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REVIEW

Efficacy of pharmacogenetic (PGx)-guided antidepressant treatment on functional outcomes and quality of life in adults with anxiety and affective disorders: A systematic review and meta-analysis

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ABSTRACT

We conducted a systematic review and meta-analysis to estimate the efficacy of pharmacogenetic (PGx)-guided antidepressant treatment compared to treatment as usual (TAU) on functional outcomes and quality of life (QoL) in people with anxiety and affective disorders. A PRISMA-compliant systematic search was performed up to 26/06/2025 to identify relevant prospective, randomised controlled trials (RCTs) in seven databases. The revised tool for Risk of Bias (RoB2) was used to assess the methodological qualities of the included studies (PROSPERO CRD42024518683). Of 2774 records, six studies were included comprising 2285 adult patients (PGx group: n = 1395, Mean age = 48.14 years; 55.68 % females; TAU group: n = 890, Mean age = 47.83 years, 58.22 % females). Three studies were included in random-effect meta-analyses. In these, PGx-guided antidepressant treatment significantly decreased functional disability, measured by the Sheehan Disability Scale/Inventory (SDS/I), compared to TAU (k = 3, Mean Difference = -2.85, SE = 1.32 [95 % CI: -5.44, -0.26], p = .031). The Hartung-Knapp adjustment of p-values yielded non-significant effects. Individually, one of these three studies reported a significant effect of PGx-guided treatment on overall SDS score, one on SDI Perceived Social Support partial score, and one no effect. Risk for bias was rated high for one study, with some concerns for the other five. Due to the small number of included trials, our ability to conduct analyses of heterogeneity, moderators and publication bias was limited. Nonetheless, our results suggest that PGx-guided antidepressant treatment may improve functioning in people with anxiety and affective disorders

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1. Introduction

With a lifetime risk of 15–18 % (Bromet et al., 2011) and 16.6 % (Somers et al., 2006) respectively, depression and anxiety disorders are common and severely impact daily life. Recurrence rates are high, often requiring long-term treatments. In addition, comorbidity between these disorders is common and associated with a worse course than either disorder alone (Penninx et al., 2011).

Pharmacotherapy, particularly antidepressants, is a mainstay in treating moderate-to-severe cases. However, treatment response and tolerability vary greatly (Rush et al., 2006; Undurraga and Baldessarini, 2012), often leading to trial-and-error process that may ultimately fail. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, for example, only 40 % achieved remission after the first step and over 30 % did not remit after four different medications (Rush et al., 2006). Treatment resistance -defined as failure after two adequate trials- remains a major challenge (Vieta and Colom, 2011).

To improve outcomes, pharmacogenetic (PGx) prescribing has emerged based on genetic variants affecting drug metabolism (van Westrhenen et al., 2020, 2021). Guidelines by the Dutch Pharmacogenetic Working Group (DPWG) (Beunk et al., 2024; Brouwer et al., 2022) and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have published PGx-based prescription guidelines for antidepressants recommended using *CYP2C19* and *CYP2D6* genotypes to guide drug selection and dosing, see Bousman et al. for a comprehensive review (Bousman et al., 2021). These genotypes determine enzyme activity, classifying patients as ultrarapid to poor metabolisers.

Since 2017, multiple studies and 18 systematic reviews (Aboelbaha et al., 2021; Fabbri et al., 2018; Health Quality Ontario, 2017; Ontario Health (Quality), 2021; Peterson et al., 2017; Rosenblat et al., 2017) and meta-analyses (Arnone et al., 2023; Bousman et al., 2019; Brown et al., 2020, 2022; Bunka et al., 2023; Ielmini et al., 2022; Milosavljević et al., 2024; Rosenblat et al., 2018; Santenna et al., 2024; Skryabin et al., 2023; Vilches et al., 2019; Wang et al., 2023) and one umbrella review (Tesfamicael et al., 2024) have assessed PGx-guided antidepressant treatment. Recent reviews report positive effects on response (Arnone et al., 2023; Bunka et al., 2023; Milosavljević et al., 2024; Skryabin et al., 2023; Wang et al., 2023), remission (Arnone et al., 2023; Bunka et al., 2023; Milosavljević et al., 2024; Santenna et al., 2024; Skryabin et al., 2023; Wang et al., 2023), and symptoms (Arnone et al., 2023; Milosavljević et al., 2024; Tesfamicael et al., 2024) though results on tolerability remain inconsistent. For instance, no clear benefit was found on adverse effects or discontinuation (Bunka et al., 2023; Milosavljević et al., 2024; Skryabin et al., 2023), except for fewer adverse reactions in the PGx group compared to treatment as usual (TAU) (Santenna et al., 2024). Only two meta-analyses reported number needed to treat (NNT): NNT = 8 for both response and remission (Bunka et al., 2023) as well as NNT = 21.1 for response and NNT = 21.3 for remission (Milosavljević et al., 2024). Possible explanations for this quite substantial gap in NNTs might be the partly different studies included in the meta-analyses due to the time of literature search and specific inclusion criteria. Also, while one study focused on outcomes at eight weeks (Milosavljević et al., 2024), the other used the longest post-treatment-initiation timepoint available (Bunka et al., 2023, 2024). Overall, despite statistical significance regarding efficacy, concerns remain regarding clinical relevance (Heilbronner and van Westrhenen, 2024; Milosavljević et al., 2024).

In addition to alleviating symptoms, restoring functioning and quality of life (QoL) is central to recovery in individuals with depression and anxiety. According to the DSM-5 (American Psychiatric Association, 2013), both disorders require the presence of functional impairment, highlighting the relevance of outcomes beyond symptom reduction. The Global Burden of Disease Study consistently ranks these conditions among the leading causes of years lived with disability (YLDs) (Ferrari et al., 2024). While symptom-based measures reflect disease-centred outcomes, QoL captures patient-centred perspectives (Peipert et al., 2025). Functional outcomes can refer to global functioning or specific domains such as social, occupational, or physical functioning, whereas QoL can encompass physical, psychological, social, economic, environmental, or overall well-being.

