Ethical Concerns in Schizophrenia Research: Looking Back and Moving Forward

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Introduction

Over the past two decades, the debate over the ethical issues involved in schizophrenia research has evolved considerably in some, but not all, respects. In general, discussions about the most important of these issues have been propelled by developments both in our understanding of schizophrenia and within the field of psychiatry itself, as well as in tandem with the evolution of standards for the protection of human research participants. Although new scientific developments, particularly those having occurred over the last decade, have required researchers to consider new and increasingly complicated ethical conundrums, there are also many issues from years past that remain only partially resolved.

The larger debate on the ethics of experimentation with human subjects essentially began during the post–World War II period with the Nuremberg trials, as the world learned about the experimentation committed by the Nazis on unwilling human subjects. The Nuremburg Code, issued in 1947, was perhaps the first official document that called for the consent of individuals participating in research.1 Here, the basic principles of ethical research were stipulated, including the importance of voluntary consent, the protection of research participants from harm, and the freedom to withdraw from participation. This was followed by the Declaration of Helsinki, adopted by the 18th World Medical Assembly in 1964,2 which added provisions on the importance of research protocols, protection of confidentiality, and professional integrity in the conduct of research and publication of results. Although organizations like the American Medical Association,3 and later the American Psychiatric Association,4 began to amend their ethics codes to address issues concerning research with human subjects, the first federal regulations on research, described in the National Research Act, were not enacted until 1974. This act required the Department of Health, Education, and Welfare to codify regulations for human research. The first broad set of federal guidelines was enacted in 1981 and was based on the principles outlined in the Belmont Report.5 This report identified three major principles in evaluating research: respect for persons; beneficence; and justice. In addition, it delineated the distinction between research and treatment, the assessment of risks and benefits, and the importance of informed consent. Several populations were also identified as needing special protections: children, pregnant women and fetuses, prisoners and, most relevant to schizophrenia research, the institutionalized mentally disabled. Regulations for all but the institutionalized mentally disabled were enacted. Objections to the proposed regulations for the mentally disabled were plentiful and strenuous, and were focused on the fact that the regulations assumed equivalence between incapacity to give an informed consent and mental illness, while neglecting the fact that non-psychiatric conditions can also produce impaired capacity. These recommendations were initially set aside, but were later revisited by several Presidential Commissions.6 Ultimately, no regulations resulted, and their helpfulness was questioned.7–8

Finally, in 1991, the Federal Policy for the Protection of Human Subjects (Title 45, Code of Federal Regulations, Part 46) was adopted across federal agencies and created a uniform approach to human research in the United States.

Ethical concerns about schizophrenia research have been raised, for the most part, because of concerns about the decision-making capacity of the potential research participants. Schizophrenia is a disorder of disturbed thinking, and so it was reasoned that if thinking is disturbed, then capacity to consent is likely to be compromised. As a result, individuals with schizophrenia have long been considered a vulnerable population in the research setting. In this article, we address five main areas where ethical issues have been, and continue to be, particularly prominent in schizophrenia research: 1. competency of participants and informed consent; 2. exclusion of suicidal patients from research on schizophrenia; 3. early intervention with prodromal patients;
of these techniques may in turn lead to a better understanding of precisely which deficits are amenable to remediation. All of these developments will ultimately help researchers make the consent process more accessible to those with severe mental illness. Some issues remain, however, even with the strides that have been made. For example, although there is a relative agreement on the minimum requirements for a determination of competency,24–25 with the exception of the MacArthur Competence Assessment measures (MaCAT-T26, MaCAT-CR27), there are few reliable and valid methods for its assessment.26 Additional data on the measures that exist would be of great value.

