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PERSPECTIVES

Issues and Solutions in Psychiatric Clinical Trial with Case Studies

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Abstract: The coronavirus disease-2019 pandemic resulted in a major increase in depression and anxiety disorders worldwide, which increased the demand for mental health services. However, clinical interventions for treating mental disorders are currently insufficient to meet this growing demand. There is an urgent need to conduct scientific and standardized clinical research that are consistent with the features of mental disorders in order to deliver more effective and safer therapies in the clinic. Our study aimed to expose the challenges, complexities of study design, ethical issues, sample selection, and efficacy evaluation in clinical research for mental disorders. The reliance on subjective symptom presentation and rating scales for diagnosing mental diseases was discovered, emphasizing the lack of clear biological standards, which hampers the construction of rigorous research criteria. We underlined the possibility of psychotherapy in efficacy evaluation alongside medication treatment, proposing for a multidisciplinary approach comprising psychiatrists, neuroscientists, and statisticians. To comprehend mental disorders progression, we recommend the development of artificial intelligence integrated evaluation tools, the use of precise biomarkers, and the strengthening of longitudinal designs. In addition, we advocate for international collaboration to diversity samples and increase the dependability of findings, with the goal of improving clinical research quality in mental disorders through sample representativeness, accurate medical history gathering, and adherence to ethical principles.

Keywords: clinical efficacy assessment, clinical trials, mental health, research design, statistical analysis

Introduction

The 2022 World Mental Health Report states that >13% of the world's population have mental disorders.[1] In 2022, the World Health Organization reported that the coronavirus-2019 (COVID-19) outbreak at the end of 2019 significantly increased the incidence of depression and anxiety worldwide by 28% and 26%, respectively.[2] One Chinese study reported that >60% of COVID-19 survivors experienced at least one long-COVID symptom, with depression and anxiety being particularly prominent.[3] Furthermore, in some patients, COVID-19 led to long-term sequelae, such as loss of taste and smell, fatigue, difficulty concentrating, and cognitive decline.[4] Beyond causing persistent negative mental effects and neurological damage, the COVID-19 pandemic has had a profound effect on society as a whole in terms of specific systemic mental syndromes.

Currently, diagnosis and treatment of mental disorders are based on scales, questionnaires, and diagnostic classification manuals compiled by Western physicians. These methods lack objective, quantifiable diagnosis, and treatment evaluation indicators.[5] The symptoms and classifications of mental disorders often overlap and are easily influenced by the subjective assessments of psychiatrists, which can lead to misdiagnosis, such as destructive mood disorder being

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misdiagnosed as bipolar disorder.[6] Medication and psychotherapy are the most frequently used treatments for mental disorders. However, due to the etiological complexity and diversity of mental disorders, identifying precise pharmacological interventions for specific symptoms remains challenging. Existing psychotropic medications often cause adverse reactions.[7] Traditional Chinese medicine and compound prescriptions, such as traditional therapies, have had a long history of use in China. For example, the traditional Chinese medicine formula, namely, Wendan Decoction, was used to treat anxiety and depression in survivors after the 2008 Wenchuan earthquake in China and to alleviate anxiety and insomnia in patients with COVID-19.[8] However, the exact clinical application of traditional Chinese medicine in mental disorders requires further clarification. The use of psychotherapy depends on symptom severity and relies on a therapist's experience; moreover, the treatment process is long and slow. These issues can hinder the diagnosis and treatment of mental disorders in the context of growing clinical demand. With the rapid development of modern technology and information science, an increasing number of new technologies, drugs, and therapies are being investigated to potentially facilitate the diagnosis and treatment of mental disorders in terms of evidence-based medicine.

Clinicians and researchers often encounter common challenges when conducting mental health-related clinical research. We aimed to discuss certain common challenges identified in various aspects of clinical trials for mental disorders, including research design and ethical considerations, sample selection and sample size estimation, clinical efficacy evaluation tools and accuracy, statistical data analysis, and quality control. Simultaneously, we aimed to explore the reasons for these issues and propose solutions to provide a reference for ensuring the standardization and professionalism of psychiatric clinical trial research.