Patients consistently prioritise regaining functioning and QoL as key treatment goals (Lam et al., 2011; Zimmerman et al., 2006). Although these outcomes remain underutilised in clinical trials, they provide distinct and complementary information to symptom severity. Indeed, depressive symptoms and functioning show only moderate correlations and are not redundant (McKnight and Kashdan, 2009). Encouragingly, a recent systematic review reported that, after cancer, mental disorders are the second most frequently studied group in QoL research (Haraldstad et al., 2019). Moreover, functioning and QoL can improve with treatment (Grassi et al., 2020; Haraldstad et al., 2019), reinforcing their importance as essential targets in clinical research and practice. Impaired social, occupational and physical functioning can be accompanied by a more passive day-to-day life and might lead to increased loneliness, which in turn can intensify symptoms of depression and anxiety (Park et al., 2020).

Although the importance of functional outcomes and QoL is widely recognised (Grassi et al., 2020; Haraldstad et al., 2019), the efficacy of PGx-guided antidepressant treatment on functioning (social relations, leisure, work) and QoL (social, environment) compared to TAU remains unclear. This systematic review and meta-analysis sought to address this gap by estimating the efficacy of PGx-guided antidepressant treatment compared to TAU on functional outcomes and QoL in adults with anxiety and affective disorders. We hypothesised that PGx-guided interventions (vs. TAU) would lead to greater improvements. Collectively, this quantitative synthesis can inform clinical practice guidelines and strategies for improving targeted interventions.

2. Methods

2.1. Protocol

The review protocol was registered on PROSPERO (CRD42024518683) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (Page et al., 2021) (see Appendices 1 and 2 in the Supplement), and the Enhancing the Quality and Transparency of Health Research (EQUATOR) reporting guidelines (Altman et al., 2008). A detailed report of all amendments to the information provided at registration or in the study protocol is presented in Appendix 3 of the Supplement. For a glossary of terms used in this work, see Appendix 0 in the Supplement.

2.2. Search strategy and eligibility criteria

A systematic literature search using multiple terms for pharmacogenetics and RCTs (see the search strategy and terms in Appendix 4 in the Supplement) was implemented up to 05/04/2024 (NEF-O, TP) on PubMed (Medline), Embase, Scopus, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science Core Collection (WoS), updated on 15/01/2025 (NEF-O) on Scopus, PsycINFO, and WoS, and updated again up to 26/06/2025 on PubMed, Embase, and ClinicalTrials.gov (NEF-O, MB) to identify RCTs on PGx-guided antidepressant treatments. Additionally, we systematically searched existing reviews and meta-analyses in this field using the same databases and manual search strategies to identify prior evidence.

A snow-balling approach (Wohlin et al., 2022) was applied to identify additional studies meeting the inclusion criteria in the reference list of studies and relevant studies already included in previous systematic reviews (Aboelbaha et al., 2021; Fabbri et al., 2018; Health Quality Ontario, 2017; Ontario Health (Quality), 2021; Peterson et al., 2017; Rosenblat et al., 2017), and meta-analyses (Arnone et al., 2023; Bousman et al., 2019; Brown et al., 2020, 2022; Bunka et al., 2023; Ielmini et al., 2022; Milosavljević et al., 2024; Rosenblat et al., 2018; Santenna et al., 2024; Skryabin et al., 2023; Vilches et al., 2019; Wang et al.,

2023), and an umbrella meta-analysis (Tesfamicael et al., 2024) were cross referenced manually (NEF-O, MB, JL).

The software Endnote was used in the initial removal of duplicates, and the software Rayyan QCRI (https://rayyan.qcri.org/) was used to manage citations, remove duplicates, and screen abstracts and titles. Titles and abstracts of articles were independently screened by NEF-O, JL, TP. After excluding those not relevant, the full texts were independently assessed for eligibility by the same authors. Discrepancies were resolved through consensus.

Only prospective RCTs published in a peer-reviewed journal in any language, examining the efficacy of PGx-guided antidepressant therapy were considered for inclusion. According to the PICO framework, studies were included if they: (i) (P) investigated adult individuals with affective or anxiety disorder according to validated diagnostic criteria, e.g., DSM (American Psychiatric Association, 2013) or ICD (World Health Organisation, 2019); (ii) (I) conducted PGx-guided antidepressant treatment (iii) (C) compared the PGx-guided intervention group with a control group, receiving TAU or any other treatment; (iv) (O) assessed the efficacy of functional outcomes, i.e., global and subdomains (e.g., social relationships, occupational functioning, independent living, leisure), and/or QoL, i.e., global and subdomains (e.g., environmental, social), or provided data that allowed effects to be calculated or on request by the authors.

Studies were excluded if they: (i) were reviews, clinical cases, abstracts alone, commentaries, letters to the editor, conference proceedings, study protocols, unpublished materials (preprints), or grey literature (thesis); (ii) only recruited participants under age 18; (iii) only investigated animals; (iv) only investigated individuals with psychotic disorders; (v) had < 10 participants in each arm; (vi) were retrospective, non-randomised designs.

2.3. Data extraction

Data were independently extracted by NEF-O, JL, and TP from eligible studies and tracked in Microsoft Excel; discrepancies were resolved through consensus.

Descriptive and clinical variables extracted included publication year, geographical region, sociodemographic characteristics and study endpoint (see full description of the extracted variables in Appendix 5 in the Supplement). For continuous outcome variables the mean and *SD* or the mean difference and *SD* (when the same instrument/measure available) were extracted jointly with the number of people diagnosed with affective and/or anxiety disorders. Corresponding authors were contacted twice by email to retrieve additional information if needed.

2.4. Study outcomes

1) Functional outcomes: global functioning or specific functioning in domains that are indicators of an individual's ability to manage everyday roles and responsibilities in key life areas, such as social, and occupational functioning. These may include hospital admissions, sick leave, employment or educational status, and interpersonal functioning (McKnight and Kashdan, 2009; Schwarz et al., 2024).
2) Quality of life (QoL): subjective evaluation of overall well-being or global QoL, including satisfaction with life across key domains such as family life, environment, health, and financial independence (Wilmer et al., 2021).

