

Willingness and Competence of Depressed and Schizophrenic Inpatients to Consent to Research

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In this study, the willingness of psychiatric inpatients to volunteer for research and their capacity to consent to and distinguish between protocols offering different levels of risk and benefit were assessed. Twenty-two inpatients with major depressive disorder, 21 inpatients with schizophrenia, and 21 community control subjects were asked to consider participation in a lower-risk study offering the potential for direct medical benefit and a higher-risk study offering no direct medical benefit. Consent-related capacities were assessed with the MacArthur Competence Assessment Tool-Clinical Research. Depressed inpatients, while having a greater degree of impairment than control subjects, still demonstrated relatively high decision-making capacity and were able to distinguish levels of risk between studies. Their pattern of preferences did not differ from control subjects. However, they were more likely to decline to participate in the research, being six times more likely to decline the lower-risk study and 1.4 times more likely to decline the higher-risk study. Schizophrenic subjects demonstrated greater impairments in decision-making capacity and were even more likely than depressed subjects to decline to participate.

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Public confidence in the adequacy of protection of human subjects in biomedical research has been shaken recently in the face of several highly publicized instances of coercive or misleading recruitment practices, financial and ethics-related conflicts of interest on the part of study investigators, and adverse events that occurred following potentially inadequate disclosures of risk during the informed-consent process.^{1–4} Although respect for the safety of human subjects is an ethical obligation in all areas of biomedical research,^{5,6} psychiatric research has received disproportionate attention from the news media and federal advisory bodies^{7–9} out of concern that individuals with mental disorders are at higher risk of

being exploited because of the effect of mental illness on decision-making capacity.^{9–11}

Many psychiatric researchers have taken issue with this assumption. They have argued that many patients with mental disorders retain substantial decision-making capacity and that to single out research involving the “mentally ill” for additional regulatory safeguards reinforces social stigma about mental illness, is impractical and expensive, and could impede important psychiatric research.^{12–16}

Severe mental illness certainly may prevent some individuals from adequately understanding and appreciating the risks that they are assuming by entering into research protocols or from rationally weighing potential risks against potential benefits. For example, patients with schizophrenia may experience delusions, apathy, lack of insight, and impaired memory and mental flexibility, all of which could contribute to impaired decision-making capacity. Similarly, more severe presentations of major depressive disorder, even when not associated with psychotic symptoms, can impair individuals’ concentra-

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tion and abstract reasoning abilities and also can be associated with nihilism and a decreased degree of concern for personal well-being.¹⁷⁻¹⁹ Further, while many research volunteers fail to appreciate important differences between clinical research and clinical treatment (for example, that the former may offer no medical benefit, may be “double-blinded,” and may follow a fixed protocol that cannot be tailored to a subject’s individual needs),²⁰⁻²² it is possible that mentally ill volunteers have even more difficulty making such distinctions, particularly when the research is conducted in the inpatient setting alongside clinical care.

In 1998 the National Bioethics Advisory Commission recommended the institution of additional federal regulations aimed at protecting research subjects with mental disorders that could affect their decisional capacity. The Commission recommended that studies that subject such individuals to “greater than minimal risk” be required to utilize an independent evaluator who would assess the capacity of all prospective participants. Further, it recommended that research studies not offering the potential for “direct medical benefit” be required to obtain the approval of an independent federal review board. With regard to the latter, the Commission expressed particular concern about studies involving the discontinuation of medication²³⁻²⁵ or the administration of pharmacological agents that might exacerbate symptoms of an individual’s illness.^{26,27}

However, whether patients with acute psychiatric illness are in fact more likely to consent to higher-risk studies than are other individuals has received little empirical study. Nor have researchers addressed whether mentally ill individuals who agree to participate in research are more impaired in their decision-making capacity than are those individuals who decline to participate. While recent research indicates that approximately three-quarters of acutely ill inpatients with major depressive disorder and half of acutely ill inpatients with schizophrenia remain capable of making informed decisions about their clinical treatment,²⁸ similar studies have not been performed regarding such individuals’ capacities to make decisions about participating in research, the latter of which may be the more challenging task.

