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Personalized Medicine in Psychiatry

Challenges and Opportunities

Edited by
Gniewko Więckiewicz

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Guest Editor

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About the Editor

Gniewko Więckiewicz

Gniewko Więckiewicz is a psychiatrist and Doctor of Medical and Health Sciences affiliated with the Department of Psychiatry, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, where he serves as a research and teaching assistant and coordinator for addiction-related care. He is a member of the Polish Psychiatric Association, the World Association on Dual Disorders, and the International Society of Addiction Medicine, where he acts as an expert within the Global Expert Network (ISAM-GEN). He completed his medical degree and doctoral training at the Medical University of Silesia, with his doctoral dissertation receiving formal distinction. His academic achievements have been recognized through prestigious fellowships from the Japanese Society of Psychiatry and Neurology and the World Psychiatric Association, as well as multiple Rector's Scholarships for academic excellence.

Dr. Więckiewicz has gained clinical and research experience both in Poland and internationally, including professional training in Brazil and Spain. He is the author and co-author of numerous scientific publications in medical sciences, with research interests focused on psychoactive substances, addiction treatment, and harm reduction. His work has been published in leading international journals, widely cited, and featured in major Polish media outlets. He collaborates with researchers from prominent universities worldwide and regularly contributes as a speaker to national and international psychiatric conferences, including the World Congress of Psychiatry.

Preface

It is a particular pleasure and privilege to introduce this Reprint of the Special Issue Personalized Medicine in Psychiatry: Challenges and Opportunities. Writing these words brings a genuine sense of excitement, as this volume brings together ten important and thoughtfully curated contributions that collectively reflect the current state, complexity, and future directions of personalized psychiatric care.

Psychiatric care occupies a crucial position in the modern world. Mental disorders contribute substantially to global disease burden, affect individuals across the entire lifespan, and intersect profoundly with social, cultural, and biological dimensions of human life. Despite remarkable scientific advances, psychiatry continues to face fundamental unknowns: heterogeneity of disorders, variable treatment response, incomplete remission, and the challenge of translating innovation into real-world care. These unresolved questions make personalization not a luxury, but a necessity.

The articles assembled in this Reprint address these challenges from complementary perspectives, spanning biological stratification, symptom dynamics, psychotherapy, digital interventions, health systems, and ethical considerations. Together, they illustrate that personalized psychiatry is not defined by a single tool or technology, but by the integration of diverse forms of evidence and clinical reasoning.

This Reprint aims to serve both as a reference point and as an invitation—to continued inquiry, interdisciplinary collaboration, and thoughtful innovation—as psychiatry advances toward more precise, humane, and effective care.

Gniewko Więckiewicz
Guest Editor

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Editorial

Personalized Medicine in Psychiatry: From Promise to Practice

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1. Personalized Medicine in Psychiatry: From Promise to Practice

The aspiration to personalize psychiatric care has long accompanied the field's scientific development, yet its realization has often lagged behind advances seen in other areas of medicine [1–3]. Psychiatric disorders are heterogeneous, multifactorial, and deeply embedded in biological, psychological, social, and cultural contexts. As a result, the translation of precision and personalized medicine concepts into psychiatry has required not only technological innovation, but also conceptual shifts in how mental illness is defined, measured, and treated. This Special Issue, "Personalized Medicine in Psychiatry: Challenges and Opportunities", was conceived to capture this moment of transition: one in which psychiatry is moving beyond uniform treatment algorithms toward stratified, data-informed, and person-centered approaches.

The contributions assembled here reflect the breadth of this transformation. Together, they illustrate how personalized psychiatry is no longer anchored to a single domain—such as genetics or pharmacology—but is instead emerging from the convergence of systems neuroscience, clinical epidemiology, psychotherapeutic science, digital health, public policy, and patient experience. Rather than offering a definitive blueprint, this Special Issue provides a multidimensional snapshot of where the field currently stands, what it has learned, and what remains unresolved.

2. Rethinking Heterogeneity: From Diagnoses to Dynamic Profiles

A recurring theme across this collection is the recognition that diagnostic categories alone are insufficient to guide personalized care. Several contributions challenge the assumption that individuals who share a diagnosis necessarily share mechanisms, symptom dynamics, or treatment needs. Instead, they highlight how symptom-level architectures, residual symptom patterns, and longitudinal trajectories are more important and informative units of personalization [4,5].

Network-based and system-level approaches exemplify this shift. By modeling psychiatric symptoms as interacting systems rather than isolated outcomes, such methods reveal how different biological or contextual factors can reshape psychopathology from within. The observation that depressive symptom networks differ according to metabolic status underscores the need to integrate somatic health into psychiatric stratification (contribution 1). Fatigue, sleep, and appetite disturbances emerge not merely as secondary symptoms, but as central nodes in specific subgroups, suggesting that personalization may depend as much on physiological context as on psychiatric diagnosis (contribution 2).

Complementing this perspective, narrative and systematic reviews addressing residual symptoms and treatment resistance emphasize how incomplete remission continues to impair functioning and predict relapse. Importantly, they expose inconsistencies in how residual symptoms are defined, measured, and prioritized. These inconsistencies are not

trivial: they shape clinical decisions, research outcomes, and patient expectations. The contrast between clinician-centered endpoints and patient-valued outcomes—such as well-being, vitality, and positive affect—highlights a persistent gap that personalized medicine must bridge if it is to be clinically meaningful.

3. Treatment Resistance as a Lens on Personalization

Treatment resistance occupies a central position in discussions of personalized psychiatry, not only as a clinical challenge but also as a conceptual stress test for existing models of care [6]. Several contributions approach resistance from complementary angles, illustrating that it cannot be reduced to pharmacological failure alone.

Quantitative syntheses of psychotherapy in treatment-resistant depression demonstrate that psychological interventions retain efficacy even after multiple treatment failures, albeit with modest effect sizes and substantial heterogeneity (contribution 3). These findings reinforce the value of multimodal care while simultaneously exposing the limits of current evidence. The scarcity of trials tailored specifically to resistant populations suggests that personalization remains more aspirational than operational in this domain [7].

At the other end of the evidentiary spectrum, psychodynamically informed case analyses remind us that treatment resistance often unfolds within relational contexts (contribution 4). Patient–physician dynamics, trust, continuity, and emotional histories can decisively shape treatment adherence and outcomes. These qualitative insights challenge technologically driven visions of personalized medicine by underscoring that personalization is not solely a matter of selecting the "right" intervention, but also a matter of sustaining therapeutic relationships capable of supporting change.

Together, these perspectives suggest that treatment resistance is best understood as an emergent property of interacting biological, psychological, and interpersonal factors. Addressing it requires flexibility not only in treatment selection, but also in clinical reasoning, care structures, and expectations of recovery.

4. Expanding the Therapeutic Landscape

Personalized psychiatry also depends on expanding the range of available interventions and understanding for whom, and under what conditions, they are most effective. The contributions in this Special Issue reflect a growing openness to both novel and non-traditional approaches, while maintaining a commitment to methodological rigor and ethical responsibility.

Interdisciplinary reviews of psychedelic research exemplify this balance [8,9]. By situating psychedelics within psychological, neuroscientific, anthropological, and philosophical frameworks, such work reframes these compounds not as isolated pharmacological agents, but as catalysts of experiential and neuroplastic change. Their potential therapeutic value lies not only in symptom reduction, but also in their capacity to disrupt rigid cognitive and emotional patterns—an effect that may be particularly relevant for treatment-resistant conditions. At the same time, calls for ethical safeguards and rigorous research designs caution against premature clinical enthusiasm (contribution 5).

Non-pharmacological interventions are receiving parallel attention. Preclinical studies demonstrating that physical exercise modulates brain metabolism following chronic substance exposure provide biological grounding for lifestyle-based personalization strategies (contribution 6). Similarly, randomized trials of brief, app-based contemplative interventions reveal that digital scalability does not guarantee universal benefit (contribution 7). Instead, individual differences in stress reactivity and resilience appear to determine who gains from low-intensity interventions and who requires more intensive, personalized support.

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These findings converge on a critical insight: personalization is not only about choosing between treatments, but also about matching intervention intensity, modality, and delivery format to individual capacities for plasticity and recovery.

5. From Evidence to Implementation: Systems Matter

Even the most sophisticated personalized approaches remain aspirational if they cannot be implemented within real-world health systems. Several contributions therefore turn their attention to the infrastructural and policy dimensions of personalized psychiatry [10].

Analyses of payer coverage decisions for pharmacogenomic testing reveal that access to personalized tools is shaped less by the absence of evidence and more by how evidence is interpreted and valued (contribution 8). Real-world evidence, case series, and observational studies play a significant role in these decisions, yet their influence varies across payer types and policy contexts. This variability underscores the need for clearer standards and dialog between researchers, clinicians, and policymakers regarding what constitutes actionable evidence in personalized care.

Digital health and informatics further extend the scope of personalization from individual encounters to population-level strategies. Electronic health records, decision support systems, prescription monitoring programs, and artificial intelligence-driven analytics offer unprecedented opportunities to identify risk, guide interventions, and reduce inequities in access. At the same time, they raise questions about data quality, privacy, algorithmic bias, and the balance between automation and clinical judgment. In this sense, personalized psychiatry becomes as much a matter of governance and ethics as of innovation (contribution 9).

6. Challenges, Opportunities, and the Road Ahead

Taken together, the contributions to this Special Issue suggest that personalized medicine in psychiatry is no longer a distant horizon, but neither is it a finished paradigm. Its most promising advances arise not from any single technology or discipline, but from their integration. Biological markers, symptom networks, psychological processes, digital tools, and relational dynamics each illuminate different facets of mental illness [11]. The challenge lies in weaving these perspectives into coherent, flexible models of care.

Several priorities emerge for future research and practice. First, greater conceptual clarity is needed regarding key constructs such as residual symptoms, treatment resistance, and remission. Without shared definitions, personalization risks becoming fragmented and inconsistent. Second, stratification efforts must move beyond cross-sectional markers to incorporate longitudinal trajectories of vulnerability, resilience, and change. Third, implementation science must be elevated to the same status as discovery science, ensuring that personalized tools are accessible, equitable, and responsive to real-world constraints (contribution 10).

Finally, personalization should not be conflated with complexity for its own sake. The ultimate measure of success lies in whether personalized approaches improve outcomes that matter to patients: functioning, well-being, dignity, and sustained recovery. Achieving this goal will require not only innovation, but also humility—an openness to revising assumptions, integrating diverse forms of evidence, and centering the lived experience of those whom psychiatry seeks to serve.

This Special Issue does not the conversation on personalized medicine in psychiatry to a close; rather, it clarifies its contours and stakes. We hope it will serve as both a reference point and a catalyst, encouraging continued interdisciplinary collaboration as the field moves from promise to practice.

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Article

Mood and Metabolism: A Bayesian Network Analysis of Depressive Symptoms in Major Depressive Disorder and Metabolic Syndrome

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Abstract: Background/Objectives: Major depressive disorder (MDD) and metabolic syndrome (MetS) are highly prevalent, bidirectionally linked conditions. Individuals with MetS are at increased risk of developing depression, while depression predisposes to metabolic dysfunction. Evidence suggests that comorbid MDD and MetS present a distinct psychopathological profile, with neurovegetative symptoms such as fatigue, sleep disturbances, and appetite dysregulation being more prominent. This study aimed to determine whether depressive symptom structures differ between MDD patients with and without MetS, applying Bayesian network methods to uncover probabilistic dependencies that may inform precision psychiatry. **Methods**: Data were drawn from 1779 adults with ICD-10-diagnosed MDD in the 2013–2020 National Health and Nutrition Examination Survey (NHANES). Using standard metabolic criteria, participants were categorized as MetS (n = 315) or non-MetS (n = 1464). Depressive symptoms were assessed with the Patient Health Questionnaire (PHQ-9). Directed Acyclic Graphs (DAGs) were estimated via a hill-climbing algorithm with 5000 bootstrap replications to ensure network stability. **Results**: MetS patients displayed a denser and more interconnected symptom network. Fatigue (PHQ4) emerged as a central hub linking sleep, appetite, cognition, and functional impairment. In contrast, non-MetS patients showed a more fragmented network dominated by affective symptoms (low mood, anhedonia) and negative self-cognitions. **Conclusions**: Depressive symptoms propagate differently depending on metabolic status. These results highlight the value of personalized medicine approaches, advocating for treatment strategies that address neurovegetative dysfunctions in MDD with MetS and affective-cognitive symptoms in non-MetS. Aligning interventions with individual symptom architectures and metabolic profiles may enhance therapeutic precision and improve clinical outcomes.

Keywords: major depressive disorder; metabolic syndrome; Bayesian network analysis; directed acyclic graph

1. Introduction

Major depressive disorder (MDD) and metabolic syndrome (MetS) are interconnected conditions with a significant global health impact. MetS is estimated to affect 25% of adults worldwide and is characterized by obesity, dyslipidemia, hypertension, and insulin resistance [1]. Depression impacts over 280 million people globally, with a lifetime prevalence of up to 20% [2].

A bidirectional relationship exists between these two conditions, with individuals with MetS being 1.5 times more likely to develop depression, while depression increases the risk of MetS by 40%. Additionally, genetic predisposition for depression is associated with an increased risk of developing MetS [3].

Emerging theories suggest that depression may not be a homogeneous disorder but rather consists of distinct subtypes shaped by metabolic dysfunction. One influential framework is the concept of "metabolic depression" or "Metabolic Syndrome Type II", which posits that depressive symptoms, particularly neurovegetative symptoms such as fatigue, anhedonia, and sleep disturbances, may stem directly from underlying metabolic dysregulation [4,5]. These subtypes are characterized by specific biological profiles, such as elevated cytokine levels, increased cortisol, and insulin resistance, which may explain differences in symptom presentation and treatment response.

In this regard, clinical practice highlights how depressive episodes in patients with MetS tend to feature more pronounced neurovegetative and cognitive symptoms compared to emotional or affective symptoms alone. A recent study by Marazziti and colleagues described the "wicked relationship" between depression and MetS, emphasizing that inflammatory markers, altered platelet serotonin, and HPA-axis dysregulation form a vicious cycle of metabolic-psychiatric comorbidity [6]. Similarly, patients with recurrent MDD have been found to show significantly higher rates of MetS compared to first-episode patients, suggesting a cumulative effect of chronic depressive episodes on metabolic health [7].

In line with this evidence, research using general linear model techniques has revealed that certain depressive symptoms, specifically anhedonia and neurovegetative symptoms such as fatigue [8,9], are particularly pronounced in individuals with metabolic syndrome compared to those without. Shared mechanisms, including low-grade chronic inflammation, neuroendocrine dysregulation, and unhealthy habits (such as poor diet, sedentary lifestyle, and smoking), underline this relationship, emphasizing the importance of targeted interventions [10].

The heterogeneity in symptom profiles across individuals with depression suggests a need for more nuanced analytical methods capable of capturing the complex interplay between depressive symptoms and metabolic status. To this end, Bayesian Network Analysis (BNA) offers a flexible, data-driven framework to model conditional dependencies among symptoms. BNA uses probabilistic graphical models, specifically, directed acyclic graphs (DAGs), to infer both symptom connectivity and directional influence, thereby enabling a more refined exploration of comorbidity structures [11,12].

BNA is particularly suited for this research context because it facilitates the identification of central nodes—or "hub" symptoms—that may act as bridges between emotional, cognitive, and somatic dimensions of depression.

The clinical relevance of this approach is profound. By distinguishing the structural organization of symptoms in patients with and without MetS, BNA can inform precision psychiatry—tailoring interventions based on a patient's specific symptom profile and underlying biological state [13,14].

Given this backdrop, the present study applies Bayesian network techniques to map and compare depressive symptom structures in MDD patients with and without metabolic syndrome, using nationally representative data from the NHANES cohort. We aim to iden-

tify divergent pathways and central symptom hubs to guide targeted, mechanism-based interventions for individuals experiencing comorbid psychiatric and metabolic conditions.

2. Materials and Methods

2.1. Participants, Procedures, and Measures

The present study used publicly available data from the National Health and Nutrition Examination Survey (NHANES), a large-scale, cross-sectional program conducted by the U.S. Centers for Disease Control and Prevention [15]. NHANES integrates comprehensive interviews, physical examinations, and laboratory data to provide a reliable picture of health and disease prevalence across the United States. The strength of this dataset lies in its standardized methodology and the diversity of the sampled population, which enhances the generalizability of findings.

For our analysis, we selected data from four NHANES cycles, spanning the years 2013–2014 through 2017–2020. These cycles were chosen due to the consistent inclusion of key variables relevant to both MDD and MetS. Specifically, the dataset included detailed information on demographic characteristics, physical parameters (such as waist circumference and blood pressure), laboratory values (including fasting glucose, HDL, LDL, and triglycerides), and mental health indicators, most notably the Patient Health Questionnaire (PHQ-9), a widely used screening tool for depressive symptoms [16].

To identify individuals affected by MDD, we focused on participants who were both taking psychotropic medications and had been assigned diagnostic codes consistent with major depressive disorder. More precisely, we included individuals associated with ICD-10 codes F32.9 (Major depressive disorder, single episode, unspecified) and F33.9 (Major depressive disorder, recurrent, unspecified). Additionally, individuals had to complete the PHQ-9 and have available metabolic data.

The diagnosis of metabolic syndrome followed established clinical criteria, consistent with guidelines from the American Heart Association and the International Diabetes Federation [17]. A participant was classified as having MetS if at least three of the following five criteria were met: elevated waist circumference ($\geq$102 cm in men or $\geq$88 cm in women), high triglyceride levels ($\geq$150 mg/dL), low HDL cholesterol (<40 mg/dL in men or <50 mg/dL in women), elevated blood pressure (systolic $\geq$ 130 mmHg or diastolic $\geq$ 80 mmHg), and impaired fasting glucose ($\geq$100 mg/dL). These thresholds align with standard definitions used in epidemiological and clinical studies, ensuring compatibility with previous findings in the field.

By combining both psychiatric and metabolic criteria, we were able to extract a subset of participants who presented with MDD, with or without concurrent metabolic syndrome. Individuals with incomplete data or with conditions potentially confounding the depressive phenotype—such as schizophrenia, bipolar disorder, or psychosis—were excluded from the analysis to ensure sample homogeneity.

2.2. Statistical Analysis

We first described the sample using classical univariate statistics (Table 1). For continuous variables such as age, weight, or PHQ-9 scores, we calculated means and standard deviations. For categorical variables like sex or medication status, frequencies and proportions were reported. To compare the MetS and non-MetS groups, we employed Student's *t*-tests for continuous data and chi-square tests for categorical data. These comparisons allowed us to identify any significant demographic or clinical differences between the two subpopulations and to quantify these differences using effect sizes such as Cohen's d and odds ratios, where appropriate.

Table 1. Sample characteristics.

Characteristic	MetS $n = 315$ [1]	Non-MetS $n = 1464$ [1]	Effect Size [2]
Gender			
Female	207 (66%)	991 (68%)	0.91
Male	108 (34%)	473 (32%)	
Age	54.902 (13.877)	53.389 (16.219)	0.095
Weight (kg)	97.023 (23.011)	87.198 (24.670)	0.402 ***
Waist circumference (cm)	113.984 (15.114)	105.225 (18.059)	0.498 ***
Body Mass Index (kg/m^2)	34.891 (7.782)	31.878 (8.503)	0.359 ***
Blood Pressure			
Systolic	128.671 (20.101)	123.456 (17.429)	0.290 ***
Diastolic	73.967 (14.136)	71.271 (11.900)	0.218 ***
Fasting Glucose (mg/dL)	134.025 (53.143)	107.407 (33.795)	0.635 ***
Triglyceride (mg/dL)	192.397 (101.430)	96.338 (50.621)	1.303 ***
Direct HDL-Cholesterol (mg/dL)	43.914 (12.172)	55.397 (16.678)	−0.720 ***
PHQ1 (*Little interest in doing things*)	1.098 (1.062)	1.083 (1.051)	0.014
PHQ2 (*Feeling down, depressed, or hopeless*)	1.219 (1.120)	1.209 (1.062)	0.009
PHQ3 (*Trouble sleeping or sleeping too much*)	1.584 (1.095)	1.374 (1.157)	0.183 **
PHQ4 (*Feeling tired or having little energy*)	1.733 (0.970)	1.633 (1.023)	0.098
PHQ5 (*Poor appetite or overeating*)	1.171 (1.092)	1.036 (1.122)	0.121 *
PHQ6 (*Feeling bad about yourself*)	0.943 (1.196)	0.850 (1.026)	0.088
PHQ7 (*Trouble concentrating on things*)	0.940 (1.111)	0.864 (1.079)	0.069
PHQ8 (*Moving or speaking slowly or too fast*)	0.552 (0.990)	0.479 (0.886)	0.081
PHQ9 (*Thought you would be better off dead*)	0.222 (0.664)	0.241 (0.627)	−0.029
PHQ10 (*Difficulty these problems have caused*)	0.848 (0.935)	0.796 (0.878)	0.057
PHQ Total Score	9.463 (5.857)	8.769 (5.800)	0.119 *

[1] *n* (%); Mean (SD). [2] Cohen's d is used for continuous variables; Odds Ratio is used for categorical variables. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; MetS = Metabolic Syndrome; PHQ = Patient Health Questionnaire.

The core of our analytical strategy centered on exploring the internal structure of depressive symptoms using BNA. This method, grounded in probabilistic graphical modeling, is particularly suited to uncovering complex interdependencies between symptoms. Unlike traditional regression models, which often assume that individual symptoms are independent contributors to a latent disorder, BNA treats symptoms as nodes in a network and allows for direct modeling of their conditional relationships.

To construct these networks, we represented the nine PHQ-9 items plus a tenth expressing a functional outcome ("*Difficulty these problems have caused*") as nodes within a Directed Acyclic Graph (DAG). Edges, or connections, between nodes indicated a statistical dependency between symptoms, with the direction of the arrow representing the potential influence from one symptom to another. The structure of the DAG was determined using a hill-climbing algorithm, a heuristic optimization technique that searches for the most plausible network by minimizing the Bayesian Information Criterion (BIC). The BIC offers a balance between model complexity and goodness-of-fit, thus avoiding overfitting [12].

To ensure the stability and replicability of the inferred network structures, we applied a robust bootstrap procedure consisting of 5000 iterations. This resampling technique

generated multiple versions of the data, allowing us to assess how consistently each edge appeared across different samples. Only the most stable connections were retained in the final graphs. Specifically, connections that appeared in at least 85% of bootstrapped networks were considered strong enough to be included, while the direction of the connection had to be consistent in at least 50% of replications to be visualized as a directed edge.

Visualizations of the resulting networks were produced to enhance interpretability. In these figures, the thickness of each edge was proportional to its strength—meaning the statistical contribution of that connection to the overall model. Stronger edges indicated that removing the connection would significantly impair the fit of the model. This approach enabled us to not only detect which symptoms were central within each population's depressive network but also to infer possible causal sequences among them.

All statistical computations were performed in R (version 4.3.2), an open-source environment widely used for data analysis and visualization. Data preparation and manipulation were conducted using the *tidyverse* package suite (version 2.0) [18]. The Bayesian networks themselves were estimated using the *bnlearn* package (version 4.9.4), a well-established tool for learning and visualizing probabilistic graphical models [11].

By employing these advanced analytical techniques, we aimed to uncover the unique ways in which depressive symptoms organize and interact in individuals with and without metabolic syndrome.

3. Results

3.1. Participants

From an initial dataset of 60,432 individuals included across four NHANES survey cycles, a total of 1779 participants met the inclusion criteria for this study. All selected individuals had a documented diagnosis of Major Depressive Disorder (MDD), as defined by ICD-10 diagnostic codes (F32.9 or F33.9), and provided complete data on PHQ-9, metabolic biomarkers, and relevant physical parameters.

Within this sample, 315 participants fulfilled the diagnostic criteria for MetS, as outlined by AHA/IDF guidelines. The remaining 1464 participants did not meet the criteria for MetS and thus constituted the comparison group.

Demographic and clinical characteristics of both groups are summarized in Table 1. As expected, individuals in the MetS group had higher body weight, larger waist circumference, elevated blood pressure, higher fasting glucose and triglyceride levels, and lower HDL cholesterol. Importantly, significant differences also emerged in depressive symptomatology between the two groups.

Specifically, individuals with MDD and concurrent MetS reported higher total PHQ-9 scores, reflecting greater overall depressive burden. Upon inspection of individual symptom items, item 3 ("Trouble falling or staying asleep, or sleeping too much") and item 5 ("Poor appetite or overeating") were significantly elevated in the MetS group, suggesting a more pronounced expression of neurovegetative symptoms in this population. However, although a statistical difference was reported, all effect size measures were low-modest (not higher than 0.2); fittingly, they have not been considered in the discussion.

3.2. Bayesian Network Analysis—Directed Acyclic Graphs (DAGs)

The resulting DAGs revealed different patterns of symptom interconnectivity between the two populations. In the MetS group, the depressive symptom network appeared densely interconnected, with multiple conditional dependencies linking affective, cognitive, and somatic domains. A particularly interesting pathway began with PHQ2 ("*Feeling down, depressed, or hopeless*"), which was connected to PHQ1 ("*Little interest or pleasure in doing things*") with a moderate arc strength of −42.72. This connection may reflect the

classic depressive dyad of low mood and anhedonia. From there, PHQ1 linked directly to PHQ4 ("*Feeling tired or having little energy*") with an arc strength of −38.37, suggesting that neurovegetative fatigue might follow or co-occur with emotional symptoms.

PHQ4 then emerged as a central hub, radiating outward to a number of other symptoms. It was connected to PHQ3 (sleep disturbances, arc strength = −29.12), PHQ5 (appetite dysregulation, arc strength = −28.47), and PHQ10 (perceived functional impairment, arc strength = −25.76). These connections suggest that fatigue not only reflects core biological disruptions but may also mediate links between mood symptoms and day-to-day functioning. Interestingly, the item expressing appetite changes was further connected to PHQ7 ("*Trouble concentrating*"), with a smaller but still notable arc strength of −21.21, pointing to a potential cascade from somatic to cognitive symptoms in the context of metabolic dysfunction.

In contrast, the network observed in the non-MetS population was sparser and more fragmented, indicating fewer strong conditional dependencies between symptoms. The first was between PHQ1 and PHQ2—anhedonia and depressed mood—with a much stronger arc strength of −266.07, suggesting that these two emotional symptoms are tightly coupled in individuals without metabolic comorbidity. The second strong connection was between PHQ6 ("*Feeling bad about yourself*") and PHQ9 ("*Thoughts that you would be better off dead*"), with an arc strength of −166.78. This pathway appears to reflect a more cognitive-affective dimension of depression, centered around self-worth and suicidality.

The full list of arc strengths, as well as detailed network statistics and bootstrapping metrics, can be found in Tables 2 and 3. Visualizations of the resulting DAGs are provided in Figure 1, where edge thickness is scaled according to arc strength, offering an intuitive representation of central and peripheral nodes in each network.

Table 2. Arc Strength in the Depressed Population *with* Metabolic Syndrome.

From	To	Strength
PHQ1	*PHQ4*	−38.3712
PHQ2	*PHQ1*	−42.7230
PHQ2	*PHQ6*	−38.7644
PHQ2	*PHQ9*	−20.4625
PHQ3	*PHQ7*	−9.5678
PHQ4	*PHQ3*	−29.1284
PHQ4	*PHQ5*	−28.4721
PHQ4	*PHQ10*	−25.7662
PHQ5	*PHQ6*	−9.1726
PHQ5	*PHQ7*	−21.2129
PHQ10	*PHQ8*	−22.1705

Label: PHQ—Patient Health Questionnaire.

Table 3. Arc Strength in the Depressed Population *without* Metabolic Syndrome.

From	To	Strength
PHQ1	*PHQ2*	−266.075336
PHQ1	*PHQ4*	−58.303795
PHQ1	*PHQ6*	−41.475119
PHQ1	*PHQ10*	−37.837109
PHQ2	*PHQ3*	−23.761115
PHQ2	*PHQ6*	−73.165437
PHQ2	*PHQ7*	−17.234737
PHQ2	*PHQ10*	−12.176333

Table 3. *Cont.*

From	To	Strength
PHQ3	*PHQ5*	−14.913171
PHQ4	*PHQ3*	−82.394517
PHQ4	*PHQ5*	−38.399162
PHQ6	*PHQ4*	−9.286942
PHQ6	*PHQ7*	−24.434691
PHQ6	*PHQ8*	−33.507499
PHQ6	*PHQ9*	−166.782370
PHQ6	*PHQ10*	−50.954734
PHQ7	*PHQ5*	−28.141069
PHQ7	*PHQ8*	−68.776081
PHQ8	*PHQ3*	−11.217882
PHQ10	*PHQ4*	−22.107131
PHQ10	*PHQ7*	−80.191290

Label: PHQ—Patient Health Questionnaire.

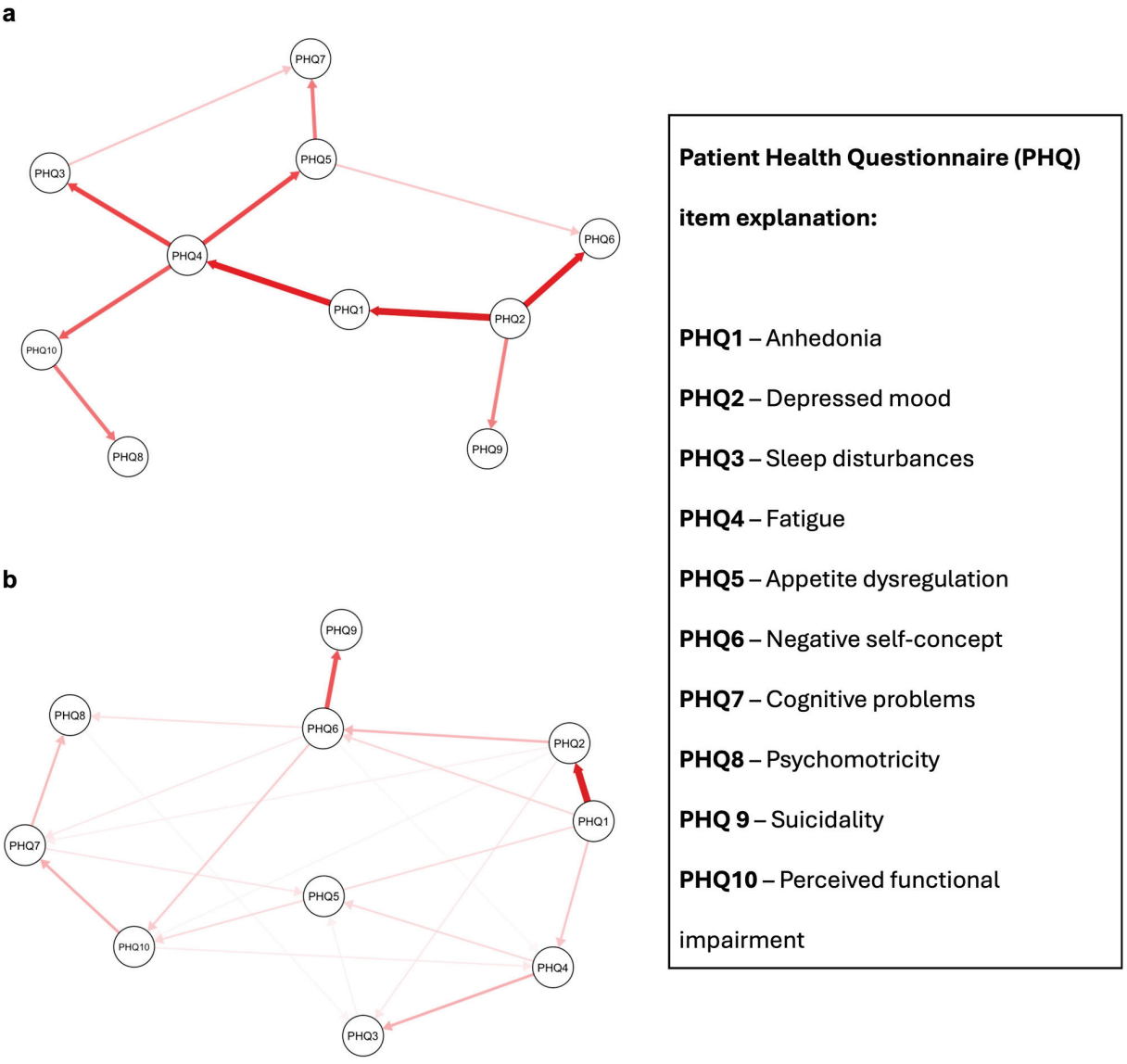

Figure 1. Proposed Directed Acyclic Graphs (DAGs) for depressed patients *with* and *without* metabolic syndrome. Red arrows indicate a causal relationship. Arrow shade refers to arc strength, with more

intense colors indicating higher relative importance of each edge in the network. Panel (**a**): depressed patients *with* metabolic syndrome. Panel (**b**): depressed patients *without* metabolic syndrome; PHQ = Patient Health Questionnaire.

4. Discussion

The findings of this study provide novel insights into the differential structure of depressive symptomatology in individuals with and without MetS. Leveraging Bayesian network analysis, we demonstrated that individuals with both MDD and MetS exhibit a denser, more interconnected symptom structure, particularly centered around neurovegetative symptoms such as fatigue, sleep disturbance, and appetite dysregulation. In contrast, those with MDD but without MetS display a sparser network, with symptom associations primarily concentrated in affective and cognitive domains.

This structural divergence reflects broader pathophysiological differences that may underlie these two subpopulations. Our findings align with recent Mendelian randomization research by Zhang et al., which showed a causal effect of genetically predicted depression on the risk of developing MetS and several of its components, including waist circumference, hypertension, and dyslipidemia [10]. These findings strengthen the evidence that depression is not merely comorbid with MetS but may actively contribute to its pathogenesis, highlighting the role of depression as a metabolic disruptor.

In individuals with MetS, our analysis revealed that fatigue (PHQ4) occupies a central node in the symptom network, forming strong connections with sleep disturbances (PHQ3), appetite changes (PHQ5), and functional impairment (PHQ10). Fatigue has been recognized as a hallmark feature in the overlap between metabolic and depressive pathology. Mechanistically, it may reflect systemic inflammation, mitochondrial dysfunction, and insulin resistance—core features of both disorders [3]. Studies suggest that chronic low-grade inflammation, particularly elevated interleukin-6 and C-reactive protein levels, may mediate both depressive fatigue and metabolic abnormalities [19].

Further supporting this interpretation is the growing body of literature on "immunometabolic depression"—a subtype of depression marked by prominent neurovegetative symptoms and inflammatory dysregulation [20]. Individuals with this phenotype often display elevated triglycerides, central adiposity, and insulin resistance, all consistent with the clinical characteristics observed in our MetS subgroup.

Interestingly, the connection between appetite disturbances (PHQ5) and cognitive symptoms (PHQ7) in the MetS group adds a novel perspective. This relationship may suggest that metabolic disruptions impact not only somatic domains but also executive function and attentional control. Metabolic dysfunction, especially insulin resistance and elevated inflammatory markers, has been linked to impaired cognitive flexibility and working memory in depressed patients [21,22]. These findings may explain the PHQ5–PHQ7 edge in our DAG, where changes in eating behavior—either as a symptom or consequence of metabolic imbalance—could influence cognitive efficiency.

In contrast, among MDD patients without MetS, symptom pathways appeared more linear and affective in nature. Strong associations were observed between core depressive symptoms such as anhedonia (PHQ1) and depressed mood (PHQ2), as well as between feelings of worthlessness (PHQ6) and suicidal ideation (PHQ9). This pattern reflects what has traditionally been considered the "classic" presentation of depression, where emotional pain and self-referential negative thoughts dominate the clinical picture. These findings also echo cognitive models of depression, which emphasize the role of maladaptive core beliefs and negative attribution styles [23].

The divergent structures in the two networks offer compelling support for the conceptualization of depression not as a monolithic disorder, but rather as a heterogeneous

syndrome composed of various overlapping subtypes. The neurovegetative-dominant profile observed in MDD with MetS supports the existence of biologically driven phenotypes that may not respond adequately to standard psychotherapeutic or antidepressant-based interventions. In fact, accumulating evidence indicates that these patients may benefit more from lifestyle modifications, anti-inflammatory agents, or metabolically neutral antidepressants [24,25].

From a clinical perspective, the identification of fatigue (PHQ4) as a central hub symptom in the MetS group holds significant implications as it may foster, similarly to other psychiatric conditions, tailored strategic interventions [26–28]. Fatigue's role as both an outcome and driver of depressive and metabolic symptoms suggests it may serve as a strategic target for intervention. Behavioral interventions such as aerobic exercise have been shown to reduce systemic inflammation and improve energy levels in this population [29]. Similarly, anti-inflammatory pharmacotherapies and dietary interventions such as the Mediterranean diet have demonstrated promise in reducing depressive symptoms in metabolically at-risk individuals [30,31].

Moreover, the increased connectivity in the symptom network of MetS patients suggests that interventions targeting one domain (e.g., fatigue or sleep) may exert downstream effects on a broader constellation of symptoms, potentially yielding a higher treatment payoff. This contrasts with the more fragmented symptom network in non-MetS patients, where symptom-focused treatments may need to be more targeted and psychologically oriented.

The use of Bayesian network analysis in this context offers distinct advantages. Traditional statistical approaches often assume symptom independence or linearity, potentially obscuring the rich interdependencies among symptoms. BNA allows us to model the probabilistic relationships between symptoms, capturing both directionality and strength of influence. In doing so, it provides a more nuanced picture of how depressive symptoms evolve and interact in differing metabolic contexts. This methodology is especially relevant in the age of precision psychiatry, where the goal is not only to diagnose but to tailor interventions based on individual symptom architecture [11,12].

Our findings also offer potential predictive value. For example, in patients with elevated metabolic markers but no current depressive diagnosis, early monitoring of fatigue and sleep disruptions may serve as early warning signs for the development of full-syndrome depression. Conversely, in patients already diagnosed with depression, identifying metabolic risk factors could inform prognosis and treatment selection.

However, although our findings rely on a large sample size, several limitations must be considered. The cross-sectional nature of our dataset precludes definitive conclusions about the causal relationships between depressive symptoms. Although DAGs allow for the inference of potential causal structures, longitudinal data are required to confirm symptom trajectories over time. Furthermore, while our DAG models were statistically robust and bootstrapped over 5000 iterations, external validation in independent datasets is necessary to confirm generalizability. Concerning BNA, DAGs can reveal conditional dependencies among symptoms. However, they cannot determine whether depression + MetS reflects (i) a distinct subtype of MDD characterized by a unique network structure, or (ii) the coexistence of two overlapping conditions, such as somatic symptoms driven by MetS superimposed on depressive symptoms. Second, depressive symptoms were assessed exclusively through the PHQ-9. Although this instrument is widely validated and commonly employed in epidemiological research, its reliance on self-report introduces potential sources of measurement bias. Factors such as social desirability, recall inaccuracies, or cultural differences in symptom expression may have influenced responses. Moreover, self-reported questionnaires may underestimate or overestimate the severity of symptoms in populations with cognitive impairment, alexithymia, or limited health literacy—conditions

that are relatively frequent among individuals with metabolic syndrome. Regarding network analysis, we must also acknowledge that a few PHQ9 items are made of a combination of symptoms (e.g., insomnia/hypersomnia or anorexia/hyperphagia, etc.), which warrants extra care when interpreting the findings. This issue might be overcome if such nodes are considered with a generic interpretation rather than a specific symptom (e.g., sleeping problems or appetite changes).

Future works may also consider directly incorporating biomarkers (e.g., CRP, IL-6, HOMA-IR) into the network to map how biological factors interact with symptom pathways. Network studies modelling psychometric measures together with laboratory analytes might help to uncover the multifaceted mechanisms that link clinical presentation and inflammatory dysregulation [32,33]. In addition to network analysis, other statistical approaches may be valuable in investigating the association between depression and MetS. For example, factor analysis could be used to distinguish latent dimensions such as "somatic" and "anhedonia" factors, which could be regressed on MetS-related features. Alternatively, biclustering methods could simultaneously group patients and symptoms to uncover enriched symptom patterns specific to the depression–MetS comorbidity.

Another promising direction is to integrate neuroimaging findings into symptom networks, particularly given that fronto-limbic connectivity has been shown to differ between melancholic and atypical depression subtypes, which may overlap with MetS-related profiles [34].

5. Conclusions

In conclusion, this study provides a detailed examination of how depressive symptoms organize differently in individuals with and without MetS, offering a unique contribution to the growing literature on the heterogeneity of depression. By applying BNA, we were able to move beyond traditional categorical or dimensional approaches and to highlight distinct symptom architectures. The denser, neurovegetative-centered network observed in the MetS group underscores the profound influence of metabolic dysfunction on the manifestation and persistence of depressive symptoms. Fatigue, sleep disturbances, and appetite dysregulation emerged as central nodes in this group, suggesting that energy dysregulation and somatic symptoms may serve as key drivers of depression when metabolic abnormalities are present. In contrast, the more affective and fragmented symptom structure identified in the non-MetS group aligns more closely with traditional cognitive-affective models of depression, where low mood, anhedonia, and self-referential negative cognitions dominate the clinical presentation.

At a research level, this study underscores the need for longitudinal and integrative designs. Future work should confirm whether the symptom dependencies identified here remain stable across time and whether targeting central nodes like fatigue can alter downstream symptom trajectories. Incorporating biological markers—such as inflammatory cytokines, cortisol rhythms, or measures of insulin sensitivity—into network models will provide an even more mechanistic understanding of the pathways that link depression and MetS. Furthermore, given the strong bidirectional relationship between these conditions, it will be critical to study whether improvements in metabolic health translate into structural changes in depressive symptom networks, and vice versa [3,22].

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Patient Life Engagement and Metabolic Profile Improve After Switching from First-/Second-Generation Antipsychotics to Brexpiprazole: A Real-World Study in Patients with Schizophrenia

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Abstract: Background: Schizophrenia is a chronic disorder requiring long-term pharmacological treatment. Many patients experience inadequate response and adverse effects, often leading to poor adherence and need for antipsychotic switch or polypharmacotherapy. In this context, brexpiprazole, an atypical antipsychotic with favorable tolerability profile, may offer clinical benefits following previous treatment failure or intolerance. However, real-world evidence after treatment switch remains limited. **Methods**: This retrospective, observational study included 50 outpatients with schizophrenia switched to brexpiprazole (2–4 mg/day) via cross-titration and evaluated over 12 weeks. Primary outcomes were changes in *Patient Life Engagement*, assessed through a 14-item subset of the Positive and Negative Syndrome Scale (PANSS), along with response/remission rates. Secondary outcomes included changes in subjective well-being, quality of life, sexual functioning (based on Subjective Well-being under Neuroleptics—Short Form [SWN-S], WHO-5 Well-Being Index [WHO-5], and Arizona Sexual Experience Scale [ASEX] scores, respectively), metabolic parameters, and prolactin levels. **Results**: Life engagement improved significantly ($p < 0.001$) across all domains, and clinical response was achieved in 40% of patients. Significant improvements were observed in SWN-S and WHO-5 scores (both $p < 0.001$). Weight and BMI significantly decreased (–2.64 kg, $p = 0.013$, and –0.91 kg/m^2, $p = 0.006$, respectively). Numerical non-significant reductions were found in ASEX ($p = 0.067$) and prolactin levels (–30.7 ng/mL, $p = 0.077$). Overall, treatment was well-tolerated. **Conclusions**: Switching to brexpiprazole was associated with improvements in psychopathological, functional, and physical health domains. These findings support its potential role in real-world, personalized therapeutic strategies for patients with schizophrenia following suboptimal outcomes with prior antipsychotic treatments.

Keywords: psychosis; brexpiprazole; pharmacological switch; life engagement; personalized medicine

1. Introduction

Schizophrenia is a severe, chronic disorder with an estimated lifetime prevalence of 0.5–1% worldwide and a substantial burden in terms of individual suffering, functional disability, and societal costs [1]. According to recent estimates, schizophrenia ranks among the top 15 leading causes of disability [2] and is associated with a reduced life expectancy

of 15 to 25 years, mainly due to comorbid medical conditions [3,4] and lifestyle factors, such as poor diet, smoking, and reduced physical activity [5,6].

Although antipsychotic medications are the cornerstone of treatment for schizophrenia, their clinical effectiveness is often limited to the reduction in positive symptoms, such as hallucinations and delusions [7]. Negative symptoms (e.g., anhedonia, apathy, avolition, and social withdrawal) and cognitive dysfunctions tend to be more treatment-resistant and represent critical barriers to functional recovery and satisfactory quality of life [8,9]. Moreover, approximately 20–30% of patients fail to respond adequately to a first-line antipsychotic trial and may require long-term polypharmacotherapy [10,11], which is often complicated by adverse effects with impaired adherence and quality of life [12,13].

In this context, switching antipsychotic treatment represents a common and often necessary strategy, typically driven by suboptimal treatment response, the emergence of adverse effects or adherence issues [10]. Lack of efficacy and poor tolerability emerge as the most frequent reasons for change, albeit with some sex-specific differences [14]. Within the range of switching strategies described in the literature, cross-titration and, particularly, the plateau method (i.e., delayed tapering of the previous antipsychotic until the new one has reached a therapeutic level) have been identified as the preferred approach to mitigate withdrawal, rebound, or dopaminergic destabilization, especially when transitioning from full D2-receptor antagonists to partial agonists [15].

Brexpiprazole is a dopamine–serotonin partial agonist [16] that combines antipsychotic efficacy with a favorable tolerability profile, including a lower incidence of extrapyramidal symptoms, metabolic disturbances, sedation, and hyperprolactinemia [7,17,18]. These characteristics, along with its flexible dosing schedule [19], make it a potential candidate for personalized treatment strategies, particularly in patients with comorbidities or suboptimal response to previous antipsychotic regimens [20–23]. Although the overall antipsychotic effectiveness is comparable to that of other atypical antipsychotics used for schizophrenia [21], treatment with brexpiprazole has been associated with lower rates of therapeutic discontinuation and fewer symptom exacerbations in clinical practice, with improved adherence and quality of life [24]. Indeed, post hoc analyses and real-world studies suggest that brexpiprazole may exert beneficial effects on domains often under-addressed by conventional antipsychotics, including subjective well-being and life engagement—a multidimensional construct encompassing emotional, cognitive, social, and physical functioning [25,26]. Life engagement has emerged as a relevant outcome reflecting patients' life-fulfillment, participation in meaningful activities, and social interactions, with potential implications for functional recovery and quality of life [27].

Nevertheless, despite its favorable clinical profile, real-world data on brexpiprazole's effectiveness and safety after switching from other antipsychotics remain limited and warrant further investigation. Therefore, this real-world, observational study retrospectively investigates the effects of switching from first-/second-generation antipsychotics to brexpiprazole in patients with schizophrenia. The primary aim was to evaluate the effects of a three-month treatment on psychotic symptoms, focusing on *Patient Life Engagement*, intended as a proxy of patients' active and meaningful involvement in daily life. Changes in sexual functioning, well-being and subjective experience with treatment, as well as the adherence and the overall safety/tolerability profile of brexpiprazole, were also evaluated.

