Assessment of the Most Relevant Symptoms Reported By Patients With Major Depressive Disorder

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Introduction

- Major Depressive Disorder (MDD) is a significant 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]
- 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 evaluating treatment benefit in clinical studies, particularly where the use of clinical indicators will be limited.
- Content valid, patient-reported outcome (PRO) measures of MDD are needed to assess treatment benefit from the patient's perspective.
  - 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 the most prevalent and meaningful symptoms associated with major depressive disorder (MDD) using concept elicitation interviews of subjects with MDD.
- To inform the item content of a new patient-reported outcomes measure of treatment benefit.

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 of MDD that are relevant and important to patients, and to gain insight into how patients experience and evaluate improvement in their condition.
- Interviews were conducted by a trained qualitative researcher and lasted approximately 60 minutes
  - Research staff used a semi-structured interview guide, designed to obtain both unprompted and prompted subject input about MDD symptoms.
  - Open-ended questions and day-reconstruction exercises were employed to elicit spontaneous reports of symptom concepts.
  - Subsequent probing was used to assess concepts not spontaneously reported by subjects.
  - Interviewers used worksheets to track and notate spontaneous and probed concepts.
- During the interviews, subjects were asked to rate their worst symptom severity on a 0 to 10 Numerical Rating Scale (NRS) – with 0 being not severe at all and 10 being as severe as they can imagine.
- After the qualitative interview, subjects were asked to complete NRS ratings for how much each of the symptoms they expressed during the interview bothered them (0 representing not bothered at all, 10 representing as bothered as they can imagine being).

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 (12-month) 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.
- The predominance of symptoms expressed by subjects was determined.
- Average ratings for severity and degree of bother ratings for each symptom expression were calculated for those subjects that provided a rating (subjects who did not express a given symptom were excluded from this calculation).

Results

Study Population:

- A total of 40 interviews were conducted (mean age [standard deviation]: 46.2 [11.8]; 67.5% female) with subjects representing a broad range of demographic and clinical characteristics (Table 1).

Table 1. Demographic and Clinical Characteristics:

Characteristic	Total N=40
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]
Prescription Medication Regimen at Screening: n (%)	
No Psychotropic Medications	20 (50.0%)
Anti-Depressant Medication Only	9 (22.5%)
Anti-Depressant and Other Psychotropic Medication	5 (12.5%)
Other Psychotropic Medication Only	5 (12.5%)

Transcript Analysis:

- Analysis of the transcripts resulted in 3022 symptom expressions.
- Expressions were coded and grouped into 105 concepts in 11 symptom domains.
- Saturation of concept was achieved after analysis of the first 32 coded transcripts.

Table 2. Symptom Prevalence and Ratings:

