ABSTRACT

Background: Patients’ decisions in relation to participation in clinical research depend on individual values and relevant outcomes. Presenting possible decisions by way of defaults (opt-in or opt-out) has been used to achieve desired outcomes. Our objective was to characterize patients willing to participate in clinical research and to assess the impact of defaults on patients with Serious Mental Illness (schizophrenia, schizoaffective disorder, major depression and bipolar disorder; Smi) during the decision process.

Methods: Patients with Smi were requested to accept or reject participation in a novel drug treatment study using either the (1) opt-in condition, wherein they were told that our center’s policy is not to include them in drug studies; (2) the opt-out condition, wherein they were told that our center’s policy is to include them in drug studies; and the (3) neutral condition that required patients to state their preference with no prior information.

Results: 311 patients with Smi completed the brief questionnaire within 48 hours of admission to a psychiatric ward. There were 227 (73%) patients suffering from schizophrenia and schizoaffective disorder, 40 (13%) suffering from bipolar disorder and 44 (14%) suffering from major depressive disorder. There were 156 men (50%) and 155 women in the sample, mean age 47.8±16.2 years. In the opt-in condition, 58% abstained, while 42% opted-in (p=0.003). In the opt-out condition, 58% participated, while 42% opted-out. In the neutral condition 51% indicated willingness to participate, 33% refused and 16% were undecided. The “willing” patient was characterized by younger age, previous hospitalizations, affective illness and more comorbid physical disorders.

Conclusion: Taken together these findings reveal the “profile” of patients with Smi willing to participate in clinical research and demonstrate an increase in participation preferences through the use of defaults.

INTRODUCTION

Serious mental illness (SMI) is a major cause of significant disability in young adults. Treatment decisions in the context of SMI are often undertaken with the perspective of long-term outcomes. The collective purpose of clinical research is to explore and understand illness and to improve the quality of life of those who suffer. In the mental health arena, there are ethical concerns that the psychiatric clinical research may expose those being studied to potential harm (1). Despite a paucity of data, a recent systematic review suggests that negative reactions to research participation occur in <10% of patients (2). Individuals with complex psychopathology are more disposed to experience distress in clinical research settings (3). Specifically, there are reservations about research among individuals diagnosed as suffering from schizophrenia (1, 4). Nevertheless, the pressing needs of patients with SMI, their families and health care providers require continuing research in order for clinicians to be able to offer hope of remission or recovery (5). The past decade has not provided novel solutions or ground-breaking discoveries in the treatment or prevention of SMI and may have resulted in despair by mental health professionals (6). In a parallel process emphasized over the past decade, the pharmaceutical industry has begun to withdraw its investment in central nervous system (CNS) research-and-development. The high cost and high risk of CNS...
drug development coupled with decreased opportunities for pharmaceutical companies to recoup their investments and make profits to reinvest in further research and development is now reaching its logical conclusion: companies curtail developing new medications for CNS diseases (7). Thus, investigating patients with SMI preferences and choices as to participation in clinical research may enable the identification of patient subgroups that are amenable to participation. In addition, characterizing the “consenting” patient with SMI may be translated into benefits for patients, drug developers, regulatory agencies and other interested parties.

Social psychologists have long been interested in decision making and several insights are relevant to the patient-physician dialogue concerning participation in research. When faced with momentous and non-trivial decisions, subjects are reluctant to make a decision and tend to avoid deciding and to rely on factors that should not affect their choice (8). Moreover, the role that patients play in decision making has shifted from physician paternalism towards informed autonomous relationships (9). The shift in the patient-physician-relationship has placed decision making in the center of this dialogue. One of the main themes in the study of decision making suggests that there are techniques that may result in better outcomes for patients. For example, defaults may be best when strong evidence suggests an option to be best for most people, but preserving patient choice is appropriate. Defaults in decision research are defined as a preselected option adopted when no alternative is specified. Alternatively, the use of environments that explicitly facilitate the optimal construction of preferences is most appropriate when choice depends on a patient’s ability to understand probabilities and outcomes (10). Respondents’ preferences, even for substantively important decisions, are influenced by factors that should not affect the choice, such as the wording used to present data (11). Social psychology demonstrates that subjects’ choice is influenced by opt-in versus opt-out presentation of decision algorithms. Defaults not only make a difference in what is chosen, they can also make decisions easier. Moreover, default decisions are optimal when subjects have a strong propensity to procrastinate (12). This factor is particularly relevant to SMI patients presented with complex and affectively loaded decisions. The impact of defaults have been emphasized in the general public by several unintended “natural experiments” in which governmental and public organizations randomly assign people to one program and then give the chance to choose among a set of alternative ones - examples include assignment to health care plans, the adoption of privacy policies and organ donation, where the stakes are high (8). These “natural” experiments show that defaults have a substantial role in determining what is chosen. In most cases, the majority of people choose the default option to which they were assigned (13).

