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Participants with schizophrenia retain the information necessary for informed consent during clinical trials

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Abstract

Objective—Cognitive impairment is a characteristic of schizophrenia. This impairment may affect the retention of information required for ongoing knowledgeable participation in clinical trials. This study monitored retention of study-related knowledge--including assessment of therapeutic misconception--in people with stable, DSM-IV schizophrenia during participation in placebo-controlled clinical trials of adjunctive agents. Stability was defined as being on an antipsychotic with no change in medication or dose over the previous 4 weeks.

Method—Individuals enrolling in one of seven clinical trials were approached for participation. Participants came from research clinics and community mental health centers. At baseline, clinical trial consent forms were reviewed and study knowledge assessed. Participants were randomized to follow-up assessments at weeks 1, 4, and 8; weeks 4 and 8; or at week 8 only. Clinical trial consent forms were not re-reviewed at any follow-up visit.

Results—Fifty-nine participants were enrolled; analysis included 52 participants with at least one follow-up visit. Study knowledge did not decrease meaningfully in any group. Therapeutic misconception was not observed in participants during the study. The group assessed most

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Conflict of Interest Statement

Drs. Fischer, McMahon, Appelbaum, and Carpenter and Mr. Slack and Mr. Meyer declare no potential conflict of interest relevant to the contents of this paper.

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frequently demonstrated significant improvement over baseline (t_{44}= 3.43, p= 0.001). Retention of study knowledge was not related to symptoms, but had a weak correlation with cognitive capacity (R= 0.28, p= 0.07). Performance did not differ between participants from research clinics and those from community mental health centers.

Conclusions—Clinically-stable people with schizophrenia enrolling in a placebo-controlled adjunctive medication study, once determined to have capacity to consent to a clinical trial, retained appropriate study knowledge for at least 8 weeks. In the absence of a specific reason to suspect a loss of decisional capacity, there appears to be no need to routinely re-evaluate participants during this type of clinical trial.

Keywords

consent; schizophrenia; clinical trials; ethics; capacity; therapeutic misconception

As a group, people with schizophrenia perform worse than healthy controls on assessments of capacity to consent[1, 2]. However, there is considerable variability in individual performance within this group[3] and previous work has shown convincingly that many people with schizophrenia have capacity to consent to research[4, 5]. Furthermore, people with schizophrenia who perform poorly on an initial assessment of decisional capacity can often considerably improve with the aid of training or other interventions[4, 6, 7]. A remaining concern is whether people with schizophrenia, once entered into a study, retain enough information about the study to participate knowledgeably—including making informed decisions about whether to terminate their involvement—as the study progresses[8].

Stroup and colleagues monitored changes in capacity to consent from enrollment to 6 and 18 months during the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[9]. Using the MacArthur Competence Assessment Tool—Clinical Research (MacCAT-CR)[10], they found nearly all (96%) of the 1,158 participants retained capacity to consent during the CATIE study. However, the CATIE study used FDA-approved antipsychotics, for their approved indication, without a placebo arm, and with clinicians allowed to adjust doses according to participants' clinical needs[11]. Despite blinding and randomization, the main study parameters were very similar to what the participants experience in clinical care--in fact, one of the strengths of the CATIE study was this direct parallel to clinical care. As a result, however, it is unclear that the findings of Stroup et al. can be generalized to the novel situation of placebo-controlled trials of medications given in addition to an individual's regular antipsychotic treatment, a frequent model for research in schizophrenia.

Another concern related to ongoing participation in research is the therapeutic misconception[12]. Therapeutic misconception can be defined as the failure of study participants to recognize that research is meant to yield generalizable information and not primarily to benefit the individual[13]. It generally takes the form of misunderstanding the differences between clinical care and what occurs in a research study--such as not understanding random assignment, prescription of placebo or fixed doses of study medication, or that a study may be designed to investigate an illness without necessarily alleviating it. Therapeutic misconception is not restricted to psychiatric research participants, but is a concern in any research setting-from critical care[14] to biobank-based

genetic research[15]. However, people with schizophrenia may be particularly vulnerable to this type of confusion.

