Do Research Procedures Pose Relatively Greater Risk for Healthy Persons Than for Persons With Schizophrenia?

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Federal regulations governing human research suggest that potential harms and discomforts of research be considered in relation to the risks normally encountered in daily life or in routine examinations. No data regarding relative risks of research exist for persons with schizophrenia. We surveyed psychiatrists (N = 68) to assess their perceptions of the risk associated with 12 research procedures in 2 categories, that is, evaluation- and intervention-type procedures. Psychi- atrists were asked to rate “risks compared to usual daily risks” for people with schizophrenia and, separately, for healthy people. For healthy research volunteers, psychiatrists rated 2 of 5 evaluation procedures and none of the intervention procedures as posing fewer risks than daily life. One evaluation procedure and 2 intervention procedures were rated as similar to daily risks for healthy research volunteers. For volunteers with schizophrenia, psychiatrists rated 4 of the 5 evaluation procedures and 1 intervention procedure as conferring less risk than everyday life. For 1 of 5 evaluation procedures and 5 of 7 intervention procedures, the risks associated with the procedures were centered close to the benchmark for those faced every day by persons with schizophrenia. Psychiatrists in this study viewed research procedure risks as closer to the daily risks encountered by persons with schizophrenia than by healthy persons. Because federal regulations benchmark research studies as “minimal risk” if they are analogous to the usual risks of everyday life, this finding may have important implications for the evaluation of psychiatric protocols.

Key words: research ethics/Institutional Review Board/ research safeguards/placebo/research risk/informed consent

Introduction

The disease burden of schizophrenia, a severe and persistent mental illness affecting 1% of all people, is immense.1–2 The imperative to engage in scientific work to better understand this illness is increasingly recognized.3–5 Toward this end, many hundreds of clinical research protocols involving many thousands of persons with schizophrenia are currently under way in the United States. As with all human studies, federal regulations have been adopted to assure, first, that the dignity and rights of study volunteers are respected and, second, that participants are not exposed to disproportionate risk and are appropriately safeguarded.6–9 A principal safeguard in this system of assurance is prospective review and oversight by Institutional Review Boards (IRBs).6, 8, 10

IRBs are responsible for evaluating the risks associated with human studies. “Minimal risk” protocols are defined in the federal regulations as those in which anticipated harms are not greater than those ordinarily faced in everyday life or during routine examinations.11–12 Studies that are deemed as posing “minimal risk” require less intensive safeguards. They may be considered in an expedited manner or, under certain circumstances, deemed exempt from further IRB review and oversight.13 For these reasons, understanding how people perceive risk in relation to those risks usually encountered in daily life is important.

However, applying the minimal risk threshold raises an as-yet unanswered question: Whose daily life serves as the “benchmark” or referent for judging what is routine? It has been suggested that the minimal risk standard be tethered to the risks normally encountered by healthy adults in daily life.14 As a rationale for raising this issue, consider that ill people may routinely encounter more risks or discomforts and would therefore be subject to less stringent protections if each subject population’s daily lives were referenced when determining what constitutes “minimal risk” for a given study. An evidence-based approach to resolving this dilemma of how to index minimal risk would help inform the discussion of these important issues and would help guide IRBs in their work. This may be particularly important in the present environment, when IRBs, pressed for time and resources,13 must review many protocols, including many

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complex and/or IRBs demonstrate variability in their review practices.15

Interestingly, no objective evidence-based standards for evaluating risk have been developed to guide IRBs in making these assessments.11 In the area of schizophrenia, no published data exist regarding how the risks of research procedures are rated relative to the risks of everyday life—whether the index life is that of a normal healthy person or that of a patient with schizophrenia. This topic has emerged as the subject of great controversy in the long-standing debate on the ethical considerations inherent to scientific study of mental illness.17–20 Concerns about psychosocial distress, physical harm, and the long-term consequences of research procedures such as genetic testing, medication washouts, and symptom provocation, for example, have been raised without resolution.21–25