2.5. Risk of bias and certainty in the evidence assessment

Risk of bias assessment was independently conducted (MB and JL) by using the revised Cochrane Rob2 tool (Sterne et al., 2019). Rated domains included: (1) risk of bias arising from the randomisation process; (2) risk of bias due to deviations from the intended interventions; (3) risk of bias due to missing outcome data; (4) risk of measurement in the outcome; and (5) risk of bias in the selection of the reported result. The quality of included studies was rated as of high risk, some concerns, or low risk related to the selection, performance, and outcome reporting procedures used; disagreements were discussed with a third reviewer (NEF-O) and resolved through consensus.

Certainty in the evidence for each outcome was assessed (NEF-O, MB) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. GRADE uses a structured approach to assign a rating of high, moderate, low, or very low certainty to the evidence. Factors affecting certainty—study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias—are considered in rating the certainty or confidence in evidence (Prasad, 2024). Disagreements were resolved through consensus.

2.6. Statistical analyses

We conducted a meta-analysis when a minimum of three studies (Higgins et al., 2024) were available. A random-effects model was employed, with the between-study heterogeneity variance estimated using the maximum-likelihood estimator (REML) (Viechtbauer, 2005). We also applied Hartung-Knapp adjustments to the pooled effect and its confidence interval as sensitivity analysis (Röver et al., 2015). If the number of available effect sizes did not allow for a quantitative synthesis, study findings were summarised and appraised qualitatively in a narrative synthesis (Popay et al., 2006).

The mean difference (MD) was used as the effect size, measuring the absolute mean difference between the two groups in a clinical trial. This outcome measure estimates the amount by which the experimental intervention changes the outcome on average compared with the control (TAU) post-treatment. We also calculated standardised mean differences (SMD) alongside the MD, as recommended by previous meta-epidemiological studies (Heimke et al., 2024; Takeshima et al., 2014). For one study (Papastergiou et al., 2021), the missing change score (MD) had to be imputed (Furukawa et al., 2006) with values (Mean and *SD* post-test) provided by authors.

As measures of heterogeneity, the percentage of variation not attributable to sampling error was quantified using Higgins' and Thompson's I^2 statistic, and the between-study variance of the underlying distribution of true effect sizes was reported using the tau-squared (τ^2) statistic (Borenstein et al., 2017).

Meta-regression, subgroup analyses, and assessments of publication bias were conducted only when a minimun of 10 studies were available (Higgins and Thompson, 2004).

All the quantitative analyses were conducted in R version 4.2.1 using the *"meta"* and *"metafor"* packages (Balduzzi et al., 2019; Harrer et al., 2022; Viechtbauer, 2010); statistical significance was set at $p < .05$ (two-tailed). Forest plots were created to show results by means of MD and SMD, although their heuristic value was necessarily limited given the low number of included studies. An overview of the risk of bias assessment was created with the "*robvis*" tool (McGuinness and Higgins, 2021).

3. Results

3.1. Study characteristics

A total of 2774 records were identified (2765 studies from databases, and 9 studies from manual searches), of which 46 eligible studies (37 from data bases and 9 from manual searches) were full text screened. After excluding 40 studies (32 from data bases and 8 from manual searches), six studies were included in the qualitative and three studies were included in quantitative syntheses (see the process of study selection in detail in Fig. 1, the full list of included studies in Appendix 6, and the full list of excluded studies in Appendix 7 in the Supplement).

The six studies included were conducted in Europe ($n = 2$), North America ($n = 2$), Australia ($n = 1$), and Asia ($n = 1$), and published

