


Review

# Gut Microbiota Research in Bipolar Disorder and Possible Implications for Precision Psychiatry: A Systematic Review

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**Abstract:** Bipolar disorder (BD) is a highly disabling condition with a chronic and relapsing nature. Despite the substantial socioeconomic burden associated with BD, there are still significant research gaps in risk stratification, diagnostic accuracy, and treatment selection, all key components of precision psychiatry. One possible strategy to increase the validity of precision psychiatry approaches in BD is to increase our knowledge of disorder-associated gut microbiota perturbations. To this end, we systematically reviewed the evidence on gut microbiota alterations in relation to precision psychiatry approaches on BD. We performed a systematic review on PubMed/MEDLINE and Web of Science to identify original articles investigating the possible clinical applications of microbiota analyses for pragmatic precision psychiatry in BD. A pearl growing strategy was employed to enlarge the scope of this review. The primary search strategy yielded one paper and an additional one was identified through reference tracking. The included studies were observational, with one study of good quality. The identified results justify the efforts devolved in this area of research and underscore the need to expand these investigations through additional larger and properly designed studies.

**Keywords:** bipolar disorder; precision psychiatry; brain-gut axis; personalized treatment; risk stratification; systematic review



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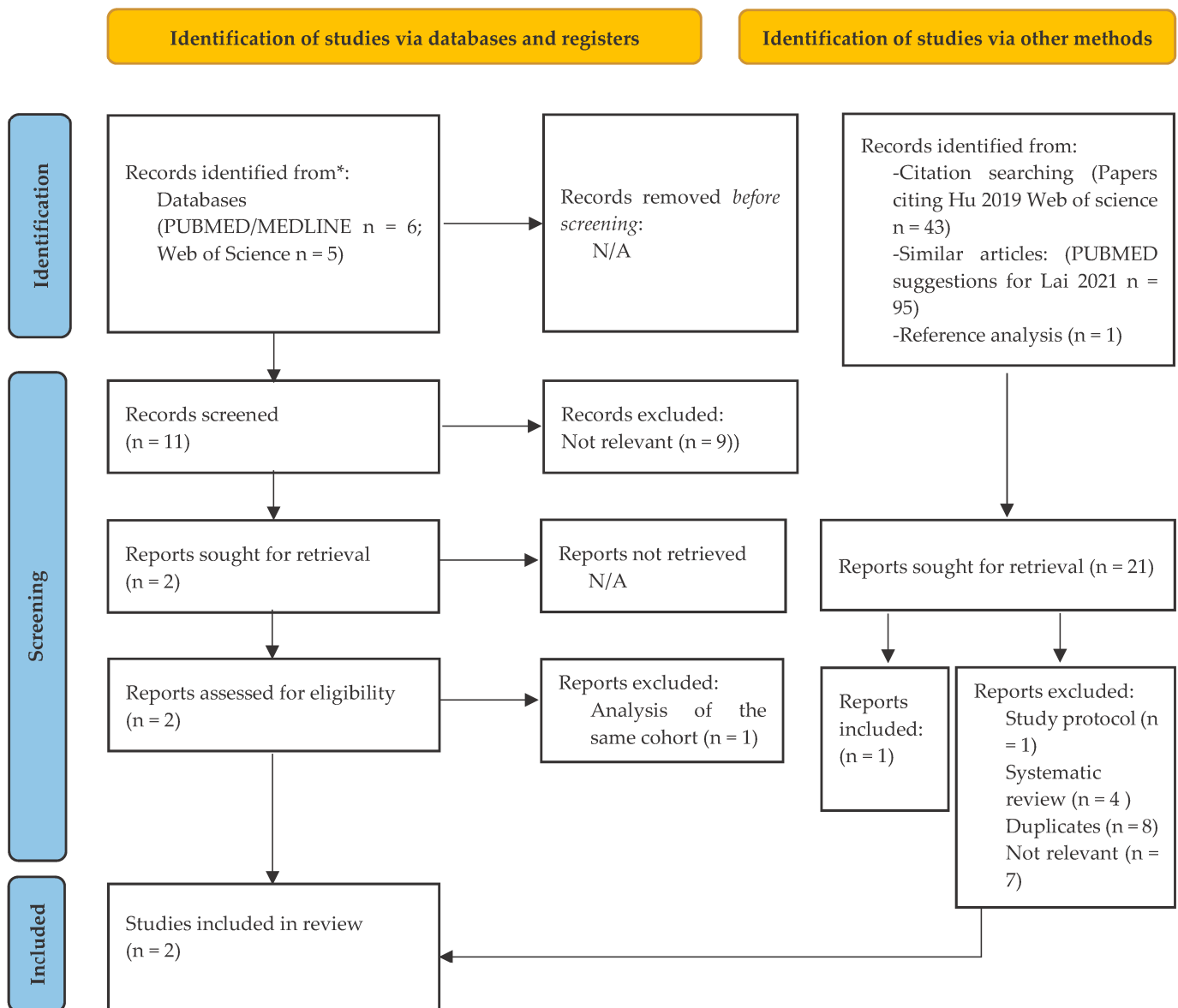
## 1. Introduction