We are facing a time of progressively more complex options in SMI research and treatment, in which data require continuous updating, and preferences and values become highly relevant. Patients are overwhelmed by information through the internet, personal contact with other patients, family physicians and patients’ organizations, while very few information sources are evidence-based, or are based on rigorous guidelines. Moreover, health messages on television and other mass media have the potential to significantly influence patients’ health-related knowledge and behavior, though little is known about patients’ ability to comprehend such messages (14). Serious ethical concerns come along with using defaults with vulnerable populations. While examining the impacts of defaults in a high-risk population like patients with SMI is addressing a gap in the literature, it must be done cautiously and any such investigation must take care to address the many ethical issues that arise, including the possibility of undue coercion of a vulnerable population.

Thus, the present study was designed to evaluate the role of defaults in patient’s with SMI decisions to participate in clinical research in real-life, with the hope that the results would aid both treating psychiatrists and researchers in characterizing those patients willing to take part in clinical research.

METHODS

SUBJECTS

Patients admitted to the Abarbanel Mental Health Center were recruited between January and June, 2012, according to the following eligibility criteria: (1) a DSM-IV diagnosis of a SMI (schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder), (2) availability to participate within 48 hours of admission and (3) aged 18 years and older. We excluded patients with cognitive impairment (mental retardation or dementia) and patients who had already participated in other studies related to informed decision making. Enrollment took place consecutively until the planned sample size was achieved.
We enrolled 311 SMI patients in this study. Patients were suffering from schizophrenia (n=166, 53%), schizoaffective disorder (n=63, 20%), MDD (n=40, 13%) or bipolar disorder (n=44, 14%). All completed the attitudes questionnaire within 48 hours following admission to an acute psychiatric ward. Patients sent for observation by court order were not included as these are not eligible to participate in research in Israel. There were 156 men (50%) and 155 women in the sample, with a mean age 47.8 ± 16.2 years.

In the “neutral” questionnaire (no stated position of researchers), 51% of 104 patients declared they would like to participate in research (45% of whom were schizophrenia and schizoaffective patients) and 33% declared they refused participation (73% of whom were schizophrenia and schizoaffective patients), and 16% were undecided if they wished to participate in research (of whom 41% were schizophrenia and schizoaffective patients).

In the opt-out questionnaire (where we declared that we are assigning them to participate as research candidates), 42% of 101 patients actively declared they wish to withdraw from participation in research (60% of whom were suffering from schizophrenia and schizoaffective disorder), while 58% did not change their assigned position (47% of whom were suffering from schizophrenia and schizoaffective disorder). The proportion of patients who opted to decline participation in research in the opt-out arm was not significantly different from chance \( (c^2=0.434; p=0.071) \). Thus, in comparison to the neutral condition, 7% more patients “adhered” to the center’s policy to participate in research.

In the opt-in questionnaire (where we declared that we do not seek research candidates), 42% of 106 patients actively sought to participate in research (43% of whom were schizophrenia and schizoaffective patients), while 58% did not change their assigned position (61% of whom were schizophrenia and schizoaffective patients). Thus, in comparison to the neutral condition 25% more patients “adhered” to the center’s policy to participate in research.

In order to achieve this 42% of the patients had to “actively” opt- in, that is, to change the default and to participate in research, and this was significant \( (c^2=9.49; p=0.004) \). This may imply that the “declared” policy not to participate in research had only a minor influence on patients’ choice.

Comparisons between the three conditions (not with “chance” but to each other) demonstrated only one significant finding. In the opt-out condition SMI patients were older than in the two other groups \( (p<0.05) \).

See Table 1 for details of patients’ preferences.

We defined a “willing” participant as a patient who chose to participate in research in the neutral arm, to actively seek participation in research in the opt-in arm and to remain in the “offered” research position in the opt-out arm. In total, there was 155/311 (50%) “willing” patients who chose to participate in research. Of these,
only 70 were suffering from schizophrenia and schizoaffective (45%) were significantly under-represented in the “willing” group (p<0.04). Compared to patients who did not choose to participate in clinical research, the “willing” participants were statistically significantly younger, with more recurrent hospitalizations, higher rates of physical co-morbidity and diagnosis of an “affective” disorder (including schizoaffective) (p<0.05).

See Table 2 for demographic details of all participants and the “willing” group.

DISCUSSION
Clinicians who treat patients with SMI may encounter a variety of ethical issues related to both treatment of patients and their participation in clinical research. Neuropsychological impairments, as well as psychotic and severe affective symptoms and lack of insight, can affect patients’ abilities to make fully informed decisions about their own research participation. Attention to the process of informed consent as an ongoing dialogue strengthens the clinician-patient relationship and helps patients clarify preferences. In addition, investigators are attuned to and aligned with research participants in many, but not all, respects on the importance of participating in clinical studies. Investigators may bring a protective bias in their predictions of the vulnerabilities of ill volunteers (15). Decision-making abilities of people with SMI in research contexts call for in depth studies (16). The present study aimed to add to the limited literature in this field.