The present study therefore explored the willingness and capacity of inpatients with major depressive disorder and schizophrenia to provide informed consent to participation in research. We addressed the

following questions: (1) Are acutely ill psychiatric inpatients more likely than community control subjects to volunteer for research protocols? (2) Are they more impaired than community control subjects in their competence to consent to research? (3) Are those patients who agree to participate in research more impaired than those who decline to do so? (4) Are psychiatric inpatients more likely than community control subjects to volunteer for higher-risk studies that offer no direct medical benefit?

Methods

The study was approved by the institutional review board and did not employ deception or misleading statements. Subjects included volunteer patients and community control subjects. Data were collected from two groups of psychiatric inpatients at the University of Virginia Health System. The first group consisted of patients admitted with the diagnosis of major depressive disorder (“depression group”). The second group consisted of patients admitted with the diagnosis of schizophrenia (“schizophrenia group”). A third group consisted of nonclinical subjects residing in the community (“control group”).

A doctoral-level research assistant, not involved in the subjects’ ongoing clinical care, approached all subjects within 48 hours of admission. Community control subjects were approached by the same research assistant. All potential participants were informed that the current study would involve hearing about two different human research protocols and then answering questions that would test their understanding of this information. In addition, they were explicitly informed that their actual consent to participate in the two protocols was not being sought at this time, only their opinion as to whether they would be likely to consent to participation in either, both, or neither of the protocols were they to be approached in the future. The interview could take up to 90 minutes to complete, although subjects could terminate the interview at any time. All subjects would be paid \$20 for their time.

Of those who were approached, 29 percent (6 of 21) of the schizophrenia patients, 91 percent (20 of 22) of the mood disorder patients, and 95 percent (20 of 21) of the community control subjects agreed to participate. All inpatients who agreed to participate in the study were administered the Structured Clinical Interview for DSM-IV (SCID) to confirm

that they met the diagnostic criteria for major depressive disorder or schizophrenia.²⁹ Symptom severity was assessed using a 17-item version of the Brief Psychiatric Rating Scale (BPRS) for the schizophrenia group,³⁰ the Beck Depression Inventory-II (BDI) for the depression group and control group,³¹ and the Mini-Mental State Exam (MMSE) for all groups.³²

Subjects were presented with detailed informed-consent information for two research protocols. The first study, which offered lower potential risk and the potential for medical benefit (“drug study”), was a six-week, placebo-controlled, phase III pharmaceutical trial, involving either a new antidepressant drug (for the depression and control groups) or a new antipsychotic drug (for the schizophrenia group). Subjects were informed that this agent had been studied in animals and healthy human volunteers and that the primary objective of the present study would be to determine the drug’s safety and efficacy in a clinical population. Subjects would have a 50 percent chance of receiving drug or placebo. The study would include an initial physical examination and blood and urine testing, as well as clinical assessment and serologic tests at weekly intervals. The consent information emphasized that this was a research project and not clinical treatment. Potential benefits included that subjects’ participation might contribute to the availability of better treatments for other patients in the future, as well as the possibility that they themselves might benefit from taking the drug in the course of the study. Potential risks included that subjects might experience side effects from the study medication, might experience discomfort due to blood draws, and might experience clinical deterioration, either while taking the study medication or while taking placebo.