Schizophrenia is characterized by cognitive impairments affecting memory and attention[16, 17] that remain static despite adequate control of psychosis. Although poor insight and prominent psychosis have been associated with decreased capacity to consent[18–20], cognitive impairment has been the strongest predictor of decisional capacity[4, 5, 21–24]. It is possible that difficulties with attention or memory could impair the ability of someone with schizophrenia to retain/recall the information needed to participate knowledgeably in an ongoing study. This may be more likely when a clinical trial contains elements not previously experienced in clinical care such as placebo. Additionally, cognitive impairment may make participants with schizophrenia more vulnerable to confusion between research and clinical care.

This study extends the findings of Stroup et al. by examining information retention during placebo-controlled clinical trials of adjunctive agents added to stable antipsychotic therapy. The goals of the study were to determine: 1) Do participants retain enough information for continued informed participation during the course of these clinical trials? 2) If not, when do they lose this information? This work was designed to yield empirical data as to when and if researchers need to remind participants about the nature of their participation in a clinical trial. We hypothesized that there would be some meaningful information degradation at 8 weeks compared to baseline. We did not make specific predictions as to when this decrease would occur, but tested some participants after 1 week and 4 weeks, as well as all participants at 8 weeks. An exploratory aim of the study was to evaluate whether therapeutic misconception was prominent at baseline or changed during the study.

Methods

This study was approved by the Institutional Review Boards of the University of Maryland, Baltimore and the State of Maryland Department of Health and Mental Hygiene. Written documentation of informed consent for this study was obtained from each participant.

Participants

All participants were diagnosed with schizophrenia or schizoaffective disorder by best estimate approach (utilizing the Structured Clinical Interview for DSM-IV (SCID-IV)[25], direct assessment, family informants, and past medical records). Individuals were approached for participation in this study after signing consent for a placebo-controlled clinical trial of at least 8 weeks duration occurring at the Maryland Psychiatric Research Center (MPRC). All participants were clinically stable on antipsychotic therapy and were enrolling in a study examining the addition of an adjunctive agent to their regular regimen. Participants came from MPRC research clinics and from community mental health centers. The clinical trials were: augmentation of clozapine by risperidone versus placebo for treatment-resistant psychosis[26], atomoxetine versus placebo for cognitive enhancement[27], atomoxetine versus placebo for weight loss in people on clozapine or olanzapine[28], varenicline versus placebo for cognitive enhancement[29], varenicline versus placebo for smoking cessation[30], rimonabant versus placebo for weight loss[31], davunetide versus

placebo for cognitive enhancement[32], and rasagiline versus placebo for persistent negative symptoms (trial recently concluded, ClinicalTrials.gov registration number: NCT00492336). Other than diagnosis and clinical trial participation, there were no inclusion/exclusion criteria for this study; however, each clinical trial had varying inclusion/exclusion criteria. All excluded potential participants for acute psychiatric instability (operationalized as recent change in medication or dose), mental retardation, if medically unstable, or if criteria for substance abuse or dependence (other than for nicotine) were met in the past 3 months or 6 months, respectively.

Assessments

Retention of consent information was measured by the modified Evaluation to Sign Consent (mESC)[33]. This 23-item Likert-type evaluation was developed with input from researchers, people with schizophrenia, and family members. The scale is used to assess participants in areas generally recognized as important in determining capacity to consent to a clinical trial: what medication is being studied, for what indication, and how it will be assigned; what is required of research participants (burdens of participation); what are the risks and benefits; and how can participants withdraw from the study. This information is also regarded as vital for ongoing consent[8]. Items are scored 0–4, with anchors at 0, 2, and 4, yielding a maximum score of 92.