Bipolar disorder (BD) is a complex and clinically heterogeneous disorder associated with a significant morbidity and disability burden. Globally, it has been estimated that BD may account for 9.9 million disability-adjusted life years (DALY), corresponding to 0.4% of total DALYs and 1.3% of years lost due to a disability (YLD) [1]. BD is in itself a well-recognized risk factor for suicide [2,3], and its association with an excess mortality associated with cancer and cardiovascular disorders is increasingly evident [3–5]. Affected individuals have, on average, a life expectancy 20 years shorter than the general population [6]. Despite the high costs in terms of individual suffering and socioeconomic impact [7,8], there are still numerous unmet needs in risk stratification, diagnostic accuracy, and treatment selection, all key components of precision psychiatry [9,10]. Precision psychiatry postulates that diagnosis and treatment selection could be made based on knowledge of the phenotypic and biological characteristics of any given individual affected by a mental disorder. A broad range of different interventions has been proven effective in improving BD symptoms [11], with pharmacotherapy representing an important component. The landmark study Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) provided invaluable data regarding illness course, treatments and assessment models for this heterogeneous disorder [12]. Bipolar depression has a prominent role in the course

of illness and in causing disability as it may occur at twice the rate observed for hypomania, manic or mixed episodes [12]. BD severity is closely linked to its chronicity, with 60% to 80% of relapses occurring in the two years following an antecedent episode, either depressive or manic [13]. The relative paucity of efficacious treatment modalities available for bipolar depression further complicates its management [14]. Diagnosing BD may be difficult, even for mental health specialists. Patients often receive an alternative diagnosis, frequently unipolar depression, substance abuse disorder or schizophrenia spectrum disorder depending on the most significant symptoms present at the time of the evaluation [15]. According to recent estimates [15], the average diagnostic delay ranges from 15 to 20 years for BD. Even when BD is appropriately identified, the choice for a particular pharmacological agent is typically based on a trial-and-error approach, as is often the case for mental health disorders in general [16]. Arguably, this factor may lead to further prolongation of the time required to achieve an adequate symptomatic amelioration. Taken together, these factors further underscore the need to develop more accurate risk stratification models, as well as reliable algorithms for treatment selection and optimization of currently available treatments to increase effectiveness and decrease safety risks [17]. This is indeed the core mission of precision psychiatry [18,19]. Psychiatry is personalized in that it relies deeply on descriptive psychopathology and phenomenology, but it remains imprecise since the integration of biological data with detailed clinical information to increase the accuracy of prediction is still in its infancy. However, it is conceivable that the brain-gut-microbial axis may represent a novel avenue for the personalization of treatment in mental health disorders [20]. Evidence deriving from preclinical data increasingly suggests that gut microbiota perturbations might contribute to pathophysiological mechanisms for mental disorders. A fecal microbiota transplant from affected human individuals to germ-free mice was associated with the development of the pathological phenotype observed in the mice model for various psychiatric and neurological conditions [21–23]. Remarkably, the transplant from healthy human donors did not result in the same changes [21], and may instead thereafter attenuate some of the induced anomalies through such paradigm [22]. With this review, we aimed to analyze the current evidence regarding possible applications of gut microbiota analyses for precision psychiatry in the treatment of BD.