The second study, which offered higher potential risk and no direct medical benefit (“ketamine study”), involved the research subjects’ receiving a positron emission tomographic (PET) scan while simultaneously performing various cognitive tasks. The entire procedure would last approximately three hours. Prior to the procedure, subjects would receive an intravenous catheter. In the course of the study, they would be exposed to a low dose of radiation and also would be administered a low dose of intravenous ketamine. Subjects were informed that high doses of ketamine cause general anesthesia, while lower doses can cause dissociative symptoms in healthy volunteers. Some patients with schizophrenia who had

been administered lower doses also had experienced brief increases in symptoms of their illness, such as hallucinations or disorganized thinking. In rare instances, they had experienced a worsening of psychiatric symptoms that had lasted from 8 to 24 hours. No subjects in earlier studies had experienced a more prolonged psychotic response due to ketamine. Clinical staff would help them to cope with such a response if it did occur. Subjects also were informed that the main purpose of the study was to gain a better understanding of the pathophysiology of their illnesses (schizophrenia or major depression), not to provide clinical treatment, and that neither the ketamine, the radioactive water, nor the PET scan image was expected to offer any direct clinical benefit to them. The only benefits of the study were that researchers might learn more about the subject’s illness, thereby potentially contributing to the development of more effective treatments. The risks included the possibility that symptoms of the illness might temporarily worsen, that they would be exposed to low-level radiation, that they might experience discomfort from intravenous injections, and that they might become frustrated or bored while lying still and having to repeat various tasks.

In the course of explaining each of the two protocols, subjects were administered the MacArthur Competence Assessment Tool—Clinical Research version (MacCAT-CR).³³ The MacCAT-CR is based on a similar instrument designed to assess competence to consent to clinical treatment.²⁸ Using a semistructured interview format that can be individualized for specific research protocols, the MacCAT-CR assesses the four most commonly accepted components of decision-making capacity: (1) understanding of disclosed information about the nature of the research project, (2) appreciation of the effects of research participation on subjects’ own life situations, (3) reasoning about participation, and (4) ability to communicate a choice about participation.

The MacCAT-CR was individualized for both research protocols. Each question was scored zero, one, or two on the basis of objective criteria. Two raters independently scored all interviews and resolved any differences through later discussion. Thirteen questions in the “understanding” section (maximum score of 26) focused on information concerning the research study’s purpose, procedure, benefits, risks, and alternative (e.g., “What is the purpose of the research project I described to you?”). Three “appre-

Table 1 Demographic Characteristics of Depression, Schizophrenia, and Control Group Subjects

Characteristic	Depression (n = 20)	Schizophrenia (n = 6)	Control (n = 20)
Sex (% female)	65.0	33.3	60.0
White (%)	85.0	83.3	80.0
African-American/ Other (%)	15.0	16.7	20.0
Age (y)	34.1 (6.9)	40.0 (7.8)	41.1 (10.3)
Education (y)	14.0 (3.5)	15.5 (5.1)	15.9 (3.5)
Number of previous hospitalizations (%)			
Never	40.0	0.0	N/A
Once	25.0	16.7	N/A
Twice or more	35.0	83.3	N/A
Previous research participation (%)	20.0	66.7	—

Age and education are expressed as the mean \pm SD.

ciation” questions (maximum score of six) focused on subjects’ beliefs about whether what they had been told actually applied to them (e.g., “Do you believe that you have been asked to be in this study primarily for your benefit?”). Four “reasoning” questions (maximum score of eight) centered on subjects’ abilities to compare research participation with other treatment options and to describe the everyday consequences of participation versus nonparticipation (e.g., “What is it that makes [the subject’s preferred option] seem better than [the nonchosen option]?”). One choice question (maximum score of two) assessed whether the patient could clearly express a choice about participating in research.

Data Analysis

Descriptive statistics were computed to describe the groups. To address each research question, separate analyses were conducted as appropriate. Chi-square tests were used to compare categorical data across the three groups. One-way analysis of variance and multivariate analysis of variance were used to compare the mean scores for significant differences among continuous variables. Further, univariate analyses were used to test group difference followed by the Scheffé *post hoc t* test, as appropriate.

Results

Subject Characteristics

The groups did not differ in their demographic characteristics with the exception of age. The mean age for the total sample was 37.9 years (SD = 9.18). Subjects in the depression group were seven years

younger on average than subjects in the schizophrenia and control groups, ($F(2,43) = 3.97, p < .04$). Subjects were 41 percent male and 59 percent female. Most were white (83.6%), the remainder being African-American (13%), or of other backgrounds (4.3%). Educational level did not differ among the three groups, with the mean number of years of education being 15 (SD = 3.77) (Table 1).

