

# The Side Effects of Antipsychotic Drugs and Patients' Quality of Life: Patient Education and Preference Assessment with Computers and Multimedia

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*Determining the relative value of novel antipsychotics such as clozapine requires measures of the utility of their different side-effect profiles. Many of these side effects (SE) are complex and difficult to describe adequately. Schizophrenic patients are also difficult to interview reliably. Even in normal subjects, utility assessment can be tedious, inconsistent, and difficult for subjects to understand. We addressed these challenges by developing a multimedia patient education and utility assessment tool.*

*SE were described using short video sequences accompanied by digitized voice descriptions. Patients' preferences were assessed using visual analog scales, pairwise comparisons, and standard gambles. These assessment techniques were carefully explained and logically integrated. Instructions were presented both by digitized voice and in print, and, if necessary, were clarified by a moderator. Animated displays were used to graphically display probability. Reminder pictures, comprehension tests and validation questions were used throughout the survey.*

*Thirty-three patients from VA and public clinic inpatient and outpatient settings took the survey. Five psychiatrists were surveyed as a reference group. Patients understood the SE and the survey (92% mean comprehension) and their answers were internally valid and consistent (74% internal consistency). The standard gamble disutilities for the SE were substantial, ranging from 12-20% decrease in their quality of life.*

*Computer-based, multimedia techniques are useful in conducting utility assessment and evaluating its validity. They allow effective patient education and elicitation of useful values, even in subjects with cognitive impairments.*

## INTRODUCTION

Assessing the value of drugs and other treatments requires quantitative measures of their relative benefits. In diseases like schizophrenia, improvement in quality rather than quantity of life is the major indicator of treatment efficacy. A comprehensive and representative measure of drug effects involves asking patients for global assessments of their impact on their quality of life (QOL). In the process, patients

become informed about their treatments and can play a more active role in therapeutic decision-making.

Measuring benefit may be particularly valuable for drugs which have both high costs and high risks. In such circumstances, the perceived magnitude of any benefit must be weighed against risks and costs on an individual basis. Clozapine is a novel antipsychotic, with significant side effects (SE) but which offers, in general, a better quality of life to patients than alternative neuroleptic agents. However, it is many times more costly. It may also be associated with an increased risk of death due to agranulocytosis. The indications and use of clozapine are limited, partly because the significance of its quality of life benefits in the face of its risks is unclear.

We sought to quantify these benefits by educating patients about the main SE differentiating clozapine from other antipsychotics and assessing their impact on patients' QOL. This allowed us to calculate relative risk-benefit and cost-utility ratios for clozapine and to gain insight into policy and individual treatment decisions for the drug therapy of schizophrenia.

## BACKGROUND

Researchers in psychiatry have traditionally used rating scales to evaluate the SE of antipsychotics. These scales ask physicians to rate the severity of various manifestations of the SE in the patient and add the ratings to provide a global score [1-3]. Since these scales measure only certain aspects of the SE, they do not provide a comprehensive rating of quality of life. They also do not address subjective dimensions of health state experience that may be critical to determining patients' perception of their QOL [4]. Since each scale is specific to a class of SE of neuroleptics, the significance of ratings on one scale cannot be compared to another or to SE caused by drugs for other illnesses.

Schizophrenics' disease-symptom related QOL has also been measured using rating scales [5,6]. Here, the physician gives a rating to various dimensions of a patient's life, such as social interactions and living environment, and adds up the ratings to provide a measure of overall quality. These scales do not correlate well with more direct measures of improvements from medication [7]. They also depend heavily

on standard of living measures, which may not correlate with patients' own assessments of well-being [8].

These traditional methods are really qualitative, not quantitative. They do not weight individual aspects for their importance to patients' lives, and they use physicians' values rather than patients'. The reliability and validity of schizophrenics' responses are often called into question. However, it may be difficult for people who have never experienced these SE to imagine what they are like. Psychiatrists may also have intrinsic biases that affect their answers; psychiatrists and patients have given very different ratings of severity for many of these SE [9].

In order to provide a quantitative, direct measure of the impact of these SE on patients' QOL, we turned to the techniques of patient utility assessment [10]. Several groups [11,12] have developed HyperCard computer-assisted utility and QOL assessment tools. However, these programs are relatively complex and difficult for patients to understand. Others [13] have used laser disks and videos of patient testimonials for patient education and support of decision-making. These programs are expensive to produce and require elaborate systems to operate. Unlike previous multimedia efforts, this survey was designed to be delivered on a "stand-alone" portable computer. The survey closely couples patient education and assessment of patient preferences using utility theory.

