Identifying patient-relevant endpoints among individuals with schizophrenia: An application of patient-centered health technology assessment

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Objectives: Schizophrenia imposes a great burden on society, and while evaluation should play an important role in informing society's efforts to alleviate these burdens, it is unclear what "endpoints" should be chosen as the objective of such analyses. The objectives of the study were to elicit endpoints directly from patients with schizophrenia, to ascertain whether patients are sufficiently cognoscente to express what endpoints are and are not important to them and to rank the relevant endpoints.
Methods: We applied principles of patient-centered health technology assessment to identify and value endpoints from the patient's perspective. Focus groups were conducted to elicit endpoints, using interpretive phenomalogical analysis (IPA) to guide the collection, analysis and interpretation of data. Patient interviews were subsequently used to elicit patient preference over endpoints. Respondents were presented with cards outlining the endpoints and asked to remove irrelevant cards. They where then asked to identify and rank their five most relevant endpoints in order of importance. Interviews were recorded for the purposed of triangulation, and data was analyzed using descriptive statistics. Patients were recruited from five geographically diverse cities in Germany. Eligibility required a diagnosis of schizophrenia by a physician and treatment with an antipsychotic medication for at least one year. Respondents were excluded if they were experiencing an acute episode.
Results: Thirteen endpoints emerged as important from the focus groups spanning side-effects, functional status, processes of care and clinical outcomes. Respondents could clearly identify relevant and irrelevant endpoints, and rank which factors were important to them. Triangulation between field notes of the ranking exercise and recordings confirmed that rankings were not arbitrary, but justified from the respondents' point of view.

Conclusions: Patients with schizophrenia can express preferences over endpoints. Our results show that qualitative methods such as IPA can be used to identify factors, but ranking exercises provide a more robust method for ranking the importance of endpoints. Future research involving patients with schizophrenia ranking outcomes is needed to identify variations across patients and methods such as conjoint analysis could prove beneficial in identifying acceptable tradeoffs across endpoints.

Keywords: Schizophrenia, Patient-preferences, Patient endpoints, HTA, Health technology assessment

When assessing potential beneficial and harmful effects, patient-relevant endpoints and not their surrogates (i.e., disease-relevant aspects) should primarily be taken into consideration. IQWiG *Methods* (2005) (15)

Schizophrenia is a severe mental illness characterized by disturbances in thinking, perceptions, and emotions, although no one symptom positively identifies schizophrenia (9). Schizophrenia is a major public health problem, affecting approximately 24 million people globally; lifetime prevalence is 1 percent (13). Schizophrenia imposes a great burden to society (16;17;30), and patients are often nonadherent to potentially beneficial treatments. Although there have been calls for more patient-centered care in evaluation (1;12;25), researchers and practitioners have been reluctant to embrace patient-centered methods, especially in mental health. It is often assumed that patients with schizophrenia lack the cognition to either form or express preferences over outcomes (11;24), hence a paternalistic approach is favored to guide treatment and research.

There are a range of treatments available for schizophrenia (19) and evaluation of their efficacy is highly influenced by the choice of treatment endpoints. A debate persists as to what endpoints are appropriate to evaluate for schizophrenia. Despite this debate, endpoints are seldom chosen on the basis of patient preferences (8). Although there has been an international movement toward the measurement of patient reported outcomes (1;12;23), the identification and valuation of these outcomes is often chosen on the basis of clinical opinion or tradition. Patient-centered evaluation requires that patients are involved in all aspects of research, including the choice of endpoints (4;5).

While Germany remains rather paternalistic toward the treatment of patients (29), the incorporation of patient preferences into economic treatment evaluations is already mandated when assessing health technologies, although it is not yet operationalized. The Institute for Quality and Efficiency in Healthcare (IQWiG) makes recommendations regarding the efficiency and efficacy of healthcare services to the Federal Joint Committee (G-BA) (10). IQWiG states that results important for patients need to be taken into account before evaluation conclusions for interventions are reached because this data can substantially alter the conclusions of a systematic review (15). Patient-relevant is described as how a patient feels, their experience or perception of their functions and activities (15;16). To assess the patient-relevant benefit of medical interventions, the clinical outcome measures mortality, morbidity, and health-related quality of life are taken into consideration.

