Identifying Disease-Defining Concepts Using Spontaneous and Probed Responses from Semi-Structured Qualitative Interviews in Patients with Major Depressive Disorder

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Introduction

- Major Depressive Disorder (MDD) is a severe mental health disorder affecting 16.9% of the U.S. adult population, nearly 340 million people worldwide, and is a leading cause of disability, with disproportionate impact on women.[1]
- It is characterized by depressed mood, hopelessness, helplessness, loss of interest or pleasure, intense feelings of sadness, guilt, decreased self-esteem and disturbed sleep or appetite, low energy and poor concentration.[2]
- Because depression is primarily experienced subjectively, and the severity of MDD symptoms is directly related to the degree of impairment that patients experience, the assessment of depressive symptoms is an essential endpoint for clinical studies, particularly where the use of clinical indicators will be limited.
- By exploring the patient experience with MDD through qualitative interviews, it is possible to better understand and document the specific depression-related concepts that are relevant to the patient as well as understand the patient's assessment of improvement in his or her condition.
- Ultimately, a well-developed instrument that has firmly established content validity (supported by qualitative data from patients) will be expected to demonstrate greater sensitivity in clinical studies of treatment benefit.

Objectives

- To identify symptoms and functional impacts associated with major depressive disorder (MDD) using concept elicitation interviews to determine the most important and relevant concepts to MDD patients for assessing treatment benefit.
- Evaluate whether these concepts were spontaneously reported by patients during open-ended interviews or in response to probes.

Methods

Concept Elicitation Interviews

- Forty qualitative interviews were conducted across 6 U.S. clinical sites representing a geographically diverse sample of adult subjects with MDD.
- The objective of the interviews was to identify and document the symptoms and impacts of MDD that are relevant and important to patients, and to gain insight into how patients experience and evaluate improvement in their condition.
- Information from the concept elicitation interviews serve to support the selection and development of appropriate PRO concepts for use in assessing treatment benefit from the patient's perspective.
- Interviews were conducted by a trained qualitative researcher and lasted approximately 60 minutes
- Research staff used a semi-structured interview guide to minimize inter- and intra- interviewer variability, designed to obtain both unprompted and prompted subject input about MDD symptoms and their impacts and how the participant feels these factors affect their ability to function.
- Open-ended questions and day-reconstruction exercises were employed to elicit spontaneous reports of symptom/impact concepts.
- Subsequent probing was used to assess concepts not spontaneously reported by subjects.
- Interviewers used worksheets to track and notate spontaneous and probed concepts.

Study Population

- Inclusion criteria (must meet all to be eligible):
  - Male or female between the ages of 18 to 65, inclusive
  - Experienced a major depressive episode within the last 6 months
  - Currently meets DSM-IV-TR criteria for MDD
  - Hamilton Rating Scale for Depression (HAM-D) score > 18
  - Currently being treated for MDD on an outpatient basis
  - Able to read, write, and speak English well enough to understand and complete an Informed Consent Form and take part in the interview process
- Exclusion Criteria (must not meet any to be eligible):
  - Current or past history of a personality disorder, bipolar disorder, schizophrenia or other psychotic disorder, obsessive compulsive disorder, post-traumatic stress disorder, mental retardation, organic mental disorders, or mental disorders due to a general medical condition
  - Subject has a significant risk of suicide (in the opinion of the investigator or as evidenced through affirmative responses to items 4 or 5 of the Columbia Suicide Severity Rating Scale (C-SSRS) within the last 12 months
  - Positive Urine Drug Screen for cocaine, methamphetamine, opiates, phencyclidine, methadone or ecstasy during the enrollment visit. (Subjects screening positive for amphetamine, barbiturate or benzodiazepine use with evidence of a current prescription can be included)
  - Recent history of clinically significant drug or alcohol abuse or dependence (excluding nicotine)
  - History of MDD treatment by electroconvulsive therapy, vagal nerve stimulation or deep brain stimulation
  - Currently enrolled in another investigational device, drug or biologics product study, or less than 30 days since receiving other investigational agent(s)
  - Clinically significant history of renal, neurologic, gastrointestinal, pulmonary, cardiovascular, hepatic, hematopoietic or endocrine disease or disorder
  - In the opinion of the site investigator or study director any medical condition or disorder than could compromise the ability of the subject to give written informed consent and/or prevent or interfere with the subject's ability to successfully participate in a face-to-face interview and provide meaningful information about their MDD experience

Analyses

- All interviews were audio-recorded and transcribed and cleaned to remove any personal identifying information.
- Transcripts were coded and analyzed using Atlas.ti and summarized by like-content. Interview guide notations were used to tag concepts offered as either spontaneous or probed report.