More subjects in the schizophrenia group (66.7%) had participated in previous research than had subjects in the depression group (20%, $\chi^2(1, n = 26) = 4.72, p = .05$). Subjects in the schizophrenia group also were more likely to have received inpatient psychiatric treatment previously than were subjects in the depression group ($F(2,24) = 19.94, p < .04$).

On the Beck Depression Inventory-II (BDI), the mean score for subjects in the depression group was 40.95 (SD = 9.5), consistent with severe depression, while the mean score for the control group was 3.3 (SD = 4.16), consistent with minimal depression. Schizophrenia subjects indicated a degree of severity of their psychotic symptoms typically found among inpatients, with scores on the Brief Psychiatric Rating Scale ranging from 36 to 47.

Are Psychiatric Patients More Likely Than Community Control Subjects to Volunteer?

Psychiatric patients in this study were less likely than community control subjects to volunteer for research protocols. Chi-square tests were used to determine patterns of volunteering for the drug and/or ketamine studies (yes/no, no/yes, yes/yes, or no/no) by group (control, depression, and schizophrenia). Table 2 shows that control subjects, depression subjects, and schizophrenia subjects demonstrated different patterns of consent ($\chi^2(6, n = 46) = 20.52, p = .002$). All control subjects (100%) consented to

Table 2 Distribution of Consent for the Drug Study Only, Ketamine Study Only, Both Studies, or Neither Study Among Control, Depression, and Schizophrenic Subjects

	Depression (n = 20)*		Schizophrenia (n = 6)		Control (n = 20)†	
	%	n	%	n	%	n
Drug study only	25	5	0	0	55	11
Ketamine study only	10	2	0	0	10	2
Both studies	15	3	17	1	35	7
Neither study	50	10	83	5	0	0

* $\chi^2(6, n = 46) = 20.52, p = .002$ for control, depression, and schizophrenia.

† $\chi^2(6, n = 40) = 13.85, p = .003$ for control & depression.

Patient Competence to Consent

Table 3 Scores on the MacArthur Competence Assessment Tool—Clinical Research Version for Control, Depressed, and Schizophrenic Participants by Agreement to Participate in the Drug Study

	Control (n = 20)		Depression (n = 20)		Schizophrenia (n = 6)	
	Yes (n = 18)	No (n = 2)	Yes (n = 8)	No (n = 12)	Yes (n = 1)	No (n = 5)
Understanding score						
25–26	83.3	100.0	87.5	66.7	—	—
23–24	5.6	—	12.5	25.0	100.0	60.0
21–22	11.1	—	—	8.3	—	—
20	—	—	—	—	—	20.0
<20	—	—	—	—	—	20.0
Appreciation score						
6	100.0	100.0	100.0	66.7	—	40.0
5	—	—	—	33.3	100.0	—
4	—	—	—	—	—	—
3	—	—	—	—	—	20.0
2	—	—	—	—	—	20.0
1	—	—	—	—	—	20.0
Reasoning score						
7–8	100.0	100.0	75.0	58.3	—	40.0
5–6	—	—	12.5	33.3	100.0	20.0
2–4	—	—	12.5	8.3	—	20.0
1	—	—	—	—	—	20.0

Data are percentage of subjects who did or did not agree to participate, according to score.

participate in one or both studies, compared with 50 percent of subjects in the depression group and 17 percent of subjects in the schizophrenia group. Among the 10 subjects in the depression group who consented to participate in one or both studies, half elected to participate only in the drug study. Similarly, 55 percent of the control subjects chose the drug study alone. Two subjects in the control group and two in the depression group chose the ketamine study alone. Among the six schizophrenia group subjects, five declined to participate in either study. The single schizophrenia subject who agreed to participation in research chose to participate in both studies.

Are Psychiatric Patients More Impaired in Their Competence to Consent?