Currently it is not clear what patient-relevant endpoints are, how they are identified or how they are valued. As such, efficiency can not be measured until such endpoints, which could transcend the traditional notion of clinical outcomes to include process issues, are identified and weighed (23). This is not just a problem in Germany, as health economists are increasingly using qualitative methods and ranking approaches to measure patient preferences (2).

Although patients have expressed different priorities for treatment in other areas of medicine, research specific to schizophrenia is scarce (27). This is potentially due to the lack of reliable tools to measure patients' subjective responses, or because patients with schizophrenia typically have disorganized thoughts and thus are perceived to be unable to provide valid responses of their treatment preferences (24). However, the majority of patients with schizophrenia can evaluate and rate their affective state, well being and quality of life when not experiencing an episode of psychosis (3;14;21). This indicates they would be able to report patient-relevant endpoints for treatment. The objective of this study was to: (i) identify endpoints directly from patients with schizophrenia; (ii) assess whether patients can express which endpoints are and are not important to them; and (iii) to rank the relevant endpoints.

METHODS

The study comprised two parts; the first consisted of focus groups, the second of individual patient interviews. Qualitative methods and ranking procedures are increasingly being used as a method to identify patient preferences. Interpretative phenomenological analysis (IPA), a qualitative approach, was used to understand how patients with schizophrenia view their treatment experience and to determine the endpoints of primary importance as related to individual objectives and priorities for treatment. IPA affords insight into patients' verbal accounts of their experience with treatment and has recently been recognized as making important contributions to the field of health psychology (7).

Sample Selection

This study was conducted in five major cities across Germany—Berlin, Düsseldorf, Frankfurt, Hamburg, and Munich. Although interviews occurred in these cities, participants may not have lived within the city limits. The ethics committee of Johns Hopkins Bloomberg School of Public Health approved the study protocol. All research was conducted in accordance with local German regulations. For both focus groups and individual patient interviews, participants were purposively selected to create a sample of individuals between the ages of 18 and 65 years old who met the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, criterion for a diagnosis of schizophrenia F20 or F25. Patients were recruited through office-based psychiatrists using a screener to determine whether inclusion criteria were met. To be eligible for the study, these individuals had to be familiar with the various aspects of treatment, therefore, currently taking a typical or atypical antipsychotic for at least one year. Because the study required individuals to verbalize their thoughts and experiences about treatment, they needed to be stable (that is, in remission) at the time of the interview.

Identifying Endpoints

Focus groups were used to elicit patients' experience with the medical treatment of schizophrenia. The groups were conducted sequentially over three months (September–November 2007) by a trained psychologist. The interview format was group discussion, each group consisting of four to five individuals. A psychiatrist was present during the entire process—to support the interpretation of the patients' statements and as a precaution in the event that discussion was stressful to any participant and triggered a reaction. The purpose of the focus groups was to bring forth the patients' perspectives of the primary endpoints associated with the medical treatments of schizophrenia and to differentiate between the positive and negative endpoints. Due to disease inherent characteristics of schizophrenia, the decision was made to not audio or video record the focus group sessions. All focus groups were conducted in German and simultaneously transcribed. A literature review and individual interviews with psychiatrists and other clinicians were conducted to validate and supplement our results.

Transcribed notes from the focus groups were reviewed several times to identify key issues that were raised during the discussion. From this list of key issues, themes were identified that best reflected the underlying meaning. These themes were then reduced to more specific endpoints of treatment. At this point, text was translated into English. To triangulate the accuracy of translations a second reviewer reassessed the transcripts to ensure the validity of translation and interpretation. Themes were aggregated across focus groups and compared; themes that were not consistent or common across focus groups were discarded.