2. Materials and Methods

2.1. Participants

Patients who had been consecutively referred to the Department of Psychiatry at Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS in Rome, between January 2019 and June 2023, with a primary diagnosis of schizophrenia according to DSM-5

criteria [28] were retrospectively screened for inclusion. Eligible participants were outpatients of both sexes who had been receiving maintenance treatment with a first- or second-generation antipsychotic at an adequate dosage for an appropriate duration, and who had subsequently been switched to flexible doses of brexpiprazole (2–4 mg/day) due to partial response and/or tolerability issues, in accordance with the locally approved Summary of Product Characteristics and relevant clinical guidelines [15,19]. Additional inclusion criteria were age between 18 and 65 years and presence of clinically relevant psychotic symptoms at baseline, as indicated by total scores on the Positive and Negative Syndrome Scale (PANSS) prior to the antipsychotic switch [29].

All patients were converted from previous antipsychotic(s) to brexpiprazole monotherapy through a gradual cross-titration over four weeks [15,30]. Specifically, brexpiprazole was administered orally once daily starting at 1 mg/day, increased to 2 mg/day after seven days and, eventually, it was further increased up to the maximum dosage according to clinicians' judgment, while the previous antipsychotic was gradually decreased using the 25% x week rule and discontinued within four weeks. Concomitantly, continuous psychosocial support was provided. The concurrent use of other psychotropic medications (e.g., anticonvulsants/mood stabilizers, antidepressants, anxiolytics/sedative-hypnotics) was permitted as long as these were not modified throughout the observation period. Exclusion criteria were: the use of any other antipsychotic agents during the study period; neurological disorders associated with cognitive impairment (e.g., intellectual disability, and all forms of dementia, including Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson's disease-related dementia, and post-traumatic brain injury); current abuse of alcohol or other psychotropic substances (except for tobacco use). By contrast, the lifetime presence of a substance use disorder was not considered an exclusion criterion.

Anonymity was guaranteed to all participants who provided a written informed consent before inclusion. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board's 'Comitato Etico Territoriale (CET) Lazio area 3' of Rome, Italy, on 14 December 2023 with protocol code 6222.

2.2. Procedures and Assessment

Patients' clinical records were consulted to retrieve sociodemographic (age, gender, educational level, occupation, marital status) and clinical information (body weight, Body Mass Index [BMI], prolactin levels, fasting glucose and lipid profile, smoking habits, history of family psychiatric illness, medical and psychiatric comorbidities, age at onset of schizophrenia, psychiatric hospitalizations, previous antipsychotic drug and class, other current psychopharmacological treatment). Clinical and psychometric data were extracted from charts according to visits regularly performed during the routine clinical practice, i.e., at first assessment (baseline) and at different timepoints, after four and twelve weeks (endpoint).

The primary outcome was the evaluation of psychotic symptoms using the Patient Life Engagement (PLE) score. Unlike the traditional PANSS subscales (i.e., positive, negative, and general psychopathology) that primarily focus on symptom dimensions, the PLE score is a composite measure derived from selected items of the PANSS that provides a multidimensional assessment of patients' engagement with daily life. It encompasses four core domains and offers a more integrated perspective on how psychotic symptoms affect everyday functioning and initiative. Specifically, it comprises 14 PANSS items grouped into cognitive (P2, conceptual disorganization; N5, difficulty in abstract thinking; N7, stereotyped thinking; G11, poor attention; G15, preoccupation), emotional (N1, blunted affect; N2, emotional withdrawal; G6, depression), social (N3, poor rapport; N4, passive/apathetic

social withdrawal; N6, lack of spontaneity and flow of conversation; G16, active social avoidance) and physical (G7, motor retardation; G13, disturbance of volition) domains.

These items were selected based on previous factor-analytic and clinical work aimed at isolating those symptoms most indicative of a patient's capacity to engage meaningfully with their internal and external environment [25,31]. For all PLE domains and total scores, higher values indicate greater symptom severity and poorer life engagement. In our sample, internal consistency of the 14 PANSS items composing the PLE was evaluated at baseline and good reliability was detected (Cronbach's α = 0.848; McDonald's ω = 0.868). Skewness values for individual items ranged between –0.76 and +0.63 (SE = 0.34), confirming approximate normality and excluding floor or ceiling effects.

At the endpoint, patients were classified as responders if they achieved a $\geq$40% reduction in the total PANSS score from baseline, a threshold representing a clinically meaningful improvement beyond minimal ($\geq$20%) or moderate ($\geq$30%) change, as previously validated [32,33]. Remission was defined as a score of $\leq$3 (mild severity or less) on each of the following items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), N1 (blunted affect), N4 (passive/apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), G5 (mannerisms and posturing), and G9 (unusual thought content) [34,35]. Given that the conventional definition requires symptom stability for $\geq$6 months, and that assessments in this study were conducted over 12 weeks, remission was accordingly classified as "early remission". PANSS and PLE ratings were performed by psychiatrists with at least five years of clinical experience and inter-rater consistency was ensured through weekly consensus meetings.

Secondary outcome measures were investigated at the same time-points through the Italian versions of the following self-report questionnaires: the Arizona Sexual Experience Scale (ASEX), a five-item instrument assessing sexual functioning across domains such as drive, arousal, and satisfaction with a total score cut-off $\geq$ 19 conventionally used for significant dysfunction [36,37]; the Subjective Well-being under Neuroleptic Scale (SWN-S), which evaluates patients' perceived well-being during antipsychotic treatment, including emotional regulation, self-control, and mental functioning [38]; and the 5-item World Health Organization Well-Being Index (WHO-5), a brief measure of overall psychological well-being and quality of life [39], with total scores of $\leq$13 and >13 indicating, respectively, poor and good well-being, and a $\geq$10-point increase from baseline representing a clinically meaningful improvement [40].

Safety and tolerability of brexpiprazole were confirmed by physical examination, measurement of body weight and vital signs, routine laboratory and instrumental clinical tests, and patients' reports of any adverse events, as recorded in clinical charts.

2.3. Statistical Analysis

Descriptive data were summarized as the number of patients and percentage (%) or mean and standard deviation (M $\pm$ SD). The outcome measures—defined as mean changes from baseline to 1 and 3 months for each efficacy variable—were analyzed using repeated measures analysis of variance (ANOVA), with time as the within-subjects factor. Age, gender, and psychiatric comorbidity were included as between-subjects covariates to adjust for potential confounding effects. Assumptions of repeated-measures ANOVA were checked: normality of residuals was verified graphically, and sphericity was tested with Mauchly's test; when the assumption of sphericity was violated, Greenhouse–Geisser corrections were applied. When the main effect of time was statistically significant, pairwise comparisons between time points were conducted with Bonferroni correction for multiple testing. Effect sizes were reported using partial eta squared (η^2). Beyond Bonferroni correction for within-outcome pairwise comparisons, multiplicity across primary and

secondary endpoints was controlled using the Benjamini–Hochberg false discovery rate (FDR) procedure (q = 0.05). For each outcome, standardized effect sizes (Cohen's d) with 95% confidence intervals were calculated for baseline-to-endpoint changes to quantify the magnitude of improvement.

Sensitivity to clinical change in the primary outcome measure (i.e., PLE) was assessed by computing paired-sample Cohen's d for baseline-to-endpoint differences, showing large effect sizes for both total (d = 3.61) and domain scores (cognitive d = 3.48; emotional d = 2.78; social d = 2.72; physical d = 1.97). Convergent validity between PLE and scales capturing subjective well-being and quality of life, conceptually related to life engagement (i.e., SWN-S and WHO-5), was tested through Pearson's correlations, which revealed significant baseline associations between PLE and SWN-S (r = –0.37, $p = 0.009$), but not with WHO-5 (r = –0.15, $p = 0.31$).

For clinical parameters (i.e., body weight, BMI, prolactin levels, fasting glucose, total cholesterol, high-density [HDL], and low-density [LDL] lipoproteins), changes from baseline to endpoint were tested using paired samples t-tests or Wilcoxon Signed Ranks Tests, according to data distribution. Post hoc exploratory analyses were performed to evaluate the potential impact of prior antipsychotic class (stratified as prolactin-elevating vs. non-prolactin-elevating profile and high vs. low/neutral metabolic liability) and concomitant psychotropic medications on specific outcomes (i.e., PLE/PANSS, ASEX, weight/BMI and prolactin levels). Between-group comparisons were conducted using repeated-measures ANOVAs with 'Time × Group' interactions (for PLE, PANSS and ASEX) and independent-samples t-tests (for Δ weight, BMI, prolactin).

Analyses were performed on all patients with at least one valid post-baseline assessment of the variables (full-analysis set, FAS). A significance level of 0.05 was used for each test. All analyses were conducted using IBM SPSS Statistics for Windows, v. 28.0.

3. Results

One hundred and sixteen patients referred for schizophrenia were screened for enrollment and, after removing those who did not fulfill the inclusion criteria (n = 32), presented missing data in their medical charts (n = 20), or refused to participate (n = 14), a total of 50 Caucasian subjects who switched to brexpiprazole from previous antipsychotic treatments were included. Of them, 17 (34%) were switched due to partial response, 24 (48%) due to adverse effects, and 9 (18%) due to both reasons. The mean brexpiprazole dose was 3.04 ± 0.71 mg/day. Demographic, clinical, and psychometric characteristics at baseline are summarized in Table 1.

Table 1. Sociodemographic and clinical characteristics at baseline.

Characteristics (n, %; M ± SD)	
Overall	50
Sociodemographic	
Age (years)	41.5 ± 15.1
Gender	
Male	30 (60)
Female	20 (40)
Educational level (years)	15 ± 3.06
Occupation	
Employed	34 (68.7)
Unemployed	16 (31.3)
Marital status	
Married	12 (23.5)
Unmarried	38 (76.5)
Clinical	

Table 1. *Cont.*

Characteristics (n, %; M ± SD)	
Smoking habits (yes)	30 (60)
Medical comorbidities (yes)	14 (28)
Weight (kg)	81.5 ± 17.6
BMI (kg/m^2)	25.7 ± 4.34
Prolactin (ng/mL)	33.2 ± 23.3
Glucose (mg/dL)	83.0 ± 7.0
Cholesterol (mg/dL)	213.2 ± 68.7
HDL (mg/dL)	56.8 ± 17.7
LDL (mg/dL)	138.2 ± 57.0
Family psychiatric history (yes)	33 (66.7)
Age at onset (years)	27.9 ± 10.9
Psychiatric hospitalizations (yes)	17 (34.5)
Previous antipsychotic drug	
Amisulpride	3 (6)
Aripiprazole	11 (22)
Asenapine	1 (2)
Clozapine	1 (2)
Haloperidol	3 (6)
Lurasidone	4 (8)
Olanzapine	19 (38)
Paliperidone	1 (2)
Quetiapine	3 (6)
Risperidone	4 (8)
Previous antipsychotic class	
Prolactin-elevating	11 (22)
Non-prolactin-elevating	39 (78)
High metabolic liability	23 (46)
Low/Neutral metabolic liability	27 (54)
Other psychopharmacotherapy (yes)	40 (80)
Antidepressants	26 (52.4)
Anticonvulsants/Mood stabilizers	27 (53.5)
Sedative-hypnotics/Anxiolytics	27 (54.8)
Psychometric	
PLE	58.5 ± 7.26
Cognitive	20.5 ± 2.43
Emotional	13.6 ± 1.98
Physical	7.96 ± 1.52
Social	16.5 ± 2.92
ASEX	20.8 ± 3.74
SWN-S	77.1 ± 6.59
WHO-5	9.54 ± 2.47

Abbreviations: ASEX, Arizona Sexual Experience Scale; BMI, Body Mass Index; M, mean; PLE, Patient Life Engagement score; SD, Standard Deviation; SWN-S, Subjective Well-being under Neuroleptic Scale; WHO-5, World Health Organization-Five Well-Being Index.

The following psychiatric comorbidities were identified in 36.7% of the sample: major depressive episodes (63.3%), anxiety disorders (18.2%), eating disorders (9.1%), and adult attention-deficit/hyperactivity disorder (9.1%). In addition, substance use disorders in current remission were detected in 46.4% of participants, specifically: polysubstance use 46.2%, cocaine 23.1%, alcohol 15.4%, and cannabinoids 15.3%.

At baseline, PANSS scores were 120 ± 11.2 for the total, 25.1 ± 4.75, 29.7 ± 4.07 and 65.7 ± 6.76, respectively, for 'positive', 'negative' and 'general psychopathology' subscales. At the endpoint, data were available for 40 subjects with all dropouts occurring after the first month (drop-out rate: 20%, n = 10, 95% CI: 11.2–33.0). According to available clinical records, none of these cases reflected pharmacological discontinuation due to inefficacy or adverse effects and were attributed to non-clinical reasons.

Changes in psychotic symptoms expressed as mean PLE total and domains scores are reported in Table 2.

Table 2. Changes in *Patient Life Engagement* scores at different time-points by age, gender and psychiatric comorbidity as covariates (ANOVA).

PLE Cognitive	**F**	***p***	**η^2p**
Within-Subjects Effects			
Time	10.82	**<0.001**	0.07
Time * Age	0.29	0.752	0.002
Time * Gender	3.95	**0.029**	0.026
Time * Psychiatric Comorbidity	0.41	0.672	0.003
Between-Subjects Effects			
Age	4.88	**0.042**	0.072
Gender	0.69	0.419	0.010
Psychiatric Comorbidity	0.53	0.478	0.008
Emotional	F	*p*	η^2p
Within-Subjects Effects			
Time	7.49	**0.008**	0.028
Time * Age	0.82	0.451	0.004
Time * Gender	0.53	0.592	0.003
Time * Psychiatric Comorbidity	0.46	0.633	0.002
Between-Subjects Effects			
Age	0.12	0.731	0.002
Gender	1.49	0.239	0.027
Psychiatric Comorbidity	0.01	0.927	0.000
Physical	F	*p*	η^2p
Within-Subjects Effects			
Time	3.47	**0.043**	0.039
Time * Age	0.49	0.616	0.005
Time * Gender	0.06	0.943	0.001
Time * Psychiatric Comorbidity	0.16	0.856	0.002
Between-Subjects Effects			
Age	0.93	0.349	0.014
Gender	0.01	0.910	0.003
Psychiatric Comorbidity	1.31	0.270	0.020
Social	F	*p*	η^2p
Within-Subjects Effects			
Time	5.84	**0.007**	0.042
Time * Age	0.25	0.779	0.002

Table 2. *Cont.*

Time * Gender	1.06	0.359	0.008
Time * Psychiatric Comorbidity	0.63	0.538	0.005
Between-Subjects Effects			
Age	0.13	0.722	0.002
Gender	0.34	0.567	0.006
Psychiatric Comorbidity	0.41	0.534	0.007
Total	F	*p*	η^2p
Within-Subjects Effects			
Time	9.45	**<0.001**	0.06
Time * Age	0.53	0.594	0.003
Time * Gender	1.41	0.258	0.009
Time * Psychiatric Comorbidity	0.09	0.912	0.001
Between-Subjects Effects			
Age	0.04	0.839	0.001
Gender	0.11	0.742	0.002
Psychiatric Comorbidity	1.18	0.294	0.020

Significant results in **bold**. Abbreviations: η^2p, partial eta-squared; ANOVA, Repeated Measures Analysis of Variance; F, between- and within-group ratio; *p*, statistical significance; PLE, Patient Life Engagement.

Given the statistically significant 'Time × Gender' interaction observed for the cognitive PLE domain ($p = 0.029$), a supplementary analysis examined gender differences in symptom trajectories across timepoints. Estimated marginal means revealed that female patients reported greater impairment in cognitive life engagement at baseline (21.7, 95% CI: 19.99–23.4) compared to males (18.9, 95% CI: 17.58–20.3). Both groups showed substantial improvements at a one-month follow-up (females: 16.7, 95% CI: 14.87–18.6 vs. males: 15.8, 95% CI: 14.34–17.3), with final scores converging at the endpoint (11.1, 95% CI: 9.42–12.7 in females; 11.3, 95% CI: 10.04–12.6 in males).

Changes in psychotic symptoms expressed as mean PANSS scores, evaluated after one and three months of treatment, are reported in Figure 1. Reductions at each timepoint were significant after Bonferroni correction ($p < 0.001$) and were the following for the 'positive', 'negative', 'general psychopathology' and total scores, respectively: 20.0 ± 0.89, 25.1 ± 0.85, 54.6 ± 1.53, 99.7 ± 2.44 after one month; 14.4 ± 1.12, 17.6 ± 1.07, 39.7 ± 1.94, 71.6 ± 3.81 at three months. None of the covariates displayed a significant interaction with symptomatic changes over time. At the endpoint, 40% of patients met response criteria defined as a $\geq$40% reduction in PANSS total score (95% CI: 27.6–53.8), 22% (95% CI: 12.8–35.2) achieved early remission, while the proportion of non-responders was 18% (95% CI: 9.8–30.8).

Exploratory analyses according to prior antipsychotic class observed a significant 'Time × Group' interaction for the PANSS total score ($p = 0.036$), indicating greater improvement among patients switched from prolactin-elevating compounds (endpoint marginal means: 63.3, 95% CI: 55.2–71.5) compared to those from non-elevating drugs (77.3, 95% CI: 72.5–82.0). A similar pattern emerged for the PLE total score ($p = 0.008$), with greater reduction (=improvement) in the prolactin-elevating group (30.2, 95% CI: 23.2–37.2) vs. the non-elevating group (34.4, 95% CI: 31.4–37.5). A modest effect was also detected by metabolic liability ($p = 0.046$), with slightly lower PLE total scores (=better) in patients switched from high-risk agents (32.9, 95% CI: 27.9–38.0) compared to low-risk agents (34.2, 95% CI: 30.8–37.6). No significant 'Time × Group' interactions were found for concomitant

medications. However, endpoint scores were slightly lower (=better) among mood stabilizer users for PLE (32.0 vs. 35.9; $p = 0.006$) and among antidepressant users for PANSS (70.3 vs. 79.6; $p = 0.044$).

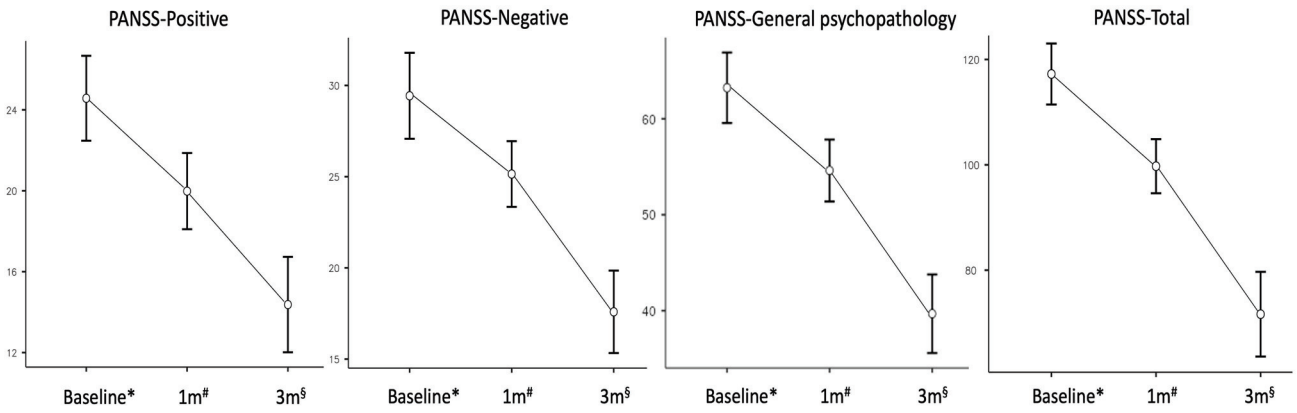

Figure 1. Changes in mean Positive and Negative Syndrome Scale scores with standard errors at different timepoints (ANOVA). Abbreviations: 1 m, one month follow-up; 3 m, three months follow-up; ANOVA, Repeated Measures Analysis of Variance; PANSS, Positive and Negative Syndrome Scale; sample size at * baseline n = 50, # one month n = 50, § endpoint n = 40.

Improvements from baseline to endpoint were also observed in all secondary outcome measures (i.e., ASEX, SWN-S, and WHO-5 scales) and are reported in Table 3. At baseline, 74% of patients were above the ASEX threshold suggestive of sexual dysfunction, which lowered to 58% at one month and to 32.3% at three months. According to the WHO-5 cut-off, the proportion of patients above the 'good well-being' threshold was only 4% at baseline, which increased to 25% at one month and to 96.8% at three months, while 25.8% achieved a $\geq$10-point improvement from baseline to endpoint.

Given the significant main effect of 'Gender' on ASEX scores, a supplementary analysis to estimate sex-stratified marginal means showed that female patients reported higher ASEX scores at baseline (23.1, 95% CI: 20.3–25.9) compared to males (19.6, 95% CI: 17.4–21.8). This pattern persisted at one month (females: 21.0, 95% CI: 18.7–23.4 vs. males: 18.2, 95% CI: 16.4–20.1) and three months (females: 19.6, 95% CI: 17.2–21.9 vs. males: 16.7, 95% CI: 14.8–18.5), despite general improvement over time in both groups.

Mean values (SD) at baseline, after one and three months of treatment for both primary and secondary outcome measures are reported in Supplementary Table S1. All improvements remained significant after controlling for multiple comparisons using the Benjamini–Hochberg false discovery rate ($q \leq 0.012$ across 12 endpoints). Effect sizes were consistently large for both primary (PLE and PANSS) and secondary (ASEX, SWN-S, WHO-5) outcomes, supporting the robustness and clinical relevance of the observed changes (see Supplementary Table S2 for d values and 95% CIs).

Mean changes (SE) from baseline to endpoint observed in laboratory parameters were −2.64 (0.91) for weight [t = −2.9; $p = 0.013$], −0.91 (0.27) for BMI [t = −3.37; $p = 0.006$], and −30.7 (11.6) for prolactin levels [t = −2.65; $p = 0.077$]. Further exploratory analyses showed no significant differences in weight, BMI, or prolactin changes based on prior treatment class or concomitant medications (all $p > 0.10$). No significant changes were observed at endpoint in fasting glucose [−2.57 (3.65), t = −0.71, $p = 0.508$], total cholesterol [−1.5 (6.48), t = −0.23, $p = 0.826$], HDL [0.5 (3.69), t = 0.13, $p = 0.898$], and LDL [−0.67 (2.58), t = −0.26, $p = 0.806$], suggesting a metabolically neutral profile over the 12-week period.

Table 3. Changes in sexual functioning, subjective well-being, and quality of life at different time-points by age, gender and psychiatric comorbidity as covariates (ANOVA).

ASEX	**F**	***p***	**η^2p**
Within-Subjects Effects			
Time	2.95	0.067	0.006
Time * Age	0.29	0.766	0.001
Time * Gender	0.381	0.686	0.001
Time * Psychiatric Comorbidity	0.351	0.707	0.002
Between-Subjects Effects			
Age	2.55	0.130	0.043
Gender	6.19	**0.024**	0.105
Psychiatric Comorbidity	0.01	0.947	0.000
SWN-S	F	*p*	η^2p
Within-Subjects Effects			
Time	11.43	**<0.001**	0.108
Time * Age	0.05	0.949	0.000
Time * Gender	0.47	0.629	0.004
Time * Psychiatric Comorbidity	1.58	0.222	0.015
Between-Subjects Effects			
Age	0.51	0.485	0.008
Gender	0.02	0.896	0.000
Psychiatric Comorbidity	0.72	0.412	0.011
WHO-5	F	*p*	η^2p
Within-Subjects Effects			
Time	24.32	**<0.001**	0.079
Time * Age	0.324	0.725	0.001
Time * Gender	0.253	0.778	0.001
Time * Psychiatric Comorbidity	1.202	0.314	0.004
Between-Subjects Effects			
Age	0.01	0.695	0.003
Gender	0.05	0.831	0.001
Psychiatric Comorbidity	1.85	0.191	0.024

Significant results in **bold**. Abbreviations: η^2p, partial eta-squared; ANOVA, Repeated Measures Analysis of Variance; ASEX, Arizona Sexual Experience Scale; F, between- and within-group ratio; *p*, statistical significance; SWN-S, Subjective Well-being under Neuroleptic Scale; WHO-5, World Health Organization-Five Well-Being Index.

A minority of patients (n = 5, 10%) reported mild side effects (i.e., akathisia, dizziness/drowsiness) within the first month of treatment that gradually disappeared over time and did not lead to treatment discontinuation in any case.

4. Discussion

In this real-world, observational study, the switch to brexpiprazole in patients with schizophrenia who had previously been treated with first- or second-generation antipsychotics was associated with improvements in both clinical and functional outcomes over the 12-week follow-up. Notably, Patient Life Engagement (PLE) significantly improved across cognitive, emotional, social, and physical domains, reflecting a broader recovery in dimensions crucial to daily functioning and autonomy. These changes were paralleled by enhanced subjective well-being and quality of life, with a trend toward improvement in sexual functioning and an overall favorable safety profile.

Life engagement refers to the degree to which individuals are actively involved in meaningful activities and social roles that support their sense of identity, purpose, and well-being [25,26]. In schizophrenia, these domains are frequently impaired due to the interplay of negative symptoms, cognitive deficits, and social dysfunctions—factors that are closely linked to reduced functional capacity, lower quality of life, and poor long-term outcomes, even when positive symptoms remit [3,8,9]. Although symptom-focused scales, such as the PANSS, remain fundamental in the clinical assessment of schizophrenia, they may not adequately capture domains related to recovery and reintegration [32,33,35]. Conversely, constructs such as PLE provide a complementary framework to traditional psychopathological evaluations by encompassing subjective well-being and functional restoration. This perspective aligns with modern paradigms of patient-centered and recovery-oriented care [41–43]. Recent studies have employed PANSS-derived proxies to operationalize PLE in schizophrenia, supporting the preliminary validity of this approach and emphasizing the increasing focus on outcomes that are personally meaningful to patients [25].

The effects of brexpiprazole on PLE, particularly in the cognitive and social domains, may reflect its distinct pharmacodynamic profile [21,24]. Unlike other compounds with a predominant dopaminergic activity, brexpiprazole exerts a partial agonism at dopamine D2 and serotonin 5-HT1A receptors, and an antagonism at serotonin 5-HT2A and noradrenergic receptors. Its mechanism of action may support executive functioning and attention regulation, as well as mood stabilization and motivational drive, potentially reflecting a reduction in negative symptom burden—typically less responsive to standard antipsychotic treatment [17,44]. Exploratory analyses suggested a greater magnitude of cognitive improvement among female patients who appeared to benefit more markedly in life-engagement–related cognitive functioning, although endpoint values were comparable with males. While this effect should be interpreted cautiously, given the post hoc nature of the analysis and warrants further investigation, it may reflect gender-related differences in baseline functioning or treatment responsiveness, as reported in prior literature [45].

The pharmacodynamic profile of brexpiprazole can provide a plausible explanation for the observed improvements in life engagement, but alternative interpretations cannot be excluded. Cognitive gains may partly reflect regression to the mean or relief from residual sedation and anticholinergic burden associated with prior treatments. Social improvements could also derive from the alleviation of adverse effects that interfere with interpersonal functioning (e.g., extrapyramidal symptoms, sexual side effects), or from non-specific factors such as enhanced clinical monitoring and support during treatment transition. Accordingly, favorable changes in patient-reported outcomes were detected with improvements in subjective well-being across both the SWN-S and WHO-5 scales, which are increasingly used to assess emotional and functional recovery [38].

Notably, the present study is among the few naturalistic investigations to employ a validated self-rated scale to assess sexual functioning in patients with schizophrenia [36]. Although the overall reduction in ASEX scores did not reach statistical significance, the

data show a potential trend toward improved sexual functioning. Additionally, female patients reported persistently higher ASEX scores, suggesting a greater burden of sexual dysfunction despite overall improvements. This exploratory observation is consistent with existing literature highlighting gender differences in the subjective experience and reporting of sexual side effects during antipsychotic treatment [46] and underscores the importance of gender-sensitive monitoring in clinical practice. Indeed, depending on the pharmacological profile and individual characteristics, sexual dysfunctions can affect up to 80% of patients treated with antipsychotics and are strongly associated with reduced quality of life and poor treatment adherence [47,48]. Nevertheless, they remain underreported and overlooked in clinical trials that generally lack systematic use of specific assessment tools. Moreover, recent expert consensus highlights that, in the context of functional recovery, improvements in domains such as depression and social interaction are often prioritized over others, including leisure and sexual functioning, by both clinicians and patients [49], thus partially explaining why sexual health is not consistently addressed in routine assessments.

In parallel, a trend-level reduction in serum prolactin concentration was observed. Given the well-established association between hyperprolactinemia and sexual dysfunction—including decreased libido, erectile and orgasmic difficulties, amenorrhea, and bone demineralization—these findings, although preliminary, hold clinical relevance [50]. Prolactin elevation is commonly induced by dopamine D2 receptor antagonism in the tuberoinfundibular pathway, which disrupts tonic inhibition of anterior pituitary secretion [51]. Brexpiprazole's partial agonism at these receptors, combined with its low intrinsic activity, may preserve dopaminergic tone and, thus, attenuate prolactin elevation [52]. Additionally, its negligible affinity for serotonergic receptors involved in prolactin release likely contributes to a favorable endocrine profile [53]. These pharmacodynamic features offer a plausible mechanistic explanation for the observed trends in both sexual and endocrine parameters, supporting the need for further investigation.

The present findings also support the overall metabolic neutrality of brexpiprazole. Reductions in weight and BMI following the switch are encouraging, considering that metabolic syndrome is a major contributor to excess mortality in schizophrenia [54]. While antipsychotic-induced metabolic disturbances are well documented, recent metabolomic and epidemiological analyses emphasize that such abnormalities in schizophrenia stem from complex interactions between genetic predisposition, environmental exposures, and disease-specific mechanisms [55,56]. Further, there is growing recognition of an intrinsic vulnerability to metabolic dysregulation in patients with schizophrenia, independent of pharmacologic exposure [3,4]. Evidence from drug-naive, first-episode patients reveals elevated prevalence of insulin resistance, dyslipidemia, and visceral adiposity, suggesting shared pathophysiological pathways involving inflammation, hypothalamic–pituitary–adrenal axis disruption, and mitochondrial alterations [22,23,57]. In this context, brexpiprazole's limited affinity for histaminergic and muscarinic receptors may underlie its lower metabolic liability, in line with prior prospective studies and meta-analyses highlighting the relative metabolic neutrality of D2 partial agonists [13]. Furthermore, in our cohort, improvements in psychotic and engagement-related symptoms appeared to be more pronounced among patients previously treated with prolactin-elevating antipsychotics, whereas changes in metabolic and endocrine parameters were largely independent of prior treatment class. This pattern may suggest that brexpiprazole's partial agonism at dopamine D_2 receptors not only mitigates hyperprolactinemia but may also potentially support global functioning in patients transitioning from potent antagonists.

Approximately one-third of patients in our sample achieved early symptomatic remission, while nearly half met the response threshold based on standard PANSS-derived

cut-offs [34]. These results are consistent with those reported in randomized controlled trials and real-world studies evaluating second-generation antipsychotics [11,33,35]. The efficacy profile of brexpiprazole appears broadly comparable to that of other antipsychotic agents examined in large-scale meta-analyses, particularly about symptom control and global functioning [7,18,44]. Nevertheless, our findings are encouraging given the naturalistic design and the inclusion of patients with partial response or poor tolerability to previous treatments. It is plausible that the observed response pattern may also reflect brexpiprazole's effectiveness in individuals with complex clinical presentations including psychiatric comorbidities, because of its multimodal receptor activity that combines antipsychotic efficacy with mood-stabilizing and anxiolytic properties [20,21]. Indeed, prior switching studies have demonstrated the feasibility and clinical benefit of transitioning to brexpiprazole, supporting its use in flexible and individualized therapeutic strategies [15]. Notably, no differential trajectories were observed according to concomitant use of antidepressants or mood stabilizers, supporting the robustness and generalizability of treatment effects across common co-therapy regimens.

Finally, although adverse events were recorded narratively based on clinical observation and patient reports without the administration of standardized rating scales for extrapyramidal symptoms or akathisia, brexpiprazole exhibited a favorable tolerability profile with minimal reports of sedation, akathisia, or extrapyramidal symptoms. This finding aligns with previous safety data and supports its suitability for long-term use, particularly in patients at risk of poor adherence due to adverse effects [16,48]. Considering the well-established association between tolerability and adherence [10], this aspect is of central importance in real-world effectiveness. Brexpiprazole's safety profile is further corroborated by its pharmacodynamic characteristics and by comparative analyses indicating superior tolerability among dopamine partial agonists [17,24,58]. Collectively, these findings support brexpiprazole as a viable treatment option for patients requiring improved balance between tolerability and efficacy. Further, although clozapine remains the gold standard for treatment-resistant cases of schizophrenia, augmentation or switching strategies are often required, and growing evidence, albeit limited, highlights the potential role of third-generation antipsychotics, including brexpiprazole, also in similar contexts [59–61].

Several limitations warrant consideration in this study. The retrospective and monocentric design, the relatively short follow-up duration of 12 weeks, the small sample size, and the absence of a control group may limit the interpretation of treatment effects. In addition, the clinical heterogeneity of prior antipsychotic exposure may have influenced outcomes and prevented comparisons between pharmacologically similar subgroups. However, exploratory subgroup and sensitivity analyses accounting for prior antipsychotic class and concomitant medications supported the robustness of the main findings, suggesting that improvements in PANSS and PLE were not merely attributable to withdrawal from previous treatments and appeared consistent across common co-therapy regimens. The sample also consisted exclusively of Caucasian patients, further limiting ethnic diversity. Another methodological limitation concerns the use of repeated-measures ANOVA rather than linear mixed-effects models, which represent the optimal analytic approach in the presence of attrition. However, in our dataset, drop-outs did not differ from completers at baseline, and sensitivity analyses (per-protocol and last-observation-carried-forward) confirmed the robustness of the primary results, mitigating concerns about attrition bias. Taken together, these aspects may constrain the external validity of the results. Nevertheless, the real-world nature of treatment decisions enhances their relevance, and future research including more diverse populations, longer follow-up periods, and controlled study designs will be essential to confirm and extend the generalizability of our findings.

Despite these aspects, the study offers several strengths. It is among the first to adopt a proxy measure of Patient Life Engagement, derived from PANSS items, alongside conventional PANSS-based response and remission criteria. The inclusion of sexual functioning evaluation through a validated self-report instrument, seldom used in naturalistic switch studies, further contributes to the originality of the work. The integration of clinical, functional, and patient-reported outcomes provides a broad and clinically relevant perspective on brexpiprazole's effects following antipsychotic switching.

5. Conclusions

Schizophrenia is a chronic and disabling psychiatric disorder often marked by persistent negative symptoms, cognitive deficits and social dysfunction, which substantially impact long-term functioning and quality of life, even in individuals achieving remission of positive symptoms [5,8]. Optimizing the balance between efficacy, tolerability, and functional recovery remains a core therapeutic goal [9].

In this real-world study, switching to brexpiprazole from other antipsychotics was associated with improvements in both psychopathological symptoms and patient-centered outcomes, like patient life engagement and subjective well-being. Metabolic parameters such as weight and BMI also showed favorable changes, alongside a trend toward reduced prolactin levels. The treatment was generally well tolerated, with a low incidence of adverse effects. Although sexual functioning did not significantly improve, a positive trend was noted, reinforcing the importance of addressing this often-neglected aspect of care. In conclusion, these findings support brexpiprazole as a treatment option for individuals requiring optimization of antipsychotic regimens and prioritizing improved tolerability and attention to patient-centered outcomes. The use of a proxy measure for life engagement, combined with standardized clinical criteria and validated self-report instruments, provides an integrated and complementary perspective on treatment response. Future, prospective research with longer follow-up and broader functional evaluations is needed to confirm and extend these results within personalized care strategies for schizophrenia.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jpm15110502/s1, Table S1: Values of primary and secondary outcome measures at different time-points; Table S2: Baseline-endpoint changes and standardized effect sizes for all outcomes.

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Review

The Role of Psychedelics in Contemporary Psychological and Interdisciplinary Inquiry

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Abstract: Psychedelic compounds are gaining renewed attention across disciplines for their profound psychological and neurobiological effects. Emerging research highlights their efficacy in treating mood disorders, PTSD, and addiction by enhancing neuroplasticity and disrupting maladaptive cognitive patterns. From a psychological standpoint, psychedelics facilitate introspection, emotional processing, and therapeutic breakthroughs. Neuroscientific findings reveal altered brain network dynamics, while anthropological and philosophical perspectives contextualize their cultural and existential significance. In medicine, they offer novel interventions for chronic pain and palliative care. The present review article underscores the need for rigorous, ethically grounded research to explore psychedelics' potential in reshaping mental health paradigms and cognitive science from a multidisciplinary perspective.

Keywords: psychedelics; interdisciplinary; anthropology; philosophy; palliative care

1. Introduction: The Psychedelic Renaissance

In recent decades, the field of psychedelic research has experienced a resurgence, often referred to as the "psychedelic renaissance". After decades of prohibition and stigmatization, substances such as psilocybin, LSD, MDMA, and ayahuasca are once again being explored for their therapeutic and scientific potential [1]. This renewed interest is grounded in both historical context and contemporary necessity. During the mid-20th century, psychedelics' potential in treating mental health conditions was investigated by researchers [2]. However, by the late 1960s, political and cultural backlash led to their criminalization and the suspension of nearly all clinical research. For over three decades, scientific engagement with these substances was minimal, with exceptions largely confined to anthropological or countercultural discourse [3].

The contemporary revival began gaining momentum in the early 2000s, driven by advances in neuroimaging technologies, shifting societal attitudes toward mental health, and an increasing body of anecdotal and historical evidence supporting the therapeutic use of psychedelics [4]. Institutions such as Johns Hopkins University, Imperial College London, and the Multidisciplinary Association for Psychedelic Studies (MAPS) have played central roles in legitimizing and advancing psychedelic science. As mental health crises escalate globally, with depression, anxiety, post-traumatic stress disorder (PTSD), and substance use disorders affecting millions, conventional pharmacotherapies often fall short in providing sustained relief [5]. Psychedelics offer a fresh perspective by targeting not only biochemical imbalances but also deeply ingrained cognitive and emotional patterns [6].

The renaissance is further fueled by a multidisciplinary approach. Neuroscientists investigate the effects of psychedelics on brain networks and neuroplasticity [7]. Psychologists

explore the substances' capacity to facilitate emotional processing and self-awareness [8]. Anthropologists and historians contextualize traditional uses in Indigenous rituals, offering insights into long-standing cultural practices [9]. Philosophers and ethicists examine the existential dimensions of psychedelic experiences, questioning notions of consciousness, identity, and healing [10]. This integrative perspective has redefined psychedelics not as mere recreational tools or dangerous substances but as potent instruments for inquiry and intervention.

Moreover, the technological and cultural landscapes of the 21st century have created a fertile ground for the revival of psychedelic science. Digital platforms and social media have amplified anecdotal reports and facilitated community-building among advocates, therapists, and researchers. At the same time, mental health professionals increasingly recognize the limitations of current treatments, particularly in resistant cases. This confluence of scientific innovation and cultural openness has established psychedelics as a promising frontier in both medicine and consciousness studies.

Nevertheless, the field remains in a formative stage, necessitating rigorous, ethically grounded research to confirm early findings and guide safe, effective applications. Regulatory frameworks are evolving, with some regions decriminalizing or legalizing psychedelic-assisted therapy [11], while others maintain strict prohibitions. The psychedelic renaissance is not only a scientific and medical movement but also a cultural and philosophical shift, one that reimagines the boundaries of mental health care and human experience.

2. Neurobiological Mechanisms of Psychedelic Action

Understanding the neurobiological mechanisms of psychedelics is essential for elucidating their therapeutic potential. Psychedelic compounds, particularly classic serotonergic psychedelics such as psilocybin, LSD, and DMT, primarily act as agonists at the 5-HT2A receptor, a subtype of the serotonin receptor system [12]. Husain suggests that this interaction triggers a series of changes that alter typical neural activity and enhance communication between separate areas of the brain. One of the most consistently observed phenomena is the temporary downregulation of the default mode network (DMN), a brain system associated with self-referential thought, rumination, and ego maintenance [13]. Hyperactivity within the DMN has been linked to various psychopathologies, including depression and anxiety [14]. Psychedelic-induced suppression of the DMN is thought to facilitate ego dissolution and a subsequent reduction in rigid, maladaptive cognitive patterns [15].

Another key neurobiological effect of psychedelics is the enhancement of neuroplasticity [16]. Preclinical studies in animal models have demonstrated that psychedelics can promote the growth of dendritic spines, synaptogenesis, and increased expression of brain-derived neurotrophic factor (BDNF) [17]. These changes suggest that psychedelics not only alter brain activity acutely but also promote long-term restructuring of neural circuits, which may underpin their enduring therapeutic effects. Human neuroimaging studies using fMRI and PET scans have corroborated these findings, showing increased global connectivity and decreased modular segregation within the brain [18].

The neurochemical effects of psychedelics also extend beyond serotonin receptors. Compounds like MDMA primarily act on serotonin transporters, leading to a surge in extracellular serotonin, as well as effects on dopamine and norepinephrine systems [19]. This pharmacological profile accounts for MDMA's empathogenic and prosocial properties, which are particularly useful in the treatment of PTSD and relational trauma [20]. Meanwhile, ketamine, a dissociative anesthetic with psychedelic-like properties, acts as an NMDA receptor antagonist and has been shown to induce rapid antidepressant effects through glutamatergic pathways and downstream mTOR signaling [21].

Importantly, these neurobiological changes do not occur in a vacuum. The phenomenology of the psychedelic experience, characterized by perceptual distortions, emotional breakthroughs, and mystical-type experiences, is deeply intertwined with its therapeutic outcomes [22]. Current theories propose that the brain under psychedelics enters a state of heightened entropy or "criticality", enabling flexible cognitive and emotional reorganization [23]. This aligns with the Relaxed Beliefs Under Psychedelics model (REBUS), which remains a hypothesis and posits that psychedelics reduce the precision of high-level priors in the brain's predictive coding hierarchy, allowing for novel interpretations and experiences [24].

Emerging research has begun to explore individual variability in response to psychedelics based on genetic, neurobiological, and psychological traits. For example, differences in 5-HT2A receptor density, baseline DMN activity, or levels of trait openness may influence the intensity and quality of psychedelic experiences [25]. This line of inquiry is critical for developing personalized therapeutic strategies that maximize benefits while minimizing risks.

Animal studies have also shed light on the molecular pathways activated by psychedelics, revealing interactions with inflammatory markers and epigenetic regulators [26]. These findings open new avenues for understanding how psychedelics might modulate not only neural circuitry but also systemic physiological processes [27]. For instance, some evidence suggests that psychedelics may reduce markers of neuroinflammation, potentially contributing to their antidepressant effects [28].

As research advances, understanding the complex neurobiological mechanisms of psychedelic action will be crucial for refining therapeutic protocols, predicting individual responses, and developing next-generation compounds with optimized efficacy and safety profiles. Integrating molecular, systems-level, and phenomenological data will be key to unlocking the full potential of these substances in modern medicine.

3. Psychological Effects and Therapeutic Insights

The psychological effects of psychedelics are central to their therapeutic potential. These substances induce profound alterations in cognition, emotion, and perception, which, when properly supported and integrated, can catalyze meaningful psychological change [29]. Key psychological phenomena associated with psychedelic experiences include introspection, emotional processing, ego dissolution, and the integration of traumatic memories. These effects are neither random nor merely hallucinatory; rather, they are shaped by the individual's psychological landscape and the context in which the substance is consumed, commonly referred to as "set and setting" [30].

One of the most consistently reported outcomes of psychedelic experiences is heightened introspection [31]. Under the influence of psychedelics, individuals often access thoughts, memories, and emotions that are typically suppressed or inaccessible in ordinary states of consciousness. This intensified self-awareness allows for the reevaluation of long-held beliefs, unresolved conflicts, and subconscious motivations [32]. In therapeutic contexts, such introspective insight can lead to breakthroughs in understanding one's behavior, identity, and life narrative.

Emotional processing is another core component of the psychedelic experience. Individuals frequently report encountering deep-seated emotions, such as grief, guilt, fear, or love, that had been repressed or insufficiently addressed [33]. Rather than bypassing these emotions, psychedelics often facilitate their full expression and resolution. This emotional catharsis is thought to play a significant role in the alleviation of symptoms in conditions like depression and PTSD, where emotional avoidance and dysregulation are prominent features [34].

A particularly important aspect of the psychedelic state is ego dissolution, which refers to a temporary loss of one's usual sense of self or identity boundaries [35]. Ego dissolution can engender a feeling of unity with others, nature, or the cosmos, often described in spiritual or mystical terms. While potentially disorienting, this state is associated with increased openness, reduced narcissism, and greater cognitive flexibility in the long term. In clinical trials, the intensity of mystical-type experiences has been positively correlated with therapeutic outcomes, suggesting that ego transcendence may be a key mechanism of healing [36].

Trauma integration under psychedelics also warrants special attention [37]. Unlike traditional psychotherapies that may take months or years to reach the roots of traumatic memory [38], psychedelics often bring these memories into conscious awareness rapidly and vividly [39]. In a supported environment, individuals can reprocess traumatic experiences with a sense of safety and detachment, facilitating their resolution. MDMA-assisted psychotherapy, for instance, has shown significant efficacy in treating PTSD by allowing patients to revisit traumatic memories without being overwhelmed by fear or distress [40].

These therapeutic effects are not merely products of suggestion or placebo. Controlled clinical trials have demonstrated sustained symptom reduction in treatment-resistant depression, anxiety, and addiction following just one or two psychedelic-assisted sessions [41]. Mechanistically, the psychological impact is believed to result from the temporary destabilization of rigid cognitive and emotional patterns, creating a window of opportunity for reorganization and growth. This capacity for psychological "reset" distinguishes psychedelics from traditional pharmacotherapies, which typically require daily administration and primarily manage symptoms.

Integration, which is the process of making sense of and incorporating insights from the psychedelic experience, is essential for lasting therapeutic benefit [42]. Without integration, the profound realizations and emotional breakthroughs may fade or become confusing. Therapeutic models increasingly emphasize preparation and post-session integration as critical components of psychedelic therapy [43]. Integration may involve psychotherapy, journaling, mindfulness practices, or community support, all aimed at reinforcing positive changes and addressing any lingering challenges.

The psychological effects of psychedelics extend far beyond hallucinations or altered perceptions. These compounds have been shown to enable access to unconscious cognitive and emotional content, facilitate emotional release, and induce a temporary dissolution of ego boundaries—processes that may underpin significant and enduring therapeutic outcomes [44]. Such findings highlight the critical need for rigorously designed therapeutic frameworks that optimize clinical efficacy while mitigating potential risks. As research continues, the challenge will be to translate these complex psychological mechanisms into standardized, scalable, and ethically robust clinical practices.