Psychiatric patients in this study were somewhat more impaired in their competence to consent to participation in research than were community control subjects. Those in the schizophrenia group were more impaired than those in the depression group. All subjects demonstrated an ability to express a

choice as to whether they wished to participate in either research study, and most subjects also performed well on the other three MacCAT-CR subscales (understanding, reasoning, and appreciation). Table 3 shows the distribution of scores for each of the three consent capacities by group and by decision to consent to the drug study (with higher scores indicating greater capacity). Table 4 shows the distribution of scores for each of the three consent capacities by group and by decision to consent to the ketamine study.

Most control subjects scored in the highest category for all three capacity scores in both study conditions. Their poorest performance was in the area of understanding of the conditions of the drug study, with two “consenters” scoring in the 21- to 22-point range (maximum score = 26). Depression group subjects also tended to score in the highest range for all three consent capacities, for both research studies. The poorest performance was in reasoning in those subjects who declined to participate in the drug study, with 58 percent of subjects receiving the top score (7–8), 33 percent ($n = 4$) falling in the second-best category (5–6), and 8.3 percent ($n = 1$) falling

Table 4 Frequency Distribution on the Three Subscales of the MacArthur Competence Assessment Tool—Clinical Research Version for Control, Depressed, and Schizophrenic Participants, by Agreement to Participate in the Ketamine Study

	Control (n = 20)		Depression (n = 20)		Schizophrenia (n = 6)	
	Yes (n = 9)	No (n = 11)	Yes (n = 5)	No (n = 15)	Yes (n = 1)	No (n = 5)
Understanding score						
25–26	100.0	90.9	60.0	86.7	—	—
23–24	—	9.1	40.0	6.7	100.0	40.0
21–22	—	—	—	6.7	—	20.0
20	—	—	—	—	—	—
<20	—	—	—	—	—	40.0
Appreciation score						
6	77.8	100.0	80.0	73.3	—	20.0
5	22.2	—	20.0	26.7	100.0	20.0
4	—	—	—	—	—	20.0
3	—	—	—	—	—	20.0
2	—	—	—	—	—	20.0
1	—	—	—	—	—	—
Reasoning score						
7–8	77.8	100.0	60.0	66.7	—	20.0
5–6	22.2	—	20.0	26.7	—	20.0
2–4	—	—	20.0	6.7	100.0	40.0
1	—	—	—	—	—	20.0

Data are as described in Table 3.

into the next to lowest category (2–4). The next worst performance among subjects in the depression group was in understanding and reasoning among those who elected to participate in the ketamine study. Although 60 percent of these subjects received scores in the top range for understanding and reasoning, the remaining 40 percent ($n = 2$) scored in the second-best category (23–24) for understanding and in the second (5–6)- and third-level (2–4) category ranges for reasoning.

Subjects in the schizophrenia group rarely achieved perfect scores for any of the three consent capacities related to either the drug study or the ketamine study. The single subject who agreed to participate in both studies scored in the second highest category range for every capacity except reasoning in the ketamine study (where the subject fell into the next to lowest category, i.e., two to four). The five subjects who declined to participate in both studies were fairly evenly distributed among the full range of capacity scores. The two subjects with the most severe levels of psychosis (scores of 47 on the BPRS) also received the lowest scores on the three capacities.

Are Those Patients Who Agree to Participate in Research More Impaired?

Capacity-to-consent scores of those subjects who agreed to participate in research were not lower than those of subjects who declined to participate. Mean consent capacity scores between groups were compared using a two \times three multivariate analysis of variance (MANOVA). The independent variables were decision to participate (yes and no) and group (depression, schizophrenia, and control). The three capacities to consent (understanding, appreciation, and reasoning) were used as dependent variables. Separate MANOVAs were run for the capacity-to-consent scores for both the drug and ketamine studies.

