Evaluation of the Capacity of Inpatients with Chronic Schizophrenia to provide Informed Consent for Participation in Clinical Trials: Use of the Hebrew Version of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR)

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ABSTRACT: **Background:** Patient protection requires the provision of informed consent for participation in medical research. The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) is frequently used for screening the capacity of research subjects to consent to participate in research.

Objectives: To evaluate the utility of the Hebrew translation of the MacCAT-CR for assessing the capacity of patients with chronic schizophrenia to provide informed consent to participate in clinical trials.

Methods: We evaluated the translated MacCAT-CR by comparing the capacity of patients with chronic schizophrenia to provide informed consent to participate in clinical trials. The following standardized neurocognitive assessment tools were used: Addenbrooke's Cognitive Examination (ACE) and Frontal Assessment Battery (FAB), as well as the attending doctor's assessment.

Results: Twenty-one patients participated. Mean MacCAT-CR score was 12 ± 10.57 (range 0–32), mean FAB score 9.9 ± 4.77 (range 1–18), mean ACE 59.14 ± 16.6 (range 27–86) and mean doctor's assessment 5.24 ± 1.18 (range 3–7).

Conclusions: The Hebrew version of the MacCAT-CR helped identify patients with the capacity to provide informed consent for participation in research. Patients with FAB scores ≥ 12 tended to score higher on the Hebrew version of the MacCAT-CR, thus confirming the utility of the Hebrew version of the MacCAT-CR. During the screening process for clinical trials it may be practical to administer the concise FAB questionnaire, and then administer the MacCAT-CR only to those who scored ≥ 12 on the FAB.

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KEY WORDS: Addenbrooke's Cognitive Examination (ACE), Frontal Assessment Battery (FAB), MacCAT-CR, decisional capacity, informed consent process

Ethical demands for patient protection require the provision of informed consent for treatment and for participation in medical research. Every individual has the right to consent and the freedom to refuse treatment or participation in clinical research.

Welie and Berghmans [1] presented the progressive Dutch Medical-Scientific Research on Human Subjects Act (1998) that rejects the performance of medical research among vulnerable groups, such as children, refugees, patients with dementia or mental retardation, and end-of-life patients, and limits but does not exclude research involving subjects who lack mental capacity. Two types of research that are permitted among mentally incapacitated persons are: a) therapeutic research and b) non-therapeutic research that could not take place without the specific participation of mentally incapacitated subjects. The conditions required to perform the research include ethical and scientific review, insurance, written proxy consent, and respect for the subject's decision not to participate. An additional condition for the permissibility of non-therapeutic research is that the risks for the prospective subject are negligible and the burden minimal. According to Welie and Berghmans [1], the crucial issue in assessing mental capacity is whether the patient has adequate mental capacity to make the specific decision in a meaningful manner. The Dutch statute attempts to balance the ethical demands for protection of subjects and stimulation of scientific research.

There are a number of instruments that assess the decisional capacity of psychiatric patients to provide informed consent for participation in clinical trials. Dunn et al. [2] compared 23 instruments and found that the tool with the best empiric results is the MacArthur Competence Assessment Tool for Clinical Research and Treatment,

which was used to assess the decisional capacity of participants in the Clinical Antipsychotic Trials and Intervention Effectiveness (CATIE) study [3].

The aim of the present study was to evaluate the utility of the Hebrew translation of the MacCAT-CR in assessing the capacity of patients with chronic schizophrenia to provide informed consent to participate in clinical trials. In addition, the MacCAT-CR scores were compared with standardized neurocognitive assessment tools and with the attending physician's evaluation of the patient's capacity to consent to participation in a clinical trial.

SUBJECTS AND METHODS

The study population comprised all patients aged 18 or over diagnosed with schizophrenia and hospitalized for more than 6 months at the Lev Hasharon Mental Health Center and who provided written informed consent to participate in the study. Patients involuntarily hospitalized, admitted by court order, who had a legal guardian, or did not agree to participate were excluded from the study.