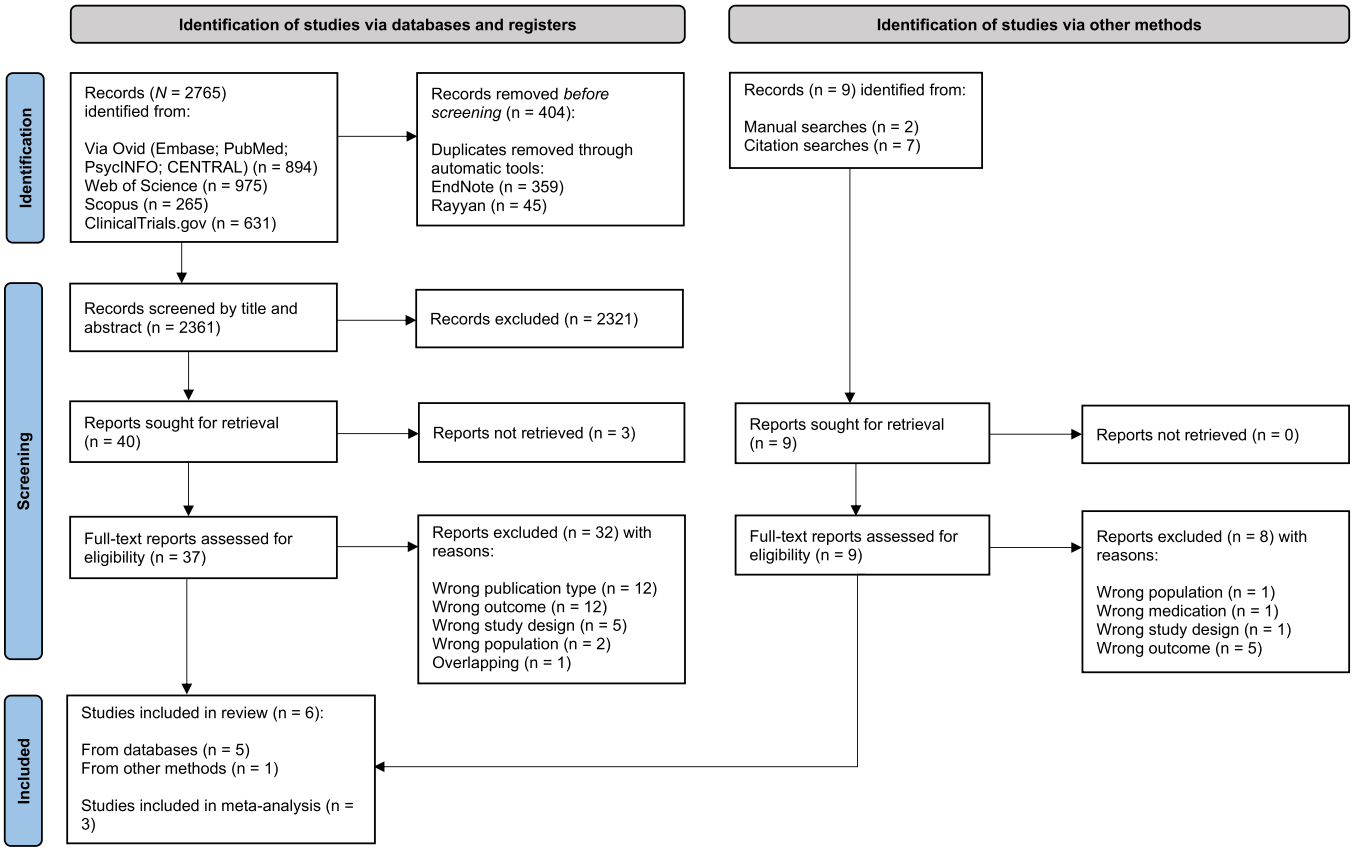

Fig. 1. PRISMA 2020 Flowchart outlining the study selection process.

between 2015 and 2021. Sample sizes ranged from 49 to 1459, compromising a total of 2285 adult participants of whom 56.67 % were females (PGx group: $n = 1395$, 55.68 % females; TAU group: $n = 890$, 58.22 % females). The mean age of the total sample was 47.99 [range = 41 –70] years.

For one study (Han et al., 2018), a corrigendum was published in 2020. In this manuscript, we always refer to the corrected version.

Five studies (Han et al., 2018; Pérez et al., 2017; Ruaño et al., 2020; Singh, 2015; van der Schans et al., 2019) were conducted in major depressive disorder (MDD), one study was conducted in a mixed sample with anxiety and MDD (Papastergiou et al., 2021).

In five of the six included studies, functional outcomes or QoL were secondary outcomes measures. The study duration ranged from four weeks to 6 months (see further descriptive characteristics of the included studies in Table 1).

The included studies varied in both the number of psychotropic medications prescribed and the manner in which this information was reported. All studies that conducted statistical comparisons found no significant differences in antidepressant treatment between study groups (Han et al., 2018; Papastergiou et al., 2021; Pérez et al., 2017; Singh, 2015; van der Schans et al., 2019). Notably, van der Schans et al. (2019) focused specifically on nortriptyline and venlafaxine, whereas the other studies assessed a broader range of antidepressants. Ruaño et al. (2020) reported on the most commonly prescribed psychotropic medications in the overall sample but did not provide group-specific data; in their sample, antidepressants were frequently augmented with antipsychotics. Further details on psychotropic medication use across studies are provided in Appendix 8 in the Supplement.

3.2. Qualitative synthesis

Functional outcomes. Five (Han et al., 2018; Papastergiou et al., 2021; Pérez et al., 2017; Ruaño et al., 2020; Singh, 2015) of the six included studies assessed functional outcomes. Three studies (Han et al., 2018; Papastergiou et al., 2021; Pérez et al., 2017) assessed functional disability/impairment with the Sheehan Disability Scale/Inventory (SDS/I) (Leon et al., 1997). The SDS is a composite of three self-rated items designed to measure the extent to which three major domains in the patient's life are functionally impaired by psychiatric or medical symptoms: work, social life/leisure activities, and family life/home responsibilities.

Results from the studies using the SDS/SDI scores paint a mixed picture. Han and colleagues did not find a significant effect of PGx-guided treatment on functional disability (Han et al., 2018). Another study (Papastergiou et al., 2021) on the other hand, reported a significant effect of PGx-guided treatment on the overall SDS score, after six months in a sample of patients with a diagnosis with MDD and/or general anxiety disorder (GAD) (time*group interaction: $F = 6.25$, $p < .001$). About 58 % of the sample fulfilled criteria for both MDD and GAD. In sensitivity analyses, the authors first selected those participants in the PGx group whose prescribers accepted the recommendations regarding dose adjustments, medication switches, addition of new medication, and medication adherence. In a second sensitivity analysis, those in both the PGx and TAU groups, whose prescribers accepted the recommendations, were selected. The results stayed statistically significant in both cases. The third study (Pérez et al., 2017) found a significant positive effect of PGx-guided treatment on the SDI Perceived Social Support partial score ($p = .048$), but not on the SDI Disability and SDI Stress partial scores.

In all three studies using the SDS (Han et al., 2018; Papastergiou et al., 2021) or SDI (Pérez et al., 2017), the authors reported a significantly larger effect of PGx-guided treatment compared to TAU on symptom measures, such as depressive symptom reduction (Han et al., 2018; Papastergiou et al., 2021) and response rate (Pérez et al., 2017) highlighting the discrepancies between symptom and functional

Table 1
Sociodemographic and clinical characteristics of included studies.