### DESIGN CONSIDERATIONS

The primary design goal was to maximize construct validity of preferences assessed for the health states. Since methods such as rating scales are not highly correlated with utilities [14], there was no standard against which we could compare our answers. We therefore emphasized careful development of SE descriptions and clear and valid assessment tasks. Since the usefulness of answers obtained from schizophrenics may be disputable, the reliability of the assessment process needed to be carefully monitored. This was addressed at several steps in the program, through monitoring by one or more moderators, and by interviewing psychiatrists as a reference group.

Schizophrenics can also easily become disinterested, frustrated, or lose concentration, so the survey process needed to be as enjoyable and easy as possible. They are often relatively uninformed about the effects of their treatments, so effective methods of patient education needed to be developed to assure understanding. Since clozapine is not available to many patients, the survey could not specifically discuss its benefits or offer patients treatment choices.

### IMPLEMENTATION

The survey was implemented in HyperCard on a Macintosh computer. Digitized voice, sound, music, and animation were used to facilitate and clarify the interview process. The program with sound and pictures occupies about 8 MB of disk space. A PowerBook 180 was used to deliver the survey. Its gray-scale high-resolution display allowed for easy portability and high-quality visual presentation. A moderator assisted patients with use of the survey. Patients used a large external trackball to indicate their responses. The moderator assisted the patient when necessary using the trackball integrated in the PowerBook.

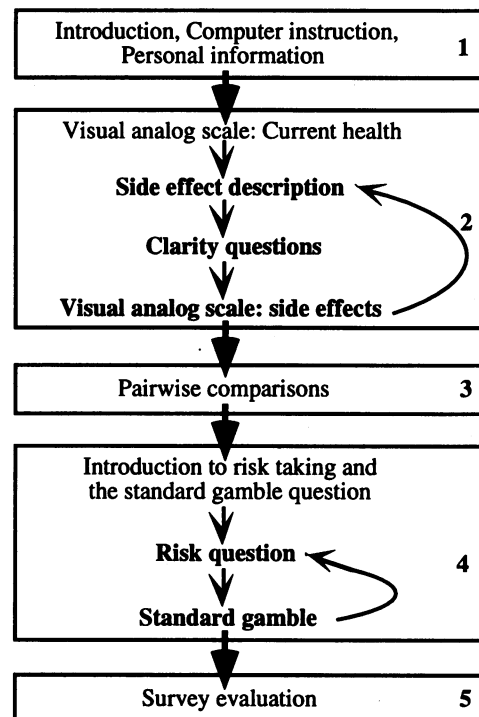


Figure 1. Structure of the program. Steps in bold are repeated for each of the three side effects.

### Presentation of the side effects

Three SE, akathisia (aka), parkinsonism (par), and tardive dyskinesia (td), were selected as the key factors in the decision through review of over 100 references and through pilot testing. Physician and patient descriptions of these SE were compiled from the literature. 25-second descriptions were recorded into HyperCard and refined through consultation with an expert and with patients until they were readily understandable and communicated the SE clearly. They were presented in the format: "This person has tardive dyskinesia. If you had this...", and included

physical and psychological factors as well as a sense of how they would affect the patient's life. Medical terms were used for the SE both because patients should be aware of the terminology their doctors may use and because they allowed for testing of subjects' understanding.

Video clips demonstrating each SE were imported onto the computer and combined using a graphics program to form large PICT files. Different portions of each file were shown in sequence or in random order to present simple animations. Combination with digitized voice descriptions allowed effective, real-time demonstration of the mouth motions of tardive dyskinesia, the stooped posture and rigid gait of parkinsonism, and the restless pacing of akathisia.

### Evaluating Understanding

Once the subject is satisfied that she understands the SE, she is tested to verify her comprehension and attention. A multiple-choice question asks her to define the SE. This question addresses several types of errors, including confusion between SE, and projection of patients' dissimilar experiences onto the SE description. The subject then rates her subjective understanding of the SE and her degree of confusion about the SE on a 5-point categorical scale. Finally, she is asked about her experience with the SE: whether she has or has ever had it herself, and whether she has ever seen it in anyone else. The moderator usually explores any positive responses to ensure that the subject's experience matches the SE presentation.