In this study, we sought to remedy a gap in the schizophrenia research literature on risks relative to everyday risks. We examined psychiatrists’ views of the risks associated with research procedures, relative to everyday or usual risks, for patients with schizophrenia and for healthy persons. We thus use the term relative risk in this article to denote the concept of respondents’ perceptions of the risks of a given procedure relative to the everyday risks faced by 2 populations, specified for the purposes of this study as (1) healthy people and (2) people with schizophrenia. This work examines a customary task that IRB members are asked to perform in the absence of clear guidelines, that is, to estimate research procedure–related risks compared to everyday risks for different subject populations. We hypothesized that psychiatrists—as medical professionals with understanding of the experiences and disease-related burdens of mental illness and as individuals who often serve on IRBs—would assess the relative risks associated with research procedures as greater for healthy individuals than for persons living with schizophrenia.

Methods

For this IRB-approved project funded by the National Institute of Mental Health, we designed a survey to assess psychiatrists’ perspectives on ethically important considerations in mental illness research.26 The instrument incorporated 120 quantitative questions related to ethical considerations in research in general, research safeguards, and research procedures with varying risks. Here we report data on psychiatrists’ perceptions of risk associated with 2 kinds of research procedures (i.e., evaluative and intervention) relative to everyday risks encountered by healthy persons and by persons with schizophrenia. For each procedure, we asked, “How do the risks of being in this study compare with the usual risks that healthy people (or people with schizophrenia) live with everyday?” Data were collected in a manner that protected participant confidentiality; data were then encoded into an electronic database with no identifiers.

Five-point rating scale responses (from 1 = “much less risk,” to 3 = “same risk,” to 5 = “much more risk”) were subjected to repeated-measures multivariate analysis of variance (MANOVA), using procedures (12 research procedures) as 1 repeated measure and population (healthy people versus people with schizophrenia) as a second repeated measure, as well as psychiatrist gender as 1 between-subjects independent variable and participant status as a second between-subjects independent variable. In the analysis, no effects of participant gender or participant status as faculty versus resident were detected.

Results

Participant Characteristics

All 105 attending psychiatrists and psychiatry residents at the University of New Mexico School of Medicine and the New Mexico Veterans’ Health Center were invited to participate. As shown in table 1, the 68 psychiatrists (41 attending physicians and 27 resident physicians) who volunteered (65% response rate) were 46% women and 54% men; 72% married or living with a partner and 28% single, divorced, or widowed; and 19% Hispanic, 13% Asian, 1% black, 74% white, and 12% unreported. Psychiatrist participants had a mean (SD) age of 42.4 (11.0) years.

Comparison of Relative Risks for Research Participant Populations

Figure 1 depicts psychiatrists’ ratings of the relative risks of 5 procedures that may be used in evaluating research participants and 7 procedures that may be employed in an intervention study. A population main effect (F[1,66] = 38.76, p < .0001) showed that psychiatrists rated the procedures overall as having greater relative risks for healthy people (mean = 3.40) than for people with schizophrenia (mean = 2.78, Cohen’s d = 0.86), consistent with our hypothesis.

Comparison of Relative Risks for Procedures

A procedure main effect (F[11,56] = 22.15, p < .0001) indicated that psychiatrists rated relative risks very
However, a population–procedure interaction effect \((F_{[11,56]} = 2.03, p < .05)\) also showed that psychiatrists rated the relative risks for each group differently depending on the specific procedure (population group \(d_s\) ranged from 0.35 to 0.79). The greatest gaps in rated relative risk between healthy people and people with schizophrenia were in 3 of the 12 items: drawing blood for a genetic test, taking head X rays, and inducing temporary symptoms of schizophrenia \((d = 0.77\) to \(0.79, all \ p < .05)\) were all rated as having greater relative risk for healthy people than for patients with schizophrenia, although the rated differences between the populations for the other 9 procedures all showed moderate effect sizes \((mean \ d = 0.56)\) consistently reflecting greater perceived risk for healthy people than people with schizophrenia.