4. Clinical Applications in Psychiatry and Mental Health

The therapeutic potential of psychedelics in psychiatry and mental health is becoming increasingly recognized as evidence mounts from both clinical trials and observational studies [45]. Substances such as psilocybin, MDMA, ketamine, and ayahuasca are being systematically studied for their efficacy in treating a broad range of psychiatric disorders, including major depressive disorder (MDD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and substance use disorders (SUDs) [46]. These applications mark a paradigm shift in psychiatric care, offering novel interventions for patients who are unresponsive to existing treatments or who experience significant side effects from conventional pharmacotherapies.

One of the most compelling areas of research involves the use of psilocybin for treatment-resistant depression (TRD) [47]. Multiple randomized controlled trials have demonstrated that a single or a few doses of psilocybin, administered in conjunction with psychotherapy, can produce rapid and sustained reductions in depressive symptoms [48]. Unlike standard antidepressants, which may take weeks to begin working and must be taken daily, psilocybin often exerts noticeable effects within hours, with therapeutic benefits lasting weeks or even months [49]. The subjective intensity of the psychedelic experience, including mystical-type encounters and emotional breakthroughs, has been positively correlated with clinical outcomes [50].

In the context of PTSD, MDMA-assisted psychotherapy has yielded particularly promising results. PTSD, a condition marked by intrusive memories, hyperarousal, and emotional numbing, is notoriously difficult to treat with existing pharmacological agents [51]. MDMA's unique pharmacological profile, enhancing empathy, emotional resilience, and fear extinction, makes it well-suited to trauma work [52]. In phase 3 clinical trials, patients undergoing MDMA-assisted therapy exhibited significant improvements, with many no longer meeting diagnostic criteria for PTSD after the treatment protocol [53].

Importantly, these results were maintained at follow-up, suggesting durable therapeutic effects. Psychedelics have also shown efficacy in treating various forms of anxiety, particularly in existential contexts [54]. Studies involving terminally ill patients with cancer have found that psilocybin can dramatically reduce end-of-life anxiety and existential distress [55]. Participants often report profound shifts in perspective, including a greater sense of peace, interconnectedness, and acceptance of mortality. These changes are attributed not merely to neurochemical alterations but to the subjective content of the psychedelic experience, which frequently includes insights related to life, death, and meaning [56].

In the realm of addiction treatment, psychedelics have demonstrated notable potential [57]. Psilocybin has been studied for smoking cessation and alcohol use disorder, with encouraging outcomes [58]. Mechanistically, psychedelics are thought to disrupt compulsive patterns of thought and behavior, enhance motivation for change, and catalyze self-reflection. Ayahuasca and ibogaine, though less studied in Western contexts, have long been used in Indigenous and therapeutic settings for the treatment of substance dependence, offering further avenues for exploration [59].

4.1. Combined Therapy Models and Integration

A key aspect of psychedelic-assisted treatment is its reliance on a holistic therapeutic model that integrates pharmacological intervention with guided psychological support [60]. This typically involves a structured protocol composed of three phases: preparatory sessions before the psychedelic experience, a supervised dosing session, and a series of post-session integration meetings [61]. The preparatory phase is designed to establish rapport between the therapist and the patient, set clear therapeutic intentions, and explore potential psychological themes or concerns that may arise. This phase helps orient the participant to the importance of mindset ("set") and physical and social environment ("setting"), which are both critical determinants of the therapeutic outcome [62].

During the psychedelic session itself, patients are often encouraged to adopt a receptive, inward-focused attitude, typically while lying down with eyeshades and listening to a curated music playlist [63]. The therapist or guide maintains a supportive, non-intrusive presence, providing emotional grounding and safety [64]. Unlike traditional talk therapy, the dosing session emphasizes internal processing, allowing the psychedelic compound to facilitate spontaneous emotional, cognitive, or somatic experiences that may emerge. These experiences can include revisiting traumatic memories, encountering symbolic imagery, confronting existential concerns, or experiencing a sense of unity or transcendence.

The final phase, post-session integration, is perhaps the most crucial for long-term therapeutic success [42]. Integration involves revisiting the experience in a coherent, structured way, using psychotherapy, journaling, body work, or creative expression to process the insights gained [65]. The goal is to translate fleeting realizations into sustainable behavioral and emotional change. Without proper integration, the psychedelic experience risks becoming disconnected from the patient's everyday life, potentially leaving them disoriented or emotionally exposed, Gorman suggests. Research increasingly supports the notion that the quality and duration of integration work are strong predictors of long-term outcomes [66]. As such, psychedelic therapy is not a one-time pharmacological intervention but an extended therapeutic process that requires careful preparation, presence, and post-experience reflection.

4.2. Challenges and Considerations

While clinical results from psychedelic research have been promising, the translation of these therapies into standard psychiatric practice involves a series of logistical, methodological, and ethical challenges. One of the most pressing issues is the standardization of treatment protocols [67]. Given the profound subjectivity of psychedelic experiences, no two sessions are alike. This variability complicates the task of creating universal guidelines for dosage, session structure, and therapeutic technique [61]. Unlike psychopharmacological treatments that act more uniformly across populations, psychedelics demand a flexible, individualized approach. However, such flexibility also presents challenges for clinical reproducibility and regulatory approval, which typically require standardized protocols and measurable outcomes [68].

Another significant barrier is the shortage of adequately trained professionals. The role of a psychedelic therapist differs substantially from traditional psychotherapists [69]. Facilitating non-ordinary states of consciousness requires specialized training in trauma-informed care, transpersonal psychology, somatic awareness, and crisis management [70]. Currently, few accredited programs exist to meet this demand, and many therapists are unfamiliar or uncomfortable with the altered states induced by psychedelics. This highlights the urgent need for formal certification pathways, clinical supervision, and ethical oversight specific to this modality.

In addition to clinical and training limitations, accessibility is an increasingly prominent concern [71]. Psychedelic therapy is time-intensive, typically involving multiple preparatory and integration sessions as well as a full-day dosing experience [72]. This format may be prohibitively expensive, especially in private clinical settings [73]. As health systems begin to consider reimbursement models, questions of insurance coverage, equity, and health justice arise [74].

Finally, there are ongoing concerns around the potential for overmedicalization or commodification of psychedelic substances, especially as commercial interest grows [75]. Without careful ethical consideration and inclusive policy frameworks, the rollout of psychedelic therapy risks becoming a service accessible only to privileged populations, potentially reinforcing the disparities it aims to address [76].

5. Pharmacology and Safety Considerations

The therapeutic promise of psychedelics is intimately tied to their unique pharmacological properties, which govern their effects, duration, and safety profiles. Understanding these factors is critical for clinicians, researchers, and policymakers to develop responsible and effective treatment protocols. Classic psychedelics encompass a diverse range of chemical compounds that interact primarily with serotonin receptor systems but differ widely in their pharmacokinetics, dosage parameters, and potential adverse effects [77]. This section

explores the pharmacological mechanisms of major psychedelics, their safety considerations, and the importance of dosage and administration context in minimizing risks.

5.1. Pharmacological Mechanisms

Classic psychedelics, such as lysergic acid diethylamide (LSD), psilocybin, and dimethyltryptamine (DMT), are primarily serotonin receptor agonists, particularly at the 5-HT2A receptor subtype [78]. Activation of these receptors leads to widespread changes in cortical activity, neural connectivity, and sensory processing, producing the characteristic alterations in perception, cognition, and mood [79].

Psilocybin is rapidly converted into psilocin after ingestion [80], which then crosses the blood–brain barrier and stimulates 5-HT2A receptors [81]. This receptor activation is thought to disrupt normal patterns of network activity such as the default mode network (DMN) [82]. LSD similarly acts as a potent 5-HT2A agonist but also binds to dopaminergic and adrenergic receptors, contributing to its longer duration and more complex psychopharmacological profile [83]. MDMA, often classified as an entactogen rather than a classic psychedelic, primarily increases the release of serotonin, dopamine, and norepinephrine, fostering empathy and emotional openness rather than vivid hallucinations [84]. Ketamine, a dissociative anesthetic used off-label as a rapid-acting antidepressant, acts as an NMDA receptor antagonist, modulating glutamate transmission and promoting synaptic plasticity through distinct mechanisms from serotonergic psychedelics [85].

5.2. Pharmacokinetics

Pharmacokinetic properties, including absorption, distribution, metabolism, and elimination, influence onset, duration, and intensity of psychedelic effects. Psilocybin is rapidly metabolized to psilocin by alkaline phosphatases in the gut and liver, with peak plasma concentrations occurring within 60 to 90 min [86]. LSD is well absorbed orally, with peak effects emerging after 1 to 2 h and a half-life of approximately 3 h [87].

MDMA's pharmacokinetics are more complex due to its dual role as a releaser and reuptake inhibitor of monoamines [88]. Its metabolism involves liver enzymes such as CYP2D6, with notable individual variability affecting duration and intensity [89]. Ketamine's rapid metabolism through the cytochrome P450 system produces active metabolites like norketamine, which contribute to its antidepressant effects [90].

5.3. Safety and Adverse Effects

While psychedelics are generally considered physiologically safe when administered in controlled environments, their potent psychoactive effects necessitate careful consideration of psychological safety. Classic psychedelics have low toxicity profiles and minimal addictive potential [91]. However, acute adverse effects may include anxiety, panic, paranoia, confusion, nausea, and transient increases in blood pressure and heart rate [92].

Psychological risks are primarily linked to "challenging experiences" or "bad trips," which can provoke distress, disorientation, or exacerbation of underlying psychiatric conditions, especially in individuals with psychotic disorders or a family history of schizophrenia [93]. Thus, thorough screening and exclusion criteria are critical in clinical trials and therapeutic settings, Schlag highlights. MDMA carries additional concerns related to hyperthermia, dehydration, and potential serotonergic neurotoxicity, particularly when used recreationally at high doses or in uncontrolled settings [94]. Clinical protocols carefully monitor vital signs and control dosing to mitigate these risks [95]. Ketamine's safety profile includes potential dissociative symptoms, transient blood pressure elevations, and the risk of abuse or dependence with frequent use [96]. Its use in clinical settings requires medical supervision and attention to dosing intervals.

5.4. Set and Setting: Crucial Determinants of Safety

Beyond pharmacology, the context of administration, often termed "set and setting", plays a decisive role in safety and therapeutic outcomes [97]. "Set" refers to the individual's mindset, expectations, and psychological preparedness, while "setting" encompasses the physical, social, and cultural environment [98]. Clinical studies emphasize that well-prepared participants, supportive therapeutic environments, and trained facilitators greatly reduce the risk of adverse psychological reactions, Haijen explains. Conversely, uncontrolled or unsupervised use increases the likelihood of challenging experiences and potential harm.

5.5. Drug Interactions and Contraindications

Psychedelics may interact with other medications, most notably selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), potentially altering efficacy or increasing side effect risk [99]. For instance, MAOIs potentiate DMT effects in ayahuasca but also raise risks of hypertensive crises when combined with certain foods or drugs [77]. Contraindications for psychedelic therapy typically include a personal or family history of psychosis, bipolar disorder, or severe cardiovascular disease [100]. These exclusions safeguard against exacerbation of symptoms or unpredictable physiological stress, Frescska highlights.

5.6. Emerging Safety Protocols and Training

As clinical research expands, formalized safety guidelines and training programs for psychedelic-assisted therapy are being developed [101]. These include standardized screening tools, monitoring protocols during sessions, and integration practices to ensure psychological support post-treatment. Professional organizations and regulatory bodies are also formulating best practices to minimize risks and maximize benefits as psychedelics transition from experimental to approved therapeutic tools [102].

6. Anthropological and Cultural Dimensions

Psychedelic substances have been intimately woven into the fabric of human culture for thousands of years, playing vital roles in spiritual, social, and healing traditions around the world [103]. The contemporary revival of interest in psychedelics within Western medicine and science stands in contrast to the rich, continuous histories of Indigenous peoples who have preserved these practices over millennia [104]. A thorough and nuanced understanding of psychedelics today requires situating these compounds within their anthropological and cultural contexts, recognizing the meanings, rituals, and communal identities they have historically shaped.

Across many Indigenous societies, psychedelics have been employed as sacraments, healing agents, and mediators of spiritual connection [105]. In the Amazon basin, for example, the ayahuasca brew, composed of the *Banisteriopsis caapi* vine combined with leaves containing the psychoactive compound DMT, has been used for centuries in shamanic ceremonies, Williams states. These rituals, guided by experienced healers or shamans, serve to diagnose illnesses, restore harmony within individuals and their communities, and facilitate communication with the spiritual world [106]. The ceremonial context, complete with chanting, drumming, and group participation, is critical to the meaning and effectiveness of the experience [107]. It is not simply the pharmacological properties of the brew that matter but also the collective framework that shapes the journey.

Similarly, peyote, a cactus containing mescaline, holds a sacred status within the Native American Church [108]. Used in religious ceremonies that aim to foster spiritual insight and moral guidance, peyote is protected under legal exemptions in some countries,

reflecting recognition of its deep cultural and religious significance. Its use within this context is highly structured and governed by communal values, serving as a living link between participants and their ancestors.

Anthropological studies highlight that psychedelic use cannot be reduced to a simple chemical interaction; rather, it is fundamentally shaped by the cultural environment and belief systems in which it occurs [109]. The significance attributed to the experience, the expectations established by ritual, and the presence of knowledgeable guides or elders profoundly influence the outcomes. This understanding forms the foundation for the contemporary concept of "set and setting," which emphasizes psychological readiness and environmental context as essential to the safety and therapeutic efficacy of psychedelics [110].

In Western contexts, the resurgence of psychedelics has often drawn heavily on Indigenous knowledge and ceremonial practices [105]. However, this borrowing has sparked important ethical debates around cultural appropriation, intellectual property, and the commodification of traditional spiritual practices. While Indigenous knowledge has undeniably enriched modern therapeutic models, questions remain about how to respect and protect the rights of source communities, ensure fair benefit-sharing, and avoid erasing the cultural origins of these substances [111].

The globalization of psychedelic use has also led to the emergence of hybrid cultural forms [112]. Western participants frequently travel to South America to take part in ayahuasca ceremonies or attend retreats that blend traditional Indigenous rituals with modern psychotherapy [113]. These cross-cultural exchanges create new practices that combine elements from multiple traditions, often reflecting a globalized spirituality that resonates with contemporary seekers. At the same time, they raise complex issues of authenticity and cultural sensitivity, as well as concerns about the sustainability and regulation of these ceremonies.

Importantly, anthropological research cautions against assuming that psychedelic experiences are universally consistent [114]. Instead, cultural frameworks significantly shape the phenomenology of the experience itself, how visions are interpreted, what emotions are evoked, and the meanings assigned to insights. Thus, the subjective effects of psychedelics are not purely pharmacological but deeply intertwined with the user's cultural background, language, and worldview.

The role of psychedelics in traditional societies often extends beyond the individual, emphasizing collective healing, social cohesion, and the reinforcement of shared values [110]. Ritual use frequently functions to maintain community harmony, address social tensions, and link participants to ancestral wisdom. This contrasts with many Western therapeutic models that prioritize individual psychological outcomes, suggesting that integrating communal and cultural dimensions could enrich modern psychedelic practices [115].

As contemporary research continues to develop, it is increasingly clear that the cultural and anthropological dimensions of psychedelics offer invaluable insights into their potential uses and limitations [116]. Respecting these perspectives challenges reductionist approaches and invites a more holistic view that incorporates spirituality, ritual, and relationality. Moreover, engaging with Indigenous communities as partners rather than mere sources of knowledge is essential for ethical progress in the field, Batchelder states.

To better understand the global landscape of psychedelic use, Table 1 provides a comparative overview of selected countries with respect to the therapeutic legality of psychedelic substances, their historical usage, and the cultural contexts in which they have traditionally been employed [117,118]. This overview highlights both the resurgence of interest in modern clinical settings and the deep-rooted cultural practices that have shaped the historical significance of these compounds across diverse societies.

Table 1. Legality, historical use, and cultural context of psychedelics [117,118].

Country	Psychedelics	Legality for Therapy	Historically Used	Cultural/Traditional Use
USA	Psilocybin, MDMA, ketamine	Partially (state-level or trial-based)	No	Modern clinical trials; underground therapy; state decriminalization (e.g., Oregon, Colorado)
Canada	Psilocybin, MDMA	Yes (limited exemptions for palliative and treatment-resistant cases)	No	Legal exemptions for end-of-life therapy; growing clinical research
Brazil	Ayahuasca	Yes (legal for religious use)	Yes	Used in syncretic religions (Santo Daime, União do Vegetal)
Peru	Ayahuasca, San Pedro	Yes (in traditional and spiritual settings)	Yes	Integral to Amazonian and Andean shamanic healing ceremonies
Mexico	Psilocybin (mushrooms)	No (religious/Indigenous use tolerated)	Yes	Sacred mushroom rituals (veladas) among Mazatec and other Indigenous groups
Netherlands	Psilocybin truffles	Yes (truffles only, not mushrooms)	No	Legal truffle sales; therapeutic retreats and guided sessions
Australia	Psilocybin, MDMA	Yes (approved for PTSD and depression as of 2023)	No	Approved under medical supervision; emerging clinical framework
India	Cannabis, datura	No	Yes	Used in spiritual rites; possible Vedic references (e.g., soma)
South Africa	Psilocybin, ayahuasca	No	Possibly	Underground use; neo-shamanic practices on the rise
Portugal	Various (decriminalized)	No (but personal use is decriminalized)	No	Decriminalized personal use; informal healing and introspective applications
Switzerland	LSD, MDMA, psilocybin, ketamine, ayahuasca	Yes (licensed therapy allowed in specific cases since 2014)	No	Clinical psychedelic therapy; psycholytic therapy history; licensed ayahuasca use in Geneva

7. Philosophical and Existential Implications

The use of psychedelics opens profound philosophical and existential questions that challenge conventional understandings of consciousness, selfhood, and reality [119]. Beyond their therapeutic and neurobiological effects, psychedelics have historically been regarded as gateways to altered states of consciousness that can transform one's fundamental sense of identity, meaning, and purpose [30]. These substances invite inquiry into the nature of subjective experience, the construction of the self, and the ways humans find significance in existence.

One of the central philosophical questions psychedelics raise concerns the nature of consciousness itself [10]. Psychedelic experiences often involve dramatic alterations in perception, cognition, and awareness, including vivid visual phenomena, synesthesia, and a dissolution of boundaries between self and environment [120]. Such states challenge Cartesian dualism, the notion that mind and body are distinct entities, and instead support monistic or non-dual perspectives that emphasize interconnectedness and the fluidity of

mental phenomena [121]. Philosophers and cognitive scientists have debated whether these experiences reveal hidden aspects of consciousness or simply result from disrupted neural processes [122]. Regardless, they highlight the profound plasticity and contextuality of conscious experience.

Closely related is the phenomenon of ego dissolution, frequently reported during high-dose psychedelic sessions [123]. Users describe a loss of the usual sense of self as a bounded, separate entity, replaced by a feeling of unity with the cosmos or an expansive awareness that transcends personal identity, Mason highlights. This experience challenges foundational ideas about the self as a continuous, autonomous subject. Philosophically, it raises questions about the nature and persistence of personal identity, inviting interpretations ranging from mystical insights into universal consciousness to neuroscientific models of transient self-representation [124]. Ego dissolution also bears significant existential implications. The experience of self-transcendence can provoke profound shifts in one's relationship to mortality, suffering, and purpose [125]. Many individuals report a newfound appreciation for life's interconnectedness and impermanence, leading to changes in values, priorities, and behavior. From this perspective, psychedelics can be seen as tools that facilitate existential exploration, helping users confront anxieties about death and meaninglessness with a sense of acceptance and awe [126].

Furthermore, psychedelic experiences often generate encounters with what users interpret as spiritual or mystical realities [127]. These may include visions of divine beings, encounters with archetypal symbols, or feelings of profound sacredness. Such phenomena align with perennial philosophical questions about the transcendent and the numinous, experiences that evoke a sense of awe and reverence beyond ordinary understanding [128]. These mystical dimensions of psychedelics have been linked to positive therapeutic outcomes, suggesting that meaning-making processes rooted in spirituality can be integral to psychological healing, Samiento writes.

Philosophically, these spiritual experiences raise challenging questions about the ontology of mystical phenomena [129]. Are these experiences mere hallucinations produced by altered brain chemistry, or do they access some deeper metaphysical truths? Scholars remain divided, with some advocating for a materialist reductionism that explains mystical states as brain states, while others propose that psychedelics may reveal aspects of reality normally inaccessible to ordinary consciousness [130]. This debate touches on broader issues in the philosophy of mind and metaphysics, including the limits of scientific explanation and the validity of subjective experience as a source of knowledge.

In addition to challenging concepts of self and consciousness, psychedelics also influence moral and ethical frameworks. The profound empathy, connectedness, and dissolution of ego boundaries reported by many users can foster a heightened sense of compassion and ethical responsibility toward others and the environment [131]. This shift in perspective is sometimes described as a "moral awakening," where users feel motivated to live more authentically, altruistically, and in harmony with the natural world [132]. Such transformations echo philosophical traditions that emphasize the interconnectedness of beings and the ethical imperative to care for others.

The existential reorientation catalyzed by psychedelics can also challenge dominant cultural narratives around individualism, materialism, and control. Many users report a diminished fixation on consumerism, competition, and ego-driven pursuits, replaced by values emphasizing connection, creativity, and presence [133]. This shift suggests that psychedelics might play a role in broader societal change by encouraging alternative ways of understanding human flourishing and well-being.

However, these profound experiences and insights are not universally transformative or positive. Psychedelics can also provoke existential crises, anxiety, or disorientation,

particularly when taken without adequate preparation or support [134]. Byock suggests that the destabilization of the self-concept can be deeply unsettling, raising philosophical questions about the stability and coherence of identity. The challenge for therapeutic and philosophical inquiry lies in integrating these experiences in a way that supports lasting psychological growth and ethical engagement.

Finally, the resurgence of psychedelic research invites a reevaluation of the role altered states of consciousness play in human cognition and culture [135]. Philosophers have long pondered the nature of imagination, creativity, and insight. Psychedelics appear to expand the boundaries of ordinary cognition, enabling novel connections, perspectives, and ways of understanding [136]. This suggests that altered states may have evolutionary significance, contributing to human adaptability and cultural innovation.

8. Medical Uses Beyond Psychiatry

The therapeutic promise of psychedelics has largely focused on psychiatric disorders such as depression, PTSD, anxiety, and addiction [137]. However, emerging evidence suggests that their potential medical applications extend beyond the domain of mental health [138]. Psychedelics may offer novel interventions for chronic pain [139], palliative care [140], and somatic conditions where conventional treatments have limited efficacy [141]. These expanded uses are supported by both mechanistic insights from neuroscience and a growing number of clinical observations, indicating that psychedelics may exert complex effects on perception, emotion, and physiological systems that intersect with physical health and healing [142].

One of the most promising frontiers in non-psychiatric psychedelic medicine is in the treatment of chronic pain [143]. Pain is not solely a sensory phenomenon but involves affective, cognitive, and emotional dimensions [144]. Psychedelics, particularly classical serotonergic compounds like psilocybin and LSD, appear to influence pain perception through both psychological and neurobiological mechanisms [145].

Beyond these neurobiological mechanisms, the subjective experience of psychedelics can shift patients' relationship to their pain [146]. In qualitative reports, individuals describe experiencing their pain from a new perspective, often with increased acceptance and reduced emotional reactivity. Bornemann highlights that this is consistent with observations in mindfulness-based pain management, where changing the cognitive appraisal of pain can significantly improve quality of life. By disrupting habitual thought patterns and promoting cognitive flexibility, psychedelics may reduce the suffering component of pain, even if the physical sensation remains.

A particularly compelling area of research involves the use of psychedelics in palliative care and end-of-life settings [56]. Patients facing terminal illness often struggle with existential distress, fear of death, and a loss of meaning, Federico explains. Traditional pharmacological treatments for such distress, such as benzodiazepines or antidepressants, are often inadequate and may dull consciousness without addressing the deeper psychological and spiritual dimensions of dying [147]. Psychedelic-assisted therapy, by contrast, has shown remarkable promise in alleviating anxiety and depression in terminally ill patients, often after just a single guided session.

Studies using psilocybin for cancer-related psychological distress have demonstrated rapid and sustained improvements in mood, anxiety, and existential well-being [148]. Participants frequently report a decreased fear of death, greater emotional acceptance, and a renewed sense of connection to life, loved ones, and the universe [149]. These effects are not simply byproducts of mood elevation but often emerge from what participants describe as deeply meaningful, even mystical experiences. Such outcomes suggest that psychedelics may uniquely address the spiritual and existential needs of patients at the

end of life, offering a level of psychological and emotional relief that is rarely achieved by conventional means.

In terms of clinical application, patient selection, dosing strategies, and integration support must all be adapted to the specific medical context. For instance, the emotional and existential needs of a terminal cancer patient differ significantly from those of a person with chronic back pain. Tailoring the therapeutic approach to fit the patient's medical, psychological, and existential profile will be key to maximizing benefits and minimizing risks.

9. Ethical and Methodological Challenges in Psychedelic Research

The recent resurgence of psychedelic research has reinvigorated scientific and medical discourse, but it has also exposed a complex landscape of ethical and methodological challenges. Psychedelics, unlike many conventional pharmaceuticals, involve deeply subjective, often unpredictable experiences that are profoundly shaped by context, expectation, and interpersonal dynamics [150]. As such, designing robust, ethical studies that meet the standards of modern scientific inquiry while honoring the complexity of these substances presents a unique set of difficulties. Addressing these challenges is critical for ensuring the safe, effective, and responsible development of psychedelic-assisted therapies.

One of the most immediate ethical concerns in psychedelic research involves participant safety and informed consent. Psychedelic substances, especially psilocybin, LSD, and DMT, can induce powerful alterations in consciousness, including emotional catharsis, perceptual distortions, and ego dissolution [151]. While these effects may contribute to therapeutic breakthroughs, they can also be psychologically destabilizing or overwhelming, particularly for individuals with a history of trauma or latent mental health vulnerabilities. Ensuring that participants are adequately screened, informed of potential risks, and supported throughout the experience is essential. Informed consent must go beyond a standard legal disclosure to include detailed preparation about the nature of the psychedelic experience, the importance of "set and setting," and the role of the guide or therapist [152].

The therapeutic environment itself presents another layer of ethical complexity [153]. Unlike conventional drug trials, which focus on standardized pharmacological testing, psychedelic therapy is not a clinical trial but a therapeutic process that relies on the interpersonal relationship between the participant and the facilitator [61]. This places significant responsibility on therapists, who must balance clinical neutrality with the emotionally intimate role often required to support participants during vulnerable states. Boundaries can become blurred, particularly when participants experience transference or come to regard the therapist as a spiritual or parental figure. Ethical guidelines must therefore emphasize therapist training, supervision, and the prevention of misconduct [61]. Historical instances of boundary violations in psychedelic therapy underscore the urgency of establishing professional standards and accountability mechanisms [154].

Methodologically, psychedelic research must contend with the challenge of placebo control [155]. The effects of psychedelics are typically unmistakable, making it exceedingly difficult to blind participants and researchers to treatment conditions, Wen highlights. This lack of blinding introduces expectancy effects and biases that can confound results. Some studies have attempted to use active placebos, such as low-dose psychedelics or other mildly psychoactive substances like niacin, but these often fail to mimic the intensity of the psychedelic experience [156]. Consequently, researchers must interpret findings with caution and consider alternative designs that account for non-specific factors, such as participant expectations and the therapeutic alliance.

Moreover, the question of what constitutes an appropriate control group in psychedelic studies remains unresolved. Unlike conventional medications that aim to produce pre-

dictable, dose-dependent outcomes, psychedelics operate in a context-dependent manner, where psychological, cultural, and environmental variables strongly influence results [157]. This complexity makes it difficult to isolate the specific contribution of the drug from the broader therapeutic framework. As a result, researchers have called for "whole-system" or "context-inclusive" approaches that evaluate not only the substance but also the setting, preparation, and integration processes as integral components of the treatment.

Another significant methodological challenge involves the integration of subjective reports into scientific analysis. Psychedelic experiences are inherently personal and often described in metaphorical or spiritual terms, which resist straightforward quantification [158]. While standardized psychometric instruments such as the Mystical Experience Questionnaire [159] and the Ego Dissolution Inventory [125] provide some structure for data collection, they cannot fully capture the richness and variability of individual experiences. This tension between subjective depth and empirical rigor calls for mixed-methods approaches that combine quantitative measures with qualitative interviews, narrative analysis, and phenomenological inquiry [160].

The growing commercialization of psychedelics introduces ethical dilemmas that must be addressed at both institutional and policy levels [161]. As pharmaceutical companies, retreat centers, and venture capitalists enter the psychedelic space, there is increasing pressure to prioritize profitability over patient welfare, scientific integrity, and equitable access [162]. Patenting of psychedelic compounds, delivery methods, or therapeutic protocols raises concerns about intellectual property monopolies that could limit public access and stifle collaborative innovation. These dynamics risk commodifying substances that have been used ceremonially by Indigenous cultures for centuries, often without their consent or benefit.

Finally, regulatory frameworks have not yet fully adapted to the unique demands of psychedelic research. Despite increasing evidence of safety and efficacy, psychedelics remain Schedule I substances under international conventions and in many national jurisdictions, meaning they are classified as having no accepted medical use and a high potential for abuse [163]. This classification imposes significant logistical and financial barriers for researchers, including complex licensing procedures, security requirements, and stigma within academic institutions, Nutt highlights. Reforming drug policy to reflect current scientific understanding is essential for advancing the field and enabling broader access to potentially life-changing treatments.

10. Conclusions

The contemporary resurgence of interest in psychedelics marks a pivotal moment in both psychological science and broader interdisciplinary thought. Once relegated to the fringes of medical and cultural discourse due to prohibition and stigma, psychedelics are now at the forefront of a paradigm shift that bridges neuroscience, psychiatry, anthropology, philosophy, and medical ethics. This renaissance is not merely a practice of mid-20th-century investigations but a data-driven and context-aware movement that seeks to responsibly integrate these potent substances into modern therapeutic and epistemological frameworks.

One of the most profound revelations from recent research is the remarkable therapeutic efficacy of psychedelics in addressing a wide range of psychiatric conditions, including treatment-resistant depression, PTSD, anxiety, and addiction. Unlike conventional pharmacotherapies that often aim to suppress symptoms, psychedelics appear to facilitate transformative psychological change by enhancing introspection, emotional processing, ego dissolution, and neuroplasticity. These therapeutic effects are often catalyzed through

just one or two experiences yet yield outcomes that can last for months, a finding that challenges the chronic treatment models underpinning much of modern psychiatry.

Equally compelling are the neurobiological underpinnings of these effects. Psychedelics modulate key brain systems, most notably the serotonin 5-HT2A receptor and the default mode network, producing a temporary loosening of rigid neural patterns that may enable more flexible cognition and emotional regulation. By promoting neural connectivity and fostering conditions conducive to the reorganization of mental frameworks, these compounds serve not only as symptom relievers but as agents of psychological restructuring.

Moreover, psychedelic-assisted therapy is inherently integrative, combining pharmacological intervention with structured psychological support. This therapeutic model emphasizes the importance of "set and setting," integration, and the relational dynamic between guide and participant, highlighting the contextual nature of healing. These elements mark a departure from traditional Western biomedical models and point toward a more holistic approach to mental health, one that recognizes the interplay between biology, emotion, meaning, and social context.

Beyond the clinic, psychedelics raise far-reaching philosophical and cultural questions. Experiences of ego dissolution, unity, and mystical insight prompt reevaluation of entrenched concepts of self, consciousness, and reality. These phenomena echo long-standing spiritual and existential inquiries found across human history and cultures, suggesting that psychedelics may have a unique role in fostering not only psychological healing but also moral reflection, creativity, and personal growth. The potential for psychedelics to catalyze shifts in values toward empathy and connectedness also implies relevance beyond individual therapy, pointing to their possible contributions to social and ecological transformation.

Anthropological perspectives further enrich this discussion by situating psychedelics within the cultural traditions from which many of them originate. Indigenous communities have long utilized these substances within ritualized frameworks aimed at healing, cohesion, and spiritual communion. Acknowledging and respecting these traditions is essential, not only for ethical integrity but also for expanding Western paradigms of medicine and healing. As psychedelic therapy enters mainstream discourse, it is imperative that it does so with cultural humility, inclusive dialogue, and mechanisms for fair benefit-sharing.

Nevertheless, the integration of psychedelics into modern health systems is not without challenges. Ethical considerations around consent, safety, and therapist conduct must be rigorously addressed. Methodological limitations, such as difficulties in achieving placebo controls or standardizing subjective experiences, complicate the evidentiary base. Furthermore, concerns about access, equity, commercialization, and overmedicalization must be met with thoughtful policy and inclusive frameworks to prevent the marginalization of vulnerable populations and the co-optation of Indigenous knowledge.

Despite these complexities, the momentum behind psychedelic research is undeniable. With growing support from academic institutions, regulatory bodies, and the public, there is an unprecedented opportunity to reimagine mental health care. This reimagining calls for a delicate balance between scientific rigor and openness to subjective, spiritual, and cultural dimensions of healing. It demands innovation in research methodologies, investment in training and ethical guidelines, and a commitment to equity and justice.

Psychedelics invite us to expand our definitions not only of therapy and medicine but also of consciousness, suffering, and what it means to be whole. Their reemergence challenges reductionist models and offers a more expansive, integrative vision of human well-being. As science, culture, and policy converge around this promising frontier, the question is no longer whether psychedelics have a role to play in contemporary inquiry but how we will responsibly shape and share that role for generations to come.

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Systematic Review

Effectiveness of Psychological Therapy for Treatment-Resistant Depression in Adults: A Systematic Review and Meta-Analysis

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Abstract: Background: Depression that is resistant to two or more adequate treatment trials—treatment-resistant depression (TRD)—is a prevalent clinical challenge. Although psychotherapies have been recommended by clinical guidelines as an alternative or adjunctive treatment strategy, the effectiveness of psychotherapy in individuals with TRD has not yet been evaluated through meta-analytic methods, primarily due to a limited number of trials. This highlights the necessity of personalized research targeting this specific population. This systematic review and meta-analysis aimed to summarize the evidence on psychotherapy in treating TRD. **Methods:** A systematic search was conducted following the Guidelines from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Articles were included if they quantitatively examined the efficacy of psychotherapy on depression symptoms in individuals diagnosed with depression who had not responded to at least two prior treatments (i.e., pharmacotherapy and/or psychotherapy). **Results:** A total of 12 studies were included. The quality of evidence was evaluated as being globally moderate. When pooling all psychotherapies, a small-to-moderate, but significant, effect on depressive symptoms was observed compared to the control group (SMD = −0.49, CI = −0.63; −0.34). The observed effect remained unchanged after removing the outlier (SMD = −0.47, CI = −0.62; −0.32). When examining depressive symptoms by type of psychotherapy, Mindfulness-Based Cognitive Therapy (SMD = −0.51, CI = −0.76; −0.25), Cognitive Behavioral Therapy (SMD = −0.53, CI = −0.92; −0.14), and Cognitive Therapy (SMD = −0.51, CI = −1.01; −0.01) showed a moderately significant effect on depressive symptoms compared to the control group. **Conclusions:** Although this potentially represents the first meta-analysis in this area, the number of studies specifically addressing this complex population remains limited, and the existing literature is still in its early stages. Research focusing on TRD is notably sparse compared to the broader body of work on depression without treatment resistance. Consequently, it was not possible to conduct meta-analyses by type of psychotherapy across all treatment modalities and by type of control group. Due to several study limitations, there is currently limited evidence available about the effectiveness of psychotherapy for TRD, and further trials are needed. Beyond the treatments usually offered for depression, it is possible that TRD requires a personalized medicine approach.

Keywords: systematic review; meta-analysis; major depressive disorder; treatment-resistant; psychotherapy

1. Introduction

The lifetime prevalence of major depressive disorder (MDD) is up to 21% and tends to increase over the years [1,2]. MDD can impact all areas of life, including professional, relational, and personal spheres [3,4]. For example, MDD is associated with a prevalence of up to 30% for work absenteeism or unemployment [5]. It also increases the risk of developing medical issues, such as cardiovascular and respiratory diseases [6]. Additionally, the lifetime prevalence of suicide attempts in MDD was estimated at 31% (95% confidence interval (CI) = 27–34%) [7]. Indeed, the risk of death by suicide was significantly higher among individuals with MDD, with a relative risk of 19.7 (CI = 12.2–32.0) compared to individuals without MDD [8]. In 2023, the societal economic burden of MDD in the United States of America was estimated to be $382.4 billion [9]. Furthermore, the World Health Organization estimates that depression is among the leading causes of disability in developed countries [10].

Treatments recommended for depression are antidepressants, psychotherapy, and their combination [11,12]. However, resistance to antidepressant treatment is a common issue in clinical practice. Studies indicate that between 30% and 55% of individuals remain symptomatic after two trials of antidepressants [13–15]. Treatment resistance in MDD leads to more severe consequences across various aspects of individuals' lives [15]. Individuals with treatment-resistant depression (TRD) experience poorer quality of life and psychosocial functioning [16,17]. They are twice as likely to attempt or complete suicide and have higher rates of hospitalization [18,19]. They also use more healthcare resources and impose a greater societal and economic burden than those with treatment-responsive depression [20,21]. Furthermore, increasing levels of TRD were associated with elevated direct and indirect costs, as well as a decline in health-related quality of life [22]. Given the high prevalence of individuals with TRD and the negative repercussions for individuals, their entourage, and society, psychotherapy has been widely recommended in clinical practice guidelines as part of the treatment for those suffering from MDD and TRD [11,12,23–25].

Although several meta-analyses have examined the efficacy of psychotherapies for treating depressive symptoms in adults, treatment resistance was rarely considered. In adults without specific criteria for treatment resistance, a large meta-analysis of 143 studies reported that psychotherapy had a moderate effect on depressive symptoms compared to treatment as usual (TAU) (g = −0.66, CI = −0.78; −0.53) [26]. Analyses by type of psychotherapy revealed moderate efficacy: Cognitive Behavioral Therapy (CBT) (k = 94, g = 0.71, CI = 0.62; 0.79), Behavioral Activation Therapy (k = 31, g = 0.74, CI = 0.56; 0.91), Interpersonal Psychotherapy (k = 31, g = 0.60, CI = 0.45, 0.75), Problem-Solving Therapy (k = 13, g = 0.83, CI = 0.45; 1.21), Nondirective Supportive Therapy (k = 18, g = 0.58, CI = 0.45; 0.72), and Short-Term Psychodynamic Psychotherapy (k = 10, g = 0.61, CI = 0.33, 0.88) [27]. Among individuals with resistance to at least one antidepressant treatment, the number of available studies was significantly reduced (k = 6), as was their efficacy [28]. Indeed, CBT combined with TAU has shown a small but statistically significant benefit compared to TAU alone (k = 3, SMD = −0.35, CI = −0.56; −0.13). However, other psychotherapies in addition to TAU, such as Dialectical Behavior Therapy (k = 1, SMD = −0.72, CI = −1.66; 0.21), Interpersonal Therapy (k = 1, SMD = 0.07, CI = −0.60; 0.74), and Intensive Short-Term Dynamic Psychotherapy (k = 1, SMD = −0.88, CI = −1.41; −0.35) have not shown significant effects compared to TAU alone. To our knowledge, no meta-analysis has specifically focused on individuals who remain symptomatic after two adequate treatment courses. Previous attempts to conduct such meta-analyses have been limited by the small number of eligible studies [28,29]. Notably, a recent meta-analysis identified only three studies, which were three different types of psychotherapy: CBT,

Long-Term Psychoanalytic Psychotherapy, and Mindfulness-Based Cognitive Therapy (MBCT). Moreover, outcomes were limited to depression remission, with no data reported on secondary outcomes such as self-esteem, anxiety, functioning, or quality of life [28]. Therefore, personalized research targeting this specific population was necessary.

For instance, systematic reviews that defined treatment resistance as non-remittent depression despite at least two antidepressant trials identified only three relevant studies [28,29]. In addition, a recent article from 2023 highlighted the issues regarding the multiple definitions of TRD and reported the need to include non-response to psychotherapies in the definition of treatment resistance in MDD [15]. Incorporating non-response to psychotherapy into the criteria for treatment resistance aligns with the established clinical guidelines for treating depression (i.e., American Psychological Association, National Institute for Health and Care Excellence, Canadian Network for Mood and Anxiety Treatments). These guidelines recommend psychotherapy as a first-line treatment, as well as an intervention for cases where patients do not respond or only partially respond to pharmacotherapy [11,12,25]. Moreover, the inclusion of non-response to psychotherapy in the definition of treatment resistance facilitates the use of real-world clinical samples, as approximately 25% of treatment modalities in clinical practice involve psychotherapy [30].

Thus, the present systematic review aimed to evaluate the effectiveness of all types of psychotherapy, both combined and separately, in individuals with TRD. All psychotherapies were initially pooled to provide an overall estimate of their effectiveness and to enhance statistical power before individual modalities were analyzed. The outcomes assessed extended beyond depressive symptoms to include associated domains such as anxiety, self-esteem, overall functioning, and quality of life. Consistently with the definitions discussed above, TRD was defined as non-response to at least two treatment courses, including pharmacotherapy and/or psychotherapy. Given that treatment effectiveness tends to decline with increasing resistance across various psychopathologies, the efficacy of psychotherapy was expected to be lower in TRD compared to non-resistant MDD.

2. Methods

2.1. Search Strategy

The search was performed in accordance with the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31] (see Table S1 in Supplementary Materials). Two graduate students (A.F. and S.G.) independently conducted a systematic search of the electronic databases PubMed (k = 3550), PsycINFO (k = 1208), Web of Science (k = 3120), and Cochrane Library (k = 264). The search included records from the inception of the databases until October 2024. Search terms were inclusive of depressive disorder (e.g., major depressive disorder, depression), treatment-resistance (e.g., refractor, nonresponse, resistant), and psychological therapy (e.g., psychotherapy, intervention, psychosocial treatment). No restrictions were applied to the setting, date, or geographical location. English and French language sources were eligible. A secondary search was conducted in Google Scholar to retrieve gray literature, and the reference lists of the included studies (k = 38) were screened to ensure that no relevant studies were missed. The specific search strategy adapted for each database is provided in Table S2 in the Supplementary Materials. The systematic review was not preregistered.

2.2. Study Eligibility

Studies were included for analyses if they met the following criteria: (1) quantitatively examined the effects of psychological therapy on depressive symptoms, (2) involved adults with depression, (3) examined treatment resistance—defined as unremitted depression despite at least two courses of treatment (i.e., pharmacotherapy and/or psychotherapy), (4) clearly involved a healthcare professional in the psychotherapy, and (5) compared psychotherapy to a control group (e.g., other psychotherapy, waiting list, TAU, pharmacotherapy). To maximize the number of studies and obtain an overall view on the subject, quasi-experimental studies were included in addition to clinical trials (e.g., randomized controlled trials (RCTs)). Studies were excluded if they (1) did not involve a healthcare professional in the psychotherapy (e.g., self-help, computer-based), (2) merged multiple types of psychotherapy into a single outcome category (e.g., reporting results for all psychotherapies combined), (3) were not peer-reviewed, (4) comprised pharmacotherapy alone without psychotherapies, and (5) involved prevention programs. Self-help and computer-based interventions were excluded, because they are not included in the recommendations of clinical guidelines for the treatment of depression [11,12,25]. Study eligibility was conducted independently by A.F., S.G., and J.A., and discussions on including meta-analyses were held with senior researchers (A.D. and S.P.) to ensure consensus.

2.3. Data Extraction

Data were extracted with a standardized form by S.G. and counter-validated by J.A. Key information related to the design of studies, types of psychosocial treatment, country of study, participants (i.e., definition of treatment resistance, sample size, gender), control group (e.g., TAU, other psychotherapy), timepoint (i.e., post-therapy, 3-month follow-up), outcomes measured (e.g., depressive and related symptoms, functioning, quality of life), study results, and adjustment for confounding factors were recorded (see Table S3 in the Supplementary Materials). The authors were contacted when data were missing to perform our analyses or when the condition of a group was unclear. In the absence of a response from the authors, their results were not included in the analysis. Furthermore, S.G. and J.A. independently assessed the quality of evidence for the effect sizes reported in the meta-analyses using a set of criteria based on the GRADE Checklist [32–34]. This widely used and recommended tool enables the evaluation of key domains of evidence quality, including risk of bias, indirectness, inconsistency, imprecision, and publication bias [35–38]. We assigned higher scores to studies that comprised a single-blind RCT, comprised larger sample sizes compared to active control (i.e., another psychotherapy), and conducted moderator analyses (e.g., number of treatment sessions, type of comparison condition, demographic predictors). Studies were assigned to the following categories: very low quality, low, moderate-to-low, moderate, moderate-to-high, and high.

2.4. Statistical Analysis

The analyses were performed using the statistical software RStudio (version 2024.12.1) with the metafor package [39]. The effect size of depressive symptoms was estimated with standardized mean differences (SMDs). For all studies, CIs were calculated based on post-treatment scores comparing the experimental group to the control group. When the CI crosses zero, it indicates that the effect was not statistically significant. Random-effects models were employed, which are more conservative than fixed-effects models and appear to address heterogeneity between studies and study samples [40]. The following qualitative descriptions of the strength of reported SMDs were used: small 0.2, medium 0.5, and large $\geq$ 0.8 [41]. When a study evaluated the effects of depression using clinician-rated and self-report measures, both were used, and a multivariate random-effect meta-analysis

with a random intercept grouped by study was fitted to the data. A meta-analysis suggested that combining self-report and clinician ratings may provide a more accurate assessment of treatment response, as different symptoms may be more suitable for self-report or ratings by clinicians [42]. Heterogeneity among study point estimates was quantified using the I^2 index, with a value of 0% indicating no effect heterogeneity. Values of 25%, 50%, and 75% correspond to low, moderate, and high heterogeneities, respectively [43]. The risk of publication bias was assessed using Egger's test and examined with funnel plots. The Egger's test is widely used in meta-analyses of psychotherapy [36,44,45]. A significant *p*-value suggests the presence of publication bias, indicating that studies with non-significant results are more likely to remain unpublished [46]. Additional analyses were also performed by type of psychotherapy. Due to the limited number of studies, all analyses were conducted irrespective of control group type. Sub-analyses were conducted without the outlier study. Analyses were performed by S.G. and validated by a statistician (C.-É.G.).

