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Review article

# Efficacy and tolerability of therapies set under pharmacogenetic tools suggestions: A systematic review with meta-analysis about mood disorders

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ABSTRACT

*Background:* Bipolar Disorder (BD) and Major Depressive Disorder (MDD) have a huge impact on functioning and quality of life; moreover, they are linked to extensive direct and indirect costs. This systematic review with meta-analysis aims to evaluate the utility of pharmacogenetic tests (PGT) in terms of efficacy and tolerability into the routine clinical treatment of mood disorders.
*Materials and methods:* The first part of the review is a qualitative overview of the PGTs used in the included studies. The second part aims to compare, in terms of efficacy and tolerability, patients affected by BD and MDD treated as usual (TAU), according to the clinicians' prescribing attitude, versus patients whose psychopharmacological treatments were set up following the PGT suggestions.
*Results:* 6 studies on MDD and 2 studies on BD were included. Regarding MDD, the meta-analysis shows a significantly higher number of patients achieving better outcome in terms of efficacy, through the evaluation of response rate and remission rate at the HDRS (Hamilton Depression Rating Scale) in the group of patients treated under the PGT suggestions; regarding BD the meta-analysis does not show any significant difference in terms of efficacy. In terms of adverse events, the available data suggest promising results about the utility of PGT to set more tolerated therapies.
*Conclusions:* Although the limited number of studies, results confirm the importance of PGT in setting up psychopharmacological therapies as a support to clinicians' choices.

## 1. Introduction

Mood disorders include Bipolar Disorder (BD) and Major Depressive Disorder (MDD). The first condition consists in a disabling and complex mental disorder characterized by shifts in energy, behavior and mood from mania or hypomania to depression, in which different subtypes can be distinguished (Bessanova et al., 2020). Its lifetime prevalence is estimated to be 4.4% in the United States; it represents a leading cause of disability among young people, and is associated with a huge impact on personal, social, and occupational functioning, and a lower quality of life (Vieta et al., 2018). The second disorder is characterized by a persistent feeling of sadness and loss of interest; it is one of the most prevalent mental disorder worldwide, as well as one of the most disabling. According to the Global Burden of Disease study, MDD represents the fourth leading cause of disability (Gutiérrez-Rojas et al., 2020). It is estimated that mood disorders are associated to extensive direct and indirect cost each year. The economic burden of depression, including MDD and BD was estimated at $83.1 billion in 2000 in the United States (Greenberg et al., 2015). In addition to the problem of the costs to society, it is fundamental exploring the individual perspective of the patients. Many people affected by depression or bipolar disorder must assume treatments from the onset of the symptoms, which for bipolar disorder is around 25–30 years, until the older age, and frequently need for hospitalizations to find the most effective and tolerated therapy (Ielmini et al., 2018a, 2018b). In the last years, pharmacogenetics testing (PGT) is spreading out as a tool for tailoring treatments. PGTs have found different applications, particularly in oncology and neurology; in psychiatry, the prescribing attitude and the information knowledge of clinicians, the pharmacogenetic analysis, and the test costs can represent limitations in the spread out of PGT (Ielmini et al., 2018a, 2018b; Pagani et al., 2019; Callegari et al., 2019); nevertheless literature seems to show promising data dealing with PGTs role in founding better

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tolerated and more efficacious therapies and managing drug-drug interactions.

This systematic review of the professional literature aims to evaluate the utility of PGT into the routine clinical treatment of mood disorders. The first part of the review provides an overview of the different PGTs used in the included studies. The second part aims to compare patients affected by BD and MDD treated as usual (TAU), according to the clinicians' prescribing attitude, versus patients whose psychopharmacological treatments were set up following the PGT suggestion in terms of efficacy and tolerability, through a metanalytic approach.

## 2. Materials and methods

A systematic review of all studies in which PGTs were used was performed. The scientific literature search was conducted from 2000 to March 2021 searching PubMed, Embase, APA PsycInfo, and Google Scholar. The combination of the following MeSH terms was screened: "pharmacogenetics", "pharmacogenomics", "test", "pharmacogenetic testing", "mood disorder", "bipolar disorder", "major depressive disorder", "clinical trial", "randomized clinical trial", "clinical application". The Boolean operators "and/or/not" were used to create different combinations for the search strategy.

Studies had to fulfill the following criteria to be included:

- Studies comparing the use of PGT to prescribe treatments versus the empirical prescribing of therapies in terms of efficacy and tolerability;
- Studies written in English;
- RCTs, observational studies, or case-control studies;
- Studies evaluating patients aged $\geq$ 16 years;
- Studies evaluating patients diagnosed with MDD or BD according to the Diagnostic and Statistical Manual of Mental Disorder (DSM), or the International Classification of Disease (ICD).