Research Design: Issues and Solutions

Sample Selection and Heterogeneity

The heterogeneity among populations with mental disorders makes sample selection complex. Solutions include increasing the sample size to enhance representation; ensuring diversity in the sample, such as including individuals of different ages, genders, disease severities, and treatment histories; and using strict inclusion criteria and random sampling methods to minimize sample selection bias (case studies, Table 1).[9]

Sample Size Calculation

During the design phase, researchers estimate effect sizes based on previous studies or their clinical experience. However, in some mental disorder-related studies, the expected effect size is unclear or difficult to estimate. Follow-up for patients with mental disorders is often more challenging than that for other patients, and the attrition rate is high, which can be addressed through increasing the sample size beyond the original estimation. Assessments of treatment efficacy in relation to psychiatric patients often involve the use of scales and the continuous collection of data at different time points, which increases the complexity of sample size calculations. Proactive planning and prioritizing primary endpoints are likely to help ensure sufficiently large sample sizes to address the primary research objectives and provide flexible handling of secondary endpoints or subgroup analyses (case studies, Table 1).[10]

Randomization and Blinding

In clinical studies concerning mental disorders, implementing a double-blind design poses challenges when the treatment intervention or outcome evaluation is associated with the disease status; that is, preferred interventions and outcome measurements vary as the disease status changes. Therefore, single-blind designs can be used where either the researcher or the participant is blinded to a specific treatment plan (case studies, Table 1).[11] In addition, objective indicators should be used to measure the intervention effects to reduce the effect of subjective bias.

Study Duration and Long-Term Follow-Up

Treatment for mental disorders often requires long-term observation and tracking, which may lead to participants' dropping out or missing data. Measures such as increasing the frequency of follow-up visits, providing appropriate

Table 1 Issues, Solutions, and Case Studies in Psychiatric Clinical Trials

Module	Methodology	Issues	Solutions	Case Studies	Reference
Study design	Participant selection	Participant selection was challenging due to heterogeneity	Increase the sample size. Ensure sufficiently diverse samples. Use strict inclusion and exclusion criteria and random sampling.	O'Connell suggested that future bipolar disorder-related research should incorporate ethnically-diverse samples to address Eurocentric bias, as well as incorporate population biobanks, registry data, and electronic health records to increase the sample size necessary for continued genetic discovery.	[9]
	Sample size estimation	Expected effect sizes are unclear or challenging to estimate. A lack of multiple endpoints or subgroup analyses Participant follow-up and the high rate of missed visits was concerning.	Increase the sample size. Set primary endpoints in advance, ensure sample size is sufficient for the primary research question, and be flexible about secondary endpoints or subgroup analyses.	In a randomized controlled trial investigating the efficacy and safety of 3.4-methylenedioxymethamphetamine (MDMA)-assisted therapy for the treatment of patients with severe post-traumatic stress disorder, the sample size was calculated using CAPS-5 as the primary study endpoint.	[10]
	Randomization and blinding	Therapeutic intervention or assessment outcomes related to the condition status complicate the double-blind status.	Use single-blind designs where necessary.	In a trial testing effectiveness and cost-effectiveness of task-shared care for people with severe mental disorders in Ethiopia, a single-blind design was used as it was not possible to mask participants or care providers.	[11]
	Follow-up phase	A long study duration. A high probability of withdrawal.	Provide appropriate incentives to increase participant motivation. Use objective indicators to assess the effectiveness of interventions and reduce the influence of subjective bias.	The previous case mentions that a lack of reimbursement for transport to attend the psychiatric clinic might have been a barrier, leading the participants to drop out of care.	[11]
	Etiological study	High genetic predisposition to mental disorders. Influence from a combination of genetic and environmental factors.	Avoid simple associations between single genes or gene variants and disease risk. Consider gene-environment interactions and gene-gene interactions.	If a biological parent has schizophrenia, the risk of the disorder developing in their offspring is significantly increased. Certain specific gene variants have also been found to be associated with the risk of developing schizophrenia. One study found that people with the COMT gene variant may have an increased risk of developing schizophrenia if they used marijuana during their teenage years. Yue et al found that individuals carrying the rs7692791 C allele or the CC genotype of KDR, as well as those with the rs9282715 T allele of IGF-1R, may be susceptible to PSD.	[12–15]

(*Continued*)

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Table 1 (Continued).