Unlike the original Evaluation to Sign Consent[34, 35], the mESC includes questions beyond a basic understanding of the facts. Participants are also asked to consider how the basic facts apply to their own situation and to manipulate those facts in order to make decisions. These latter exercises represent the domains of appreciation and reasoning, which, along with understanding, are assessed to determine decisional capacity. Additionally, 3 mESC items directly address the therapeutic misconception. The mESC is easily modified to reflect correct answers for particular clinical trials. Each clinical trial included in our study had appropriate mESC scoring anchors developed in conjunction with the clinical trial investigators (e.g., for side effect questions: “Which side effects are important to know for this clinical trial?”). Cronbach’s alpha for the mESC was 0.83. (See online supplementary material for a full copy of the mESC.)

The Brief Psychiatric Rating Scale (BPRS) total score and positive symptom items (conceptual disorganization, hallucinations, unusual thought content, and suspiciousness) were used to assess global psychopathology and positive symptoms, respectively[36]. BPRS items for emotional withdrawal, motor retardation, and blunted affect were used to evaluate negative symptoms. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[37] characterized participants’ cognitive abilities.

Design

On the day participants received their first dose of clinical trial study medication, they completed a baseline assessment of study knowledge using the mESC. At this visit, the complete consent form for the clinical trial was read aloud to participants as they followed along. Afterwards, they were offered an opportunity to ask questions or obtain clarification. The BPRS was then administered followed by the mESC. For follow-up visits, only the

BPRS and mESC were administered for our study of sustained knowledge about the trial. Although the participant had free access to their copy of the clinical trial consent form, it was not re-reviewed with them during follow-up.

Follow-up visits occurred after 1, 4, and 8 weeks to determine the timing of any loss of information. To evaluate the possible learning effects from repeatedly asking clinical trial-related questions, participants were randomly assigned to have follow-up assessments at all three time points (Group 1), only at weeks 4 and 8 (Group 2), or only at week 8 (Group 3).

The investigators of this study were in regular communication with the clinical trial investigators. No formal criteria have been established as to what information a participant needs to retain to continue knowledgeable participation in the study. However, to address IRB concerns, it was decided a priori that any individual who seemed incapable of remaining in the clinical trial (based on the impression of our study rater) would be referred to the clinical trial investigator. The clinical trial investigator would then determine whether the participant would be withdrawn from the clinical trial or be re-educated about the clinical trial. Individuals withdrawn from the clinical trial could still remain in our consent study. However, to avoid biasing our results, if an individual received additional education regarding the information on the consent form during the clinical trial, they would be withdrawn from our study.

Statistical Methods

Paired t-tests were used to assess within-group changes from baseline on mESC scores at all visits where it was administered. Analysis of covariance, adjusting for baseline score, was used to test for differences at week 4 between Groups 1 and 2, and at week 8 between Groups 1, 2 and 3 in changes in the mESC, BPRS total score, and BPRS psychosis score. Spearman rank correlations were calculated between the baseline mESC total score and the RBANS total score and baseline BPRS symptom measures (total score, psychosis score, and negative symptom score), as well as between changes in the mESC score and changes in the symptom measures from baseline to week 8.

Results

Demographics

Fifty-nine participants enrolled in the study. Data analysis was restricted to participants with at least one follow-up visit. Demographics are presented in Table 1. Group 2 was slightly more highly educated than Group 1, but there were no other group differences.

Retention of Study Information

Changes in study knowledge for each group are presented in Table 2. Group 1 (assessed at 1, 4, and 8 weeks) improved from baseline at each assessment culminating in a 6.2 point improvement (about 8%) from baseline to week 8. This increase was both clinically meaningful and statistically significant (t_{44}= 3.43, p= 0.001). Group 2 (assessed at weeks 4 and 8) and Group 3 (assessed at week 8 only) demonstrated no clinically meaningful change in their study knowledge (changes of 1% and 3%, respectively, at week 8).