Exclusion of Suicidal Patients in Research

In contrast with the longstanding debate on informed consent, an area that has only begun to attract attention at both the professional and federal level is that of the inclusion of suicidal patients in clinical research studies. Suicide and attempted suicide occur at a high rate in individuals with schizophrenia.29 Yet most basic biological and intervention research on schizophrenia excludes those at risk for suicide. Although very few papers in the literature address this issue, researchers have recently begun to question this wisdom of this policy, recognizing that there are very few empirically validated treatments for suicidal patients.30 In recognition of the importance of conducting suicide intervention research and the complex array of clinical and ethical issues associated with these types of studies, NIMH and the federal government have also recently addressed the issue with several high-profile developments. For example, in 1999, the surgeon general of the United States issued a Call to Action to Prevent Suicide,31 and soon thereafter presented a comprehensive assessment of future goals and objectives to combat suicide.32 In 2002, recognizing that the research community was in need of guidelines for the development of protocols that addressed the needs of suicidal patients, NIMH commissioned a panel to study the issue. As a result, the Committee on Pathophysiology and Prevention of Adolescent and Adult Suicide issued guidance for researchers interested in conducting this type of research.33 Finally, in late 2003, NIMH published a Request for Applications for the development of research infrastructure aimed at developing and testing interventions for suicidal patients with mental illnesses (RFA MH-04-003).

Suicidal patients are typically excluded from research protocols because of their high-risk status. While there are certainly important reasons to be cautious about including suicidal patients in clinical research, there are also important, and often overlooked, consequences. Perhaps most importantly, the exclusion of suicidal patients inevitably limits the generalizability of what we learn from intervention and basic biological research. By systematically excluding suicidal patients, we will of
course be unable to empirically demonstrate whether any interventions are effective in treating these patients, who are often among the most severely ill patients that we encounter. Although a percentage of participants in clinical trials for cancer treatment are also at high risk for death, they are not routinely excluded from clinical trials for cancer treatments. In fact, these trials are often conducted with patients for whom other treatments have failed, invariably making the sample representative of the sickest patients, rather than the healthiest. There are certainly good reasons for this methodology, such as the high toxicity of anticancer medications, and the ethical implications of giving them to patients who have a reasonable chance of improvement with existing drugs. But even if we consider these differences, we should not regard high-risk patients with mental illnesses any differently than high-risk medical patients, simply because they have a disorder that may affect their capacity to give informed consent. Ethical and responsible research is routinely conducted with patients in emergency medical situations who are also at times unable to provide consent. In these situations, the FDA's decision to allow a waiver of consent (in certain circumstances) until it can be obtained by a participant or legal representative is an example of an appropriate balance between the need to improve care through research and the need to protect vulnerable populations from exploitation.

This type of blanket exclusion is reminiscent of the routine exclusion of women of childbearing years in the 1960s and 1970s, as well as the exclusion of children until the past decade. While the intent of the exclusion was to protect potentially vulnerable groups, the result of such exclusion was that the research knowledge gained was applicable only to adult males. We eventually discovered that what applied to adult males did not automatically hold true for adult females of childbearing years or for children. It was not until the affected populations or their representatives protested the lack of research knowledge that their exclusion had to be justified rather than presumed. In a similar way, suicidal patients may represent a unique subgroup of schizophrenic individuals. Although the discussion of the ethical implications of including or excluding suicidal patients from research protocols is in its early stages, the needs of this subgroup of very ill patients demand that the dialogue continue.

Medication Withdrawal and Medication-Free Research

In addition to the patient-related issues in schizophrenia research, there has also been debate about the ethics of several research designs typically employed by schizophrenia researchers. The debate over medication withdrawal, medication-free research designs, and placebo use followed the earlier papers on informed consent, but also coincided with several larger developments. One particularly important influence was the allegations of research misconduct that appeared in the popular press after the families of two research participants filed formal ethics complaints against the University of California–Los Angeles, charging that the investigators had inadequately informed the participants of the risks associated with relapse from medication discontinuation (see articles by P. J. Hilts, The New York Times, March 10, 1994, and May 24, 1994). Others were the rediscovery of clozapine in 1989 and the large-scale clinical trials that were necessary for the development and testing of the several atypical antipsychotic medications that are currently available. Interest in medication-free research designs also increased with the rapidly growing interest in the study of cognition in schizophrenia, as well as with neuroimaging researchers. At the national and even international level, the standardization of research methods and ethical considerations was being considered as well, as indicated by the formation of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in 1990.