Table 1: Characteristics of Interview Participants

Characteristic	Total N=40 (100%)
Age in years: mean (SD); [range]	46.2 (11.8); [21-63]
Gender: Female: n (%)	27 (67.5%)
Marital status: n (%)	
Married	13 (32.5%)
Living with Partner	3 (7.5%)
Widowed	1 (2.5%)
Separated	4 (10.0%)
Divorced	9 (22.5%)
Never Married	10 (25.0%)
Racial and Ethnic Group: n (%)	
White (Non-Hispanic)	18 (45.0%)
White (Hispanic)	9 (22.5%)
White	1 (2.5%)
Black/African American	9 (22.5%)
Asian	1 (2.5%)
Other: Mixed Race	2 (5.0%)
Highest Level of Education Completed: n (%)	
High School	9 (22.5%)
Some College	17 (42.5%)
Bachelor's Degree	7 (17.5%)
Graduate or Professional School	7 (17.5%)
Employment outside home: n (%)	
Not Employed Outside Home	3 (7.5%)
Full-Time	14 (35.0%)
Part-Time	7 (17.5%)
Retired	1 (2.5%)
Not Employed	15 (37.5)
Clinical Characteristics	
Years since Diagnosis with MDD: mean (SD); [range]	7.8 (8.7); [0-40]
Years since most recent MDE: mean (SD); [range]	1.0 (1.8); [0-8]
HAM-D Total Score at Screening: mean (SD); [range]	24.4 (4.3); [19-39]

Results

- A total of 40 interviews were conducted (mean age: 46.2±11.8; 67.5% female) with subjects representing a broad range of demographic characteristics (Table 1).
- Analysis of the transcripts resulted in 3022 symptom expressions and 830 impact expressions.
- Expressions were coded and grouped into 105 concepts in 11 symptom and 4 impact domains (Tables 2 & 3).
- Saturation was achieved after the first 32 coded transcripts.

Table 2: Symptom Concept Expressions

Domain	Concept	Total (N=40) Spontaneous: n (%)	Probed: n (%)	Not Reported: n (%)
Anxiety	Anxiety	**22 (55.0%)**	3 (7.5%)	15 (37.5%)
	Nervousness	6 (15.0%)	4 (10.0%)	**30 (75.0%)**
	Panic Attack	9 (22.5%)	1 (2.5%)	**30 (75.0%)**
	Stress	7 (17.5%)	9 (22.5%)	**24 (60.0%)**
	Worry	13 (32.5%)	7 (17.5%)	**20 (50.0%)**
Cognitive Issues	Cognitive Lethargy	7 (17.5%)	4 (10.0%)	**29 (72.5%)**
	Intrusive Thoughts	9 (22.5%)	7 (17.5%)	**24 (60.0%)**
	Memory Issues	6 (15.0%)	0	**34 (85.0%)**
	Poor Concentration	**17 (42.5%)**	7 (17.5%)	16 (40.0%)
Disturbed Eating Behavior	Decreased appetite	10 (25.0%)	4 (10.0%)	**26 (65.0%)**
	Increased appetite	11 (27.5%)	3 (7.5%)	**26 (65.0%)**
	Weight Gain	13 (32.5%)	4 (10.0%)	**23 (57.5%)**
	Weight Loss	3 (7.5%)	1 (2.5%)	**36 (90.0%)**
Low Energy	Fatigue/Exhaustion	**20 (50.0%)**	3 (7.5%)	17 (42.5%)
	No/Low Energy	4 (10.0%)	0	**36 (90.0%)**
	Tiredness	**26 (65.0%)**	4 (10.0%)	10 (25.0%)
Motivation	Lack of Interest	13 (32.5%)	6 (15.0%)	**21 (52.5%)**
Negative Affect	Guilt	**17 (42.5%)**	8 (20.0%)	15 (37.5%)
	Helpless	10 (25.0%)	4 (10.0%)	**26 (65.0%)**
	Hopeless	9 (22.5%)	3 (7.5%)	**28 (70.0%)**
	Loneliness	**18 (45.0%)**	10 (25.0%)	12 (30.0%)
	Shame	11 (27.5%)	1 (2.5%)	**28 (70.0%)**
Negative Emotions/ Bad Mood	Anger	**23 (57.5%)**	6 (15.0%)	11 (27.5%)
	Irritability/Hostility	**17 (42.5%)**	6 (15.0%)	17 (42.5%)
	Mood Swings	9 (22.5%)	6 (15.0%)	**25 (62.5%)**
	Sadness	**21 (52.5%)**	11 (27.5%)	8 (20.0%)
Physical Symptoms	Bodily Pain	10 (25.0%)	2 (5.0%)	**28 (70.0%)**
	Chest Pressure	4 (10.0%)	4 (10.0%)	**32 (80.0%)**
	Dizziness	4 (10.0%)	5 (12.5%)	**31 (77.5%)**
	GI Problems	10 (25.0%)	4 (10.0%)	**26 (65.0%)**
	Headaches	12 (30.0%)	6 (15.0%)	**22 (55.0%)**
	Heart Palpitations	9 (22.5%)	3 (7.5%)	**28 (70.0%)**
	Stomach Discomfort	5 (12.5%)	3 (7.5%)	**32 (80.0%)**
	Tingling in Extremities	0	4 (10.0%)	**36 (90.0%)**
Sense of Self	Low Self-Efficacy	6 (15.0%)	6 (15.0%)	**28 (70.0%)**
	Low Self-Esteem	13 (32.5%)	13 (32.5%)	14 (35.0%)
Suicide/ Self-Harm	Self-Harm	2 (5.0%)	1 (2.5%)	**37 (92.5%)**
	Thoughts of Death	7 (17.5%)	4 (10.0%)	**29 (72.5%)**
Sleep Disturbances	Difficulty Falling Asleep	**22 (55.0%)**	5 (12.5%)	13 (32.5%)
	General Sleep Difficulty	14 (35.0%)	10 (25.0%)	16 (40.0%)
	Oversleeping	16 (40.0%)	3 (7.5%)	**21 (52.5%)**