Studies conducted on single-nucleotide polymorphism (SNP) or in laboratory generic analysis were excluded to evaluate the utility of PGT already available for the routine clinical practice.

Quality of available studies was evaluated as follows:

- Non-randomized case-control studies (comparing outcomes in a PGT group vs. TAU group): Cochrane risk of bias tool for non-randomized studies (Sterne et al., 2016);
- Observational studies: Good ReseArch for Comparative Effectiveness (GRACE) Checklist (Dreyer et al., 2014);
- RCTs: Cochrane Collaboration risk of bias Tool (Higgins et al., 2011).

Ratings were completed by two reviewers independently.

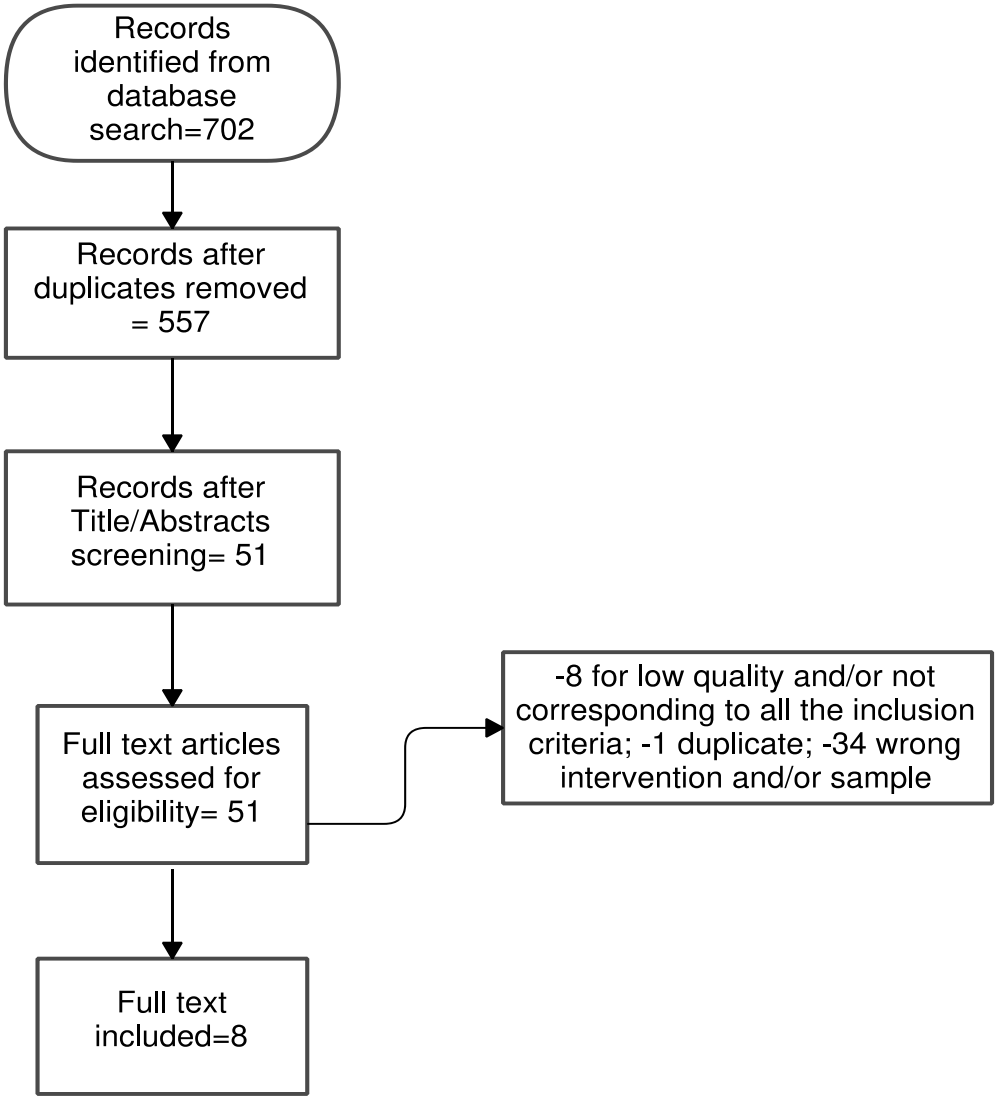


**Fig. 1.** Flow chart on the search strategy, screening, evaluation of eligibility, and inclusion of the studies.

Disagreements were solved by consensus or involving a third author.