3. Results

3.1. Description of Studies Included

The PRISMA flowchart for study inclusion is presented in Figure 1. The systematic search identified 4561 potential articles, which were screened for eligibility after duplicates were removed. Among these, twelve studies were included, comprising a total of 723 adults with depression and a non-response to at least two treatment courses (65% women, mean age = 43.87, SD = 2.68). Eleven of these studies reported the presence of psychiatric comorbidities (e.g., anxiety disorder, personality disorder, substance use disorder). Moreover, eleven studies were randomized, seven controlled, and eight had evaluators blinded to the type of intervention. Psychotherapy comprised MBCT (k = 3), CBT (k = 2), cognitive therapy (k = 2), long-term psychoanalytic psychotherapy (k = 1), group compassion-focused therapy (k = 1), trauma-focused cognitive behavioral therapy (k = 1), group-based interpersonal psychotherapy and occupational therapy (k = 1), and body-oriented psychological therapy (k = 1). Control groups varied across studies, including TAU (k = 6), eye movement desensitization and reprocessing (k = 1), waiting list (k = 1), CBT combined with rehabilitation treatment (k = 1), rehabilitation treatment alone (k = 1), pharmacotherapy (k = 2), and a health-enhancement program (k = 1). Studies have been carried out in various countries (Canada (k = 1), England (k = 1), Iceland (k = 1), Iran (k = 1), Italy (k = 1), Japan (k = 1), Netherlands (k = 1), United Kingdom (k = 2), United States of America (k = 3)). Findings were mostly evaluated as having moderate quality evidence. See Table S3 in Supplementary Materials for a summary of the quality of evidence provided by the included studies. The study by Foroughi et al., 2020 [47] was found to be an outlier since they were two standard deviations below or above the composite effect size.

3.2. Effects of Psychological Interventions

The pooled analysis of all studies showed a small-to-moderate, but significant, post-intervention effect on depressive symptoms (SMD = −0.49, CI = −0.63; −0.34) in favor of the psychotherapy compared to the control group (Figure 2). There was no heterogeneity (I^2 = 0.00%) between studies. Upon examination of the funnel plot, no publication bias was observed (Figure 3). Egger's test also suggested that there was no publication bias for the overall database (t = −1.69, p = 0.11). Some of these studies assessed depressive symptoms with self-reports, involving clinical judgment, or using both questionnaires. After removing the outlier study [47], the effect on depressive symptoms remaining stayed stable (SMD = −0.47, CI = −0.62; −0.32).

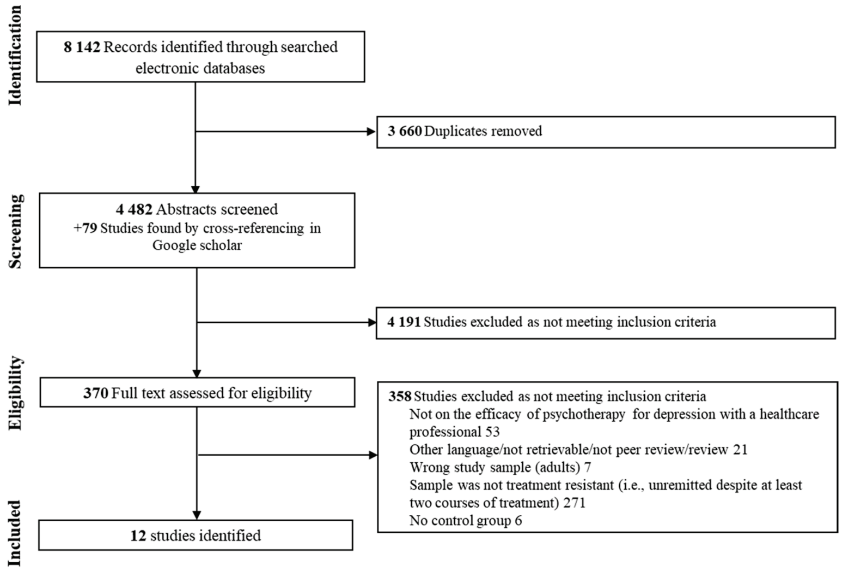

Figure 1. Flow chart of the study selection process.

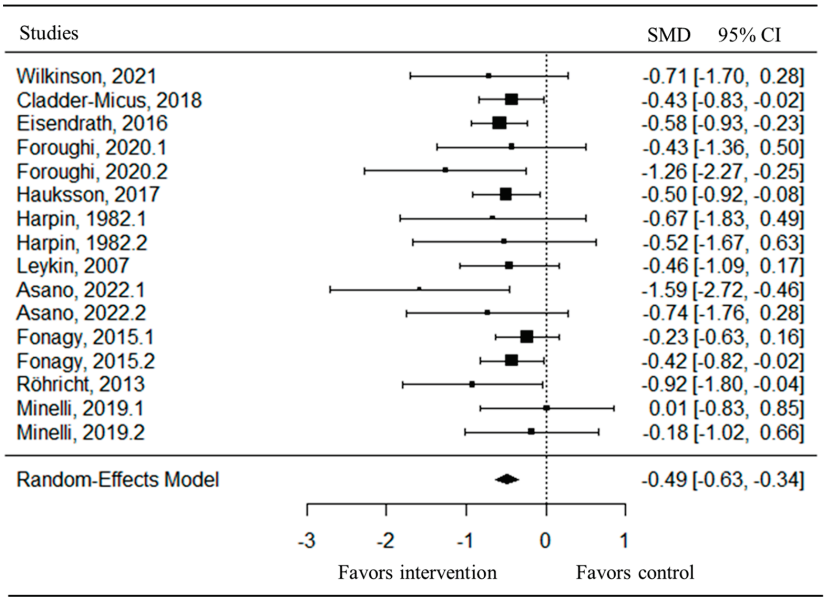

Figure 2. Forest plot of the effect size of the psychotherapy compared to the control group on depressive symptoms [47–57].

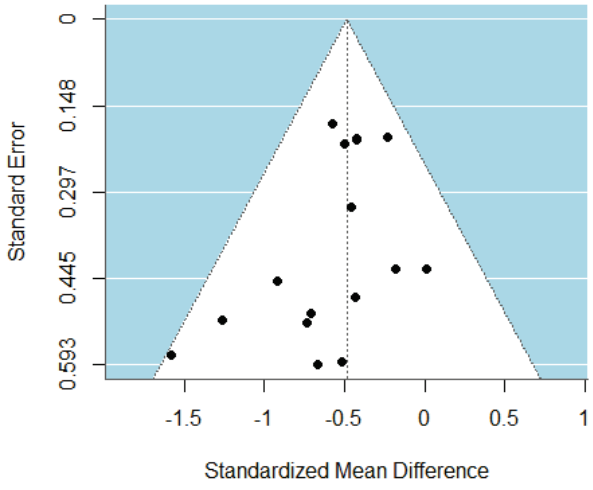

Figure 3. Funnel plot of the meta-analysis of psychotherapy for TRD.

3.3. Effects of Psychological Interventions by Type of Intervention

3.3.1. Mindfulness-Based Cognitive Therapy

An RCT compared eight sessions of MBCT, delivered in groups of 8–12 participants in addition to TAU (n = 44), with TAU alone (n = 52) [48]. Participants were included if their current depressive episode had lasted at least 12 months, had moderate-to-high levels of depressive symptoms, and had at least one trial of antidepressant (appropriate dose for ≥four weeks) and a previous CBT or interpersonal therapy (≥10 sessions) during the current depressive episode. The TAU condition was a naturalistic condition consisting of mental healthcare for depression. It included antidepressant medication, psychological treatment excluding mindfulness-based treatment, support by a psychiatric nurse, and day hospital treatment. At post-therapy, a small but significant improvement was observed in depressive symptoms measured using the Inventory of Depressive Symptomatology-Self Report (SMD = −0.43, CI = −0.83; −0.02) and in quality of life (SMD = 0.45, CI = 0.03; 0.88), favoring MBCT plus TAU. Additionally, moderate improvements were found in mindfulness skills (SMD = 0.67, CI = 0.24; 1.10) and self-compassion (SMD = 0.52, CI = 0.09; 0.95). There was no significant difference between groups in rumination (SMD = −0.38, CI = −0.80; 0.05). Apart from higher baseline rumination, which was associated with a greater reduction in depressive symptoms in the MBCT plus TAU condition compared to TAU alone, most moderators had no significant treatment effect (e.g., sex, age, childhood trauma, number of previous episodes, duration of the current episode, treatment resistance, baseline depression severity). The authors reported no difference between groups in the mean number of treatment sessions or in the number of patients who received TAU. The quality of evidence is graded as moderate.

A second large RCT of eight sessions of MBCT delivered in groups of 6–12 individuals (n = 67) was compared to a health-enhancement program (n = 64), which included behavioral activation [49]. Participants included had a diagnosis of MDD, had a score of 14 or greater on the 17-Hamilton Depression Rating Scale (HDRS), and had undergone two or more adequate antidepressant medication trials during the current episode. At post-therapy, a moderate reduction was found in depressive symptoms measured using the HDRS (SMD = −0.58, CI = −0.93; −0.23) in favor of MBCT. The MBCT showed no significant difference in mindfulness skills (SMD = 0.15, CI = −0.01; 0.30), rumination (SMD = 0.05, CI = −0.39; 0.29), and experiential avoidance (SMD = 0.00, CI = −0.34, 0.34) compared to the health-enhancement program group. In both groups, participants were allowed to make medication changes during treatment, but no significant difference was found between the groups for this variable. The moderators, such as anxiety, presence of a personality disorder, and emotional abuse in childhood, had a significantly higher depressive symptom severity. The quality of evidence was graded as moderate.

A randomized trial compared eight sessions of MBCT in addition to receiving antidepressants (n = 9) to receiving antidepressants alone (n = 9) (i.e., 60 mg citalopram/4–6 weeks, 200 mg sertraline/4–6 weeks plus bupropion (dose and duration not mentioned)) [47]. The participants had a diagnosis of MDD, a minimum of a moderate level of depression, and were resistant to at least two antidepressants. After therapy, compared to the control group, participants receiving MBCT combined with antidepressants showed a large improvement in depressive symptoms measured using the Beck's Depression Inventory II (BDI-II) (SMD = −1.26, CI= −2.27; −0.25), but no significant change was observed when symptoms were assessed using the HDRS (SMD = −0.43, CI = −1.36, 0.50). However, at the 1-month follow-up, a significant difference between groups was found for depressive symptoms assessed with the HDRS (SMD = −2.45, CI= −3.67; −1.23), but not when assessed using the BDI-II (SMD = −0.91, CI = −1.88; 0.06). In addition, post-therapy, the MBCT group showed significant improvements in rumination (SMD = −1.06, CI = −2.04; −0.07) and mindfulness

skills (SMD = 2.16, CI: 1.00; 3.32) compared to the control group. These improvements were maintained at the 1-month follow-up. Finally, no significant change in self-compassion was observed after therapy (SMD = 1.14, CI = −0.57; 2.86). However, a large improvement in favor of the MBCT group was found at the 1-month follow-up (SMD = 3.09, CI = 1.73; 4.46). The quality of evidence was graded as low.

At post-therapy, the pooled analysis of these three studies, including 245 participants, showed a moderate improvement in depressive symptoms (SMD = −0.55, CI = −0.80; −0.31, I^2 = 0.00%) and a small improvement in mindfulness skills (SMD = 0.30, CI = −0.05; 0.55, I^2 = 63.27%) in favor of MBCT compared to the control group. However, there was no significant difference in rumination (SMD = −0.32, CI = −0.72; 0.09, I^2 = 49.18%) and self-compassion (SMD = 1.14, CI = −0.57; 2.86, I^2 = 96.79%) when compared to an active control group. The analysis excluding the outlier study, which included two studies totaling 227 participants, showed that the effect remained unchanged in depressive symptoms (SMD = −0.51, CI = −0.78; −0.25, I^2 = 0.00%), mindfulness skills (SMD = 0.22, CI = 0.03; 0.40, I^2 = 36.21%), rumination (SMD = −0.19, CI = −0.50; 0.12, I^2 = 26.71%), and self-compassion (SMD = 0.31, CI = −0.06; 0.68, I^2 = 44.96%) in favor of MBCT compared to the control group. However, the heterogeneity between studies was reduced by removing the outlier study.

3.3.2. Cognitive Behavioral Therapy

A large randomized trial compared 12 sessions of individual CBT (*n* = 59) and group CBT (*n* = 86; groups of 12–15)—which both included rehabilitation treatment—and rehabilitation treatment alone (*n* = 36) [50]. Participants were inpatients diagnosed with MDD (83.9%) or dysthymia (36.5%) and failed to respond to at least two antidepressant trials of adequate doses and duration. The rehabilitation treatment consisted of psychoeducation, behavioral activation, occupational therapy, relaxation, counseling by a member of the professional health or social care, and medication as needed. Most participants received high doses of antidepressants on arrival, and the medication was continued throughout the study. At post-therapy, a moderate improvement in depressive symptoms was observed on the BDI-II (SMD = −0.50, CI = −0.92; −0.08) and hopelessness (SMD = −0.53, CI = −0.95; −0.11) in favor of individual CBT plus rehabilitation treatment compared to rehabilitation treatment alone. However, these benefits were not maintained at the 18-month follow-up (SMD = −0.14, CI = −0.66; 0.38; SMD = −0.36, CI = −0.88; 0.17). There was no difference between these two groups in anxiety (SMD = −0.17, CI = −0.59; 0.24) and automatic thoughts (SMD = −0.31, CI = −0.72; 0.11), at either post-therapy or 18-month follow-up. No significant difference was found between group CBT plus rehabilitation treatment and rehabilitation treatment alone, or between individual CBT plus rehabilitation treatment and group CBT plus rehabilitation treatment, at either post-therapy or 18-month follow-up. Most comorbidities (i.e., generalized anxiety disorder, panic disorder, post-traumatic stress disorder, hypomanic episode, obsessive–compulsive disorder, psychotic disorder, bulimia, and anorexia) showed no significant impact on treatment outcomes, except for social phobia and substance dependence, which were associated with worse depression severity after the therapy. The quality of evidence ranged from low-to-moderate to moderate-to-high depending on the control group and follow-up duration.

A pilot study began with six ketamine infusions over three weeks, and then the 28 individuals who achieved a clinical response were randomized to 16 sessions of CBT (*n* = 14) or TAU (*n* = 14) [51]. TAU consisted of weekly or every-other-week visits with a study physician for the management of medication and adverse events. The study did not report if there was a difference between groups in medication management. Participants included had a diagnosis of MDD, severe depressive episodes, and were resistant to two

or more adequate courses of antidepressants. At post-therapy, no significant difference was found in depressive symptoms measured with the Montgomery-Asberg Depression Rating Scale (MADRS) (SMD = −0.65, CI = −1.82; 0.55) nor with the Quick Inventory of Depressive Symptomatology-Self Report (SMD = −0.71; CI = 0–1.70; 0.28). The quality of evidence was graded as low-to-moderate.

At post-therapy, the pooled analysis of these two studies (n = 209) showed a significant moderate reduction in depressive symptoms (SMD = −0.53, CI = −0.92; −0.14) in favor of CBT compared to the control group. There was no heterogeneity between studies (I^2 = 0.00%).

3.3.3. Cognitive Therapy

An RCT was conducted comparing 20 to 28 sessions of Cognitive Therapy with 16 weeks of pharmacological treatment on individuals with a diagnosis of MDD and a score of 20 or greater on 17-HDRS [52]. A subanalysis was conducted using data from several prior antidepressant trials. Among those with two or more prior antidepressant trials lasting at least 4 weeks, 15 participants received cognitive therapy, while 29 participants were assigned to the pharmacotherapy group. In the pharmacotherapy group, paroxetine treatment was initiated at 10–20 mg daily for the first week and subsequently increased to a maximum dose of 50 mg daily by week six of therapy. Paroxetine non-responders received additional augmentation therapy with lithium carbonate and/or desipramine after week 8. At post-therapy, depressive symptoms measured with the HDRS were not significantly different between groups (SMD = −0.46, CI = −1.09; 0.17). The quality of evidence was graded as moderate.

A small pilot study included 12 participants experiencing a depressive episode and with a minimum score of 20 on the HDRS. All had previously failed to respond to antidepressants and any other form of therapy. This study compared 26 to 36 sessions of Cognitive Therapy (n = 6) with a waiting list (n = 6) [53]. In the Cognitive Therapy group, a significant person currently living with the participant also took part in therapy sessions. In both groups, participants were monitored by a psychiatrist throughout the treatment period. They received a subclinical dose (25 mg per day) of a tricyclic antidepressant that they were already taking. Those taking no medication at the start of the program were prescribed 25 mg of imipramine per day. At post-therapy, depressive symptoms measured using the Wakefield Depression Scale (SMD = −0.67, CI = −1.83; 0.49) and the HDRS (SMD = −0.52, CI = −1.67; 0.63) were not significantly different between groups. In addition, there was no significant difference between groups in social anxiety (SMD = −0.21, −1.34; 0.93), assertiveness (SMD = −0.22, CI = −1.35; 0.92), as well as adjustment and social behavior (SMD = −0.44, CI = −1.58; 0.71). The quality of evidence was graded as low.

At post-therapy, the pooled analysis of these two studies, involving 56 participants, showed moderate significant difference in depressive symptoms (SMD = −0.51, CI = −1.01; −0.01) between the Cognitive Therapy group and the control intervention. There was no heterogeneity between studies (I^2 = 0.00%).

3.3.4. Long-Term Psychoanalytic Psychotherapy

An RCT was conducted to compare 60 sessions of Long-Term Psychoanalytic Psychotherapy in addition to TAU (n = 67) with TAU alone (n = 62) [54]. The TAU group received care as determined by the referring practitioner or through referrals to specialized services, which could include prescribed medication, but excluded Psychoanalytic Psychotherapy. In the Long-Term Psychoanalytic Psychotherapy group, the participants could not undertake any form of short-term psychological therapy according to National

Institute for Clinical Excellence guidelines. Participants included had a diagnosis of MDD with a minimum duration of two years of the current depressive episode, a minimum score of 14 on 17-HDRS and of 21 on the BDI-II, and at least two failed treatment attempts. HDRS scores assessing depressive symptoms showed no significant difference between the two groups at any time point (i.e., post-therapy, 6-, 12-, and 24-month follow-up). A small decrease in BDI-II scores was observed at post-therapy (SMD = −0.42, CI = −0.82; −0.02) and 6-month follow-up (SMD = −0.50, CI = −0.91; −0.09), and a moderate decrease at 24-month follow-up (24-month: SMD = −0.73, CI = −1.15; −0.31) in favor of Long-Term Psychoanalytic Psychotherapy. Compared with the control group, the Long-Term Psychoanalytic Psychotherapy group displayed significant improvements in social functioning at all time points (SMD ranging from 0.49 to 0.69), fewer well-being deficits at 24-month follow-up (SMD = −0.66, CI = −1.08; −0.24), and a better quality of life at 6-month (SMD = 0.57, CI = 0.16; 0.98) and 24-month follow-ups (SMD = 0.68, CI = 0.27; 1.11). In both groups, the average number of medications increased from two to five during the study, with no significant difference between groups. The quality of evidence was graded as moderate-to-high.

3.3.5. Group Compassion-Focused Therapy

A small pilot RCT was conducted to assess the efficacy of 12 sessions of a group compassion-focused therapy for 4–6 individuals (n = 9), compared to TAU (n = 7) [55]. In addition to a primary diagnosis of MDD (82%) or dysthymia (18%), participants were required to have at least a moderate level of depressive symptoms and to be refractory to two selective serotonin reuptake inhibitors. The TAU group continued to receive their regular medical appointments and may have participated in rehabilitation day care programs. Still, they were asked to refrain from receiving psychological interventions such as counseling or psychotherapy during the study. At post-therapy, while GRID-HDRS scores assessing depression symptoms did not differ between groups (SMD = −0.74, CI = −1.76; 0.28), BDI-II scores significantly decreased in compassion-focused therapy (SMD = −1.59; CI = −2.72; −0.46). No significant difference was observed between the groups in self-compassion (SMD = 0.33, CI = −0.66; 1.33). A large effect was found in favor of group compassion-focused therapy in compassionate engagement both for self (SMD = 1.48, CI = 0.37; 2.60) and for others (SMD = 1.20, CI = 0.13; 2.27); no effect was found for compassionate engagement from others (SMD = 0.30, CI = −0.69; 1.29). The evidence was graded as low-to-moderate quality.

3.3.6. Trauma-Focused Cognitive Behavioral Therapy

A small pilot RCT was conducted to compare 24 sessions of Trauma-Focused Cognitive Behavioral Therapy (n = 10) to eye movement desensitization and reprocessing (n = 12) [56]. Both groups received drug TAU, and adjustments were permitted based on the clinical judgment of the treating physicians. Inclusion criteria were a diagnosis of MDD, a history of at least three lifetime traumatic events, failure to respond to two or more adequate trials of antidepressants from different classes, and an adequate trial of a tricyclic antidepressant. At the post-therapy and 1-month follow-up, there was no difference between the two groups in depressive symptoms measured using the MADRS (SMD = 0.01, CI = −0.83; 0.85; SMD = −0.31, CI = −1.15; 0.54) and the BDI-II (SMD = −0.18, CI = −1.02; 0.66; SMD = −0.33, CI = −1.17; 0.52) in scores of anxiety (SMD = −0.33, CI = −1.18; 0.51; SMD = −0.25, CI = −1.09; 0.59), sleep quality (SMD = −0.26, CI = −1.11; 0.58; SMD = −0.17, CI = −1.01; 0.67), and psychosocial functioning (SMD = −0.08, CI = −0.91; 0.76; SMD = −0.28, CI = −1.12; 0.56). The quality of evidence was graded as moderate.

3.3.7. Group-Based Interpersonal Psychotherapy and Occupational Therapy

A randomized trial was conducted to compare 16 sessions of Group-Based Interpersonal Psychotherapy and Occupational Therapy plus medication management (augmentation and combination strategies) (n = 34) with TAU (n = 30) [58]. In the TAU condition, participants received treatment using available community services. Participants included had a diagnosis of chronic MDD, dysthymic disorder with superimposed MDD (double depression), or MDD in partial remission, had an episode duration of two years or more, and had at least moderate severity of depressive symptoms. Participants had a history of a mean of 2.9 (SD $\pm$ 1.0) failed medication trials, and the majority (85.9%) had previously undergone psychotherapy. At post-therapy, no significant differences were observed in depressive symptoms measured with the de BDI-II (SMD = -0.29, CI = -0.82; 0.25) and in common psychiatric symptoms (i.e., somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety) (SMD = -0.23, CI = -0.77; 0.30). The quality of evidence was graded as moderate.

3.3.8. Body-Oriented Psychological Therapy

An RCT was conducted to compare 20 sessions of Body-Oriented Psychological Therapy (n = 12) to a waiting list (n = 10) [57]. Both groups received TAU, which consisted of ongoing antidepressant medication and outpatient clinical management. Participants had an MDD diagnosis, a duration of the current episode of depression of more than two years, and a total score of $\geq$20 on HDRS, and had failed at least two antidepressant trials and one psychological therapy before the study. At post-therapy, a large significant decrease was found in depressive symptoms measured with the HDRS (SMD = -0.92, CI = -1.80; -0.04) in the Body-Oriented Psychological Therapy group compared with the control group. No significant difference was observed between groups in quality of life (SMD = 0.28, CI = -0.57; 1.12) and self-esteem (SMD = 0.34, CI = -0.52; 1.20). The authors reported no clinically relevant medication change (i.e., drug change within four weeks before entering the study and/or more than 30% dose increase) and/or other psychological treatments. The quality of evidence was graded as moderate.

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis assessing the efficacy of psychotherapy in TRD, which is defined as the failure of at least two treatment trials involving either pharmacotherapy or psychotherapy. In summary, when pooling all kinds of psychotherapies, our meta-analysis revealed a small but significant effect on depressive symptoms (SMD = -0.49, CI = -0.63; -0.34) in favor of the psychological intervention compared to the control group. There is currently no clear consensus regarding the effect size required to determine clinical significance. One study proposed an effect size of SMD = 0.24 as a preliminary threshold for clinical relevance in the treatment of depression [59], while another suggested that effect sizes below d = 0.5 should be considered clinically irrelevant [60]. Although psychotherapy demonstrates statistically significant effects in TRD, the clinical meaningfulness of these effects remains uncertain. Future research should place greater emphasis on evaluating the clinical significance of the outcome. When possible, separate meta-analyses were conducted by type of psychological intervention. MBCT, CBT, and Cognitive Therapy showed a moderate reduction in depressive symptoms compared to active control. These three psychotherapies may share overlapping therapeutic techniques (e.g., identifying cognitive distortions and ruminative thinking patterns). Moreover, the effect sizes associated with these psychotherapies appear to be of similar magnitude. Due to the limited number of studies available (i.e., only one study was identified for each of the treatment modalities), meta-analyses could not be conducted for

other types of psychotherapy. Specifically, Trauma-Focused Cognitive Behavioral Therapy and Group-Based Interpersonal Psychotherapy and Occupational Therapy did not show statistically significant differences compared to active control conditions on depressive symptoms. A large reduction in depressive symptoms was found for Body-Oriented Psychological Therapy compared to an inactive control. Finally, Long-term Psychoanalytic Psychotherapy and Group Compassion-Focused Therapy have mixed results depending on the type of questionnaire used for assessing depressive symptoms. Moreover, most psychotherapies did not show significant effects on secondary outcomes (i.e., rumination, self-compassion, anxiety, and self-esteem) compared to the control interventions. The lack of significant effects on certain secondary outcomes may be partly explained by limited statistical power, as several included studies had small sample sizes. It is also possible that these psychotherapeutic interventions are less effective for these specific outcomes. Future studies with larger samples and targeted outcome measures are needed to clarify these findings.

In comparison, a meta-analysis of 143 studies in depression without specific criteria for treatment resistance showed that psychotherapy had a larger effect (g = −0.66, CI = −0.78; −0.53) compared to TAU [26]. Accordingly, the efficacy of psychotherapeutic interventions appears to be slightly lower in TRD relative to those with non-treatment-resistant depression. However, as the number of studies is not comparable, it is currently not possible to draw conclusions [27,61]. However, one notable finding was the diversity of countries conducting studies, reflecting a widespread global interest in treating TRD, and allowing for the inclusion of diverse cultural perspectives in the research. While this geographic diversity strengthens the generalizability of findings by encompassing a wide range of cultural and healthcare contexts, it also introduces variability that may influence treatment outcomes. A previous meta-analysis on psychotherapy for depression found a significant regional difference in effect sizes ($p < 0.001$), with the lowest effect sizes reported in North America, Europe, and Australia, and the highest in East Asia, South Asia and the Middle East, and North Africa [62].

Although this meta-analysis is clinically relevant, its findings should be interpreted with caution due to several limitations. Firstly, the small number of studies included in this meta-analysis constitutes an important methodological limitation. It limits the robustness of the conclusions that can be drawn. Therefore, it was not possible to conduct meta-analyses by type of psychotherapy for all treatment modalities or by type of control group (i.e., waiting list, TAU, other psychotherapy), which may have led to either underestimation or overestimation of the findings. Previous meta-analyses showed that effect sizes are generally smaller when interventions are compared to active control groups (such as pharmacotherapy or psychotherapy) rather than to TAU or waiting list control groups [63]. Thus, heterogeneity in control conditions across studies may have biased the aggregated outcomes. Furthermore, future studies should include comparisons between psychotherapy and emerging treatments for TRD, such as electroconvulsive therapy, ketamine, and virtual reality-based psychotherapy, to better position psychotherapy within the broader treatment landscape and identify optimal, patient-centered care pathways. Additionally, it was not possible to determine whether one psychotherapy is more effective than another, as no study directly compared different kinds of psychotherapy. A meta-analysis on the response rates in depression without criteria for treatment resistance observed that different psychotherapy modalities (i.e., CBT, Behavioral Activation, Interpersonal Psychotherapy, Problem-Solving Therapy) seemed to have a comparable effect [61]. Nevertheless, all these points underscore the need for further high-quality studies to build a stronger evidence base, particularly for TRD to at least two treatment trials. Indeed, research on TRD is comparatively scarce relative to the larger body of studies on depression without criteria for

resistance to treatment [26,61,64]. Therefore, increased personalized research targeting this specific population is necessary. At present, it would be premature to assess the potential efficacy of specific components of psychotherapies. However, as more studies become available, it will be necessary to examine these components in greater detail to identify the most effective therapeutic elements for treating TRD. It would also be of interest, once more studies become available, to explore whether a dose–response relationship exists between the number of sessions and the effectiveness of psychotherapies. Among the included studies, none reported patient-reported outcomes. Future research should incorporate these measures to better capture the patient's perspective.

Secondly, due to the limited number of studies included, it was not possible to perform sub-analyses based on different characteristics of the sample (e.g., criteria for TRD, TRD severity, sex, comorbidity). The sample was characterised by a higher proportion of women (65%) than men. This is consistent with the literature, which shows that depression is two times more prevalent in women and has significantly higher treatment-seeking rates [65–67]. Sex does not appear to be a significant predictive factor in the therapeutic response to depression [68,69]. However, this sex imbalance may limit the external validity of the findings, particularly regarding their applicability to males with TRD. A dedicated analysis would be relevant to determine whether this holds specifically in the context of TRD. In addition, only one study excluded all comorbidities (e.g., anxiety disorder, personality disorder). Our findings may be underestimated, as comorbidity appears to reduce the effectiveness of psychotherapy relative to what might be observed in a more diagnostically homogeneous TRD population [70]. Thus, the presence of comorbidities may obscure treatment-specific effects and complicate the identification of optimal therapeutic strategies for more homogeneous TR-MDD subgroups. In addition, comorbidities may introduce greater heterogeneity into study samples, potentially increasing variability in outcomes. However, as comorbidity is highly prevalent in individuals with MDD, this allowed a better representation of the population with a depressive disorder [71–73]. Indeed, the inclusion of individuals with comorbidities enhances the generalizability of the results to typical clinical settings, where strict diagnostic exclusions are rarely feasible. Regarding the inclusion criterion for TRD, which requires at least two courses of treatment, the lack of consensus on its definition and, particularly, what constitutes an adequate dose and duration, results in heterogeneity across populations enrolled in clinical trials and observed in real-world practice [15,74]. While this variability may limit the interpretation of findings, it may also better reflect the heterogeneity observed in real-world clinical practice [74]. All the limitations discussed may affect the extent to which the findings can be generalized. Thirdly, it was not possible to assess the medium- and long-term effectiveness of psychotherapy, as only two studies analyzed the effect beyond a 6-month follow-up [50,54]. Consequently, the sustained effects of psychotherapy cannot be determined. This highlights the need for future trials to incorporate longer follow-up periods to evaluate the durability of treatment effects better.

Fourthly, although concurrent pharmacotherapy could represent a potential confounding factor on the independent effect of psychotherapies, the majority of studies controlled for this by assessing medication changes during the trials and allowing pharmacotherapy use in both groups. Furthermore, combined treatment approaches (psychotherapy and pharmacotherapy) are recommended in current guidelines for the management of TRD and represent the typical trajectory of care for this population [11,23–25,75]. Consequently, the sample provides a more representative depiction of individuals with TRD.

Fifth, restricting the inclusion to studies published in French and English may have introduced a potential language bias, as relevant studies in other languages may have been excluded.

Finally, findings were mostly evaluated as having moderate-quality evidence. However, it is important to note that the quality of evidence varied considerably, ranging from very low quality in quasi-experimental trials to moderate-to-high quality in single-blind RCTs. Several factors contributed to the lower quality of evidence across trials, including the absence of blinding and controlled randomization procedures, small sample sizes that may lead to limited statistical power and the generalizability of the findings, and a lack of long-term follow-up. This is critical, as an RCT with methodological limitations is insufficient to support evidence-based practice. Therefore, the quality of included studies must be carefully considered when interpreting the efficacy of interventions. To overcome all of these limitations, further studies are needed with larger sample sizes, longer follow-up periods, and comparison to other psychotherapies. The literature on this topic remains in its early stages, highlighting the clear need for further research that generates high-quality evidence using gold-standard methodologies, including adequately powered sample sizes to detect treatment superiority and follow-up periods exceeding six months to assess the durability of psychotherapeutic effects [76] and the generalizability of the findings. Future research should explore the feasibility and effectiveness of implementing psychotherapies for TRD in real-world clinical settings. This includes evaluating potential barriers (e.g., accessibility, clinician training, patient adherence) as well as facilitators (e.g., acceptability, integration into multidisciplinary care). Among the studies included in this meta-analysis, cost-effectiveness evaluations were available for CBT and long-term psychoanalytic psychotherapy. Augmented CBT for TRD has been shown to be cost-effective for patients currently experiencing moderate-to-severe symptoms, both in secondary mental health care and in primary care settings [77,78]. In contrast, long-term psychoanalytic psychotherapy was not found to be cost-effective when compared with TAU [79]. Further cost-effectiveness studies are needed to assess other psychotherapy modalities for TRD.

5. Conclusions

Given the high prevalence of individuals with TRD who have undergone at least two treatments, and considering that TRD is a leading cause of disability and societal economic burden, prioritizing further research into effective treatments for TRD are essential. This systematic review and meta-analysis aim to summarize the literature on the efficacy of psychotherapies for TRD. However, due to the number of study limitations, there is currently limited evidence available about the effectiveness of psychotherapy for depressive symptoms in TRD. When pooling all the psychotherapy studies, the meta-analysis showed a small to moderate effect compared to control interventions (mainly TAU). Ultimately, further research on psychotherapies is necessary to enhance treatment strategies for this complex population. New avenues have also been emerging in the field for MDD, such as the use of virtual reality personalized for each patient, which, to our knowledge, has not yet been investigated explicitly in TRD. Standard treatments for depression may be insufficient for TRD, which could necessitate the implementation of personalized medicine approaches.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jpm15080338/s1, Table S1. PRISMA Checklist; Table S2. Electronic search strategy for the systematic review conducted; Table S3. Details of the retrieved studies included.

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An Assessment of Real-World Evidence and Other Sources Supporting Payer Coverage Decisions for Pharmacogenomic Testing in Psychiatry

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Abstract: Background: Sources and evidence cited to inform payer coverage decisions on pharmacogenomic (PGx) testing in psychiatry are presently underexplored. **Methods:** We conducted a qualitative and quantitative assessment of publicly available coverage policies from 14 US payers, examining the number and both the type and source of citations across policies and coverage decisions. Payers were classified as for-profit or mutual fund versus non-profit or government, and their coverage decisions were categorized as either coverage (limited or specified) or no coverage. **Results:** Among 32 unique sources cited, peer-reviewed literature as a single source was most frequently cited across all policies. Of 207 peer-reviewed papers cited across all policies, 40% (n = 83) were psychiatry-specific real-world evidence (RWE) studies. No statistically significant relationships were observed when comparing variance in the number of citations per policy by payer type (p = 0.22) or coverage decision (p = 0.75; unadjusted variance of 61.25 and an adjusted variance of 60.98 for both comparisons). For-profit or mutual fund payers and/or payers providing no coverage cited systematic reviews and non-randomized controlled cohort RWE studies most often. Non-profit or government payers and/or payers providing coverage cited case series or case-control RWE studies most often. Six psychiatry-specific RWE studies and contributions from 13 distinct sources were often cited, regardless of payer type or coverage decision. **Conclusions:** RWE, among several sources, are cited in many forms and to varying degrees among payers providing coverage decisions for PGx testing in psychiatry, with coverage determinations being largely based on how certain payers interpret evidence on the clinical value of testing.

Keywords: pharmacogenomics; psychiatry; payer coverage; precision medicine; real-world evidence

1. Introduction

Pharmacogenomic (PGx) testing is a molecular diagnostic strategy that tailors medication and dosage selection based on a patient's genetic profile or drug metabolism phenotype. Accumulating research indicates that PGx testing in psychiatric care settings has

the potential to improve the pharmacological management of mental health conditions by optimizing medication and dosage selection, decreasing adverse drug events, and reducing healthcare spending per patient [1]. In fact, the Clinical Pharmacogenetics Implementation Consortium (CPIC) offers prescribing guidelines based on substantial high to moderate evidence for seven (7) psychiatric drugs with US Food and Drug Administration (FDA) labeling (i.e., CPIC Level A status for PGx biomarkers *CYP2D6* and *CYP2C19* and respective drug-gene pairs with citalopram, escitalopram, amitriptyline, atomoxetine, nortriptyline, paroxetine, and vortioxetine; see Supplementary File S1 in Supplementary Materials).

In additional to variable clinical recommendations from the above sources, access to and adoption of PGx testing in psychiatric care settings vary significantly due to a myriad of patient, provider, and health system factors, with cost being a major contributor [2]. Moreover, recent conversations among payers, bioethicists, and clinicians reflect ongoing uncertainty about the value and clinical utility of PGx testing in psychiatry [3]. Current psychiatric treatment often relies on both trial and error and polypharmacy approaches, further complicating efforts to establish PGx testing as standard care. While further evidence is needed to validate the real-world effectiveness of PGx testing psychiatry, the pace of evidence generation is closely tied to implementation factors such as insurance coverage. For many patients, access to genetic testing is primarily determined by cost, making insurance coverage a critical factor in ensuring the affordability of clinical-grade testing.

A prior analysis found variations in insurance coverage for PGx testing in oncology, with the evidence cited within insurance coverage policies playing a significant role in influencing payer coverage decisions [4]. In oncology, payer decisions often reflect the availability of strong clinical evidence—especially randomized controlled trials and large-scale real-world studies—that demonstrate consistent benefit and are backed by clinical guidelines or regulatory endorsements. These features help create a clearer path to coverage. In contrast, evidence supporting PGx testing in psychiatry is more diffuse if not inconclusive as evidence bases supporting the utility of PGx testing in psychiatry remain provisional or under development for 32 drug–gene pairs (see Supplementary File S1 in Supplementary Materials).

Considering this, there is a present lack of research directly examining payer coverage decisions for PGx testing in psychiatry and sources and evidence cited in those decisions. To address this gap, we evaluated citations listed within and across a national sample of payer coverage policies and characterized evidence cited and organized by US payer types and decisions to better understand the role of evidence and types of evidence in coverage decisions for testing in psychiatry [5,6]. We did not assess the rationale behind payer evidence selection and underlying decisions in each payer policy. Specifically, we assessed payer types and coverage decisions for PGx testing in psychiatry, categorized evidence, and sources cited in policies to support payers' coverage decisions, assessed the potential relationships that exist between payer type or coverage decisions and the number of sourced cited, and, lastly, summarized evidence cited in coverage policies.

2. Methods

2.1. Payer Policy Search and Selection

A systematic search was conducted in October 2024 online via Google, payer websites, and a commercial database (PolicyReporter, Morrisville, NC, USA) using any combination of the following terms to identify US payer coverage policies effective during that time: pharmacogenomic, pharmacogenetic, genetic, psychiatry, mental, behavioral, coverage, policy, and insurance. Information sought/sourced publicly available payer coverage policies from national, regional, state, and local payers in the US.

Our search initially identified 14 unique payers and 38 payer plans serving Medicare, Medicaid, individual, commercial (parent company and subsidiaries), self-funded or employer-sponsored, or unspecified markets. From there, policies were consolidated to ensure adequate representation across national, regional, state, and institutional payers, market share, and for-profit versus non-profit status. Policies were included in the sample if the policy represented the parent company (commercial payers only) and contained a policy effective date, a PGx test, or Current Procedural Terminology code (billing code for medical services and procedures) relevant to psychiatry or a biomarker with a current PGx US Food and Drug Administration labeling section [7], and a coverage decision for a single or multi-panel genetic test with claims of effectively guiding psychiatric medication selection or dosage was specified in the policies.

Policies focused specifically on genetic testing for intellectual disabilities (e.g., autism spectrum disorder), substance use, or abuse disorders (e.g., prediction for opioid use disorder), or central nervous system disorders associated with age-related decline (e.g., dementia) were excluded from the analysis.

2.2. Policy Content Analysis

The following information was extracted and catalogued from each policy selected for inclusion to closely evaluate evidence base and sources cited alongside coverage decisions:

- Policy type (general or psychiatry specific)
- Payer type
  - For-profit or mutual fund: entity with a tax filing status based on individual shareholder investments or an investment fund.
  - Non-profit or government: entity with a tax filing status based on public benefit, charity, or social cause.
- Coverage determination
  - No coverage
  - Coverage
    - Specified (i.e., coverage for a specific test/subpopulation).
    - Conditional (i.e., coverage based on meeting clinical or prior authorization criteria).
- Active company subsidiaries (when applicable and when information was freely available online) to exclude non-parent or subsidiary policies with redundant or boilerplate language seen in parent company policies (commercial payers only).
- References cited
  - For policies specific to PGx testing for mental health or psychiatric purposes, all references were quantified and catalogued.
  - For policies non-specific to PGx testing for mental health or psychiatric purposes, only references relevant to mental health or psychiatry were quantified and catalogued.

2.3. Evaluation of Payer Types and Coverage Decisions

Payers were categorized by type (for-profit or mutual fund versus non-profit or government) and analyzed coverage decisions (covered [conditional or specified] versus not covered). Summary statistics (the average number of citations) were obtained for general comparison (for-profit or mutual fund versus non-profit or government; covered [conditional or specified] versus not covered) using Microsoft Excel. Given, the non-normal distribution of data, Wilcoxon rank-sum (Mann–Whitney) tests were conducted at a 95%

confidence interval (CI) using STATA to determine if statistically significant relationships exist between payer type/coverage decision and the number of sources cited.

2.4. Assessment of Sources Cited in Payer Policies

Peer-reviewed sources cited in payer policies were further evaluated by two authors (R.M.H.-S. and M.N.) along the following criteria until >95% agreement was reached, with a third author (C.Y.L.) available to resolve potential disagreement and assess inter-rater reliability: publication year, Oxford Centre for Evidence-Based Medicine 2011 (OCEBM) Evidence Level (see Supplementary File S2 in Supplementary Materials), psychiatry-specific, and classification as an RWE study according to a detailed definition of RWE and RWE classification criteria described by Rahman et al. [8,9]. There is increased interest and consideration among regulators, payers, and health systems in using RWE to address research questions concerning the clinical and economic utility of medical products, including but not limited to PGx testing [9–12]. For this reason, a descriptive summary of peer-reviewed sources classified as RWE studies and psychiatry-specific studies was generated to determine OCEBM Level of Evidence therein and date range. Microsoft Excel software was used to assess and summarize quantitative findings and key findings from the most commonly cited psychiatry-specific RWE studies.

2.5. Ethics Statement

Our work was not intended as human subjects research and solely involved a review of publicly available information online. Payer entity names were omitted for privacy and can be made available upon direct request.

3. Results

3.1. Payer Assessment and Coverage Analysis

Upon closely evaluating payer policies to exclude non-parent/subsidiary policies with redundant or boilerplate language seen in parent company policies (commercial payers only), our final analyses included 14 unique payers and policies. Variations in coverage for PGx testing were observed (no coverage [n = 7], conditional coverage [n = 3], and specified coverage [4]) among for-profit or mutual fund (n = 7) and non-profit or government (n = 7) payers. These policies together had 346 total citations from 32 distinct sources across all payer policies applicable to PGx testing in psychiatry (see Table 1). The number of citations per unique payer ranged from zero (0) to 77.

Table 1. Overview of number and source of citations across payer coverage policies for pharmacogenomic (PGx) testing in psychiatry, organized by payer type and by coverage decisions.

	Number of References per Payer Type (For-Profit or Mutual Fund [n = 7] and Non-Profit or Government [n = 7]) and per Coverage Decision (Covered [n = 7] and no Coverage [n = 7])			
Source Cited (Total of 32)	**For-Profit or Mutual Fund (215 Total References)**	**Non-Profit or Government (131 Total References)**	**Covered (Specified or Partial; 146 Total References)**	**Not Covered (200 Total References)**
Centers for Medicare and Medicaid Services (CMS; 16 total citations)	4 (2%)	12 (9%)	11 (8%)	5 (3%)
Centers for Disease Control and Prevention (CDC; 8 total citations)	3 (1%)	5 (4%)	6 (4%)	2 (1%)
United States (US) Food and Drug Administration (FDA; 14 total citations)	10 (5%)	4 (3%)	5 (3%)	9 (5%)
UptoDate (4 total citations)	3 (1%)	1 (1%)	1 (1%)	3 (2%)
National Institute of Health (NIH; 9 total citations)	9 (4%)	0 (0%)	3 (2%)	6 (3%)

Table 1. *Cont.*

Source Cited (Total of 32)	Number of References per Payer Type (For-Profit or Mutual Fund [n = 7] and Non-Profit or Government [n = 7]) and per Coverage Decision (Covered [n = 7] and no Coverage [n = 7])			
	For-Profit or Mutual Fund (215 Total References)	Non-Profit or Government (131 Total References)	Covered (Specified or Partial; 146 Total References)	Not Covered (200 Total References)
Department of Energy (2 total citations)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Federal Register (1 total citation)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)
PharmGKB (2 total citations)	1 (0.5%)	1 (1%)	1 (1%)	1 (0.5%)
American College of Medical Genetics and Genomics (ACMG; 10 total citations)	10 (5%)	0 (0%)	9 (6%)	1 (0.5%)
International Statements or Guidelines (1 total citation)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Peer-reviewed literature (207 total citations)	132 (61%)	75 (57%)	78 (53%)	129 (65%)
Industrial or market solution [a] (13 total citations)	2 (1%)	11 (8%)	9 (6%)	4 (2%)
Clinical Pharmacogenetics Implementation Consortium (CPIC; 12 total citations)	6 (3%)	6 (5%)	9 (6%)	3 (2%)
News article (1 total citation)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Canadian Agency for Drugs and Technologies in Health (CADTH; 2 total citations)	1 (0.5%)	1 (1%)	1 (1%)	1 (0.5%)
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH; 1 total citation)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
International Society of Psychiatric Genetics (1 total citation)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Agency for Healthcare Research and Quality (AHRQ; 1 total citation)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)
Payer Technology Evaluation Center (4 total citations)	4 (2%)	0 (0%)	0 (0%)	4 (2%)
PGx test provider webpage (3 total citations)	3 (1%)	0 (0%)	0 (0%)	3 (2%)
Academic resources [b] (1 total citation)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)
Association for Molecular Pathology and/or College of American Pathologists (6 total citations)	4 (2%)	2 (2%)	2 (1%)	4 (2%)
ClinKey (1 total citation)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)
Emergency Care Research Institute (ECRI) Institute (7 total citations)	7 (3%)	0 (0%)	0 (0%)	7 (4%)
Hayes Knowledge Center (6 total citations)	6 (3%)	0 (0%)	0 (0%)	6 (3%)
Payer health guidelines (4 total citations)	3 (1%)	1 (1%)	2 (1%)	2 (1%)
Subject Matter Panel and Advisory Committee [c] (4 total citations)	2 (1%)	2 (2%)	3 (2%)	1 (0.5%)
American Association for Clinical Chemistry (1 total citation)	0 (0%)	1 (1%)	0 (0%)	1 (0.5%)
American Psychiatric Association (1 total citation)	0 (0%)	1 (1%)	0 (0%)	1 (0.5%)
International Society of Psychiatric Genetics (1 total citation)	0 (0%)	1 (1%)	0 (0%)	1 (0.5%)
Government agency health technology assessment (2 total citations)	0 (0%)	2 (2%)	0 (0%)	2 (1%)
National Society of Genetic Counselors (1 total citation)	1 (0.5%)	0 (0%)	1 (1%)	0 (0%)

[a] Company advertising and selling operational or consultative services and solutions to healthcare service providers. [b] Academic-derived teaching or reference tool for healthcare providers and researchers. [c] Convened panel or committee of subject matter experts.