Ranking Endpoints

Individual in-depth patient interviews were used to validate the results of focus groups. Participants were presented with all endpoints printed on cards and asked to explain the meaning of each endpoint in relation to their own treatment experience. Cards were presented in groups of four or five cards to avoid overwhelming the participant with too many tasks at once. After the presentation of all endpoints the participants were asked to remove the cards whose topic was irrelevant to them. From the remaining cards that contained the relevant attributes, participants were asked to choose the five that were most important to them and rank them from most to least important. Interviews occurred sequentially across the five locations and vernacular changes were made on five of the thirteen cards during the early interviews. From the focus group experience, it was decided that audio recording the interviews was possible. Each individual interview was audio recorded for later analysis.

The results from the card ranking exercise during the individual in-depth interviews were evaluated by calculating three summary measures for each endpoint. The first is the percentage of respondents that selected the endpoint as relevant and ranked it in their top five (denoted "important"). The second is the percentage of respondents that ranked the endpoint as relevant but did not rank it in their top five (denoted "relevant"). The third is the percentage of respondents that selected the endpoint as being irrelevant for them (denoted "irrelevant").

RESULTS

A total of 30 patients with schizophrenia between the ages of 18 and 65, average age 36.6 and in therapy for an average of 4.8 years, participated in the five focus groups. We found that the key themes could be summarized by thirteen endpoints. Table 1 exemplifies these endpoints with direct quotes from the respondents. Although medication was associated with negative side-effects, it was simultaneously viewed as a means to achieve one's desired functionality in daily activities, cognitive capabilities, and reinstatement of social activities.

Side-effects that were hardest to tolerate and mentioned the most are weight gain, emotional flattening and sexual side-effects. One participant said, "*I have a real potbelly; 10–20 kilograms; I know some who gain 50 kilograms...*", and the entire group was in agreement. Another described their inability to feel emotion and function on a daily basis, "*...I only function now, I know from my previous life how I should behave... when I should smile to show happiness... but my gut feelings are completely gone.*" Concerning sexual side-effects, another said, "*...a decreased libido is not a nice side-effect to deal with.*"

Additional negative side-effects of treatments included mood swings, excessive tiredness, sleep disturbances, and

Table 1. Patient-Centered Endpoints

Endpoint	Patient quote
My bodyweight	"I gained about 40 kilograms"
Relapse/acute symptoms	"I had delusions and thought someone wanted to kill me"
Problems with intimate relationships	"My sexual life does not function anymore".
Social activities	"I only go out when I have appointments"
	"I have barely any social contact"
Problems sleeping	"I have light superficial sleep"
	"I wake up and can't fall back asleep"
Fatigue/listlessness	"A bit of energy is missing that I had before"
	"I have more energy – physically and mentally"
Uncontrollable movements	"In the evening I have the feeling that I must move my feet"
	"I had serious unrest in my legs and could not hold them still"
Clear thinking	"I am sure that I cannot think as well"
Group therapy	"I would like it if there was a self-help group in my area, but there is not"
Daily activities	"I am able to live an almost normal life"
Supportive physician	"I go to the doctor, he prescribes something, but the conversation is missing"
	"I don't get any information when I ask the doctor"
Minimization of disease symptoms	"The disease does not come out anymore"
Involuntary drooling	"One has an increased amount of saliva"

slow or delayed thinking. Side-effects experienced varied by individual, even when referring to the same medication. There was little to no agreement across participants regarding the side-effects that were most difficult to tolerate or had the greatest negative impact on their quality of life.

Limited or no social contact was commonly reported, particularly during acute phases of the illness. During stable periods, social contact was described as limited to one or a small number of individuals whom they trusted. As one individual described the change in their life upon initial diagnosis, "*it was as if at 20 I was thrown out of my life*." The participants clearly believed, upon their diagnosis with schizophrenia, a loss of their identity and equated losing their social connections to a losing their life before diagnosis. Another participant said, "*One feels isolated, because you can not relate to others anymore*." Loss of social contact was not believed to be one-sided. Many thought that they had "*less social contact because people do not know how to act around them*."

