Schizophrenia Bulletin Open
https://doi.org/10.1093/schizbullopen/sgab046

Patient Preferences for Antipsychotic Drug Side Effects: A Discrete Choice Experiment

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Background: **Development of pharmaceutical interventions for schizophrenia emphasizes clinical efficacy and subsequent effectiveness and cost-effectiveness. However, given the many side effects of antipsychotic medication, it is important to consider the importance of different side effects on the preferences that people with schizophrenia have for different drugs. This study aims to use a discrete choice experiment to elicit patient preferences for antipsychotic medication with different side effects profiles.** ***Method:*** **Preferences for antipsychotic side effects were investigated using a discrete choice experiment conducted in south London. 297 participants with a schizophrenia diagnosis who had been in receipt of anti-psychotic medication for a minimum of one month were included. Participants were presented with a sequence of choices involving five antipsychotic side effects (attributes) each with four levels. Conditional logit models were used to determine the side effects most (and least) likely to be preferred by people prescribed antipsychotics. Subgroup analyses explored the impact of side effects by gender, ethnicity, age, and symptoms.** ***Results:*** **As expected, participants tended to value antipsychotic medications offering the least side effects, and the model coefficients were in the expected direction. For the whole sample and subgroups, memory and fatigue were the most important side effects, whereas palpations and mobility were the least important.** ***Conclusions:*** **Participants had a strong preference for medications with the least side effects on memory and fatigue. These findings should inform drug development by pharmaceutical companies and prescribing practice by clinicians.**

Key words: schizophrenia/psychosis/antipsychotics/discrete choice experiment/patient preferences

Background

Pharmaceutical development places understandable attention on clinical efficacy and subsequent effectiveness and cost-effectiveness. Side effects of drugs are also assessed. However, if an efficacious and effective drug is going to be widely used and accepted then patient preferences should also be considered during development. Understanding how importantly patients regard side effects is crucial for many reasons. A drug that produces side effects that are highly detrimental to patients is less likely to be adhered to and may be avoided by prescribers. A useful tool for drug developers would be a simple algorithm for taking forward medications that minimizes the most troublesome side effects from the patient's point of view.

Antipsychotic medications although beneficial in relieving positive psychotic symptoms, do produce troublesome side effects, and patients and prescribers make trade-offs between their benefits and adverse effects. This is because they have an impact on clinical outcomes, quality of life, adherence, treatment attrition, and relapse.[1–3] Adverse effects include extrapyramidal symptoms for most first-generation antipsychotic drugs, and problems linked to metabolic syndrome for second-generation drugs, especially olanzapine and clozapine.[1] Other side effects include weight gain, sexual dysfunction, restlessness/akathisia, and cardiovascular effects.[4,5] However, it is important to emphasize that all these drugs have side effects and rather than the simple dichotomization not those associated with first- and second-generation antipsychotics, it is more reasonable to view the side effects on a continuum that includes both generations.

It is well known that average life expectancy is lower for people with schizophrenia, but while antipsychotic

medication can contribute to medical comorbidity, this may be balanced to a greater or lesser extent by their impact on mortality via there efficacy in treating positive symptoms.[19]

Side effects range in intensity and duration, and patients have varying tolerance levels for different side effects and their choices are not necessarily linked to their frequency and severity.[5] These individual reports of distressing side effects differ from the list of side effects generally monitored by healthcare professionals which are more often those that have implications for long-term health. A better understanding of patient preferences for side effects may assist the development of medicines with better tolerability and which may therefore be more effective in clinical settings and aid recovery.

Although we can assess distressing side effects from clinical interviews or self-report,[5] the heterogeneity of individual responses does not allow more general weightings of preference for one type of effect against another. However, patient's preferences can be evaluated using discrete choice experiments (DCEs) which are sometimes called stated preferences discrete choice modeling or under the more general term conjoint analysis. These are increasingly being adopted in healthcare evaluations to determine what drives people's preferences for different ingredients or effects of interventions.[6,7] DCEs help to reveal individuals' implicit choice processes by breaking up a treatment or service into its key characteristics and observing the choices made between different scenarios when the levels are varied. They also allow an integration of responders' values on varying aspects of care into one measure.[8] People with psychosis have previously taken part in these sorts of choice experiments,[9,10] including those focusing on side effects of antipsychotics.[11]

This study used a DCE to elicit patient preferences for different side effects of antipsychotic medication and subsequent models explored the importance of specific sides effects for different subgroups within our sample.

Methods

Design

This is an observational study where participants were asked to make choices between different combinations of side effects with varying severity, known as a Discrete Choice Experiment. Participants randomly received one of three blocks of questions, from which they had to select one alternative based on the perceived side effects (figure 1). They were invited to consider hypothetical scenarios (choice sets) and to indicate their preferred drug. The survey was administered by interview with research assistants. The study was given ethical approval by the NRES Committee London—Dulwich (12/LO/2034).

