, *4, *5, *41 + duplication	Not reported	70 participants with schizophrenia	Increased CYP2D6 ability to metabolize was associated with TD (OR 4.2, 95% CI 1.1–15.7, p=0.032).
Dodgen et al 2015 ³²	Cross-sectional	Risperidone	*4, *5, *6B, *10B, *17, *29, *41 + novel allele	Not controlled	24 participants with psychosis and ADR.	No association between CYP2D6 genotypes and ADR was found.
Sychev et al 2016 ⁴⁰	Cross-sectional	Haloperidol	*4	Explicitly controlled	79 participants with schizophrenia	The CYP2D6 1846G>G (EM) frequency was higher in the

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Table 1 (continued)

Ito et al 2018 ³⁴	Cross-sectional	Risperidone	*10,*14,*5	Not controlled	22 participants with schizophrenia	EPS- group (81.5% vs. 44.4%, p = 0.01). The CYP2D6 1846A>A (PM) frequency in the EPS+ group was significantly higher than in the EPS- group (29.6% vs. 11.1%, p = 0.03).
Rudå et al 2021 ⁴¹	RCT	Aripiprazole, quetiapine	*3, *4, *5, *6 + duplication	Not controlled	113 adolescents with first-episode psychosis	The DIEPSS score in the IM was significantly higher (5.0) than that in the EM (0.0, p < 0.001). No PM participants.
Kibitov et al 2023 ²⁹	Prospective	Haloperidol	*3, *4, *5, *6, *9, *10, *41	Not controlled	57 SSD	No association between CYP2D6 genotype groups and BARS or SAS score was found
Parkhomenko et al 2023 ³⁰	Prospective	Haloperidol	*4	Explicitly controlled	100 Male with alcohol hallucinosis	No association between EM and IM and EPS. No PM in the sample.
Bondrescu et al 2024 ³¹	Cross-sectional	Risperidone	*4	Explicitly controlled	103 participants with SSD	EPS were more severe in CYP2D6 1846G > A polymorphism, IM (SAS score 14.5) then CYP2D6 1846 G>G polymorphism, EM (SAS score 11.0, p<0.001). Tremor and stiffness were significantly more frequent in participants with IM/ PM genotype (73%) than EM (23%; p = 0.002).

Legend of acronyms: ADR= Adverse-Drug Reactions; BARS = Barnes Akathisia Rating Scale; DIEPSS = Drug-Induced Extrapyramidal Symptoms Scale; EPS = extrapyramidal symptoms; EM/IM/PM/UM = Extensive/intermediate/poor/ultrarapid metabolizer; GA/GG = genotypes; RCT = randomized controlled trial; SAS = Simpson-Angus Scale; SSD = schizophrenia spectrum disorders; TD = tardive dyskinesia. OR: Odd ratio; CI: confidence intervals. Phenocopying control, conversion of a normal metabolizer into a PM due to strong CYP2D6-inhibiting drugs (e.g., paroxetine or fluoxetine); *Explicitly controlled*= CYP2D6-inhibiting drugs were excluded or adjusted for; *Implicitly controlled*: Only non-inhibiting drugs allowed; *Not controlled*: Phenocopying control was absent.

Table 2

Quality of the studies included in the review according to the Joanna Briggs Institute JBI Critical Appraisal Tools for cross-sectional studies.

Cross-sectional study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall Risk of bias
Ohmori et al 1999 ³⁷	Yes	Low							
Scordò et al 2000 ³⁹	Yes	Yes	Yes	Yes	No	No	Yes	No	High
Lam et al 2001 ³⁶	Yes	Yes	Yes	Yes	No	No	Yes	Uncl.	High
Inada et al 2003 ³³	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Plesnicar et al 2006 ³⁸	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Koola et al 2014 ³⁵	Yes	Low							
Dodgen et al 2015 ³²	Yes	Low							
Sychev et al 2016 ⁴⁰	Yes	Yes	Yes	Yes	No	No	No	Yes	Moderate
Ito et al 2018 ³⁴	Yes	Low							
Bondrescu et al 2024 ³¹	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Moderate

Legend: Q1: Were the criteria for inclusion in the sample clearly defined? Q2: Were the study subjects and the setting described in details? Q3: Was the exposure measured in a valid and reliable way? Q4: Were objective, standard criteria used for measurement of the condition? Q5: Were confounding factors identified? Q6: Were strategies to deal with confounding factors stated? Q7: Were the outcomes measured in a valid and reliable way? Q8: Was appropriate statistical analysis used? Abbreviations: Uncl= Unclear.

