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An Investigation of the Relationship between Bipolar Disorder and Menopause

In Search of a Refined Treatment

This project investigated the relationship between bipolar disorder and menopause in 41 research participants at the University of Massachusetts Medical School, as part of an on-going study in the Department of Psychiatry. Investigated was mood symptom manifestation across the menopausal stages and association with endocrinological assessments. This was accomplished with the use of standardized, validated, reproducible, diagnostic data. Database descriptive analyses and correlational statistics were used to assess demographic description of subjects and preliminary association of mood and menopausal stage and reproductive hormones. Due to the small sample size of the on-going study, the strength of correlations ranged from insignificant to inconclusive. Thus it was concluded that further research and a larger sample size would be needed to make strong correlations between menopause and the exacerbation of bipolar disorder symptoms.

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AN INVESTIGATION OF THE RELATIONSHIP BETWEEN BIPOLAR DISORDER AND MENOPAUSE:

IN SEARCH OF A REFINED TREATMENT

A Major Qualifying Project Report

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Abstract

This project investigated the relationship between bipolar disorder and menopause in 41 research participants at the University of Massachusetts Medical School, as part of an on-going study in the Department of Psychiatry. Investigated was mood symptom manifestation across the menopausal stages and association with endocrinological assessments. This was accomplished with the use of standardized, validated, reproducible, diagnostic data. Database descriptive analyses and correlational statistics were used to assess demographic description of subjects and preliminary association of mood and menopausal stage and reproductive hormones. Due to the small sample size of the on-going study, the strength of correlations ranged from insignificant to inconclusive. Thus it was concluded that further research and a larger sample size would be needed to make strong correlations between menopause and the exacerbation of bipolar disorder symptoms.

Introduction

During transitional menstrual periods there is an increase or alteration of normal endocrine levels which often leads to a flux in mood. This change takes place in women as a result of a slew of neurochemical and endocrinological changes that take place in the brain and bodies of women on a monthly basis. At the same time, women who have been diagnosed with bipolar disorder, already experience mood fluctuations that are deviations from the norm due to the manic and depressive episodes that characterize their syndrome. It is hypothesized that during transitional menstrual periods, women with bipolar disorder are more susceptible to the exacerbation of their bipolar symptoms. This exacerbation is a result of the bipolar symptoms being compounded with the rising and decreasing endocrine levels coupled with neurochemical alterations stemming from menstrual transition. The purpose of the present investigation is to validate the hypothesis by making correlations between mood rating scales, menopausal stage, age and the bipolarity index.

Background

The reproductive life for a woman is marked by the presence of the menstrual cycle. Menarche (onset of menses) begins during puberty. Unless pregnancy occurs, the menstrual cycle continues until menopause. The cycle periodicity is approximately 28 days, and culminates with the shedding of the uterine lining. However, as a woman approaches menopause, the cycle becomes irregular and fertility decreases. This naturally occurring physiological process is associated with an ultimate decrease in gonadal hormone levels, specifically estrogen and progesterone. Menopause is defined as one year since the final menstrual period (Curie, 2006). This is a clinical diagnosis and is not reliably assessed by hormonal levels as they vary considerably through the transition. The average age of menopause in the United States is 51 (Benazzi, 2000).

The Menstrual Cycle

To better understand the effects of menopause on women, one has to understand how the menstrual cycle functions. This 28 day cycle is comprised of three different phases: follicular phase, ovulatory phase, and luteal phase. **Figure 1** shows an illustration of the menstrual cycle phases and common length variations. Variations in cycle length occur as a result of the lengthening of the follicular phase (light blue). Ovulation begins by stimulation of the ovarian follicles to produce an increase in estrogen production in granulosa cells. The body responds to the estrogen rise by stimulating the pituitary gland to release luteinizing hormone (LH), responsible for ovulation. This process is referred to as the ovulatory phase (blue arrow in the figure). The lining of the womb thickens as progesterone is produced in the corpus luteum, marking the commencement of the luteal phase (dark blue). Failure of fertilization induces a decline in both progesterone and estrogen, while increasing the amount of follicular stimulating hormone (FSH). Menstruation then occurs due to the fluctuation in endocrine levels (Currie, 2006). The follicular phase serves as the body's mechanism for preparing for pregnancy with the aid of the endocrine system. Menstruation occurs when the body disposes of the nutrient rich lining that would support an embryo, marking the end of the body's preparation for conception.