The details of the search strategy are shown in Fig. 1.

The first part of the review is a qualitative overview of the PGTs used in the included studies. For each PGT the following information were extracted: name, producing, company, included genes, genetical process used.

The quantitative phase of the review aims to analyze patients affected by BD and MDD treated as usual (TAU), according to the clinicians' prescribing attitude, versus patients whose psychopharmacological treatments were set up following the PGT suggestion in terms of efficacy and tolerability.

Patients affected by depression were compared in terms of efficacy evaluating two outcomes:

- The primary outcome considered corresponded to the response rate, that is the reduction of at least 50% of the score obtained at the preliminary determination of the Hamilton Depression Rating Scale (HDRS);
- The secondary outcome corresponded to remission rate, that is the reduction of the HDRS score to a value $\leq 7$.

For BD, number of respondents was assessed using the Clinical Global Impression Scale (CGI).

Tolerability was evaluated comparing the percentage of treatment emergent adverse events (TEAEs) (Callegari et al., 2016) reported in the two groups of patients.

Data extracted included: means, standard deviation (SD), and sample size for both PGT and TAU patients, in addition to methodological and participants' characteristics. When authors did not provide original data, they were also extracted from bar chart using Enguage Digitizier (http://markummitchel 2021).

Meta-analysis of the quantitative part of the review was conducted using Review Manager Software (RevMan – Version 5.4). To assess heterogeneity across the studies, authors performed the Cochran Q test and quantified the heterogeneity with the I2 statistic (Higgins et al., 2011). An I2 $\langle$ 25% indicates a low grade of heterogeneity across studies, whereas an I2 ranging from 25 to 75% was deemed to have a moderate grade of heterogeneity, and an I2 $\rangle$ 75% indicates a high degree of heterogeneity. Whenever the heterogeneity across studies was low ($<$ 25%), authors used a fixed-model effect. A $p$-value $<$ 0.05 was considered statistically significant.

## 3. Results

The process of identification, screening, eligibility evaluation and inclusion is described in Fig. 1 according to PRISMA guidelines (Liberati et al., 2009). The search initially identified 702 potentially relevant studies. After removing duplicate records and screening according to the prespecified criteria, 8 studies were ultimately included. Among them, 6 studies deal with MDD (Bradley et al., 2018; Greden et al., 2019; Han et al., 2018; Perez et al., 2017; Thase et al., 2019; Winner et al., 2013) and 2 with BD (Huilei et al., 2020; Ielmini et al., 2018a, 2018b).

The evaluation of patients with depression and the characteristics of the sample are listed in the Table 1. The majority of trials lasted 8 weeks (range, 8–12 weeks). 7 studies (Bradley et al., 2018; Greden et al., 2019; Han et al., 2018; Perez et al., 2017; Thase et al., 2019; Winner et al., 2013; Huilei et al., 2020) included two groups, that is, TAU versus PGT, and 1 study (Ielmini et al., 2018a, 2018b) included one group, divided into two subgroups in a sub-analysis (one of patients with a therapy concordant to the PGT and the other group with patients with a therapy discordant to the PGT after a sub-analysis). Among these, 2 studies were conducted in Europe (Perez et al., 2017; Ielmini et al., 2018a, 2018b), 4 studies in the USA (Winner et al., 2013; Thase et al., 2019; Bradley 2017 and Greden 2019), 1 study in China (Huilei et al., 2020) and 1 study in Korea (Han et al., 2018). Hamilton Depression Rating Scale (HDRS) was used to assess efficacy of treatment for depression and Clinical Global Impression (CGI) for bipolar disorder. TEAEs were estimated as present or not by the majority of the authors; only 2 studies used a scale to evaluate this outcome (Fibser scale used by Perez et al., 2017 and DOTES used by Ielmini et al., 2018a, 2018b) (Table 2).