Study Sample

Participants aged 18–65 were recruited from three mental health hospital trusts: South London and Maudsley NHS Foundation Trust, Oxleas NHS Foundation Trust and South West London and St. George's Mental Health Trust. They were required to have a diagnosis of psychosis or a schizophrenia-spectrum disorder and to receive antipsychotic medication for a minimum of one month. Patients were excluded if they lacked the capacity to consent to research as judged by care staff, as well as an inability to communicate fluently in English. There are no accepted rules for determining sample size for a valuation exercise such as a DCE. A sample of 300 was considered suitable and was similar to other studies reported in the literature.

These two drugs have the same effect on symptoms, but they differ on their side effects. Based on this information would you choose drug 1 or drug 2?

Side effect	Drug 1	Drug 2
Memory problems	Moderate	Mild
Putting on weight	Severe	Moderate
Feeling tired	None	Mild
Rapid or irregular heartbeat	Moderate	None
Slowness in moving around	None	Mild
If you were offered one of these drugs, which would you prefer (please tick a box below)?	Drug 1 ☐	Drug 2 ☐

Fig. 1. Example of a choice set presented to patients.

DCEs: Choice of Attributes and Levels

In the experiment, patients were presented with six questions and were asked to select a preferred alternative from a pair of specified profiles that contained varying levels of side effects. Five side effects considered to be the most personally important were identified from a previous study.[5] They were memory problems, putting on weight, feeling tired, palpitations, and slowness in moving around. The severity of each side effect was categorized into four levels: not present, mild, moderate, and severe. Side effects (attributes) and their severity (levels) (table 1) were used to generate possible combinations of pair-wise choices. Full factorial investigation produced 1024 profiles (four raised to the power of five) and so to present a manageable number, an efficient experimental design of 18 profiles was obtained using D-efficiency in SAS.[12] To reduce the cognitive burden on respondents further, three blocks of six sets were produced, and participants were required to choose between two alternative drugs with different profiles of side effects (Drugs 1 and 2), with no opt-out option.

Survey Instruments

We included questions on key demographic characteristics as well as clinician reported diagnoses and current psychiatric medication. Participants completed the Maudsley Side Effects measure to determine the severity, life impact and distress associated with their side effects over the previous four weeks.[5] The Brief Psychiatric Rating Scale (BPRS) was administered to assess psychiatric symptoms over the previous seven days.[13]

Table 1. Attributes and Levels of Antipsychotics used in the Survey

Attributes	Levels
Memory problems	Not at all Mild Moderate Severe
Putting on weight	Not at all Mild Moderate Severe
Feeling tired	Not at all Mild Moderate Severe
Rapid or irregular heart beats	Not at all Mild Moderate Severe
Slowness in moving around	Not at all Mild Moderate Severe

Statistical Analysis

Data were analyzed using STATA 15. The assumption in random utility theory underlying DCEs is that an individual will choose a profile that in economic terms maximizes their "utility function" compared to an alternative set. Utility in this sense can be defined as well-being or desirability. In analyzing the DCE data, we assumed that the value of side effects could be represented in a nonlinear model and that the error of variance was not constant. A conditional logit model was used to estimate the impact on utility or desirability of the antipsychotic if it resulted in more severe side-effects.[14] Dummy variables representing mild, moderate, or severe side effects were entered with each compared to having no side effects. A model was produced for the full sample and then subgroup analyses were conducted for gender, ethnicity (White British or Black and Minority Ethnic), age group (21–40, 41–50, 51 and over), and symptoms (BPRS score of 24–47 or 48–168).

Results

Participant Socio-demographic and Clinical Characteristics

About 297 participants had complete DCE data. Background demographic and clinical characteristics are presented in table 2. Participants were on an average of 45 years old, predominantly male (67%), with a schizophrenia diagnosis and 32% were severely (22%) or extremely symptomatic. Just under half of participants had been in receipt of one of their current antipsychotic medications for at least six years. One (0.3%) person was recorded as not being in current receipt of an antipsychotic drug, 55 (18.5%) were receiving first-generation antipsychotic drugs only, 233 (78.5%) were receiving second-generation drugs only, and eight (2.7%) received both. The Maudsley Side Effects Measure revealed that the most common side effects were feeling tired (80%), putting on weight (66%), memory issues (63%), finding it hard to concentrate (62%), being thirsty (61%), passing urine frequently (61%) and finding it hard to get out of bed (60%). The *most important* side effects were a dry drooling mouth (23%), feeling tired (20%), putting on weight (14%), vertigo (10%), memory issues (10%), finding it hard to fall asleep (9%), blurry vision (9%), and joints that hurt (9%). They reported a mean of 22 side effects among which 7 (mean) were distressing. 84% of the participants reported that they thought the benefits from their medication outweighed the negative side effects.

