

# **Operational Challenges of a New Indication: MDD with Anxious Distress**

**ISCTM Fall Meeting, Philadelphia 2013**

**September, 2013**

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# Disclosures

- Full-time employee of Janssen Research & Development, LLC
- Shareholder of J&J stock

## Outline:

- Defining the patient population
- Validity of sub-population as a target for treatment
- Clinical Trial Challenges
- Regulatory Challenge
  - Impact of DSM-V With Anxious Distress Specifier

# Definition of Patient Population

Term Used	Definition
Dimensionally-defined Anxious Depression	ICD or DSM Axis 1 diagnosis of MDD, plus high levels of anxiety symptoms defined by a cut-off score on a standardized scale.  <div style="border: 1px solid green; padding: 5px; display: inline-block;">e.g. HAMD anxiety/somatization factor score &gt;7</div>
Syndromally-defined Anxious Depression	ICD or DSM Axis 1 diagnosis of MDD, plus ICD or DSM Axis 1 diagnosis of an anxiety disorder

modified according to Ionescu et al., submitted; Silverstone and von Studnitz, *Can J Psychiatry*, 2003; Goldberg, *Compr Psychiatry*, 2000; Rao and Zisook, *Curr Psychiatry Rep*, 2009

# Definition of the Patient Population

## Dimensional Approach

HAM-D Anxiety somatization  
factor  $\geq 7$

IDS-C  
Anxiety subscale  $\geq 8$

HAM-D Psychic Anxiety item  
Moderate  $< 2$   
Severe:  $\geq 2$

HAM-A cut-off  
 $\geq 18$  or  $20$

?Other

## Validity of Subpopulation as a Target for Treatment

**Slide 6**

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**CMC13**

**consider deleting slide**

Canuso, Carla M [JRDUS], 9/30/2013

## Background/Rationale:

- It is suggested the key to better antidepressant therapy is tailoring treatment to meet needs of specific depression subpopulations
- MDD with significant anxious features is one such subpopulation
  - >50% of the MDD population suffers significant concurrent anxious symptom
- Patients with anxious depression (vs. non-anxious depression):
  - have an earlier age of onset;
  - experience a more persistent course (more and longer depressive episodes);
  - are more severely depressed;
  - have an increased risk of suicidal ideation and suicidal behavior;
  - report poorer quality of life & role functioning, & overall greater functional impairment;
  - incur greater personal and socioeconomic costs;
  - higher rates of treatment failure, lower remission rates

# Treatment Outcomes for Anxious Depression

- Presence of significant anxiety symptoms is a negative predictor for treatment outcomes in MDD as well as a negative moderator of treatment response
  - higher rates of treatment failure, lower remission rates
- No specific antidepressant treatment for this subpopulation
  - frequent polypharmacy, most commonly with the addition of a benzodiazepine or atypical antipsychotic to an SSRI/SNRI
- Significant unmet need for
  - a more effective monotherapy agent, or
  - a safer, effective adjunctive agent to be used with SSRIs/SNRIs

# STAR\*D Level 1 Outcome Data: Anxious vs. Non Anxious

TABLE 2. Remission and Response in Patients in Level 1 of STAR\*D, by Presence of Anxious Depression

Outcome	Anxious Depression				Total (N=2,876)		p	Adjusted p
	No (N=1,346)		Yes (N=1,530)		N	%		
	N	%	N	%	N	%		
Remission (score ≤7 on 17-item HAM-D)							<0.0001	0.0010 <sup>a</sup>
No	896	66.6	1,190	77.8	2,086	72.5		
Yes	450	33.4	340	22.2	790	27.5		
Remission (score ≤5 on QIDS-SR)							<0.0001	0.0018 <sup>b</sup>
No	822	61.1	1,105	72.5	1,927	67.1		
Yes	523	38.9	420	27.5	943	32.9		
Response (≥50% reduction from baseline on QIDS-SR)							<0.0001	<0.0001 <sup>b</sup>
No	634	47.2	887	58.3	1,521	53.1		
Yes	709	52.8	634	41.7	1,343	46.9		
	Mean	SD	Mean	SD	Mean	SD		
QIDS-SR								
Exit score	7.9	5.4	10.2	6.1	9.1	5.9	<0.0001	<0.0001 <sup>b</sup>
Change in score	-7.3	5.7	-6.8	6.1	-7.0	5.9	0.0298	<0.0001 <sup>b</sup>
% Change in score	-46.6	35.3	-39.4	34.8	-42.8	35.2	<0.0001	<0.0001 <sup>b</sup>

<sup>a</sup> Adjusted for regional center and baseline severity of depression (Hamilton Depression Rating Scale without anxiety factor).