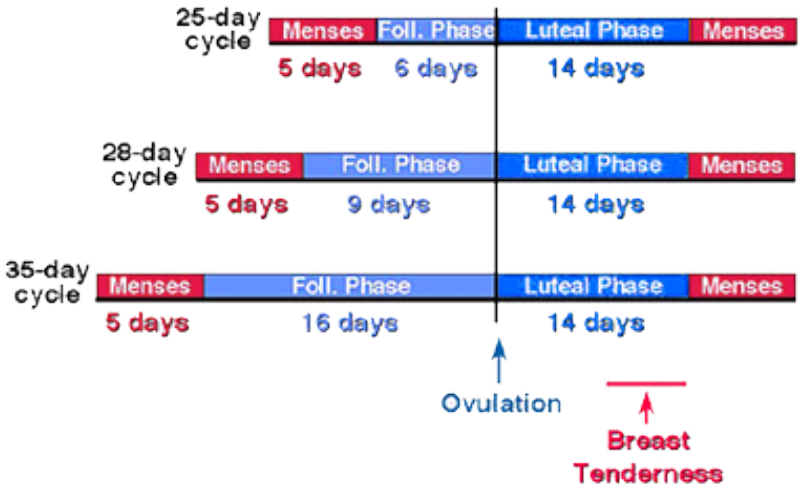

Figure 1: Diagram of the Menstrual Cycle Phases and Length Variation

Shown are three example cycle lengths of 25, 28, and 35 days, and the length of the three main phases, menses (red), follicular phase (light blue), and luteal phase (dark blue) (Ferin, 1993).

Figure 2 shows a graphical representation of the complex endocrine and physical changes occurring throughout the menstrual cycle. The act of menstruating, often called menses, marks the first day of the cycle and the first phase of the cycle: the follicular phase. When the sloughing of the uterine lining (menses) ceases, the levels of estrogen, specifically estradiol (E2), soon increase. Menstruation lasts an average of three to seven days to expel the uterus collapsed. Levels of estradiol continue to increase throughout the follicular phase. As the endometrium (lining of the uterus) re-thickens, follicles in the ovaries develop and mature. A follicle houses the oocyte, or "egg" that contains the woman's half of the genetic material for her offspring. Approximately from day 7 to day 14, one follicle becomes dominant and matures into a viable oocyte, while the rest become polar bodies and degenerate. Once mature, an LH surge induces the follicle to burst and release the egg, a process called ovulation. After ovulation the luteal phase begins. The follicle responsible for ovulation morphs into the corpus luteum, which functions to produce progesterone. Meanwhile, hair-like structures termed fimbria maneuver the egg from the ovary into the fallopian tubes to await fertilization. Failure to obtain proper implantation onto the uterine wall causes a decline in estradiol levels. The drop in estrogen levels reciprocates a rise in the release of FSH and LH hormones. However, the body utilizes a feedback mechanism to decrease the levels of FSH and LH once sufficient progesterone is secreted to signal an increased production of estrogen. Thus, the body begins to prepare for another menstrual cycle (Ferin, 1993).