The Impact of Side Effect Severity on Participant Choices

The results of the conditional logit models are shown in table 3. The coefficients report the impact on the desirability of the antipsychotic if the side effect is present

Table 2. Background and Clinical Characteristics of Participants

Characteristic	Number of respondents (N = 297)	Percentage of respondents
Gender		
Women	98	33.0
Men	199	67.0
Study site		
South London and Maudsley NHS Trust	126	42.4
Oxleas NHS Trust	55	18.5
ST George's NHS Trust	116	39.1
Ethnicity		
White British	130	43.8
Black and minority ethnic	167	56.2
Diagnosis		
Schizophrenia	268	90.2
Schizo-affective disorder	23	7.7
Psychosis	6	2.0
Illness severity[a]		
Mildly ill	8	2.7
Moderately ill	76	25.7
Markedly ill	117	39.5
Severely ill	66	22.3
Extremely ill	29	9.8
Duration on antipsychotic medication		
Under 1 month	2	0.7
1–6 months	20	6.8
7–12 months	27	9.2
1–5 years	104	35.3
Over 6 years	142	48.1
	Mean (Range)	Standard Deviation
Age (in years)	45.5 (21–66)	9.7
Brief Psychiatric Rating Scale[a] total score	49.3 (27–96)	13.6
Total side effects reported	22.2 (0–47)	10.3
Distressing side effects reported[a]	7.1 (0–38)	9.0

Note:
[a]One missing case for these variables.

compared to it being absent, so a lower number indicates a reduced desire for a drug with that level of side effect. Findings for the full sample revealed that for each domain the desirability of the drug went down as side effect severity increased. For example, if the antipsychotic caused severe memory problems then utility/desirability reduced by 2.6 compared to a situation where memory was not impaired. (It should be noted that utility is not bounded by 0 and 1 as is common in some economic evaluations.) The largest impacts on drug desirability were for memory problems and problems with fatigue. Problems with mobility and palpitations had the smallest impact, although the impact of moderate and severe levels of these problems was still statistically significant.

Are There Any Other Factors that Affect Choices?

Both memory and fatigue problems had the largest negative impact on desirability for the drug for men and women, although the impact of fatigue was particularly strong in women. But mobility problems only had a statistically significant impact on drug desirability for men, and although weight problems were important there were no differences between genders.

For both White British and BME participants the impacts of memory and fatigue problems were again greater than impacts of problems in other domains. Fatigue and mobility problems were slightly more important for BME participants than for White British participants. The groups were similar on the other domains.

For older participants, severe fatigue problems and memory problems were most important but for the younger group severe memory problems alone had large impacts on desirability. Once again, mobility and palpitation problems seemed to have the smallest impact.

Finally, for those with more severe symptoms, fatigue and memory problems again had the highest impacts on desirability with the largest effects being for the group with higher symptoms. Severe weight problems had a similar effect for both groups. "Other" side effects were also more important for the group with higher symptom scores.

Discussion

As expected, for all antipsychotic side effects there was a reduced level of desirability for the drug that would result in side effects. It is also clear that the decrement in desirability increased as side effects increased. The side effects that had the most impact on drug desirability were memory problems and fatigue. Weight problems were also important, but problems with palpitations or mobility less so. The subgroup analyses did not reveal consistent differences between groups, although there were some differences between men and women, and the different age groups.

The side effects that would be the most influential in determining choices between antipsychotics also tended to be the most likely to actually occur and be rated as most important for participants aside from the choices made in this exercise. This was particularly the case for tiredness, weight gain, and memory issues were both common and important for participants personally concurs with the choices that they made about antipsychotics as reported in these analyses. It should of course be recognized that some of these side effects may also be associated with the underlying illness itself and disentangling symptoms from drug side-effects can be challenging.

Previously, Achtyes et al reported that problems with thinking were for a sample of service users the most important side effect associated with antipsychotics and that weight gain, physical restlessness and somnolence were the

Table 3. Conditional Logit Models.