<sup>b</sup> Adjusted for regional center and baseline severity of depression according to the Quick Inventory of Depressive Symptomatology–Self-Report.

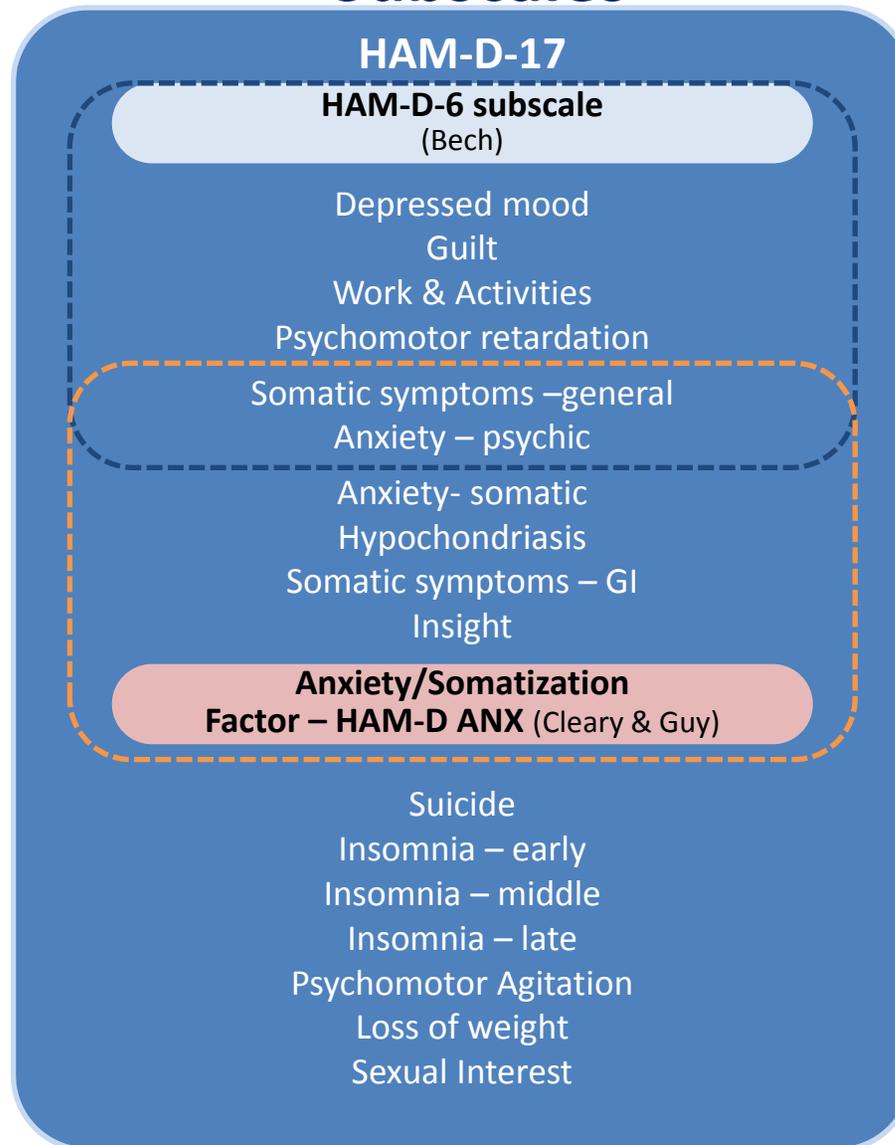
## Conclusion:

- Anxious Depression is a well-established and recognized, clinically relevant subtype of MDD
- Recognized as such within DSM-V with the addition of an anxious distress specifier to the MDD diagnostic criteria
- Persistent and recurrent condition with significant unmet need

