Patient Preference and Adherence

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ORIGINAL RESEARCH

Patient preferences for important attributes of bipolar depression treatments: a discrete choice experiment

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Purpose: The purpose of this study was to assess patient preferences regarding pharmacological treatment attributes for bipolar depression using a discrete choice experiment (DCE).

Methods: Adult members of an Internet survey panel with a self-reported diagnosis of bipolar depression were invited via e-mail to participate in a web-based DCE survey. Participants were asked to choose between hypothetical medication alternatives defined by attributes and levels that were varied systematically. The six treatment attributes included in the DCE were time to improvement, risk of becoming manic, weight gain, risk of sedation, increased blood sugar, and increased cholesterol. Attributes were supported by literature review, expert input, and results of focus groups with patients. Sawtooth CBC System for Choice-Based Conjoint Analysis was used to estimate the part-worth utilities for the DCE analyses.

Results: The analytical sample included 185 participants (50.8% females) from a total of 200 participants. The DCE analyses found weight gain to be the most important treatment attribute (relative importance =49.6%), followed by risk of sedation (20.2%), risk of mania (13.0%), increased blood sugar (8.3%), increased cholesterol (5.2%), and time to improvement (3.7%).

Conclusion: Results from this DCE suggest that adults with bipolar depression considered risks of weight gain and sedation associated with pharmacotherapy as the most important attributes for the treatment of bipolar depression. Incorporating patient preferences in the treatment decision-making process may potentially have an impact on treatment adherence and satisfaction and, ultimately, patient outcomes.

Keywords: bipolar depression, treatment preference, adverse events, weight gain

Introduction

Bipolar I disorder is characterized by periods of severe mood episodes that fluctuate between clinical depression, mania, and mixed episodes and are associated with significant disability and functional impairment.[1] In the US, the lifetime prevalence of bipolar I disorder is 1%, with a 12-month prevalence of 0.6%.[2] Patients diagnosed with bipolar I disorder have been found to experience depressive symptoms three times more often than manic symptoms.[3,4] Depressive episodes in bipolar disorder (ie, bipolar depression) tend to last longer, occur more frequently, and are associated with higher suicide rates and work-related disability compared to manic episodes.[5]

Although several treatment options are available for the management of bipolar I disorder, there are currently only three US Food and Drug Administration (FDA)-approved atypical antipsychotic treatments for bipolar depression: quetiapine, olanzapine in combination with fluoxetine, and lurasidone.[6] These medications have also received regulatory approval for the treatment of bipolar depression in other

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localities such as Canada (lurasidone and quetiapine), the European Union (quetiapine), and Japan (olanzapine). As a class, atypical antipsychotics have unique efficacy and tolerability profiles but are usually associated with considerable adverse effects, including weight gain, type 2 diabetes, and hyperlipidemia.[7]

Approximately 60% of patients with bipolar disorder do not sufficiently adhere to their medication.[8–11] According to a recent systematic literature review of observational studies, one of the most commonly reported reasons for medication nonadherence in bipolar disorder is adverse effects of treatment, such as weight gain, sedation, tremors, and perceived cognitive impairment.[12,13] In addition, residual depressive symptoms may also negatively impact medication adherence.[14] Using a stated-preference approach, side effects of weight gain or cognitive impairment were similarly identified as major considerations for the treatment of nonadherence in bipolar disorder.[15] The management of bipolar disorder includes proactive monitoring of these adverse effects, such as weight gain, through encouragement of lifestyle and behavioral modifications.[16]

Treatment nonadherence in bipolar disorder remains a continuous challenge with both clinical and economic consequences.[8,11,17] Nonadherence is associated with decreased treatment effectiveness, increased relapses, escalated morbidity, and increased hospitalizations and other health care utilization,[8,11,17] which can lead to higher health care costs and decreased quality of life. Identifying patient treatment preferences by allowing patients to trade-off the benefits and risks associated with the treatment of bipolar depression may lead to a better understanding of the patients' perspective for both physicians and patients and, ultimately, increase medication adherence rates.[18]

One way to assess patient preferences is to conduct a discrete choice experiment (DCE), a methodology that resembles real-life decision making.[19] In a DCE, participants are asked to choose between scenarios describing realistic treatment options and where they make trade-offs between different treatment attributes. This differs from a survey-only approach where patients may be asked to answer questions about independent treatment features, including side effects, without taking into account the trade-offs required to choose between multiple treatment characteristics at once.