Domain	Concept	Total N=40 Prevalence	Severity Rating*	Bother Rating*
Physical symptoms	Restlessness	8%	9.0	9.3
	Body Pain	45%	8.5	8.1
	Muscle Stiffness	15%	8.0	8.0
	GI problems	33%	7.3	7.1
	Stomach discomfort	45%	7.2	4.8
	Chest Pressure	13%	7.0	6.5
	Headaches	45%	7.0	5.4
	Heart Palpitations	30%	6.1	6.3
	Tingling in extremities	13%	6.0	2.0
	Dizziness	18%	5.3	5.2
	Other physical symptoms	20%	7.0	8.0
Low Energy	No/low energy	48%	9.5	9.1
	Fatigue/Exhaustion	43%	8.0	8.2
	Daytime Sleepiness	28%	8.0	na
	Tiredness	75%	7.4	8.0
	Drained	18%	7.0	5.0
	Lethargic	10%	6.0	na
Low motivation	No interest in activities	20%	10.0	8.0
	Not wanting to get out of bed	58%	9.1	7.2
	Desire to be alone	58%	8.4	9.1
	No interest in self-care	15%	8.0	7.0
	Less/lack of interest	48%	7.6	6.6
	Lack of drive	63%	7.5	8.3
	No interest in leaving home	18%	7.5	6.0
	Other motivation symptoms	10%	2.0	7.4
Emotions/Mood	Mood swings	40%	9.2	7.0
	Frustration	33%	8.0	7.3
	Sadness	80%	8.0	7.6
	Anger	68%	7.9	7.5
	Crying	35%	7.8	6.1
	Irritability/Hostility	73%	7.5	7.1
	Numbness	5%	7.5	8.0
	Decreased pleasure in things	28%	6.4	7.9
	Other emotions/mood symptoms	43%	9.0	7.0
Negative affect	Worthlessness	28%	9.0	9.0
	Hopeless/Helpless	45%	8.3	8.0
	Feeling lonely	70%	8.1	7.6
	Guilt	55%	7.7	7.6
	Focus on negative	25%	6.0	8.7
	Shame	33%	6.0	7.3
Cognition	Feeling overwhelmed	63%	8.7	8.5
	Cognitive Lethargy	20%	8.5	9.0
	Impulsivity	8%	8.5	8.0
	Racing thoughts	35%	8.2	7.7
	Poor concentration	55%	7.0	8.6
	Fixation on problems	30%	6.7	8.0
	Intrusive thoughts	35%	5.5	7.7
	Day dreaming	13%	5.0	6.5
	Memory issues	40%	4.8	6.5
	Other cognitive symptoms	3%	9.0	6.5
Sleep disturbances	General Sleep Difficulty	58%	9.0	7.6
	Difficulty falling asleep	65%	8.7	8.4
	Insomnia	18%	7.5	6.3
	Difficulty remaining asleep	65%	7.0	6.8
	Oversleeping	38%	6.8	5.9
Sense of self	Low self-efficacy	33%	9.5	8.3
	Hate self	18%	9.0	10.0
	Low self-esteem	60%	7.9	7.5
Self-harm/suicide	Self-harm	3%	10.0	10.0
	Thoughts on death	43%	6.5	10.0
Eating behavior	Weight gain	38%	9.5	7.0
	Under eating	35%	9.0	8.5
	Overeating	48%	7.9	7.7
	Increased appetite	18%	7.0	6.0
	Decreased appetite	35%	6.1	6.9
	Weight loss	23%	6.0	7.0
Anxiety	Nervousness	23%	8.5	7.0
	Worry	58%	8.4	7.1
	Anxiety	70%	8.1	7.9
	Stress	48%	8.0	7.7
	Panic attack	25%	7.7	7.8

Ratings were obtained only from those subjects who reported a given symptom.* ***Note:* *All shaded cells indicate prevalence in the majority of participants. Orange shading indicates prevalence in the majority of participants and an average severity or bother rating of 8.0 or greater.*

Symptom Predominance and Ratings:

- The following 12 concepts had an average NRS score of 8.0 or higher either on severity or degree of bother and were expressed by the majority of subjects during the concept elicitation interviews (Table 2):
  - Tiredness
  - Not wanting to get out of bed
  - Desire to be alone
  - Lack of drive
  - Sadness
  - Feeling lonely
  - Feeling overwhelmed
  - Poor concentration
  - General sleep difficulty
  - Difficulty falling asleep
  - Worry
  - Anxiety

Limitations

- Although the symptoms identified through this qualitative research may be applicable for the majority of the subjects, these symptoms may not reflect the full breadth of concepts experienced by all patients with MDD; 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 with other patient phenotypes.

Conclusions

- Patient-relevant symptoms 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 to patients.
  - 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).
  - Subject ratings of the severity and/or bother of symptom concepts provide support of the importance of the symptom to understanding treatment benefit.
- 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 MDD.
  - Information from the concept elicitation interviews serve to support the selection and development of items for appropriate PRO concepts for use in assessing treatment benefit from the patient's perspective.

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