

Ethical Issues in Schizophrenia Research: A Scoping Review and Qualitative Interview Study

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ABSTRACT

Schizophrenia is a major research focus due to its complex etiology and treatment challenges. Ethical issues in schizophrenia research include informed consent, decision-making capacity, and the protection of vulnerable populations. Not all schizophrenia patients can provide ethical consent, highlighting the need for careful consideration in research practices. This study examined empirical studies on these ethical domains, identifying significant gaps and offering recommendations. We aimed to synthesize ethical issues from the literature and understand ethics committee members' perspectives through a mixed-methods approach, including a scoping review and qualitative interviews with three ethics committee members. For the review, four major databases were systematically searched for studies related to ethical issues in schizophrenia research. As a result, 35 of 5,222 moderate and high-quality records were included in the scoping review. Eight themes emerged from the scoping review and interview process: informed consent and decision-making capacity; willingness to participate and compensation in research; risk-benefit consideration and perception; therapeutic misconception; participants safeguard; ethical issue in various study designs; research guidelines; and recommendations for the involved parties in schizophrenia research. We conclude that individuals with schizophrenia should actively participate in research decision-making, ensuring dignity and respect.

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Introduction

Schizophrenia, a profound and enduring mental disorder, impacts around 1% of the global population [1], leading to significant disruptions in cognitive, emotional, relational, and occupational aspects of life [2]. Disability-adjusted Life Years (DALYs) related to schizophrenia have seen an 11.4% increase from 1990 to 2019 [3]. The ongoing prevalence of schizophrenia presents substantial challenges to both neuropsychiatric research and healthcare systems, as well as to individuals and their families.

Advancements in treating schizophrenia partly depend on the willingness of its survivors to take part in research. The widespread occurrence and impact of schizophrenia, coupled with the imperative to enhance current prevention and treatment approaches, collectively offer an ethical rationale for delving into scientific investigations of this severe mental disorder. Nevertheless, conducting studies involving individuals with schizophrenia raises ethical concerns related to the risks in vulnerable populations, making the process of obtaining research consent challenging [4].

In the last two decades, discussions surrounding the ethical dimensions of schizophrenia research have progressed significantly. The ethical apprehensions related to schizophrenia research primarily stem from concerns about the compromised cognitive abilities and decision-making capacities of potential participants [4]. Consequently, individuals with schizophrenia are categorized as a vulnerable population in research. Ensuring that valuable scientific studies on schizophrenia are conducted without subjecting vulnerable individuals to unnecessary risks is a crucial consideration. Fundamental ethical principles, such as respect for autonomy, beneficence, non-maleficence, and justice, play a vital role in guiding research involving human subjects [5].

Adherence to ethical principles mandates researchers to alleviate both physical and psychological harm to study participants. Ethical considerations in schizophrenia research are indispensable for safeguarding the rights and well-being of participants, upholding the integrity and validity of research outcomes, and accounting for broader societal implications [6]. Demonstrating a commitment to ethical conduct is not only a moral obligation but also an essential element in generating trustworthy and accountable scientific knowledge in schizophrenia research.

A synthesis of previous studies suggests that numerous unanswered scientific questions regarding schizophrenia persist. These encompass ethical issues related to aspects such as informed consent, decision-making capacity, volunteerism, risk perception, misconceptions about therapy, and the careful balancing of risks and benefits [7], [8], [9], [10]. Furthermore, the design of schizophrenia research studies introduces additional ethical challenges that warrant attention [11], [12].

Despite the extensive body of literature on bioethics and biomedical research, there has yet to be a systematic review specifically focused on the ethical considerations in schizophrenia research. This article offers a review grounded in data, examining the current literature on ethical considerations in schizophrenia research. The review delves into how empirical research on each aspect addresses ethical questions while also posing new inquiries. The study not only emphasizes significant knowledge gaps in understanding the ethical dimensions of schizophrenia research but also aims to uncover the viewpoints of ethics commission members on these issues through semi-structured qualitative interviews.