Comparing changes from baseline across groups, the improvement in Group 1 at week 8 was significantly greater than changes in both Group 2 (t_{45}= 2.66, p= 0.011) and Group 3 (t_{45}= 3.22; p= 0.002).

No participants performed so poorly on any mESC that they were referred to the clinical trial investigator for evaluation of the appropriateness of their remaining in the trial.

Inter-rater agreement for the mESC was good, with an intraclass correlation (ICC) of 0.98 (95% CI: 0.96–0.99).

Therapeutic Misconception

Out of a maximum score of 12 for the three mESC items representing the therapeutic misconception, baseline averages were Group 1: 9.0±3.6, Group 2: 11.3±1.0, and Group 3: 10.6±1.9. Mean changes from baseline over the 8 weeks ranged from −0.4 to +1.9, indicating no prominent worsening of therapeutic misconception during the study.

Symptoms

There was little change in BPRS total score or psychosis subscore during our study. There were no group differences in change in symptom ratings at weeks 4 or 8.

Baseline BPRS total scores did not correlate with baseline mESC scores (R= −0.02, p= 0.88), nor did week 8 change in BPRS total score correlate to week 8 change in mESC score (R= −0.19, p= 0.22). The baseline BPRS psychosis subscore did not correlate with baseline mESC scores (R=−0.13, p= 0.37), nor did the week 8 change in BPRS psychosis subscore correlate with the week 8 change in mESC score (R= −0.12, p= 0.42). Baseline BPRS negative symptoms did not correlate with baseline mESC scores (R= −0.13, p= 0.36), nor did week 8 change in these items correlate to week 8 change in the mESC score (R= −0.11, p= 0.48).

Cognition

The RBANS correlation with baseline mESC score did not reach significance (R=0.28, p= 0.07).

Research Experience

To assess the impact of having had prior research experience, participants recruited from the research clinics of MPRC were compared to participants recruited from non-research-related community mental health centers (see Table 3). There were no significant differences in mESC change scores over the 8 weeks between research-experienced and non-research-experienced participants.

Discussion

Contrary to our hypothesis, participants did not show any appreciable, clinically relevant decreases in knowledge about the clinical trials in which they were enrolled. In fact, Group 1, which was questioned about the study at weeks 1, 4, and 8, actually showed a significant

improvement in study knowledge. This was despite the fact that the consent form was not re-reviewed at any follow-up session.

The improvement in Group 1 may indicate that repeatedly asking questions of the participant may enhance study-related knowledge in the absence of lengthy re-reviews of consent forms. Some problems people with schizophrenia may experience in the retention of consent-related information may therefore reflect memory retrieval impairment rather than impairment in initial encoding. Perhaps strengthening retrieval pathways by repeatedly asking the individual to remember previously reviewed information could be a strategy for enhancing capacity to consent. These data suggest that beginning the process soon after consent (i.e., 1 week) is more efficacious than waiting longer. This finding merits further investigation.

Although testing participants in a different type of clinical trial, our result is consistent with the overall findings of Stroup and colleagues. An exception is that Stroup et al. found that positive and negative symptoms were correlated with change in the understanding subscale of the MacCAT-CR, while we found no relationship between symptoms and the mESC. This may be because of the increased power to detect such correlations in the much larger CATIE study, the longer follow-up period in CATIE, or the different scales used in the studies (mESC versus MacCAT-CR and BPRS versus the Positive and Negative Symptom Scale). Additionally, all of the participants in our consent study were clinically stable and on antipsychotic therapy. Patients in CATIE followed a randomized plan for switching medications when symptoms were not adequately controlled by the initial medication or patients stopped that medication. Patients with acute exacerbations[19, 20] are one subgroup in which relationships have been observed between psychotic symptoms and decisional capacity. Stroup and colleagues also found a relationship between performance on neuropsychological assessments and MacCAT-CR understanding subscores and, similarly, we found a weak correlation approaching significance between the RBANS and the baseline mESC.