Module	Methodology	Issues	Solutions	Case Studies	Reference
Study outcome	Outcomes assessed subjectively	Multi-dimensional outcomes, such as degree of symptom reduction, functional improvement, and quality of life. Involvement of subjective experience, psychological state, patient self-report, and clinical observation. Mostly subjective self- or other-rated scales used as assessment tools.	Use multiple relevant scales and assessment tools to obtain information on different dimensions for a more comprehensive assessment. Use objective indicators such as neuroimaging and biomarkers to provide objective information about the condition and treatment outcomes. Consider applicability, sensitivity, specificity, and cultural adaptation of the scale to ensure its reliability and validity according to each specific research context.	In Mitchell's study, outcome measures included the CAPS-5, SDS, the BDI-II, the Alcohol Use Disorders Identification Test (AUDIT), the Drug Use Disorders Identification Test (DUDIT) and the Adverse Childhood Experiences (ACE) Questionnaire. This solution is currently challenging. For example, in Autism Spectrum Disorder (ASD), there is insufficient evidence providing molecular biomarkers for clinical trials, or technological advances regarding neuroimaging and other physiological measurements for this disorder. Skaczkowski et al developed a contextually and culturally appropriate scale to assess farmers' barriers to health-related help-seeking. Nie et al designed a new cognition assessment tool, namely, Thoven cognitive self-assessment (TCSA) and evaluated its validity and reliability.	[10] [16,17] [18]

Data analysis	Missing data	Frequent use of questionnaires, high number of follow-up visits, and susceptibility to missing data. Types of missing data: MCAR, no systematic differences between the missing values and the observed values. MAR, any systematic difference between the missing values and the observed values can be explained through differences in observed data. MNAR, despite considering observed data, systematic differences remain between the missing values and the observed values [12].	Use descriptive analysis to calculate the amount and pattern of missing data and identify the extent and nature of the missing data to determine subsequent treatments. Use only samples with complete data for full case analysis results in a reduced sample size with caution, and recognize the introduction of selection bias. Use a variety of interpolation methods, namely, mean interpolation, last observation interpolation, linear interpolation, and multiple interpolation. Use sensitivity analysis to assess the effect and robustness of different interpolation methods on the results. Estimate and analyze missing data using advanced statistical methods such as mixed effects modeling and generalized estimating equation modelling. Consider strategies for data collection and management at the study design stage to reduce the incidence of missing data.	Schober proposed that missing data reduce statistical power, which may bias the analysis results, and should therefore be appropriately described and addressed in any research report. In Hanlon's study, missing data from a modified intention-to-treat set, which was based on reasons for post-randomization withdrawal, were described. Sterne considered that results of such analyses can be biased, leading to a substantial loss of precision and power. In Guilleminite's study, some data were missing for several variables, which the authors addressed using multiple imputation. In Robinson's statistical analysis report (SAR), which was a sensitivity analysis around the multiple imputation model, a complete case analysis of the primary outcome with the addition of significant predictors for missingness as covariates was performed. In Hanlon's study, linear regression analysis was conducted in addition to Poisson regression and mixed effects linear regression modelling. Little et al considered that certain measures could be taken at the study design stage to minimize the occurrence of missing data.	[19] [11] [20–22] [11] [23]
	Multiple comparisons	Including multiple treatment groups or control groups (such as comparisons of treatment methods or drugs). Focusing simultaneously on multiple outcome indicators (such as symptom relief, quality of life improvement and the incidence of side-effects) with each indicator undergoing separate hypothesis testing. Repeatedly measuring the same outcome indicator at different points in time (such as scale).	Statistical methods correction, namely, Bonferroni correction, Holm-Bonferroni correction, and false discovery rate correction, to control for the probability of Type I errors. Post hoc tests are required when using analysis of variance for multiple group comparisons. Clarification of the study purpose and design of the necessary clinical follow-up nodes and endpoints.	In one study, authors examined whether mean grade point average and specific school subjects were associated with diagnosis of nonaffective psychoses, bipolar disorder and depression. Bonferroni correction was used for 21 tests performed to diagnose the disorders. Chen et al considered that Tukey's, Schefft's, and other post-hoc tests were all adjusted for such multiple comparisons to ensure correct type I errors in multiple testing; however, this was not always guaranteed to work. Robinson's SAP identified the trial's primary and secondary objectives, and the trial design prior to implementing the trial.	[24,25] [22]

Abbreviations: BDI, Beck Depression Inventory, Second Edition; CAPS-5, Clinician-Administered PTSD Scale for DSM-5; SAP, statistical analysis plan; SDS, Sheehan Disability Scale.