Material And Methods

This study employed a combination of two research methods, including 1) a scoping review and 2) semi-structured qualitative interviews with members of the research ethics committee. The purpose of the semi-structured interviews was to supplement the research findings by gaining insights into the actions and viewpoints of the research ethics committee concerning ethical considerations in studies involving individuals with schizophrenia.

A. Scoping review

The exploration of the literature was directed by the following research query: what ethical concerns are raised in studies involving individuals with schizophrenia?

1. Search strategy

The search strategy was based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) approach [13]. Articles were searched using the Boolean operators "OR/AND". The keywords used in the article search were ("ethics" OR "ethical issues" OR "bioethics" OR "medical ethics" OR "moral" AND "research" OR "study" OR "trial" AND "schizophrenia"). PubMed, Science Direct, Wiley Online Library, and Psych Info were searched using the abovementioned keywords.

2. Study selection

The selected articles consisted of journal publications addressing ethical concerns in schizophrenia research from PubMed, Science Direct, Wiley Online Library, and Psych Info. Articles written in English and published before October 2023 were gathered. This study analyzed original research articles employing qualitative, quantitative, or mixed methods. Commentaries, hypotheses, and letters to the editors were excluded from this review. Based on the quality assessment, only articles that fell into the high and moderate-quality categories were included, whereas low-quality articles were excluded from this investigation.

3. Quality assessment

An article quality assessment was carried out based on the Joanna Briggs Institute (JBI) Critical Appraisal tools [14] to determine the quality of each selected article. The critical

appraisal tools provided by JBI are specific to different types of research designs, including randomized controlled trials, qualitative research, cross-sectional studies, cohort studies, and more. Each tool typically includes a set of questions or criteria that users can apply to assess the strengths and weaknesses of a particular study. An article is considered to be low-quality if it meets less than 33% of the total JBI criteria, medium-quality if it meets 33%-66% of the criteria, and high-quality if it meets higher than 66% of the total JBI criteria [15], [16].

B. Qualitative interview

1. Participants

Individuals serving on the research ethics committee were deemed suitable to offer insights into the study's inquiries. Inclusion criteria for respondents involved current membership on the research ethics committee, past involvement in reviewing research proposals related to individuals with schizophrenia, and willingness to consent as indicated by the informed consent form. The recruitment process employed a purposive sampling approach and three members of the Research Ethics Commission constituted the respondents.

2. Interview process

Data was acquired from a qualitative study using one-on-one semi-structured interviews. The data collection process involved virtual interviews, each lasting approximately 30-45 minutes. The interview inquiries focused on three key themes: viewpoints on ethical issues in schizophrenia research, proposed research guidelines, and advice for involved stakeholders.

3. Interview guide

A semi-structured interview guide was developed for three major themes: ethical issues in schizophrenia research, guidelines for reviewing such research, and recommendations for stakeholders. The interview questions are detailed in Table 1.

Table 1. Interview guiding questions

Thematic Areas	Guiding Questions
Perception of ethical issue	What ethical considerations are you considering in research involving individuals with schizophrenia? What comes to your mind in this context? Based on your professional experience, what ethical principles do you primarily consider when reviewing research involving schizophrenic participants? In your opinion, what ethical issues could potentially arise in research involving schizophrenic participants?
Guideline in reviewing research	If you were faced with a moral or ethical dilemma in the review process, what guidelines would you use to resolve it?
Recommendation	What recommendations or suggestions can you give to parties involved in the research process involving participants with schizophrenia in order to achieve ethical research?

C. Data Analysis

A hybrid thematic analysis incorporating both inductive and deductive approaches was employed to examine data from scoping reviews and qualitative interviews. Fig. 1 provides a concise outline of this process. Subsequently, the research findings are presented narratively in a discussion, elucidating the themes derived from the data analysis.

