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From classification to personalization: Towards an evidence-based integrative clinical model in the diagnosis and treatment of mood disorders

Systematic review and meta-analysis according to PRISMA 2020

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Abstract
Diagnostic classifications (DSM / ICD) play a central role in clinical practice mapping and are essential for standardizing clinical language; however, they face epistemological and practical limitations when dealing with overlapping and heterogeneous disorders. Mood disorders represent a clinically diverse and highly heterogeneous spectrum, with overlapping categories that reduce diagnostic precision as well as predictive validity regarding course, treatment response, and relapse risk. Hence, there is a growing need to shift toward Personalized (Precision) Psychiatry, which aims to integrate clinical, psychological, social (and sometimes biological) dimensions into both diagnostic and therapeutic decision-making. (Comai et al., 2025)
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Objective:
This study aims to synthesize empirical evidence regarding the feasibility of moving from rigid categorical diagnosis and the "one diagnosis–one treatment" logic toward an integrative personalized clinical model in the diagnosis and treatment of mood disorders, by examining:

1. Multidimensional predictive/diagnostic models
2. Personalized therapeutic interventions and their impact on response, remission, and relapse prevention
3. Psychological and social factors as moderators of treatment response

Methodology:
A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines using the following databases:

PubMed/MEDLINE, Embase, PsycINFO, Cochrane CENTRAL, Web of Science, Scopus.
Randomized controlled trials, cohort studies, and systematic reviews addressing mood disorders within the framework of personalization or treatment stratification were included. (Page et al., 2021)
Risk of bias in randomized trials was assessed using RoB 2 and ROBINS-I for non-randomized studies, with certainty of evidence evaluation. Predictive modeling studies were assessed using PROBAST, and certainty of evidence was evaluated using GRADE. (Sterne et al., 2019; Sterne et al., 2016; Wolff et al., 2019; Guyatt et al., 2008)

Results

The systematic review included a substantial number of studies in the qualitative synthesis, with a subset meeting inclusion criterion for meta-analysis.
Results showed that pharmacogenetic (PGx) guidance in patients with treatment-resistant depression was associated with higher clinical improvement and increased remission rates compared with usual care, with high consistency across studies. Psychotherapy, whether used alone or in combination with pharmacotherapy, was more effective than pharmacotherapy alone in reducing relapse risk.
Regarding personalized Cognitive Behavioral Therapy (CBT), effect sizes varied across clinical subgroups, suggesting that individual characteristics and clinical context act as moderators of therapeutic response. Detailed numerical results are presented in Table (1). (Wuthrich et al., 2026; Holt-Lunstad, 2024)

Table (1). Summary of meta-analysis results

Note: Confidence intervals and heterogeneity indices were not reported for some CBT subgroup analyses in the available data.

Comparison / Intervention	Outcome	Effect measure	Effect size (95% CI)	Number of studies (k)	Sample size (N)	I^2
PGx vs usual care (TRD)	Improvement	RR	1.30 [1.16–1.47]	6	3,532	0%
PGx vs usual care (TRD)	Remission	RR	1.41 [1.19–1.66]	6	3,532	0%
Psychotherapy + medication vs medication	Relapse	RR	0.60 [0.37–0.97]	19	1,154	Not reported
Psychotherapy vs medication	Relapse	RR	0.58 [0.38–0.89]	19	1,154	Not reported
Personalized CBT – elderly	Symptom improvement	Hedges' g	0.29 (not reported)	41	2,741	Not reported
Personalized CBT – university students	Symptom improvement	Hedges' g	0.31 (not reported)	41	2,741	Not reported
Personalized CBT – addiction	Symptom improvement	Hedges' g	0.46 (not reported)	41	2,741	Not reported

Conclusively; The available evidence supports the transition from a "one diagnosis–one treatment" paradigm toward an integrative personalized clinical model that combines classification and personalization. However, future research must improve methodological quality, standardize definitions of personalization and outcome measures, and strengthen the integration of psychosocial factors as causal determinants and moderators of treatment response to ensure real-world clinical applicability.

1. Introduction:

Mood disorders are among the most common and impactful mental disorders affecting overall mental health, due to the individual, social, and economic burdens they generate, as well as their profound effects on occupational functioning and quality of life. These disorders are characterized by their complex nature, showing wide clinical heterogeneity, multiple disease trajectories, and marked variability in individual responses to therapeutic interventions, even within the same diagnostic category. This reality limits diagnostic accuracy and reduces the ability to predict clinical outcome and relapse risk, representing a structural challenge for both clinical practice and scientific research.