incentives, and establishing support systems can enhance participant cooperation and research sustainability (case studies, Table 1).[11]

The Design of Genetic Epidemiological Studies

Despite being highly hereditary, the specific pathogenesis and etiology of various mental disorders remains unclear. Genetic epidemiology has been applied extensively to determine specific associations. For example, a Hardy-Weinberg equilibrium test has been used to evaluate whether genotype frequencies in the population conform to the Hardy-Weinberg equilibrium principle.[26] This method has helped researchers assess whether genotype frequencies align with theoretical expectations and provides preliminary evidence of genetic correlation. Considering the complexity of etiological mechanisms of mental disorders, a simple association between a single gene or gene mutation and disease risk should be avoided. Furthermore, the occurrence of mental disorders is often influenced by both genetic and environmental factors, and the possibility of gene-environment and gene-gene interactions should be considered (case studies, Table 1).[12–15]

Study Outcomes: Issues and Solutions

In clinical trials concerning mental disorders, efficacy evaluation requires effective and reliable assessment tools. The most frequently used tools are self-rating and observer-rating scales. As previously mentioned, the diagnostic scales are often developed by Western physicians. There are inequalities in access, treatment, and quality of mental health care that could imply a bias toward Western medical practices. In fact, in addition to Western medical techniques, there are a variety of traditional medical techniques that have their own insights into diagnosing mental health disorders.[27] It's important to consider the application of diverse cultural and medical practices in mental health care worldwide. One approach to diagnosis could be the use of cross-cultural diagnostic tools: the development and use of diagnostic tools that have been culturally adapted to take into account the manifestations of mental health problems in different cultural backgrounds. These tools may more accurately reflect the actual conditions of patients from diverse cultural backgrounds.[28,29] In addition, evaluations of these scales should focus primarily on their reliability, validity, sensitivity and specificity.[18]

Assessments of the therapeutic effects of mental disorders must consider multiple dimensions, such as the degree of symptom relief, improvements in function, and quality of life. Given mental disorders involve subjective experiences and psychological states, assessments are usually subjective and involve patient self-reports and clinical observations. Various methods can be adopted to mitigate this subjective influence. For example, using multiple related scales and assessment tools to obtain information from different dimensions can provide a more comprehensive assessment result.[10] Furthermore, objective indicators, such as neuroimaging technology and laboratory examinations, can be used to provide objective information concerning conditions and treatment effects, although this option is challenging at present.[16] Regular reviews or long-term follow-up evaluations can indicate trends in symptoms and functional changes; thus, reducing the subjective effect of evaluations at a single time point. Comprehensive information can be obtained using clinical observations of doctors, patient self-reports, and family feedback to achieve more thorough and objective evaluation results. By providing an appropriate evaluation environment and good communication, participants can be encouraged to express their experiences and feelings fully, thereby reducing the bias of subjective assessments (case studies, Table 1).[17,18]

Data Analysis: Issues and Solutions

The statistical approach typically relies on hypothesis testing to assess whether an approach fits the study requirements and on the selection of appropriate data analysis methods. Two issues frequently arise in psychiatric clinical trials, namely, missing data and multiple comparisons.

Missing data patterns can be categorized in several ways, such as missing completely at random (MCAR), which means that missing data are unrelated to other variables and do not have a specific pattern; missing at random (MAR), which means that missing data are related to other variables and present a certain pattern; or missing not at random (MNAR), which refers to the presence of specific identifiable reasons or mechanisms for the missing data.[20] For example,

at a certain point in time, due to personal factors for some patients, the evaluation of a scale may not reach completion, leading to partially missing data for that measurement. This may occur with other measurement items at other times, forming an MNAR pattern.

Different solutions have been developed to correspond to these different patterns and situations with missing statistical data. Descriptive analysis calculates the number and pattern of missing data, thereby helping researchers to identify the degree and nature of missing data for determining subsequent treatment methods. Only samples with complete data are used for complete case analysis. However, this method may lead to a decrease in sample size and introduce selection bias; therefore, it should be used cautiously. Instead, the use of various imputation methods, such as mean imputation, last observation carried forward, linear interpolation, and multiple imputations, is recommended. Pedersen et al[30] considered that multiple imputations, available in most statistical software, can generally be used for resolving the issue of missing data under the MAR assumption. The process of multiple imputations addresses uncertainty in relation to missing data by creating several plausible datasets and appropriately combining the results obtained from each dataset. When using imputation methods to handle missing data, the effectiveness and robustness of different imputation methods on the results should be evaluated using sensitivity analysis.[20] Other advanced statistical methods, such as mixed effects models and generalized estimating equation models, are used to estimate and analyze missing data based on available data. Regardless of the method, researchers should transparently report how they addressed the matter of missing data and note the potential effects of missing data when interpreting their results. Additionally, it is recommended that data collection and management strategies be fully considered at the research design stage to minimize the occurrence of missing data in as far as possible (case studies, Table 1).[11,19–23]