## 2. Materials and Methods

We performed a systematic review on PubMed/MEDLINE and Web of Science using the following search string: “(precision psychiatry) AND (microbiota OR microbiome) AND (bipolar disorder OR BD)”. The last search was performed on the 15 February 2022. A PRISMA flowchart describes the screening procedure for the retrieved records (Figure 1). Two authors (MM and PP) independently evaluated the obtained records and selected the papers for this review. Any cases of discrepancy were resolved through direct confrontation until a consensus was reached. A comprehensive pearl growing strategy was employed to enlarge the scope of the review further. We included studies reporting on: (1) original research, (2) focusing on BD, (3) with interventional or observational study designs, (4) written in English. Review papers were consulted with the purpose of analyzing the reported references to retrieve additional records that might have remained otherwise uncovered through the primary search strategy [24]. The Newcastle-Ottawa Quality Assessment Scale (NOQAS) [25] was applied to evaluate the quality of the included papers.



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [26] flowchart. Hu et al., 2019 [27], Lai et al., 2021 [28].

### 3. Results

Our search strategy led to the identification of two studies reporting on the possible applications of gut microbiota analysis in precision psychiatry for BD. Both have been performed in East Asia and by the same research group. The study characteristics and main findings for the included papers have been extrapolated from the full papers and are summarized in Table 1.

**Table 1.** Summary of the main findings of the included papers.

First Author, Year	Lai et al., 2022 [28]	Zheng et al., 2020 [29]
Study characteristics	<ul style="list-style-type: none"> <li>- Prospective-cohort study</li> <li>- Diagnostic criteria and instruments: DSM-IV-TR criteria, MINI</li> <li>- Rating scales: HDRS-24, MADRS, YMRS, HAMA</li> <li>- Total sample <math>n = 122</math></li> <li>- 62 BD-ABD (HDRS <math>\geq 14</math>; 11 inpatients, 51 outpatients; BDI = 12, BDII = 45, BDNOS = 5), F = 23/62 (37.1%)</li> <li>- 60 HC, F = 31/60 (51.7%)</li> </ul>	<ul style="list-style-type: none"> <li>- Case-control study</li> <li>- Diagnostic criteria and instruments: DSM-IV-TR criteria</li> <li>- Rating scales: HDRS, MADRS, YMRS, HAMA</li> <li>- Total sample <math>n = 599</math> (discovery set <math>n = 462</math>, validation set <math>n = 137</math>)</li> <li>- MDD <math>n = 165</math>, BD <math>n = 217</math>, HC <math>n = 217</math></li> </ul>
Studied variables	<ul style="list-style-type: none"> <li>- Fecal sample (whole sample) at baseline and after 4 weeks quetiapine monotherapy for all BD patients</li> <li>- Baseline rs-fMRI (for a subset of patients)</li> </ul>	<ul style="list-style-type: none"> <li>- Fecal samples from all participants</li> </ul>
Region of studies	East Asia	East Asia
Main findings	<ul style="list-style-type: none"> <li>- <math>\uparrow</math> alpha microbial diversity described in pre-vs. post-treatment BD, and BD vs. HC.</li> <li>- <math>\uparrow</math> microbial diversity in HC and BD responders (<math>\geq 50\%</math> score reduction in baseline HDRS) vs. non-responders.</li> </ul>	<ul style="list-style-type: none"> <li>- <math>\downarrow</math> alpha diversity in BD vs. HC.</li> <li>- Beta diversity MDD, BD and HC could be differentiated at the OTU level</li> <li>- Four OTUs were associated with <math>\uparrow</math> HDRS.</li> </ul>

Abbreviations: ABD, acute bipolar depression; BD, bipolar disorder; BDI, bipolar disorder type 1; BDII, bipolar disorder type 2; BDNOS, bipolar disorder not otherwise specified; F, female gender; HC, healthy controls; HAMA, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; M, male gender; MADRS, Montgomery–Asberg Depression rating scale; MDD, major depressive disorder; OTU, operational taxonomic units; rs-fMRI, resting-state functional magnetic resonance imaging; SD, Standard Deviation; YMRS, Young Mania Rating Scale.