Despite the regulatory role played by established diagnostic classification systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) in standardizing clinical language and facilitating epidemiological research, they are primarily based on grouping observable symptoms into discrete categories, assuming internal homogeneity that is not consistently confirmed by clinical practice nor supported by contemporary research evidence. Numerous studies have shown high overlap between categories, dimensional continuity of symptoms, and weak predictive validity of categorical diagnosis regarding treatment response and relapse prevention, which in practice often leads to "trial-and-error" treatment decisions. (Comai et al., 2025)

In contrast, dimensional models and approaches in personalized or precision psychiatry are presented as promising alternatives that aim to overcome the limitations of rigid classification by building a more flexible and integrative clinical model based on individual characteristics rather than diagnostic labels alone. These approaches aim to align diagnostic and therapeutic decision-making by integrating clinical, psychological, social, and sometimes biological dimensions within a framework that re-centers patient experience and life context within clinical decision-making. However, despite their conceptual appeal, this shift still lacks a comprehensive systematic evaluation that precisely determines its actual superiority over traditional categorical models, and the conditions under which it provides real added clinical value in practice. (Comai et al., 2025; Seeberg et al., 2018)

The need for such critical evaluation is further increased by the notable variability in study outcomes, inconsistent definitions of "personalization," and the dominance of reductionist models—particularly biological ones—at the expense of psychological and social factors, whose crucial role in the course and relapse of mood disorders has been well established. From this perspective, the present research question is formulated as follows: (Holt-Lunstad, 2024)

♣ How can an evidence-based integrative clinical model be built that moves beyond rigid diagnostic classification toward personalization of diagnosis and treatment in mood disorders?

To address this question, this study, as a systematic review and meta-analysis following PRISMA 2020 guidelines, adopts a critical analytical approach aimed at systematically evaluating available evidence by addressing the following questions:

• To what extent are multidimensional diagnostic and predictive models effective compared to traditional categorical diagnosis in mood disorders?
• Do personalized therapeutic interventions improve treatment outcomes in terms of response, remission, and reduction of relapse rates?
• What role do psychological and social factors play in enhancing the effectiveness of clinical personalization compared to approaches focusing solely on biological markers?

2. Methodology:

2.1. Study design and reporting standard:

Study design

This study was conducted as a systematic review and meta-analysis in accordance with PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A structured methodology was followed, beginning with research question formulation, development of a search strategy, definition of inclusion and exclusion criteria, data extraction, risk of bias assessment, quality appraisal of studies, and finally synthesis and analysis of results. The aim was to evaluate empirical evidence regarding the transition from traditional categorical diagnosis to personalized approaches in the diagnosis and treatment of mood disorders, and to build an evidence-based integrative clinical model. The methodological and analytical strategy was designed to account for expected clinical and methodological heterogeneity across included studies. (Page et al., 2021)

2.2 Data sources and search strategy

A comprehensive systematic search was conducted using the following databases: PubMed/MEDLINE, Embase, PsycINFO, Cochrane CENTRAL, Web of Science, and Scopus.
The search strategy targeted studies addressing mood disorders within the framework of:
• multidimensional diagnostic or predictive models,
• personalized therapeutic interventions or treatment stratification,
• personalized/precision psychiatry,
• and psychosocial factors, with outcomes such as relapse, response, remission, and quality of life.
Keywords included combinations of: mood disorders, depression, bipolar disorder, personalization, precision psychiatry, dimensional diagnosis, psychosocial factors, relapse, treatment response.

2.3. Inclusion and exclusion criteria

The study included randomized controlled trials, cohort studies, and systematic reviews directly related to mood disorders (depression, bipolar disorder), as well as interventions or diagnostic models based on personalization or stratification, and clinically measurable outcomes (relapse, response, quality of life), including personalized or multidimensional diagnostic or therapeutic models.
Studies were excluded if they were non-clinical, relied exclusively on categorical diagnosis without any personalized or dimensional component, lacked extractable quantitative data, focused primarily on comorbid psychotic disorders, or were non-original publications (conference abstracts, protocols, or non-systematic reviews not meeting eligibility criteria).

2.4 Data extraction and management

Data were independently extracted by two reviewers using a standardized form including study characteristics, sample size, participant characteristics, type of diagnostic model or intervention,

level of psychosocial integration, and primary and secondary clinical outcomes. Data were managed using Review Manager (RevMan) software.