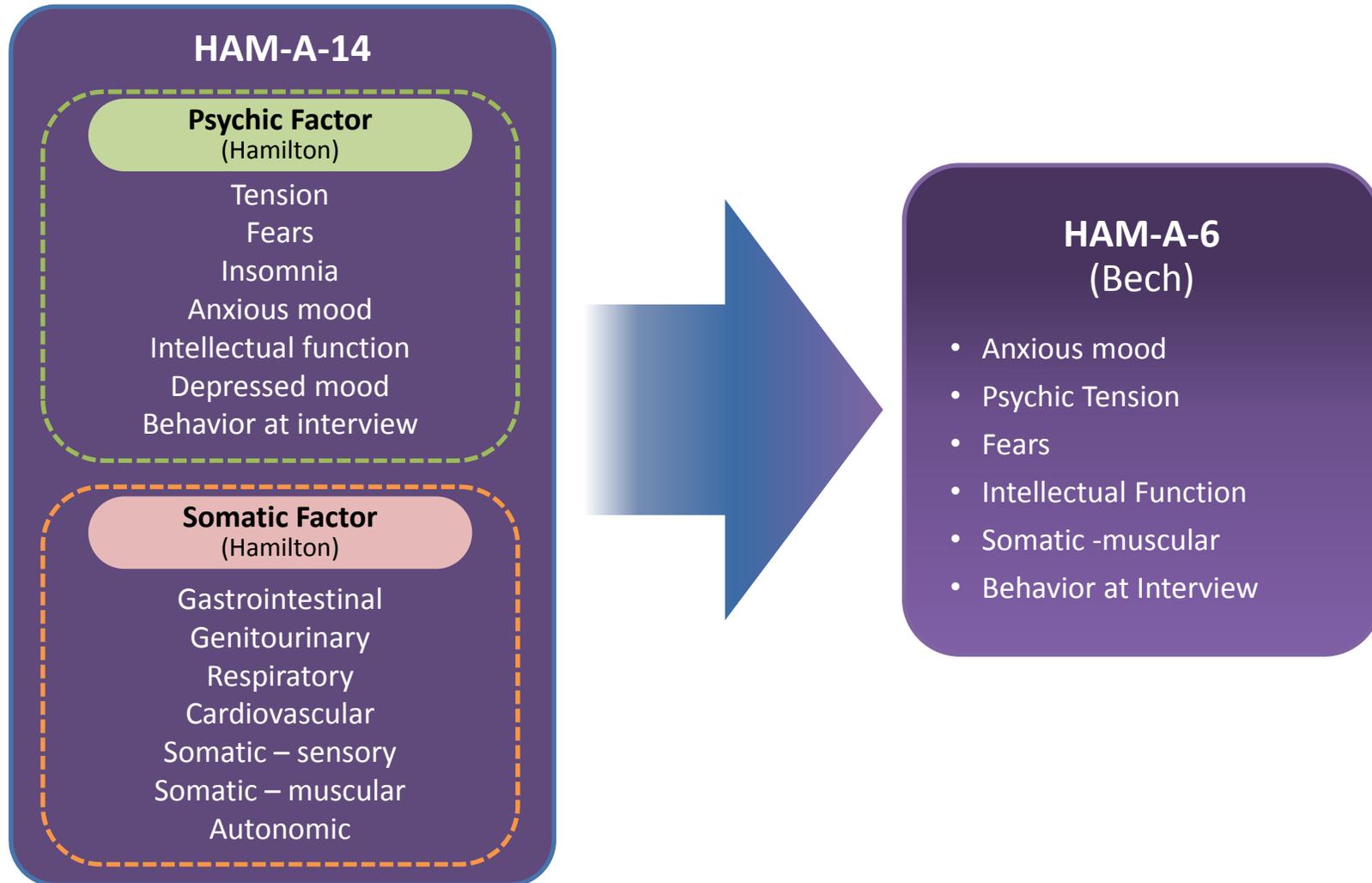
“The addition of an *anxiety severity dimension* may increase clinical awareness and increase the focus of treatment on the severity of co-morbid anxiety as a part of treatment planning, and possibly to the development of more effective treatments for co-morbid anxiety in the mood disorders and perhaps other disorders.”