Lai et al. [28] reported on microbiota analysis to discriminate BD responders from non-responders during an acute bipolar depressive episode. They further expanded the scope of their research by recruiting age, sex, and BMI-matched healthy controls (HC) and by comparing the eventually detected differences in microbial composition between pre- and post-treatment, as well as between BD and HC. Exclusion criteria included chronic diseases, recent use of probiotics or antibiotics and pregnancy. They performed a resting state-functional Magnetic Resonance Imaging (rs-fMRI) scan on a subsample of untreated BD individuals, but no specific mention of the selection criteria employed to select this group of patients is provided in the paper, limiting the significance of the reported findings. Among BD individuals, seven were new cases whilst the rest had an established BD diagnosis and were experiencing a recurrent episode of depression. All BD patients underwent a 4-week treatment course of quetiapine titrated from 50 mg quaque die to 200–300 mg daily. All recruited individuals also underwent a basal fecal sample at recruitment and at the end of the 4-week follow-up period. A significant difference in the alpha diversity (Shannon, Simpson and Obs) has been reported between post-treatment BD and HC, albeit none was detected between pre-treatment and HC. An increased microbial diversity was also observed among BD patients in post-treatment when compared to pre-treatment. Interestingly, BD responders ( $\geq 50\%$  score reduction from baseline HDRS) and HC had higher baseline microbial diversity compared with non-responders. A positive correlation was described for baseline abundance of *Clostridium barlettii* and hippocampal indices among untreated BD patients ( $n = 15$ ). Zheng et al., 2020 [29] described a case-control study focus-

ing on the analysis of possible microbiota markers able to differentiate major depressive disorder (MDD) patients from BD and HC. The exclusion criteria included the presence of physical or mental health disorders or the use of antibiotics, prebiotics, and probiotics in the preceding month. The study design allowed for the development of a discovery group and a validation group with the declared purpose of verifying the eventual findings in an independent cohort. In the discovery group ( $n = 425$ ), controls were matched by age and sex to cases, but no matching was performed in the validation group. The resulting model discriminated between the three study groups, with four OTUs belonging mainly to the Lachnospiraceae family associated with a greater degree of symptom burden, as defined according to the Hamilton Depression Rating Scale (HDRS) score. Alpha diversity (Ace and Chao indices) was decreased in BD compared to HC, but no difference was described between HC and MDD. Beta diversity analysis suggested MDD, BD and HC could be differentiated at the OTU level, with 26 differently expressed OTUs among the analyzed groups. These OTUs belonged for the most part to the Lachnospiraceae (eight OTUs), Pseudomonadaceae (three OTUs), Ruminococcaceae (three OTUs) and Bacteroidaceae (seven OTUs) families. Differences in the relative abundance of microbial composition have also been described between the MDD and BD groups at the phylum level.

Table 2 summarizes the results for the quality assessment of the included studies. One study [28] was judged of good quality, due to the use of a structured interview in the definition of cases, adequate length of follow-up for the analyzed outcomes and selection of HC from the same community as cases. The comparability between study groups was also judged fair for the selection of an adequate matching strategy for controls. The other study [29] was instead judged of poor quality for the absence of a structured instrument for the diagnosis of cases and the impossibility of establishing a clearer link between the reported findings and the included diagnostic categories due to the study design.