A few published studies of DCEs were conducted in mental health populations. However, a previous research has found that patients with severe mental illness, such as schizophrenia or major depressive disorder, may be able to appropriately complete DCE tasks and make meaningful decisions about preferred treatment scenarios based on different attributes.[19] DCE methodology has previously been used in a bipolar disorder population to assess factors associated with nonadherence to treatment. The results demonstrated that patients were more likely to be adherent to medications if they reduced the severity of their depressive episodes and did not cause weight gain or cognitive side effects.[15] However, this prior work did not focus on bipolar depression.

The objective of this study was to assess patient preferences regarding pharmacological treatment attributes for bipolar depression via a DCE.[20]

Methods

The DCE involved a series of systematic steps, including 1) development of treatment attributes, and 2) implementation of the DCE. All study activities were conducted in English.

Development of treatment attributes

Relevant treatment attributes and conceptualizations of treatment scenarios were developed through literature reviews and focus groups. A targeted literature review of articles that described bipolar depression treatments and a review of recent product inserts were conducted. PubMed and Embase were used to conduct the literature search, and the search strategies are included as a supplement to the manuscript. Product inserts for 29 medications used to manage bipolar disorder/depression were reviewed, including nine typical antipsychotics, 12 atypical antipsychotics, seven anticonvulsants, and lithium. Information related to dosing characteristics, need for monitoring, efficacy (eg, time to improvement, remission rates), adherence rates, and common adverse events was extracted from these review sources.

Following the literature review, one expert clinician interview and two focus groups with 16 adult patients[21] were conducted. The purpose of the expert interview was to draw on the clinician's experiences to identify key issues and concerns in bipolar depression, with a greater emphasis on treatment side effects and reasons for continuing or discontinuing treatment. The interview was conducted using a semi-structured interview guide.

The focus groups enrolled adult participants from two clinical sites in the US (n=8 per site). All focus group participants had a clinician-confirmed diagnosis of bipolar I disorder, a history of ≥1 major depressive episode within the last 12 months, a lifetime history of ≥1 manic or mixed manic episode, and currently or previously received antipsychotic drug therapy for bipolar disorder. Mean age of focus group participants was 47.9 years (SD =6.0 years), and

69% were females. Mean time since the participants' initial bipolar I disorder diagnosis was 15.7 years (SD =11.4 years), and their mean duration of atypical antipsychotic use was 4.9 years (SD =4.7 years). The focus groups were conducted using a semi-structured interview guide to elicit information regarding expectations of treatment, treatment experiences, and potential barriers to treatment for bipolar depression. Audio recordings of the focus groups were transcribed and analyzed for themes that patients described as being related to their expectations and preferences for bipolar depression treatment using ATLAS.ti (version 7.5.3).

The most important medication attributes identified from the expert clinician interview and patient focus groups are given in Table 1. Efficacy and weight gain were reported as important treatment attributes for patients with bipolar depression. Patients also defined "time to improvement" as the time from treatment initiation to when they began to observe improvements in their symptoms. Findings from the qualitative research were used to determine the relevant attributes and attribute levels for the DCE scenarios to be used in the pilot and main DCE studies. In determining the final list of attributes, greater emphasis was placed on factors identified by patients as being important in influencing their treatment decisions. Levels of attributes were determined based on results of clinical trials reported in the product inserts, including incidence rates of each event and time to improvement of depressive symptoms.

Implementation of DCE

The DCE was implemented via a one-time, cross-sectional, web-based survey. Prior to full implementation, one-on-one pilot interviews were conducted via web conference.

Participants

For the pilot and main web-based surveys, members of MedPanel,[22] an Internet survey panel, with self-reported bipolar depression were invited via e-mail to participate.

Table 1 Important medication attributes for the treatment of bipolar depression identified via interviews[a]

Expert clinician	Patient focus groups
Efficacy	Efficacy
Metabolic side effects	Increased blood sugar
Sedation	Increased cholesterol
Sexual dysfunction	Risk of becoming manic
Weight gain	Sedation
	Time to improvement
	Weight gain

Note: [a]Medication attributes are listed alphabetically.

MedPanel specializes in the life science industry and maintains a large patient panel across various diseases, including bipolar disorder. MedPanel members were originally recruited through patient associations, patient support groups, and physician referrals. Interested patients answered a series of screening questions to determine study eligibility.