Mood Disorders Work Group, DSM-V  
American Psychiatric Association

# Selection of Primary Endpoint: HAM-D-17 factors and Subscales



# Selection of Primary Endpoint: HAM-A Factors and Subscales



# Anxious Depression Study Design

## Key Inclusion Criteria:

- DSM-IV diagnosis of Major Depressive Disorder (MDD)
  - Subjects with a co-morbid diagnosis of GAD, SAD, or PD may be included
- Hamilton Depression Rating Scale- 17 item (HDRS<sub>17</sub>) total score  $\geq 18$
- HDRS<sub>17</sub> Anxiety /Somatization Factor Score  $\geq 7$
- At Screening, must be receiving an antidepressant at optimized dose

# Anxious Depression: Study Design

## Key Exclusion Criteria:

- A current DSM-IV axis I diagnosis other than MDD
  - comorbid GAD, Social Anxiety Disorder, or Panic Disorder allowed
- > 1 prior failed antidepressant (of adequate dose & duration) in the current episode (not including current antidepressant)
- History of treatment resistance ( $\geq 3$  lifetime Tx failures)
- Benzodiazepines prohibited for at least 1 week prior to screening and for the duration of the study

# Operational Challenges

Ensuring appropriate subjects enrolled:

- Using independent rater telephone interview at Screening
  - Site concerns
  - logistics of scheduling
- Enriching population for those with Anxious Depression

Ensuring high quality and consistency of ratings:

- Rater training
  - Initial adherence to use of scales and then return to usual practice
- Data monitoring and feedback

# Operational Challenges - Recruitment

- Enrollment challenges:
  - Summer start
  - Exclusion of benzodiazepines
- Positive impact of visits to sites by Clinical Team
- Screen failure – 23% SF rate

# Regulatory Challenges of New Indication

- Need to establish that the (sub)population is a valid target for treatment based on:
  - Different clinical course vs. those with MDD without anxious distress
  - Different clinical outcomes vs. those with MDD without anxious distress
  - Recognized unmet Clinical need
- Regulatory preference is that target population be one for which there is an established diagnosis
  - ? DSM-V specifier

## DSM-V

# Major Depressive Disorder

- A. 5 (or more) symptoms present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure
- Depressed mood most of the day,
  - Markedly diminished interest or pleasure in activities most of the day,
  - Significant weight loss when not dieting or weight gain
  - Insomnia or hypersomnia
  - Psychomotor agitation or retardation
  - Fatigue or loss of energy
  - Feelings of worthlessness or excessive or inappropriate guilt
  - Diminished ability to think or concentrate, or indecisiveness
  - Recurrent thoughts of death, suicidal ideation with or without specific plan, suicide attempt
- B. Symptoms cause distress or impairment
- C. Episode not attributable to a substance or other medical condition

**Removal of Bereavement exemption**

DSM-V

# Major Depressive Disorder

- Specify:
  - With anxious distress
  - With mixed features
  - With melancholic features
  - With atypical features
  - With mood-congruent psychotic features
  - With mood-incongruent psychotic features
  - With catatonia
  - With peripartum onset
  - With seasonal pattern

# Use of the *Anxious Distress* specifier

Anxious distress is defined as the presence of ***at least 2 of the following symptoms*** during the majority of days of a major depressive episode:

1. Feeling keyed up or tense
2. Feeling unusually restless
3. Difficulty concentrating because of worry
4. Fear that something awful may happen
5. Feeling that the individual might lose control of himself or herself

Assessment of Current Severity:

Mild: 2 symptoms

Moderate: 3 symptoms

Moderate-severe: 4 or 5 symptoms

Severe: 4 or 5 symptoms with motor agitation

## Excerpt from EU Guideline on MDD:

“The frequent co-occurrence of depressive and anxious symptoms in MDD requires a specific approach. The issue is twofold: anxiety symptoms may be a part of MDD or due to a co-morbid disorder like Generalised Anxiety Disorder (GAD).