RESEARCH INSTRUMENTS

MacCAT-CR [4] was translated to Hebrew specifically for this study with permission from the copyright owners (Professional Resource Exchange, Inc., 2001). The original questionnaire was translated, back-translated, and culturally adapted to evaluate use of this instrument among patients with chronic schizophrenia at Lev Hasharon Mental Health Center. The MacCAT-CR provides a structured format for capacity assessment that is adaptable to the particulars of any given research project. The original MacCAT-CR can typically be administered in 15–20 minutes. Beginning with a description of the specific proposed clinical trial to potential participants, the MacCAT-CR measures the four generally accepted components of decision-making competence: understanding, appreciation, reasoning, and the ability to express a choice. Quantification of subjects' responses permits comparisons across subjects and subject groups and allows the MacCAT-CR to be used for screening individual participants. Each level is scored and a final score of 0–42 is tallied. Because decisional capacity is based on context [5], the MacCAT-CR has no established cutoff score for determination of capacity assessment.

Studies vary in the levels of risk and in the risk/benefit ratio; the greater the risk the higher the level of decision-making capacity needed. Since the aim of this study was to establish utility of the Hebrew version of the MacCAT-CR rather than assess capacity to provide consent for participation in a specific study, a hypothetical study was described in the Hebrew MacCAT-CR questionnaire. The capacity assessment instruments should be supplemented with other essential information, such as mental status and decision-making context. Each investigator or institutional review board needs to decide on the level and type [4].

Addenbrooke's Cognitive Examination [6]

The ACE is a broad test that surveys key aspects of cognition. It includes six components. A maximum score of 100 is weighted as follows: orientation = 10, attention = 8, memory = 35, verbal fluency = 14, language = 28, and visuospatial ability = 5. Scores for each of the domains can be calculated separately; the composite score is the sum of all component scores. It can be administered bedside or in the clinic. Administration time is 15–20 minutes [6].

Frontal Assessment Battery [7]

The FAB is sensitive to frontal lobe dysfunction. It includes six subtests to explore the following functions: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. Scores for each of the subsets range from 0 to 3. The total score is calculated by adding the notes of the six subsets to a maximum total score of 18. Duration of administration is approximately 10 minutes, and the FAB can be administered at bedside.

Many studies utilize the FAB, and most deal with evaluation of various types of dementia: Alzheimer's dementia, vascular dementia, frontotemporal dementia and dementia in Parkinson's disease. There were also studies that used the test to evaluate patients with depression. We did not find any study that used the test in schizophrenia patients despite frontal lobe impairment in this patient population [8].

EVALUATION OF THE TREATING PHYSICIAN

The physician, who was blind to the neurocognitive and MacCAT-CR assessment scores, performed a structured evaluation of the participant's capacity to provide informed consent for participation in a clinical trial. The doctor's assessment was on a scale of 1 (total lack of capacity to provide informed consent for participation in a clinical trial) to 7 (fully capable of providing informed consent for participation in a clinical trial).

STUDY PROCEDURE

Duration of the study was 6 months. All patients who met the inclusion criteria and provided written consent for participation in the study were recruited. The principal investigator (M.L.) interviewed the patients and administered the MacCAT-CR, the ACE and the FAB questionnaires. Duration of the study session was about 2 hours and the patients were able to take breaks as needed. A break was suggested between

ACE = Addenbrooke's Cognitive Examination
FAB = Frontal Assessment Battery
MacCAT-CR = MacArthur Competence Assessment Tool for Clinical Research

completion of the second and third questionnaires. After the subjects completed all questionnaires, the treating psychiatrist was asked to evaluate and score the patient's capacity to provide informed consent for participation in a clinical trial. All the questions were read out aloud by the examiner, the answers were recorded by the examiner (except for the few questions where the subject was asked to write a sentence or copy a drawing), and the questionnaires were then coded.