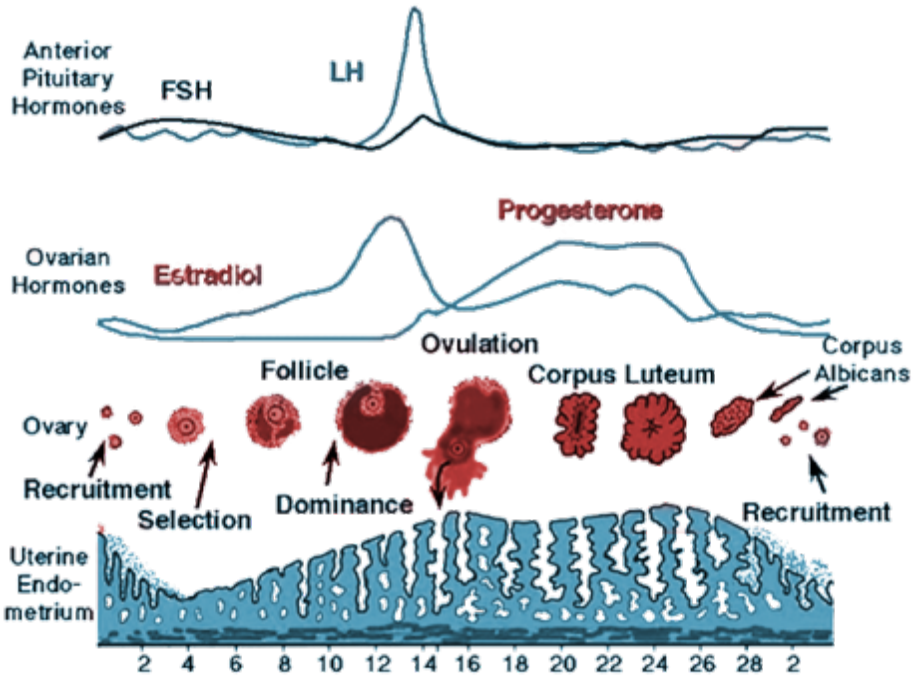

Figure 2: Diagram of Hormonal Changes in the Menstrual Cycle

Shown are the main hormonal changes throughout the cycle, relative to the status of the egg (lower diagram) (Ferin, 1993).

The egg cell count (oocytes) in women begins to decline starting at birth. At menopause the egg cell count is drastically reduced. Eventually the ovaries cease to produce estrogen and progesterone, resulting in a difference in the ratio of progesterone and estrogen endocrine levels relative to that of FSH and LH; progesterone and estrogen levels decrease, while the FSH and LH levels increase. Upon completion of the menopausal transition, menstrual cycle stops and a woman is no longer fertile (Currie, 2006).

Menopause

Menopausal diagnosis is based on changes in menstrual cycle frequency. Menopause is divided into three stages, including: i. late pre-menopause (late reproductive years when fertility declines); ii. early and late peri-menopause combined (commonly referred to as menopause); iii. early post-menopause.

Menopausal symptoms are common and may include: hot flashes (sudden warmth sensations which may cause profuse sweating), night sweats, palpitations, insomnia, weight gain, breast tenderness, and headaches. Women usually do not experience all these symptoms at once, as the symptoms may appear throughout any of the stages (Currie, 2006). The criteria for distinguishing the stages of menopause were established in July of 2001 during the Stages of Reproductive Aging Workshop detailed in the STRAW section of this paper.

The reproductive years may be described as pre-menopause, and include menarche to the onset of peri-menopause. When menstrual cycle frequency naturally becomes irregular, it marks the onset of

peri-menopause. The term menopause is reserved for the occurrence of the last menstrual cycle, often called climacteric, defined as one year after last menstruation. The conclusion of menopause marks the beginning of post-menopause, lasting the remainder of a woman's life. Menopausal symptoms may be experienced postmenopausal such as vaginal dryness and hot flashes (University of Rochester Medical Center, 2012).

Ovarian composition undergoes significant endocrinological changes that lead up to reproductive senescence and the cessation of the menses. Etiologically, the reduction in oocytes and the depletion of follicles in the ovary ultimately change the morphology of the ovary. Figure 3 shows a histological representation of the change in ovarian tissue and follicles, before and after menopause. The left panel shows circular formations that simulate the ovary of a baby that is one year of age. The middle panel represents the ovary throughout a female's fertile reproductive ages. The last panel represents the ovary depleted of its follicular reserve after menopause.