Authors, publication year	Country/ region	N	Diagnosis	n PGx	Sex PGx (% female)	Age PGx [M(SD)]	n TAU	Sex TAU (% female)	Age TAU [M (SD)]	Outcome	Instrument	Outcome primary or secondary	Study time frame	Main results
Han et al. 2018	Korea/Asia	100	MDD	52	76.90	44.20 (16.10)	48	72.90	43.90 (13.80)	Functional disability	SDS	Secondary	8 weeks	PGx-guided treatment appears to be a more effective and tolerable option for managing MDD compared to TAU. Patients in the PGx group showed significantly greater improvements in HAMD-17, FIBSER, and some of the secondary outcomes (response rate, CGI-S, GAD-7; $p = .014$ –0.047), but not for PHQ-9, PHQ-15, SDS total scores, and CGI-I. Additionally, fewer patients in the PGx group discontinued treatment due to adverse events (30.8 %) compared to the TAU group (50.0 %).
Papastergiou et al. 2021	Canada/North America	213	MDD, GAD	105	73.33	41.90 (14.55)	108	75.93	43.46 (15.26)	Functional disability	SDS	Secondary	6 months (26 weeks)	Participants with MDD or GAD randomised to receive PGx-guided treatment reported greater improvements in depression severity (PHQ-9) over a 6-month period compared to those randomised to receive TAU. Participants receiving PGx-guided treatment also reported greater improvements in two secondary outcomes, i.e., generalised anxiety (GAD-7) and in disability (SDS), over this period compared to those receiving TAU. Treatment satisfaction did not differ across groups. Significant results were not only statistically robust but also clinically meaningful.
Pérez et al. 2017	Spain/Europe	316	MDD	155	63.90	51.74 (12.05)	161	63.40	50.74 (13.12)	Functional disability	SDI	Secondary	12 weeks	PGx-guided treatment resulted in significant improvement of MDD patient's response at 12 weeks, dependent on the number of previously failed medication trials, but not on sustained response during the study period. Burden of side effects was also significantly reduced. Significant results favouring the PGx-guided treatment group were found in clinician-rated CGI-S, all three FIBSER indices and SATMED-Q total and partial scores, as well as the SDI Perceived Social Support partial score, but not in patients rated CGI-S.
Ruaño et al. 2020*	USA/North America	1459	MDD	982	51.30	NA	477	50.30	NA	LOS and RAR 30 days after discharge	Clinical record	Primary and Secondary	30 days after discharge (4 weeks)	Results did not reveal differences in hospital LOS or RAR post hospitalisation discharge between Group PGx-guided group and standard therapy group, but potential confounders, such as comorbid medical illness or lack of suitable community placement, may have obscured the effects of PGx guidance.
Singh 2015*	Australia/ Oceania	148	MDD	74	58.00	44.2	74	61.00	44.3	Proportion taking sick leave and number of sick days due to depression	Interview with blinded rater	Other**	12 weeks	Patients receiving genetically guided prescribing had a 2.52-fold greater likelihood of achieving remission. Participants in the PGx-guided treatment group also had a significantly lower risk of taking sick leave and, when necessary, experienced shorter durations of leave. However, the strict exclusion of individuals with almost any psychiatric comorbidities (e.g., bipolar, substance use, and personality disorders) may limit the generalisability of these findings.
Van der Schans et al. 2019*	The Netherlands/ Europe	49	MDD	27	51.90	70.20 (7.30)	22	63.60	68.50 (5.10)	QoL	EQ5D-3 L / EQ-VAS	Secondary	4 weeks	Results did not support PGx CYP2D6 screening to accelerate dose adjustment for nortriptyline and venlafaxine in older patients with depression. No significant differences were observed in the MD between visit 2 and visit 3 of the trial of self-reported functional health status and general and disease specific QoL or severity of depression.

Note: *studies fulfilling inclusion criteria but not included in meta-analysis; **not specified as an outcome in the registration (ACTRN12613001135707); *n* data is based on the Intention to Treat analyses (ITT) that measured the intervention effect as randomised. Abbreviations: CGI-*S* = Clinical Global Impression-Severity; EQ5D-3 L / EQ-VAS = The 3-level version of EQ-5D (EQ-5D-3 L), including the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS); FIBSER: Frequency, Intensity, and Burden of Side Effects Ratings; GAD = Generalised anxiety disorder; LOS = Length of Stay; MD = Mean difference; MDD = Major depressive disorder; NA = Not available; PGx = Pharmacogenetics; PHQ = Patient Health Questionnaire; QoL = Quality of Life; RAR = *Re*-Admission Rate; SATMED-Q: Treatment Satisfaction with Medicines Questionnaire; SDI/S: Sheehan Disability Inventory/Scale; TAU = Treatment As Usual.

measures. It is important to note, that none of these studies found significant differences regarding SDS/SDI scores at baseline between groups, which might have biased the results.

One study (Ruaño et al., 2020) reported functional outcomes in terms of hospitalisation, including length of stay (LOS) and re-admission rate (RAR) 30 days after discharge based on hospital electronic records, therefore focusing on behavioural measures in contrast to the self-report measures used in most of the included studies ($n = 4$). This study also differs to others in terms of the randomisation ratio, which was 2:1 to PGx vs. TAU. Despite the large sample ($n = 1459$), no significant effect of PGx-guided treatment was on LOS and the RAR 30 days after discharge observed; 9.5 % of the whole sample were readmitted within 30 days of discharge (Ruaño et al., 2020).

Finally, one study (Singh, 2015) reported on functional outcomes in terms of sick leave, including either the proportion of participants taking sick leave or the average number of days taken off from work or studies due to depression. This study had a time frame of 12 weeks and found a significant favourable effect of the PGx-guided treatment on both the proportion of patients taking sick leave (PGx-guided: 4 % vs. TAU: 15 %) and the average number of sick days, when the latter were needed (PGx-guided: 4.3 days vs. TAU: 7.7 days).

Quality of life. One study (van der Schans et al., 2019) assessed QoL via the self-rating scales EuroQol, including the 5D-3 L (EQ5D-3 L) and the EuroQol visual analogue scale (EQ-Vas) (EuroQol Group, 1990). The EQ-5D-3 L descriptive system describes patient́s health state and comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The study was conducted in a sample of elderly patients (60 years or older) initiating with either nortriptyline or venlafaxine. In contrast to the other studies described in this review, only patients with the phenotype poor metaboliser, intermediate metaboliser or ultra-rapid metaboliser were randomised to the PGx or TAU group. There was an additional sample with the extensive metaboliser phenotype, which was not randomised, and also received TAU ($n = 57$). Changes in QoL were compared between visit 2 (two weeks after baseline) and visit 3 (four weeks after baseline) between all three groups. No significant differences between the PGx and TAU groups were reported regarding the effect on QoL, yet this study was based on a small sample. At baseline, 27 and 22 individuals with a deviating genotype were in the PGx and TAU groups respectively. The non-randomised additional control group consisted of another 57 individuals with extensive metaboliser status.