The first MANOVA was used to assess group differences in capacity related to the drug study. It showed a significant main effect of group in the drug study condition (Wilks' $F(6,76) = 3.02, p < .01$). Univariate analyses showed that groups were significantly different in all three capacities to consent: understanding ($F(2) = 6.30, p < .05$), appreciation ($F(2) = 6.30, p < .05$), and reasoning ($F(2) = 6.30, p < .05$). Scheffé *post hoc t* tests revealed that the depression patients scored significantly lower in reasoning than the control subjects ($p < .02$). Schizo-

phrenia patients scored significantly lower on understanding, reasoning, and appreciation than both depression and control subjects (all $p < .05$). However, the main effect for decision to participate was nonsignificant, as was the interaction effect for group by decision to participate. Capacity to consent was not related to decision to participate in the drug study in any group.

The second MANOVA assessed group differences in capacity related to the ketamine study. This analysis also revealed a significant main effect for group (Wilks' $F(6,76) = 4.18, p < .001$). Univariate analyses showed that groups were significantly different in understanding ($F(2) = 8.00, p < .001$), appreciation ($F(2) = 7.27, p < .05$), and reasoning ($F(2) = 9.42, p < .001$). Scheffé *post hoc t* tests revealed that schizophrenia patients scored significantly lower on all three of the capacity tests than depression and control subjects (all $p < .001$). Again, however, consent to participate and the interaction of group by decision to participate both were nonsignificant. Capacity to consent was not related to decision to participate in the ketamine study for any group.

In the depression group, a one-way analysis of variance (ANOVA) was used to test for differences in level of depression (as measured by the BDI) based on four levels of research participation preference (drug study only, ketamine study only, both studies, or neither study). No differences were found in level of depression by level of participation preference ($F(3) = 1.08, NS$). Therefore, depressed subjects who chose to participate in research studies, including higher risk studies offering no direct medical benefit, were not more severely depressed than were patients who declined to do so.

Are Psychiatric Patients More Likely to Agree to Higher Risk Studies With No Direct Medical Benefit?

Psychiatric patients in this study were no more likely to volunteer to participate in a higher-risk study with no medical benefit than were community control subjects. We compared psychiatric subjects and control subjects with regard to their pattern of agreeing to or declining to participate in the two research protocols. Control and depressed subjects who agreed to participate in either or both protocols were compared, based on three possible levels of consent ("drug study only," "ketamine study only," and "both studies"). Subjects who declined to participate

in either study were excluded from this analysis to assess directly the depression group subjects' ability to distinguish between the drug and ketamine protocols independently from their overall greater reluctance to participate in either study. In addition, the single schizophrenia subject who consented to both studies was excluded from this analysis.

No significant difference was found in study preference by group ($\chi^2(2, n = 30) = .58, NS$). For both groups, "drug study only" was the most common preference (50% of subjects in the depression group versus 55% of subjects in the control group), followed by "both studies" (30% in the depression group, 35% in the control group) and "ketamine study only" (20% in the depression group, 10% in the control group).

Discussion

This study found that psychiatric inpatients currently being treated for depression and schizophrenia were not more likely to volunteer to participate in research than were community control subjects. Rather, the opposite proved to be the case. Depressed subjects were six times more likely to decline participation in a phase III pharmacology trial (60% versus 10%) and 1.4 times more likely to decline participation in a functional neuroimaging study involving the administration of a "pharmacologic challenge" (75% versus 55%) than were control subjects. Subjects with schizophrenia were even more likely to decline participation in research, with 96 percent of the patients that we approached declining any type of research involvement altogether. Seventy-three percent (16 of 22) refused to consider participating even in the present study, while of the six patients who agreed to participate, only one agreed to consider enrolling in either of the two proposed research protocols.

Depressed individuals who agreed to participate in a research protocol were not found to be more impaired in their decision-making capacity than depressed individuals who declined to do so, and they were no more likely to agree to participate in higher-risk studies offering no potential for direct medical benefit than were control subjects.