*In the first situation the anxiety symptoms are seen as secondary to depression and therefore they will clear with the improvement of the depression. In this case the effect is therefore a part of the antidepressant effect and no additional claim can be granted.”*

30 May 2013

EMA/CHMP/185423/2010 Rev. 2 previously (CPMP/EWP/518/97, Rev. 1)

# Level 1 of STAR\*D

Those with Anxious Depression had greater reduction in anxiety somatization scores, but had higher scores after citalopram treatment, *suggesting anxiety symptoms were not completely addressed by antidepressant treatment.*

Table 1: Differences in HAM-D Anxiety/Somatization Score Before and After Citalopram Treatment Between Patients With Anxious Depression and Patients With Nonanxious Depression (N=2,876)

Measure	Nonanxious Depression (N=1,346)		Anxious Depression (N=1,530)		p
	Mean	SD	Mean	SD	
Anxiety/somatization factor from Hamilton Rating Scale for Depression 17-item					
Baseline total score	4.8	1.2	8.5	1.5	<0.0001
Exit total score	3.3	2.4	5.1	3.1	<0.0001
% change in total score	-25.7	61.5	-39.4	35.6	0.0002

## Back-up Slides

# Hamilton Depression Rating Scale: HAM-D17

1. DEPRESSED MOOD (Sad, blue, gloomy, weepy, pessimistic, helpless, hopeless, worthless.)
  - 0 Not depressed.
  - 1 Feeling states elicited only on questioning.
  - 2 Occasional weeping. Spontaneously reports feeling states.
  - 3 Frequent weeping. Obvious behavioral evidences in face, posture, voice. Speaks mostly about feeling states.
  - 4 Exhibits *virtually only* these feeling states verbally and nonverbally. May have "gone beyond weeping".
2. GUILT FEELINGS AND DELUSIONS
  - 0 Absent.
  - 1 Self-reproach, feels he/she has let people down.
  - 2 Expresses guilt regarding past errors or misdeeds.
  - 3 Present illness is deserved punishment. Ruminations over past errors and sins.
  - 4 Severe self-reproach. Guilty delusions, e.g., is making other people ill. Deserves to die. May have accusatory or denouncing auditory or visual hallucinations.
3. SUICIDE
  - 0 Absent.
  - 1 Feels life is empty, not worth living.
  - 2 Recurrent thoughts or wishes about death of self.
  - 3 Active suicidal thoughts, threats, gestures.
  - 4 Serious suicide attempt.
4. INITIAL INSOMNIA (As part of present illness.)
  - 0 Absent.
  - 1 Mild, infrequent; more than 1/2 hour occasionally.
  - 2 Obvious and severe; more than 1/2 hour usually.
5. MIDDLE INSOMNIA
  - 0 Absent (rate 1 if hypnotic is being used).
  - 1 Complains of feeling restless and disturbed during night.
  - 2 Wakes during the night; any reading or smoking in bed or getting out of bed except to void.
6. DELAYED INSOMNIA
  - 0 Absent.
  - 1 Wakes earlier than usual but goes back to sleep.
  - 2 Wakes 1 - 3 hours before usual; unable to sleep again.
7. WORK AND INTERESTS (Apathy: loss of interest in work, hobbies, social life. Anhedonia: unable to feel pleasure.)
  - 0 No disturbance.
  - 1 Feels incapable, listless, less efficient. (Rate fatigue, loss of energy under item 13.)
  - 2 Has to push to work or play. No active interests, gets little satisfaction, feels listless, indecisive.
  - 3 Clearly decreased efficiency. Spends less time at usual work. In hospital, rate 3 if no spontaneous activity or marked loss of personal tidiness.
  - 4 Stopped working because of present illness. Doesn't shave, bathe, etc. Avoids ward activities: works only with urging.
8. RETARDATION (Psychomotor slowing of thought, speech, and movement. May vary diurnally.)
  - 0 Absent.
  - 1 Slightly flattened affect, fixed facial expression.
  - 2 Monotonous voice, delayed answering, sits motionless.
  - 3 Interview difficult and prolonged. Moves slowly.
  - 4 Depressive stupor. Interview impossible.
9. AGITATION (May co-exist mildly with retardation.)
  - 0 Absent
  - 1 Fidgety. Clenching fists or chair arm, kicking feet.
  - 2 Wringing hands, pulling hair, picking at hands or clothes. Restless on the ward, some pacing.
  - 3 Can't sit still; much pacing on ward.
  - 4 Interview conducted "on the run". Constant pacing. Pulling off clothes, tearing at hair, picking at face.
10. PSYCHIC ANXIETY (As part of present illness. NOT part of previous disposition. Includes feeling tense, irritable, apprehensive, fearful, phobic, or panic attacks.)
  - 0 Absent.
  - 1 Minimal distress, admitted only on direct questioning.
  - 2 Spontaneously expresses discomfort; worries over trivia.
  - 3 Obviously apprehensive in face and speech.
  - 4 Severely anxious, panicky, forgetful.
11. SOMATIC ANXIETY (Physiological concomitants of anxiety such as: fainting, tinnitus, blurred vision, headache, tremor, sweating, flushing, hyperventilation, palpitations, indigestion, belching, diarrhea, urinary frequency.)
  - 0 Absent.
  - 1 Trivial.
  - 2 Mild.
  - 3 Moderate.
  - 4 Severe.
12. APPETITE
  - 0 Normal appetite.
  - 1 Eats spontaneously, but without relish or pleasure.
  - 2 Marked reduction of appetite and food intake. Eats only with urging. Requests or requires laxatives.
13. SOMATIC ENERGY
  - 0 Normal.
  - 1 Occasional, mild fatigue, easy tiring, aching.
  - 2 Obviously low in energy, tired all the time: frequent backache, headaches, heavy feelings in limbs.
14. LIBIDO (Rate only definite change with illness.)
  - 0 Normal for age and marital status.
  - 1 Mildly decreased drive and satisfaction.
  - 2 Definite loss of desire: functional impotence.
15. HYPOCHONDRIASIS
  - 0 Absent.
  - 1 Mildly preoccupied with bodily functions and physical symptoms.
  - 2 Moderately concerned with physical health.
  - 3 Morbid convictions of organic disease, e.g., brain tumor, cancer.
  - 4 Bizarre delusions (often with guilty associations) e.g., worms eating head, rotting inside, bowels blocked, terrible odor.
16. LOSS OF INSIGHT
  - 0 Acknowledges being depressed and ill.
  - 1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest.
  - 2 Denies being ill at all.
17. WEIGHT LOSS (Rate either A or B.)
  - A. When rated by history.
    - 0 No weight loss.
    - 1 Probable weight loss associated with present illness.
    - 2 Definite weight loss.
  - B. When rated by weekly weight measure.
    - 0 Less than 1 lb. during past week.
    - 1 Greater than 1 lb. during past week.
    - 2 Greater than 2 lb. during past week.