### 3.1. Qualitative review: description of the PGTs used

The present part of the review describes the PGT used for the genetic analysis in the different studies. The PGT described are already available in routine clinical practice. This choice was made to have more homogeneous genetic evaluation and useful results for the real world of clinical practice

**Table 1**
Socio-demographic and clinical baseline characteristics of patients with MDD.

| Study | Group | Sample | Average age, (SD) | Gender *N*, (%) | HDRS baseline Mean, (SD) | PGT used | Weeks of Follow up |
|---|---|---|---|---|---|---|---|
| Bradley et al. (2018) | PGT | 352 | 47.8 (14.5) | F 257(73)<br>M95 (27) | 20 (5.8) | NeuroIDgenetix | 8 |
| | TAU | 333 | 47.3 (15.2) | F 241 (72)<br>M 92 (28) | 20 (5.6) | | |
| Greden et al. (2019) | PGT | 681 504 | 46.9 (14.5) | F 489 (71.8)<br>M192 (28.2) | 21.1 (4.2) | GeneSight | 8–12 |
| | TAU | 717<br>607 | 48 (14.5) | F498 (69.5)<br>M219 (30.5) | 21.4 (4.22) | | |
| Han et al. (2018) | PGT | 52 | 44.2 (16.1) | F 40 (7.69)<br>M 12 (23.1) | 24.5 (4.6) | Neurofarmagen | 4–8 |
| | TAU | 48 | 43.9 (13.8) | F 35 (72.9)<br>M 13 (27.1) | 23.1 (5) | | |
| Perez et al. (2017) | PGT | 155 | 51.7 (12.05) | F 99 (63.9)<br>M 56 (36.1) | 19.47 (5.9) | Neurofarmagen | 6–12 |
| | TAU | 161 | 50.74 (13.2) | F 102 (63.4)<br>M 59 (36.6) | 19.01 (5.71) | | |
| 2019<br>PGT | PGT | 439 | 48.4 (14.7) | F 311 (70.8)<br>M128 (29.2) | 20.37 (4.52) | GeneSight | 8 |
| | TAU | 473 | 48.9 (14.7) | F 335 (70.8)<br>M138 (29.2) | 20.66 (4.86) | | |
| Winner et al. (2013) | PGT | 26 | 50.6 (14.6) | F 18 (6.9)<br>M 8 (31) | N.R | GeneSight | 4–6–10 |
| | TAU | 25 | 47.8 (13.9) | F 23 (9.2)<br>M 2 (8) | N.R | | |

**Legend:** N.R.= not reported.

**Table 2**
Sociodemographic and clinical baseline characteristics of patients with BD.

| Study | Group | Sample | Averge age | Gender | CGI baseline mean score | PGT used | Weeks of Follow up |
|---|---|---|---|---|---|---|---|
| Huliei (2020) | PGT | 100 | N.D. | F 32; M 68 | N.R. | Hangzhou | 12 |
| | TAU | 100 | N.D. | F 30; M 70 | | | |
| Ielmini (2019) | PGT | 13 | 55 | F 5; M 8 | N.R. | Neurofarmagen | 12 |
| | TAU | 10 | 55 | F 7; M 3 | | | |

*3.1.1. NeuroIDgenetix*

It is a pharmacogenetic test used for Drug Response and Therapeutic management for anxiety and major depression disorder. It evaluates Pharmacokinetic and Pharmacodynamic variants associated with 11 genes tested, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, SLC6A4 [NM_001045.5:c.-1760C > T], SLC6A4 [5-HTTLPR], COMT [NM_000754.3:c.472 G > A], HTR2A [NM_000621.4:c.-998 G > A], HTR2A [NM_000621.4:c.614e2211T > C], MTHFR [NM_005957.4:c.665C > T], MTHFR [NM_005057.3:c.1286A > C]. Molecular methods used for detection included end-point PCR, real-time PCR for CYP2D6 copy number variation determination, and capillary electrophoresis for the genotyping of SLC6A4 5-HTTLPR (Pratt et al., 2010). In the case of CYP genes, genotypes are translated into diplotypes and then diplotypes are assigned a metabolic phenotype for clinical management. Complementing this pharmacogenetic analysis, the IDgenetix® algorithm also screens for potential metabolic interactions between concomitant medications as well as a variety of lifestyle factors, including the use of alcohol, tobacco, and herbal supplements. The NeuroIDgenetix® report classifies therapeutically related medications as one of two options; "Use as Directed" or "Use with Caution and/or Increased Monitoring". The medications classified as "Use as Directed" may be administered in accordance to the standard prescribing information since no genetic variants or metabolic interactions were identified as variant that could need increased caution or dose adjustment. Medications classified as "Use with Caution and/or Increased Monitoring" have been identified by the IDgenetix® algorithm as having one or more reasons for avoidance, including possible drug-gene and drug-drug interactions. These warnings are accompanied by brief descriptions of the reasons for caution (e.g., lack of efficacy or toxicity) along with recommendations for appropriate clinical action.

