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Research paper

Treatment effectiveness and tolerability outcomes that are most important to individuals with bipolar and unipolar depression

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ABSTRACT

Objective: To evaluate patient-reported determinants of treatment effectiveness and tolerability amongst persons with major depressive or bipolar disorders.

Methods: The Depression and Bipolar Support Alliance (DBSA) conducted an online survey February 2016–April 2016 asking participants about which outcomes are most important in determining subjective treatment effectiveness and tolerability.

Results: In total, 896 participants completed the survey [49.9% unipolar depression (n = 447) and 50.1% bipolar depression (n = 449)]. Survey respondents reported several previous medication trials with the minority (25% of depression and 29% of bipolar group) of respondents reporting that their current treatment plan was completely effective. When asked how they know that the treatment is working, for both groups, the highest rated response was, "I don't feel overly anxious, agitated or irritable." Weight gain was the adverse effect that most commonly led respondents to discontinue a medication. Lethargy, emotional blunting, shaking/trembling and anxiety were also identified as common treatment-emergent experiences leading to medication discontinuation in greater than one-third of respondents. The bipolar group more frequently identified several signs that suggested treatment was working (e.g., improved neurocognitive function, improved sleep), as well as more frequently reported several reasons to discontinue medications (e.g., weight gain, trembling).

Conclusion: Numerous factors emerged as important to patients when evaluating treatment effectiveness and tolerability. Some of these factors are inadequately assessed by current standard clinical trial outcome measures. Considering these important patient-centred outcomes in future clinical trials, treatment guidelines and direct patient care may serve to improve patient satisfaction, quality of life and the therapeutic alliance.

1. Introduction

Bipolar and unipolar depression are chronic brain disorders associated with significant functional impairments, morbidity and mortality. As the leading cause of disability, depression affects over 350 million people worldwide, making the identification of effective treatments a global priority (WHO, 2017). Current treatments for bipolar and unipolar depression are often ineffective and poorly tolerated, with high rates of treatment discontinuation, treatment resistance and frequent relapses and recurrences of mood episodes (Gaynes et al., 2009; Grande et al., 2016). Further, when a treatment is reported to be 'efficacious' and 'well-tolerated' in clinical trials, in clinical practice, patients frequently report experiencing persistent and problematic symptoms and adverse effects which belies patient acceptability (Samalin et al., 2016; Szmulewicz et al., 2017; Woo et al., 2016).

When evaluating treatments for depressive symptoms, clinical trials will typically assess efficacy based on change in mean total depressive symptom severity scores (e.g., Hamilton Depression Rating Scale) from baseline to the primary endpoint. 'Response' or 'remission' is typically defined by depressive symptom severity scores decreasing by 50% or returning to the 'normal' range (i.e., scoring in the 'not depressed' range), respectively. However, numerous studies have reported that clinician-rated depressive symptom scores are not the best proxy of the subjective experience of affected persons. Patients will frequently

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report persistently poor quality of life and functional impairment, despite remission of clinician-rated depressive symptoms (IsHak et al., 2011; Shimizu et al., 2013). Moreover, with regards to prioritizing therapeutic objectives in the treatment of depression, patients assign greater priority to quality of life, return to pre-morbid functioning, vitality and positive mental health over symptom reduction (Zimmerman et al., 2006, 2012; Zimmermann et al., 2013). Measurement of adverse effects in clinical trials may also be incongruent with patient priorities as adverse effect reporting does not capture subjective experience of tolerability which is likely of greater importance to patients (Flynn et al., 2013).

Indicators of treatment effectiveness and tolerability may differ when comparing the patient's perspective with that of the provider's. As such, patient-centred outcomes are being increasingly recognized as important in the assessment and treatment of bipolar and unipolar depression (Valderas et al., 2008). The discrepancy between how patients, providers and researchers define 'treatment effectiveness' and 'tolerability' has become increasingly apparent (Ahmed et al., 2012; Wells, 1999). Therefore, the importance of patient-centred outcomes and understanding patient perspectives on treatments has been emphasized by numerous patient advocacy groups along with the National Institute of Health (NIH) (Cella et al., 2007). Accordingly, the Depression and Bipolar Support Alliance (DBSA) conducted an online survey to better understand which factors are most important to patients with bipolar and unipolar depression in evaluating treatments. The specific objectives of the current study were to determine: (1) how patients subjectively determine treatment effectiveness and (2) which adverse effects are most influential in choosing to discontinue or change treatment.