To our knowledge, this is the first study to examine therapeutic misconception in people with schizophrenia actually participating in clinical trials. Although Dunn and colleagues reported on therapeutic misconception in older adults with schizophrenia and found it somewhat prevalent, they used a hypothetical clinical trial rather than assessing people during real study participation[38]. The indication from the present study is that therapeutic misconception—at least according to the definition we used—may not be prominent in people with schizophrenia when clinically stable and does not appear to change during the actual experience of a clinical trial.

This study has several limitations. The first is that while the mESC possesses excellent inter-rater reliability (ICC=0.98), strong face validity, and good internal consistency (Cronbach's alpha = 0.83), it is not the gold standard for assessing capacity to consent, including understanding of study-related information. Additional research on the instrument needs to determine the relationship between the mESC and the MacCAT-CR. A larger sample size will also be needed to determine the internal factor structure of the scale and whether items representing "appreciation" or "reasoning" represent separable subscales. Furthermore, the

mESC is an information-based assessment tied to the details of a consent form. It does not reflect the possibility that someone may choose to participate or remain in a study without full information, i.e., respect for autonomy may require consideration of what level of information is truly sufficient for 'informed consent.' Second, this study was not designed to examine ongoing capacity to consent; rather we examined the retention of consent-related information among research subjects. Even with regard to information retention, our findings may not be applicable to studies where participants with schizophrenia may receive placebo instead of standard of care treatment or to symptom provocation studies (e.g., placebo-controlled antipsychotic or ketamine challenge studies). Therefore, although these results extend the findings of Stroup et al., the question of both knowledge retention and ongoing capacity to consent during a study where psychotic exacerbation is expected remains unanswered. Likewise, as our assessments were only conducted up to 8 weeks, we cannot predict whether study-related knowledge would have significantly degraded beyond 8 weeks. Third, every participant had free access to their own copy of the clinical trial consent form and could have reviewed it in expectation of our follow-up visits. However, our experience in the study was that participants did not actively prepare for our follow-up visits and many only remembered that our assessment was due when we met with them after they finished their clinical trial assessments. Finally, although we found no difference between the participants recruited from research clinics and those recruited from community mental health centers, the sample was weighted towards research-experienced participants.

In summary, our finding that people with schizophrenia demonstrated no meaningful loss of consent-related information over the course of 8 weeks is reassuring. Assessment of decisional capacity at the time of consent is appropriate, but we found no evidence that people with schizophrenia require additional assessment of their understanding of a study within the first 8 weeks of a placebo-controlled clinical trial of an adjunctive agent. Nor did we find prominent therapeutic misconception during the trials. Presuming these findings are confirmed, it appears that, as with any other adult, once a clinically-stable participant with schizophrenia consents to a protocol, it can be assumed that he or she retains an understanding of the information related to participation unless there is a specific reason to suspect otherwise.

The mESC is available as supplementary material for review on the Journal of Clinical Psychiatry website. The scale is not copyrighted and is in the public domain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Points

- People with schizophrenia who have stable psychotic symptoms have no meaningful loss of consent-related information during the first 8 weeks of participation in a clinical trial.
- Therapeutic misconception, or confusion between research and clinical care, was not prominent in this sample of people with stable schizophrenia.

Table 1

Basic Demographics.

	Group 1		Group 2		Group 3	
	Re-Tested at: 1, 4, & 8 Weeks		Re-Tested at: 4 & 8 Weeks		Re-Tested at: 8 Weeks	
	N		N		N	
Age, Years [Mean (SD)]	17	42.5 (10.2)	17	44.7 (8.9)	18	44.0 (11.1)
Male Gender n (%)	17	13 (76)	17	13 (76)	18	9 (50)
Non-white n (%)	17	8 (47)	17	5 (29)	18	10 (56)
Education, Years [Mean (SD)][a]	17	11.5 (2.4)	17	13.4 (1.7)	18	12.1 (2.1)
RBANS [Mean (SD)][b]	11	82.0 (12.5)	17	80.9 (12.3)	14	79.4 (12.6)

RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SD = Standard Deviation

[a] Years education Group 2 > Group 1, $F_{2,29} = 3.92$, $p = 0.02$.