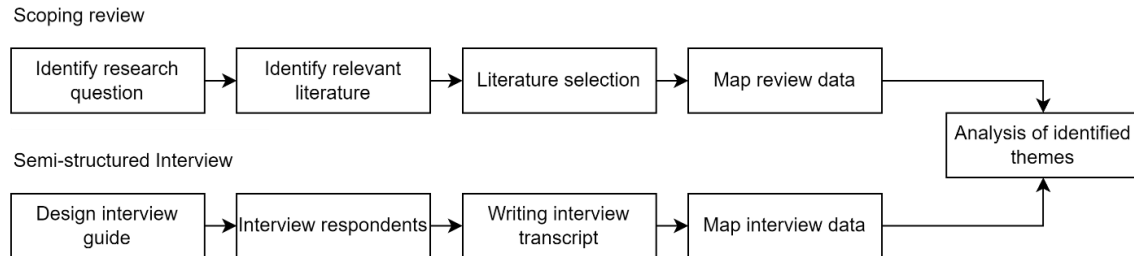


Fig. 1. Research data analysis.

Results

A. Scoping Review

1. Study selection

Based on search results using Boolean logic, a total of 5,122 articles were found. Among those, 99 duplicate data were excluded. Following an examination of titles and abstracts, 4,968 articles were eliminated due to records deemed irrelevant, editorial content, review papers, or the absence of an available full text. Of the 55 articles reviewed in full-text, 38 were identified as meeting inclusion criteria. The details of this process are presented in Fig. 2.

2. Quality assessment

After conducting a comprehensive quality assessment of the articles using JBI's Critical Appraisal Tools, 3 cross-sectional articles were found to be of low quality and would not be included in further analysis, leaving 35 articles to be reviewed in this study.

3. Article identification

Our findings revealed that the predominant research topics focused on the willingness of individuals with schizophrenia to participate in research, along with discussions on informed consent and the participants' decision-making capacity. The analyzed articles are categorized in Table 2 according to six identified themes from the scoping review study.

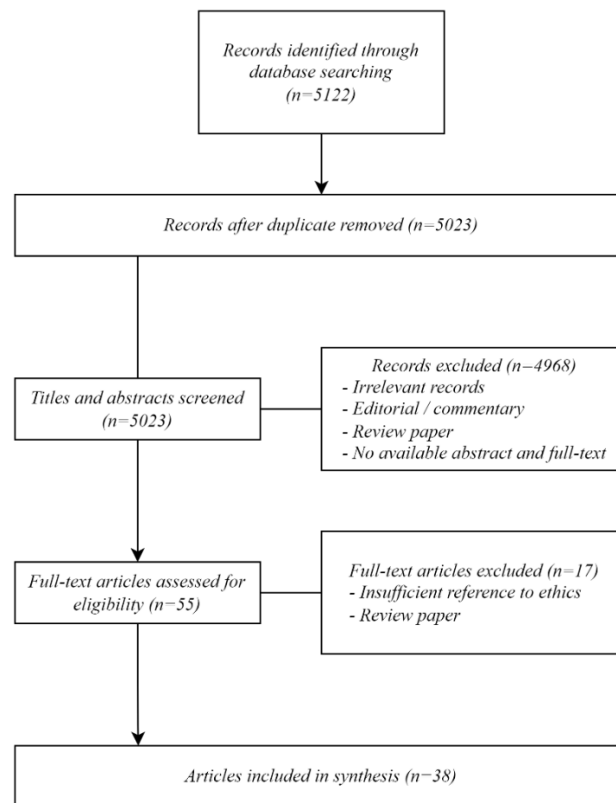


Fig. 2. Prisma flow diagram.