While these findings in themselves do not provide conclusive evidence that individuals with mental illness are at no greater risk for inappropriate research recruitment than are individuals without mental illness, neither a greater severity of psychiatric symp-

toms nor a greater degree of impairment in decisional capacity was associated with a greater propensity to agree to participate in either of the research protocols. Further, a comparison of depressed subjects and control subjects demonstrated equivalent patterns of preferences, suggesting that the depressed patients' symptoms did not have a significant impact on the nature of their choices beyond possibly contributing to their greater tendency to decline any involvement in research in general. (In the case of the schizophrenia group, the small number of patients prevented our performing a similar analysis.)

Subjects with depression and schizophrenia scored somewhat lower on standardized measures of decision-making capacity than did control subjects, with members of the schizophrenia group demonstrating a greater degree of impairment. This finding is consistent with earlier studies that have examined the capacity of psychiatric inpatients to make decisions about clinical treatment.²⁷ In that context, evidence of some degree of decisional impairment was found in about a quarter of depressed patients and half of schizophrenic patients. Our finding that decisional capacity among the subjects with depression was not associated with the severity of depressive symptoms also comports with those of earlier studies that have suggested that decisional capacity is associated less with the severity of an individual's depressive or psychotic symptoms than with illness-related deficits in cognitive and reasoning abilities.^{28,34-38}

The capacity of patients with schizophrenia to consent to participate in research has received the most attention in the ethics literature, and we therefore included this group in our pilot analysis, despite the small sample size. Our finding that individuals with schizophrenia were much less likely to volunteer for biomedical research than were other individuals, while preliminary, is bolstered by the difficulties we faced merely in recruiting schizophrenic inpatients for the present study, a far less daunting protocol than the two protocols that we were asking the subjects to consider. The present study required only that the subject engage in a brief interview and also offered financial compensation for their time. Despite this, of 21 inpatients with schizophrenia whom we approached, only 6 (29%) agreed to participate, versus 20 (91%) of 22 mood-disorder patients and 20 (95%) of 21 community subjects, all of whom were approached by the same research assistant.

Perhaps those individuals with schizophrenia who declined to participate in the present study did so as a result of greater symptom severity, for example greater suspiciousness or social withdrawal. As our study was conducted on a psychiatric unit that does not routinely assess symptom severity using standardized research measures, we could not formally test this hypothesis. However, consistent with this theory, almost all of the individuals with schizophrenia who declined to participate in the present study refused even to engage in a basic exploratory discussion, typically commenting: "I'm not interested," "I don't know," or "I don't need to do it." One individual who did engage in an initial conversation became much more suspicious and refused to participate any further when asked to sign a consent form.

Our finding that patients with depression or schizophrenia are less inclined to volunteer for research than are individuals without these conditions has several important implications. First, concerns that individuals with depressive or psychotic symptoms will be disproportionately recruited into higher-risk research as a result of their symptoms may be excessive. Consistent with earlier studies,³⁴⁻³⁸ we found that a high proportion of individuals with mental disorders retain the capacity to make discerning choices with regard to research participation, even in the midst of an episode of illness severe enough to necessitate inpatient hospitalization.

Second, the present study also assessed what Roberts⁴¹ has termed the "capacity for volunteerism." This latter capacity includes not only decision-making capacity but also an individual's ability to make "authentic" decisions that truly reflect his or her core values, prior history, and present situation. A variety of factors can affect whether an individual chooses to volunteer for a research protocol, including developmental factors, psychological issues, cultural or religious values, and the presence of external coercive pressures. In addition, symptoms of mental illness (e.g., nihilism, delusions, impaired concentration, or memory) may affect an individual's degree of volunteerism, shifting it in either a positive or negative direction. Our finding that individuals with depression and schizophrenia were less likely to volunteer for research than were non-ill individuals suggests that the influence of their illness on their capacity for volunteerism may be predominantly in the negative direction.