The physician is the primary contact for patients concerning their treatment, which is important as improved mental health provider-patient communication has resulted in improved adherence to medication in the field (6). Participants commonly reported dissatisfaction with their physicians. Respondents believed that physicians were failing to appropriately address various treatment issues, such as duration, potential side-effects, and were unwilling to change treatment based on intolerable side-effects. Better communication between physicians and patients about the entire treatment process was desired. In addition, most patients expressed the desire to play a more active role in deciding on their treatment regimen. "*When patients bring up an issue, then the physician should take it seriously and give information.*" One participant believed that it is "*often underestimated what the patients understand.*"

Participants spoke about episodes of psychosis and the symptoms of schizophrenia and the effect of treatment on these. These included hearing voices, hallucinations, lost concept of time, difficulty discerning reality and issues of apathy and anhedonia toward every day living. On medication, patients agreed that "*the disease does not come out anymore.*" Before treatment, one patient said they experienced, "*extreme inner unrest, a nervous breakdown. Now I am much more relaxed, better.*" Patients explained that over time they experienced fewer relapses every year.

Rankings of Endpoints

A total of 25 patients with schizophrenia across the five German cities participated in the individual interviews. On average, participants were 40.6 years old and were in treatment for 7.4 years. Forty-two percent ($n = 11$) of respondents were employed full time, 19 percent ($n = 5$) worked part-time, 19 percent ($n = 5$) were unemployed, one was studying at the university level, one was retired (12 percent did not report employment status). Almost half of the patients lived alone, 46 percent ($n = 12$), 15 percent ($n = 4$) were married and living with their partner, 11.5 percent ($n = 3$) lived with their parents or sibling, 8 percent ($n = 2$) lived in a group home and 19 percent ($n = 5$) did not report their living situation.

The proportion of respondents selecting the endpoints as important, relevant, and irrelevant are presented in Figure 1. Preference studies have previously shown that nonhealth endpoints and processes should be taken account of in utility studies (26;28). Our study also serves as evidence that there is utility beyond the traditional health outcome. The endpoint *ability to think clearly* was selected as important by 80 percent ($n = 20$) of the sample, relevant for 20 percent ($n = 5$), and was never selected as irrelevant. *Social activities* and *minimization of disease symptoms* were each viewed as important for 76 percent ($n = 19$) of the sample, relevant 20 percent ($n = 5$ and $n = 4$) and irrelevant 4 percent and 8 percent ($n = 1$ and $n = 2$), respectively. Having a *supportive physician* with whom the patient could openly and comfortably discuss their treatment with was ranked as important by 60 percent ($n = 15$), 20 percent ($n = 5$) as relevant, and
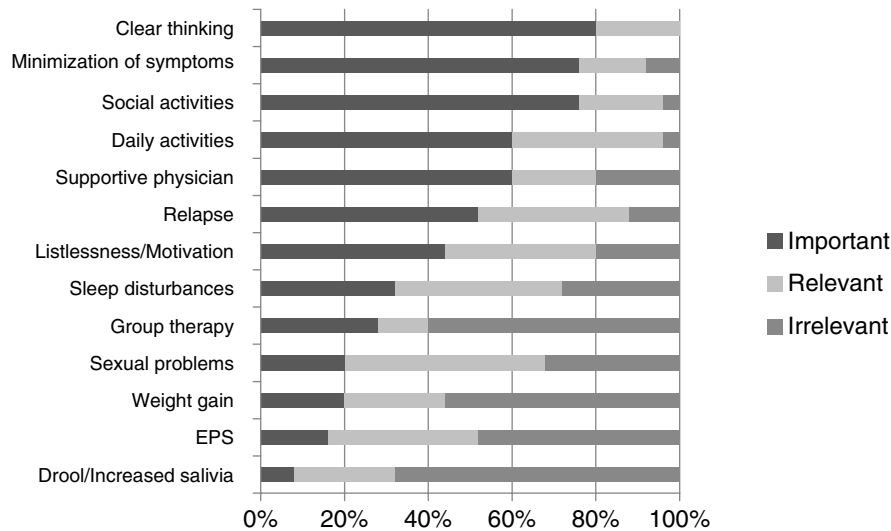
Figure 1 Frequency of relevance and irrelevance of endpoints.