The DBSA has conducted several previous surveys in an effort to understand the experience of depression as perceived by patients and their families (Murnane et al., 2016; Simon et al., 2016). As the world's largest mood disorder advocacy group, the DBSA believes understanding the answers to these questions would serve patients, providers and researchers to improve the design of clinical studies to capture outcomes important to patients, rather than exclusively focusing on conventional clinician-rated outcomes defined by researchers and regulators (e.g., depressive symptom severity rating scales). These results may also have important implications for clinical practice guidelines which are largely based on efficacy studies that primarily evaluate change in depressive symptom severity scores, drug safety profiles and overall treatment discontinuation rates.

2. Methods

The DBSA is an education, advocacy, and support organization for people living with mood disorders, governed, staffed and run primarily by people with lived experience of depression and bipolar disorder. The DBSA's outreach activities include periodic constituent surveys regarding affected individuals' and family members' views regarding clinical, research, and policy issues. These surveys are available on the DBSA website, DBSAlliance.org. All surveys are anonymous; respondents are not asked to provide any identifying information. Notably, no demographic information was obtained and diagnosis was based on self-report without verification by clinician or any validated questionnaires or scales. All survey questions are available as supplementary materials. Respondents were allowed to skip questions, as no questions were mandatory. The current study evaluated a subset of the survey questions related to the primary objective of evaluating patient-reported determinants of treatment effectiveness and tolerability. For clarity, results from other questions will be reported in separate publications.

For the current study, the DBSA conducted an online survey February 2016—April 2016 asking participants about their current treatments, perceived effectiveness and reasons for changing/discontinuing treatments. Individuals were invited to complete the survey through DBSA's online monthly newsletter, chapter network and social media pages. The survey link was also shared with several other mental health organizations to be distributed to their members. The survey was not limited to DBSA members. Notably, respondents were not asked if they were DBSA members.

Herein response rates for relevant survey questions were reported for participants reporting a history of MDD or BD. As part of a secondary analysis, response rates for the MDD group were compared with the BD group. After pooling frequencies of responses, response rates for the two groups (i.e., BD and MDD) were compared using a two-tailed chi-squared test to determine if there was a statistically significant difference between groups.

All respondents were advised regarding the goals and content of the survey, including intent to publish survey results. Because all responses were anonymous and no protected health information was collected, written informed consent was not required. The local research ethics board (REB) at University Health Network (UHN) in Toronto, ON, Canada verified that REB approval was not required for the current study (under section 2.2.b - http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter2-chapitre2/). Frequency of survey responses were tabulated using Microsoft Excel.

3. Results

3.1. Characteristics and treatment history of survey participants

In total, 896 participants completed the survey. Based on self-report, 49.9% had unipolar depression ('depression group'; $n = 447$) and 50.1% had bipolar depression ('bipolar group'; $n = 449$). No demographic or identifying data was obtained in the survey to further characterize this sample. As shown in Table 1, the majority of participants were receiving medications as part of their current treatment plan. The majority of participants in the depression group had five or fewer previous medication trials to treat depression, while the majority of the bipolar group had three or more medications to treat their depression. Over a third of the bipolar group reported trying 10 or more medications to treat their symptoms of depression. Of note, number of current and previous medications was not separated so it is unknown how many medications respondents were currently taking. Therefore, we were unable to evaluate the degree of polypharmacy in our sample. Psychotherapy was the most common non-pharmacologic treatment component reported. In both groups, the minority of respondents felt their current treatment plan was completely effective, with the majority (>70%) reporting that treatment was only partially or not at all effective.

3.2. How respondents determined subjective treatment effectiveness

When asked how respondents know that the treatment is working (i.e., treatment effectiveness), for both groups, the most common response was, "I don't feel overly anxious, agitated or irritable." Respondents identified numerous other changes that would indicate that treatment was effective, as summarized in Table 2. Of note, respondents were allowed to select multiple answers to describe the experiences which were suggestive of subjectively effective treatment. In both groups, decreased negative cognitions (e.g., "My negative self-talk goes down" and "I don't dwell as much on negative experiences") were also commonly reported signs that suggested the treatment was achieving its therapeutic objective. There were statistically significant differences between response rates, comparing the bipolar and unipolar depression groups, as summarized in Table 2, with the bipolar group more frequently selecting several signs that indicted for them that 'treatment is working.' For example, the bipolar group reported improved neurocognitive function (e.g., ability to make decisions, ability to concentrate) as a significant indicator of treatment effectiveness, whereas these factors were reported as indicators of improvement relatively less frequently in the unipolar depression group ($p < 0.001$).