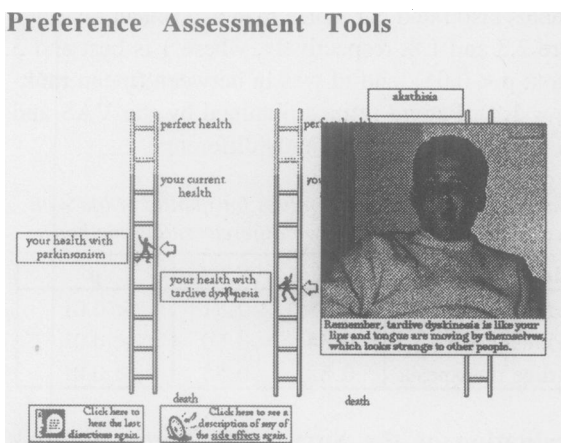


Figure 2. Visual analog scales for the SE.

**The visual analog scales.** The visual analog scales (VAS) were represented as ladders with climbing figures on them. The subject moves the figure up and down the scale, accompanied by a musical scale, to indicate her rating for the health

state. The subjects are introduced to the VAS by rating their current health-related QOL. After they view each SE description and answer questions about it, they are asked to imagine what their health would be like if they had that SE. They are then asked to move the box for that SE down the scale to what they believe their QOL would be if they had the side effect. After viewing all three side effects, subjects can re-adjust their ratings for QOL.

**Pairwise comparisons (PWC).** Subjects are asked, for each of the three possible combinations, which of two SE they think is worse. These were included as a check on subjects' consistency and to help them reconsider their ratings.

**Utility assessment.** The final task is a tradeoff for each of the SE using the standard gamble (SG). Here, subjects are asked to make a choice between a certain outcome (the SE) and an uncertain outcome (a risk). Since schizophrenics often have no control of money or other personal belongings, the only meaningful and standardizable tradeoff is what risk of death they would be willing to take to avoid a SE.

Subjects are first introduced to the concept of taking risks in order to achieve benefits. They are then given practice with the SG method with some simple health states. For each SE in turn, they are asked whether they would be willing to take any risk of an immediate, painless death to avoid the SE. If they are, they are asked to quantify their risk.

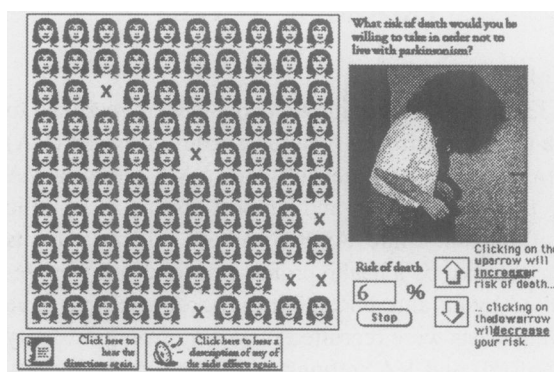


Figure 3. SG with wall of faces risk representation.

Since many patients are unfamiliar with concepts of probability, two visual representations were developed to illustrate the subjects' responses. The wall of faces, conceived during earlier work in this lab, shows a box with a hundred faces, either male or female, depending on the gender of the subject. For each 1% increase in the probability of death, one face is randomly replaced by an X. The more traditional piechart

representation is shown on the following card and the subjects are given a chance to change their answers.

### Reminders

At any stage in the program, there is always an icon that the subject can click on to repeat the instructions they have just heard. The moderator is also present at all times to ensure understanding, answer any questions, or rephrase instructions. Once she has viewed the description, the subject can review it at any time by clicking on a button which appears on each card. Each time that a question is asked about a SE, a visual icon and either a short written or a digitized voice description are included to improve recall. In the VAS and PWC, the icon appears when the pointer is over the name of the SE.

### Possible biases

One potential difficulty is that subjects' rankings of subsequent health states may be affected by the order in which they are presented. To minimize this, each health state was presented distinctly and was evaluated on a separate VAS. SE presentations and assessments were also randomly ordered.

Written and digitized voice instructions were carefully edited several times to remove as much negative framing as possible and to maximize consistency of wording throughout the survey. The standardized program avoided much of the variation of a personalized interview. In order to minimize bias, four different moderators administered the survey.

## PROGRAM STATUS

### Evaluation

33 chronic schizophrenic patients were recruited to take the survey from a Veteran's Administration (VA) open inpatient psychiatric ward, a VA clinic, a VA day treatment center, and support groups at a public mental health clinic. Approximately half the patients were referred by a health professional and half were recruited by an announcement in a group setting. Five psychiatrists were recruited in writing from university (Stanford) and VA settings and from the community to serve as a reference group.