**Table 2.** Quality assessment of the included papers with the Newcastle-Ottawa Quality Assessment Scale.

First Author, Year	Selection	Comparability	Outcome	Overall Score
Lai et al., 2022 [28]	***	*	**	Good
Zheng et al., 2020 [29]	*	*	*	Poor

#### 4. Discussion

Precision psychiatry is a promising but still unachieved healthcare model. This delay has been mainly determined by the lack of definitive data on risk stratification and prediction in mental disorders, and BD is not an exception in this regard. It is plausible that the analysis of brain-gut microbiota influence on BD disease trajectories might increase the levels of precision needed to make this construct clinically applicable. Indeed, how the host genetic factors may interact with the gut microbiota may represent an additional layer of complexity to be considered, either in predicting treatment efficacy or the tolerability profile of existing treatments. A recent example derives from rheumatoid arthritis research [30], where the authors report on a significant association for rheumatoid arthritis polygenic risk score, *Prevotella* spp. and the presence of preclinical rheumatoid arthritis phases. Remarkably, the host genotype was associated with an increased probability of microbiota perturbations that might predate the onset of the disease. A paper [31] reported on the possible association of gut microbiota perturbations with the inflammatory status, tryptophan/kynurenine levels, oxidative stress, and metabolic syndrome using a cross-sectional design. The authors described the association between a relative group difference in genus *Faecalibacterium*, at the phylum of Actinobacteria and at the family level for *Coriobacteriaceae* among BD patients as compared with healthy controls. The findings regarding *Faecalibacterium* were partly in line with a previous report [32] and deserve further replication. Tryptophan levels, inflammation status and anthropometric indices (e.g., body mass index) were instead associated with increases in the relative abundance

in the family of Lactobacillaceae, among the others. These data offer interesting prospects regarding the possible role played by gut microbiota in the complex interplay between lifestyle, metabolism, and mood levels in BD. A largely untapped area of research is the potential bidirectional relationship between oral microbiota derangements and mental health. A cross-sectional study [33] described the association of variations of oral microbiota composition with depressive and anxiety symptoms among adolescents. The study participants have been recruited from the participants of a prior study investigating the efficacy of a mindfulness-based intervention in preventing the onset of depression in at-risk individuals. Intriguingly, the relative abundance of Spirochaetes and its member family Spirochaetaceae was associated with anxiety and depression symptoms, whilst several families and species were associated solely with depressive symptoms. Considering the study design, it was impossible to establish any causal link for the observed associations. However, if replicated in prospective studies, these results would represent a significant turning point in the research for a viable biomarker as oral microbiota could be even more easily probed as compared with intestinal microbiota. A recent meta-analysis [34] reported on the results of 59 case-control studies, finding that microbiota perturbations could be associated with a pro-inflammatory state transdiagnostically. Our systematic review confirms this impression, highlighting the presence of only two studies using gut microbiota analysis for precision approaches. This should lead to an increase in research in this area. Indeed, several lines of evidence suggest a possible bidirectional role for microbiota alterations as a possible environmental factor contributing to BD relapses. Bengesser et al. [35] reported on a cross-sectional study investigating the possible association between microbial alpha diversity and aryl hydrocarbon receptor nuclear translocator-like gene (ARNTL) methylation profiled in BD. Bacterial diversity correlated significantly with ARNTL methylation status and the mood phase of BD, further underscoring the need to explore the possible intricate relationship between the microbiota and how it might affect the host. An intensified synergy between preclinical and clinical research might be helpful in developing more useful cross-species approaches which are instrumental to improving our chances of closing the ever-increasing gap between basic research and clinical applications for neuroscience [36]. For example, a recent study [37] on combined human and clinical models investigated the impact of gut microbiota in regulating the tetratricopeptide repeat and ankyrin repeat containing 1 gene (TRANK1) expression, a gene that has been associated with an increased risk of BD and encoding for a protein secreted mainly by immunocytes. Interestingly, the authors reported that while TRANK1 mRNA expression appears higher in bipolar depression, fecal transplantation from these individuals to mice also resulted in greater expression of TRANK1 mRNA. Despite requiring validation and replication and notwithstanding the significance of these findings, the approach itself may be important in this sense. More recently, it has been increasingly evident how epigenetic changes of bacteria may be significant in determining their virulence. Hopefully, it will be possible in the future to estimate better the eventual impact of microbiota epigenetic changes on host health status [38] and how these modifications may interact with individual predisposition to develop an illness (or in-treatment response) rather than on influencing just the microbiota composition itself.