3.3. Risk of bias and certainty in the evidence rating

One study (Han et al., 2018) was rated as high risk for bias due to high risk in one domain, namely missing outcome data. It is important to note that this study reported a higher overall dropout rate, and a higher dropout associated with adverse events in the TAU group compared to the PGx group. Since dropouts in a study can be associated with higher symptom burden, which is correlated to functioning, we agreed there is a risk that the missingness in the outcome (SDS) could depend on the true value of the outcome. The remaining five studies had an overall rating of some concerns (Papastergiou et al., 2021; Pérez et al., 2017; Ruaño et al., 2020; Singh, 2015; van der Schans et al., 2019). A source of some concern for bias in the domain "deviations from intended interventions" (ITT) was the fact that treating physicians could not be blinded in any study. However, since all studies used either a behavioural measure like hospital LOS and RAR 30 days after discharge (Ruaño et al., 2020), blinded raters (Singh, 2015) or patient-reports (Han et al., 2018; Papastergiou et al., 2021; Pérez et al., 2017; van der Schans et al., 2019) and participants were blinded in all studies, there is low risk of bias in the assessment of the outcome (see Fig. 2).

The overall certainty of the evidence was very low. Results of the GRADE rating are shown in Appendix 9 in the Supplement. In addition to the risk of bias described above, there are other reasons for the low certainty of evidence. Firstly, there are inconsistency indicated by the high heterogeneity between studies ($I^2 = 73.6$ %) as well as imprecision indicated by a large confidence interval in the meta-analysis. Secondly, the low number of studies raise several issues. The generalisability of the findings in clinical settings might be limited for all outcomes. For the outcomes hospitalisation, sick leave, and QoL multiple domains could not be rated because there was only one study per outcome. Publication bias could not be assessed for any outcome because of the small number of studies.

3.4. Meta-analyses

Random-effect meta-analyses showed that PGx-guided antidepressant treatment significantly decreased SDS/I-measured functional disability compared to TAU by 2.85 points on average ($k = 3$; $n = 3$; MD $= -2.85$, $SE = 1.32$ [95 % CI −5.44, −0.26], $p = .031$); with substantial heterogeneity ($I^2 = 70.46$, $\tau^2 = 3.65$, $p = .023$). The results of Knapp-Hartung analyses showed non-significant effect of PGx-guided treatment on functional disability compared to TAU (MD $= -2.85$, $SE = 1.26$ [95 % CI −8.26, 2.58], $p = .151$), see Fig. 3.

SDS/I outcomes were assessed post-treatment in all included studies, at varying time points (Mean = 15.3 weeks, $SD = 9.5$; range: 8–26 weeks).

Similar results were obtained using SMD (SMD $= -0.33$, $SE = 1.15$ [95 % CI −0.62, −0.04], $p = .026$), heterogeneity ($I^2 = 66.8$, $\tau^2 = 0.04$, $p = .04$). The results of Knapp-Hartung analyses also showed non-significant effect of PGx-guided treatment on functional disability compared to TAU (SMD $= -0.33$, $SE = 1.14$ [95 % CI −0.93, 0.27], $p = .144$), see Fig. 4.

4. Discussion

We conducted a systematic review and meta-analysis to explore the efficacy of PGx-guided antidepressant treatment compared to TAU on functional outcomes and QoL in adults with anxiety and affective disorders. A total of six studies fulfilled the inclusion criteria, out of which three used comparable outcome measures (SDS/SDI) and were eligible for meta-analysis.

As a main result, PGx-guided antidepressant treatment significantly decreased functional disability compared to TAU. However, heterogeneity was high, and the study time frame varied considerably. Notably, we found that the direction of estimates was consistent, and a conventional method showed results were statistically significant. However, when we applied the Hartung-Knapp method (Jackson et al., 2017; Röver et al., 2015), a more conservative method that accounts for uncertainty in estimation of the between-study heterogeneity, this resulted in a wider CI and non-significant result (despite individual studies suggesting significant results). The small number of studies may lead to a wide uncertainty in between-study heterogeneity. Nevertheless, this result gives a first indication that PGx-guided treatment may also be beneficial for functional outcomes compared to TAU.

We acknowledge that the effect size observed (SMD $= -0.33$) is considered small by Coheńs benchmarks (Cohen, 1988). However, this magnitude is consistent with the typical effect sizes seen in antidepressant RCTs (0.3) (Cipriani et al., 2009; Wiesinger et al., 2023), which have been argued to represent clinically meaningful change, especially in domains such as functioning and QoL. Moreover, PGx-guided treatment seeks to optimise response and minimise trial-and-error prescribing, so even modest enhancements in functional outcomes at the individual level can lead to significant cumulative benefits at the population level (Hieronymus et al., 2020).

The low number of studies we found is in line with the observation that functional and QoL measures are underrepresented in clinical trials on depression compared to clinical symptom scales (Brockow et al., 2004; McKnight and Kashdan, 2009). The three studies using the SDS (Han et al., 2018; Papastergiou et al., 2021) or SDI (Pérez et al., 2017), paint a mixed picture. In all three studies, the authors reported a

significantly larger effect of PGx-guided treatment compared to TAU on depressive symptom reduction (Han et al., 2018; Papastergiou et al., 2021) and response rate (Pérez et al., 2017), but only one found a significant effect on functional disability as measured by the overall SDS score (Papastergiou et al., 2021) and one on the SDI Perceived Social Support partial score (Pérez et al., 2017). This discrepancy underlines the notion that symptom reduction, even though often correlated with, does not equate regaining of functioning and/or QoL. Future PGx trials in psychiatry should focus more on functional and/or QoL outcomes.

Currently, PGx trials in psychiatry are underway that assess functional outcomes, even though not as primary endpoints. One example is the PSY-PGx clinical study (Pelgrim et al., 2024; van Westrhenen et al., 2025), a PGx trial including patients with a depressive episode (MDD or bipolar disorder), anxiety disorder, or psychotic disorder. In the PSY-PGx study, general well-being and QoL is assessed with the EuroQol 5 Dimensions-5 levels questionnaire (EQ-5D-5 L) as well as psychosocial functioning with the Functioning Assessment Short Test (FAST) (Rosa et al., 2007). The primary endpoint is the RAS, the recovery assessment scale as assessed by the patient (Law et al., 2012; Shanks et al., 2013). Another example is the PANDORA trial, a PGx study in patients with MDD (Minelli et al., 2021). In this study, psychosocial functioning is assessed via the MINI-ICF-APP. A third study that is currently ongoing, the PRESIDE (PhaRmacogEnomicS In DEpression) Trial (Saya et al., 2023) uses the Assessment of Quality of Life (AQoL-4D) measure and also assessed hospitalisations.