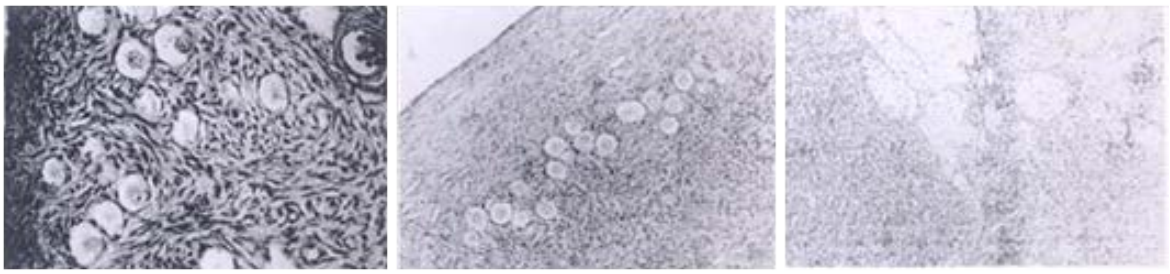

Figure 3: Diagram of Ovarian Histology Before and After Menopause

Shown are diagrams of the ovary at year-1 (left panel), reproductive years (middle panel), and post-menopause (right panel) (Ferin, 1993, page 94.)

Stages of Reproductive Aging Workshop (STRAW)

On July of 2001, the stages of menopause were classified by the Stages of Reproductive Aging Workshop (STRAW) sponsored by the American Society of Reproductive Medicine (ASRM) and the North American Menopause Society (NAMS). The workshop served to set forth a series of criteria for identifying the staging system, characterizing the aging of the female reproductive life. The staging system divided a woman's reproductive life into seven stages. The commencement of menopausal transition is identified by a change in the menstrual cycle of approximately 7 days. The STRAW criteria also took into consideration both the frequency and the length of menstrual cycles, which are associated with fluctuations in estradiol and progesterone. At the time, researches chose FSH as the most suitable marker associated with the onset of the peri-menopause (Soules et al., 2001).

The data was based on studies of endocrine changes throughout the menstrual cycle in 77 study subjects. The study consisted of measuring serum hormone levels three times a week on women who were in their reproductive ages to peri-menopausal stages (Soules et al., 2001).

Final Menstrual Period

Stages:	-5	-4	-3	-2	-1	+1	+2
Terminology:	Reproductive			Menopausal transition		Postmenopause	
	Early	Peak	Late	Early	Late	Early	Late
				Perimenopause			
Duration of stage:	variable			variable	1 yr[a]	4 yrs[b]	until demise
Menstrual cycles:	variable to regular	regular	regular	variable cycle length *(>7 days different from normal)*	≥2 skipped cycles and an interval of amenorrhea *(≥60days)*	*Amen. x 12 month*	
Endocrine:	normal FSH	normal FSH	↑FSH	↑FSH		↑FSH	

Figure 4: STRAW: Stages & Nomenclature of Normal Reproductive Aging in Women

The stages are characterized by the length of the menstrual cycle. Irregularities in the menstrual transitioning are induced by a rise in FSH endocrine levels experienced during late reproductive ages (Soules et al., 2001).

During reproductive years, menstrual cycling has a regular frequency and FSH levels slightly fluctuate throughout the cycle. FSH levels rise above reproductive levels during the transition into menopause. Levels of FSH remain elevated throughout peri-menopause and post-menopause. **Figure 4** above presents the physical changes that ensue as a result of transitioning through different menstrual phases up to post-menopause. Other endocrine levels that declined while transitioning into menopause were inhibin-B and anti-Mullerian hormone (Hale et al., 2007).

Symptomatic Treatment of Menopause

Throughout the peri-menopausal and early post-menopausal years, women may suffer from vasomotor symptoms consisting of hot flashes and night sweats. Vasomotor symptoms occur during abrupt dilations of blood vessels near the epidermis. Statistics show that hot flashes affect 60-84% of menopausal women in the United States (Currie, 2006). Menopause may also be associated with vaginal dryness, sexual changes, urinary discomfort, sleep disturbance, mood swings, and cognitive disturbances (Nelson et al., 2005).