Means within each population for each procedure that deviated more than 0.26 higher or lower than the neutral point of the rating scale \((3 = “same risk as everyday life”)\) were significantly different from everyday risk. For healthy people, psychiatrists rated 2 of the 5 evaluation procedures and 5 of the 7 intervention procedures as posing greater risk than daily life \((range \ of \ m = 3.40 \ to \ 4.20 > “same risk,” p < .05)\). In contrast, psychiatrists rated only 1 intervention procedure (i.e., stopping usual medication for 2 weeks) as posing greater risk than daily life \((m = 3.69 > “same risk,” p < .05)\) for people with schizophrenia.

For healthy people, psychiatrists rated only 2 of the evaluation procedures, filling out questionnaires \((m = 2.26)\) and having a tube of blood drawn \((m = 2.72)\), and none of the intervention procedures as posing less risk than those experienced every day \((all \ p < .05)\). For persons with schizophrenia, psychiatrists rated 4 of the 5 evaluation procedures \((range \ of \ m = 1.83 \ to \ 2.61)\) and 1 intervention procedure (showing an upsetting word or picture; mean \(= 2.36\)) as conferring fewer risks.

**Table 1. Psychiatrist Participant Characteristics \((N = 68)\)**

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*Note: Age—mean years (SD) = 42.4 (11.0). Three respondents did not report Hispanic ethnic status, and 1 did not report marital status.*

**Fig. 1. Psychiatrists’ \((N = 68)\) Ratings of Relative Risks of Research Procedures for 2 Study Populations: Healthy People and People With Schizophrenia.**
than everyday life (all $p < .05$). For healthy people, psychiatrists rated 1 evaluation procedure (head X ray) and 2 intervention procedures (showing an upsetting word or picture and giving a placebo) as similar to daily risks ($m = 2.92$ to $3.23$). For persons with schizophrenia, psychiatrists rated the risks associated with the procedures centered close to the benchmark for those faced every day for 1 of 5 evaluation procedures and 5 of 7 intervention procedures ($m = 2.88$ to $3.25$). No significant differences in response were identified in relation to the gender or to attending versus resident physician role of respondents.

**Discussion**

Psychiatrists in this study assessed research procedure-related risks as being more comparable to the daily risks encountered by persons with schizophrenia than to those encountered by healthy persons. Specifically, when considering the daily lives of people with schizophrenia as the reference point, psychiatrists rated most procedures as conferring less than or about the same level of risk as everyday life. On the other hand, when asked about relative risks for healthy people, respondents more frequently rated risks as greater than those routinely encountered.

Federal regulations benchmark research studies as “minimal risk” if they pose burdens and harms analogous to those normally encountered in daily life, without specifying whose daily lives should be used as the benchmark. This lack of clarity has left a vacuum for IRBs, which may be applying the “minimal risk” standard inconsistently. Thus, the pattern in our data may have implications for understanding how investigators and Institutional Review Board members evaluate psychiatric protocols. It is possible that identical protocols involving the same research procedures may be viewed as “minimal risk,” potentially requiring fewer safeguards, when an ill population is involved and as “greater than minimal risk,” calling for more intensive oversight, when a healthy population is involved. This finding may seem paradoxical, given that mentally ill research participants are often considered a potentially vulnerable population. These data therefore support the need for guidance for IRBs in interpreting the minimal risk definition.

To our knowledge, this is the only study that has explicitly examined ratings of protocol relative risk for patients with schizophrenia. Our respondents indicated that none of the evaluation procedures exceeded the risks of everyday life experienced by people with schizophrenia, though both blood drawn for genetic test and spinal tap exceeded this level of risk when healthy persons’ daily lives were used as the indexed daily life. Most of the intervention procedures were seen as exceeding routine risks for healthy persons, while most fell in the “same as usual” risk range for people with schizophrenia. Only medication “washout for 2 weeks” clearly surpassed everyday risk levels for schizophrenia volunteers, in the eyes of psychiatrists. An analogous study examining how IRB chairs evaluate the risks of pediatric research protocols was performed by Shah et al., however, who found that risk assessments varied depending on a number of factors, including the respondent’s age and the type of procedure. Interestingly, in the case of lumbar puncture without conscious sedation, when the research participant was described as an ill child who had had previous lumbar punctures, the procedure was more often rated as “minimal risk” than when the subjects were described as healthy children.