Only one of the outcomes that we analysed, was used in more than one study. Interestingly, the study that found a significant effect of PGx-guided treatment on the overall SDS score was the one with the longest follow-up period, namely 6 months (Papastergiou et al., 2021). In their review relating symptoms and functioning in depression, McKnight and Kashdan conclude that functioning might "be less responsive to treatment; thus, functional outcomes might lag behind symptom outcomes" (McKnight and Kashdan, 2009). In one meta-analysis, PGx-guided treatment had a positive effect on response and remission rates at weeks 8 and 12, but not after 4 and 24 weeks (Wang et al., 2023). However, only two studies had follow-up measurements at 24 weeks, so it is not clear, whether the non-significant finding is due to a limited sample size or whether the favourable effect of PGx-guided treatment just disappeared over time. Studies with longer duration of follow-up, such as the PSY-PGx clinical study with a duration of 24 weeks (Pelgrim et al., 2024) and symptom as well as functional outcomes are needed to explore this further. In addition to the long follow-up period, it is important to note that the study by Papastergiou and colleagues was the only one including participants with a diagnosis of GAD in addition to patients with MDD, many of whom (about 58 %) had both diagnoses (Papastergiou et al., 2021), limiting the comparability of the results.

The negative findings regarding the effect of PGx guided treatment on hospital LOS and the 30-day RAR (Ruaño et al., 2020), raises the question what time period would be necessary to see effects on behaviour criteria such as a RAR. A recent publication of the PREPARE Study, a trans-diagnostic PGx study with a follow-up time of up to 18 months, reports a significantly shorter duration of initial hospitalisation, 40.5 % less re-admissions, and a shorter duration of hospitalisation upon readmission in patients with an actionable genotype belonging to the PGx group compared to the TAU group (Skokou et al., 2024). Since this study uses a cluster-randomised study design, it was excluded from our review. Nevertheless, the results are promising. Behavioural criteria like a RAR have the benefit that raters bias can be avoided but also come with their own challenges. For example, in countries without fully centralised hospital databases, it might be hard to track whether patients have been hospitalised in another clinic. As Ruaño et al. report, they did not assess whether patients had been hospitalised elsewhere during the 30-day period, which might have influenced the results (Ruaño et al., 2020). Whether or not a patient is hospitalised might also differ between countries, clinics within a country, or even depend on the treating physician, which might make data like this less comparable than standardised scales.

Singh reports a significant effect of PGx-guided treatment compared to TAU both on the outcomes related to occupational functioning (proportion of participants taking sick leave and average number of sick days) and remission rates (Singh, 2015). These results are encouraging, given that this outcome is highly relevant to patients and relatively easy to assess. However, it should be interpreted with caution, because in this study almost any psychiatric comorbidity was an exclusion criterion. Given that comorbidities are common in depressive disorders, the results might not be generalisable.

As previously reported (Bunka et al., 2023), it is noteworthy that only one study assessed the outcome QoL. The non-significant finding might be due to the very small sample ($n = 49$ randomised in total; $n = 57$ in a non-randomised control group). Also, QoL was compared between two visits that were only two weeks apart, which might be too short to detect any differences between the groups.

The main sources of potential bias in the included studies were missing in the follow-up data that might depend on the true outcome, since higher symptoms and poorer functioning can be associated with higher dropout. Finally, the overall certainty of the evidence was very low at this point, which is not surprising given the small number of studies included. Also, in none of the studies the treating physician was blinded, which –as we would like to acknowledge –is hard or even impossible in a PGx trial. However, it still constitutes a risk of bias. The certainty of evidence was further limited by the fact that neither inconsistency nor imprecision could not be assessed for the three of the

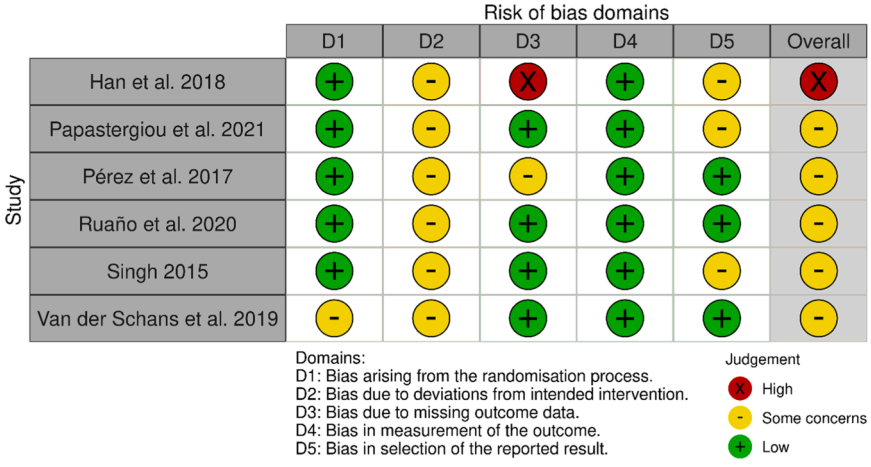

Fig. 2. RoB2 Traffic plot for functional outcomes and QoL.

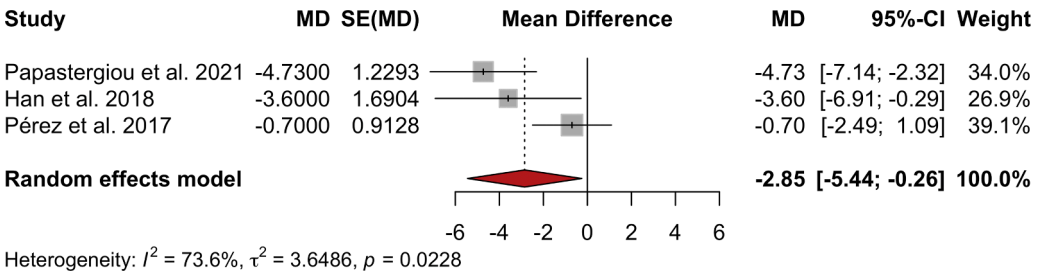

Fig. 3. Forest plot showing the efficacy of PGx-guided antidepressant treatment on functional disability in adults with anxiety and affective disorders (MD).