All these issues seemingly converged in the late 1990s, and resulted in several papers debating the ethics of these approaches. Carpenter et al. published a widely cited paper in 1997 in an effort to respond to some of these issues, and outlined the ethics of medication-research designs. The authors documented the strengths of research designs utilizing either placebo-control or medication-free study period. Although several authors, in response to this publication, voiced the view that more safeguards were necessary to protect research participants during medication-free periods, refinement of the ethical foundations of these methods continued over the next several years through the publication of several additional papers on the issue. Perhaps in response to the strong opinions on both sides of the debate, the ICH published guidelines on placebo use in clinical trials in 2001. Although the guidelines are specifically designed to standardize research practices for new drug development, they have relevance to other medication-free research designs as well. The guidelines state: "When there is no serious harm, it is generally considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort as a result, provided the setting is noncoercive and patients are fully informed about available therapies and the consequences of delaying treatment." Recent research has shown that schizophrenia patients who have demonstrated the capacity to give consent can identify salient aspects of medication-free research designs, including the consequences of relapse and the interventions that may be required, and make informed decisions about participation.

The use of medication-free research designs clearly has direct benefits for researchers through increases in study power, as well as indirect benefits to patients via several
pathways, such as more efficient drug development. However, questions over the implications of adverse events related to these designs remain unanswered. For example, as Fins asked in a commentary on this topic, how are we to judge competency in a patient who becomes incapacitated during a medication-free phase of a research protocol? Does the patient retain the capacity to accurately judge risks associated with the research? Although there is evidence that some aspects of decision-making capacity are stable over short medication-free periods, more research is needed to determine whether capacity is stable over lengthy periods without medication. Also, are there consequences associated with drug discontinuation-associated relapse? Although patients who relapse due to medication withdrawal or placebo use generally return to baseline, given enough time to recover, it is still unknown how repeated episodes of psychotic symptoms affect the brain. For example, there is evidence suggesting that a longer duration of untreated psychosis (DUP) in first-episode patients is associated with a poorer long-term course of illness. However, DUP is also con- founded with a more insidious onset of illness, also a known indicator of a more severe illness course. As research findings continue to accumulate on the implications of medication-free research designs, this debate will certainly continue to evolve.

Early Intervention Protocols

Unfolding mainly over the past ten years has been a new dialogue that is perhaps the most complex and challenging debate the field has faced thus far. The promising, and yet controversial, research on early interventions in schizophrenia has not only presented several new ethical issues that demand consideration, but also rekindled debate on earlier issues. In the early 1990s, articles began to appear suggesting that the course of illness for patients might be less severe if there were intervention during the prodromal phase of illness. These assertions seemed to have followed a period of interest in studying more targeted approaches to medication use during the illness course and were based on several factors, including preliminary findings of beneficial results with early interventions as well as the appearance of atypical medications with more benign side-effect profiles. Although some questions were being raised about the various fundamental assumptions of the approach, such as the predictive validity of prodromal symptoms, several articles appeared in the literature outlining the rationale for early intervention programs and proposing methodology for research programs. In the wake of these early papers, additional researchers began to raise questions about these proposals, thus opening the ethical debate.