*3.1.2. Genesight*

The GeneSight® Psychotropic test from Assurex Health, Inc. (Mason, OH) was used for pharmacogenomic testing by Greden et al. (2019), Thase et al. (2019) and Winner et al. (2013). It evaluates the genotypes of 59 alleles and variants across 8 genes (CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2B6, CYP2D6, HTR2A, SLC6A4;). This is a proprietary test based on licensed technology disclosed in issued patents (US patent no. 8401801 and US patent no. 8688385). In brief, the algorithm weighed the combined influence of each individual genotype on patient response to each individual medication. 38 psychotropic medications were categorized based on three levels of gene-drug interaction: 'use as directed' (no detected gene-drug interactions), 'use with caution' (moderate gene-drug interactions; i.e. medications may be effective with dose modification), 'use with increased caution and with more frequent monitoring' (severe gene-drug interactions that may significantly impact drug safety and/or efficacy).

*3.1.3. Neurofarmagen test*

Neurofarmagen was used for pharmacogenetic analysis by Perez et al. (2017), Ielmini et al. (2018a, 2018b) and Han et al. (2018). This test is a pharmacogenetic test for the specific analysis of genetic polymorphisms related to the pharmacokinetics and pharmacodynamics of principles commonly used in neuropsychiatry.

The test evaluates more than 60 polymorphisms present in 25 different genes (ABCB1, CES1, CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP3A4, EPHX1, UGT2B15, AKT1, BDNF, AL157359, COMT, DDIT4, FCHSD1, GRIK4, HLA-A, HTR2A, HTR2C, LPHN3, OPRM1, RPTOR, SLC6A4) related to pharmacokinetics and pharmacodynamics of 59 prescribed drugs. All genetic variants tested are selected according to all available evidence to date, and are routinely reviewed.

The test report encloses a part with all pharmacological principles match with a color: Green, expectation of good response to treatment or a good tolerability profile; White, index of a standard response, not different from the general population; Yellow, requiring careful monitoring; Red for high risk of adverse effects or not expected efficacy.

The test then allows to locate the most appropriate dosage for each patient by consulting in advance information on possible side effects of the drug. The genetic polymorphisms analyzed can be grouped into three different categories, depending on its possible effect:

Drug Response

The proteins encoded by these genes are direct or indirect targets of drugs (receptors, signaling pathways, etc.). These genes are crucial for the evaluation in terms of drug efficacy.

Risk of unwanted effects

Genes that should be considered to evaluate the potential side effects of the treatment.

Dose (metabolism)

Genes involved in drug activation, in penetration and in its elimination rate; genes controlling the drus' blood levels.

The administration of the genetic test is carried out on a patient's saliva sample, through the Genomic DNA Isolation Kit. AB-BIOTICS S.A. is in possession of the required authorization to operate as a health laboratory (code E17867643) and to import biological samples. DNA isolation is performed through the Genomic DNA Isolation Kit (NorgenBiotek Corp. Thorold, ON, Canada). The DNA is evaluated by a 2000 nanodrop microvolume spectrometry. All analyses are evaluated in quadruple with Real Time PCR system through the master mix TaqMan (Life Technologies Inc) genotyping system. Quantification is made with the Software Copy Caller (Life Technologies Inc.) using the CT Comparative Method.

3.2. Quantitative review

*3.2.1. Meta-analysis of the studies evaluating MDD: comparison between PGT patients versus TAU patients in terms of efficacy*

Dealing with efficacy, the six studies evaluating patients suffering from depression have been processed through a meta-analysis (Figs. 2–4).

This first meta-analysis included the six studies evaluating patients with MDD in terms of response rate at HDRS after 8–12 weeks of follow up, including a total of 1824 patients in the PGT group versus 1898 patients in the TAU group. As shown by the Forest Plot, the studies with a higher weight on the metanalysis results (as shown by the weight column) are Thase et al. (2019) (36.4%) and Greden et al. (2019) (29.3%) due to larger samples and a smaller interval of confidence. Since that the heterogeneity was small (I2=0%), the Fixed model was used; this forest plot shows a statistical significance at the meta-analysis level with an overall improvement achieved by PGT patients compared with TAU patients, as shown by the diamond on the right part of the forest plot [OR 1.49, CI (1.29,1.73)], due to the fact that the outcome of interest is desirable, the results to the right of the vertical line favours the treatment (PGT) over the control (TAU).