Table 2. Six identified themes from the scoping review

Authors (year)	Study Objective
Informed consent and decision-making capacity	
López-Jaramillo, et al., 2016 [17]	Evaluate the relationship between insight and capacity to consent to participation in research in patients with bipolar and schizophrenia.
Palmer, et al., 2013 [18]	Determine the impact of understanding after a feedback session and examine the stability of decision-making capacity.
Candilis, et al., 2009 [19]	Compare decision-making by subjects with schizophrenia or schizoaffective disorder with physical illness and healthy subjects.
Kim, et al., 2007 [20]	Assess methods for determining the capacity status of potential participants in schizophrenia research.
Dunn, et al., 2007 [21]	Evaluate the impact of changes in levels of understanding, appreciation, and reasoning on determining decision-making ability.
Palmer, et al., 2006 [22]	Evaluate the influence of cognitive deficits on dimensions of decision-making capacity evaluated by neuropsychological tests and examine the extent to which repeated presentation of information improves understanding.
Dunn and Jeste, 2002 [23]	Identify problems in consent by schizophrenic patients compared with normal subjects.
Benson, et al., 1985 [24]	Compare what prospective subjects are told and what they understand.
Kovnick et al., 2003 [25]	Compare competence in people hospitalized for schizophrenia with a comparison sample of people from the community who had never had a psychiatric hospitalization.
Therapeutic misconception	
Fischer, et al., 2013 [26]	Monitor retention of study-related knowledge-including assessment of therapeutic misconceptions.
Dunn, et al., 2006 [27]	Assess the prevalence and factors influencing therapeutic misconceptions among patients with reference to hypothetical studies.
Perception of risk and benefit	
Roberts, et al., 2002 [28]	Understand the perspectives of schizophrenia patients and psychiatrists regarding ethical aspects of relapse during participation in psychopharmacological research.
Roberts, et al., 2002 [29]	Assess potential harms and factors influencing participation decisions in a hypothetical schizophrenia study protocol from the perspectives of patients and psychiatrists.

Authors (year)	Study Objective
Dunn, et al., 2009 [30]	Assess factors influencing willingness to participate in research, with respect to perceived risks and benefits, among people with schizophrenia.
Willingness to participate	
Dufva, et al., 2021 [31]	Investigate the behavior and motivations of patients with schizophrenia and healthy individuals toward participation in genetic research.
Leickly, et al., 2018 [32]	Explore the motivations of individuals with serious mental illness to participate in research and identify influencing factors.
Taylor, et al., 2010 [33]	Investigating subjective experiences of participation in research.
Alexis, et al., 2003 [34]	Investigate factors influencing willingness to participate in schizophrenia research.
Sugawara, et al., 2015 [35]	Assess attitudes toward participation in a placebo-controlled clinical trial in schizophrenia patients in Japan.
Roberts, et al., 2015 [36]	Assess the views of healthy and ill clinical research participants regarding the ethical acceptability of human research.
Roberts, et al., 2006 [37]	Examine participants' attitudes regarding schizophrenia protocols regarding the importance of medical research, key aspects of research participation, and acceptability of research involvement.
Roberts, et al., 2006 [38]	Understand factors that may influence willingness to participate in research.
Warner, et al., 2003 [39]	Assess psychiatrists' predictions regarding the reported experiences, attitudes, and motivations of individual schizophrenia research volunteers.
Roberts, et al., 2002 [40]	Understand how individuals with serious mental illness and psychiatrists view the ethically important aspects of biomedical research participation.
Kim and Roberts, 2005 [41]	Present views of ill and healthy individuals in clinical research as a test of initial research hypotheses.
Participants safeguard	
Roberts, et al., 2004 [42]	See how people involved in research or stakeholders view efforts to ensure the rights and welfare of participants.
Roberts, et al., 2003 [43]	Assess participants' perspectives and preferences regarding ethically important aspects of protection during the schizophrenia research process.
Roberts, et al., 2003 [44]	Assess psychiatrists' attitudes toward 12 ethically relevant elements of protection in conducting clinical research.
Ethical issues in various study design	
Fischer and George, 2010 [45]	Assess whether there are differences in experiences with IRBs (Institutional Review Boards) and attitudes between researchers in schizophrenia research.
Laar, et al., 2001 [46]	Examine the long-term effects of a placebo period in a group of inpatients with chronic schizophrenia.
Wyatt, et al., 1999 [47]	Examine the long-term effects of a placebo period in a group of chronic schizophrenia patients.
Dunn, et al., 2005 [48]	Investigate whether schizophrenia patients' understanding of placebo controls can be improved by a brief educational intervention.
Noordraven, et al., 2008 [49]	Assess the attitudes and ethical considerations of patients and physicians participating in RCT trials.
Lahti, et al., 2001 [50]	Review the safety of ketamine during the study period in a group of patients and compare long-term outcomes with a group of patients who did not receive ketamine.
Kumra, et al., 2005 [51]	Examine the risks and benefits of medication-free periods for pediatric patients with refractory schizophrenia in research.