Over the past decade, there has been a dramatic increase in the study of early intervention paradigms and the associated aspects of the approach, as well as several preliminary clinical trials with atypical neuroleptics and psychosocial interventions. Along with these developments, a spirited debate on the ethics of early intervention research has unfolded. There have been several excellent reviews of these issues, as well as well-reasoned ethical arguments for and against undertaking these types of studies based on our current scientific understanding. A full review of this literature is beyond the scope of this article, but several main issues have shaped the debate. Most of the ethical concerns fall into four interrelated categories: defining the at-risk population; the issue of false positives and the consequences of intervention for these individuals; problems with stigma and loss of autonomy; and type and duration of intervention/treatment. For example, one of the most important issues concerns how we define the population that is at risk for developing schizophrenia. Although there appears to be a growing consensus on the use of McGorry’s “At Risk Mental State” criteria for the determination of psychosis risk, the fact that studies have shown that patients diagnosed with these criteria have a 40–50% chance of becoming psychotic over 12–24 months raises concerns about inappropriately treating patients who would not otherwise require intervention. Also, there are important concerns about stigmatizing young adults and adolescents who are in a sensitive development period. However, while several authors have emphasized the consequences that can result from giving the label of “prodromal” to an adolescent, McGlashan reported anecdotal findings that approximately 70% of adolescents, when faced with the information about their diagnosis and schizophrenia risk, were accepting of the information to some extent (results from the PRIME clinic intervention study).

As these types of research programs would require even more explicit disclosure about risks and potential benefits, as well as a thorough overview of the limitations of our current ability to accurately predict who will ultimately progress from prodromal or subsyndromal symptoms to full-blown psychosis, our views on informed consent must also continue to evolve. The workshop on Informed Consent for Early Intervention Research sponsored by NIMH in 2000 was an important step toward addressing some of these dilemmas, but more work seems warranted.

Genetic Studies of Schizophrenia

In addition to the issues described above, the rapid progress that is being made in cutting-edge areas will bring with it new ethical challenges. Of particular relevance to schizophrenia is the field of molecular genetics. With estimates of the heritability of schizophrenia ranging as high as 81%, there has long been interest in identifying the genetic influences on schizophrenia. Although...
there were many disappointments in the early quest for single-gene influences on the disorder, several candidate genes have recently been identified, and some of these linkages have been replicated73 (see Owen, Williams, and O’Donovan 2004 for a review of this research). As our understanding of the genes associated with increased schizophrenia risk increases, a range of ethical issues will need to be addressed.

There have been several comprehensive articles written in the past several years that have outlined some of the major ethical issues involved in psychiatric genetics.74–76 Although varied in focus and content, the issues addressed by most authors apply to many psychiatric disorders, and have fallen into three main categories: genetic testing and screening; discrimination based on genetic information; and sharing of information collected for research purposes. Although it is not yet possible to speak about the genetic influences on schizophrenia with certainty, there will come a time when we will have a much fuller understanding of the relationship between genes and the disorder. As our ability to make predictions based on the information obtained in genetic studies increases, other interested third parties will increasingly request access to the information. For example, advancements in our understanding may lead to family members, health insurance providers, or employers requesting information that may raise ethical concerns, such as information on genetic susceptibility to schizophrenia.75 Making this information available to third parties could increase the chances of discrimination against those individuals with the genetic liability. In addition, as we identify genes that increase risk for schizophrenia, there may be increasing pressure to conduct prenatal screenings for these genes.76 In addition to these general issues, which apply to any disorder with potential genetic risk, there are also issues that specifically pertain to schizophrenia. For example, although research has demonstrated that patients with schizophrenia are typically able to understand the risks and benefits of research when they are presented in an accessible manner,17 it is unknown at this point whether patients with schizophrenia, and particularly those with significant cognitive impairment, will be able to fully appreciate the implications of participating in a genetic study. Special care will be necessary to ensure that these patients fully understand the purpose of the study and the reason(s) for collecting genetic material. Information about the genetic influences on schizophrenia will almost certainly guide our treatment choices in the future. As our knowledge of these influences expands, so must our attention to the implications of our findings.

Conclusions

The ethical issues in schizophrenia research are both longstanding (e.g., competency and inclusion/exclusion criteria) and new (e.g., inclusion of suicidal patients and early intervention research). All remain fluid and continue to evolve as new research approaches are developed and as advances are made in our understanding of schizophrenia. An increased emphasis on empirical research focusing on ethical issues will be helpful in advancing these debates, and will prepare us for future dilemmas. In addition to the debates in the literature, inclusion of the affected individuals in the ethical dialogue will be of great value going forward.

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