This second forest plot includes the six studies evaluating patients suffering from MDD, compared PGT versus TAU in terms of remission

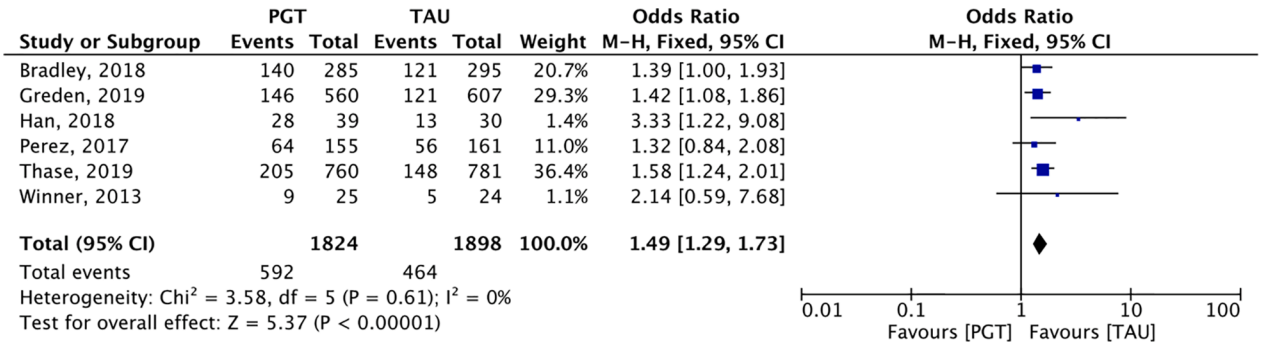


**Fig. 2.** Forest plot of comparison: PGT vs TAU among patients affected by MDD; outcome: Response rate (HDRS≤ 50%).

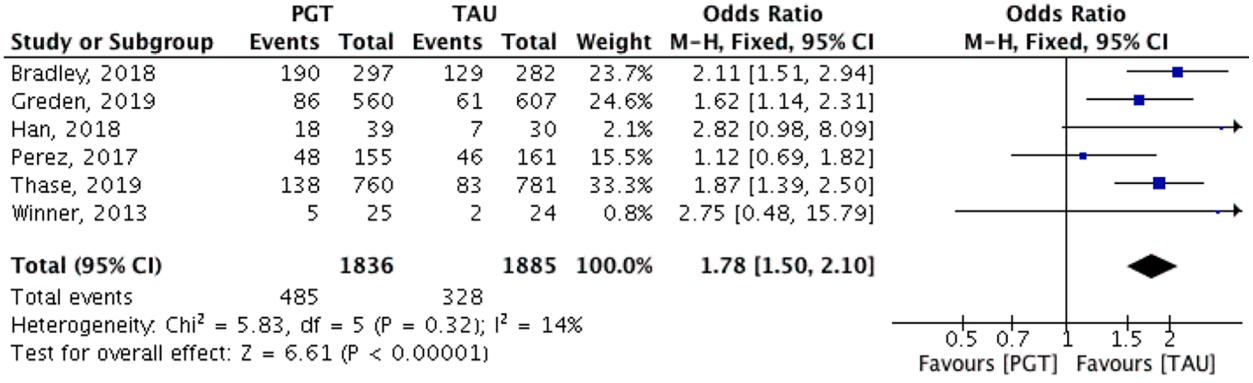


**Fig. 3.** comparison of PGT versus TAU in terms of Remission Rate (HDRS ≤ 7) at HDRS in patients suffering from MDD.

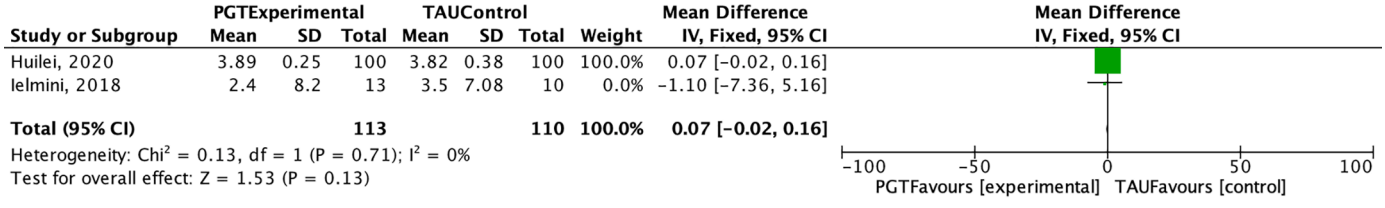


**Fig. 4.** comparison of PGT versus TAU in terms of efficacy at CGIs in patients suffering from BD.

rate at HDRS after 8–12 weeks of follow up. As shown by the weight column, Thase et al. (2019) and Greden et al. (2019) are the studies with a higher weight (respectively 33.3% and 24.6%). Since the heterogeneity was small ($I^2$=14%), the Fixed model was used; this forest plot shows a statistical significance at the meta-analysis level with an overall improvement achieved by PGT patients compared with TAU patients [OR 1.70, CI (1.50,2.10)], as shown by the diamond on the right part of the forest plot. The diamond is on the right part due to the fact that the outcome of interest is desirable; for this reason the results to the right of the vertical line favours the treatment (PGT) over the control (TAU).