## 5. Conclusions

In summary, the available evidence from preclinical and clinical models appears particularly promising for this area of research. However, the current literature is scant. Additional studies are needed to elucidate further the potential that these gut microbiota analyses may hold for predicting disease trajectories and treatment responses for BD patients.

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## References

- Ferrari, A.J.; Stockings, E.; Khoo, J.P.; Erskine, H.E.; Degenhardt, L.; Vos, T.; Whiteford, H.A. The prevalence and burden of bipolar disorder: Findings from the Global Burden of Disease Study 2013. *Bipolar Disord.* **2016**, *18*, 440–450. [CrossRef]
- Dome, P.; Rihmer, Z.; Gonda, X. Suicide Risk in Bipolar Disorder: A Brief Review. *Medicina* **2019**, *55*, 403. [CrossRef] [PubMed]
- Goldstein, B.I.; Baune, B.T.; Bond, D.J.; Chen, P.H.; Eyler, L.; Fagiolini, A.; Gomes, F.; Hajek, T.; Hatch, J.; McElroy, S.L.; et al. Call to action regarding the vascular-bipolar link: A report from the Vascular Task Force of the International Society for Bipolar Disorders. *Bipolar Disord.* **2020**, *22*, 440–460. [CrossRef]
- Leboyer, M.; Soreca, I.; Scott, J.; Frye, M.; Henry, C.; Tamouza, R.; Kupfer, D.J. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J. Affect. Disord.* **2012**, *141*, 1–10. [CrossRef] [PubMed]
- Almeida, O.P.; McCaul, K.; Hankey, G.J.; Yeap, B.B.; Golledge, J.; Flicker, L. Risk of dementia and death in community-dwelling older men with bipolar disorder. *Br. J. Psychiatry* **2016**, *209*, 121–126. [CrossRef]
- Chesney, E.; Goodwin, G.M.; Fazel, S. Risks of all-cause and suicide mortality in mental disorders: A meta-review. *World Psychiatry* **2014**, *13*, 153–160. [CrossRef] [PubMed]
- Bessonova, L.; Ogden, K.; Doane, M.J.; O’Sullivan, A.K.; Tohen, M. The Economic Burden of Bipolar Disorder in the United States: A Systematic Literature Review. *Clin. Outcomes Res. CEOR* **2020**, *12*, 481–497. [CrossRef]
- Ekman, M.; Granstrom, O.; Omerov, S.; Jacob, J.; Landen, M. The societal cost of bipolar disorder in Sweden. *Soc. Psychiatry Psychiatr. Epidemiol.* **2013**, *48*, 1601–1610. [CrossRef] [PubMed]
- Goodwin, G.M.; Haddad, P.M.; Ferrier, I.N.; Aronson, J.K.; Barnes, T.; Cipriani, A.; Coghill, D.R.; Fazel, S.; Geddes, J.R.; Grunze, H.; et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. *J. Psychopharmacol.* **2016**, *30*, 495–553. [CrossRef]