This novel area of inquiry raises many unanswered questions that require further investigation. How do we interpret these perspectives on relative risk? Is it that research procedures pose unexceptional risk when viewed against the background experience of living with a serious illness, given the burden of disease, with its concomitant emotional, interpersonal, occupational, and economic repercussions? Is it that the notion of risk itself is unclear, particularly in relation to psychosocial as well as biological components? Further, how should those entrusted with clinical care and research endeavors interpret and apply the risk-related concepts articulated in the federal regulations? Federal regulations do not specify exactly whose ordinary daily life is to be used as a benchmark, and controversy exists regarding whether it is meant to be anchored in the life experiences of the study population or of healthy adults. Concerns have been previously expressed about probable inconsistencies in how this standard is applied.

In light of this ambiguity, should measures of absolute risk be developed and tested? Should different standards exist, depending on the qualities of the individual, the illness under study, or the context? Moreover, is risk a matter of perspective? Do clinicians and clinical researchers have certain views, with IRB members, protocol participants, family members, and other stakeholders making different assessments, as some studies suggest? It would be valuable to understand how IRB members in particular make relative risk judgments about real protocols, what sort of training they receive for this task, whether they themselves have concerns about making these judgments, and whether the descriptions and framing of risks and benefits by investigators in protocol descriptions affect IRB members’ assessments. This early project highlights the need for evidence-oriented efforts to clarify such important safeguard-related issues in schizophrenia research.

Our data should be interpreted in light of several project limitations. First, we sampled only psychiatrists at only 1 institution. To what degree the responses of psychiatrists track judgments made by IRB members is unclear. Given that psychiatrists are probably more familiar with the lives of patients with schizophrenia than many, if not most, IRB members, their estimates may be more
accurate. Second, we did not assess how research or clinical care experience may have affected risk judgments, although ratings in our study did not vary by whether the psychiatrist was an attending or resident physician. As this was an exploratory study, we chose to focus on a limited number of questions, rather than broadening the analysis to encompass all possible confounding variables. Third, we did not focus on absolute risks and how they compare for different populations; rather, we explicitly examined a conceptually distinct issue—namely, how professionals who might conduct, review, or refer patients to research studies see relative risks for various research procedures involving 2 different populations. This emphasis was chosen so that our results could help inform ongoing discussion about interpretation of existing federal regulatory requirements. Fourth, our questionnaire did not address the underlying bases for respondents’ relative risk ratings. It is unknown whether respondents view patients with schizophrenia as living with a higher baseline level of risk compared to healthy people or whether there may be other explanations for the divergent relative risk estimates. In addition, in terms of the survey instrument, we provided only brief descriptions of research projects and procedures; we do not know whether relative risk estimates would have differed if we had provided full-length protocol descriptions, such as those reviewed by IRB members. Finally, as IRBs are asked to examine protocols’ risks in relation to anticipated benefits, it would be enlightening to ask about relative risk for protocols with varying levels of anticipated benefits. For these reasons, this project should be seen as exploratory and as a springboard for further empirical efforts in this area.

Acknowledgments

Dr. Roberts wishes to thank the National Institute for Mental Health for support in the form of a KO2 Career Scientist Development Award (1K02MH01918). Dr. Dunn is supported by the National Institute for Mental Health in the form of a K23 Mentored Career Development Award (K23MH66062), as well as by the Greenwall Foundation. We also gratefully acknowledge support from the National Institute of Drug Abuse (1R01DA13139). We thank Mr. Mark Talatzko for his assistance in preparing this manuscript.

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