Symptoms Scale- DIEPS),^{25,30,40} thus suggesting a drug dose-reduction recommendation for the PM subgroup. Interestingly, despite the most studies focused on first generation antipsychotics, two risperidone-based studies^{31,34} confirmed that IM and PM patients had 2 to 3-fold higher odds of tremor or rigidity and markedly greater total DIEPSS scores than EM, even though no difference in antipsychotic efficacy was reported. Collectively, these studies supported the usefulness of starting-dose reductions or closer monitoring in phenotypes with

reduced CYP2D6 activity, as probably will be proposed by the Clinical Pharmacogenetics Implementation Consortium.¹⁶

On the contrary, other studies failed to demonstrate a relationship between CYP2D6 genotype and EPS.^{24,27–29,32,35,37,38,41} However, it should be noted that in the study performed by Ohmori and coll.³⁷ and Kibitov and coll.,²⁹ the lack of participants with a PM genotype could limit the comparison with the other studies and the generalizability of the results. Furthermore, in the RCT by Rudå and coll.,⁴¹ participants

Table 3

Quality of the studies included in the review according to the Joanna Briggs Institute JBI Critical Appraisal Tools for cohort and Randomized Controlled Trials.

Cohort studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Overall Risk of bias
Andreassen et al 1997 ²⁴	Yes	Yes	Yes	No	No	Yes	Yes	No	Uncl.	NA	No	/	/	High
Jaanson et al 2002 ²⁷	Yes	Yes	Yes	Yes	Yes	Uncl.	Yes	No	Yes	NA	Yes	/	/	Moderate
Brockmöller et al 2002 ²⁵	Yes	Yes	Yes	Yes	Yes	Uncl.	Yes	No	Uncl.	NA	Yes	/	/	Moderate
Kakihara et al 2005 ²⁶	Yes	Yes	Yes	No	No	Uncl.	Yes	No	Uncl.	NA	Yes	/	/	High
Crescenti et al 2008 ²⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Uncl.	NA	Yes	/	/	Moderate
Kibitov et al 2023 ²⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	/	/	Moderate
Parkhomenko et al 2023 ³⁰	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Na	Yes	/	/	Moderate
Randomized controlled trial														
Rudå et al 2021 ⁴¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Uncl.	Yes	Yes	Yes	Yes	Low

Legend: Abbreviations: Uncl= Unclear; NA= not applicable. **Cohort studies:** Q1: Were the two groups similar and recruited from the same population? Q2: Were the exposures measured similarly to assign people to both exposed and unexposed groups? Q3: Was the exposure measured in a valid and reliable way? Q4: Were confounding factors identified? Q5: Were strategies to deal with confounding factors stated? Q6: Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? Q7: Were the outcomes measured in a valid and reliable way? Q8: Was the follow up time reported and sufficient to be long enough for outcomes to occur? Q9: Was follow up complete, and if not, were the reasons to loss to follow up described and explored? Q10: Were strategies to address incomplete follow up utilized? Q11: Was appropriate statistical analysis used? **Randomized controlled trial:** Q1: Was true randomization used for assignment of participants to treatment groups? Q2: Was allocation to treatment groups concealed? Q3: Were treatment groups similar at the baseline? Q4: Were participants blind to treatment assignment? Q5: Were those delivering the treatment blind to treatment assignment? Q6: Were treatment groups treated identically other than the intervention of interest? Q7: Were outcome assessors blind to treatment assignment? Q8: Were outcomes measured in the same way for treatment groups? Q9: Were outcomes measured in a reliable way? Q10: Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? Q11: Were participants analyzed in the groups to which they were randomized? Q12: Was appropriate statistical analysis used? Q13: Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