Our findings demonstrate that half of the acutely admitted patients declare their wish to participate in clinical research; the great majority of those who do not wish to participate are suffering from schizophrenia and schizoaffective disorder. Using the opt-out questionnaire, the percentage of SMI patients who actively remove themselves from participation decreases by more than 12%. Although not a huge drop, it lays the ground for psychoeducation and possibly other interventions to increase patients’ participation in research. Patients’ decisions depend on individual values and relevant outcomes. One obvious explanation may be that patients were not paying attention, or did not understand what they were consenting to.

Patients’ reports about their participation preferences in medical decisions can be predicted to a considerable extent. For patients with SMI, poor treatment satisfaction, negative attitudes toward medication, better perceived decision making skills and higher education were related to higher participation preferences. Patients with SMI who want to participate in decision making are often dissatisfied with care or are skeptical toward medication. Patients who judge their decisional capacity as poor or who are poorly educated prefer not to participate in decision making (17).

Research has repeatedly shown that the process of deciding is often difficult and even enigmatic. When faced with a decision that may impact our future significantly many of us circumvent the need to decide. The impediment to decision-making may often be the cost of making a decision. Since people consider this question aversive, there is some utility to choose the default, which allows people not to make choices, because making a decision is cognitively costly (18). In this context it should be pointed out that the assumption that people have reached a decision is frequently mistaken. Instead of expressing well-articulated preferences, the preference in regards to a medically significant decision is not well formed, suggesting the possibility that decisions are often constructed in response to the pertinent question. As a result, the form of the question influences the response (19, 20).

One advantage of the present study is that it uses a

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<tr>
<th>Table 1. Details of patients’ preferences</th>
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<td>Neutral n=104</td>
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<td>Yes</td>
</tr>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>No</td>
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<tr>
<td>Schizophrenia</td>
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<td>Undecided</td>
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<td>Schizophrenia</td>
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<th>Table 2. Demographics</th>
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<tr>
<td>Age (Mean ± SD)</td>
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<tr>
<td>All (N=311)</td>
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<tr>
<td>“Willing” (N=155)</td>
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*Willing” participant - a patient who chose to participate in research in the neutral arm, to actively seek participation in research in the opt-in arm and to remain in the “offered” research position in the opt-out arm.

MDD – major depressive disorder
sample of patients for whom the choice to be made has important consequences. In that sense, this is a valuable field study. Patients with SMI actively participated in the decision-making process and specifically chose active options. Only a few (16% of patients in the neutral condition) could not make a definite choice. It is conceivable that the guidelines presented to the patients in the default conditions had swayed the hesitant patients into a clear-cut decision. While the neutral condition revealed that half of the SMI patients are inclined towards research participation, the opt-out default increased patients’ research participation choice moderately. On the other hand, in the opt-in condition more than 40% of the patients had indeed acted “against” the recommendations of our center’s physicians gravitating towards participation in research.

Social psychology demonstrates that subjects’ choice is influenced by opt-in versus opt-out presentation of decision algorithms. Defaults not only make a difference in what is chosen, they can also make decisions easier. Moreover, default decisions are optimal when subjects have a strong propensity to procrastinate (12). This factor is particularly relevant to SMI patients presented with complex and affectively loaded decisions. The impact of defaults have been emphasized in the general public by several unintended “natural experiments” in which governmental and public organizations randomly assign people to one program and then give the chance to choose among a set of alternative ones – examples include assignment to health care plans, the adoption of privacy policies and organ donation, where the stakes are high (8). These “natural” experiments show that defaults have a substantial role in determining what is chosen. In most cases, the majority of people choose the default option to which they were assigned (13). However, it has not been conclusively demonstrated that in real-life situations, where patients have to commit a major disease-related act (start treatment, undergo surgery or participate in research), defaults play a significant role. A growing literature has examined how these findings may be placed within the context of the therapeutic relationship. Researchers involved in these studies suggest that many patients do not seek the level of involvement which the bioethics literature suggests they should wish. The strong preference for a shared role – physician-patient cooperation – suggests that patients wish to understand their disease and the choices available to them, and to be involved in aspects of decision-making that will affect their quality of life. However, they are willing to leave much of the responsibility for tasks that require expertise to the treating physician (21).

In conclusion, this study evaluated a sample of inpatients facing an important medical decision. The impact of defaults is an important subject of current research and adding to our knowledge of the magnitude of their effects “in the field” is valuable. Unlike lay persons required to decide on important medical matters, patients with SMI take a stand preferring research participation moderately swayed by defaults presentation. We hope that the results would aid both treating psychiatrists and researchers in characterizing those patients willing to take part in clinical research.

References