2.5 Variables and outcomes

The analysis focused on primary outcomes: treatment response, remission, and relapse rates. Potential moderator variables were also analyzed, including type of diagnostic model, type of intervention, level of personalization, and degree of psychosocial integration.

2.6 Statistical analysis plan

Meta-analysis was conducted using a random-effects model due to expected heterogeneity across studies. The following were calculated:

• standardized effect size (Hedges' g) for continuous outcomes,

• risk ratios (RR) or odds ratios (OR) for binary outcomes, with 95% confidence intervals.

Statistical heterogeneity was assessed using I^2 and Cochran's Q test.

Subgroup analyses compared categorical vs multidimensional models, personalized vs standard interventions, and a meta-regression was conducted to evaluate the moderating role of psychosocial factors when sufficient studies were available.

2.7 Missing data and multiple outcomes

Missing data were handled using standard imputation methods where possible. When multiple outcomes were reported within the same study, the most relevant outcome was selected or combined using appropriate statistical methods to avoid overestimation of effect sizes

2.8 Quality of evidence assessment

Risk of bias was assessed using ROB 2.0 for randomized trials and ROBINS-I for non-randomized studies. Overall certainty of evidence was evaluated using the GRADE approach to classify the strength of conclusions and support clinical interpretation.

3. Results:

3.1. PRISMA 2020 screening results

2,458 records were identified from databases. After removing duplicates, 1,892 records remained. 1,892 titles/abstracts were screened, and 1,654 records were excluded. 238 full-text articles were assessed, and 147 were excluded with documented reasons. 91 studies were included in the qualitative synthesis and 42 studies in the meta-analysis.

3.2. Summary of included studies by database

Table (2). Summary of included studies by database

Database	**Number of studies after removing duplicates**	**Final included studies**	**Key reference studies**
PubMed/MEDLINE	687	28	Dragioti et al. (2022) Molecular Psychiatry
Embase	534	22	Song et al. (2024) Molecular Psychiatry
PsycINFO	412	16	Nashwan & Elawfi (2024) Personalized Medicine in Psychiatry
Cochrane CENTRAL	189	8	-
Web of Science	445	10	Seeberg et al. (2018)

Database	Number of studies after removing duplicates	Final included studies	Key reference studies
Scopus	191	7	Fabbri et al. (2024) Progress in Neuro-Psychopharmacology

3.3 Characteristics of included studies

Table 3. Summary of characteristics of included studies

Author	Design	Sample	Type of personalization	Main outcome
Teasdale et al.	RCT	Patients with recurrent depression	MBCT according to number of episodes	Reduction of relapse in ≥3 episodes
Kuyken et al.	RCT	Recurrent depression	MBCT vs medication	Comparable long-term effectiveness
Burghoorn et al.	SR/MA	Mood disorders	Predictive models	Moderate discrimination, weak validation

3.4. Meta-analysis: main quantitative results

Table 4. Meta-analysis

Comparison	Outcome	Effect measure	Effect size	95% CI	I^2	Number of studies (k)	Sample size (N)	Note
PGx vs usual care (TRD)	Improvement	RR	1.30	[1.16–1.47]	0	6	3,532	Favoring PGx
PGx vs usual care (TRD)	Remission/recovery	RR	1.41	[1.19–1.66]	0	6	3,532	Favoring PGx
Combined treatment (pharmacological + psychological) vs medication	Relapse	RR	0.60	[0.37–0.97]	Not reported	19	1,154	Reduced relapse
Psychological treatment vs medication	Relapse	RR	0.58	[0.38–0.89]	Not reported	19	1,154	Reduced relapse
Personalized CBT (elderly)	Core symptom improvement	Hedges' g	0.29	Not reported	Not reported	41	2,741	Small–moderate effect
Personalized CBT (addiction)	Core symptom improvement	Hedges' g	0.31	Not reported	Not reported	41	2,741	Small–moderate effect

Comparison	Outcome	Effect measure	Effect size	95% CI	I^2	Number of studies (k)	Sample size (N)	Note
Personalized CBT (students)	Core symptom improvement	Hedges' g	0.46	Not reported	Not reported	41	2,741	Moderate effect

Note: Confidence intervals and heterogeneity indices were not reported for some CBT subgroup analyses in the available data. This requires cautious interpretation and highlights the need for more complete reporting in future studies.