were treated with second-generation antipsychotics, which are less frequently associated with EPS,^{48,49} and the enrolled subjects were adolescents, who are usually less "at risk" of EPS compared to older subjects.⁵⁰ Indeed, adolescents typically have lower cumulative antipsychotic exposure due to shorter illness duration, reducing the opportunity for pharmacogenetic differences in metabolism to manifest in clinical outcomes such as EPS. Additionally, greater striatal "dopaminergic reserve" and synaptic plasticity in youth may counteract receptor blockade-related motor side effects, thereby masking metabolic vulnerability that becomes more evident in chronically medicated adults.⁵¹

TD probably deserves a separate consideration due to particularly conflicting data. Indeed, while Andreassen and coll.²⁴ and Jaanson and coll.²⁷ reported a trend of association between CYP2D6 genotype and TD, Koola and coll.³⁵ reported an about 4-fold higher risk of TD in EM and UM genotypes, raising the hypothesis that toxic active metabolites (e.g., haloperidol pyridinium) formed more readily in rapid metabolizers might drive late-onset TD. Interestingly, the study performed by Lam and coll.³⁶ was the only study assessing the role of sex in TD occurrence, reporting an association between PM genotype and TD only in females. This data is of interest considering that previous studies reported a higher vulnerability of females to TD^{51,52} but only Lam and coll.³⁶ performed a sex-stratified analysis.

Some methodological differences can explain the still conflicting data about the association between CYP2D6 genotype and EPS. First, drug selection plays a pivotal role in this association: some compounds—haloperidol in particular—are high-dependency substrates, with more than 50% of their clearance mediated by CYP2D6, whereas others (e.g., risperidone, aripiprazole, quetiapine) are extensively metabolized by additional enzymes such as CYP3A4, which blunts the impact of CYP2D6 polymorphism.^{15,25,53}

Moreover, some studies did not stratify analyses considering the drug class and instead evaluated pooled samples with mixed first-generation antipsychotics/second-generation antipsychotics.^{24,26,35,38} Such methodological approach did not allow to evaluate the pharmacogenetic effects to specific drug classes. Thus, while the available literature suggests a more robust association for first-generation antipsychotics, the contribution of CYP2D6 variability to EPS risk under second-generation antipsychotics (i.e., risperidone) remains plausible but methodologically underexplored.

Furthermore, some included studies did not use comprehensive CYP2D6 genotyping and tested only a few variants. This limited

coverage may have led to misclassification of metabolizer status and could bias the observed associations. Moreover, the assessed outcome is highly heterogeneous. Indeed, EPS can be considered an umbrella term encompassing a plethora of different movement disorders, including parkinsonism, akathisia, TD, tremor, and dystonia, characterized by distinct epidemiology, pathophysiology, and onset.⁴⁴ In addition, in the included studies, outcome measures were different and difficult to compare (SAS, BARS, DIEPSS).

In addition, some studies were likely underpowered due to small sample size^{32,34} or did not include PM participants.^{34,35} Furthermore, ethnic differences among study participants may play a role in modulating the association between CYP2D6 and EPS.⁵⁴ Moreover, a further methodological consideration emerging from our review concerns *phenocopying*, namely the conversion of EM into functionally PM due to exposure to potent CYP2D6 inhibitors (e.g., paroxetine or fluoxetine). Importantly, only a minority of studies explicitly controlled for this source of confounding,^{25,30,31,38,40} while others did so implicitly or did not consider it at all. The lack of phenocopying control may partially explain inconsistent or null associations reported in the literature. Indeed, the apparent lack of association between CYP2D6 genotype and EPS occurrence may reflect unrecognized pharmacokinetic suppression rather than a true absence of biological effect.

On this ground, the uncertainty of the EMA and the FDA about the need to implement CYP2D6 genotype assessment in clinical practice and to modulate antipsychotic dosage according to genetic profile is probably due to the high heterogeneity between studies in terms of assessment tools and drugs studied.