Note: Shaded cells indicated whether a symptom was or was not more commonly reported by subjects. **Bold** text indicates which category was most commonly reported.

Symptom Concepts (Table 2)

- Emotions/Mood, Negative Affect, Fatigue/Tiredness and Sleep Disturbances were the symptoms most commonly reported by subjects.
- Poor Concentration was the most reported Cognitive concepts – which was most frequently offered spontaneously.
- Disturbed Eating Behaviors and Physical Symptoms were not experienced by the majority of subjects. However, when they were reported they tended to be offered spontaneously.

Impact Concepts (Table 3)

- Impacts on Daily Activities (including impacts at work, leisure activities and household chores) and Impacts on Relationships were more commonly reported than Coping Abilities and Increased Substance Use.
- In addition to being reported by the majority of subjects, many of these concepts were most often reported spontaneously.
- Taking care of one's self and one's household were more frequently reported following probing, which may be due to social desirability.

Table 3: Impact Concept Expressions

Domain	Concept	Total (N=40) Spontaneous: n (%)	Probed: n (%)	Not Reported: n (%)
Coping Abilities	Lower Tolerance Level	7 (17.5%)	9 (22.5%)	**24 (60.0%)**
	Diminished Ability to Cope	8 (20.0%)	10 (25.0%)	**22 (55.0%)**
Difficulty with Daily Activities	Household Activities	12 (30.0%)	**19 (47.5%)**	9 (22.5%)
	Leisure Activities/Hobbies	**22 (55.0%)**	11 (27.5%)	7 (17.5%)
	Personal Care	7 (17.5%)	**19 (47.5%)**	14 (35.0%)
	Work Activities	**21 (52.5%)**	5 (12.5%)	14 (35.0%)
Social/ Relationship Changes	Arguments/Bickering	**15 (37.5%)**	14 (35.0%)	11 (27.5%)
	Isolation	**23 (57.5%)**	10 (25.0%)	7 (17.5%)
	Negative Impact on Relationships	**26 (65.0%)**	11 (27.5%)	3 (7.5%)
Substance Use	Increased Use of Alcohol and Drugs	2 (5.0%)	8 (20.0%)	**30 (75.0%)**

Note: Shaded cells indicated whether an impact was or was not more commonly reported by subjects. **Bold** text indicates which category was most commonly reported.

Limitations

- Although the symptoms and impacts identified through this research may be applicable for many patients with MDD, they may not reflect the full breadth of concepts experienced by all patients; in particular patients with more marked severity (e.g., psychosis, severe psychomotor slowing, and/or loss of insight) who did not meet inclusion/exclusion criteria for this study.
  - Further qualitative research would be required to ascertain the salience of these results and identification of any other relevant symptoms and impacts with other patient phenotypes.

Conclusion

- Patient-relevant symptoms and functional impacts associated with MDD were elicited through qualitative interviews.
  - The robustness of these results are supported by evidence of concept saturation.
- Content valid measures of treatment benefit in MDD require evidence of patient importance and relevance.
  - Concepts reported spontaneously provide good support for relevance.
  - Probing can help to identify relevant concepts that subjects may have some reluctance to speak freely about (i.e. Social desirability).
  - However, some probed concepts and concepts that are experienced by few subjects may not offer the best candidates for assessment .
- Concepts identified through this research can provide the basis for the development of a patient-reported outcome measure that is "fit for purpose" in use in clinical trials for major depressive disorder.

References

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