	Full sample	Women	Men	White British	BME	Age 21–40	Age 41–50	Age 51–	BPRS 24 < 47	BPRS 48–168
Memory problems										
Mild	−0.27*	−0.12	−0.37*	−0.38*	−0.22	−0.49*	−0.11	−0.33	−0.29	−0.23
Moderate	−0.67***	−0.98**	−0.65***	−0.85***	−0.61***	−0.93***	−0.47*	−0.78**	−0.88***	−0.61**
Severe	−2.60***	−2.83***	−2.63***	−2.52***	−2.96***	−2.99***	−2.36***	−3.14**	−2.55***	−3.50**
Weight problems										
Mild	−0.81**	−1.12*	−0.77**	−0.82*	−0.92*	−0.26	−1.36**	−0.95	−1.00**	−1.05
Moderate	−0.85***	−0.94	−0.96***	−0.58	−1.17**	−0.82	−1.10**	−0.93	−0.96**	−1.30*
Severe	−1.54***	−1.54***	−1.66***	−1.62***	−1.59***	−1.29***	−1.82***	−1.74***	−1.61***	−1.88***
Fatigue										
Mild	−0.30	−0.47	−0.29	−0.35	−0.31	0.03	−0.81**	−0.07	−0.46	−0.33
Moderate	−0.63***	−1.17**	−0.52**	−0.73**	−0.59**	−0.57*	−0.74**	−0.70**	−0.80**	−0.68**
Severe	−1.97***	−2.48**	−1.86***	−1.89***	−2.34**	−1.79*	−2.05***	−2.70**	−1.84***	−3.05*
Palpitations										
Mild	0.00	0.39	−0.11	0.24	−0.24	−0.22	0.18	−0.14	0.38	−0.49
Moderate	−0.87**	−0.73	−0.93**	−0.45	−1.37*	−0.96	−0.93**	−1.09	−0.34	−2.01*
Severe	−1.11***	−1.44***	−1.03***	−1.13***	−1.17***	−1.18***	−1.22***	−1.06***	−0.92***	−1.50***
Mobility problems										
Mild	−0.18	0.64	−0.44	−0.06	−0.44	−0.44	−0.06	−0.36	0.28	−1.12
Moderate	−0.54*	−0.13	−0.69*	−0.35	−0.83	−0.53	−0.60*	−0.78	−0.30	−1.26
Severe	−0.85**	−0.32	−1.07**	−0.66*	−1.21*	−1.12	−0.74*	−1.15	−0.55	−1.85*

Note: figures in table are regression coefficients. Significance of coefficients: *** $P < .001$, ** $P < .01$, * $P < .05$.
BME = Black and minority ethnic, BPRS = Brief Psychiatric Rating Scale.

side effects most likely to influence a treatment switch.[15] Elsewhere, it has been demonstrated that side effects are an important (but not exclusive) reason for drug discontinuation,[16] and that patients may have scepticism about the long-term use of medication because of issues around social recovery.[17] Few studies have explored preferences for medication side effects, and as far as we know, ours is the first to examine preferences for antipsychotic side effects. Our results are consistent with those presented in a previous study which reported on preferences for drug adverse effects in epilepsy.[6] Participants in that study also indicated a stronger preference for less severe drug adverse effects.

Limitations

Choice questions may be generally cognitively challenging and a diagnosis of schizophrenia often leads to some cognitive problems this might have produced some unreliable responses. Although participants did not seem to lack the ability to take part in this simple task (judging by the completion of it), we mitigated potential effects by using a manageable number of choice sets based on a simple experimental design. It may be though that challenges with insight may impact on reporting of side effects, with some effects perhaps not recognized. Related to this is the possibility that the range of symptoms as measured with the BPRS may be different to those measured with other measures.

We did not include an opt-out question on the profiles. This has been recommended in some studies. Furthermore, we did not include a cost attribute and so we could not estimate the marginal willingness to pay for attributes. A study that compared forced and unforced (with opt-out question) choice models reported small differences between the models and recommended less complexity in choice models to reduce the proportion of those who opt out.[18] In addition, exploration of external validity to determine whether individuals behave as they state in a hypothetical context was not undertaken.

The side effects included in the analysis were chosen following a survey of people with lived experience of mental health problems. This was deemed appropriate for this study, but it should be recognized that other side effects may be seen as important by clinicians. These may be those with impacts on long-term health outcomes rather than those which cause subjective distress. It is also important to recognize that only five side effects were included in the survey. These were deemed to be the most important in the earlier survey. Others while of less importance are often reported, such as sexual dysfunction.

The subgroup analyses were informative but could have been improved with the availability of more extensive data. For example, length of time on treatment could have been influential but we only had data of duration on current medication.

Finally, we opted for a particular form of analysis (a conditional logit model) and included various subgroup analyses. Latent class analysis could have been used to further investigate underlying relationships and in future work this would be a useful approach to consider.

Implications for Research and Policy

Our results are likely to be useful in informing the prescription of antipsychotics, and to some extent pharmaceutical companies involved in drug development. The findings that the most important domains attributes were memory and fatigue were clear and should influence practice and drug development.

Funding

This study was funded through a grant from the Maudsley Charity with support from the National Institute for Health Research (NIHR) Biomedical Research Centre in Mental Health, South London and Maudsley NHS Foundation Trust and King's College London.

Acknowledgments

T.W. would also like to cite the support from her NIHR Senior Investigator award. The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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