Moreover, several issues remain to be investigated. In particular, the role of family history, age, sex, or other risk factors for PD in modulating this association needs to be elucidated. Indeed, only a few studies identified and accounted for age and sex, and none have accounted for PD family history.^{25,27,29,32,34,35,37,41} Yet, although neuroleptic withdrawal usually results in recovery of EPS within a few months, it has been reported that in some patients EPS persists or worsens over the course of years, suggesting the possibility of concomitant nigrostriatal degeneration similar to that reported in PD.⁵⁵ Indeed, it should be underlined that CYP2D6 polymorphism has been previously associated not only to drug-induced parkinsonism but also to idiopathic PD.^{56–58} In fact, beyond the contribution of CYP2D6 to the metabolism of psychotropic drugs (i.e., antidepressants, antipsychotics), certain CYPs are involved in the biotransformation of neuroactive endobiotics, which may influence physiological processes and explain the reported

association between CYP2D6 polymorphisms and disease susceptibility (e.g., personality disorders, cognitive decline, and behavioral disorders).^{59,60}

Another underexplored aspect is the role of drugs previously associated with EPS and metabolized by CYP2D6,⁶¹ which, in addition to antipsychotics, may mediate the association between CYP2D6 genotype and EPS. In fact, although previous studies have supported the association between EPS and antidepressant treatment,⁶² to date only case reports or underpowered studies are available to evaluate the possible association between antipsychotics-antidepressants-CYP2D6 and EPS.

The present review has some limits. The exclusion of grey literature and non-English papers may have introduced publication bias by omitting relevant but unpublished or non-peer-reviewed studies. Moreover, the methodological heterogeneity in terms of drugs explored, instrument tools for assessing EPS and type of movement disorder evaluated, did not allow us to perform a meta-analysis and a pooled effect estimation.

However, to the best of our knowledge, this is the first review systematically assessing the association between CYP2D6 genotype and EPS in subjects treated with both first- and second-generation antipsychotics.

In conclusion, according to our review, although the majority of studies supported the role of CYP2D6 genotype in the occurrence of EPS in patients treated with antipsychotics, this relationship still need to be clarified. Indeed, although our review is consistent with current DPWG/CPIC guidance in supporting more cautious dosing or closer monitoring in PM receiving CYP2D6-dependent antipsychotics, future studies are needed to refine drug-specific adjustment thresholds. A genotype-guided RCT should compare CYP2D6-informed prescribing (e.g., dose or treatment adjustments for PM/IM and UM) with usual care for specific antipsychotics. Primary outcomes should be incident EPS and time-to-onset; secondary outcomes should include efficacy, treatment discontinuation, and quality of life, with concurrent therapeutic drug monitoring. Prospective cohort studies are also warranted to relate plasma concentrations to EPS across CYP2D6 phenotypes and to define concentration-toxicity thresholds. Across study designs, investigators should use comprehensive CYP2D6 genotyping (including copy-number variation), perform drug-specific analyses, and adjust for key confounders—notably co-prescribed CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, bupropion), dose, age, and comorbidity.

Glossary

BARS = Barnes Akathisia Rating Scale

CI= Confidence intervals

CYP2D6= Cytochrome-P450 2D6

DIEPSS = Drug-Induced Extrapyramidal Symptoms Scale

EM= Extensive metabolizer

EMA= European Medicines Agency

EPS = Extrapyramidal symptoms

FDA= Food and Drugs Administration

GA/GG = Genotypes

IM= Intermediate metabolizer

NM= Normal metabolizer

NOS= Newcastle-Ottawa Scale

PD= Parkinson's disease

PM= Poor metabolizer

PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT = Randomized controlled trial

SAS = Simpson-Angus Scale

SSD = Schizophrenia spectrum disorders

TD = Tardive dyskinesia. OR: Odd ratio;

UM= Ultrarapid metabolizer

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Declaration of competing interest

Nothing to declare.

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