In terms of multiple comparisons, study designs may include multiple treatment or control groups, such as comparisons of treatment methods or drugs, and focus on multiple outcome indicators, such as symptom relief, improvement in quality of life, and the incidence of side-effects. Each indicator requires independent hypothesis tests and repeated measurements of the same outcome indicator at different time points (such as using scales), all of which are likely to introduce the issue of multiple comparisons.

In multiple comparison analysis, performing multiple intergroup comparisons will increase the possibility of Type I errors, and appropriate statistical methods should be used for correction, such as Bonferroni correction, Holm-Bonferroni correction, and the false discovery rate correction, to control for the probability of Type I errors (case studies, Table 1).[24,25] However, there are disadvantages with multiple comparisons. Unclear research goals and attempts to mine data through numerous comparisons may lead to over-interpretation and mis-direction. In addition, interim analysis can lead to studies concluding prematurely. It is important to adjust nominal *P*-values and plan study endpoints related to interim analysis in the statistical analysis plan.

Ethical Considerations: Issues and Solutions

In studies concerning mental health disorders, distinctive ethical challenges arise due to the specificities of the population. Patient comprehension and decision-making may be affected, complicating informed consent. This challenge necessitates additional efforts by researchers to ensure participants understand the study and its potential risks, potentially involving legal guardians.[31] Patient privacy is essential as are data protection measures. For example, a common challenge in adolescent mental health research is the breach of confidentiality. Psychologists or researchers may need to disclose information to parents or schools, particularly in cases involving suicidal ideation or other behaviors that could potentially cause serious harm to adolescents.[32,33] In addition, the use of placebos in trials raises ethical concerns because participants may be deprived of effective treatments. Critics of the use of placebos in psychiatric research argue that the crucial question is not necessarily whether a new treatment is better than a placebo, but rather whether it is better than existing treatments. In addition, there's a moral dilemma in using placebo groups when effective treatments are already available.[34] We believe that improvements in trial design to better reflect clinical practice, greater clarity in the informed consent process, a renewed focus on suicidality, and careful attention to vulnerable populations can strengthen the field.

Conclusion and Perspectives

Distinctive challenges related to mental disorders have been identified through clinical research. For example, the classification, definition, and efficacy evaluation of mental disorders often rely on patient symptom presentation, self-rating scales, or other rating scales. A lack of precise biological diagnostic standards makes it challenging for researchers to establish and implement inclusion and exclusion criteria and evaluate efficacy. Aside from drug treatment, psychotherapy (such as cognitive behavioral therapy) may play a key role in efficacy evaluation. Resolving these issues requires a combined effort from both researchers and relevant institutions. Through adopting appropriate methods and assessment tools, ensuring the representativeness of samples, accurately obtaining medical history information, and adhering to ethical principles, the quality and reliability of clinical research on mental disorders can be improved. Moreover, interdisciplinary collaboration should be encouraged to promote exchange and cooperation among psychiatrists, psychologists, neuroscientists, epidemiologists, and statisticians to address these issues collectively.

Future research should focus on the following aspects of study design: the development of more accurate and reliable clinical assessment tools, such as integrating artificial intelligence technology[35,36] to better capture symptoms and changes in mental disorders; utilizing new technologies and biomarkers, such as magnetic resonance imaging (MRI), electroencephalography (EEG)[37] and genetic analysis,[38] to assist in research; strengthening longitudinal study designs to better understand disease development and the long-term effects of treatment; and enhancing international cooperation and data sharing to broaden sample diversity and the reliability of research results for dissemination.

Abbreviations

COVID-19, coronavirus disease 2019; MCAR, missing completely at random; MAR, missing at random; MNAR, missing not at random; GEE, generalized estimating equation; FDR, False Discovery Rate; SAP, statistical analysis plan.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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