[b] RBANS ranges: Group 1: 56–92; Group 2: 60–102; Group 3: 52–101.

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Table 2

Retention of Study Information and Symptoms during Clinical Trials.

		Group 1 Re-Tested at: 1, 4, & 8 Weeks		Group 2 Re-Tested at: 4 & 8 Weeks		Group 3 Re-Tested at: 8 Weeks		Between Group Comparisons		
		N	M (SD)	N	M (SD)	N	M (SD)	F	df	p
Modified Evaluation to Sign Consent	**Baseline**	17	73.9 (14.1)	17	79.9 (7.5)	18	81.6 (6.5)	-	-	-
	ΔWeek 1[a]	13	3.1 (5.9)	-	--	-	--	-	-	-
	ΔWeek 4	14	2.6 (5.2)	13	−0.8 (5.1)	-	--	1.20	1, 24	0.28
	ΔWeek 8	14	6.2 (5.5)[2]	17	−1.4 (6.6)	18	−3.1 (8.0)	5.58	2, 45	0.007[c]
BPRS total score	**Baseline**	17	34.4 (8.0)	16	31.6 (7.2)	16	33.1 (7.8)	-	-	-
	ΔWeek 1	13	−0.5 (3.8)	-	--	-	--	-	-	-
	ΔWeek 4	14	−0.6 (5.1)	13	−0.8 (4.8)	-	--	0.03	1, 24	0.86
	ΔWeek 8	14	−0.4 (4.9)	15	1.1 (6.4)	16	−0.6 (7.5)	0.23	2, 41	0.80
BPRS Psychosis Subscale	**Baseline**	17	10.5 (4.7)	16	8.5 (4.1)	16	7.9 (3.3)	-	-	-
	ΔWeek 1	13	0.3 (1.4)	-	--	-	--	-	-	-
	ΔWeek 4	14	−0.8 (2.0)	13	0.4 (1.8)	-	--	1.35	1, 24	0.26
	ΔWeek 8	14	−0.3 (1.4)	15	1.2 (3.3)	16	0.1 (3.2)	0.94	2, 41	0.40

BPRS = Brief Psychiatric Rating Scale; df = Degrees of Freedom; M = Mean; SD = Standard Deviation

[a] ΔWeek 1, ΔWeek 4, and ΔWeek 8 rows represent changes from baseline at each week.

[b] Group 1: Significant change from baseline, t_{44}= 3.43, p= 0.001.

[c] Group 1 had a significantly greater change in the modified Evaluation to Sign Consent from baseline to 8 weeks compared to both Group 2 (t_{45}= 2.66, p = 0.011) and Group 3 (t_{45}= 3.22; p = 0.002).

Table 3

Participants from Research Clinics versus Non-research Clinics.

		Research Clinic		Non-research Clinic		Between Group Comparisons		
		N	M (SD)	N	M (SD)	F	df	p
Modified Evaluation to Sign Consent	**Baseline**	33	80.3 (8.4)	19	75.5 (12.5)	-	-	-
	ΔWeek 1[a]	8	1.4 (6.7)	5	5.8 (3.0)	1.89	1, 10	0.20
	ΔWeek 4	18	0.1 (5.2)	9	2.8 (5.3)	0.56	1, 24	0.46
	ΔWeek 8	32	−0.1 (5.1)	17	0.6 (11.5)	0.06	1, 46	0.81

df = Degrees of Freedom; M = Mean; SD = Standard Deviation

[a]ΔWeek 1, ΔWeek 4, and ΔWeek 8 rows represent changes from baseline at each week.