irrelevant by 20 percent ($n = 5$). Participants who believed *having a supportive physician* was irrelevant explained that one should change their physician if not satisfied. Lastly, recognizing the effect that schizophrenia can have on ones daily activities, which was described as maintaining a household, employment, and attending and finishing university was important 60 percent ($n = 15$) of the time, relevant 36 percent ($n = 11$) and irrelevant only 4 percent ($n = 1$) of the time.

DISCUSSION

The results of this study indicate that patients diagnosed with schizophrenia have distinct preferences for treatment endpoints and can prioritize them. Our results show that traditional clinical measures of treatment endpoints do not always coincide with patient priorities for treatment endpoints, results that are consistent with recent research findings (26). The majority of participants experienced weight gain, which is one of the most frequent side-effects of antipsychotic medication, and in particular the atypical agents (18;20;22). We find that weight-gain is not a priority for patients as they rank other endpoints as more important, despite weight gain and its metabolic consequences being important to physicians treating these patients.

When empowering patients' to take a more active role in their treatment, this research found that it is important for them to feel supported by their physician. The majority of patients were not satisfied with the way their physician addressed potential medication side-effects or dealt with how the patient tolerated the medication side-effects. Improving patient-physician communication has the potential to increase adherence to treatment (6). Individuals respond differently to medication such that one medication may be

successful for one patient but for another the side effects can not be tolerated. Thus, individualized treatment is a key aspect of the pharmacotherapy management of patients with schizophrenia.

The success of a treatment is commonly measured by remission of disease symptoms, yet this does guarantee that the patient returns to a normal life, that is, life before diagnosis. However, studies have shown that utility beyond the traditional health outcome exists (28). Patients described postdiagnosis as being forced to begin a new life; *thrown out* of their previous life and had difficulty functioning as before. This is an important aspect of the chronic management of schizophrenia, and one that was significant for the patients in this study. This demonstrates that the successful treatment of schizophrenia involves not only the remission of symptoms, but also patients' objectives for resuming their activities and functions. To the extent that physicians can work with patients to set goals and expectations that allow them to resume a life that is as close as possible to their former existence may be an important factor in improving the patients' quality of life.

CONCLUSIONS

Although traditional clinical endpoints such as the minimization of symptoms are important, there also are patient-relevant endpoints that can be equally important for general social well-being. The patient-relevant endpoints such as the *ability to think clearly, participation in social activities, ability to conduct daily activities* and the process of care *having a supportive physician* would not be captured and evaluated using traditional clinical endpoints. Increasing patient satisfaction with treatment through shared decision making and the valuation of patient-relevant endpoints in HTA, offers

considerable potential for improving disease management, patient compliance and further treatment outcomes (26;29).

We have shown that patients with schizophrenia do have preferences over treatment outcomes and have shown that these preferences can be validated by patients through a ranking exercise, a result that is consistent with recent findings by Pyne and Labbate (26). The next research step is to develop a method for measuring attributes on a cardinal scale. Cardinal measurement would show to what degree one attribute is preferred over another, which would allow more precise estimation of preferences. Future research should focus on developing cardinal measurement tools for patient-relevant endpoints and advancing the inclusion of patient-relevant endpoints into evaluation. Here patient preference methods such as conjoint analysis show real promise in the search for patient-relevant endpoints. Such methods could not only be used to identify and value patient-relevant endpoints, but they can be used to identify acceptable tradeoffs across endpoints. Further research is needed using such methods in health technology assessment, both in the case of schizophrenia and beyond.

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