### Results

**Patient Population.** The mean age of the patients was 43 (range 23 - 73). 94% were male, and 25% were African-American or Hispanic. 90% of the patients had never used a computer before. 78% of the patients had had at least one of the SE themselves, and 88% had seen at least one in someone else. The

psychiatrists had a mean age of 50 (range 38 - 62), and all were white males.

**Comprehension.** 92% of the multiple-choice clarity questions were answered correctly. Patients performed significantly better on aka than on par (100% correct answers vs. 84% correct), and td was in between (91% correct). More patients reviewed the video description for par than for aka or td (23% vs. 5 and 9%, respectively;  $p < 0.09$ ). For the different SE, patients reported about the same mean rate of understanding (3.6 - 3.8, where 1 = not at all and 5 = very well) and confusion (2.1 - 2.3, where 1 = not at all confused and 5 = very confused).

**Internal Validity.** Internal validity was measured by determining the order of rankings on the VAS, PWC, and SG, and measuring their consistency. The mean rate of patient consistency between methods was 76%. Psychiatrists had 100% consistency.

**Ratings.** The values obtained from the VAS and SG are shown in Table 1. The values obtained from patients and psychiatrists were relatively equivalent. In the VAS ratings, patients rated the SE differently ( $p < 0.05$ ); aka was the highest, and par the lowest ( $p < 0.01$ ). Psychiatrists' ratings were similar, but in a different order; td was the highest, and par the lowest ( $p < 0.06$ ).

The same trends were relatively consistent in the SG, but were not as significant. Patients rated par as the worst SE here as well ( $p < 0.09$ ). In the PWC, patients also rated par worse than aka (mean rankings were 2.3 and 1.8, respectively, where 1 is best and 3 worst;  $p < 0.05$ ), and td was in between (mean ranking = 1.9). Patient ratings obtained by the VAS and SG methods were significantly different.

Table 1. Patients' mean values for quality of life with each side effect for the two different rating methods.

Side effect	SG	VAS	p
Akathisia	0.88	0.61	< 0.01
Parkinsonism	0.84	0.50	< 0.01
Tardive dyskinesia	0.88	0.55	< 0.01

**Evaluation of the Survey.** The program took from 15 - 30 minutes to complete. On average, patients reported that they understood the survey "pretty well" (mean = 3.9, where 5 = "very well"), and were only a little confused (mean = 1.7, where 1 = not at all confused). They also enjoyed the survey, rating it an average of 8.5 (10 was a very positive experience and 0 was a very negative one). Psychiatrists also ap-

proved of and enjoyed the survey; they gave it an average rating of 8.9 on the 10-point scale.

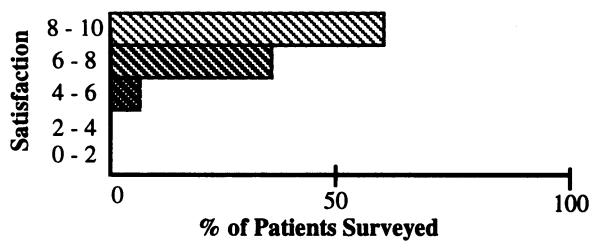


Figure 4. Patient satisfaction with the survey experience.

## DISCUSSION

The survey enabled schizophrenic patients to understand complex SE and answer difficult questions about their QOL. Patients' answers were relatively consistent. Most patients enjoyed taking the survey.

The values obtained from the VAS were significantly lower than those from the SG. This agrees with earlier work showing variation among methods for measuring well-being [15]. These different methods may be measuring different dimensions of QOL. The VAS appears to be a better indicator of perceived severity, while the SG incorporates considerations of risk and time that make it more comparable to real clinical situations. When the SG values were combined with data from earlier work [16], the relative risk-benefit ratio for clozapine appeared favorable in most situations. Clozapine may also be cost-effective for many schizophrenic patients with severe SE.

Preference assessment with computers and multimedia can allow effective patient education and value assessment, even in subjects with cognitive impairments. These techniques can make the process enjoyable enough that patients can learn, concentrate, and participate, while keeping the process meaningful so that they give reliable and useful answers.

## FUTURE WORK

Different degrees of SE severity may be associated with variation in values that might impact the estimated the risk to benefit ratio. Patients' utilities and ratings of the severity of their own SE should be compared to values determined by physician assessments using rating scales. The methods of education and preference assessment applied in this study are also currently being applied to other medical decisions where the QOL is an important factor [17].

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