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An assessment of the understanding and motivations of patients with schizophrenia about participating in a clinical trial ☆

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ABSTRACT

Enrollment of an adequate number of subjects for a clinical trial is a perennial challenge and this might arguably be even more difficult and complex in trials involving patients with schizophrenia. In this paper, we used a modification of the Prospective Preference Approach (PPA) as a prelude to an actual randomized placebo-controlled trial of a cognitive-enhancing agent for patients with schizophrenia. This approach sought to test and enhance subjects' understanding of the key concepts of the trial, and administered the PPA at baseline and following a brief educational module. The motivations and concerns regarding potential participation in the proposed trial were also elicited by the PPA. Of one hundred ninety patients with schizophrenia recruited for this PPA study, only 12 (6.3%) were assessed to have understood all key trial-related concepts after the initial explanation and baseline PPA administration (prior to the educational module).

Following the education module, however, there was significant increase in the number of patients who understood all key trial elements. Younger age and higher level of education were significant factors associated with better understanding of the proposed trial. The main reasons cited for wishing to participate in clinical trials were personal medical benefits and altruistic desire to help others. Concerns regarding the safety of the trial medication were expressed in over 80% of the subjects. PPA administration with educational module supplementation may provide a valuable addition to clinical trial procedures in patients with schizophrenia.

1. Introduction

One of the most important factors in achieving the successful conduct and interpretable outcome of a clinical trial is the twin problem of under-enrollment and selective enrollment [1]. This has the scientific implications of inadequate statistical power and volunteer bias, and possibly ethical ramifications [2]. Perhaps central to these issues is the fact that concepts of risk-benefit, voluntary participation, randomization, blinding, and the use of placebo, while familiar to researchers and clinicians, may be difficult concepts for research subjects to grasp initially [3]. These issues may be even more of an ethical concern among individuals with schizophrenia, since this is a severe mental illness that impairs cognition and hence might affect decisional capacity. Decisional capacity among patients with schizophrenia is heterogeneous and not necessarily "static", as demonstrated by studies that have shown that decisional capacity can be improved with various educational interventions [4–6]. Halpern (2002) first

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suggested the potential use of an approach called the Prospective Preference Approach (PPA). The goal of the PPA is to elicit potential participants' views on the proposed research design, including their motivations and reasons for considering participation or non-participation, and their willingness to participate in a study. It comprises 5 sequential stages: (i) a brief protocol describing a clinical trial, (ii) ensuring the interviewee understands the trial design, (iii) using a list of questions to evaluate motivations and concerns, (iv) administering an ordinal response written questionnaire to evaluate the interviewee's willingness to enroll, and (v) assessing the interviewee's willingness to enroll by systematically varying one or more factors deemed important to him/her. The PPA has been utilized successfully as a prelude to trials involving antihypertensive drugs [7] and arthroscopic knee surgery [8]. This strategy – to our knowledge – has not been employed to date in patients with schizophrenia although [9] its use has been recommended in trials involving participants with schizophrenia as an ethical means of exploring some of the issues pertaining to participation.

Here, we used an adaptation of the PPA combined with an educational module in patients with schizophrenia to explore the extent of their comprehension of key elements of a randomized placebo controlled trial. We hypothesize that: (1) There would be a significant proportion of patients with schizophrenia who would have difficulty in understanding the key concepts of a randomized controlled trial that could be rectified with a brief educational module, and (2) The most prevalent reasons for wanting to participate in the subsequent trial are either altruistic in nature or for personal benefits.

2. Methods

2.1. Setting and participants

Singapore is an island state in Southeast Asia with a total population of 4.2 million. The largest ethnic group is the Chinese (76.8%), followed by Malays (13.9%), Asian Indians (7.95%), and others (1.4%). This study was carried out in the country's only state mental health treatment facility. Participants meeting DSM-IV criteria for schizophrenia were consecutively recruited from the outpatient clinics of the Institute of Mental Health.

2.2. Assessments and procedures

The study was approved by the relevant Institutional Review Boards. Since the PPA interview is procedurally simpler and has minimal risk compared to the relatively greater complexity and risk of participation in an RCT, we used the "sliding scale" concept of capacity as described by [10]: accepting as "adequate understanding" the subject's ability to understand that participation is voluntary, that they are not enrolling in a real clinical trial as yet, and therefore the risk is minimal (consisting primarily of possible discomfort with specific questions, boredom during the assessment, etc). Patients were those with a DSM-IV diagnosis of schizophrenia, English-speaking and did not have a history of mental retardation, epilepsy, substance abuse or dependence (other than nicotine), or neurological or other organic brain disorders. All provided written informed consent.

The hypothetical clinical trial was then described following a written script. The script described the randomized controlled trial as an adjunctive or "add-on" treatment to their current medication regimen i.e., they were told that they would continue with their current medications as prescribed by their attending psychiatrists however, they would receive either the active compound or the placebo, which was described as "a sugar pill, with no active compound" – the appearance of which would be identical to the active compound. It was emphasized to them that this "add-on" is part of the research in which they are participating. The rationale of randomization was described as the best method for determining whether the active compound works (i.e. helps to alleviate symptoms), and the procedures of randomization and double-blinding were likened to "flipping a coin" to decide on the choice of treatment, which neither the patients nor the investigators would know until the end of the study.

An assessment of the subject's understanding of the trial design was then made using a questionnaire which we developed ourselves. This questionnaire comprised a combination of 7 close-ended questions (eg, "Is this part of your regular treatment ?" and "and "Will you know if you are taking drug X or the placebo ?" and probing open-ended questions that covered the risk-benefit aspects, the voluntary nature of participation, randomization, blinding, use of placebo, duration of the trial, and frequency of visits (eg, "What do you understand by the term randomization ? ". The research assistants administering the assessment were trained to probe for clarification of any unclear responses, and the responses were then assessed by the research assistants as either correct or incorrect.

Subjects who did not answer all 7 questions correctly subsequently viewed an educational module. The subjects were not told of the results of the test questionnaire prior to being given the educational module. The educational module was presented in the format of a 15-minute PowerPoint presentation, in which the consent agreement and research terminology concepts were presented in a simple and straightforward way. Research staff were available to further clarify the any aspects of the trial as necessary subsequent to the education module. The same PPA assessment questionnaire was then readministered. In addition to assessing the knowledge and understanding of participants with regard to possible trial participation, another component of the PPA evaluated motivations and concerns, also via patient self-administered questions which listed the possible motivations and concerns with respect to the clinical trial. The patient was asked to rank, in order of personal importance, the factors that might motivate him to participate in the study or would cause concerns. These factors include "inconvenience fee", "helping other patients like myself", "the possibility that I might get well", "I do not know if the new drug is safe", and "I do not like to take a placebo".

There were 3 experienced research assistants who administered and scored the tests. Trainings were held to ensure general consistency among all the 3 research assistants. Further, the most senior research assistant was available for consultation throughout the study in cases when there was some uncertainty with the scoring or responses.