- Fountoulakis, K.N.; Vieta, E.; Young, A.; Yatham, L.; Grunze, H.; Blier, P.; Moeller, H.J.; Kasper, S. The International College of Neuropsychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 4: Unmet Needs in the Treatment of Bipolar Disorder and Recommendations for Future Research. *Int. J. Neuropsychopharmacol. Off. Sci. J. Coll. Int. Neuropsychopharmacol. (CINP)* **2017**, *20*, 196–205. [CrossRef] [PubMed]
- National Institute for Health and Care Excellence [NICE]. Available online: <https://www.nice.org.uk> (accessed on 21 February 2022).
- Bowden, C.L.; Perlis, R.H.; Thase, M.E.; Ketter, T.A.; Ostacher, M.M.; Calabrese, J.R.; Reilly-Harrington, N.A.; Gonzalez, J.M.; Singh, V.; Nierenberg, A.A.; et al. Aims and results of the NIMH systematic treatment enhancement program for bipolar disorder (STEP-BD). *CNS Neurosci. Ther.* **2012**, *18*, 243–249. [CrossRef]
- Geddes, J.R.; Miklowitz, D.J. Treatment of bipolar disorder. *Lancet* **2013**, *381*, 1672–1682. [CrossRef]
- Yalin, N.; Young, A.H. Pharmacological Treatment of Bipolar Depression: What are the Current and Emerging Options? *Neuropsychiatr. Dis. Treat.* **2020**, *16*, 1459–1472. [CrossRef] [PubMed]
- Lubloy, A.; Kereszturi, J.L.; Nemeth, A.; Mihalicza, P. Exploring factors of diagnostic delay for patients with bipolar disorder: A population-based cohort study. *BMC Psychiatry* **2020**, *20*, 75. [CrossRef]
- Kessler, R.C.; Luedtke, A. Pragmatic Precision Psychiatry—A New Direction for Optimizing Treatment Selection. *JAMA Psychiatry* **2021**, *78*, 1384–1390. [CrossRef] [PubMed]
- Salagre, E.; Dodd, S.; Aedo, A.; Rosa, A.; Amoretti, S.; Pinzon, J.; Reinares, M.; Berk, M.; Kapczinski, F.P.; Vieta, E.; et al. Toward Precision Psychiatry in Bipolar Disorder: Staging 2.0. *Front. Psychiatry* **2018**, *9*, 641. [CrossRef]
- Denny, J.C.; Collins, F.S. Precision medicine in 2030—seven ways to transform healthcare. *Cell* **2021**, *184*, 1415–1419. [CrossRef] [PubMed]
- Ashley, E.A. Towards precision medicine. *Nat. Rev. Genet.* **2016**, *17*, 507–522. [CrossRef] [PubMed]
- Ahmed, E.; Hens, K. Microbiome in Precision Psychiatry: An Overview of the Ethical Challenges Regarding Microbiome Big Data and Microbiome-Based Interventions. *AJOB Neurosci.* **2021**, 1–17. [CrossRef] [PubMed]
- Zheng, P.; Zeng, B.; Zhou, C.; Liu, M.; Fang, Z.; Xu, X.; Zeng, L.; Chen, J.; Fan, S.; Du, X.; et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host’s metabolism. *Mol. Psychiatry* **2016**, *21*, 786–796. [CrossRef] [PubMed]
- Sampson, T.R.; Debelius, J.W.; Thron, T.; Janssen, S.; Shastri, G.G.; Ilhan, Z.E.; Challis, C.; Schretter, C.E.; Rocha, S.; Gradinaru, V.; et al. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson’s Disease. *Cell* **2016**, *167*, 1469–1480.e12. [CrossRef] [PubMed]