3.2. Statistical Assessment of Sources Cited

Statistical analyses showed high variation in the mean number of references cited according to payer type and coverage decision, as well as comparatively large and unequal variance in number of sources cited across policies, but these were not statistically significant. An average of 30.71 references were cited by for-profit or mutual fund compared to an average of 18.71 references cited by non-profit or government payers. An average of 28.86 references were cited by payers providing some form of coverage compared to 28.57 references cited by payers providing no coverage.

On average, 24.71 citations were observed across all policies (95% CI: 10.9 to 38.53) with variance in the number of references cited per policy and across all policies, regardless of payer type and coverage decision, being 572.37 (95% CI: 300.82 to 1485.57). When comparing the number of citations per policy according to payer type, Mann–Whitney tests showed a non-statistically significant ($p = 0.22$) unadjusted variance of 61.25 and an adjusted variance of 60.98. Upon comparing the number of citations per policy according to coverage decision, Mann–Whitney tests showed a higher level of statistical insignificance ($p = 0.75$) for the same unadjusted variance of 61.25 and an adjusted variance of 60.98.

3.3. Assessment of Sources Cited Across Payer Types

We observed overlap in terms of for-profit or mutual fund and non-profit or government payers citing at least one (1) reference from the same source. Specifically, both for-profit or mutual fund and non-profit or government payers cited work from the following eleven (11) sources: US Centers for Medicare and Medicaid Services (CMS), US Centers for Disease Control and Prevention (CDC), US FDA, UptoDate, PharmGKB, industrial or market solutions (which do not disclose or cite discernable evidence), Clinical Pharmacogenetics Implementation Consortium (CPIC), Canada's Drug Agency (CDA) formerly known as Canadian Agency for Drugs and Technologies in Health (CADTH), Association for Molecular Pathology and/or College of American Pathologists (AMP/CAP), payer health guidelines, and subject matter panel and advisory committees (see Table 1). Payers providing some form of coverage or no coverage cited work from the following thirteen (13) sources: US CMS, US CDC, US FDA, UptoDate, National Institute of Health (NIH), PharmGKB, Industrial or market solution, CPIC, CADTH, AMP/CAP, American College of Medical Genetics and Genomics (ACMG), payer health guidelines, and subject matter panel and advisory committees (see Table 1).

3.4. Assessment of Peer-Reviewed Literature Cited Across Payer Types

Peer-reviewed literature was cited most frequently, compared to all other reference sources, and in similar proportion among both for-profit or mutual fund and non-profit or government payer types (132 out of 215 total references [61%] and 75 out of 131 total references [57%], respectively). Likewise, peer-reviewed literature was most cited across all payers, with payers providing no coverage cited peer-reviewed literature at a higher proportion (129 of 200 [65%]) than payers providing some form of coverage (78 of 146 [53%]).

3.5. Assessment of RWE in Peer-Reviewed Literature Cited Across Payer Types

Of all peer-reviewed article citations ($n = 207$), 82 citations were determined upon assessment by the authors (R.M.H.-S. and M.N.) as psychiatry-specific RWE studies (40%). Publication years for these studies ranged from 2005 to 2024 and publications spanned OCEBM Levels of Evidence ranging from 1 to 5 (see Figure 1). When stratified for coverage decision (Figure 1A), payers choosing to cover testing most frequently cited RWE studies at OCEBM Level of Evidence 4 (13 out of 29 citations). Payers declining coverage most frequently cited RWE studies at OCEBM Levels of Evidence 1 and 3 (19 out of 53 and 18

out of 53 citations, respectively). When stratified by payer type (Figure 1B), non-profit or government payers most frequently cited RWE studies at OCEBM Level of Evidence 4 (12 out of 34 citations). For-profit or mutual fund payers most frequently cited RWE studies at OCEBM Levels of Evidence 1 and 3 (17 out of 48 and 16 out of 48 citations, respectively).

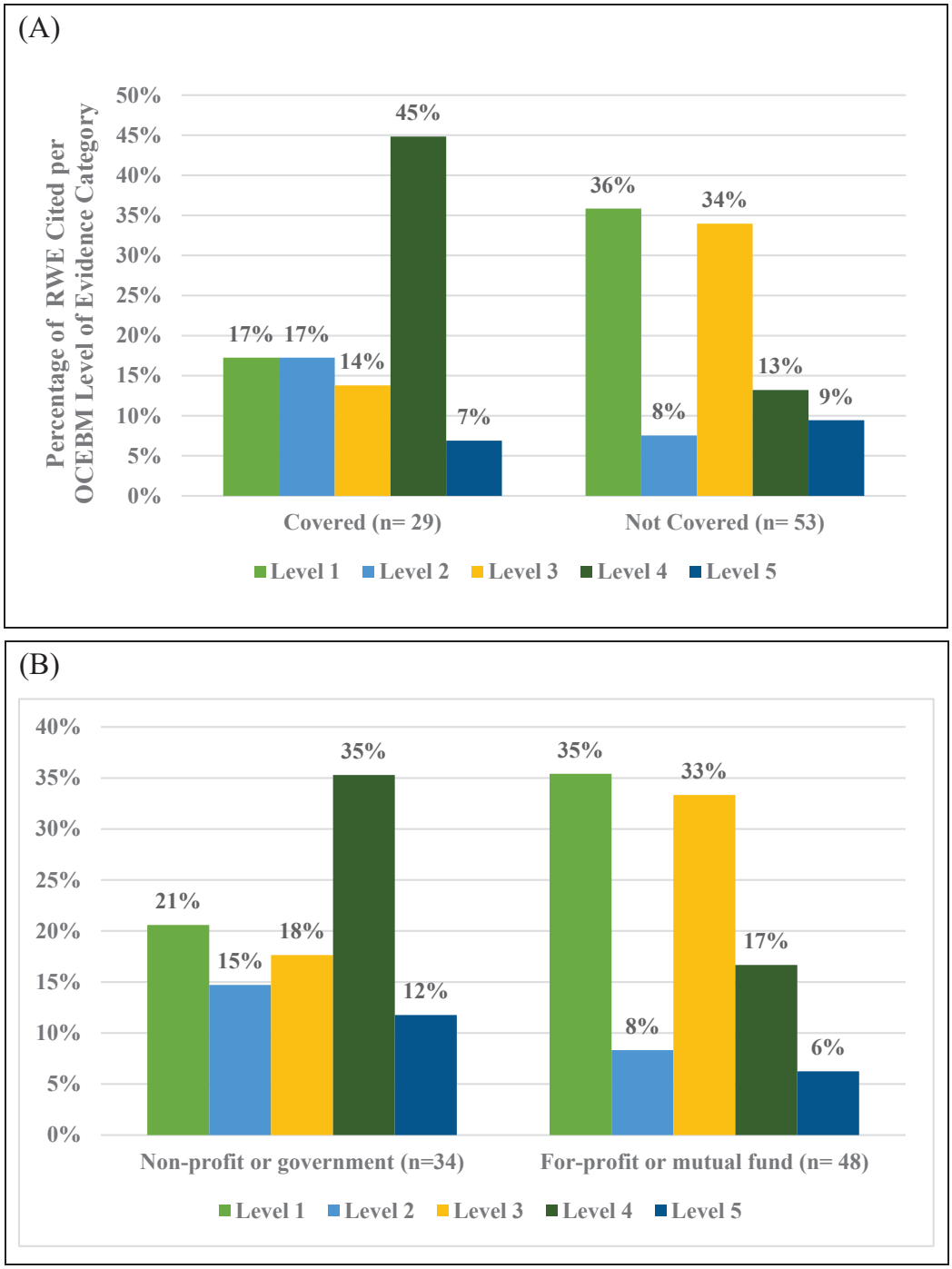

Figure 1. Summary of real-world evidence (RWE) cited in payer policies for PGx testing in psychiatry, categorized by Oxford Centre for Evidence-Based Medicine 2011 (OCEBM) Level of Evidence category and stratified by coverage decision (**A**) and payer type (**B**). Level 1: Systematic review of studies reflecting local and current random sample or censuses. Level 2: Systematic review of surveys that can be matched to local circumstances (includes randomized trials and observational studies with dramatic effects). Level 3: Local non-random sample studies (includes cohort studies and non-randomized controlled cohorts). Level 4: Case series studies (includes case-control and historically controlled studies). Level 5: Studies reflecting mechanism-based reasoning.

We identified six (6) psychiatry-specific RWE studies cited more than once and in more than one payer policy and within the most frequently categorized OCEBM levels in Figure 1 (i.e., studies categorized in Levels 1, 3, and 4; PMID 22198443, 23047243, 24018772, 25686762, 26445691, and 29690793; see Table 2) [13–17]. Key findings from each study identified are summarized in Table 2. No studies were identified based on this description at OCEBM Level 4. With the exception of one (1) paper (PMID 22198443, OCEBM Evidence Level 3, Not Covered), most papers (n = 5) cited were accompanied by either a Covered or Not Covered payer decision and published between 2021 and 2018 [13]. Also, with the exception of one (1) paper (PMID 29690793, OCEBM Evidence Level 1, Both Covered and Not Covered), most papers (n = 5) conveyed results indicating therapeutic benefit associated with PGx testing (i.e., changes in medication dose due to PGx biomarker status, reduction in psychiatric symptoms and medication side effects following PGx-guided treatment, measurable effect of PGx-guided treatment based on treatment severity, and increase in quality of life [12].

Table 2. Key findings or conclusions within psychiatry-specific RWE studies (n = 6) cited more than once and in more than one payer policy and at the top Oxford Centre for Evidence-Based Medicine 2011 (OCEBM) Evidence Levels observed across all policies.

Study PMID (OCEBM Evidence Level)	Publication Year	Payer Coverage Decision(s)	Key Findings or Conclusions
22198443 (Level 3)	2012	Not Covered (2 policies)	Poor metabolizers and ultra-rapid metabolizers received significantly higher chlorpromazine equivalent doses than extensive metabolizers and intermediate metabolizers. There was a tendency that the increase primarily was caused by CYP2D6-dependent antipsychotics and not as expected by CYP2D6-independent antipsychotics.
23047243 (Level 3)	2012	Both Covered (1 policy) and Not Covered (3 policies)	A greater reduction in overall Quick Inventory of Depressive Symptomatology, Clinician Rated (QIDS-C16), and Hamilton Rating Scale for Depression (HAM-D17) scores were achieved with PGx-guided treatment.
24018772 (Level 3)	2013	Both Covered (1 policy) and Not Covered (1 policy)	Study replicated the magnitude of effect previously observed in a prior smaller prospective pilot study (23047243). Reduction in depression scores from the baseline to the 8-week visit was greater in the PGx-guided group than in the PGx-unguided group.
25686762 (Level 1)	2015	Both Covered (1 policy) and Not Covered (1 policy)	8-week improvement in depressive symptoms in the three studies assessed displayed the same trend, with clinical outcomes differing overall as a function of the most severely categorized medication patients was prescribed at the study baseline.
26445691 (Level 3)	2015	Both Covered (1 policy) and Not Covered (1 policy)	Majority of patients showed clinically measurable improvement (rated as very much improved, much improved, or minimally improved), with most demonstrating clinically significant improvement. Among individuals with $\geq$ 2 prior treatment failures, the majority showed clinically measurable improvement. Patients also reported significant decreases in depression, anxiety, and medication side effects and increases in quality of life.
29690793 (Level 1)	2018	Both Covered (1 policy) and Not Covered (2 policies)	At present, there are insufficient data to support the widespread use of combinatorial pharmacogenetic testing in clinical practice, although there are clinical situations in which the technology may be informative, particularly in predicting side effects.

PMID: PubMed identification number (https://pubmed.ncbi.nlm.nih.gov/ (accessed on 25 May 2025)).

4. Discussion

Here, we report high variance in the number of citations per payer coverage policy for PGx testing, regardless of payer type and coverage decision. Although no statistically significant relationships were observed between payer type or coverage decision and the number of references cited per payer policy, a higher level of statistical insignificance was observed when assessing this relationship according to coverage decision (versus payer type). We also observed that payers may consider a variety factors, including but not limited to peer-reviewed studies containing RWE, to support their decisions around coverage for PGx testing in psychiatry. Next, we observed that non-profit or government payers often cited RWE studies at OCEBM Level of Evidence 4, whereas for-profit or mutual fund payers often cited RWE studies at OCEBM Levels of Evidence 1 and 3. Payers choosing to cover testing often cited RWE studies at OCEBM Level of Evidence 4, whereas payers declining coverage often cited RWE studies at OCEBM Levels of Evidence 1 and 3. Lastly, where matters of payer alignment might arise, both for-profit or mutual fund and non-profit or government payers cited references from the same 11 same sources (US CMS, US CDC, US FDA, UptoDate, PharmGKB, industrial or market solutions, CPIC, CDA, AMP/CAP, payer health guidelines, and subject matter panel and advisory committees). Payers, regardless of type or coverage decision, cited six (6) psychiatry-specific RWE studies more than once (PMIDs 22198443, 23047243, 24018772, 25686762, 26445691, and 29690793).

Alongside these findings, we provide the scientific community with a methodological approach that may be useful to help individuals understand evidence and other sources cited in payer coverage policies for PGx testing in psychiatry. We anticipate that these methods can be applied across other therapeutic areas outside of psychiatry and for similar investigational purposes, particularly in situations where patients are unable to obtain direct to consumer (DTC) or cash price negotiation pathways to access PGx testing.

Notwithstanding one payer with zero sources cited and regardless of payer type, payers cited peer-reviewed literature most frequently in their policies, demonstrating general payer alignment around the use of peer-reviewed literature to substantiate coverage decisions. We observed that for-profit or mutual fund payers or payers providing no coverage for PGx testing cited peer-reviewed literature most often and psychiatry-specific RWE studies at OCEBM Levels of Evidence 1 and 3 more frequently than payers providing coverage. Non-profit or government payers or payers providing coverage for PGx testing most frequently cited psychiatry-specific RWE studies at OCEBM Levels of Evidence 4. These patterns suggest that for-profit or mutual fund payers and payers denying coverage may either weigh or favor interpretations based on a totality of evidence (i.e., systematic reviews) and RWE generated through non-randomized controlled cohort studies more than non-profit or government payers and payers providing coverage who may either weigh or favor RWE in case series studies.

Regardless of payer type or coverage decision, payers seemed to consult many of the same additional sources (i.e., US CMS, US CDC, US FDA, UptoDate, PharmGKB, etc.). Also, among the six studies cited at the most common Oxford Centre for Evidence-Based Medicine 2011 (OCEBM) Evidence Level, classified as both RWE studies and psychiatry-specific, and with two or more citations among payers in our sample, no specific patterns were observed with respect to a payer coverage decision based on key study outcomes or conclusions. Yet, given that payers deciding to cover or not cover testing frequently cited these six RWE studies, it is possible that these studies might serve as useful sources to support engagement among payers. This could be useful to support payer engagement as (1) payers continue to discuss or deliberate evidentiary needs and considerations for PGx testing in psychiatry, and (2) as evidence on the clinical utility of PGx testing in psychiatry continues to develop.

Overall, our findings underscore the need for solutions that have been proposed in prior work, such as the development of standardized data and evidence review processes among payers, payer engagement in RWE study design, use of incentives and partnerships to lower barriers to RWE generation, education of payers and providers concerning the use of RWE and PGx testing, learning payer preferences for RWE with respect to PGx testing, and frameworks for conducting outcome-based contracting for PGx testing [12,18,19]. In addition, given that clinical outcomes appear to be a key consideration for payers, future RWE studies should prioritize investigating the impact of PGx testing on psychiatric treatment selection and outcomes, particularly for specific beneficiary populations rather than the total population [18,20,21].

As efforts grow to engage payers more directly in the design and execution of real-world evidence (RWE) studies, it is important to remain attentive to the potential for bias that such collaborations might introduce. Payers can bring practical insight into coverage criteria and patient access, which can potentially strengthen the relevance of study design. However, their involvement could also lead to concerns about undue influence on study outcomes or selective emphasis on evidence that aligns with business objectives. To mitigate these risks, future research partnerships should prioritize independent oversight, transparency in protocol development, and pre-specified analytic plans. Multi-stakeholder governance models that include neutral third parties—like academic researchers, clinicians, and patient representatives—may help ensure that payer priorities inform but do not dominate the scientific process. Establishing clear boundaries around payer involvement can foster mutual trust while safeguarding the integrity and credibility of the resulting evidence base.

Amid growing demand for public transparency, and as beneficiaries may have questions or hold concerns about how payer entities engage in the selection, listing, or preponderance of scientific evidence, the presence or absence of certain economic or business interests that could favor a specific payment approach holds tremendous beneficiary and provider interest. Payers, like clinicians, hold an obligation or right to deny any rendering of services, including molecular testing, where risks of potential harm due to conflicting or inconclusive evidence, and thus a lack of interpretation around medical necessity, outweigh the uncertainty of benefit. Patients today, however, have access to DTC genetic testing mechanisms that allow market demand and forces to elevate the patient, if not solely clinical, value of PGx testing in psychiatry. Amid this push-and-pull dynamic between payers and patients, prescribing clinicians have an ethical obligation to withhold recommendations for testing that could pose unnecessary or disproportionate risks of harm (e.g., health risk due to prescribing or de-prescribing) while also respecting and upholding competent patient autonomy. All these factors should be considered to mitigate or avoid any negative influence on the scientific integrity of future investigations that will involve payer engagement in RWE development and implementation and that affect clinical care or patient choices.

Today, and as observed herein, payers consider systematic reviews and other study types, all of which can be evaluated or disseminated within emerging or existing evidentiary frameworks that serve to enhance study rigor and reproducibility and control for bias. Frameworks include, for example, the Institute for Clinical and Economic Review's evidence rating matrix, which exists alongside its industry partnership to generate "decision-grade" RWE and mission to "expand use of RWE to complement other sources of information used in its value assessments" [22,23]. Also, an RWE study registry exists under our Real-World Evidence Transparency Initiative, whereas all study registrations therein require an uploaded study protocol, and registrants are encouraged to follow a study template developed by the International Society for Pharmacoepidemiology (ISPE)

and the Professional Society for Health Economics and Outcomes Research (ISPOR) joint task force that has been endorsed and recently adapted by the US CMS for public consideration and comment [21,24]. For this reason, payers might consider evidence evaluated under these rigorous frameworks and registries that may endorse them [25].

Moving forward, it will be important to consider our findings herein to support this ongoing work and related initiatives focused on building a general understanding of whether or how, and the process through which, payers engage in the consideration and subsequent selection or development of (real-world) evidence. Clinical practice areas where PGx testing is relevant, such as psychiatry, would be a key clinical and therapeutic use case for consideration, given its complexity, for payers managing pharmacy care [20]. Importantly, future work should also explore payer rationale for our observed administrative and stylistic differences in payer policy drafting and online publication of evidentiary sources on PGx testing in psychiatry.

Our findings are accompanied by limitations that should be noted to inform both practice and future work. First, payers may require additional payment guidelines or prior authorizations for coverage that are not captured in this analysis. Also, parent companies may have subsidiary plans that might also vary in terms of coverage and sources cited in their policies, especially in cases where subsidiary plans are population-specific. Thirdly, our findings are exclusive to the practice of psychiatry and may, therefore, not be generalizable to other clinical or therapeutic areas outside of psychiatry. Lastly, coverage is often mandated based on applicable legal requirements of a state or the federal government, which might also affect local coverage determinations; this analysis does not capture these. We note that for certain areas outside the immediate scope of our present analysis (i.e., rationale behind payer evidence selection and decisions and assessment of methodological rigor and quality of each article included in each payer policy), future qualitative or contextualizing work is needed.

5. Conclusions

Our findings highlight substantial variation among payers in both coverage decisions and sources and evidence cited concerning the clinical utility of PGx testing in psychiatry. Peer-reviewed studies of various OCEBM Evidence Levels, inclusive of RWE, are highly cited among payers to substantiate their coverage decisions for PGx testing psychiatry. The observed variation in payer coverage and underlying rationale for coverage can be expected at this time given that relevant, reliable, and conclusive RWE on PGx testing in psychiatry is still emerging. Our assessment supports broader efforts and lays foundational work toward an understanding of payer perspectives and preferences for key sources and evidence concerning the clinical value of PGx testing in psychiatry.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jpm15060232/s1, Supplementary File S1: Table of Pharmacogenomic Biomarkers in Drug Labeling and Corresponding Clinical Pharmacogenetics Implementation Consortium Information, and Supplementary File S2: Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence [8].

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Case Report

Psychodynamic Insights into Treatment-Resistant Pharmacotherapy: A Case Study Exploring Patient–Physician Dynamics and Adherence to Evidence-Based Practices

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Abstract: Background: Pharmacological resistance in severe recurrent mood and anxiety disorders remains a significant challenge in modern biological psychiatry. This case report investigates the intricate decision-making process employed by physicians when managing patients resistant to conventional pharmacotherapy. Methods: Informed consent was obtained from the patient. Following this, the case report was developed using the CARE checklist (2013) to ensure a comprehensive and systematic documentation of the treatment process and outcomes. Results: The patient's treatment history highlights the complex nature of pharmacological resistance and the impact of minor medication adjustments versus established clinical practices. A crucial aspect of this case was the patient–physician relationship, particularly addressing the patient's past grievances towards physicians, which played a significant role in the treatment process. Despite efforts to improve the physician's confidence and approach, challenges such as lack of continuity and a fragile therapeutic relationship contributed to treatment failure. Conclusions: This case underscores the importance of psychodynamic models in overcoming pharmacologic challenges. A deeper understanding of the patient–physician dynamics and addressing underlying emotional factors can enhance treatment efficacy and patient outcomes, providing valuable lessons for managing complex cases of treatment resistance.

Keywords: treatment resistance; psychodynamic pharmacology; behavioral pharmacology; insomnia; depression; anxiety; personality disorders

1. Introduction

In an era where an increasing number of individuals grappling with depression and anxiety seek solace in pharmacologic treatment, the inevitability of encountering treatment failure looms large. While some cases simply necessitate judicious adjustments to medications, leading to eventual stabilization, a unique subset of patients exhibit treatment failure due to psychodynamic aspects. Unraveling the complex psychodynamics using appropriate models is critical to connect the biologic psychiatry mindset and the psychoanalytical approach.

Beyond the conventional realm of pharmacological considerations, these instances demand a nuanced exploration of underlying causes contributing to treatment resistance. Thase and Rush created a five-stage strategy to properly identify and discuss treatment resistance [1]. In stages III and IV of resistance, they discuss how the therapeutic relationship is extremely valuable. In these very complex cases, the patients may exploit physician emotions through countertransference and dictate treatment. Delving deeper into this realm becomes imperative as it may reveal intricate therapeutic relationship dynamics, such as patients subconsciously transferring their anger to the physician, thereby undermining the prescribed treatment regimen.

The literature widely recognizes the advantages of combining pharmacotherapy and psychotherapy to optimize treatment outcomes [2]. Shapiro and Plakun were pioneers in using psychoanalytical dimensions to optimize pharmacologic treatment [3].

This case report centers on a patient displaying elevated resistance to conventional psychotropic medications, empowering them to influence treatment decisions and deviate from traditional evidence-based approaches. Our case report expands on the concept of psychodynamic psychopharmacology, which was described by Mintz and Belnap [4]. Additionally, the report delves into the influence of transference on physician confidence, highlighting the significance of a physician's assurance in effectively managing challenging patients. Maintaining confidence is essential as it prevents the patient's subconscious emotions from unintentionally steering the course of treatment, underscoring the need for a mindful and informed approach in such therapeutic scenarios.

2. Methods

This case report presents a 45-year-old woman with treatment-resistant anxiety and depression, shaped by complex psychodynamic factors. Informed consent was obtained, and the patient's psychiatric history, treatment responses, and psychodynamic interactions were thoroughly documented. CARE guidelines were followed throughout to ensure a systematic and comprehensive review of the case. The analysis focused on the qualitative examination of the therapeutic relationship, particularly the impact of transference and countertransference on treatment outcomes.

Data collection involved a detailed review of medical records, psychiatric evaluations, and medication history, emphasizing the psychodynamic aspects of the patient's condition. We drew upon the works of Gabbard to guide our psychodynamic analysis. Specifically, the psychodynamic model chosen for our case was object relation theory. Ethical considerations were strictly observed, with patient privacy and confidentiality protected throughout.

3. Patient Information

This case involves a 45-year-old married woman, currently unemployed, residing with her husband and children. She voluntarily admitted herself to a psychiatric hospital following presentation at a nearby emergency room, where she reported symptoms of anxiety and vague suicidal ideation. Of particular concern to the patient was her severely disrupted sleep, despite an extensive medication regimen. The patient met criteria for admission due to her suicidal ideation. The goal of inpatient treatment was to ensure patient safety and better control her acute psychologic symptoms.

Along with the suicidal thoughts, the patient reported generalized anxiety and occasional panic attacks marked by chest tightness. She reported an extensive history of insomnia due to the anxiety. However, she denied other panic attack symptoms such as shortness of breath, palpitations, a sense of doom, or tingling in her hands.

The patient revealed a history of a distressing childhood. The patient recalls her father being absent for much of her early childhood especially before she was 2 years old. Her mother served as the primary caregiver, while her father, a surgeon, was predominantly focused on his career. Thus, when her mother was diagnosed with amyotrophic lateral sclerosis (ALS) when she was 11 years old, it had a profound impact on her. The subsequent deterioration and eventual passing of her mother during the patient's senior year of college had a substantial impact, leading to ongoing difficulties in fully comprehending and coping with this loss. Notably, there were no reports of emotional, physical, or sexual abuse, and the patient denied experiencing symptoms commonly associated with post-traumatic stress disorder (PTSD), such as nightmares or flashbacks.

Further exploration revealed a prolonged struggle with mental health challenges. While the patient experienced multiple traumatic events during childhood, she did not pursue mental health treatment until age 30. From the age of 30 until 44, the patient was consistently treated for anxiety and depression. The treatment during this 14-year period was self-reported as "fairly consistent". The patient did report occasional changes

in the specific selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) during this time. Before the age of 44, the patient found the most consistent benefit with paroxetine. The patient could not recall any specific stresses that could have preceded the onset of anxiety and depression. She reports having great relationships with her husband and children. However, she did not mention having any strong friends outside of her immediate family. It was unclear whether the patient had any social support outside of her husband.

Approximately a year ago, the patient was hospitalized for suicidal ideation. In the months leading up to this hospitalization, the patient found her medication regimen to be much less helpful. During the hospitalization she was stabilized and advised that her response to medications may change during the perimenopausal timeframe. In addition, the patient underwent psychological testing during this hospitalization and the patient was formally diagnosed with cluster B personality disorder with features of borderline and histrionic personality. Once discharged from the hospital she underwent nearly a year of intensive outpatient therapy without improvement. Of note, she refused dialectical therapy on multiple occasions in the outpatient setting. Thus, her outpatient therapy seemed to largely revolve around medication management rather than psychotherapy. The patient reported seeing her psychiatrist extensively over the past year. She was never able to go more than 6 weeks without an appointment to change the medication regimen. When asked about her experience with therapy, the patient was largely dismissive. On review of the last discharge, it was advised for her to complete a partial hospitalization program where she would have had group and individual therapy every weekday for 2 weeks. However, the patient refused and would only agree to seeing a therapist weekly. When questioned about her experience with this therapy, the patient was dismissive stating that she "tried for months and it did nothing".

The patient's medication management over the last 18 months had extreme fluctuations. Specifically, her anxiety and insomnia were not adequately controlled with more than three different classes of anti-depressants, including a tricyclic anti-depressant (TCA) and ketamine. All of these classes were taken for an adequate duration with proper dosing. She was unable to recall if she had ever taken a monoamine inhibitor (MAOi). She has never had ECT for her symptoms.

Her outpatient provider seemed to be at a loss after 12 months of medication changes, many of which were trials that did not follow evidence-based practices. Consequently, she was referred to a specialist on treatment resistance in the area. Before the appointment with the specialist, the patient felt extremely helpless and presented in the emergency room. In the ER, she was given Ativan for her anxiety and helplessness, but reported that this "made everything worse". When questioned further, she was not able to describe how the lorazepam worsened her symptoms other than just repeating "it made me more anxious".

During discussions about treatment options, a common pattern of dictating treatment and switching drugs also was evident. It was not evident whether the patient had a history of non-adherence or rather just was constantly frustrated with the medication regimen.

4. Diagnostic Assessment

Upon admission, a physical examination was conducted by a medical doctor, leading to diagnoses of hypertension and gasteroesophageal disease (GERD). These conditions were deemed adequately managed, and outpatient follow-up was recommended. Lab work, including complete blood count (CBC), complete metabolic panel (CMP), thyroid panel, lipid panel, and vitamin D levels, was also performed. Slightly elevated lipid levels were noted but did not require medication at this time. A deficiency in vitamin D was identified with a level of 20.7, prompting the initiation of vitamin D replacement. All other lab results were within normal limits.

The previous psychological testing from an earlier hospitalization was reviewed. The DSM-5-based diagnoses included generalized anxiety disorder, panic disorder, recurrent

severe major depressive disorder without psychosis, moderate benzodiazepine use disorder, and a cluster B personality disorder with borderline and histrionic features.

A psychiatrist evaluated the patient upon admission and confirmed the diagnoses of generalized anxiety disorder, recurrent moderate major depressive disorder without psychosis, and moderate benzodiazepine use disorder. While the history of cluster B personality disorder and panic disorder was noted, these were not initially apparent during the interview.

Daily evaluations throughout the hospitalization revealed a more pronounced presence of cluster B personality disorder, particularly with borderline features such as splitting. The severity of benzodiazepine use disorder was reassessed as severe rather than moderate. After a week of inpatient treatment, the prognosis was extremely poor due to significant issues with insight and adherence. Resistance to individual psychotherapy emerged as a major barrier to successful treatment.

5. Hospital Course

The objective of inpatient treatment was to stabilize the patient, address suicidal ideations, and alleviate feelings of helplessness. Additionally, hospitalization aimed to reduce acute symptoms and provide guidance for her subsequent outpatient care. Notably, due to her extensive psychiatric history, the prognosis of completely resolving her symptoms during this hospitalization was poor.

The patient's history of extensive psychotropic medication trials guided the selection of the most appropriate regimen. She was unwilling to start with any evidence-based medications that she had previously deemed unsuccessful. She was started on imipramine due to refusing all SSRIs and SNRIs. Additionally, she had been discharged on imipramine at her last hospitalization with positive response. Along with the imipramine, gabapentin and mirtazapine were deemed suitable to help with her sleep and anxiety.

Daily interactions with the patient primarily revolved around medication discussions as she was very resistant to any therapy. The patient consistently expressed dissatisfaction and pressured the physician for changes well before the therapeutic benefits could be thoroughly assessed. This persistent push for alterations is reflected in Table 1, illustrating extensive deviations from standard clinical practice. Subsequently, the patient was exposed to many more side effects than if a consistent medication regimen had been properly adhered to.

The therapeutic relationship and physician behavior, particularly countertransference, were clear during this hospitalization. A thorough interview revealed a difficult upbringing contributing to a personality disorder and medication resistance, emphasizing unresolved anger towards her absent father, who was a physician, and suppressed memories.

Post-interview, it was clear that dialectical therapy would benefit the patient; however, she was very resistant to anything other than medications, as seen in her prior refusals of dialectical outpatient therapy. She refused to attend group and individualized therapy. On the 8th day, a suitable long-term inpatient facility was found, emphasizing psychotherapy. Despite some progress and the physician identifying what the patient truly needed, the patient sought another doctor, resumed clonazepam, and refused the medications that had contributed to her slight improvement. The weak therapeutic relationship was detrimental in this case because the physician was not able to provide the best care for this patient. Over the week there were slight improvements, but the patient's self-sabotaging behavior ultimately was not able to be overcome.

The course of treatment underscores the interplay of psychotropic medications, patient autonomy, and the therapeutic relationship. Comprehensive approaches considering both pharmacological and psychoanalytical dimensions are crucial. The patient's recovery ultimately hinges on securing proficient professionals who guide treatment confidently, avoiding patient-driven decisions for successful outcomes.

This highlights the necessity for a comprehensive approach that takes into account physician emotions in medication management. The extensive medication changes illus-

trated in Table 1 show how the patient dictated treatment and deviated from standard practice. This unique situation shows how a lack of continuity in care can be detrimental to treatment.

Table 1. Summarized hospital course.

Day	Patient Events	Medication Changes	Dose Changes	Patient Status
0	• Required clonazepam at night	Imipramine Gabapentin Mirtazapine		Poor
1	• TCA made her suicidal • Learned never fully stopped benzo use • Refused to take benzo • Received psychotherapy		Dec imipramine Inc gabapentin	Poor
2	• Wanted to see another doctor • Passive aggressive towards doctor • Required many PRNs ○ Diphenhydramine ○ Trazadone ○ Propranolol		Inc gabapentin Inc mirtazapine	Very poor
3	• Called outpatient provider • No longer experiencing depression • Focused on insomnia	2 changes D/C imipramine Start nortriptyline		Improvement
4	• Experiencing more depression	4 changes D/C mirtazapine Start propranolol Start quetiapine Start ramelteon		Stable
5	• Stated she "disliked all the medication" • Hypotensive • Slept 7 h	1 change D/C ramelteon	Inc quetiapine	Significant improvement
6	• Patient appears more rested with improved mood and affect • States "feels weird"	1 change D/C propranolol	Inc gabapentin Inc quetiapine	Poor
7	• Switched doctor • New doctor restarted clonazepam	4 changes D/C nortriptyline D/C gabapentin Start lithium Start clonazepam		Very poor

D/C: Discontinue, TCA: Tricyclic acid, Benzo: benzodiazepine, PRN: As needed medications.

6. Follow-Up and Outcomes

Throughout the hospitalization, the patient displayed poor adherence and tolerability to medications. Multiple adverse events, including severe suicidal ideation and dissatisfaction with the psychiatrist, were reported. Despite a week of inpatient management and numerous medication changes, the patient's symptoms remained largely unchanged. Clinical improvement was minimal, and the prognosis for this patient is deemed extremely unfavorable due to lack of insight, poor judgment, and resistance to psychotherapy. The weak therapeutic relationship and excessive polypharmacy, and not following evidence-based guidelines, contributed to the overall poor outcomes. The patient's resistance to treatment and the impact of physician emotions on decision-making are evident in this challenging case.

7. Discussion

The patient's trauma and overreliance on concrete means to manage internal distress had a significant impact of the pharmacologic effectiveness in this case. Specifically, her own fantasies of what medications would do for her influenced her requests and impacted the physician's management. Additionally, this case report underscores the profound influence of physician emotions on medication management. In an ideal scenario, physicians should make decisions impartially, but a lack of confidence may lead them toward the path of least resistance, jeopardizing the best interests of the patient. Straying from evidence-based clinical practices exposes patients to considerable side effects without apparent benefits, as highlighted by the significant adverse effects our patient encountered during hospitalization. Not adhering to evidence-based practice also may present as a pseudo-resistance. Additionally, the patient's non-compliance could compound a pseudo-resistance [5]. A nuanced comprehension of the patient–physician relationship is essential for adeptly addressing challenging cases characterized by treatment resistance, especially in the later stages described by Thase and Rush [1].

One noteworthy takeaway from this case report is the importance of a resilient physician who acknowledges their own emotions and avoids yielding to the patient's preferences. Furthermore, maintaining continuity in care is imperative for this subset of patients. Given the complexity of their psychiatric history and underlying symptoms, a substantial amount of time is required to gain a comprehensive understanding and provide optimal treatment. Even with significant advancements in psychiatric pharmacology, this case report highlights how a biological framework is not always effective. Vlastelica emphasizes the importance of identifying dynamic factors that may be interfering in pharmacologic treatment [6].

This specific scenario aligns with the literature on the psychodynamics of psychopharmacology. Mintz and Belnap were pioneers in this field and discuss how the use of many psychodynamic models can have a significant impact on pharmacologic benefit [4]. They found that an understanding beyond the biologic perspective increases overall clinical effectiveness of the medication. Building on this concept, the paper by Silvio and Condemarin explores how, over the past 20 years, there has been an increased focus on how incorporating medications can affect individuals psychologically [7]. In their paper, they recognize the importance of interpersonal factors in patient adherence and ultimate success. A similar study by Li confirmed the importance of being mindful of various psychodynamic models and utilizing them in clinical practice in conjunction with medications [8].

In this case, unaddressed psychodynamic factors rooted in object relations theory likely played a crucial role. According to the theory first described by Klein, early relationships, internalized during infancy, continue to shape interpersonal dynamics throughout life [9]. The patient may have struggled with transitioning from Klein's "paranoid-schizoid position"—a state characterized by splitting the world into "good" and "bad" objects—to the "depressive position," where an integration of these split elements occurs [10]. This failure to integrate could have led to the patient projecting hostility onto the medical team, fueled by primitive anxieties or a fear of psychological disintegration. Such dynamics, if unrecognized, may have exacerbated the patient's resistance to treatment. Addressing these underlying psychodynamic issues within the therapeutic relationship might have alleviated some of the patient's hostility and improved the overall treatment outcome. A common theme within the realm of psychodynamics of psychopharmacology is the therapeutic alliance. This is a concept that has been researched extensively and is agreed to be integral in the success of treatment. The meta-analysis by Martin et al. in 2000 showed the significance of a positive therapeutic relationship [11]. Taking these concepts and applying them in clinical practice can be a challenge. The book by Reba and Balon focuses on combining pharmacotherapy and psychotherapy [12]. They emphasize the importance of a comprehensive initial diagnostic assessment. In practice, a comprehensive assessment can be extremely challenging when patients are resistant, as in our case report. The concepts in their book were confirmed by the meta-analysis performed by Karyotaki

et al. in 2016 [13]. Nonetheless, it is important to still understand the psychodynamic aspects even if psychotherapy is not an option for treatment. For example, Forrest talks about how being aware of certain character styles can improve the therapeutic alliance and medication regimen [14].

We can delve deeper into the specific nuances that contributed to the poor therapeutic relationship in our case report. Psychodynamic formulation was first described by Perry et al., which focuses on central conflicts such as transferences and resistances [15]. Their paper discusses how psychodynamic formulation is important in guiding psychiatric treatment. Transference is a prominent coping mechanism used by the patient. Her subconscious deep-seated anger towards her father was transferred to the physicians treating her. Therefore, multiple physicians proceeded to deviate from traditional practice and made excessive medication changes due to the patient's demands. These excessive medication changes were also likely compounded by the physicians feeling helpless themselves from the patient's countertransference of her emotions.

Transference, initially introduced by Freud and further developed by Carl Rogers, has evolved and been applied to the therapeutic alliance. A comprehensive review of transference by Horvath in 2000 explores its current implications in clinical practice [16]. The primary takeaway emphasizes the critical importance of identifying transference early in the therapeutic relationship and recognizing the collaborative framework's significance in determining the most effective therapy [2]. Similar papers by Marcus in 2007 and Gabbard in 2020 echoed many of the same concepts but delved deeper into how physicians should use their emotions to better understand their patient's subconscious [17,18]. The paper by Marcus specifically explored the transference and countertransference related to medications. He concluded that both of these ego defenses are highly specific diagnostic indicators [18]. While this case report was not successful in treating the patient, the identification of countertransference was used to understand the underlying emotions and create a plan for a future physician to follow. This unique case underscores the impact of subconscious emotions on the success of treatment in patients with underlying personality disorders.

Our case report underscores the importance of integrating psychoanalytic and pharmacological approaches in the treatment of borderline personality disorder. A significant factor in the therapeutic failure was the patient's refusal to engage in cognitive behavioral therapy (CBT) or dialectical behavior therapy (DBT). The patient exhibited a pronounced splitting mechanism, categorizing physicians as either idealized figures who acceded to her demands or devalued figures when they prescribed medications associated with adverse effects. This splitting behavior, characterized by cycles of idealization and devaluation, severely disrupted the therapeutic alliance. Each time alternative treatment modalities were proposed, the patient exhibited marked distress, further complicating her clinical management and contributing to the overall therapeutic impasse.

If CBT or DBT cannot be accomplished, understanding the principles can still be beneficial in optimizing the pharmacological treatment. To understand how to apply these concepts to management, we can draw upon the "A View from Riggs" publication series, particularly focusing on the psychodynamic approach to understanding treatment resistance. In Plakun's foundational paper, he underscores the necessity of tolerating negative transference as a frequent component associated with treatment resistance [19]. Plakun argues that recognizing the provider's own negative emotions in countertransference is crucial. Furthermore, the paper highlights the importance of not relinquishing authority to the patient, emphasizing the need for maintaining control over treatment strategies and admission terms.

In another publication from the same series, Shapiro delves into the dynamics of the patient's living situation and authority [3]. The paper highlights the risk of physicians adhering solely to the current treatment paradigm, neglecting the individual's personality and psyche. Without a comprehensive psychological understanding, biological interventions offer limited benefits. For these patients, resistance to treatment may not only be a

reenactment of painful experiences, but also a mode of communication. Their resistance may be a coping mechanism for suppressed anger, allowing them to assert control over providers they deem untrustworthy.

Both our case report and the "A View from Riggs" publication series exemplify how recognizing individuals' subconscious psychodynamics can transform physicians into competent allies, leading to a shift in their own perspectives.

Our case report highlights the inherent challenges in managing patients with complex medical conditions. When a therapeutic alliance is weak, the repercussions of excessive polypharmacy become particularly pronounced. In such instances, clinical pharmacologists play a pivotal role as a crucial safeguard. The study conducted by Stuhec and Zorjan underscores the significance of an external perspective in evaluating reported benefits and clinical relevance within a specified timeframe [20].

Clinical pharmacists, as demonstrated in their interventions with ambulatory psychogeriatric patients, contribute valuable insights to the decision-making process. Their specialized knowledge enables a more comprehensive and well-informed approach to combining different medications [20]. This collaborative strategy not only adds an additional layer of scrutiny to medication choices, but also serves to counterbalance the potential influence of physician emotions on decision-making. The outcome is a more objective and patient-centered approach to care.

8. Conclusions

In conclusion, the optimal care for challenging cases necessitates the integration of psychopharmacological and psychodynamic models. Recognizing and addressing transference and splitting mechanisms early in the therapeutic relationship are crucial to successful treatment. This case report underscores the active role of patients in influencing treatment decisions. To mitigate variance from evidence-based practice, physicians must confidently navigate these dynamics. A strong therapeutic relationship and a multidisciplinary approach are pivotal for the proper management of these unique patients. Therefore, adopting a holistic approach that considers both pharmacological and psychoanalytical dimensions is essential for ensuring comprehensive and effective care in challenging cases.

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Institutional Review Board Statement: The informed consent procedure for this case report commenced with the healthcare professional approaching the patient, acknowledging them by their name and date of birth. A comprehensive explanation of the report's purpose, content, and potential implications was provided to the patient. Emphasis was placed on the voluntary nature of participation, ensuring the patient understood that their decision would not affect their medical care. Discussions encompassed protective measures for anonymity, potential impacts on the scientific community, and the opportunity for the patient to seek clarification by asking questions. The patient's comprehension and agreement were meticulously documented, and contact information was furnished for any subsequent inquiries or withdrawal of co-sent. This approach was employed to uphold ethical standards in obtaining informed consent for participation in the case report. In alignment with ethical guidelines, the Institutional Review Board (IRB) was contacted regarding the need for formal approval. The IRB reviewed the case report and determined that it constitutes a medical/educational activity rather than research as defined by the Department of Health and Human Services (DHHS). According to the DHHS definition, research involves a "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge". Given that this case report does not meet this definition, formal IRB approval was not required.

Informed Consent Statement: Upon completion of the case report, the patient was given the opportunity to examine the comprehensive document. Subsequent to review, they expressed consent for the publication of the final case report in an open-access journal, including any identifiable information present in the manuscript and accompanying images.

Data Availability Statement: The data supporting this case report are available upon request, subject to Institutional Review Board (IRB) approval. Requests for data access should be directed to the corresponding author at alexbaur123@gmail.com. Data will be de-identified to ensure patient privacy. Access is granted for research purposes only, pending IRB approval and compliance with ethical guidelines.

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Review

The Search for Consistency in Residual Symptoms in Major Depressive Disorder: A Narrative Review

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Abstract: Residual symptoms are prevalent in major depressive disorder (MDD), encompassing a wide spectrum of symptoms such as sleep disturbances, changes in weight and appetite, cognitive impairment, and anxiety. These symptoms consistently impair daily functioning, diminish quality of life, and forecast disease relapse. Despite their clinical significance, residual symptoms lack a unified definition, potentially leading to confusion with treatment-emergent symptoms and ambiguity across studies, thereby hindering the generalizability of research findings. While some research identifies insomnia and mood disturbances as critical indicators, other studies emphasize different symptoms or find no significant correlation. Inconsistencies in defining residual symptoms, as well as methodological differences across studies, contribute to these conflicting results. While clinicians focus on alleviating negative symptoms to improve functional status, patients often prioritize achieving positive affect and overall well-being as essential components of successful treatment. It necessitates a comprehensive approach to patient care in depression. This review explores the phenomenon of residual symptoms in MDD, focusing on the ambiguity in definitions, clinical characteristics, and their impact on long-term outcomes. The lack of a standardized regulatory or academic definition for residual symptoms leads to varied interpretations among clinicians, underscoring the need for standardized terminology to guide effective treatment strategies and future research.

Keywords: residual symptoms; depression; major depressive disorder; predictor; functional impairment; recovery; relapse

1. Introduction

Neuropsychiatric conditions impose the most substantial global burden of disease. Prominently, major depressive disorder (MDD) affects nearly 300 million individuals worldwide [1]. Annually, up to 60% of patients with MDD may experience work-related impairments, leading to an average loss of over four workdays per week due to the disease [2]. The public health implications stem from the well-established link between MDD and several common chronic physical diseases [3,4]. For instance, MDD is a known risk factor for cardiovascular disease, obesity, and type 2 diabetes mellitus, particularly in individuals with more severe or persistent depressive syndromes [5].

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which primarily utilized traditionally acting antidepressants (TAAD), remission rates for the first, second, third, and fourth acute treatment steps were 36.8%, 30.6%, 13.7%, and 13.0%, respectively. The overall cumulative remission rate was 67%. Patients who required multiple treatment steps experienced higher relapse rates during the naturalistic follow-up phase [6]. Notably, 90% of participants who reached remission and response status experienced at least one residual symptom with appetite/weight disturbance, sad mood, decreased energy, and decreased concentration among the most common residual symptoms [7,8].

A significant number of patients experience treatment-resistant depression (TRD), defined as the failure to respond to two adequate pharmacological treatments [9]. Its

prevalence varies due to differing definitions [10] but remains substantial globally, contributing significantly to the economic burden of MDD due to higher indirect costs and greater psychosocial impairment [11]. For instance, nearly 3 million adult patients suffer from TRD in the United States, which contributes to almost USD 44 billion annually [12]. Consequently, there has been increased interest in recent advancements, including rapid-acting antidepressants (RAAD) such as ketamine, noted for its antidepressive, antisuicidal, and antianhedonic effects [10,13,14], as well as a burgeoning interest in psychedelics as prospective therapeutic agents [15], particularly for patients who do not respond to TAAD.