*3.2.2. Meta-analysis of the studies evaluating BD: comparison between PGT patients versus TAU patients in terms of efficacy*

Regarding Bipolar Disorder, only two studies were included in the review: Huilei et al. (2020) and Ielmini et al. (2018a, 2018b).

Between the two studies Huilei et al. (2020) was the only one with a weight in the meta-analysis; the $I^2$ was 0 so the fixed model was used. The meta-analysis was not significative, due to the included studies and as shown by the diamond on the vertical line [OR 0.07 (CI -0.02,0.16)].

*3.2.3. Tolerability results*

A metanalytic approach has not been possible regarding tolerability because of TEAEs were considered only by 5 studies using heterogeneous approaches. To complete our evaluation we are reporting their evidence in a descriptive way.

Starting from the studies evaluating depressed patients we found the following results:

- Greden et al. (2019) did not found any statistically significant difference between the PGT group and the TAU group regarding the mean number of side effects at week 8 (0.243 vs 0.237, $p = 0.855$) or the proportion of patients who experienced side effects [15.6% (88/560) versus 15.3% (93/607), $p = 0.881$]. They also reported that when patients taking incongruent medication at baseline were evaluated separately, those who switched to congruent medications by week 8 had a significantly lower mean number of side effects compared to those who remained incongruent (0.065 versus 0.242, $p = 0.002$). Significantly fewer patients who switched to congruent medications experienced side effects compared to those who did not [6.5% (5/77) versus 16.5% (22/136), $p = 0.045$];
- Bradley et al. (2018), did not find any statistical difference between the control and experimental group ($p = 0.21$). They also reported that only 6% of the reported TEAEs were severe and equally distributed across the control and experimental groups;

- Perez et al. (2017), assessed the TEAEs through the FIBSER (Frequency, Intensity, Burden of Side Effects Rating) scale analyzing subjects with a FIBSER sub score $\geq 1$ at the baseline ($n = 177$). At baseline, this tolerability subpopulation did not display significant differences among groups in the FIBSER Burden domain score. The likelihood of reaching a FIBSER Burden score $\leq 2$, indicating no changes needed for side effects, was significantly higher in the PGT group after 6 weeks (66.7% versus 50%, $p = 0.029$) and was maintained after 12 weeks;

The authors evaluating patients affected by bipolar disorder founded that:

- Huilei et al. (2020), founded a statistically significant difference between the PGT group and the TAU group, with fewer side effects among the PGT group' patients. The mean rank difference between the PGT group and the reference group was 13.86 ($p = 0.047$) at 2 weeks after, 13.38 ($p = 0.057$) after 4 weeks, 15.42 ($p = 0.027$) at 8 weeks after and 17.39 ($p = 0.005$) after 12 weeks;
- Ielmini et al. (2018a, 2018b), described that after the sub analysis, with a small effect size, patients with a therapy incongruent to the PGT at baseline and receiving a change in therapy congruent to the PGT within the follow-up, showed a significative improvement in terms of tolerability (from 9/10 patients presenting TEAEs at baseline to 3/10 patients presenting TEAEs after 8 weeks, $p = 0.031$).

Overall, the PGT group showed better or comparable results compared to the TAU group in terms of tolerability, in both MDD and BD.

## 4. Discussion

This systematic review concerns the utility of PGT use in the treatment of mood disorders in term of efficacy and tolerability. The review shows that there are still few studies on the argument, particularly for the use of PGT in the treatment of BD; more results on depression are already available.

Lack of experimental validation or the poor evidence of effectiveness and save costing are the major obstacles to the proceeding of PGx in the routine clinical practice (Gratten et al., 2014); for these reasons, the study aims to evaluate the available data about the use of PGT tools in the treatment of the mood disorder. This review focuses on the use of PGTs, in order to evaluate the usefulness of PGx through the use of practical tools that can be used in routine clinical practice.

The first part of the review describes the PGTs used in the included studies, showing four different kinds of them. All of these tools give both pharmacokinetic and pharmacodynamic details about the pharmacotherapies commonly used for mood disorders and different SNPs of patients, but obviously they differ in the polymorphisms analyzed and in the kind of genetic analysis approach.