B. Semi-structured Interview

1. Characteristics of respondent

Interviews were carried out in December 2023 with three members of the Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing of Universitas Gadjah Mada, Indonesia. The interviews were conducted through online video conferencing, lasting approximately 30-45 minutes. Among the respondents, two are experts in psychiatry and psychology, while one is a layperson contributing to the ethics commission's review of research, particularly in safeguarding research participants. All

respondents possess over five years of experience as ethics committee members and have diverse educational backgrounds, ranging from bachelor's to doctoral degrees, including master's and specialist degrees.

2. Interview result

The scoping review and the interview produced eight themes. The grouping of categories and themes can be seen in Table 3.

Table 3. Grouping of eight categories from interview

Theme	Category
Protection of the rights of research participants involving schizophrenia participants	The rights of people with mental disabilities must be fulfilled as in research in general. Patients with schizophrenia also have the same decision-making rights as participants with physical illnesses. One of the underestimated ethical principles is related to participant privacy due to the influence of societal culture.
Consideration of physical and psychological benefits and harms arising from research involving schizophrenic participants	Side effects that arise as a result of research must be anticipated by researchers. One of the harms that needs to be considered is psychological stress. The impact of extracting information in research can cause danger in the form of increasing positive symptoms. Considerations of harms and benefits should be reviewed prior to the informed consent process. The duration of collecting research data in the form of interviews can be dangerous for participants and researchers.
Compensation and the risk of harm in research	Compensation and benefits are not just money. The benefits that research participants get can be in the form of appropriate compensation. Benefits that can be provided to participants include counseling.
The process of informed consent for research by participants with schizophrenia	Guardian assistance is needed in the research approval process. Informed consent can be given by participants on the condition that they truly understand it. Informed consent cannot only be given by the patient's family. Researchers must be able to understand the competencies of their research participants before asking for consent. In research involving patients in acute conditions, consent can be sought from the family, and repeated informed consent can be obtained from the participants.
Competence to make decisions about participating in research	The assessment of participants' competence to make decisions and provide informed consent can be assessed objectively by experts. People with schizophrenia have reduced cognitive and emotional abilities that affect comprehension.
Ethical obstacles encountered in research involving schizophrenic participants	Socialization is needed for reviewers regarding the ethical review of research with schizophrenia cases. The ethics commission does not have the authority to monitor the research process directly, so cases of ethical violations in research cannot be monitored. There are still differences in perceptions between researchers regarding the ethics of schizophrenia research.
Ethical guidelines for research involving participants with schizophrenia	There are currently no guidelines regarding the ethics of research involving people with schizophrenia. However, the World Health Organization (WHO) has issued guidelines containing the human rights of people with mental disabilities called WHO QualityRights. There are no guidelines for reviewing schizophrenia research. IRB members review research based on their experience and knowledge in their field because their references are limited to general medical cases (mild or severe illnesses).
Recommendations for related parties	It is necessary to provide certification for researchers who will involve participants with mental disabilities. Training and discussion are needed for ethical commissions and reviewers regarding ethical issues in research involving people with schizophrenia.

Discussion

The ultimate objective of this study is to examine and map recognized ethical concerns associated with research involving individuals with schizophrenia by utilizing scoping reviews and qualitative interviews. The synthesis of results from both scoping reviews and interviews reveals eight key thematic areas of ethical issues, along with recommendations for stakeholders engaged in schizophrenia research.

A. Informed Consent and Decision-making Capacity

In vulnerable populations, diminished autonomy among individuals can result in a compromised ability to make independent decisions, a concern raised by interview respondents in this study. The ethical challenges surrounding the informed consent process for individuals with schizophrenia were acknowledged by interview respondents, given the diverse conditions of participants, ranging from acute to stable. This necessitates researchers to assess participants' conditions and competence.

MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) has been a widely used tool for evaluating decision-making capacity in individuals with schizophrenia. Severe mental illness was linked to poorer performance on MacCAT-CR sub-scales, indicating potential difficulties in research consent capacity [20]. Cognitive test scores, especially in understanding and appreciation, exhibited strong correlations with decisional capacity, alongside negative symptoms and general psychopathology in schizophrenia patients [22]. Decision-making capacity is significantly influenced by cognitive capacity, physical functioning, mental illness, and education level across diagnoses, with psychotic symptoms correlating with lower scores [19]. Schizophrenia participants faced challenges in responding to open-ended questions about study details [23]. Additionally, emphasizing therapeutic aspects might compound subjects' problematic understanding of research purposes and methodology [24].

Recognizing the significance of insight, Ref. [17] suggests its inclusion in capacity assessments. Ref. [25] proposed a correlation between competence to consent and insight, mediated by cognitive impairments in schizophrenia. The stability of decisional capacity in schizophrenia implies an ongoing informed consent dialogue during study visits [18]. Researchers using capacity assessment instruments should carefully set cut-offs for further evaluation [21].

Due to the vulnerability of schizophrenia patients, layperson respondents recommended that, during the informed consent process, participants should be accompanied by a guardian to prevent the exploitation of their vulnerability by researchers. Another respondent added that involving witnesses who understood the participant's medical condition was also necessary. Furthermore, the three respondents emphasized that researchers are obliged to

include participants in informed consent, and consent must not only be given by the family or guardian.

B. Willingness to Participate and Compensation in Research

In the realm of schizophrenia research, individuals diagnosed with this condition frequently express altruistic motivations for their active participation, thereby challenging prevailing stereotypes. Ref. [31] underscores the schizophrenia participants' eagerness to contribute to genomic research, advocating for their inclusive involvement. Schizophrenia respondents in a study by Ref. [37] affirmed their support for medical research, citing autonomy and altruism as key motivators. In the domain of mental health and suicide research [33], participants' opinions were generally positive, although some participants found the experience challenging.

Participants enrolled in schizophrenia research protocols often endorsed hope and altruistic motives, aspects that were occasionally underestimated by psychiatrists [40]. Ref. [41] observed that individuals with mental illness demonstrated deeper connections and a more nuanced ethical perspective in their participation compared to healthy volunteers. Psychiatrists tended to underestimate the influence of altruism and the role of research staff [39]. Acceptance of research participation declined with an increasing burden on participants [36].

Patients involved in biomedical research accentuated psychosocial benefits, with half expressing potential resource gains [34]. Decision-making factors included perceived societal helpfulness, inversely correlated with perceived harmfulness [38]. In research on supportive housing and community experiences [32], contributing to scientific advancements emerged as a common motivation. Expectations for disease improvement, assurance of hospital treatment, and encouragement from family or friends played significant roles in influencing participation in clinical trials, while concerns about time presented hindrances [35].

Participants in the interviews conducted for this research emphasized the significance of researchers comprehending the perspective of patients. They underscored the necessity for effective communication among researchers, healthcare professionals, and participants to ensure ethical and well-informed engagement in research studies. Evaluating the comprehension and perceptions of potential research participants regarding the risks, benefits, and alternatives to participation plays a crucial role in fulfilling the mission of informed consent and upholding ethical principles.

C. Risk-benefit Consideration and Perception

Patients' viewpoints regarding the risks and benefits associated with research participation are pivotal for making ethically sound decisions in psychiatric research, as emphasized by participants in this study. Numerous investigations have delved into how individuals with schizophrenia perceive the potential risks and benefits linked to research protocols.

Patients and psychiatrists exhibited significantly disparate perceptions of harm across four protocols, with medication washouts or placebo treatments associated with greater harm. Protocols perceived as more harmful correlated with reduced participant willingness to enroll in a research study [29]. While psychiatrists generally accurately predict patient responses, the significance of elucidating individual patient perspectives on specific protocols is underscored.

Psychiatrists commonly underestimate harm and overestimate decision difficulty from the viewpoint of schizophrenia patients. Although patients and psychiatrists shared similar rationales for participation decisions, their approaches differed. This implies that decisional-making capable schizophrenia patients possess strengths in evaluating ethically significant design elements of psychopharmacological trials [44].