Regardless of the severity, chronicity, or stage of depression, it is imperative that treatment focuses on promoting functional recovery, emphasizing the restoration of everyday activities and overall well-being [16]. Despite positive responses to pharmacological treatment and even formal remission in cases of TRD, residual symptoms persist in nearly all patients [7,8,16]. These persistent symptoms significantly burden patients, impacting their quality of life and daily functioning. Consequently, there is a crucial need for continued treatment optimization to achieve full symptom resolution and functional recovery, ensuring that patients can be free from the lingering effects of depression.

However, the area of residual symptoms remains under-researched. Current reports are relatively scarce, and the existing literature is not well-established in terms of defining residual symptoms, their incidence, and how they impact patients, often presenting conflicting results. This review aims to explore the phenomenon of residual symptoms, with a specific focus on the ambiguity in definitions, clinical characteristics, and their impact on long-term outcomes.

2. Methodology

Electronic databases, PubMed and Web of Science, were searched from their inception until June 2024. Only English-language papers were considered. There were no restrictions on the publication date. The following keywords were used in various combinations: residual symptoms, relapse, recurrence, functional impairment, depression, major depression, and major depressive disorder. Inclusion criteria encompassed (1) adult subjects, (2) MDD diagnosis with residual symptoms, and (3) data on incidence or functional impairment or relapse/recurrence prediction. Exclusion criteria included: (1) patients below 18 years of age, (2) diagnosis other than MDD, (3) lack of residual symptoms. Titles and abstracts of relevant papers were subsequently screened, with the most prominent papers included in the review.

3. Residual Symptoms

3.1. Inconsistency in Definitions

Characterizing change during the treatment of depression is defined diversely. For example, formal remission is characterized by cut-off scores in standardized scales (e.g., $\leq$10 points in Montgomery–Åsberg Depression Rating Scale (MADRS)), and treatment response is defined as a reduction of at least 50% from the baseline score or partial response, typically defined as an improvement between 25 and 50% [17].

Nevertheless, the identification of residual symptoms is inconsistent across the literature. Examples of these definitions are summarized in Table 1. For instance, patients were considered to exhibit residual symptoms if they met the criteria for formal remission on the Beck Depression Inventory (BDI) [18] the 17-item Hamilton Depression Rating Scale (HAM-D) [19–21], the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR16) [8,22], 16-item Quick Inventory of Depressive Symptomatology-Clinician (QIDS-C16) or Harvard Department of Psychiatry/National Depression Screening Day (HANDS) [23]. Another common method for classifying residual symptoms is based on treatment response in the QIDS-SR16 [7,24], MADRS [25], HAM-D [26], or the Visual Analogue Scale (VAS) [27,28]. The next definition includes partial response; however, some studies do not explicitly state what definition they followed [29,30]. Additionally, there are studies that do not fit into any specific category. For instance, two studies used the Psy-

chiatric Status Rating (PSR) scale with different thresholds [16,31]. Another study defined partial remission as subjectively reported improvement in symptoms over at least 2 months with a BDI score of less than 20 [32]. Other studies employed different cut-off scores for residual symptoms on the HAM-D than the score required for formal remission [33] or did not explicitly describe criteria for the presence of residual symptoms in the non-remitters group, i.e., it is not clear if this group consisted of responders only or all patients without formal remission [34].

Table 1. Definitions of residual symptoms used in the literature.

Study	Presence of Residual Symptoms Definition
Paykel et al., 1995 [18]	Formal remission in BDI
Judd et al., 1998 [31]	Score of 2 on PSR Scale
DeBattista et al., 2003 [29]	Partial response *
Fava et al., 2005 [30]	Partial response *
Fava et al., 2006 [23]	Partial or full remission (both considered as response to treatment) Response defined as score < 9 on HANDS
Dombrovski et al., 2008 [20]	Remission defined as HDRS-17 score ≤ 7
Iovieno et al., 2010 [19]	Formal remission in HAM-D17 (score < 7)
Nierenberg et al., 2010 [8]	Formal remission defined as a QIDS-SR16 score of $\leq$5
McClintock et al., 2011 [7]	Treatment response defined as a 50% or greater reduction in the baseline QIDS-SR16
Fekadu et al., 2011 [16]	Subthreshold PSR score of 3 to 4
Britton et al., 2012 [32]	Partial remission was defined by a subjectively reported improvement in symptoms in the last 2 months, BDI score $\leq$ 20 and the exclusion of individuals with severely depressed mood/anhedonia, or active suicidal ideation
Romera et al., 2013 [26]	Improvement above 50% in HAM-D
Mowla et al., 2015 [33]	Score in HDRS < 10
Hiranyatheb et al., 2016 [34]	Remission defined as HDRS-17 score ≤ 7 Criteria for non-remitters group not stated
Sakurai et al., 2022 [21]	Remission was defined as a QIDS-C16 total score of $\leq$5
Xiao et al., 2018 [27]	Patients who responded to antidepressant drug treatment reporting improvement of depressive symptoms of $\geq$50% on the VAS were divided into 'remitters' (QIDS-SR total score of $\leq$5) and 'non-remitters' (QIDS-SR total score of >5)
Wang et al., 2020 [28]	Residual symptoms were considered present if patient felt to have recovered by 50% or more via VAS assessment
Lambrichts et al., 2022 [25]	Decrease in MADRS score of at least 50%
Sakurai et al., 2022 [21]	Score of $\leq$7 on the HAMD17
Hart et al., 2023 [24]	Decrease in QIDS-SR16 composite score of $\geq$50% from baseline to at least one follow-up QIDS
Zhou et al., 2024 [22]	Remission was defined as a QIDS-SR16 total score of $\leq$5

* Definition not clearly stated, common definition delineates partial response as improvement between 25 and 50% [28]; ADT—antidepressant therapy; BDI—Beck Depression Inventory; HAM-D17—17-item Hamilton Depression Rating Scale; HANDS—Harvard Department of Psychiatry/National Depression Screening Day; HDRS-17—17-item Hamilton Depression Rating Scale; PSR—Psychiatric Rating Status; QIDS-C16—16-item Quick Inventory of Depressive Symptomatology—Clinican; QIDS-SR16—16-item Quick Inventory of Depressive Symptomatology—Self Report; VAS—Visual Analogue Scale.

3.2. Clinical Characteristics

3.2.1. Patient-Reported Outcomes

In the aforementioned STAR*D study, among patients who achieved remission after 12 weeks of treatment with citalopram, less than 10% reported complete resolution of depressive symptoms in QIDS-SR16. The most frequent complaints among the remain-

ing remitters included weight gain (71.3%), middle insomnia (54.9%), increased appetite (50.6%), difficulty falling asleep (29.5%), and persistent sad mood (27.1%) [8]. Conversely, among patients who responded to treatment but did not achieve remission, the most frequently persistent depressive symptoms were mid-nocturnal insomnia (81.6%), sad mood (70.8%), and decreased concentration/decision-making (70.6%) [7].

In a study conducted by Xiao et al. [27], individuals who achieved remission, as measured by the Visual Analogue Scale (VAS), commonly experienced residual symptoms in the QIDS-SR16 with at least minimal intensity, including middle insomnia (39.4%), early insomnia (32.8%), decreased energy (32.3%), and decreased concentration (31.3%). Conversely, among non-remitters (i.e., patients who responded by at least 50% but did not achieve remission), the most prevalent residual symptoms were decreased concentration (82.4%) and decreased energy (79.6%). Additionally, among the 15 somatic symptoms assessed using the Patient Health Questionnaire (PHQ), individuals achieving remission most commonly reported feeling tired (35.5%), trouble sleeping (32.6%), headache (31.9%), intestinal problems (31.3%), palpitations (26.3%), gastric discomfort (22.3%), dizziness (22.2%), and stomach ache (20.6%). Similar results were observed for non-remitters [27]. Another study found that "concentration/decision making" was the most prominent and thus the core residual symptom [22]. In another study, the most frequently reported residual symptoms included sleep disorders, depressed mood, biological symptoms, inattention, poor self-esteem, loss of interest, decreased energy, and mental anxiety. These symptoms were reported with higher frequency in patients with functional impairment [28].

3.2.2. Clinician-Rated Outcomes

In a randomized controlled trial (RCT) involving fluoxetine, over 90% of patients in remission had at least one residual depressive symptom, with the most common being sleep disturbances (both insomnia and hypersomnia) and anxiety [19]. Another RCT aimed at verifying the effectiveness of gabapentin and clonazepam for residual sleep disturbances found that patients suffered from significant sleep issues at baseline, as measured by the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI) [33]. In a study that included MDD and/or dysthymic disorders patients, the most common symptom domains were core mood symptoms, insomnia symptoms, anxiety symptoms, and somatic symptoms [34]. Similarly, Romera et al. [26] reported that the most frequent residual symptom was anxiety, followed by core mood symptoms, residual insomnia, and somatic symptoms.

3.2.3. Patient-Reported and Clinician-Rated Outcomes

There are discrepancies between clinicians' and patients' perspectives, with patients reporting symptoms as more severe than clinicians do [35], therefore it is pragmatic to combine both perspectives. For example, residual symptoms among patients diagnosed with MDD who underwent repetitive transcranial magnetic stimulation (rTMS) were evaluated using both the QIDS-SR16 and the 28-item Hamilton Depression Rating Scale (HAM-D28). The most commonly reported residual symptoms in the QIDS-SR16 included mid-nocturnal insomnia (70.6%), sad mood (64.7%), decreased concentration/decision-making (61.8%), and low energy (51.5%). Similarly, the most frequently reported residual symptoms in the HAM-D28 were depressed mood (61.8%), diurnal variation (54.4%), and feelings of guilt (50.0%) [21].

Although there is a greater volume of data on self-reported residual symptoms compared to clinician-rated outcomes, likely due to practical reasons related to data collection, there appears to be a notable overlap in the reporting of residual symptoms from both perspectives. A summary of the most consistently and commonly reported symptoms is presented in Figure 1.

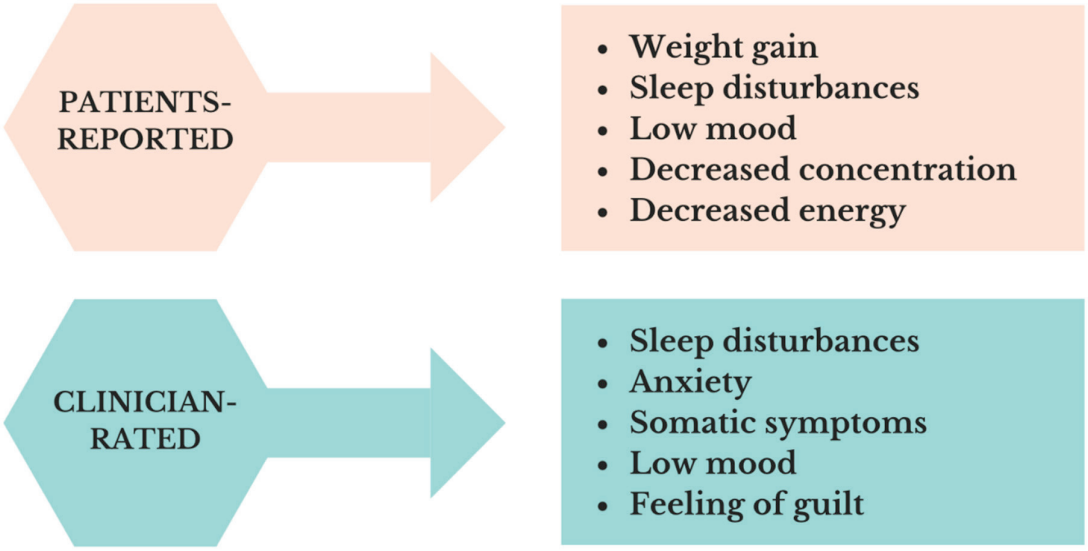

Figure 1. The diagram depicts the prevalence of the five most frequently reported residual symptoms from both patients' and clinicians' perspectives across standardized depression rating scales.

3.3. Functional Impairment

Residual symptoms contribute greatly to impairment in professional and leisure time activities. For example, non-remitters exhibited notably higher levels of functional impairment compared to remitters across general functioning and all three functional domains in the Sheehan Disability Scale (SDS), i.e., work, social life, and family life. Non-remitters experienced more frequent occurrences of days lost due to illness and underproductivity in both general functioning and across all three domains [27]. The factors most closely related to functional impairment included loss of interest, anxiety, and sleep disorders [28]. Patients with non-remitted MDD, particularly those experiencing more severe residual somatic symptoms, exhibit pronounced impairments in quality of life and increased clinical symptomatology [36].

A single study explored the correlation between specific residual symptoms and patient functioning. This study identified a stronger association with residual core mood symptoms. Residual insomnia showed a weaker relationship with patient functioning, while residual somatic symptoms were not associated. Importantly, residual insomnia was found to have a significantly weaker association with patient functioning compared to residual core mood symptoms. The absence of pain significantly increased the likelihood of normal functioning, regardless of residual anxiety. However, the absence of residual anxiety improved the chances of normal functioning only in the absence of pain. The link between residual symptoms and particular domains of functional impairment was not studied [26].

3.4. Predictors of Relapse and Recurrence

Residual symptoms in psychiatric disorders like depression signal ongoing illness activity and suggest a heightened risk of relapse, making them crucial for identifying patients who are more likely to experience a recurrence. Consistent findings in the literature suggest that the presence of residual symptoms leads to a quicker relapse of depressive episodes, highlighting their role in the active phase of the illness. Moreover, the characteristics and number of residual symptom domains further influence the likelihood of relapse. Research indicates that individuals with a broader range of lingering symptoms following initial treatment are at a higher risk of experiencing a relapse [8]. The impact of these residual symptoms on relapse risk appears consistent across different methods of assessment, whether self-reported or clinician-rated [37]. For instance, research shows that sleep disturbances and feelings of lassitude significantly increase the likelihood of relapse

following electroconvulsive therapy in older adults with depression [25]. Similarly, residual symptoms such as restlessness, insomnia, and changes in weight are recognized as markers that can better pinpoint individuals with MDD susceptible to relapse [37]. Studies have highlighted insomnia specifically as a significant predictor of recurrence in individuals recovering from recurrent major depression [20]. Furthermore, broader aspects of the depressive mood spectrum, including residual obsessive-compulsive and phobic anxiety symptoms, also contribute to an elevated risk of relapse [38–40]. In contrast, patients who achieve asymptomatic recovery tend to experience a longer period before any recurrence of depressive episodes occurs [18,31].

However, there are areas of controversy in the literature regarding whether the total number of residual symptoms predicts relapse or recurrence universally. Some studies suggest no significant predictive value for overall symptom burden [19,20], indicating variability in how residual symptoms may impact the course of depression. In addition, there are contradictory findings regarding the predictive value of residual mood and anxiety symptoms across different studies [20], as well as inconsistencies in the role of sleep disturbances in predicting relapse [8,19]

The field of relapse prediction is characterized by inconsistent findings. Supportive data is frequently contradicted by subsequent studies. It is undoubted that residual symptoms signal an increased risk of relapse in depressive episodes, and their identification and overall clinical characterization are necessary. However, there is controversy regarding the designation of a single symptom or symptom group as definitive indicators of relapse.

3.5. Discontinuation Syndrome and Residual Symptoms

The distinction between treatment-emergent symptoms, discontinuation symptoms, and residual symptomatology remains ambiguous. Practitioners often consider many of these symptoms as residual. The primary challenge lies in differentiating overlapping complaints such as emotional blunting and anhedonia, since both conditions share phenotypic similarities. However, anhedonia is a core symptom of depression, whereas emotional blunting is a side effect of selective serotonin reuptake inhibitors (SSRIs) [41]. Despite the complexities in distinguishing these symptoms, both treatment-emergent and discontinuation symptoms significantly impact patients' quality of life [42]. To achieve this, it is essential to employ systematic and quantitative monitoring of depressive symptoms using standardized assessment tools. These tools help to provide a clear and objective measure of symptom presence and severity, facilitating better differentiation between symptom types. One such tool is the Discontinuation-Emergent Signs and Symptoms (DESS) inventory, which is particularly beneficial in routine psychiatric practice. The DESS inventory is designed to specifically assess symptoms that emerge during SSRI discontinuation, thereby aiding in the effective evaluation of the effects of drug tapering. Its use allows clinicians to distinguish between discontinuation symptoms and residual depressive symptoms more accurately [43].

3.6. Successful Outcome Measure

With the advancement of pharmacological treatments for depression, the measurement of treatment success has evolved from simply assessing response to aiming for remission and ultimately achieving full functional recovery [44,45]. Response is defined as a significant reduction in depressive symptoms, typically a 50% decrease from baseline on a standardized rating scale. It offers a quantifiable measure of short-term improvement and guides treatment adjustments; however, it may not capture the full resolution of symptoms or the impact on quality of life. Remission is defined as a period where depressive symptoms fall below a specific threshold, signaling substantial symptom reduction and improved overall functioning; however, it may still leave residual symptoms affecting daily life and suffers from variability in criteria across studies and settings. Full functional recovery involves achieving both symptom remission and the restoration of normal functioning in personal, social, and occupational domains. It offers a comprehensive measure of

treatment success by focusing on overall quality of life but is more challenging to measure and requires alignment with individual patient goals and expectations. According to Canadian Network for Mood and Anxiety Treatment (CANMAT) guidelines, full remission should be considered both in terms of short-term and long-term effects, as short-term remission must lead to sustained full recovery in the long term [46]. The best chance for full recovery from a depressive episode occurs within the first 3–6 months. After one year, the likelihood of full recovery decreases to approximately 10–15%, and after two years, the likelihood of full recovery drops to a single-digit percentage [47]. Therefore, the earlier treatment is initiated, the better the prospects for future outcomes. However, healthcare professionals and patients have differing expectations regarding the definition of remission and recovery. Physicians aim to alleviate and minimize depressive symptoms, considering formal remission with residual symptoms as a promising outcome. However, patients prioritize positive affect and have distinct expectations compared to physicians [48]. Therefore, not only the symptom-centered approach, but patients' values, needs, and preferences should be considered when making treatment decisions and assessing outcomes to ensure patient-centered and individualized care [49].

4. Discussion

This review provides a comprehensive overview of the literature on residual symptoms in MDD. Residual symptoms lack a standardized definition and are defined diversely by clinicians. Sleep disturbances, changes in weight and appetite, cognitive impairment, low mood, anxiety, decreased energy, and somatic symptoms consistently emerge as the most common residual symptoms, regardless of whether they are reported by patients or assessed by clinicians. Residual symptoms such as sleep disturbances, cognitive impairments, and mood disturbances have a profound impact on individuals' daily functioning and overall quality of life. They often result in reduced productivity at work or school due to difficulty concentrating, making decisions, or maintaining motivation. Moreover, these symptoms frequently lead to increased absenteeism from work.

The field of relapse prediction is characterized by inconsistent findings. Interestingly, the symptoms contributing to this risk vary between studies. This variability can result in differing conclusions about which residual symptoms are most crucial for predicting relapse. The lack of a well-grounded and commonly used definition is a confounding factor. Since some studies use formal remission as a threshold for the presence of residual symptoms [8,21], others use the response as a criterium [7,25], and some studies use yet another criterium [32], it must be acknowledged as a confounding factor in the research of residual symptoms. The complexity increases when considering that remission and response outcomes are defined from multiple perspectives—clinician versus patient—and assessed using various tools that may not encompass the same aspects of the illness. Clinicians and patients may have differing views on what constitutes remission or response, leading to potential discrepancies in treatment evaluations. Furthermore, assessment tools used by clinicians may focus on specific symptom domains or severity thresholds that do not align with those considered by patients, resulting in incomplete or inconsistent coverage of the disease spectrum. This divergence complicates the accurate assessment of treatment outcomes and the development of tailored treatment strategies.

Residual symptoms are evaluated through both self-report measures [7,8] and clinical assessments [25], which may result in differing evaluations of the final outcome. From a clinical perspective, patients in formal remission and those who respond to treatment might differ significantly, presenting distinct spectra and intensities of depressive symptoms. This suggests that residual symptoms in remitters and responders could represent two clinically distinct phenomena, with responders exhibiting somewhat different but still active forms of the disease. Patients who continue to experience residual depressive symptoms often exhibit a higher disease burden and increased functional impairment compared to those who have achieved full remission. Remitters, by definition, do not meet the criteria for a depressive episode and typically experience fewer symptoms and

less impairment. However, comparing these two groups can be challenging due to the differences in symptom profiles, severity, and impact on daily functioning. Consequently, the assessment and management of residual symptoms in patients with ongoing depressive symptoms must be approached with caution, recognizing the complexities and variabilities inherent in these conditions. Potentially, patients who respond to treatment but continue to exhibit residual symptoms may require management similar to that of patients with active depression. In contrast, remitters with residual symptoms, who present with a more limited symptom profile, need a distinctly individualized treatment approach. Furthermore, with the advent of rapid-acting antidepressants (RAADs) and the increasing interest in psychedelic treatments, the standard criteria for residual symptoms may not always be applicable. For example, when patients show significant improvement within hours after receiving ketamine or 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) [10,50], it is debatable whether symptoms that persist shortly after such rapid improvement should be classified as residual. However, there has not yet been an established timeframe for the onset of residual symptoms. It could be argued that a standardized definition of residual symptoms should include a specific cut-off score on depression scales that preferably reflects formal remission and covers a particular timeframe, making it applicable for use in RAAD research.

Among all depressive symptoms, sleep disturbances are the most consistently reported residual symptom [7,8] with mid-nocturnal insomnia being the most common presentation [51]. While statistics vary, anxiety, low mood, cognitive impairment, and weight changes are also frequently reported in the literature. However, few studies distinguish and report the prevalence of treatment-emergent symptoms [7,8]. This distinction is essential because, as McClintock et al. [7] report, insomnia is both the most common residual symptom and a common treatment-emergent symptom. If treatment-emergent symptoms are not analyzed separately from residual symptoms, the incidence of some residual symptoms may be inaccurately elevated. Patients with TRD experience a high disease burden, low health-related quality of life, and reduced functioning and productivity, with a significant proportion being unable to work [2]. In this context, patients with residual symptoms exhibit similarities to those with TRD, as both groups experience significant functional impairment and a lowered quality of life [27,36]. Given that residual symptoms are widely recognized as predictors of relapse and recurrence, it is prominent that the primary goal of treatment should be functional recovery. Research indicates that functional recovery is achievable even in patients with TRD [16,18]. This underscores the importance of addressing residual symptoms comprehensively to improve long-term outcomes and overall quality of life in depressive disorders as depicted in Figure 2.

Clinicians typically measure the success of depression treatment by achieving remission and recovery, which they define primarily as the reduction or elimination of depressive symptoms. This clinical perspective focuses on quantifiable changes in symptom severity, using standardized scales and assessment tools to determine whether a patient no longer meets the criteria for depression. The ultimate goal from the clinician's viewpoint is to alleviate the negative symptoms that define the disorder, thereby improving the patient's functional status and overall quality of life. However, patients often have a different perspective on what constitutes successful treatment. While the absence of depressive symptoms is undoubtedly important, many patients place a higher value on the presence of positive affect—experiencing joy, interest, and engagement with life. For them, functional recovery is not just about reducing or eliminating negative symptoms but also about regaining a sense of well-being and the ability to enjoy life fully. This emphasis on positive affect highlights a more holistic view of recovery, one that encompasses both the removal of distress and the promotion of positive emotional experiences.

This review has its limitations. Firstly, electronic databases were not searched systematically, potentially omitting relevant studies that could have added value. Secondly, the domain of residual symptoms is highly inconsistent, complicating the ability to draw definitive conclusions. Nevertheless, the review has strengths, including the identification

of discrepancies in definitions, an overview of the incidence and impact of residual symptoms on patient functioning and relapse risk, and a contextualization of these symptoms in light of recent advancements in RAADs. Further research should focus on establishing a common regulatory and/or academic definition for residual symptoms to improve the quality and clarity of research in this area. This would allow for a unification of findings and provide more comprehensive outcomes in the field. Only by ensuring we use consistent terminology can we develop and implement appropriate treatment strategies. Otherwise, the range of treatment options may remain as diverse and under-researched as seen in residual insomnia [51]. Additionally, since residual symptoms are typically of mild severity, it is important to develop a tool that can accurately capture these symptoms and their impact on functioning, even at low levels. Developing a sensitive and comprehensive tool to capture residual symptoms mild in severity and their impact on functioning will provide a more nuanced understanding and management of the patient's condition.

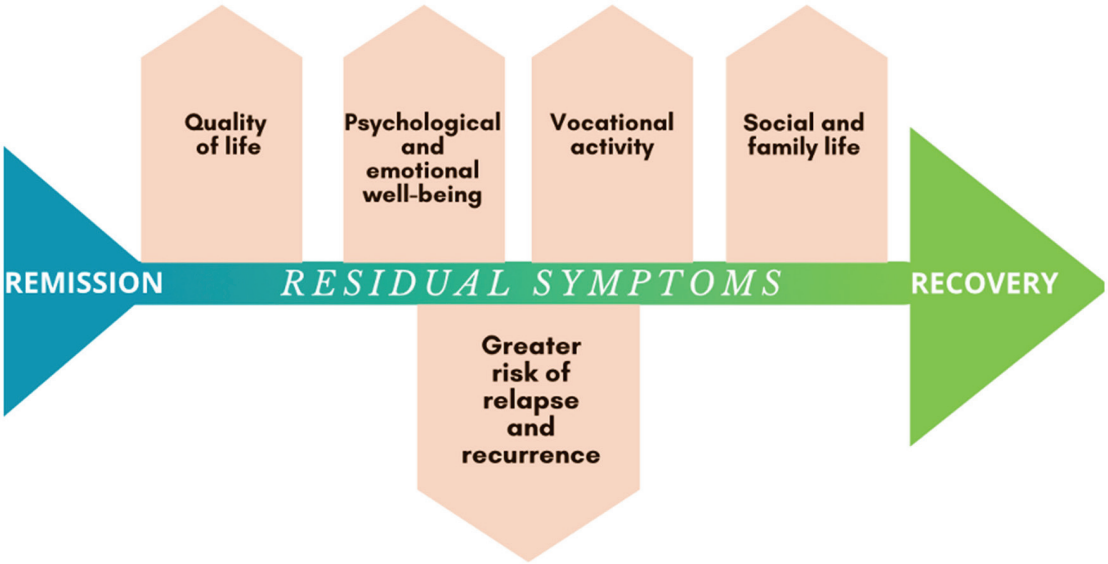

Figure 2. The diagram illustrates how residual symptoms influence various domains of life. Despite achieving remission, the presence of residual symptoms can increase the risk of relapse and recurrence, impeding full recovery and negatively affecting overall well-being.

5. Conclusions

Common residual symptoms such as sleep disturbances, changes in weight and appetite, cognitive impairments, low mood, anxiety, decreased energy, and somatic complaints consistently appear in both patient reports and clinician assessments, significantly impacting daily functioning and overall quality of life. The field of relapse prediction is marked by inconsistent findings, with the most robust evidence relating to sleep disturbances. Despite the conflicting literature, substantial evidence suggests that residual symptoms, especially when numerous, are strong predictors of relapse and recurrence in depressive episodes. However, the lack of a standardized definition for residual symptoms leads to varied interpretations among clinicians, and the predictive value of specific symptoms remains controversial. It can be assumed that overall symptom burden is a more significant factor, and only by standardizing terminology can we develop and implement effective treatment strategies.

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Review

Exploring Health Informatics in the Battle against Drug Addiction: Digital Solutions for the Rising Concern

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Abstract: Drug addiction is a rising concern globally that has deeply attracted the attention of the healthcare sector. The United States is not an exception, and the drug addiction crisis there is even more serious, with 10% of adults having faced substance use disorder, while around 75% of this number has been reported as not having received any treatment. Surprisingly, there are annually over 70,000 deaths reported as being due to drug overdose. Researchers are continually searching for solutions, as the current strategies have been ineffective. Health informatics platforms like electronic health records, telemedicine, and the clinical decision support system have great potential in tracking the healthcare data of patients on an individual basis and provide precise medical support in a private space. Such technologies have been found to be useful in identifying the risk factors of drug addiction among people and mitigating them. Moreover, the platforms can be used to check prescriptions of addictive drugs such as opioids and caution healthcare providers. Programs such as the Prescription Drug Monitoring Program (PDMP) and the Drug and Alcohol Services Information Systems (DASIS) are already in action in the US, but the situation demands more in-depth studies in order to mitigate substance use disorders. Artificial intelligence (AI), when combined with health informatics, can aid in the analysis of large amounts of patient data and aid in classifying nature of addiction to assist in the provision of personalized care.

Keywords: drug addiction; substance abuse; electronic health records; Prescription Drug Monitoring Program

1. Introduction

Addiction is a chronic, relapsing disease that causes functional alterations in the brain's networks related to stress and self-control. Long after a person stops using the addictive substance, those changes might persist [1]. Addiction has pervasive impact on various aspects of life, including physical health, mental well-being, relationships, legal status, work, and finances, thus affecting the overall quality of life. Americans lose more than 700 billion dollars annually due to enhanced medical treatment costs, criminality, and diminished productivity due to the use and abuse of prescription drugs, nicotine, and illicit drugs [2–4]. In 2018, almost 70,000 deaths were attributed to overdoses of prescription and illicit drugs [4,5].

Since drugs have the most harmful and potentially fatal effects on both the user and others around them, they are typically the first and most prominent thing that comes

to mind when someone thinks of addiction. Around 19.7 million adults in the US went through a period of substance abuse in 2017 [6]. Furthermore, over 23 million adult Americans have battled with substance abuse issues. Remarkably, it is said that 10% of adults in their lifetime have experienced a drug-use disorder, but 75% of this population have been found to have never received any treatment [6].

Individuals with addiction frequently have one or more comorbid medical conditions, such as lung or heart disease, stroke, cancer, or mental health disorders. Accidental drug overdose has been found to be a major cause of mortality among persons below the age of 45 years. In the US, drug overdose deaths account for over 70,000 deaths per year and the National Centre for Drug Abuse Statistics (2020) has reported that the yearly rate of increase in overdose deaths is 4.0% [7].

The co-occurrence of mental illness and drug use is common. Addiction may lead to mental health issues like psychosis, depression, or anxiety. In other situations, drug use—especially in those with particular vulnerabilities—may cause or exacerbate mental health conditions [8]. Additionally, one in ten HIV cases are related to drug injection. According to Cone et al. (2015), injection drug use can result in endocarditis and cellulitis and is a significant contributing factor in the spread of hepatitis C [9]. It is crucial to acknowledge the availability of FDA-approved medications for opioid-use disorder, and utilizing these in conjunction with behavioral interventions aids individuals in their recovery processes. However, detoxification alone, without further care, usually results in a return to drug use [10]. Given the current increase in drug addiction cases in the US, it is essential to incorporate other interventions in order to prevent and manage addiction effectively.

The use of digital and information technology in healthcare has grown significantly during the first two decades of the twenty-first century. Through data management, personalization, innovative interventions, clinician support, and improved treatment accessibility, information technology offers opportunities for the enhancement of healthcare [11,12]. Health information technology is improving in the US as a result of healthcare reform and a greater focus on performance monitoring. According to Wisdom et al. (2010), these technologies can reduce cost, save time, and improve quality. Increased incentives, data, and implementation guidelines can help improve the facility of health IT in drug addiction treatment [13]. While health informatics' role in cost-cutting and preventive care has received much attention, its potential for treating addiction remains unexplored. Electronic health records (EHRs), telemedicine, and clinical decision support systems (CDSS) are examples of platforms that show great promise for tracking drug use and providing individualized clinical interventions [12]. Electronic health records (EHR), a clinical decision support system (CDSS), and hospital information management systems (HIM) can aid in the detection of wrong prescriptions and overdose prescriptions of drugs, leading to the prevention of addiction. Moreover, machine learning (ML) algorithms, through brain imaging, behavioral kinematics, and memory analysis, aid by providing insights as to substance use and its associated disorders.

This review entails a description of the current crisis scenario of drug addiction in the US and the relevant ongoing treatment strategies. This study focusses on how health informatics can be utilized to prevent, monitor, and treat patients with drug addiction, helping them to achieve positive outcomes. The novelty of the review lies in exploring this new side of health informatics in managing a global crisis.

A thorough review of the literature was undertaken across prominent research databases such as PubMed, Scopus, and Google Scholar. Given the focus of this article on computers and the modern world, only articles published after 2001 were included. We specifically considered full-length research articles, systematic reviews, and narrative reviews for analysis, while excluding case reports, case series, letters to the editor, and commentary articles. Two authors screened the databases separately for articles by using the title/abstract method. The search process was meticulous and comprehensive, utilizing keywords such as drug addiction, substance abuse, health informatics, electronic medical records, and electronic health records. Figures were generated using BioRender.com (accessed on 5 January 2024).

2. The Growing Drug Addiction Crisis

Drug addiction presents a burgeoning crisis in the US, posing a threat not only to the physical well-being of the youth, but also to their mental health. Given the longstanding nature of this issue, it is imperative to examine past policies while formulating new strategies to address it.

2.1. Current Status of Drug Addiction in the US and Related Regulations

Drug addiction has long been a concern in the United States. According to the National Epidemiologic Survey on Alcohol and Related Conditions, men, white people, Native Americans, and those who were single or divorced were more likely to suffer from a drug-use disorder. A higher risk also applied to younger people and those with lower incomes and educational levels [13]. Table 1 represents the 2020 statistics for the US population aged 12 or older as to addiction to various addictive drugs, and their health consequences.

Table 1. Statistics of people in the US (aged 12 or above) affected by substance abuse in 2020, and the associated physical and mental health consequences.

Substance	Estimated Number of People Affected	Physical/Mental Health Consequences	References
Marijuana	5.1% (or 14.2 million)	Alterations in senses, Mood swings, Diminished bodily movement, Difficulty in problem-solving, Decreased memory, Hallucinations, Psychosis	[14,15]
Opioids	1.1% (or 2.7 million)	Falling unconscious, Slow and shallow breathing, Choking, Vomiting, Slower heart rate	[14,16]
Cocaine	0.5% (or 1.3 million)	Weight loss, Damage to cardiovascular system, Risk of stroke, Intracerebral hemorrhage, Ulcerations in the GI tract, Cognitive impairments	[14,17]
Heroin	0.3% (or 902,000)	Hot flashes, Dry mouth, Lack of concentration, Slower heart rate, Coma and Permanent brain damage	[14,18]
Stimulant use disorder	0.2% (roughly 500,000)	Decreased appetite, Anxiety, Jitteriness, Headaches, Weight loss, Insomnia, Psychosis.	[14,19]
Benzodiazepines	2% (5 million)	Respiratory depression, Respiratory arrest, Drowsiness, Confusion, Syncope, Nausea/vomiting, Diarrhea.	[14,20]
Barbiturates	0.2% (or 500,000)	Lack of consciousness, Bradycardia, Difficulty in coordination, Vertigo, Weak muscles	[14,21]

The Controlled Substances Act (CSA) of 1970 designated many opioids (fentanyl, hydromorphone, morphine, and oxycodone, among others) as Schedule II drugs, and they are currently approved for use in medicine as a form of treatment in the United States, albeit with stringent limitations. According to Chou et al. (2009), the CSA has classified opioids as possessing a highly addictive nature, one that may lead to critical psychological and physical dependency [22].

2.2. The Growing Opioid Epidemic

Opioids reduce pain by slowing signal transmission through the central nervous system. This causes the brain to reduce the sense of pain exponentially [23]. Opioids cause the neurotransmitter dopamine to be released, which is what actually causes physiological and psychological dependence and has given rise to the street term "dope". Although this is the main goal of the medication, it also causes other physiological effects, including nausea, lack of appetite, and euphoria due to the increased release of dopamine [16]. The overall physical side effects of opioids on the human body are depicted in Figure 1.

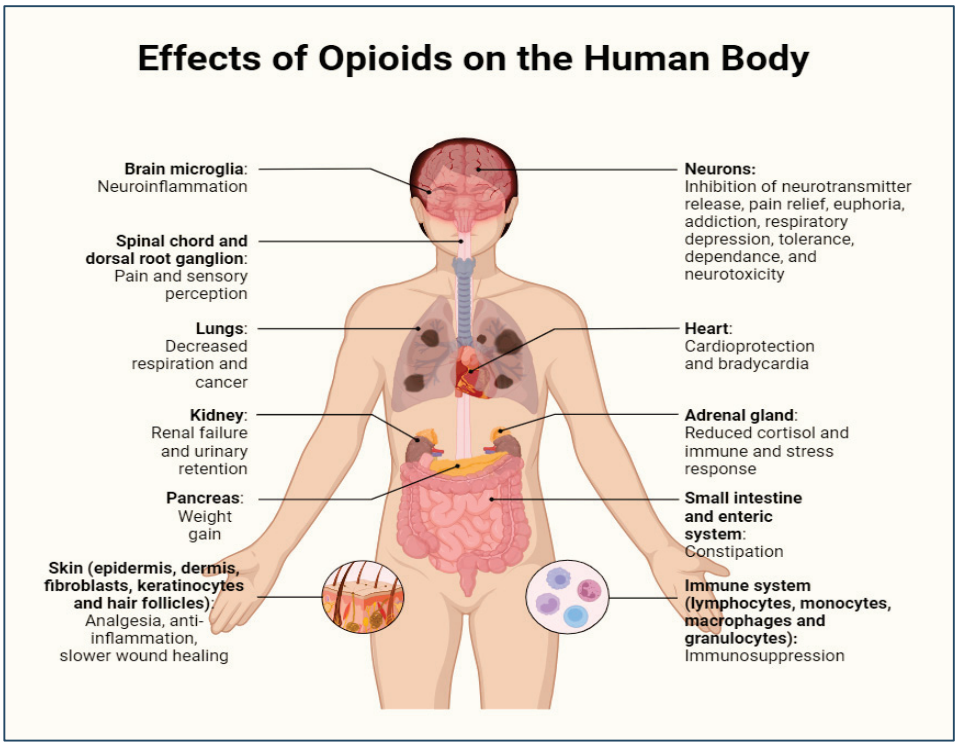

Figure 1. Effects of opioid addiction on the various systems of the human body. https://app.biorender.com/illustrations/65c9b7c73e5b86ada6bdc65d?slideId=39b528df-f03a-4593-a240-a47e2ef7540d (accessed on 5 January 2024).

Physical dependence, a medical term often used interchangeably with addiction, can develop within a few days of taking opioids, depending on the dosage and duration of use [24]. Because more and more people are becoming addicted to opioids, the number of prescriptions for these drugs has increased, which has led to an increase in addiction rates. As a result, people are frequently prescribed opioids for a much longer duration than necessary. In 2014, 10.3 million people reported using prescription opioid drugs for purposes other than those for which they were prescribed, or, alternatively stated, 10.3 million people reported taking opioids solely for the euphoric high they produced [25]. The most concerning trends were the 153% increase in emergency room visits related to prescription opioid misuse or abuse between 2004 and 2011, as well as the more-than-quadrupling of patient admissions to substance use treatment programs between 2002 and 2012 [26]. Most alarmingly, in progressing from 1.5 to 5.9 deaths per 100,000 people, morbidity and death from opioid overdoses increased by nearly a factor of four between 2000 and 2014. The DHHS designated opioid addiction as a major public health epidemic in 2014 after over 165,000 prescription-opioid-related deaths were reported [26].

2.3. The Mental Health Consequences and Social Impact

Addiction to substances is linked to numerous immediate and long-term health consequences. They can differ based on the medication type, dosage, and frequency of use, as

well as the individual's overall health [27]. In general, drug use and dependence can have a wide range of consequences, affecting nearly every organ in the human body. Moreover, they can lead to difficulties with memory, focus, and decision-making which impede day-to-day functioning. Changes in mood, thought, or behavior are often indicative of mental disorders [28]. They can make daily tasks challenging and hinder a person's capacity to work or perform well in school, engage with family, and carry out other important life-tasks [29].

There are various ways that drugs can impact mental health. Drug use can cause long-term mental health issues. Cannabis use on a regular basis may raise your risk of depression or anxiety [30]. Increased levels of cannabis use have also been connected to the development of schizophrenia or psychosis [31]. People may experience anxiety and depression following the use of stimulants. Stimulants like cocaine have the potential to exacerbate pre-existing psychological issues and schizophrenia [32]. "Magic mushrooms" and other hallucinogenic substances can induce frightening or upsetting flashbacks and a sense of detachment from your surroundings. Combining medication with alcohol or other drugs can pose serious risks, including those of potential harm or fatality. The present-day mind is more knowledgeable about the potential consequences of combining various medications.

2.4. Associated Risk Factors of Drug Addiction

The chance of becoming addicted to drugs varies from person to person, just as with other illnesses and disorders, and there is no one factor that can predict whether someone will develop an addiction. Generally speaking, the likelihood that using drugs will result in drug use and addiction increases with an individual's number of risk factors. Conversely, protective factors lower an individual's risk. Environmental and biological factors can act as risk and protective factors (Figure 2). The majority of people who use drugs at some point in their lives do so without ever developing a substance-use disorder, despite the fact that numerous studies have identified factors that predict the likelihood of disorders associated with substance use. For instance, it is estimated that 46.9% of Americans have used marijuana at some point in their lives, but only 9.9% of US adults will experience a drug-use disorder at some point in their lives [33,34]. Any age, gender, or socioeconomic background can develop addiction. The likelihood and rate at which addiction develops can be influenced by various factors.

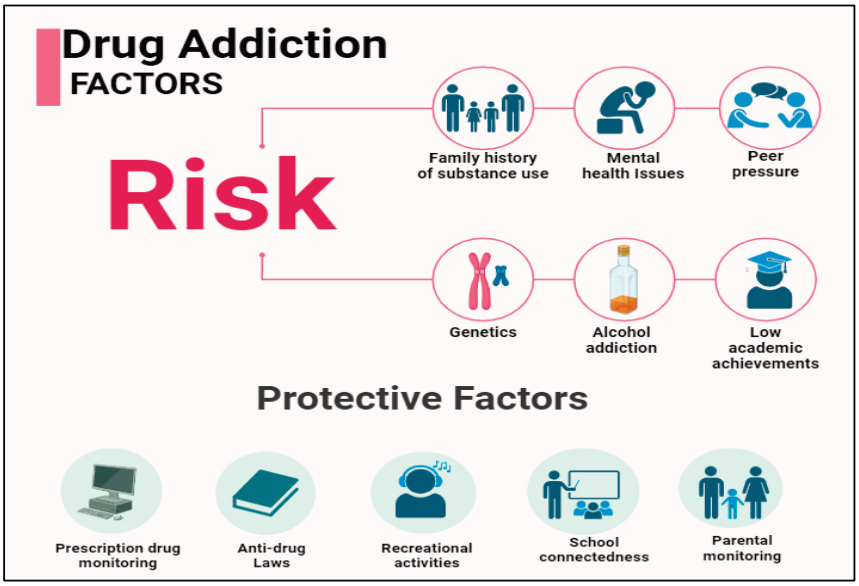

Figure 2. Protective and risk factors associated with drug addiction among individuals. https://app.biorender.com/illustrations/65c9bf623838038a35e0a3a6?slideId=212350a7-bd36-4a9a-baa9-8e46347669a1 (accessed on 5 January 2024).

2.4.1. Record of Addiction within a Family

Drug addiction has been found to be more prevalent in certain families and is probably associated with a higher risk in some cases due to genetics. You run a higher risk of becoming addicted to drugs if you have a blood relative, like a parent or sibling, who is addicted to alcohol or drugs [35]. Meier et al. (2016) created a cumulative risk index, for instance, by adding up the presence of nine risk factors that are associated with childhood and adolescence: being male, having a lower socioeconomic status in the family, having a family history of drug addiction, having depression as a child, being exposed to substances at an early age, and frequently using alcohol, tobacco, and cannabis as a teenager [35].

2.4.2. Mental Health Disorder

Addiction to drugs is more common in those with psychological issues like depression, attention-deficit/hyperactivity disorder, or post-traumatic stress disorder. One of the most well-researched indicators of the likelihood of developing a substance use disorder as an adult is receipt of a mental health diagnosis early in life. Attention-deficit/hyperactivity disorder, conduct disorder or oppositional defiant disorder, and depression diagnosed in childhood or adolescence were linked to an increased risk for adult addiction, according to a meta-analytic review [36].

2.4.3. Peer Pressure, Lack of Family Involvement and Early Use

Peer pressure plays a significant role in the decision to start using and abusing drugs, especially for young people [37]. Addiction risk factors include challenging family circumstances, a lack of attachment to parents or siblings, and inadequate parental supervision. Drug use during adolescence can alter the brain's development and raise the risk of developing a drug addiction [38].

3. Health Information Management and Addiction

With the increasing incidence of drug addiction among individuals in the US, it is time for health information technology to be explored, allowing it to attain its full benefits in monitoring and preventing addiction.

3.1. Health Informatics and Various Platforms

Health information technology (IT) includes a wide array of devices, programs, and networks that facilitate patient-centric care or self-management among patients [39]. Clinical alerts, computerized order entry, clinical decision support systems, electronic prescribing and test results, patient decision support, administrative and financial systems, and other electronic exchanges of health information are a few of the instances of applications related to health informatics [40]. Information on the clinical and behavioral conditions of clients, as well as information about finances, regulations, and other mandated reporting, are all included in health information.

Hospital settings that have to handle data from several departments (like radiology, pharmacy, and intensive care) and various types of quantitative data (like lab results and prescription orders) will undoubtedly benefit from these essential capabilities [41]. Health informatics improves the quality of preventive care by providing providers with patient-centric alerts on issues like vaccine schedules. Quality indicators can be measured by aggregating data from multiple patients. After entering data from hand-filled forms, staff members can immediately increase productivity [12]. By permitting electronic invoicing, billing schedules can be optimized, and communication delays caused by paper invoices being mailed or faxed can be minimized. According to Ekstrom and Johansson (2019), health IT can also lower medical errors brought on by a lack of communication, incomplete information, or illegible handwriting [42].

These advantages are seen in health IT systems that track a large number of patients. These systems allow large hospitals to take advantage of economies of scale that might not be available to treatment programs, which typically have fewer patients [41]. Enhanced

vaccination rates and decreased post-operative infections are two examples of preventive care measures for which decision support systems have been linked to adherence to protocol-based care [40]. Harpaz et al. (2013), for instance, developed interventions to lessen the frequency of adverse drug events by using electronic medical records to identify them [43]. However, Liu and colleagues (2013) discovered that because of data fragmentation and a poor human–machine interface, putting in place a computerized order-entry system increased the risk of medication errors [44].