A qualitative metanalysis was possible for the studies concerning patients with MDD (Bradley et al., 2018; Greden et al., 2019; Han et al., 2018; Perez et al., 2017; Thase et al., 2019; Winner et al., 2013), showing better outcomes in terms of efficacy among patients treated according to the PGT suggestions. In detail, the meta-analysis about response rate (HDRS $\leq$ 50%) shows a statistically significant overall improvement in the PGT group, with more patients achieving a HDRS score decreasing by more than 50% from the baseline score in the group of patients treated under the PGT suggestions (49% more often, OR 1.49).

Also regarding remission rate (HDRS $\leq 7$), the meta-analysis showed a significative difference in terms of efficacy, with superior outcome for patients treated under the PGT suggestions, reaching an HDRS score $\leq 7$ more often than in the TAU group (78% more often in the PGT group, than in the TAU group, with an OR of 1.78).

These results confirm the importance of pharmacogenetic support in setting up antidepressant therapy, as already claimed by different authors (Cuéllar-Barboza et al., 2020; Weinshilboum and Wang, 2017). It is known how the response to antidepressant is strongly influenced by individual factors, which can only be investigated with an accurate pharmacokinetic and pharmacodynamic analysis; the setting of a tolerated and effective therapy, calibrated on the individual patient, greatly influences the compliance of the patient with substantial implications in terms of clinical improvement (Solomon et al., 2019). As evidence of this, the FDA suggests for the evaluation of polymorphisms of CYP2C19 before starting antidepressant treatment with citalopram, suggesting a maximum dose limited to 20 mg/day in poor metabolizers patients due to the risk of QT prolongation (Pharmgkb.org, 2021). In light of this points, the review has taken into consideration also if the therapies set under the PGT suggestions were more tolerated. This point was evaluated through a descriptive approach because this outcome was assessed in different ways by some of the studies included in the review. Dealing with MMD, contrasting results emerged because Bradley et al. (2018) and Perez et al. (2017) found a decrease of the TEAEs when patients had therapies congruent to the PGT, while Greden et al. (2019) did not find any significant statistical difference between the two groups.

Dealing with BD, carrying out a meta-analytical approach to the studies has been more complex, first of all because there were only two studies available (Huilei et al., 2020; Ielmini et al., 2018a, 2018b), and between these only one (Huilei et al., 2020) presented a significant sample size. However, since the lack of data dealing with bipolar disorder, we have taken into consideration all the available evidence. Both the studies showed a significant clinical improvement in the arm of patients treated under the PGT suggestion, but, since the given the paucity of the data deriving almost entirely from one study, further evidence is needed to confirm these results. Also dealing with tolerability, both the studies showed fewer TEAEs when the therapies were set according to the PGT. Regarding the use of PGT in the clinical practice of patients suffering from bipolar disorder that are often treated with polypharmacotherapy, who often require changes in therapy according to the different phases of the disease and who often have to take drugs for a long time, it is undoubted that a careful genetic analysis could be a useful tool to support clinicians in setting up better tolerated and more effective therapies and in managing the problem of drug-drug interactions (Wang et al., 2012).

In light of the problems arising both in terms of direct and indirect costs and in terms of the impairment deriving from the unresponsive symptoms and for the frequent adverse reactions to polypharmacotherapy, we think that it is of undoubted benefit to deepen the knowledge of the patient through genetic analyzes, before setting up a therapy that often, between various changes and additions, patients should continue for many years.

There is also no doubt, as already discussed in a recent publication (Ielmini et al., 2021), that to provide training programs for clinicians to facilitate the use of PGTs in psychiatric clinical practice, and to identify PGx guidelines could be crucial.

The issue of the costs is certainly even more difficult: demonstrating cost savings is even harder in relation to the different reporting systems of health services, to the calculation of indirect and direct costs linked to the pathologies (Menchetti et al., 2010, 2014) and to the diversity of costs of available PGTs. Surely this topic may be subject to a further review, always aiming to objectifying the real usefulness of the use of PGX in clinical practice.

The limitation of the review is represented by the lack of data on bipolar disorder, considering the more relevant contribute by the study performed by Huilei et al. (2020); moreover, studies evaluating tolerability have a short duration follow-up. Have long term studies could be useful to have more information about tolerability, late adverse events and their role on adherence to therapy. This last point could represent another future study proposal; particularly the impact of PGT versus TAU on adherence to psychopharmacological therapies through the

evaluation of drop-outs could be the aim of a future review. In conclusion, more evidences are needed to detail the topic and, when available, they will be object of an update.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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