In a study by Ref. [28], the majority of patients responded negatively to research participant protocols due to uncertainty regarding risks, benefits, and side effects. This significant finding highlights the importance of beneficence and non-maleficence compared to autonomy in patients' research decision-making. This aligns with statements from respondents in this study, emphasizing researchers' duty to prioritize patient autonomy while considering risks and benefits.

D. Therapeutic Misconception

Therapeutic misconceptions, involving misunderstandings about the distinctions between clinical care and research, play a crucial role in assessing the informed consent process in schizophrenia research. Ref. [26] study on participants with schizophrenia engaged in placebo clinical trials demonstrated their ability to differentiate between research and clinical treatment objectives. It highlights the capacity of individuals with schizophrenia to comprehend the primary research goal, which is contributing to scientific knowledge.

Another investigation [27] identified the prevalence of therapeutic misconceptions in older adults with schizophrenia, particularly in those with lower education levels or cognitive impairments. The degree of therapeutic misunderstanding correlated with scores on the MacCAT-CR tool related to understanding, appreciation, and reasoning, but not with the severity of psychopathology.

A study underscored the significance of cognitive elements in mitigating therapeutic misconceptions among individuals with schizophrenia, emphasizing the necessity for clear communication during the informed consent process [26]. This aligns with the insights shared by interview respondents in this study, indicating that patients' cognitive and emotional functioning can influence their understanding of research procedures.

E. Participants Safeguard

In general, the protection of participants, including those with schizophrenia, and the fulfillment of participants' rights in research are similar. The importance of maintaining well-being and autonomy in schizophrenia research was emphasized by the respondents in this study. Valuable insights from existing schizophrenia studies indicated that safeguards instill confidence in potential research volunteers, and clear information about these measures facilitated protocol recruitment [42].

In a 2004 study by Ref. [43], both individuals with schizophrenia and psychiatrists assessed the protectiveness and impact of five safeguards—namely, informed consent, alternative decision makers, institutional review boards, data safety monitoring boards, and confidentiality measures. All safeguards were perceived as protective by both participants with schizophrenia and psychiatrists. The ratings of protectiveness given by both groups correlated with their willingness to participate in studies.

Individuals with schizophrenia interviewed in a project [43] revealed interesting perspectives and preferences related to ethically important aspects of recruitment, consent, and debriefing in clinical research, offering insights for making research processes more participant-oriented. Participants strongly endorsed debriefing practices and expressed a desire to be informed if a health problem was discovered during the protocol.

Ref. [44] also examined the ethically relevant attitudes of psychiatrists toward human research. Safeguards and scientific merit were identified as the most prominent considerations for psychiatrists who are faculty members and residents. Significantly, residents attributed greater significance to almost every factor (including Safeguards and Scientific Merit, Investigator Integrity and Relationship, and Patient Benefit) when compared to faculty members.

F. Ethical Issues in Various Study Designs

In general, respondents in this study believed that individuals must thoroughly comprehend the treatment in experimental drug testing. Participants should be in a non-acute state and exhibit good cognitive capacity for effective communication. Researchers must carefully assess the risk-benefit ratio and anticipate potential side effects of drug administration, with a notable example being placebo research.

In a placebo-controlled study [46], adverse events for a patient group were modest, with most not experiencing a statistically significant increase during the placebo phase. Analyzing behavioral rating scores in a double-blind placebo study for chronic schizophrenia patients revealed variable recovery speeds [47]. Performance on the placebo post-test correlated positively with decisional capacity and neurocognitive abilities but negatively with the severity

of negative symptoms, underscoring the impact of the consent process on understanding research design-related information [48].

To address concerns about ketamine usage in schizophrenia research, Ref. [50] found that administering subanesthetic doses in a controlled environment caused no adverse events and minimal distress for schizophrenic volunteers, indicating no alteration in the course of their illness. In another study design, research on children and adolescents with treatment-refractory schizophrenia determined that a medication-free period of at least four weeks in inpatient settings was safe, highlighting the importance of hospitalization for observation during this phase [51].