3.2. Applications of Health Informatics in Drug Addiction Management

There are studies available on the cost-effectiveness of substance use treatment and the cost of implementing health IT. Research examining these problems in medical facilities and physician practices has usually focused on how health IT has affected service utilization [45]. On the other hand, medical interventions are less common in substance use treatment programs (29 percent test for HIV and 21 percent test for other STDs); instead, the majority of programs (99% offer individual therapy and 96% group therapy) focus primarily on psychosocial interventions [14]. Health IT offers organizational opportunities in addition to information administration. It can assist in monitoring client health statistics over time, giving a clear picture to support the management of addiction.

Electronic health record (EHR) systems facilitate the retrieval of comprehensive patient data, encompassing medical history, prescriptions, and records of substance use treatment. Data on substance use disorders (SUDs) can be integrated into electronic health records (EHRs) to support coordinated care and guarantee continuity between healthcare settings [46] (Figure 3). Remote addiction treatment and support services can be conveniently provided through telemedicine platforms and mobile health apps. Individuals with addiction can receive medication-assisted treatment, peer support networks, and counselling via secure communication channels and virtual consultations [47].

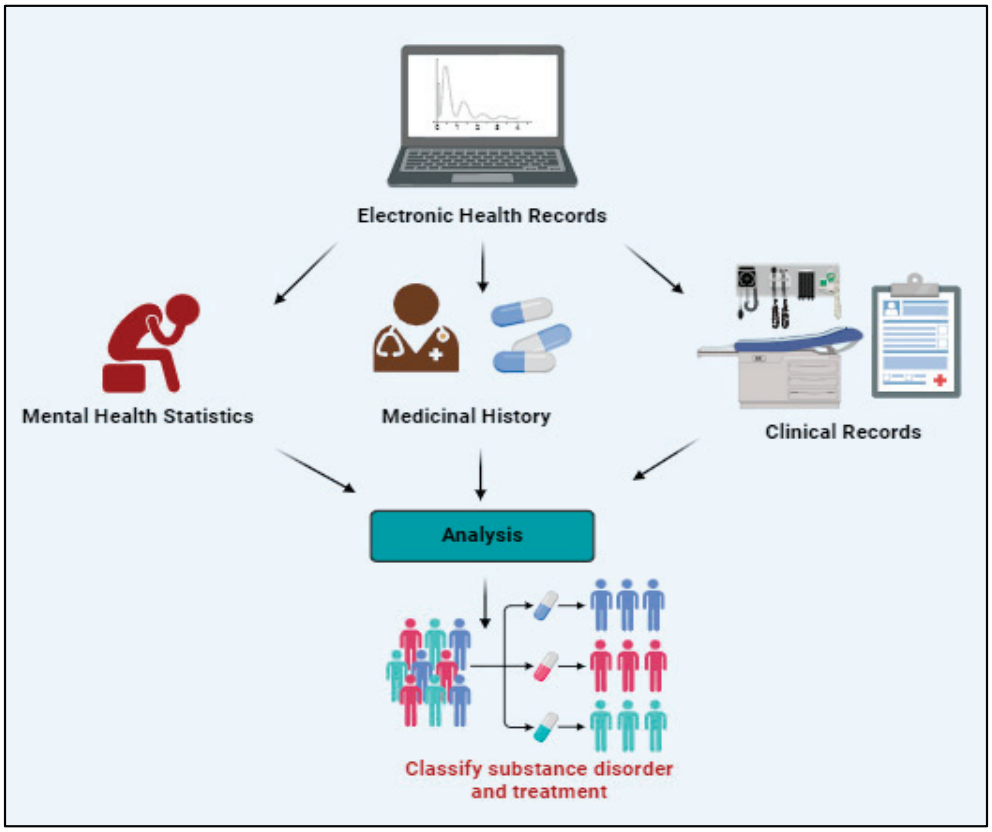

Figure 3. Role of electronic health records in the management and treatment of drug addiction. https://app.biorender.com/illustrations/65c9d39fe1ecacdd7c66b249 (accessed on 5 January 2024).

Predictive analytics is another tool that health informatics uses to identify people who may return to use or develop drug-use disorders. In order to lower high-risk prescribing behaviors, opioid medication use, and mortality rates, Valdes et al., 2023 set out to use the recently developed Opioid Risk Stratification Tool to identify people who might be at risk for abusing opioids. They also sought to investigate the effects of implementing a mailing and engagement intervention to this population and their prescribers [48]. According to Valdes et al. (2023), there was a higher decline in the number of people in the intervention group who also had prescriptions for benzodiazepines and opioids [48]. In addition, Prescription Drug Monitoring Programs (PDMPs) also keep track of prescriptions for controlled substances in order to spot possible misuse or diversion. By enabling real-time data analysis, alerts for questionable prescribing patterns, and interoperability with EHRs for smooth information exchange, health informatics tools improve the functionality of prescription drug monitoring programs (PDMPs) [49].

3.3. Prescription Drug Monitoring Programs (PDMPs) and Their Effectiveness

Prescription drug monitoring programs (PDMPs) are presently in use in a majority of the American states to identify providers who overprescribe opioids and to discourage patients from doctor shopping, which is the practice of routinely obtaining duplicate prescriptions for opioids. According to Yokell et al. (2012), PDMPs include a plethora of data on demographic trends, prescription drug-use patterns, overdoses, and poisonings. These data can be analyzed to identify shifts in prescribing practices and patterns that are influencing the changing trends [50].

Incorporating the first significant health information management tool to be used for both diagnosing and preventing prescription drug addiction, this strategy was historic. Despite the fact that the PDMP was first created for law enforcement [51], prescribing physicians were able to view a patient's medicinal history in real time, and, on occasion, at the time of an urgent necessity. According to a 2012 study by Dormuth et al., PharmaNet, the PDMP databases used in Canada, led to a sharp decline in the prescription of opioids [52].

The frequency of PDMP use by doctors in pain management, psychiatry/behavioral health, internal medicine, and dentistry was studied by Hildebrand et al. in 2014 [53]. The study's findings showed that while not all prescribers use a PDMP consistently, patients needing pain management frequently received the same prescriptions. In contrast, doctors with different specializations mainly used PDMP for first-time clients, or for patients who appeared to be seeking drugs.

A PDMP utilization survey was carried out by Irvine et al. (2014) on 1065 Oregon physicians who were currently employed in pain clinics, emergency medicine, and primary care [51]. Around 95% of the prescribers who took part in the survey at the time said they had used the PDMP while treating a patient who may have been using illicit drugs. As for first-time patients, who are not suspected of having drug-use disorders, about half of the prescribers surveyed said they utilized the PDMP. Referrals for psychological help or addiction therapy were made 54% of the time.

In 2014, Islam and McRae revealed that physicians not willing to suggest opioids to specific patients due to concerns about abuse were likely to receive low ratings, which may have an impact on their ability to receive payment and keep their jobs [54]. These studies show that Health IT platforms such as PDMP can aid in identifying patients struggling with drug addiction, even though the PDMP has its own benefits and drawbacks (Figure 4). Further investigation is required to enhance and optimize the methods by which medical practitioners use health informatics to identify and address both suspected and confirmed drug abuse.

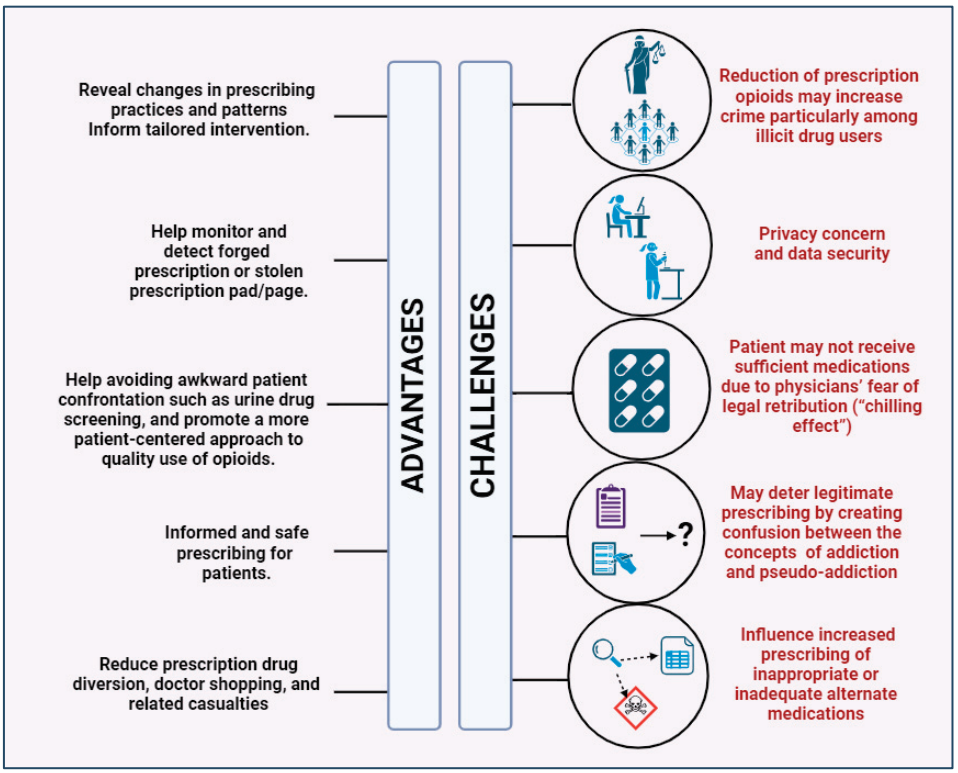

Figure 4. Advantages and challenges related to the use of a prescription drug monitoring system in controlling prescribing addictive medications. https://app.biorender.com/illustrations/65c9d4930b30aa000ee90ce5?slideId=7e85bb6c-29d1-44fe-a542-a5fb3b97cb51 (accessed on 5 January 2024).

4. Development of Novel Interventions

Apart from PDMP, there are a few novel interventions that have been developed involving health information technology. These include Drug and Alcohol Services Information Systems and AI-based interventions.

4.1. Drug and Alcohol Services Information Systems (DASIS)

In recent years, addiction treatment has been affected globally by the use of health information management. These database structures are often known as Substance Dependency Treatment Information Systems (SDTIS) or Drug and Alcohol Services Information Systems (DASIS), and are health information management systems that gather, process, and disseminate data about addiction [26]. Since substance abuse and addiction have such widespread effects on modern society, the WHO (World Health Organization) ranks drug addiction among the most pressing challenges confronting our generation, along with hunger, criminal activity, and pollution of the environment [55]. This validates the need for these specific databases.

It is crucial to implement the right care schedules for each patient, just as it is for the prevention and management of any psychological or physical condition. The System Data Set, Minimum Data Set, and Supplementary Data Set are the three subsets of data that the US uses to treat addiction using the DASIS system. The goal of this information system is to give data regarding drug abuse and addiction therapy, including patient demographics, hospitalization and discharge records, and program efficacy metrics [56].

4.2. Developing a Collaboration between EHRs and AI

Currently, there is very little computational support available for carrying out extensive research that can measure each of these medications' effects on an individual basis, whether they are taken alone or in combination. This is mostly because different people

respond to these medications differently, which frequently leads to conflicting findings in scientific cohort studies.

Using a socioeconomic status survey dataset from Bangladesh, Shahriar et al., 2019 used Neural Networks, Random Forests, Support Vector Machines, and feature importance to differentiate between people who were addicted and those who were not [57]. Conversely, Dong et al., 2021 employed deep networks to forecast drug addiction, employing the Cerner EMR dataset [58]. While both offer insightful information and showcase the application of state-of-the-art computational technology, neither investigates the potential for creating a patient-level metric that is proportionate to the person's propensity towards substance use. Ovalle et al., 2021 evaluated the risks of abuse based on four bio-markers: HIV, amphetamines, methamphetamines, and tetrahydrocannabinol (THC, a constituent of cannabis) [59]. They obtained data from social media sites. Additionally, Barenholtz et al. (2020) identified several aspects that can be improved to incorporate computational strategies, including machine learning, into the understanding and management of substance abuse [60].

The standardization of data and procedures is one of these elements. Quantifying the impact of addictive prescription drugs on individuals through the use of objective data is one potential solution to these problems [61]. Therefore, it may now be possible to use biological data to quantify substance effects using Electronic Medical Record (EMR) data [62]. Additionally, the use of informatics like the SEI can help to advance research and diagnosis related to substance abuse. When the SEI is completed, it could be used in conjunction with the psychometric scores to (i) give the treating physician a more comprehensive and insightful profile of the patient's substance abuse; and (ii) promote the use of standardized methods and measures, which will advance research on substance use [62].

According to research described in [63], machine learning (ML) algorithms can aid in drug-addiction determination through various factors. Brain-related factors, behavioral phenotypes, and functional differentiation of the brain can express a great deal about disorders. These findings also identify the insights into various research levels, classification techniques, performance measures, challenges, and future directions related to use of ML. Random Forests models are largely used, due to their better performance.

Through the integration of electronic health records (EHR) in healthcare systems, the details of the journey of a patient through treatment can be easily monitored. The details as to the various prescribed medicines and their doses can be tracked at any point, and through the interoperability of systems, by any other hospital. This can aid in detecting unnecessary opioid prescription and improper dosing.

Moreover, through Clinical Decision support systems (CDSS), dosing can be tracked. Dosing errors account for over 60% of all prescribing mistakes [64]. But through CDSS, the software component can generate a personalized list of recommended dosages for a specific medicine. Moreover, the CDSS can address the problem of duplicate therapy by comparing a newly introduced medication with the active ingredients of drugs in a patient's profile. If a similarity is detected, the system generates an alert, eliminating the chance of an overdose. This can be beneficial, too, in restricting opioid overdoses. People working at hospitals who are engaged in healthcare management need to have the proper training as to the handling and supervision of these forms of software.

5. Challenges in Implying Health Informatics for Drug Addiction

The application of health informatics to drug addiction treatment presents a number of obstacles, despite the possible advantages. It is crucial to protect sensitive patient data, which requires strong data encryption, controlled access, and adherence to privacy laws [39]. Coordinated care and information sharing are hampered by the fragmentation of healthcare data across different systems. To enable data sharing between agencies and providers, standardization and interoperability initiatives are required [65].

Furthermore, unequal access to technology could worsen already-existing healthcare inequalities by restricting the use of health informatics interventions in marginalized communities [39]. Furthermore, there are moral conundrums associated with the use of patient data for surveillance, research, and predictive modelling; thus, procedures for informed consent are required [65].

These health informatics systems need to be carefully designed to keep matters only between the healthcare provider and patient. The software applications need to adhere to high security standards, specifically those involving HIPAA compliance, and need to be blockchain secured for increasing privacy and mitigate data theft. In the revised manuscript we have added this data, as highlighted in [66].

6. Conclusions and Future Prospects

The field of health informatics has enormous potential to change how drug addiction is treated in the United States. Healthcare stakeholders can improve prevention efforts, optimize therapy pathways, and encourage sustained recoveries among people who suffer from substance use disorders. To fully utilize health informatics in the fight against the growing problem of opioid and other drug addictions, however, issues of confidentiality, connectivity, and fairness must be resolved [67].

Future initiatives should concentrate on collaboration among healthcare sectors, government bodies, technology developers, and community members to create inventive informatics in order to maximize the impact of health informatics on drug addiction management [39]. Furthermore, it is crucial to carry out thorough investigative research to determine the efficacy of health information technology in the treatment of drug addiction [67]. Drug addiction treatment can undergo a revolution if data analytics and machine learning algorithms are used to design therapies based on an individual patient's unique risk profile, treatment preferences, and socioeconomic background.

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Exercise Influences the Brain's Metabolic Response to Chronic Cocaine Exposure in Male Rats

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Abstract: Cocaine use is associated with negative health outcomes: cocaine use disorders, speedballing, and overdose deaths. Currently, treatments for cocaine use disorders and overdose are non-existent when compared to opioid use disorders, and current standard cocaine use disorder treatments have high dropout and recidivism rates. Physical exercise has been shown to attenuate addiction behavior as well as modulate brain activity. This study examined the differential effects of chronic cocaine use between exercised and sedentary rats. The effects of exercise on brain glucose metabolism (BGluM) following chronic cocaine exposure were assessed using Positron Emission Tomography (PET) and [18F]-Fluorodeoxyglucose (FDG). Compared to sedentary animals, exercise decreased metabolism in the SIBF primary somatosensory cortex. Activation occurred in the amygdalopiriform and piriform cortex, trigeminothalamic tract, rhinal and perirhinal cortex, and visual cortex. BGluM changes may help ameliorate various aspects of cocaine abuse and reinstatement. Further investigation is needed into the underlying neuronal circuits involved in BGluM changes and their association with addiction behaviors.

Keywords: 18F-FDG fluorodeoxyglucose; positron emission tomography; aerobic exercise; glucose metabolism; statistical parametric mapping; cocaine

1. Introduction

Cocaine use is associated with a wide range of negative health outcomes [1]. The number of deaths involving cocaine has also increased steadily since 2015, with 24,486 deaths reported in 2021. Currently, there is no approved treatment for cocaine overdose. In the United States, there are an estimated 2 million regular users of cocaine, with no approved medication for the treatment of cocaine use disorder (CUD) [2]. Cocaine is often used with alcohol, opioids, and benzodiazepines, making overdose and treatment failures more likely. Psychosocial treatment of CUD has high dropout and recidivism rates, and no pharmacological treatments have been approved [2]. Researchers are currently investigating both pharmacological and non-pharmacological approaches to treating addictions and substance use disorders such as CUD [2–5].

Previous studies have shown that aerobic exercise alters BGluM in regions associated with sensory processing, motor function, and motivated behavior, both alone [6] and in response to acute cocaine [7].

In female Lewis rats, exercise has been shown to increase brain glucose metabolism in a range of sensorimotor regions [6–8]. In rats chronically exposed to cocaine, exercised rats showed activation in the secondary visual cortex, lateral area (V2L) compared to their sedentary counterparts [8,9]. Our group previously found the modulation of BGluM in sensory cortical areas following both exercise alone and acute cocaine [6,7]. Other sensorimotor regions, such as the central nucleus of the inferior colliculus (CIC), caudate putamen (striatum) (CPu), and primary auditory cortex (Au1), have been found to be activated in response to chronic aerobic exercise alone [6]. In chronically exercised female rats exposed to an acute dose of cocaine, activation has been observed in the temporal association area (TeA), entopeduncular nucleus (EP), Crus 1 of the ansiform lobule (crus 1), and substantia nigra. The visuospatial demand required for exercise may explain the activation of sensorimotor regions and coincides with the acute effects of exercise proposed by the "transient hypofrontality hypothesis" [10]. This hypothesis proposes that metabolic resources are redirected from regions not pertinent to exercise performance to structures that are required for motor patterns, the assimilation of sensory inputs, and the coordination of autonomic regulation. Increased BGluM in the sensorimotor regions has also been observed in works from the literature investigating the effects of physical exercise on humans, indicating potential clinical relevance [11]. In contrast, various sensorimotor regions have been observed to be inhibited in female rats exposed to both chronic exercise and chronic cocaine. BgluM inhibition has been observed in relation to the paraflocculus (PFL), the eighth cerebellar lobule (8cb), the paramedian lobule [2], the copula of the pyramis (COP), the stria terminalis (st), the stria medullaris of the thalamus, the medial and posteromedial parts of the bed nucleus of the stria terminalis (stmpm), the ventrolateral thalamic nucleus, (VL), the primary somatosensory cortex, hindlimb region (S1HL) [8].

The literature suggests that glucose metabolism differs based on the history of cocaine use. This has been demonstrated in a study on BgluM changes in Rhesus monkeys after the administration of an acute cocaine injection, 60 sessions of self-administration under limited-access conditions (1 h/day), 60 sessions under extended-access conditions (4 h/day), and 4 weeks of abstinence [12]. BgluM inhibition was observed in the prefrontal cortex, expanding to other regions of the frontal cortex with higher levels of cocaine consumption. In humans, cocaine abuse is associated with decreased glucose metabolism in the frontal cortex, which persists for 3–4 months after abstinence [13]. The frontal lobe itself is acutely affected by cocaine, and the effects persist the longest in the region during withdrawal. As previously mentioned, a range of sensorimotor regions have been shown to be inhibited in female rats exposed to chronic cocaine and chronic exercise [8]. The inhibition of regions outside of the frontal lobe could help correct the biased inhibition of the frontal lobe observed In humans and non-human primates following chronic cocaine use, particularly if regions are functionally connected to the frontal lobe. Furthermore, regions associated with motivated behavior have been shown to be modulated in our group's previous findings [8]. Inhibition in cPu, st, and the thalamus are of particular interest because they are a part of the brain's reward cascade [14], which may impact response to cocaine. These results in female rats imply that exercise could help balance the bGluM changes observed following chronic cocaine [15] or psychostimulant use [16,17]. The functional connectivity of regions affected, as well as the role of specific regions in addiction, should also be considered [9].

Based on the previous literature, changes in basal ganglia activity associated with cocaine would be expected to be attenuated. The activation of the caudate putamen (striatum) (CPu) in chronically exercised female Lewis rats compared to sedentary controls [8] is of particular interest because the region is a part of the basal ganglia, which has been implicated in various aspects of cocaine-induced behavioral [18] effects. In female rats administered chronic cocaine in conjunction with the same exercise regimen as used in the current study, various regions of the basal ganglia were inhibited. Due to the role of the

basal ganglia in reward-seeking [19], the modulation of BGluM in this region is of interest in terms of determining the efficacy of exercise in attenuating addiction behavior. While previous work by our group demonstrated results supporting these mechanisms of action in female rats, male rats remain to be investigated, which is the purpose of the current study. Due to sex differences in the effects of cocaine and susceptibility to abuse [20–22], sex-specific studies are required to assess the use of exercise as an intervention [23].

Behavioral results support the hypothesis that exercise has a beneficial role in drug addiction, as exercise has been shown to decrease drug maintenance and the acquisition of cocaine self-administration [24] in adolescent and adult rats [25]. Binge use of alcohol in adult rats has also been shown to be reduced by exercise [26]. Alcohol consumption in a two-bottle choice model has been shown to be reduced in mice given access to running wheels [27]. Maintenance of methamphetamine self-administration in rats is attenuated when given access to running wheels; however, this is only the case if access is available at the start of self-administration [28].

The impact of exercise on addiction behavior has been shown to depend on the phase of the addiction process when used as an intervention [29]. The protective effects of exercise during initiation and withdrawal are attributable to its effect on dopaminergic transmission. Physical exercise has been shown to attenuate withdrawal symptoms as well as increase abstinence rates when used as an intervention in various substance use disorders [30]. In rats, exercise has been shown to reduce cocaine place preference, cue-induced reinstatement, and locomotor responses [4,5]. Aerobic exercise has been shown to reduce rates of cocaine acquisition and have a protective effect on cocaine-seeking at both low and high doses of self-administration [25].

At a neuronal signaling level, exercise has been shown to have a range of beneficial effects on drug-induced changes in neurotransmission. During drug use, exercise has been shown to help normalize glutamatergic and dopaminergic transmission in the reward pathway and reverse the modification of chromatin [31–34]. Aerobic exercise has been shown to produce rewarding effects by activating glutamate neurons in the red nucleus, which project to dopaminergic neurons in the VTA [35]. Chronic drug exposure is also associated with glutamatergic over-stimulation of the reward system, which may be corrected by exercise and has been shown to decrease striatal and hippocampal glutamate concentrations [35,36]. Exercise produces non-drug reward-producing changes in the mesolimbic reward pathway, which is associated with altered sensitivity to drugs of abuse [37]. However, the effect of exercise on the reward system is not completely beneficial, as exercise-induced plasticity has been shown to intensify drug associations if drug exposure occurs after a chronic exercise regimen. For example, a history of chronic voluntary exposure to wheel running has been shown to enhance conditioned place preference for morphine and cocaine in rats [38,39]. Chronic drug exposure is associated with reduced dopamine release, which may promote further drug use and withdrawal symptoms to correct for a lack of dopaminergic signaling [40,41]. Cocaine dependence, in particular, is associated with dopamine depletion [42,43]. The increased dopaminergic signaling caused by exercise may help correct the dysfunction seen in chronic drug exposure and reduce withdrawal symptoms. The potentiation of dopaminergic signaling has been shown to attenuate alcohol self-administration [44,45], and exercise may help in a similar manner.

Understanding the underlying mechanisms of the effects of exercise on cocaine-related behavior can be facilitated by gaining more insight into how exercise modulates various circuits in the brain. Positron Emission Tomography (PET) has the ability to assess how exercise modulates specific brain regions, assisting our understanding of the underlying mechanisms that dictate how exercise affects cocaine and addiction-related behavior. [18F]-Fluorodeoxyglucose (FDG) was used in the current study to assist in observing the changes in brain glucose metabolism (BGluM). This experiment served to advance our understanding of the underlying mechanisms by which aerobic exercise impacts subsequent cocaine exposure, identifying potential targets for further anatomical investigation in the ongoing research looking at exercise for addiction treatment. The data suggest that chronic aerobic

exercise helps attenuate the effects of hypoactivation in the frontal cortex in addition to impacting regions involved in addiction behavior. This study aims to identify if similar regions are involved in the exercise-mediated inhibition of addiction behavior observed in male rats using an identical protocol that has been previously used for females.

2. Materials and Methods

2.1. Animals

Eight-week-old young adult male rats (N = 16) were obtained from Taconic (Hudson, NY, USA). The animals were split into an exercised group (N = 8) and a sedentary group (N = 8). The animals were individually housed at room temperature ~22 °C on a 12 h reverse light/dark cycle. The dark cycle was from 6 a.m. to 6 p.m. The rats were given unlimited access to food and water in their home cages and were handled daily. The animals weighed approximately 250–285 g at the start of the study. They were allowed one week to habituate to their environment before beginning the assigned group regimens. This experiment was conducted in accordance with the National Academy of Sciences Guide for the Care and Use of Laboratory Animals (1996) and approved by the University at Buffalo Institutional Animal Care and Use Committee (Approval code: RIA 13095Y; Approval date: 1 July 2023).

2.2. Exercise

Exercise was the experimental variable. The animals in the exercised group (N = 8) underwent the following regimen: Forced running was performed on a customized treadmill divided into individual plexiglass running lanes. The exercise regimen started at 10 min a day at 10 m/min, increasing by 10 min each day until a maximum time of 1 h was reached, as per the standard exercise protocol [6,8]. The animals were given a ten-minute break after 30 min of running. This exercise regimen was maintained for 5 days per week for six weeks [8]. Sedentary rats remained in their home cages for the duration of the exercise regimen, receiving no treadmill exercise, as previously described [4,6,46,47].

2.3. Chronic Cocaine Treatment

Prior to imaging, all of the rats underwent chronic cocaine exposure. The cocaine was dissolved in 0.9% saline and injected via the intraperitoneal route at 25 mg/kg, consistent with previous experiments administering chronic cocaine over similar time periods [48], and with publications using the current exercise protocol [8]. Cocaine administration occurred daily for 8 days, alternating every other day with saline. Four total cocaine injections were administered.

2.4. PET Imaging

The rats were food-restricted for 8 h prior to imaging to normalize blood glucose levels. The rats were then given 500 ± 115 μCi of 18F-FDG via intraperitoneal injection. A 30 min uptake period followed the injections, and the animals were anesthetized immediately after. The rats were anesthetized with 3% isoflurane, maintained at 1% throughout the scan. PET imaging was completed using a microPET® Focus120 scanner (Concorde microSystems Inc. (Knoxville, TN, USA), transaxial resolution: 1.3 mm full-width at half maximum, transaxial field view: 8.0 cm). Anesthetized rats were secured to the scanner bed for 30 min, as per the standard imaging protocol.

2.5. PET Image Analysis

Analysis was conducted as previously described [6,49,50]. The scans were reconstructed using the MAP algorithm (15 iterations, 0.01 smoothing, 256 × 256 × 256 resolution). The reconstructed scans were manually coregistered onto a rat brain MRI template (63 slices, Paxinos and Watson Stereotaxic coordinates) in PMOD imaging software. (Version 2.85, PMOD technologies, Fällanden, Switzerland). Automatic coregistration and spatial normalization were carried out using MATLAB software (MATLAB, R2018b). Sta-

tistical Parametric Mapping (Voxel Threshold, K > 50) in MATLAB was then used to find significant differences in cluster size between the exercise and sedentary groups. Using PMOD software, significant clusters were again fitted onto the rat brain MRI template. Clusters were then mapped and labeled using "The Rat Brain in Stereotaxic Coordinates" atlas [51]. A complete experimental timeline can be viewed in Figure 1.

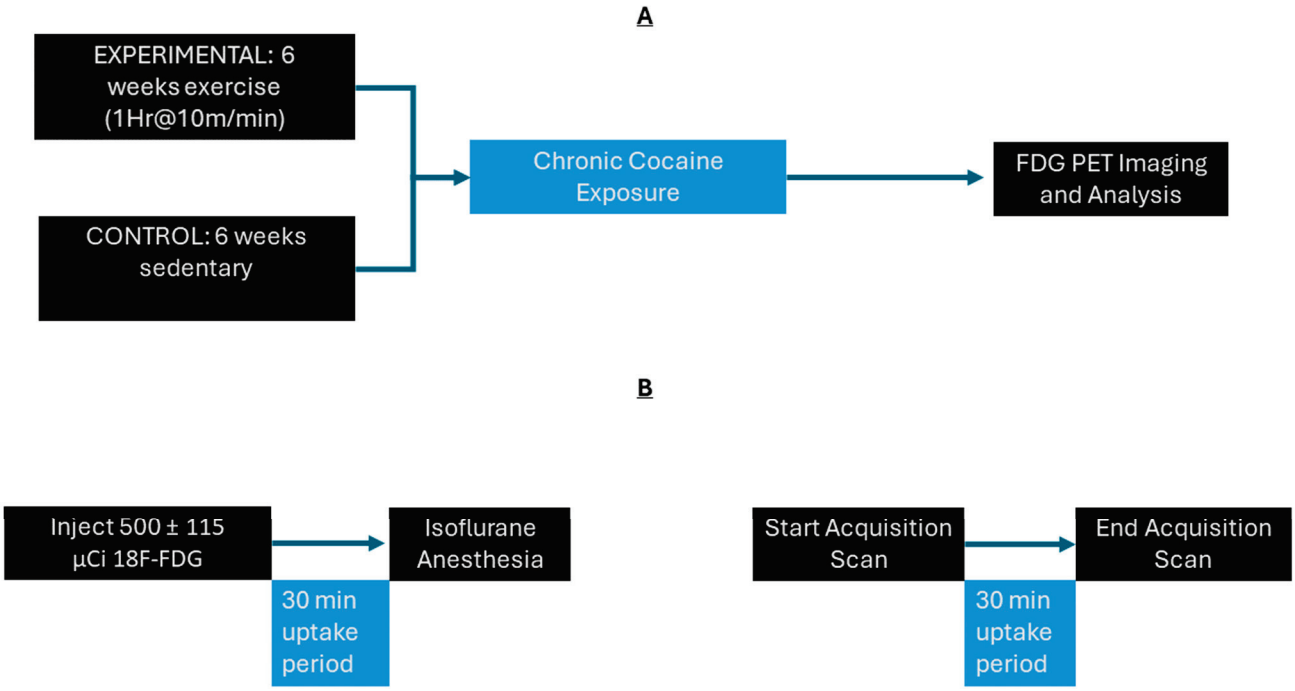

Figure 1. Experimental timeline: (**A**) The rats were split into exercise and sedentary groups. Exercise group rats underwent 6 weeks of exercise, and sedentary rats remained in their home cages. All animals underwent chronic cocaine exposure for 8 days followed by microPET scans. (**B**) Timeline of PET scans: rats were given [18F]-Fluorodeoxyglucose (FDG). Then, a 30 min uptake period followed. Animals were then anesthetized with isoflurane (3%), maintained throughout the duration of the 30 min PET scan (1%). This was based on a standard protocol, as described in [8].

3. Results

Statistics

A two-sample t-test revealed that the exercised rats showed significantly increased BGluM ($p < 0.001$, K > 50) compared to sedentary rats in the following regions (See Figure 2): amygdalopiriform transition area (t = 6.39; z = 3.83; KE = 244), basolateral amygdaloid nucleus/dorsal endopiriform nucleus piriform cortex layer 1 (t = 6.53; z = 3.87; KE = 94), trigeminothalamic tract (t = 5.57; z = 3.58; KE = 178), perirhinal cortex/rhinal fissure (t = 4.58; z = 3.21; KE = 112), and secondary visual cortex, lateral area (t = 4.17; z = 3.03; KE = 50). The only region with a significant decrease (See Figure 2) in BGluM was the SIBF primary somatosensory cortex (t = 4.85; z = 3.32; KE = 99). Information regarding cluster location, size, and statistical significance is reported in Table 1.

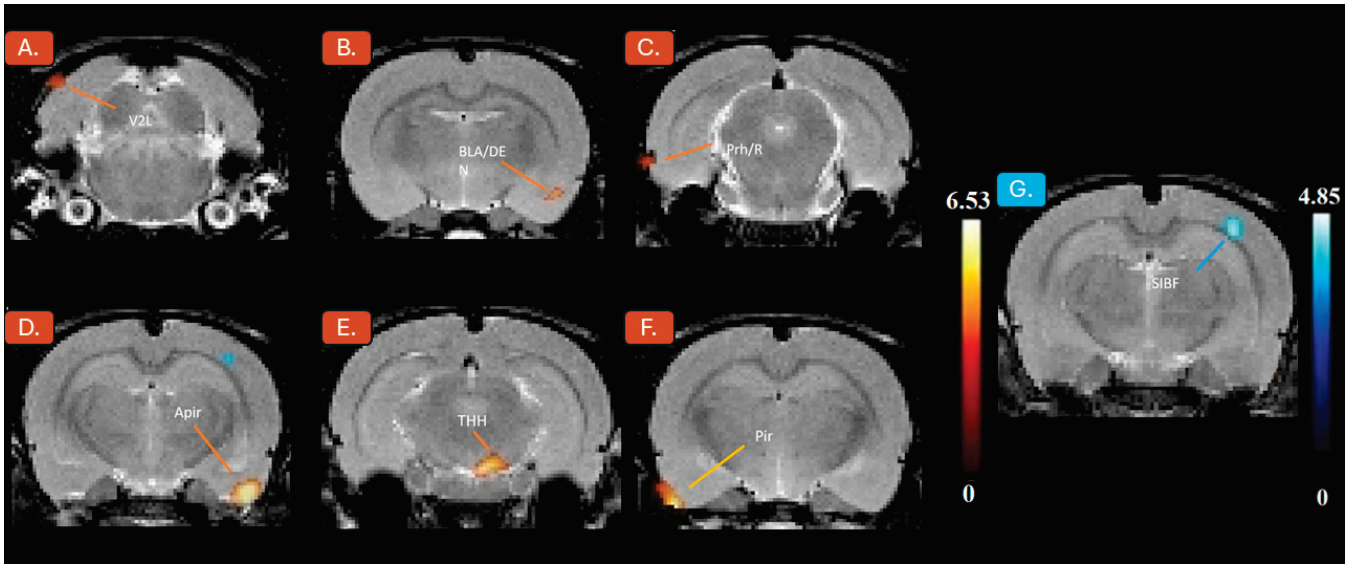

Figure 2. Significant activation clusters: coronal PET images showing brain regions with significant ($p < 0.001$, K > 50) metabolic increases (**A**–**F**) in exercised rats compared to sedentary rats labeled in orange. T-values represent peak activation (t = 6.53). Hot scale clusters illustrate BGluM activation in the (**A**) V2L, (**B**) BLA/DEN, (**C**) Prh/R, (**D**) Apir, (**E**) THH, and (**F**) Pir. Significant inhibition clusters: coronal PET images showing brain region with significant ($p < 0.001$, K > 50) metabolic decreases (**G**) in exercised rats compared to sedentary rats labeled in blue. T-values represent peak inhibition (t = 4.85). Cold-scale clusters illustrate BGluM reduction in (**G**) SIBF.

Table 1. Brain regions with significant decreases at $p < 0.001$ and voxel threshold K > 50 in BGluM between exercised and sedentary groups following chronic exercise and chronic cocaine exposure are labeled as inhibited. Regions with significant increases ($p < 0.001$, K > 50) in BGluM are labeled as activated. Increases are interpreted as activation while inhibitions are interpreted as deactivation. Cluster location is indicated by coordinates in stereotaxic space (medial-lateral, anterior–posterior, and dorsal–ventral). The t-values and z-scores were calculated from the average BGluM of all voxels within the significant clusters. KE represents the number of voxels in the respective cluster. Each cell under "Brain Region(s)" represents a separate cluster.

Brain Region (s)	Activated or Inhibited	ML (mm)	DV (mm)	AP (mm)	t Value	z-Score	KE
Primary somatosensory cortex (SIBF)	Inhibited	44	26	−44	4.85	3.32	99
Piriform cortex (Pir)	Activated	−58	104	−28	6.53	3.87	94
Piriform cortex	Activated	−58	104	−28	6.53	3.87	94
Amygdalopiriform transition (Apir)	Activated	56	100	−42	6.39	3.83	244
Trigeminothalamic tract (TTH)	Activated	10	84	−60	5.57	3.58	178
Basolateral amygdaloid nucleus, dorsal (BLA/DEN)	Activated	52	90	−20	4.56	3.2	67

4. Discussion

The results of the FDG PET analysis of male rats found differential activation in the exercised group compared to the sedentary group under chronic cocaine treatment. While sample size may be considered a limitation, it is consistent with previous publications [8]. Housing and PET imaging protocols were identical between the groups to minimize methodological bias. The animals were also handled daily to minimize stress.

Regions associated with drug cue-induced reinstatement, drug cue-induced conditioning, and compulsive drug use appear to be normalized. Additionally, a handful of affected regions border and project into the frontal lobe, which may imply the prevention of the more acute effects of cocaine. The SIBF primary somatosensory cortex (SIBF) was found to be inhibited in the exercised group. Increased activation was observed in the amygdalopiriform transition area (Apir), piriform cortex layer 1, trigeminothalamic tract (TTH), perirhinal cortex rhinal fissure (Prh/Rf), basolateral amygdaloid nucleus dorsal endopiriform nucleus (BLA/DEN), and secondary visual cortex, lateral area (V2L). Our group conducted the same protocol with female rats and found the exercised group to only have significant activation in the V2L compared to sedentary counterparts. Inhibition occurred in the paraflocculus (PFL), the eighth cerebellar lobule (8cb), the paramedian lobule [2], the copula of the pyramis (COP), the stria terminalis (st), the stria medullaris of the thalamus, the medial and posteromedial parts of the bed nucleus of the stria terminalis (stmpm), the ventrolateral thalamic nucleus, (VL), and the primary somatosensory cortex, hindlimb region (S1HL) [8].

In female cohorts subjected to the same protocol [8], sensorimotor regions were more activated in the exercised group compared to the sedentary group following chronic cocaine exposure. In contrast, in the male rats of the current study, sensory regions such as the V2L and Pir were found to be activated. These are associated with visual [52] and olfactory [53] sensory processing, respectively. Regions associated with higher-order sensory processing were also found to be activated. Prh/Rf, which is involved in object recognition memory [54], was found to have increased BGluM. Apir, which is associated with the processing of olfactory and gustatory information [55], was activated. The BLA/DEN is associated with integrating sensory stimuli and emotional responses [56]. TTH was found to be more activated in the exercised group, and it provides motor innervation to the jaw and is involved in orofacial nociception [57,58].

An interesting similarity between sexes is the inhibition of the somatosensory cortex. In the somatosensory cortex, acute cocaine is known to decrease spontaneous background neuronal activity [59]. Exercise appears to enhance the ability of the somatosensory cortex to ignore background stimulus [60], which may exacerbate the above-mentioned effects of cocaine. However, it is unclear if the observed exacerbation of inhibition will result in adverse effects on cocaine addiction as connectivity between other regions is also a factor associated with addiction behavior. Chronic cocaine self-administration is associated with hypoconnectivity between the somatosensory cortex and dorsal anterior cingulate, with higher consumption correlating to increased hypoconnectivity [61]. Exercise is associated with increased plasticity and neuroprotection in the region [61,62]. Interpretation of the inhibition of the region seen in the current studies exercised group would be facilitated by an investigation into the effect on connectivity and behavior to determine if exercise helps or harms susceptibility to cocaine addiction. A hypothesized brain circuit of regions found to have modified BGluM is pictured in Figure 3; however, further investigation is critical to validating or correcting this hypothesized circuit. This study cannot concretely identify functional connectivity.

The activation of the basal lateral amygdala observed in the males of the current experiment and nearby regions may have some implications for addiction behavior. The amygdala has been found to be involved in responses to drug cues and the reinstatement of cue-induced drug seeking [63,64]. The activation of the region is associated with relapse to drug-seeking, particularly by way of glutamatergic transmission [65,66]. Drug use has been found to decrease glutamate levels in the brain while sensitizing glutamatergic response to drug administration [67]. While the activation observed in the current study may imply increased susceptibility to relapse following exercise, the mechanism of action by which activation occurs hinders drawing concrete conclusions. In addition to increased activation, altered connectivity has been observed in the amygdala following cocaine abuse [68]. Dysfunction in connections with the prelimbic cortex has been implicated in cocaine reinstatement [69,70]. Exercise has been shown to induce plasticity [71,72] in the

amygdala, which may help correct dysfunction; however, further research is necessary. Cocaine has also been shown to dysregulate glutamate signaling in the amygdala [67]. Glutamate agonism has been shown to help reduce the rewarding effects of cocaine [73,74] and enhance the extinction of cocaine CPP [75]; however, agonism has also been shown to enhance the reconsolidation of cocaine-associated memories [76]. Exercise has been shown to enhance glutaminergic transmission in the amygdala [77], which could have helpful or harmful effects on cocaine addiction. Behavioral evidence shows that exercise decreases relapse potential [77], but the role of the amygdala, its connections, and glutamatergic transmission require further investigation.

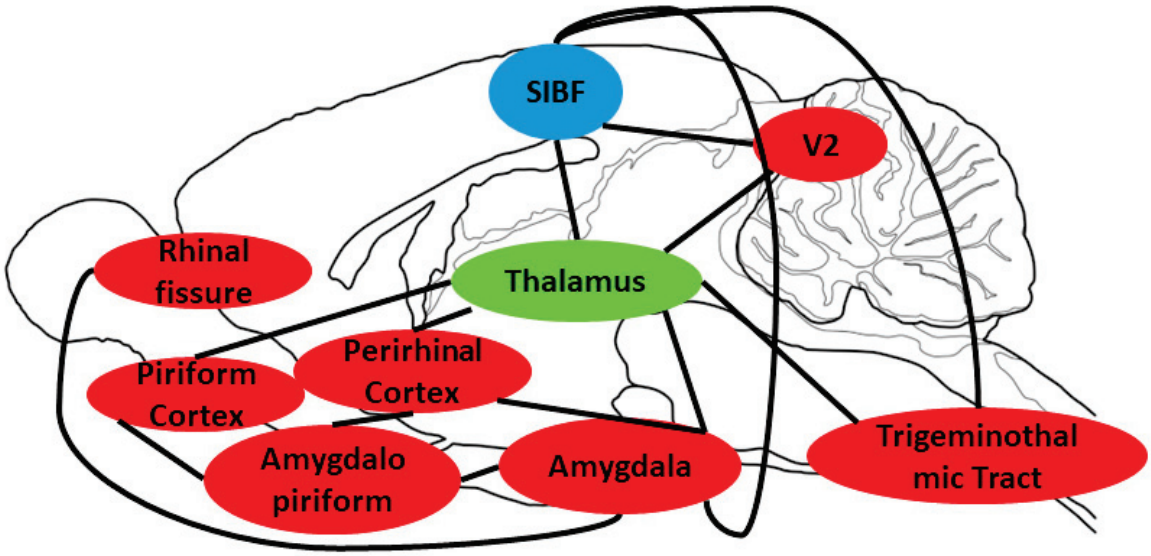

Figure 3. Hypothesized brain circuitry following chronic cocaine and exercise on a sagittal drawing. Activated/increased BGluM clusters are shown in red, while the inhibition of BGluM is shown in blue. Green boxes are brain regions that may serve as connection points between clusters.

The observed activation of V2L may have a beneficial impact on cocaine abuse. In the visual cortex, cocaine has been found to reduce activity [78], gray matter [79], and 123 I uptake, indicating impaired function [80]. However, in response to cocaine cues, increased activation has been observed in comparison to food cues, indicating involvement in drug conditioning by facilitating the establishment of cocaine–stimulus associations [81,82]. Increased sensitivity to drug cues in this cortex has been observed for a wide array of drugs [83] in addition to cocaine [81,82], contributing to compulsive drug use. In the current study, exercise helped to ameliorate inactivation of the visual cortex by cocaine. The activation of the visual cortex via exercise may be able to disrupt drug cue conditioning and affect relapse susceptibility due to its ability to influence visual cortex plasticity [84,85]; however, further behavioral research is necessary.

The piriform cortex was observed to be significantly more activated in the exercised group. In the piriform cortex, acute cocaine use has been found to decrease octanoate labeling, which is associated with decreased function [86], in addition to reducing both dopamine and 5-HT synthesis [87]. Similarly, withdrawal (at 6 h and 72 h from cessation) [85] from the self-administration of cocaine ($\geq$7 days for 3 h, followed by 12 h binge before) has been found to reduce regional cerebral metabolic rate for glucose [88] in the piriform cortex, which is associated with decreased function [88]. Exercise appears to impact this region in humans, as it has been observed that following exercise, regional cerebral blood flow in the region is decreased [89]. Connectivity between the piriform cortex and other regions is associated with cue-induced drug reinstatement and self-administration. For example, disconnection of projections between the piriform cortex and the orbitofrontal cortex has been found to reduce cue-induced fentanyl restatement [90]. Connectivity to the lateral habenula has been found to be differentially involved in compul-

sive methamphetamine-taking based on rats' sensitivity to punishment [91]. Compulsive drug-taking was assessed using methamphetamine self-administration along with concomitant footshock. Connectivity between the piriform cortex and lateral habenula was positively associated with compulsive intake in punishment-resistant rats; the opposite was found in punishment-sensitive rats. Based purely on BGluM, it would appear that exercise would help attenuate cocaine's effects on the piriform cortex; however, its impact on connectivity to regions, such as the lateral habenula and orbitofrontal cortex, should also be considered and investigated.

The observed activation of the trigeminothalamic tract of the exercised group may potentially influence the sensitivity of rats and thereby affect compulsive drug intake via the mechanism proposed for the piriform cortex. The trigeminothalamic tract is involved in orofacial nociception and motor innervation in the jaw [57,58]. The activation of this region suggests enhanced pain signaling, which would imply that the exercised group is more akin to the punishment-sensitive group seen in [91] in relation to orofacial pain. Past research following the same chronic exercise regimen as the current paper has linked acute cocaine administration with insular cortex activation [7]. In particular, chronic aerobic exercise and acute cocaine was found to increase BGluM in the granular and dysgranular regions of the insular cortex. Granular activation is also involved in orofacial proprioception and motor activation of the jaw [92]. The similarity between the trigeminothalamic tract and the granular region of the insular cortex raises the question of whether their involvement in cocaine-induced modification of orofacial nociception is related. The involvement of both in jaw movement may be related to cocaine-related jaw tension and vasoconstriction, as previously suspected [7]; however, more research is necessary.