23. Zhu, F.; Guo, R.; Wang, W.; Ju, Y.; Wang, Q.; Ma, Q.; Sun, Q.; Fan, Y.; Xie, Y.; Yang, Z.; et al. Transplantation of microbiota from drug-free patients with schizophrenia causes schizophrenia-like abnormal behaviors and dysregulated kynurenine metabolism in mice. *Mol. Psychiatry* **2020**, *25*, 2905–2918. [[CrossRef](#)] [[PubMed](#)]
24. Horsley, T.; Dingwall, O.; Sampson, M. Checking reference lists to find additional studies for systematic reviews. *Cochrane Database Syst. Rev.* **2011**, MR000026. Available online: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.MR000026/full> (accessed on 21 February 2022). [[CrossRef](#)] [[PubMed](#)]
25. Wells, G.A.; Shea, B.; O'Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Ott. Hosp. Res. Inst.* **2011**, *2*, 1–12.
26. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [[CrossRef](#)] [[PubMed](#)]
27. Hu, S.; Li, A.; Huang, T.; Lai, J.; Li, J.; Sublette, M.E.; Lu, H.; Lu, Q.; Du, Y.; Hu, Z.; et al. Gut Microbiota Changes in Patients with Bipolar Depression. *Adv. Sci.* **2019**, *6*, 1900752. [[CrossRef](#)] [[PubMed](#)]
28. Lai, J.; Li, A.; Jiang, J.; Yuan, X.; Zhang, P.; Xi, C.; Wu, L.; Wang, Z.; Chen, J.; Lu, J.; et al. Metagenomic analysis reveals gut bacterial signatures for diagnosis and treatment outcome prediction in bipolar depression. *Psychiatry Res.* **2022**, *307*, 114326. [[CrossRef](#)] [[PubMed](#)]
29. Zheng, P.; Yang, J.; Li, Y.; Wu, J.; Liang, W.; Yin, B.; Tan, X.; Huang, Y.; Chai, T.; Zhang, H.; et al. Gut Microbial Signatures Can Discriminate Unipolar from Bipolar Depression. *Adv. Sci.* **2020**, *7*, 1902862. [[CrossRef](#)]
30. Wells, P.M.; Adebayo, A.S.; Bowyer, R.C.E.; Freidin, M.B.; Finckh, A.; Strowig, T.; Lesker, T.R.; Alpizar-Rodriguez, D.; Gilbert, B.; Kirkham, B.; et al. Associations between gut microbiota and genetic risk for rheumatoid arthritis in the absence of disease: A cross-sectional study. *Lancet Rheumatol.* **2020**, *2*, e418–e427. [[CrossRef](#)]
31. Painold, A.; Morkl, S.; Kashofer, K.; Halwachs, B.; Dalkner, N.; Bengesser, S.; Birner, A.; Fellendorf, F.; Platzer, M.; Queissner, R.; et al. A step ahead: Exploring the gut microbiota in inpatients with bipolar disorder during a depressive episode. *Bipolar Disord.* **2019**, *21*, 40–49. [[CrossRef](#)]
32. Evans, S.J.; Bassis, C.M.; Hein, R.; Assari, S.; Flowers, S.A.; Kelly, M.B.; Young, V.B.; Ellingrod, V.E.; McInnis, M.G. The gut microbiome composition associates with bipolar disorder and illness severity. *J. Psychiatr. Res.* **2017**, *87*, 23–29. [[CrossRef](#)] [[PubMed](#)]
33. Simpson, C.A.; Adler, C.; du Plessis, M.R.; Landau, E.R.; Dashper, S.G.; Reynolds, E.C.; Schwartz, O.S.; Simmons, J.G. Oral microbiome composition, but not diversity, is associated with adolescent anxiety and depression symptoms. *Physiol. Behav.* **2020**, *226*, 113126. [[CrossRef](#)]
34. Nikolova, V.L.; Hall, M.R.B.; Hall, L.J.; Cleare, A.J.; Stone, J.M.; Young, A.H. Perturbations in Gut Microbiota Composition in Psychiatric Disorders: A Review and Meta-analysis. *JAMA Psychiatry* **2021**, *78*, 1343–1354. [[CrossRef](#)] [[PubMed](#)]
35. Bengesser, S.A.; Morkl, S.; Painold, A.; Dalkner, N.; Birner, A.; Fellendorf, F.T.; Platzer, M.; Queissner, R.; Hamm, C.; Maget, A.; et al. Epigenetics of the molecular clock and bacterial diversity in bipolar disorder. *Psychoneuroendocrinology* **2019**, *101*, 160–166. [[CrossRef](#)] [[PubMed](#)]
36. Corlett, P.R.; Schoenbaum, G. Leveraging Basic Science for the Clinic-From Bench to Bedside. *JAMA Psychiatry* **2021**, *78*, 331–334. [[CrossRef](#)] [[PubMed](#)]
37. Lai, J.; Zhang, P.; Jiang, J.; Mou, T.; Li, Y.; Xi, C.; Wu, L.; Gao, X.; Zhang, D.; Chen, Y.; et al. New Evidence of Gut Microbiota Involvement in the Neuropathogenesis of Bipolar Depression by TRANK1 Modulation: Joint Clinical and Animal Data. *Front. Immunol.* **2021**, *12*, 789647. [[CrossRef](#)] [[PubMed](#)]
38. Payelleville, A.; Brillard, J. Novel Identification of Bacterial Epigenetic Regulations Would Benefit From a Better Exploitation of Methylomic Data. *Front. Microbiol.* **2021**, *12*, 685670. [[CrossRef](#)]