Regarding medication adherence, a study discovered that patients viewed financial incentives positively and considered them effective. The study concluded that Money for Medication (M4M) interventions are ethically acceptable under certain conditions, emphasizing the need for additional research on benefits, motivation, and preferred incentive size and duration [49]. Similar to previously discussed ethical issues in research designs, qualitative research methods, typically conducted through participant interviews, also present potential risks. Respondents in this study emphasized that dangers could arise from psychological pressure during information extraction. Additionally, researchers must consider the duration of interviews, as prolonged sessions may trigger symptoms of patient aggression.

G. Research Guidelines

No ethical guideline discussion was identified in the scoping review search results. Similarly, interview respondents in this study admitted the absence of guidelines addressing the ethics of schizophrenia research for both IRB reviewers and researchers, highlighting the necessity for outreach and training in this area.

One interview respondent mentioned that, to the best of their knowledge, the WHO offers training and guidance on human rights in mental health facilities, known as WHO Quality Rights. Respondents believed that such training could enhance researchers' understanding of the rights of individuals with mental disabilities, including those participating in research.

Currently, research reviews rely on the expertise and knowledge of field experts, limited to general medical cases. This creates conflicts due to differing perceptions among researchers regarding the ethics of research involving individuals with schizophrenia. Respondents use various general research guidelines, such as the Helsinki Declaration, Good Clinical Practice (GCP) guidelines, and guidelines from The Council for International Organizations of Medical Sciences (CIOMS) clinical research. However, these guidelines are not specific to severe mental disorders, emphasizing the need for outreach and training to address ethical conflicts.

H. Recommendations

Implementing the principles of beneficence, maleficence, and justice in research necessitates an understanding of the perspectives and experiences of those engaged in the research protocol. Examining ethical motivators and barriers aids in comprehending the decision-making process of individuals with illnesses participating in research [34].

Modifications in information delivery are recommended in research to enhance decision capacity among participants with schizophrenia [48]. For instance, researchers could provide modules to participants. It underscores the importance of viewing capacity as a modifiable trait, even if initially deemed insufficient.

In addressing the challenges of obtaining consent from schizophrenia patients in research, emphasizing insight is crucial [17]. Experts should develop or refine psychometric tools that incorporate insight as a variable. Assessing consent capacity without considering insight is inadequate and poses a risk to the autonomy of the subjects. Respondents in this study proposed that a certification method for researchers involved in studies with participants having mental disabilities like schizophrenia is necessary. This aims to ensure the protection of participants' rights and prevent unethical research practices. Involving ethics commissions facilitating discussions and sharing experiences with researchers, addressing emerging ethical dilemmas is deemed beneficial. To achieve this objective, collaborative efforts among ethics commissions, researchers, and policymakers are essential.

Conclusion

The ethical considerations in research with individuals diagnosed with schizophrenia carry significant importance due to their vulnerability. It is imperative to involve individuals with schizophrenia in the decision-making process, emphasizing dignity and respect throughout the research journey. Researchers bear the responsibility of striking a balance between autonomy, participant welfare, and the ethical assessment of potential risks and benefits. Upholding informed consent, safeguarding privacy and confidentiality, and addressing long-term impacts are crucial aspects. Currently, the lack of specific guidelines for ethical research involving individuals with schizophrenia necessitates ongoing outreach and training. Ethical review boards, adherence to established guidelines, and collaboration with mental health experts are vital in navigating these complexities and ensuring the moral conduct of research with individuals diagnosed with schizophrenia.

Study Limitation

This study offers an overview of ethical considerations in schizophrenia research. Nevertheless, certain limitations should be acknowledged. While the scoping review method provides a broad understanding of the research topic, it may lack in-depth analysis. Subjectivity may impact inclusion criteria and result interpretation, introducing potential bias.

Additionally, this qualitative research, relying on semi-structured interviews, presents a single perspective – that of ethics commission members. Given the complexity of ethical issues, a comprehensive and balanced depiction necessitates insights from various perspectives.

Conflict of Interest

The authors declare that there is no conflict of interest.

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