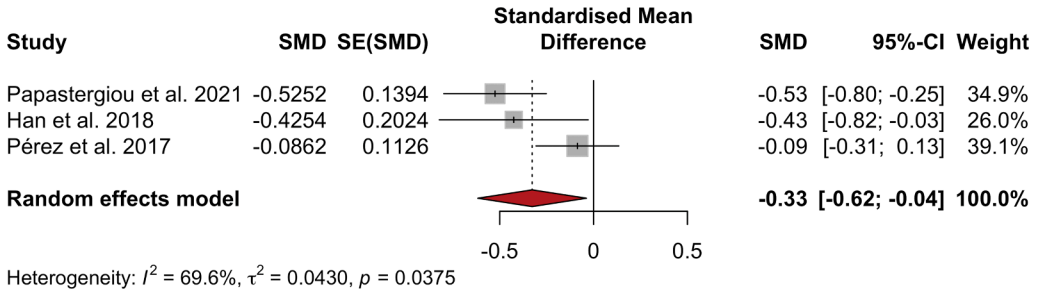

Fig. 4. Forest plot showing the efficacy of PGx-guided antidepressant treatment on functional disability in adults with anxiety and affective disorders (SMD).

six studies that reported unique outcomes. The meta-analysis revealed high heterogeneity between the studies (inconsistency) and a large confidence interval (imprecision).

4.1. Clinical implications

Due to the small number of studies, clinical implications can only be drawn very cautiously at this point. Given the importance of functioning and QoL for patients (Zimmerman et al., 2006), it would be desirable to assess functional outcomes in addition to clinical symptoms in any future RCTs on treatment efficacy, especially in PGx trials, to better understand the relationship between disease- and patient-centred outcomes as well as the treatments necessary to affect these. Therefore, it would be ideal if response and remission criteria were based on both types of outcomes. However, is should be carefully considered which domains of functioning and QoL to assess with which instruments. There needs to be a balance between covering domains important to the patient and feasibility in the clinical setting. Also, a high heterogeneity among QoL measures in depression has been found (Peipert et al., 2025). Our results give a first indication that PGx-guided treatment may also be beneficial for functional outcomes compared to TAU.

4.2. Strengths and limitations

We performed an up-to-date systematic review, allowing the inclusion of studies exploring the efficacy of PGx-guided antidepressant treatment on functional/QoL outcomes in common mental disorders. This is the first meta-analysis in the field of pharmacogenetics with a functional outcome approach. Although there was some variability in which outcomes were reported, the quality of the included studies was fair, and three studies used the same standard and validated instrument to assess functional disability. Other strengths of this study include the rigorous methodology of the systematic search, study selection, and data extraction performed by independent researchers.

Our work also includes some limitations. First, we performed meta-analyses when data from at least three studies were available for a given outcome (Higgins et al., 2024). However, given the small number of studies in some comparisons, these results should be interpreted with extra caution due to potential instability of the estimates and increased risk of bias (Jackson and Turner, 2017). As the number of relevant studies was limited, no meta-regressions or subgroup analyses could be conducted, which precludes a reliable investigation of heterogeneity and potential moderators. Due to the small number of studies (<10) no publication bias was assessed (Higgins et al., 2024). Second, while the exclusion of grey literature and unpublished studies may help reduce heterogeneity in study quality, it also carries the risk of omitting relevant findings and may introduce publication bias, favouring studies with statistically significant or 'positive' results. Grey literature can offer timely, practice-based, or otherwise unpublished evidence that complements peer-reviewed publications. Conversely, the inclusion of such data may introduce other forms of bias, particularly related to unclear methodology or selective reporting (Boutron et al., 2023). Third, four of the six studies used self-rating scales to assess functioning. While self-rating scales have the two advantages that the patient's perspective is captured and patients are blinded to their treatment group, clinician ratings and behavioural measures of functioning are needed to cover more facets of functioning, including work, cognitive functions, leisure, and social relationships. Forth, except for LOS (Ruaño et al., 2020), none of the outcomes we considered were primary outcomes. Fifth, the substantial differences in trial duration (4 weeks - 6 months) may affect the heterogeneity of the results. Lastly, we acknowledge that the overall certainty of the evidence is very low at this point, which together with the limitations above, highlights the need to study functional and QoL outcomes in PGx trials.

5. Conclusion

Evidence relating to functional outcomes and QoL is particularly limited and further investigation on the efficacy of PGx-guided antidepressant interventions on specific functional outcomes (social, leisure, work) for people with anxiety and affective disorders is urgently needed. Nonetheless, our results suggest that using PGx-guided antidepressant treatment may benefit functioning and thus well-being in adult patients.

CRediT authorship contribution statement

Protocol registration: TP, NEF-O, EV, RvW. Term, Conceptualisation, Methodology: NEF-O, TP, EV, RvW. Data collection, data curation: NEF-O, MB, JL, TP. Writing –original draft: NEF-O, MB. Writing –reviewing & editing: All the authors. Formal analysis, Software, Validation: NEF-O,

MH. Visualisation: NEF-O, MB, MH. Interpretation of the data: All the authors. Investigation: NEF-O, MB, JL, TP. Supervision: NEF-O, EV, RvW. Resources, funding acquisition: RvW, AP, UH, EV, The PSY-PGx Consortium. All the authors approved the final version of the submitted manuscript.

Data availability

NEF-O, MB, and MH have full access to all the data in the study. Open materials: https://github.com/MathiasHarrer/meta-pharmacogenetics.git

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Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2025.08.003.

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Note: Articles marked with an asterisk were included in this systematic review and meta-analysis.

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