In the exercised group, increased BGluM was observed in the perirhinal cortex. Cocaine withdrawal is associated with increased activity in the perirhinal cortex as well as increased c-fos expression [93]. Acute cocaine use has been shown to increase dopamine and 5-HT [94]. Cocaine has been found to enhance memory consolidation by D2R agonism, which may contribute to cocaine conditioning [95]. Cocaine also induces tPA mRNA in the perirhinal cortex. tPA is related to plasticity and may be involved in behavioral changes observed with cocaine use [96]. This information on the effects of cocaine on the perirhinal on its face would appear to show that exercise would have an adverse effect on drug abuse. However, research suggests that the effect of activation may be more complex and not simply additive. Chemogenetic activation of the perirhinal cortex has been found to reverse methamphetamine-induced NOR task impairment as well as reduce relapse [97]. Similarly, mGlu5R activation in the perirhinal cortex reduces methamphetamine relapse while recovering NOR test performance [98]. Exercise appears to influence the perirhinal cortex in a similar manner, as evidenced by observed improvements in NOR tasks [99,100]. Corticotropin-releasing factor 2 receptors have been implicated in NOR task deficits seen during cocaine withdrawal [93]. Exercise is known to impact the corticotropin system and could potentially counteract the effects of cocaine via this mechanism. This evidence supports further investigation into the ability of exercise to ameliorate perirhinal cortex-mediated cocaine relapse and NOR deficits akin to that observed in methamphetamine via perirhinal activation.

A meta-analysis of the effectiveness of short-term exercise on drug rehabilitation found improvements in drug craving, cognitive functioning, and perceived stress among exercised individuals [101]. This indicates that animal models investigating the effects of exercise on drug addiction have some translatability into humans. The current study provides anatomical targets for further investigation into the underlying mechanisms involved in the observed improvements in drug rehabilitation. An important note is that for cocaine specifically, the use of exercise as an intervention for cocaine intake has mixed results in humans. Treadmill running has been found to non-significantly improve cocaine abstinence and reduce craving [102]. Non-significance could be attributed to methodological limitations such as the small sample size; however, mechanisms by which exercise may enhance cocaine response, such as the activation of the amygdala and perirhinal

cortex, should also be considered. Identifying potential mechanisms by which exercise may enhance cocaine response can help develop more specific interventions. These may include altered type and intensity of exercise or coadministration of pharmacological agents to minimize and/or inhibit mechanisms by which exercise could exacerbate cocaine response. A higher-powered study demonstrated the beneficial effect of exercise on stimulant rehabilitation [103], though benefits are reduced among black participants who are known to use cocaine at higher rates. While many other factors may be involved, the limitation of exercise as an intervention for cocaine use specifically must be considered. While it is critical to identify limitations, it is also important to note that the literature overall demonstrates a beneficial effect of exercise in reducing cocaine response in humans [101–105].

5. Conclusions

Treatments, even adjuncts to treatment, are needed for patients with cocaine use disorders. Exercise, such as in vigorous physical regimens, rather than sitting and going to meetings, has been discussed in recovery forums and by celebrities who have used this method to recover. Eminem credited exercise with his recovery from cocaine and other drug addictions [106]. The dose, duration necessary, how to monitor fidelity to the protocol and brain plasticity are all questions we need to ask in laboratory models and translate to humans.

The results demonstrated that compared to sedentary controls, chronically exercised rats were observed to have modulated brain glucose metabolism in seven regions. The SIBF primary somatosensory cortex was found to be inhibited in the exercised group. Increased brain glucose metabolism was observed in the amygdalopiriform transition area, piriform cortex layer 1, trigeminothalamic tract, perirhinal cortex rhinal fissure, basolateral amygdaloid nucleus dorsal endopiriform nucleus, and secondary visual cortex, lateral area. The literature shows that the regions modulated are involved in cocaine response. However, further research is needed to elucidate changes in behavior and regional connectivity, especially in humans.

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Conflicts of Interest: The authors declare no conflicts of interest.

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Resilient Stress Reactivity Profiles Predict Mental Health Gains from Online Contemplative Training: A Randomized Clinical Trial

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Abstract: Low-dose app-based contemplative interventions for mental health are increasingly popular, but heterogeneity in intervention responses indicates that a personalized approach is needed. We examined whether different longitudinal resilience–vulnerability trajectories, derived over the course of the COVID-19 pandemic, predicted differences in diverse mental health outcomes after mindfulness and socio-emotional dyadic online interventions. The CovSocial project comprised a longitudinal assessment (phase 1) and an open-label efficacy trial (phase 2). A community sample of 253 participants received 12 min daily app-based socio-emotional dyadic or mindfulness-based interventions, with weekly online coaching for 10 weeks. Before and after the intervention, participants completed validated self-report questionnaires assessing mental health. Stress reactivity profiles were derived from seven repeated assessments during the COVID-19 pandemic (January 2020 to March/April 2021) and were categorized into resilient (more plasticity) or vulnerable (less plasticity) stress recovery profiles. After both interventions, only individuals with resilient stress reactivity profiles showed significant improvements in depression symptomatology, trait anxiety, emotion regulation, and stress recovery. Those with vulnerable profiles did not show significant improvements in any outcome. Limitations of this study include the relatively small sample size and potential biases associated with participant dropout. Brief app-based mental interventions may be more beneficial for those with greater levels of stress resiliency and plasticity in response to stressors. More vulnerable individuals might require more intense and personalized intervention formats.

Keywords: mindfulness; socio-affective; dyads; mental training; mental health; personalization; plasticity; stress reactivity

1. Introduction

Contemplative interventions, including mindfulness- and compassion-based training, have well-documented benefits for mental health and wellbeing [1,2]. Although traditionally, mindfulness-based contemplative interventions relied on in-person courses supported by teachers, recently, lower-dose web- and app-delivered mindfulness and socio-affective interventions have gained popularity for promoting mental health [3,4]. Meta-analytic evidence supports the effectiveness of online contemplative interventions in reducing depression and anxiety and enhancing resilience [5–8]. However, despite promising findings, small-to-medium effect sizes indicate heterogeneity in responses to these interventions, suggesting that perhaps some individuals might benefit more than others [9–11]. Therefore, efficacy investigations of these interventions are now needed to identify which groups of individuals benefit most from these low-dose online contemplative interventions. Accordingly, recent advances in clinical sciences advocate for a personalized approach to mental health interventions [12].

Thus far, however, most studies have investigated time-stable moderators of intervention responses, such as personality traits, socio-demographic variables, dispositional mindfulness and response styles, or baseline symptom levels [8,10,13]. However, the prevailing models of resilience conceptualize resilient mental wellbeing as a dynamic process

of stress recovery that evolves over time in response to encountered life stressors, and not as a mere reflection of specific time-stable psychological aspects [14,15]. Consequently, it can be extrapolated that dynamic stress recovery profiles, derived from an ecologically valid assessment of reactivity to naturalistic stressors, might be more uniquely suited to predicting individual differences in intervention gains since they index the individual capacity for plasticity in response to dynamic contexts, explaining who shows responsivity in a mental training context [16]. To explore this, we examined whether individual variations in adapting to multiple stressors over time could predict differences in mental health benefits from online contemplative interventions. We employed longitudinal resilience and vulnerability profiles, generated over the course of the COVID-19 pandemic and associated lockdowns [17], to predict who would show greater mental health benefits after online mindfulness-based and socio-emotional partner-based interventions [18].

Dynamic stress response profiles have been shown to predict the future state of mental health in prior studies, with more resilient profiles of stress reactivity (i.e., better recovery after stressor, indicating more flexibility in response) being associated with better mental wellbeing at future timepoints as compared to chronic (i.e., poor stress recovery) or delayed dysfunction (i.e., delayed onset of difficulties in stress recovery after stressor) profiles [19]. This indicates that profiles associated with more plasticity in response to stressful situations may be a good indicator of mental wellbeing in the future. Building upon these insights, it is reasonable to anticipate that individuals displaying greater plasticity or more dynamic reactivity in response to naturalistic stressors over extended durations in daily life might also exhibit enhanced plasticity with respect to learning gains during mental interventions. Such a view would align with empirical findings supporting the capitalization view of treatment gains, i.e., those with existing strengths are able to capitalize on them to reap greater benefits from a treatment [20,21]. Accordingly, the compensation versus capitalization model [21] suggests that an intervention could be more effective either (1) for individuals with the greatest difficulties in the areas targeted by the intervention (compensation) or (2) if it builds on the individual's existing strengths (capitalization). Contrastingly, the compensation approach would suggest that those who show less plasticity over time in response to stressors are those who can profit more from mental training, with empirical support showing that baseline deficiencies predict greater treatment benefits [22,23].

In the present study, we explored whether those showing more vulnerable (less plastic) or more resilient (more plastic) dynamic stress recovery profiles [17] showed greater mental health benefits from low-dose online mindfulness-based and socio-affective interventions. Using data from both phases of the CovSocial project [18], the first goal was to investigate whether longitudinal resilience–vulnerability profiles, identified through repeated assessments of stress reactivity during the COVID-19 pandemic in phase 1 [18] (January 2020–March/April 2021; see Figure 1), predicted baseline levels of depressive symptom severity, anxiety vulnerability and symptomatology, emotion regulation (ER) difficulties, and stress recovery and resilience assessed prior to intervention delivery in phase 2 [4]. The second goal of this study was to investigate whether these longitudinal profiles then predicted individual differences in training-related changes in depressive symptoms, anxiety vulnerability and symptomatology, ER difficulties, and resilience after the online socio-emotional or mindfulness-based intervention. The hypotheses for the present study were preregistered on the Open Science Framework as part of the "Mental Health and Resilience" complex of phase 2 of the CovSocial project (osf.io/3nsjc).

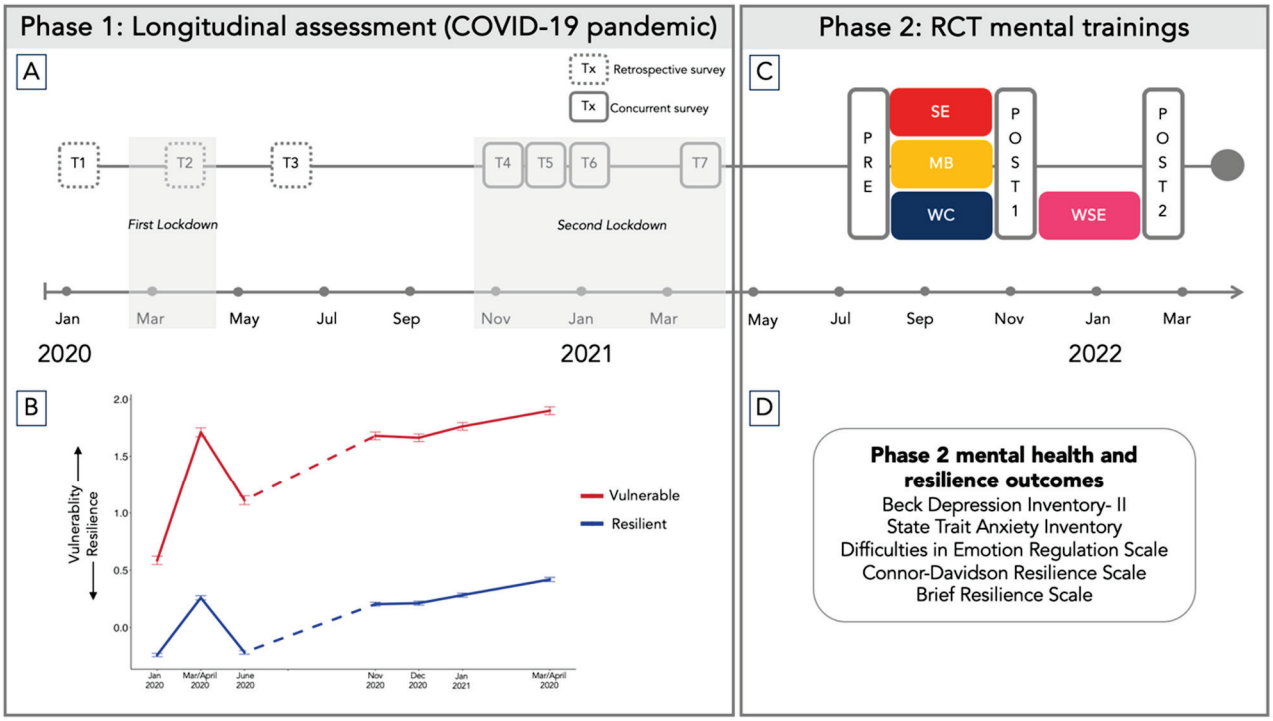

Figure 1. The design of the CovSocial project. (**A**) Phase 1 of the project involving repeated assessment of stress reactivity to various phases of the COVID-19 pandemic in Berlin, Germany. Grey panels indicate phases of state-mandated lockdowns in Germany. Dotted lines indicate retrospective assessment and solid lines represent concurrent assessment. (**B**) The depiction of overall resilience–vulnerability trajectories derived over the seven assessment timepoints in phase 1 of this study. (**C**) The design of the randomized controlled trial (phase 2) conducted with a sub-sample of individuals from phase 1 of this study. SE = socio-emotional intervention group, MB = mindfulness-based intervention group, WC = waitlist control group, WSE = waitlist socio-emotional intervention group, PRE = pre-intervention assessment, POST1 = post-intervention assessment 1, POST2 = post-intervention assessment 2. (**D**) Study measures assessing mental health at pre- and post-intervention stages of phase 2.

2. Materials and Methods

2.1. Recruitment and Study Design

The data for the present study originated from the CovSocial project, which aimed during its initial phase to evaluate shifts in psychological wellbeing amidst the COVID-19 pandemic, and in a subsequent second phase, examined the efficacy of two distinct forms of online mental training (see Figure 1). In phase 1, participants (n = 3522) completed assessments of multiple aspects of mental health, resilience, and social cohesion at seven timepoints: T1 (before lockdown in January 2020), T2 (during first lockdown from mid-March to mid-April 2020), T3 (in June 2020 when restrictions were eased), T4 (November 2020, start of second lockdown), T5 (December 2020), T6 (January 2021), and T7 (mid-March to mid-April 2021, end of second lockdown). In phase 2, as part of a randomized control trial (RCT), a sub-sample of participants from phase 1 (n = 285; see Figure 2 for recruitment flow) were assigned to one of two interventions, partner-based socio-emotional training (SE) or attention-based mindfulness training (MB), or to a waitlist control (WC) group who later underwent socio-emotional training (WSE).

Interested individuals from phase 1 had to meet the following inclusion criteria to take part in phase 2: age between 18 and 65 years, resident of Berlin, access to a smartphone, and proficiency in German language. Participants were pre-screened to exclude vulnerability, educational background in psychology, current or prior meditation practice, experience with stress management programs, chronic illnesses or pain, and

history of or current psychiatric diagnosis. Participants were also screened for clinically relevant levels of psychopathology using the Standardized Assessment of Severity of Personality Disorder [24] and Composite International Diagnostic Screener [25].

Power analysis for phase 2 of the project was performed prior to sample recruitment based on biological measures that were part of the phase 2 of the CovSocial project [18]. The a priori effect size was determined and power calculations were performed based on prior work [26], which validated the interventions applied in the present study. Power analyses were conducted using G*Power [27] based on an analysis of variance with repeated measurements and interactions between group and intra-group variables. This comprised the following elements: $\alpha = 0.05$, power = 0.80, 3 groups, 2 measurements, $r = 0.39$, and $f = 0.10$. The result was a total sample size of n = 297. Therefore, we aimed to recruit around 300 individuals, 100 per intervention group.

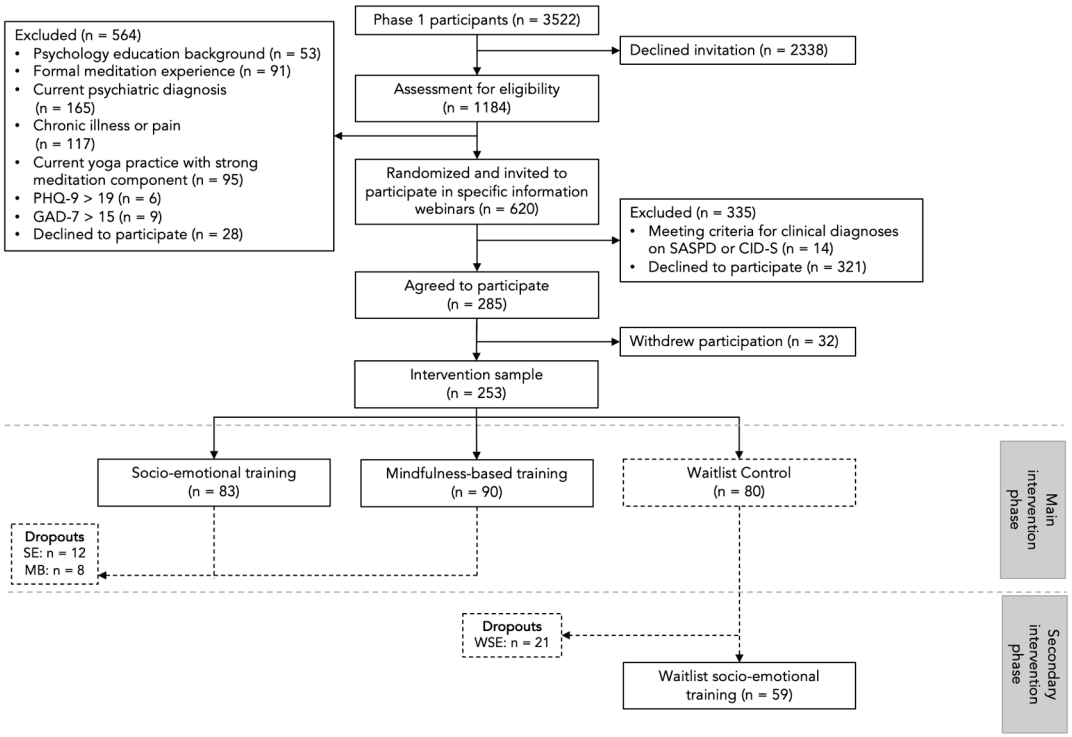

Figure 2. The CONSORT recruitment flow. PHQ-9 = Patient Health Questionnaire-9 [28], GAD-7 = Generalized Anxiety Disorder-7 [29], SASPD = Standardized Assessment of Severity of Personality Disorder [24], CID-S = Composite International Diagnostic—Screener [25], SE = socio-emotional intervention group, MB = mindfulness-based intervention group, WSE = waitlist socio-emotional intervention group. This figure is adapted from a prior study from the CovSocial project [4].

We utilized a block randomization technique that was generated by a senior researcher in the project. Participants were randomized in a parallel-group design, with 1:1:1 allocation, using computer-generated numbers. Interventions were assigned to the participants by the study coordinator. The SE and MB groups were tested on the outcome measures at 2 timepoints (pre-test and post-test 1). Meanwhile, the WC group completed the measures at pre-test, post-test 1, and at a third timepoint (post-test 2) after undergoing the intervention. After exclusion and dropouts, 253 participants completed the pre-intervention measures: 83 individuals in the SE group, 90 in the MB group, and 80 in the WC group (sample descriptives in Table 1). For further details, see the study protocol [18]. We invited the first participants to be informed about the interventions in phase 2 of the study on 27 May 2021, and data collection for all phase 2 measures was completed on 31 March 2022. This study was approved by the Ethics Commission of Charité –Universitätsmedizin

Berlin (EA4/081/21) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Table 1. An overview of the intervention sample (n = 253). This table is adapted from a prior study from the CovSocial project [4]. SE = socio-emotional, MB = mindfulness-based, WC = waitlist control.

Characteristic	SE	MB	WC
N	83	90	80
Mean age (SD)	43.14 (11.80)	44.14 (11.44)	45.86 (11.15)
Female participants, N (%)	65 (78.3%)	64 (71.1%)	62 (77.5%)
Migration background (to current country of residence), N (%)	4 (4.8%)	10 (11.1%)	3 (3.8%)
Years of education, mean (SD)	18.49 (3.97)	17.06 (3.52)	18.41 (3.21)
Married or cohabiting, N (%)	27 (32.5%)	32 (35.6%)	32 (40%)
Lifetime prevalence of psychiatric disorder	17 (21.0%)	16 (17.8%)	18 (22.5%)
Income > Berlin average monthly net income (EUR 2175 (as reported by the Department of Statistics of Berlin-Brandenburg (2019)))	52 (62.7%)	61 (67.8%)	56 (70.9%)
Full-time employment, N (%)	42 (50.6%)	57 (63.3%)	46 (57.5%)

2.2. Measures

2.2.1. Longitudinal Stress Recovery Profiles

From the phase 1 data, dynamic stress reactivity profiles in response to the COVID-19 pandemic stressors were obtained, which were validated in a multi-step procedure in a prior publication from the project [17]. In the prior study, in the first step, 13 distinct measures of mental health, vulnerability, and resilience (e.g., perceived stress, loneliness, health burden, psychosomatic complaints, life satisfaction, self-efficacy, and coping approaches) were used to extract a latent factor of resilience–vulnerability at each of the seven timepoints of phase 1. A combination of validated scales and self-generated questions was employed, which included the Perceived Stress Scale (PSS-4) for stress perception, the Patient Health Questionnaire-2 (PHQ-2) for depressive symptoms, the Generalized Anxiety Disorder Scale (GAD-2) for anxiety symptoms, and the General Self-Efficacy Short Scale (ASKU) for beliefs about self-efficacy. Additionally, self-generated questions captured pandemic-specific aspects of resilience and vulnerability, such as pandemic-related burdens, psychosomatic complaints, loneliness, stress recovery, coping approaches, optimism, life satisfaction, and the perception of the pandemic as an opportunity. The data were gathered via online surveys conducted repeatedly at seven different time intervals from January 2020 to April 2021. Missing data were addressed using predictive mean matching through the multivariate imputation by chained equations (MICE) method, and a measurement model was specified for each timepoint using confirmatory factor analyses. In the next step, using growth mixture modeling, 4 distinct latent profiles of stress reactivity were identified, which were termed: "most vulnerable", "more vulnerable", "more resilient", and "most resilient". These profiles were based on longitudinal changes in stress responses to dynamic phases of the COVID-19 pandemic in Germany, such as the first lockdown, re-opening, and second lockdown. The optimal number of classes was determined based on model fit indices and theoretical plausibility. These analyses were conducted using R (version 4.0.3) with the packages mice and lavaan for missing data imputation and measurement model analysis, respectively. Additionally, Mplus (version 8) was employed for growth mixture modeling.

Given the smaller sample size in phase 2, participants in the more and most vulnerable groups were merged into one category termed 'vulnerable' (n = 79), and the more and most resilient groups were merged into one 'resilient' group (n = 174). Given that we grouped the profiles to ensure adequate statistical power for the present analysis, we tested

the mean latent resilience–vulnerability scores for these new 'vulnerable' and 'resilient' profiles across the 7 timepoints. Within-class comparisons revealed that the vulnerable class did not recover to pre-lockdown levels of vulnerability at re-opening ($p < 0.001$), while in the resilient class, participants recovered to the baseline ($p > 0.1$). When compared to individuals with the resilient profile, individuals with the vulnerable profile had greater levels of vulnerability at the start of the second lockdown ($p < 0.001$), and they showed a steeper increase in vulnerability during the second lockdown ($p = 0.03$). Figure 1B illustrates the resilience–vulnerability time courses of these two groups.

2.2.2. Intervention Outcomes

From the phase 2 data, all intervention outcomes that formed part of the Mental Health and Resilience complex (as outlined in the preregistered strategy on OSF osf.io/3nsjc) were obtained: depressive symptom severity (Beck Depression Inventory-II (BDI-II) [30]), trait anxiety vulnerability and state anxiety symptomatology (State-Trait Anxiety Inventory (STAI-T and STAI-S) [31]), and resilience (Connor Davidson Resilience Scale (CD-RISC [32]) and Brief Resilience Scale (BRS [33])). Moreover, recognizing the significance of emotion regulation (ER) difficulties in mental health [34], we also considered the Difficulties in Emotion Regulation Scale [35] to be a primary outcome in the present study.

2.3. Interventions

The SE group, and in the secondary intervention phase the WSE group, engaged in daily 12 min sessions of the Affect Dyad [36], pairing up with a different partner each week, who was randomly assigned to them by the CovSocial mobile app designed for the study. During the Affect Dyad sessions, participants took turns recounting a recent (in the last 24 h) challenging emotional experience and exploring the sensations associated with it in their bodies, followed by sharing a gratitude-inducing moment and reflecting on the bodily sensations evoked by gratitude. The listening partner remained empathetic and non-judgmental but without offering any verbal or non-verbal responses. Meanwhile, participants in the MB group practiced daily 12 min sessions focusing on attention-based mindfulness techniques. Guided by audio meditations, they directed their attention to their breath or to the sounds in their surroundings, or engaged in open awareness meditation, tuning into sensations within themselves and their environment. Both groups were encouraged to practice their respective techniques six times weekly at home, facilitated through the CovSocial mobile app over a 10-week period. Additionally, participants attended weekly two-hour online coaching sessions led by mindfulness and dyad experts, providing a platform with which to discuss and enrich their practice experiences (refer to the supplementary information for the coaching session details). Before the intervention began, every participant underwent a comprehensive 2.5 h introductory session on contemplative training. Additionally, they attended two 2.5 h onboarding webinars designed specifically for the interventions they would receive (refer to the supplementary information "File S1: Mental training protocol for phase 2 of the CovSocial project" for more specifics).

2.4. Statistical Analysis

To investigate the first goal, we employed linear models with the stress recovery profile (vulnerable or resilient) as the predictor of pre-test levels of depressive symptom severity, trait anxiety, state anxiety severity, ER difficulties, and resilience (CD-RISC and BRS). To investigate the second goal, we employed separate linear mixed-effects models to assess whether intervention-related changes in each of the outcome measures were predicted by the type of dynamic profile. Each model included a 3-way interaction term between the intervention (SE or MB), time (pre-test or post-test 1), and recovery profile (vulnerable or resilient). A random intercept for the participant was included to account for individual variability in baseline levels of the outcome variables. This allowed for the estimation of individual-specific deviations from the overall group mean, enhancing the accuracy and robustness of the model. Separate models were implemented for the WSE

group with a 2-way interaction term between the time of assessment (pre-test, post-test 1 and post-test 2) and recovery profile and a random intercept for the participant. Age and sex were included as covariates in all models, and *p*-values were Bonferroni-adjusted for multiple comparisons. Analyses were conducted in R version 4.3.1 [37] using the *lme4* [38] and *multcomp* [39] packages.

3. Results

First, we found that at the pre-intervention stage, individuals displaying the resilient dynamic recovery profile had significantly lower levels of depressive symptoms ($\beta = -8.10$, $p < 0.001$, d = 1.08), trait anxiety ($\beta = -8.57$, $p < 0.001$, d = 0.92), state anxiety ($\beta = -6.03$, $p < 0.001$, d = 0.66), and ER difficulties ($\beta = -8.10$, $p < 0.001$, d = 1.08) and higher levels of resilience on the CD-RISC ($\beta = 6.07$, $p = 0.002$, d = 0.48) and BRS ($\beta = 0.46$, $p < 0.001$, d = 0.58; see Figure 3).

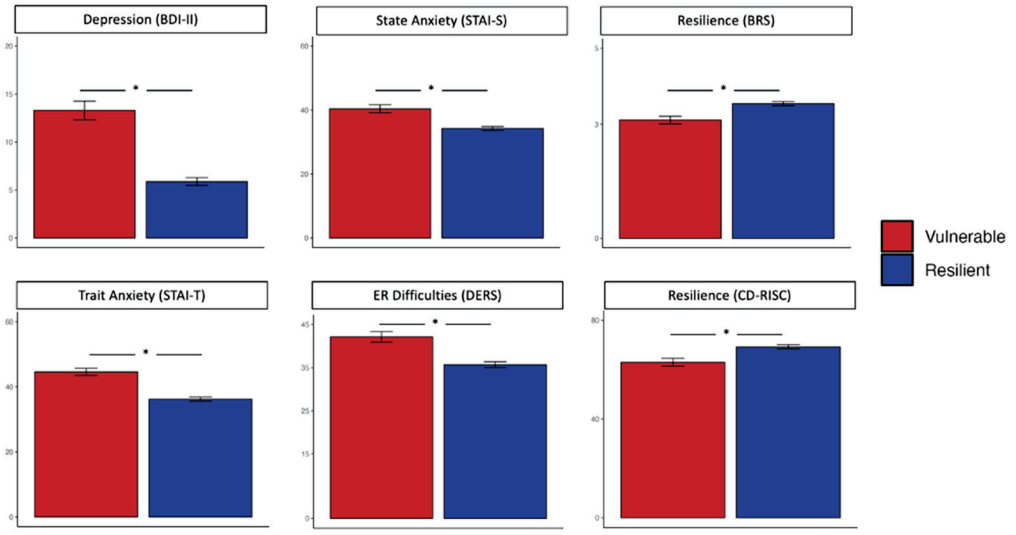

Figure 3. Pre-intervention levels of depressive symptoms, trait anxiety, state anxiety, emotion regulation (ER) difficulties, and resilience (CovSocial project phase 2) stratified by longitudinal vulnerable and resilient response profiles during the COVID-19 pandemic (phase 1). BDI-II = Beck Depression Inventory—II, STAI-T = State Trait Anxiety Inventory—Trait, STAI-S = State Trait Anxiety Inventory—State, DERS = Difficulties in Emotion Regulation Scale, CD-RISC = Connor Davidson Resilience Scale, BRS = Brief Resilience Scale. A significant difference between vulnerable and resilient profiles is indicated by an asterisk (* indicates $p < 0.05$ after adjustment for multiple comparisons).

Second, mixed-effects models revealed significant three-way (intervention, time, and recovery profile) interactions for depressive symptoms ($F = 9.37$, $p < 0.001$), trait anxiety ($F = 6.16$, $p < 0.001$), state anxiety ($F = 5.26$, $p < 0.001$), ER difficulties ($F = 10.56$, $p < 0.001$), and the BRS ($F = 7.12$, $p < 0.001$), but not for the CD-RISC ($F = 1.04$, $p = 0.385$). The findings are depicted in Figure 4. Post hoc comparisons indicated that the effect of the interventions over time was significantly moderated by the recovery profiles, such that only individuals displaying the resilient recovery profile showed significant decreases in depressive symptomatology in both the SE ($\beta_{SE} = -2.08$, $p < 0.002$, d = 0.34) and MB ($\beta_{MB} = -3.13$, $p < 0.001$, d = 0.51) interventions. Similar findings were observed for trait anxiety ($\beta_{SE} = -1.52$, $p = 0.044$, d = 0.18 and $\beta_{MB} = -3.11$, $p < 0.001$, d = 0.36) and ER difficulties ($\beta_{SE} = -2.29$, $p = 0.007$, d = 0.26 and $\beta_{MB} = -4.42$, $p < 0.001$, d = 0.51). Individuals displaying the vulnerable recovery profile did not show significant changes after either intervention in depressive symptoms ($\beta_{SE} = -0.43$, $p > 0.5$, d = 0.07 and $\beta_{MB} = -0.82$, $p > 0.5$, d = 0.14), trait anxiety ($\beta_{SE} = -0.87$, $p > 0.5$, d = 0.10 and $\beta_{MB} = -0.94$, $p > 0.5$, d = 0.11), or ER difficulties ($\beta_{SE} = -1.86$, $p = 0.12$, d = 0.21 and $\beta_{MB} = -1.35$, $p = 0.42$, d = 0.16). Interestingly, individuals displaying the vulnerable profile showed an increase in state anxiety symptoms in the MB ($\beta_{MB} = 3.11$, $p = 0.023$, d = 0.34) but not the SE

(β_{SE} = 1.25, p = 0.53, d = 0.14) intervention. Those with the resilient profile did not show any significant changes in state anxiety in either intervention (β_{SE} = −0.12, p > 0.5, d = 0.01 and β_{MB} = −1.27, p > 0.5, d = 0.14). For changes in resilience on the CD-RISC, we found no significant effect of either stress recovery profile after either the SE ($\beta_{vulnerable}$ = 0.63, p > 0.5, d = 0.05 and $\beta_{resilient}$ = 0.95, p > 0.5, d = 0.06) or MB ($\beta_{vulnerable}$ = 0.95, p > 0.5, d = 0.08 and $\beta_{resilient}$ = 1.56, p > 0.1, d = 0.13) intervention. Contrastingly, only individuals displaying the resilient profile showed significant increases in stress recovery on the BRS in both interventions (β_{SE} = 0.17, p = 0.017, d = 0.23 and β_{MB} = 0.33, p < 0.001, d = 0.44), which was not the case for individuals with the vulnerable profile (β_{SE} = 0.13, p > 0.1, d = 0.17 and β_{MB} = 0.17, p > 0.1, d = 0.23).

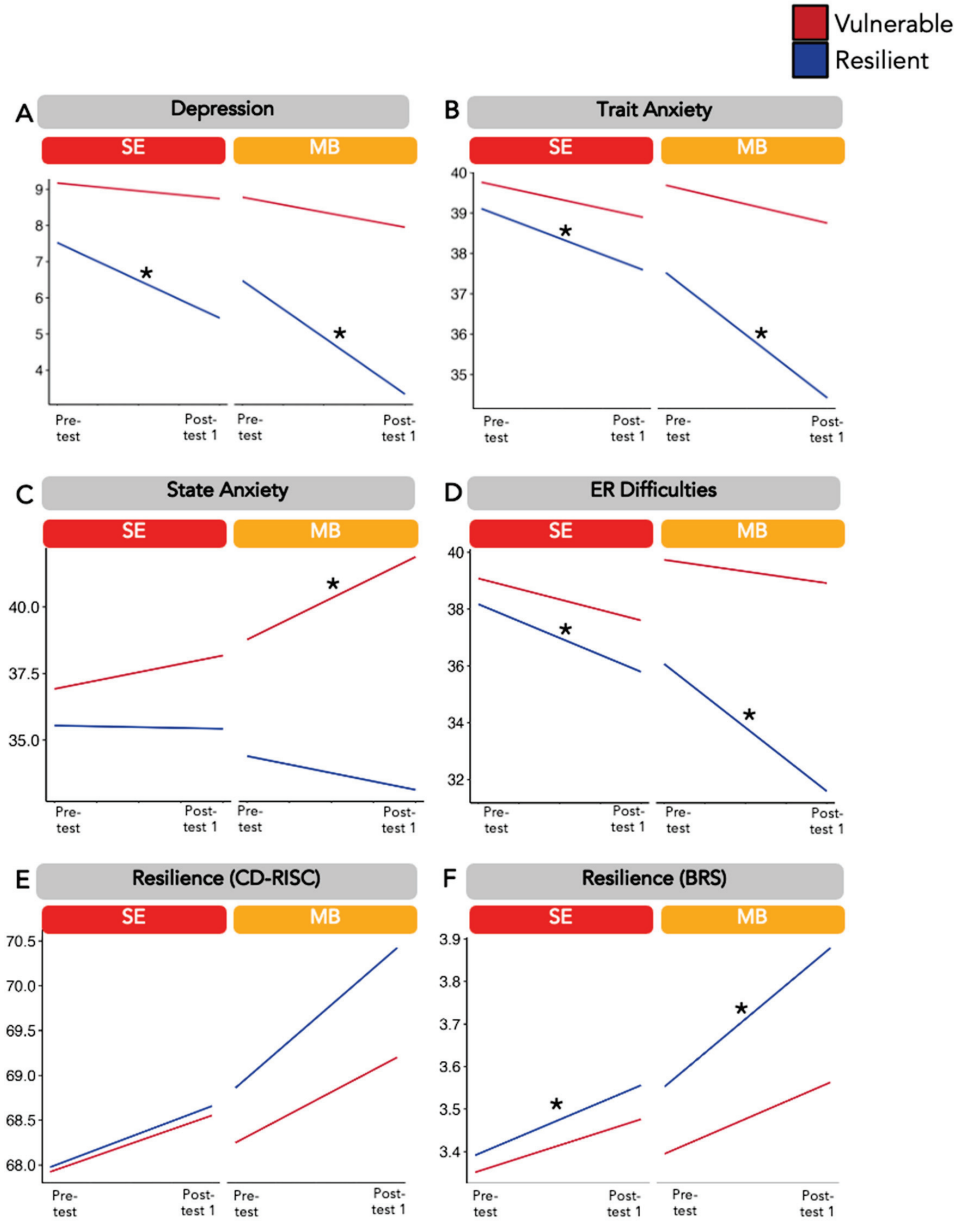

Figure 4. Pre- to post-intervention changes in (**A**) depressive symptoms, (**B**) trait anxiety, (**C**) state anxiety, (**D**) emotion regulation (ER) difficulties, and (**E**,**F**) resilience (CovSocial project phase 2) examined within the context of longitudinal vulnerable and resilient response profiles during the COVID-19 pandemic (phase 1). SE = socio-emotional dyadic intervention, MB = mindfulness-based intervention, CD-RISC = Connor Davidson Resilience Scale, BRS = Brief Resilience Scale. A significant change from pre- to post-intervention is indicated by an asterisk (* indicates p < 0.05 after adjustment for multiple comparisons).

A similar pattern of findings emerged for the underpowered WSE group. We found significant pre- to post-intervention decreases in depressive symptomatology only in the resilient profile ($\beta_{WSE} = -1.06$, $p = 0.007$, d = 0.14) and not in the vulnerable profile ($\beta_{WSE} = -0.13$, $p > 0.5$, d = 0.02). Similar findings were observed for decreases in ER difficulties ($\beta_{vulnerable} = -1.12$, $p > 0.1$, d = 0.12 and $\beta_{resilient} = -1.10$, $p = 0.02$, d = 0.13). On the other hand, there were significant increases in resilience on the BRS only in the resilient profile ($\beta_{WSE} = 0.11$, $p = 0.02$, d = 0.14) and not in the vulnerable profile ($\beta_{WSE} = -0.03$, $p > 0.5$, d = 0.03). There were no significant differences between the two profiles in changes in trait or state anxiety and resilience on the CD-RISC (all $p > 0.5$). Please see the supplementary information's Figure S1 for a pictorial depiction.

4. Discussion

The present study aimed to investigate the predictive power of dynamic longitudinal stress recovery profiles, derived in conditions of naturalistic stressors during the COVID-19 pandemic in Germany, for explaining individual differences in mental health gains after online mindfulness and socio-affective dyadic interventions in the context of the CovSocial project [18]. We explored whether those with more vulnerable or more resilient longitudinal response profiles benefitted more from low-dose online contemplative training programs.

First, we found that individuals displaying more resilient profiles, i.e., those who had lower levels of experienced vulnerability during the COVID-19 pandemic and showed better recovery after stressors (during the period from March 2020 to April 2021), had significantly lower levels of depressive symptoms, trait anxiety, state anxiety, and ER difficulties and higher levels of resilience pre-intervention (in July–August 2021). These findings are in line with prior research that has employed dynamic stress resilience trajectories to predict the future mental health status [19,40].

Second, we found that only individuals displaying resilient profiles showed significant intervention-related decreases in depressive symptomatology, trait anxiety, and ER difficulties and significant improvements in stress recovery after both 10-week online MB and SE interventions. Individuals displaying a vulnerable profile did not show significant improvements after either intervention in any outcome. This indicates that individuals who showed more resilience and plasticity in response to repeated naturalistic stressors during the pandemic were also the ones who benefited more from the online mental training. This aligns with the capitalization view of the compensation versus capitalization model of treatment gains [21]. On the other hand, those showing more vulnerable profiles (less plasticity) during the pandemic did not show significant training-related improvements in mental wellbeing in most measures.

Our findings have crucial theoretical and practical implications. First, the present work adds to the rather limited field of precision contemplative science. Very few prior studies have used data-driven methods, especially dynamic longitudinal profiles, to identify who benefits from app-based contemplative interventions for mental health. A recent study by Webb and colleagues [10,41] employed a machine-learning-based algorithm utilizing baseline characteristics of the individuals, such as baseline levels of distress, depression, and stress. The algorithm identified that those with more baseline levels of distress and psychopathology benefitted more from use of a meditation app. This is in contrast with our findings. While prior studies have typically employed baseline characteristics, or machine learning algorithms based upon baseline characteristics, to predict intervention outcomes, our study diverged by focusing on longitudinal stress recovery profiles. This methodological difference likely accounts for the contrast in findings between our study and previous research. By considering how individuals dynamically respond to varied stressors over a period of time and recover from them longitudinally, our study captures a more nuanced picture of who benefits from contemplative interventions. We investigated the predictive link between long-term adaptability to stressors, evaluated over months, and short-term cognitive plasticity in the context of a 10-week mental intervention, examining how the former impacted the ability to learn and benefit from the latter. Our findings

suggest that using data-driven indices that capture this long-term plasticity or dynamic stress recovery process may offer a more comprehensive and accurate prediction of individual differences in intervention responses compared to static baseline characteristics. This underscores the importance of considering dynamic processes in predicting contemplative intervention responses and highlights the potential of precision contemplative science to guide personalized intervention strategies. Building from this, the present findings also hold practical relevance. It can be extrapolated that individuals with more vulnerable response profiles may benefit from more extended and intensified intervention programs, potentially supported by in-person weekly coaching sessions with mindfulness experts, enabling them to fully experience the mental health benefits of the online contemplative interventions utilized in this study.

Interestingly, we found that individuals displaying vulnerable profiles showed an increase in state anxiety after the MB but not the SE intervention. This finding supports the Monitor and Acceptance Theory, which suggests that mindfulness-based interventions that enhance the monitoring of bodily sensations without including acceptance components can, in fact, lead to a worsening of anxiety symptomatology [42]. Supporting this view, the SE intervention, which incorporates both monitoring and acceptance aspects of contemplative interventions [36], did not lead to significant increases in anxiety symptomatology for the vulnerable group, indicating a buffering effect.

5. Limitations

Some limitations of the present work must be considered. Foremost, due to the longitudinal design of this study, the final sample size of individuals displaying vulnerable profiles was rather small. Therefore, it is possible that the vulnerable group was not sufficiently powered for us to detect significant effects. This limitation could have contributed to the null findings observed in certain analyses, suggesting the need for caution when interpreting these subgroup effects. Furthermore, we observed participant dropouts over the course of phase 2 of the study, particularly between study onboarding and the pre-intervention assessment phase, constituting approximately 11.2% of the initial sample (32 out of 285 participants). There was also specific attrition in the waitlist control group between the pre-intervention and post-intervention 1. This dropout phenomenon reflects the challenges inherent in longitudinal research involving contemplative interventions, such as the one implemented here, which required daily practice and weekly 2 h coaching sessions. However, to address this issue and ensure the integrity of the randomized design, an intention-to-treat approach was employed, which involves analyzing participants according to their original assigned group, regardless of dropout. This provides a more conservative estimate of intervention effects and accounts for potential biases introduced by dropout. Moreover, participants from phase 1 who further volunteered to participate in the intervention study of phase 2 may have been more motivated or interested in contemplative interventions than the general population, leading to self-selection bias. Although we tried to control this aspect of the self-selection bias through our use of a randomized controlled study design and the inclusion of demographic variables as covariates in our statistical analyses, self-selection bias cannot be ruled out. However, it is important to acknowledge that in contrast to most mental training studies involving mindfulness-based interventions, here, participants were initially recruited for a large-scale COVID-19-related mental health study based on random draws of addresses from the Berlin city register, rather than specifically for an intervention study. Additionally, this study's longitudinal design in phase 1 and rather heterogeneous sample may have helped to capture a broad range of perspectives and experiences, thereby partially addressing potential self-selection biases. Note, as well, that we excluded any person with prior experiences with any sort of contemplative interventions or practices. Future studies could benefit, however, from larger sample sizes, more heterogenous samples, more objective measures, and additional follow-up periods. Future research should also explore whether brief in-person interventions and more person-tailored training approaches are needed in vulnerable populations. Addition-

ally, an intentionally wide age range of participants was recruited for this study, to enhance the generalizability of our findings across different age groups. However, this approach may have introduced age-related heterogeneity within the sample, potentially influencing the results. While our study considered age and gender as covariates, their inclusion did not yield significant findings, suggesting that age or sex differences may not have substantially impacted our findings. However, it is plausible that other socio-demographic factors or individual characteristics, such as socio-economic status, educational level, or cultural background, could have influenced the intervention outcomes but were not explored in the current study. Thus, future research could benefit from a more comprehensive examination of these factors, to further our understanding of their roles in shaping the effectiveness of personalized mental health interventions. Additionally, investigating other potential moderators, such as personality traits or coping styles, may provide further insights into how individual differences impact intervention responses. Moreover, exploring the interplay between socio-demographic factors and intervention outcomes could inform the development of more tailored and culturally sensitive interventions, to address mental health needs effectively across diverse populations.

6. Conclusions

Our study's strength lies in the employment of data-driven longitudinal stress response profiles, indexing dynamic stress recovery in response to the COVID-19 pandemic, to predict who reaps more mental health benefits from low-dose online contemplative interventions in a community sample. Our findings highlight the importance of targeting interventions to specific stress recovery profiles, as the effectiveness of the interventions could vary depending on the individual's plasticity profile. In line with the Precision Medicine Initiative® led by the National Institute of Health (NIH) and the National Institute of Mental Health (NIMH) Strategic Plan [43], this suggests that a one-size-fits-all approach to mental health and app-based contemplative interventions may not be effective. These findings suggest that interventions targeted towards individuals with a more vulnerable stress recovery profile may need to be tailored differently from those for individuals with a more resilient profile. Individuals with a vulnerable profile may require more intensive, longer-term, or in-person interventions, whereas those with a resilient profile can benefit from a relatively low-dose 10-week online intervention.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jpm14050493/s1. File S1: Mental training protocol for phase 2 of the CovSocial project. Figure S1: Post-test 1 to post-test 2 changes in intervention outcomes in WSE group stratified by longitudinal stress reactivity profiles.

Author Contributions: Conceptualization, M.G. and T.S.; data curation, M.G.; formal analysis, M.G.; funding acquisition, T.S.; investigation, T.S.; methodology, M.G. and T.S.; project administration, T.S.; resources, T.S.; software, M.G.; supervision, T.S.; visualization, M.G.; writing—original draft, M.G.; writing—review and editing, T.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by the Ethics Committee of Charité—Universitätsmedizin Berlin (EA4/081/21, approved on 15 April 2021) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: All participants provided written informed consent prior to participation.

Data Availability Statement: Data will be made available upon request.

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Conflicts of Interest: T.S. was honorary co-founder and scientific and curriculum advisor for Humanize from 2021 to summer 2023. Humanize is a start-up that is inspired by T.S.'s mental intervention research as well as her ReConnect Masterclasses and courses focusing on dyadic interventions, including the Affect Dyad, and is releasing modified and extended versions of these dyad intervention programs on a commercial digital platform and app. These additional roles of T.S. have been formally approved by the Max Planck Society. T.S. no longer has an active role or shares in Humanize.

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