HAM-D ANX items  
circled in red

# Hamilton Anxiety Rating Scale: HAM-A

The Hamilton Anxiety Scale (HAM-A) is a rating scale developed to quantify the severity of anxiety symptomatology, often used in psychotropic drug evaluation. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe).

0 = Not present to 4 = Severe

Score

**1. ANXIOUS MOOD**

- Worries
- Anticipates worst

**2. TENSION**

- Startles
- Cries easily
- Restless
- Trembling

**3. FEARS**

- Fear of the dark
- Fear of strangers
- Fear of being alone
- Fear of animal

**4. INSOMNIA**

- Difficulty falling asleep or staying asleep
- Difficulty with Nightmares

**5. INTELLECTUAL**

- Poor concentration
- Memory Impairment

**6. DEPRESSED MOOD**

- Decreased interest in activities
- Anhedoni
- Insomnia

**7. SOMATIC COMPLAINTS: MUSCULAR**

- Muscle aches or pains
- Bruxism

**8. SOMATIC COMPLAINTS: SENSORY**

- Tinnitus
- Blurred vision

**9. CARDIOVASCULAR SYMPTOMS**

- Tachycardia
- Palpitations
- Chest Pain
- Sensation of feeling faint

**10. RESPIRATORY SYMPTOMS**

- Chest pressure
- Choking sensation
- Shortness of Breath

**11. GASTROINTESTINAL SYMPTOMS**

- Dysphagia
- Nausea or Vomiting
- Constipation
- Weight loss
- Abdominal fullness

**12. GENTOURINARY SYMPTOMS**

- Urinary frequency or urgency
- Dysmenorhea
- Impotence

**13. AUTONOMIC SYMPTOMS**

- Dry Mouth
- Flushing
- Pallor
- Sweating

**14. BEHAVIOR AT INTERVIEW**

- Fidgets
- Tremor
- Paces