An alternative explanation is that individuals who have a serious illness are less inclined than are control subjects (asked to imagine themselves as having that illness) to take risks with their health, such as forgoing standard therapy in favor of an experimental protocol. Future studies might attempt to distinguish between these two hypotheses. For example, volunteerism could be compared between individuals with a mental illness who currently are in the midst of an acute exacerbation versus individuals with the same illness currently in remission. Similarly, individuals with a serious medical illness that does not directly affect mood and cognition (e.g., nondepressed individuals with coronary artery disease) could be compared with community control subjects.

Third, our finding that subjects with depression and schizophrenia were less likely to volunteer for research protocols than were community control subjects may be relevant when considering the generalizability of research findings to actual clinical populations. It is commonly acknowledged that many research trials have limited external validity due to their strict recruitment criteria. For example, an antipsychotic or antidepressant medication found in clinical trials to be superior to placebo may demonstrate much lower effectiveness in "real world" settings, where excluded symptoms (e.g., suicidality) and excluded comorbid psychiatric and medical conditions are the rule rather than the exception.⁴² The present study suggests that another factor that should be considered when attempting to interpret the validity of research studies is the possible presence of subtle factors that influenced whether only a particular subset of individuals with the illness in question volunteered for the protocol.

For example, it is likely that recruitment rates are lower in research involving some clinical conditions (e.g., acute mania, first-break schizophrenia) than in research involving other conditions (e.g., generalized anxiety disorder, dysthymic disorder). Despite this, the nature of this "recruitment bias" and how and why it varies between various psychiatric disorders has received scant attention. This pilot study suggests that recruitment may be much more difficult in protocols involving schizophrenia than in those involving depression, such that researchers may need to exercise greater caution when drawing conclusions from a study involving schizophrenia. This subject is deserving of further research.

Fourth, qualitative analysis of the reasons offered by subjects in the present study for preferring one protocol over another raises questions about the validity of distinctions that have been made between research that offers the possibility of “direct medical benefit” and research that does not.⁹ Although the majority of subjects in both the depression and control groups agreed to volunteer for the pharmaceutical study (which presumably offered lower risk as well as the potential for direct medical benefit) but not for the ketamine challenge study (which presumably offered higher risk and no potential for direct medical benefit), a minority of subjects expressed the exact opposite preference (i.e., to participate only in the ketamine study). These individuals were not found to be more impaired in their decision-making. Rather, out of altruism, they were willing to risk a brief exacerbation of their symptoms, but they were unwilling to forgo standard treatment and risk longer-term clinical deterioration while receiving either a placebo or an experimental drug over several weeks. Our finding that patients were capable of making such distinctions is consistent with those of previous studies suggesting that psychiatric patients often can offer highly discerning opinions with regard to such matters.^{24–26,43}

The present study had several limitations. First, this was a pilot study involving a small number of patients, and replication with larger samples is needed. Second, our finding of impaired decisional capacity among acutely ill psychiatric inpatients probably overestimates the degree of impairment encountered by researchers conducting actual pharmaceutical or neuroimaging protocols, particularly in the outpatient setting. For example, outpatient research subjects with moderate, nonpsychotic depression who were examined during the course of an actual clinical protocol generally performed quite well on the MacCAT-CR.³⁶ Further, although we approached all patients who had been admitted to an inpatient psychiatric unit with a diagnosis of major depressive disorder or schizophrenia, researchers typically approach a patient only after having consulted with the patients’ treating clinicians to identify those particular patients who are most likely to meet the study’s inclusion and exclusion criteria, are likely to be willing to volunteer for the study, and are likely to be capable of providing informed consent. They also might delay approaching more severely ill patients until the patients have been at least partially treated.²⁸ Many

investigators also recruit patients from a pool of chronically ill individuals who have been previously identified due to having already participated in other protocols. Had we engaged in similar prescreening practices, our patient sample may have demonstrated greater decisional capacity and a greater willingness to agree to research participation.

Third, we did not investigate the effect of supplying additional education on either decisional capacity or willingness to volunteer for research. Several studies have found that such efforts can bolster the ability of some potential research subjects to provide adequate informed consent.^{34,35,44}

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