Inclusion criteria were adult subjects (18–75 years), self-reported diagnosis of bipolar depression (bipolar I disorder with most recently documented depressive episode within the last 12 months), lifetime history of ≥1 manic or mixed manic episode, and currently or previously received antipsychotic drug therapy for bipolar disorder. Exclusion criteria were hospitalization for a manic or mixed episode within the 60 days prior to screening, participation in any other clinical trial, or had received study medication ≤45 days from study screening. Diagnosis of bipolar depression was self-reported by patients, and symptoms of depression were further verified through patients' responses to screening questions related to use of medications to manage bipolar disorder and symptoms of depression and/or mania.

Institutional review board approval was obtained from Ethical and Independent Review Services on October 16, 2015 (study number: 15127-01) for the study protocol and recruitment materials. All participants provided electronic informed consent, and each eligible participant received $20 for completing the study.

A pilot study with four participants was conducted using the preliminary DCE scenarios to assess the clarity and understanding of the web-based survey questions. Based on participants' feedback, minor changes were made to the attribute names and the order of tasks. Participants understood the DCE task and were able to complete the web-based survey with minimal difficulty. The final treatment attributes and levels used for the DCE scenarios are given in Table 2. In the main DCE, eligible participants completed only the web-based survey.

Survey instrument

Eligible participants were asked to complete up to 10 sets of DCE scenarios, sociodemographic and clinical questions, the self-reported Montgomery–Åsberg Depression Rating Scale (MADRS-S),[23,24] the WHO-5 Well-Being Index (WHO-5),[25] and the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Instrument (GHI).[26]

In each DCE scenario, two hypothetical bipolar depression medications comprising different attributes (time to improvement, risk of becoming manic, weight gain, risk of sedation, increased blood sugar, and increased cholesterol)

Table 2 Final DCE attributes and levels

Attribute	Description	Levels
Time to improvement	The time until you feel an improvement in your depressive symptoms (ie, sadness, crying, feeling of isolation) after you start taking the medication	1 week 2 weeks 4 weeks
Risk of becoming manic	The chance that taking the medication when you are in a depressive episode will cause you to become manic instead	Fewer than one in 100 of depressed patients will switch to being manic after taking the medication Five in 100 of depressed patients will switch to being manic after taking the medication Eight in 100 of depressed patients will switch to being manic after taking the medication
Weight gain	The amount of weight gain you will experience after taking the medication	Patients experience a minimum weight gain of less than 3lbs after taking the medication Patients experience an average weight gain of 3–10 lbs after taking the medication Patients experience an average weight gain of 10–20 lbs after taking the medication Patients experience an average weight gain of more than 20lbs after taking the medication
Risk of sedation	The chance that you will experience excessive sleepiness or drowsiness after taking the medication	Fewer than 10 in 100 of patients will experience excessive sleepiness or drowsiness after taking the medication 10–24 in 100 patients will experience excessive sleepiness or drowsiness after taking the medication 25–50 in 100 patients will experience excessive sleepiness or drowsiness after taking the medication More than 50 in 100 patients will experience excessive sleepiness or drowsiness after taking the medication
Increased blood sugar (glucose)	The chance that your blood sugar (glucose) levels will change from normal to high after taking the medication	Fewer than five in 100 patients will experience increased blood sugar (glucose) after taking the medication 10–15 in 100 patients will experience increased blood sugar (glucose) after taking the medication
Increased cholesterol (fat in the blood)	The chance that cholesterol levels will change from normal to high after taking the medication	Fewer than five in 100 patients will experience increased cholesterol levels after taking the medication 10–15 in 100 patients will experience increased cholesterol levels after taking the medication

Abbreviation: DCE, discrete choice experiment.

and corresponding levels for each attribute were presented (Table 2 and Figure 1). Participants were instructed to review the treatment pairings and select the medication they would prefer to take at the present time given the options. Each participant responded to only 10 choice pairs in order to both minimize the cognitive burden on participants and maximize the efficiency of the study design, given the number of attributes and levels included in the DCE. One of the discrete choice scenarios presented was a fixed-choice question and was not included in the final analysis. The fixed-choice question presented a clearly favorable medication choice to establish that participants understood the DCE task. Those who responded incorrectly were excluded from the analysis. To prevent potential biases in responses, the fixed-choice question was presented as part of the full set of scenarios. In addition to the discrete choice task, participants were also asked to directly rank the six attributes in order of importance on a scale of 1 (most important) to 6 (least important).