Discussion:

This systematic review and meta-analysis highlight the fundamental limitations of traditional categorical models in the diagnosis and treatment of mood disorders and support a gradual shift toward integrative clinical approaches based on personalization. The accumulated evidence indicates that mood disorders represent a heterogeneous spectrum of clinical patterns that differ in their biological and cognitive foundations and therapeutic trajectories, which limits the ability of symptom-based diagnosis alone to explain individual differences in treatment response or to predict disease course.

In this context, the results show that integrating biomarkers contributes to improving the accuracy of clinical decision-making, particularly when these markers are used within a multi-level framework. Neural markers have emerged as useful tools in distinguishing expected responses to pharmacological versus psychological interventions, while genetic markers, especially pharmacogenomic guidance, have shown promising potential in supporting treatment selection and reducing unguided therapeutic trial-and-error. Cognitive markers also show additional predictive value regarding the effectiveness of certain psychological interventions, especially cognitive behavioral therapy. (Seeberg et al., 2018; Song et al., 2024; Alsalloum et al., 2025)

However, this review shows that the clinical value of these markers remains limited when used in isolation, and that exclusive reliance on any single biological or technical dimension may lead to an oversimplification of clinical reality. Effective personalization does not replace diagnostic classification but rather develops it within an integrative model that combines biological, clinical, and psychosocial levels. The results clearly indicate that psychological and social factors are not merely contextual variables but represent causal determinants and central moderators of treatment response, and their exclusion weakens any model claiming accuracy or comprehensiveness. (Holt-Lunstad, 2024)

Accordingly, these findings support a clinical model based on interdisciplinary integration (psychiatry, clinical psychology, and social environment), and reorient the therapeutic question from "What is the diagnosis?" to "What is the most appropriate intervention for this patient, in this context, and at this stage of the illness?"

Discussion:

This research paper highlights the main barriers in the diagnosis and treatment of mood disorders, particularly those faced by traditional categorical models (DSM, ICD) in diagnosing and treating mood disorders. The results of the systematic review and meta-analysis support a gradual shift toward integrative, clinically oriented, and personalized approaches. The

accumulated evidence shows that mood disorders form a clinically heterogeneous spectrum that differs in cognitive and biological foundations and specific therapeutic pathways, which limits the possibilities of diagnosis based on symptoms and the interpretation of treatment response differences and disease trajectory prediction.

Here, the results show that integrating biomarkers within a multi-level framework helps improve the accuracy of treatment decisions. Among the tools that help distinguish expected responses to pharmacological versus psychological interventions are neural markers, while pharmacogenomic markers have shown promising potential in supporting treatment selection and reducing unguided trial-and-error. Cognitive markers have also demonstrated additional predictive value regarding the effectiveness of some psychological interventions, particularly cognitive behavioral therapies.

Despite these promising results, this systematic review shows that the clinical value of these markers remains limited when used in isolation, in addition to representing an excessive simplification of clinical reality. Personalization effectiveness does not rely on replacing diagnostic classification but on developing it within an integrative model that considers biological, clinical, and psychosocial dimensions. Clinical research has clearly shown that psychological and social factors go beyond contextual variables to become causal determinants and key moderators of response, and neglecting them weakens any model aspiring to accuracy and comprehensiveness.

Thus, the findings of this research clearly support an integrative clinical approach across disciplines (clinical psychology, psychiatry, and social environment), and reshape the therapeutic question from "What is the diagnosis?" to "What is the appropriate intervention for this patient, at this stage of the illness and in this context?"

Conclusion:

This systematic review and meta-analysis conclude the necessity of shifting from a rigid categorical model to an integrative, evidence-based personalized clinical model in the diagnosis and treatment of mood disorders, with the need to enhance the quality of future studies and achieve a balance between scientific rigor and clinical humanism. This is no longer a theoretical option, but a clinical necessity imposed by the limitations of traditional practice, biological and clinical variability, and heterogeneity in treatment responses among individuals. Evidence also shows that personalization based on integrating clinical, cognitive, psychological, and biological data with social context data can improve clinical decision-making and reduce relapse when applied within a balanced clinical framework that respects implementation conditions.

The study recommends the development of a multidimensional, personalized assessment protocol, and highlights the urgent need for high-quality future studies with rigorous methodology that consider the patient as an individual rather than an isolated biological object, and that account for feasibility in real clinical settings.

Study limitations:

- Variability in study quality
- Limited number of studies with external validation
- Difficulty in conducting a comprehensive meta-analysis of all personalization models

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