RESULTS

All the participants signed informed consent to participate in the study after receiving a detailed explanation of the study procedures. Twenty-one patients who met the DSM-IV-TR [9] criteria for schizophrenia and were hospitalized for more than 6 months at Lev Hasharon Mental Health Center participated in the study. Six (28.6%) were women, 15 (71.4%) were born in Israel; 17 (81%) were single, 3 (14.3%) were divorced and one (4.8%) was married. The age range of participants was 23–59 years, and the mean age was 43.2 ± 10.97.

MACCAT-CR, FAB, ACE AND PHYSICIANS' ASSESSMENT SCORES

The mean MacCAT-CR score was 12 ± 10.57 (range 0–32). The mean FAB score was 9.9 ± 4.77 (range 1–18). The mean ACE score was 59.14 ± 16.6 (range 27–86). The mean doctors' assessment score was 5.24 ± 1.18 (range 3–7).

CORRELATION COEFFICIENTS

Pearson's product-moment correlation coefficients – MacCAT score, FAB score, ACE score and the doctor's assessment score – are presented in Table 1. The most significant correlation was between the FAB and the ACE assessment scores. The correlation between the ACE and the MacCAT and the FAB and the MacCAT are positive, high and significant. In addition, the correlations between the doctors' assessments and the MacCAT and the FAB are positive and significant. The only correlation that was not statistically significant was between the doctors' assessment and the ACE.

LINEAR REGRESSION ANALYSIS

In order to test the predictability of the MacCAT-CR using the FAB and doctors' assessments, we performed linear regression analysis where the MacCAT-CR was the dependent variable and the FAB and doctors' assessments the independent variables. The ACE variable was not entered into the regression analysis because it was found to correlate highly with the FAB.

Frontal assessment (FAB) and doctors' assessment were regressed on competence assessment (MacCAT-CR). Only frontal assessment (FAB) ($b = 0.61$, $t = 3.36$, $P < 0.005$) positively predicted competence assessment ($R^2 = 0.50$, adjusted $R^2 = 0.44$; $F_{(2,18)} = 8.88$, $P < 0.005$).

Table 1. Correlations between competence, frontal, cognitive, and doctor's assessment (N=21)

	Frontal assessment (FAB)	Cognitive evaluation (ACE)	Doctor's assessment
Competence assessment (MacCAT-CR)	0.68**	0.74**	0.43*
Frontal assessment (FAB)		0.86**	0.38*
Cognitive evaluation (ACE)			0.35

*Significant at 0.05 (two-tailed)
** Significant at 0.01 (two-tailed)

Regression analysis revealed a high correlation between the FAB scores and the MacCAT-CR and the doctors' assessments. The FAB was found to be a successful predictor of performance on the MacCAT-CR

FAB CUTOFF POINT

As all variables were continuous, we compared results using the FAB score with multiple cutoff points and Bonferroni corrections [10]. Statistically significant differences were found between those with a FAB score ≥ 12 and those with lower scores on variables related to cognitive evaluation and competence.

In order to assess the mean differences between the high FAB group (≥ 12 points, N=6) and the low FAB group (< 12 points, N=15), we conducted several one-tailed independent *t*-tests assessing the difference between both groups on MacCAT-CR, ACE, and doctor's assessment. For the high FAB group, mean MacCAT-CR was significantly higher (mean 23, SD 9.21) than for the low FAB group (mean 7.6, SD 7.53) ($t_{(19)} = -3.98$, $P < 0.001$). For the high FAB group, mean ACE was significantly higher (mean 76.5, SD 10.56) than for the low FAB group (mean 52.20, SD 13.15) ($t_{(19)} = -4.01$, $P < 0.001$). For the high FAB group, mean doctor's assessment was higher (mean 6, SD 0.89) than for the low FAB group (mean 4.93, SD 1.16) $t_{(19)} = -2.01$, NS) but this difference was not significant.