The MADRS-S is a nine-item self-report scale assessing depressive symptoms over the past 3 days.[23,24] Patients were asked to rate the severity of each of the symptoms assessed on a scale ranging from 0 to 6. The total score for the MADRS-S was then calculated by summing the ratings of the nine items, which ranged between 0 and 54, with higher scores indicating greater impairment.

The WHO-5 is a measure of emotional well-being developed from the World Health Organization-Ten Well-Being Index[25] and consists of five positively worded items assessing emotional well-being over the past 2 weeks. Each item is rated on a 6-point Likert scale ranging from 0 (not present) to 5 (constantly present). Individual item ratings are summed to obtain a raw score ranging from 0 (worst possible quality of life) to 25 (best possible quality of life), which may be transformed into a percentage score ranging from 0 (worst possible quality of life) to 100 (best possible quality of life). A raw score ≤13 has been found to be indicative of depression.

Now keeping in mind the features you just read through, please read each option carefully and choose which medication you would prefer for the treatment of your bipolar depression.

If you need to review the description of the medication features again, click here: **Glossary**

Time to improvement	Four weeks	Four weeks
Risk of becoming manic	**Less than 1% (fewer than 1 in 100)** of depressed patients will switch to being manic after taking the medication.	**8% (8 in 100)** of depressed patients will switch to being manic after taking the medication.
Weight gain	Patients experience an average weight gain of **10–20 lbs** after taking the medication.	Patients experience an average weight gain of **10–20 lbs** after taking the medication.
Risk of sedation	**Less than 10% (fewer than 10 in 100)** of patients will experience excessive sleepiness or drowsiness after taking the medication.	**25%–50% (25 to 50 in 100)** of patients will experience excessive sleepiness or drowsiness after taking the medication.
Increased blood sugar (glucose)	**Less than 5% (fewer than 5 in 100)** of patients will experience increased blood sugar (glucose) after taking the medication.	**Less than 5% (fewer than 5 in 100)** of patients will experience increased blood sugar (glucose) after taking the medication.
Increased cholesterol	**10%–15% (10 to 15 in 100)** of patients will experience increased cholesterol levels after taking the medication.	**Less than 5% (fewer than 5 in 100)** of patients will experience increased cholesterol levels after taking the medication.

Figure 1 DCE question sample.
Abbreviation: DCE, discrete choice experiment.

The PROMIS Global Health Questionnaire[26] comprises 10 questions covering the global domains of physical health and mental health. Severity questions assess the respondent's current state using a response scale of "excellent, very good, good, fair, and poor". Frequency questions assess the past 7 days using a response scale of "never, rarely, sometimes, often, and always".

Statistical analyses of DCE

Descriptive analyses were conducted on sociodemographic and patient-reported outcome questionnaire data. For the DCE data, preference weights (part-worth utility values) were estimated using a random-effects multinomial logit model.[27] The model estimated the probability of a patient choosing an alternative i (over a set of possible alternatives I in the given choice set) with the βs representing the estimated part-worth utilities.

$$P_i = \frac{\mathrm{Exp}\,(V(\beta, X_i))}{\sum_{j=1}^{I} \mathrm{Exp}\,(V(\beta, X_j))}.$$

A positive part-worth utility indicated that the attribute level was preferred over levels with negative values, and larger part-worth utilities indicated a higher degree of preference for one level over another. The part-worth utilities were scaled to have a mean value of zero and then used to calculate the relative importance of each attribute. The relative importance of each attribute was then calculated using the following formula:

$$\text{Relative importance} = \frac{\text{Overall utility for each attribute}}{\text{Total utility}}$$

Overall utility value for each attribute equaled the range of part-worth utilities within each attribute, and total utility value equaled the sum of overall utility values across all attributes. The relative importance of each attribute was expressed as a percentage, reflecting the proportion of the variance in the overall medication decision that was accounted for by each attribute. Utilities and relative importance were evaluated for each DCE attribute. Sawtooth CBC System for Choice-Based Conjoint Analysis (version 7; Sawtooth Software, Inc., Provo, Utah, USA) was used to generate the DCE survey questions and to estimate the part-worth utilities for the DCE analyses. SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to conduct all other analyses.

Subgroup analyses

Participant preferences were stratified by gender and age (using a median split). The subgroups were determined based on a priori hypotheses that there may be gender differences

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