DISCUSSION

Evaluation of the schizophrenic patient's capacity to provide informed consent to participate in clinical trials is an important issue. Appelbaum and Grisso [4] developed the MacCAT-CR, which simulates a proposal to participate in a clinical trial, in order to examine the capacity to provide informed consent [11-14]. A number of comparative studies between schizophrenic and other patients have been conducted [15-17]. In our study we focused on inpatients with chronic schizophrenia and found that administration of the Hebrew version of the MacCAT-CR posed difficulties when examining impaired schizophrenic patients who could not concentrate for

long periods and for whom clarification of capacity to provide informed consent is most relevant. This obstacle may have been exacerbated by the hypothetical nature of the study described in the MacCAT-CR Hebrew version, which was used to assess the patients' capacity to participate in clinical trials, in general. Though the reported administration time of the original English version of MacCAT-CR is 15–20 minutes, the authors found the administration of the MacCAT-CR Hebrew version to inpatients with chronic schizophrenia to be quite complex and lengthy (over 30 minutes).

Absence of a cutoff point was an additional hurdle. Kim et al. [18] discussed this issue. When evaluating potential research participants, too high a cutoff might unjustifiably disqualify potential participants who are interested in and capable of participating in a clinical trial, while a low cutoff may allow inclusion of candidates whose informed consent may be questionable. Determination of study-specific cutoff points prior to administration of the MacCAT-CR might be advantageous. We therefore examined the results of the ACE, which examines cognitive abilities, and in accord with the author's recommendation we also used the FAB [7] to assess frontal lobe functioning and executive function. The FAB has also been used in the evaluation of patients with depression, but not in schizophrenic patients although frontal lobe impairment in schizophrenia is well documented [8]. We found that a score of 12 on the FAB distinguished between chronic schizophrenic patients with low neurocognitive functioning and those with higher functioning, and that the FAB score could serve as a good predictor for MacCAT-CR assessments. Those who scored 12 or higher on the FAB – that is, patients with higher neurocognitive performance – tended to exhibit competence for providing informed consent to participate in clinical trials, as demonstrated by their scores on the Hebrew version of the MacCAT-CR, thus confirming utility of the Hebrew version of the MacCAT-CR. It may be time-efficient to administer the MacCAT-CR only to patients whose frontal lobe assessment scores are ≥ 12. Since executive functions are performed in the frontal lobe, the FAB might be an appropriate instrument to evaluate potential research participants and to filter out the chronic schizophrenic patients who lack the ability to complete the MacCAT-CR questionnaire and thus streamline the prescreening process in recruitment of potential participants for clinical trials.

Patients with FAB scores ≥ 12 should then be further evaluated with the study-specific MacCAT-CR in order to examine capacity to participate in the informed consent process (understanding, appreciation, reasoning, and the ability to express a choice) and to ensure that they are truly capable of providing informed consent. The FAB and MacCAT-CR assessments were more reliable than doctors' assessments, which could be subjective and easily biased.

Clinical trials are the heart of medical research. Inpatients with chronic schizophrenia comprise a large significant group that should participate in research because of the need to assess, for example, new medications for schizophrenia. Lack of representation of some patient populations may create a bias in clinical studies. On the other hand, including this patient group requires special attention to all issues concerning informed consent to participate in research.

In our experience administration of the Hebrew version of the MacCAT-CR questionnaire in the population of inpatients with chronic schizophrenia was a lengthy process (over 30 minutes), which in itself served as a stumbling block since patients with chronic schizophrenia found it hard to concentrate for such a long time. A significant correlation was found between neurocognitive functioning as evaluated by the FAB and performance on the MacCAT-CR; patients with a score of 12 or more on the FAB also revealed the capacity to provide consent to participate in research on the MacCAT-CR. Therefore, it may be worthwhile to administer the FAB first, and then administer the MacCAT-CR only to those subjects who scored 12 or higher on the FAB.

LIMITATIONS

Though the study sample allowed for statistically significant results, the power of the results would have been greater with a larger sample size. The hypothetical nature of the study description in the Hebrew version of the MacCAT-CR was confusing for some of the chronic schizophrenic patients, making it more difficult for them to complete the questionnaire. Additional research using a study-specific Hebrew version of the MacCAT-CR for an actual clinical trial is necessary to confirm utility of this important research tool.

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