The menopausal transition is a natural reproductive change in a woman's life. Thus, for example, the Mayo Clinic notes that no treatment exists for menopause; however, menopausal symptoms can be disruptive. So medication management is often utilized. One of the most effective treatment approaches is the administration of estrogen. Hormone therapy (HT) may include estrogen and/or

progesterone. Estrogen is considered to be the most effective treatment for menopausal symptoms. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have also shown to decrease hot flashes and improve depressive symptoms. However, doctors recommend using only low dosages of antidepressants, enough to relieve menopausal symptoms (Mayo Foundation for Medical Education and Research, 2011). Estrogen is an evidence-based treatment for vaginal dryness and discomfort and improves bone mineral density (Mayo Foundation for Medical Education and Research, 2011).

Bipolar Disorder

The Diagnostic and Statistical Manual of Mental Disorders, Edition IV (DSM-IV) defines bipolar disorder as a mood disorder characterized by the incidence of mania or manic episodes and depression or depressive episodes. Mania refers to the presence of atypically elevated energy, cognition or mood levels. If the mood episode is slighter than typical mania, the DSM-IV refers to this sate as hypomania. Those experiencing manic episodes are susceptible to depressive episodes, with the possibility of a mixed state in which characteristics of both episodes appear simultaneously. In some cases the alternation between the states of mania and depression occur quickly. This is known as rapid-cycling. In other instances, individuals can experience periods of normal mood; dividing the manic and depressive episodes. When the severity of manic episodes increases, individuals may display psychotic symptoms, coupled by delusions.

Components of Bipolar Disorder

There are four main components to bipolar disorder that present themselves in different intensities and in turn define a subtype based on their prevalence. The hallmark of bipolar disorder is the manic episode. The severity of which is often used to determine the classification of the disorder.

Mania

The term mania refers to an interval of elevated mood, sometimes manifesting itself as euphoria. Individuals experiencing mania frequently exhibit and increase in energy, with decreased need for sleep. Some individuals only sleep for a few hours while some may last for days without sleep (American Psychiatric Association, 2000). Other common symptoms of mania are racing thoughts and pressured speech (Mayo Clinic, 2012). Severity of a manic episode may be monitored by scales such as the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978).

Criteria for Manic Episode

A manic episode is a period marked by irregularity and continual irritable, expansive and elevated mood, persisting for a minimum of one week. The duration of the episode becomes less important if hospitalization is required as the severity of the episode trumps the durative component of the criteria (American Psychiatric Association, 2000). During a manic episode, an individual may experience exaggerated self-esteem or grandiosity, in addition to decreased need for sleep (in which case the individual feels rested with far less than eight hours of sleep). Individuals may also be more talkative, distractible, or experience flight of thoughts. Lastly, the individual may be involved in goal-directed or pleasurable activities, with the time spent on these activities being disproportionate to time spent on other activities. To meet the criteria of a manic episode, three or more of the aforementioned

symptoms must have endured (four if the mood displayed was irritability). The other caveat is that persistence of the symptoms must be significant to meet the criteria (American Psychiatric Association, 2000).

It should be noted that the criteria for a mixed episode are not the same as the criteria for mania. The symptoms of a manic episode must be independent of any medication or narcotic. In addition, the symptoms have to be severe enough to interrupt or preclude the completion of everyday activities or result in hospitalization or psychosis (American Psychiatric Association, 2000).

Hypomania

Hypomania is a less severe manifestation of mania. While these symptoms appear to be the same as those of mania, their expression is mild to moderate.

Criteria for Hypomanic Episode

The criterion for a hypomanic episode is very similar to that of the manic episode with a few alterations. Different to a manic episode, a hypomanic episode requires only four days of mood elevation, expansiveness or irritability. The criteria for hypomania require that during a hypomanic episode, the same amount of symptoms must last and persist significantly, analogous to the criteria of a manic episode. While the severity of the symptoms is less intense, the symptoms of hypomania are the same as mania in definition and classification. One of the most notable differences between mania and hypomania is that the symptoms are not debilitating, thus they do not prevent the individual from completing tasks that they unusually would. Nonetheless, the symptoms are obvious enough that bystanders can notice the difference in the individual's behavior. Once again these symptoms may not be induced by drugs to count as a hypomanic episode.

Depression

A depressive episode is characterized by feelings of sadness and or anhedonia (loss of interest in activies) plus at least five of nine other symptoms. These include suicidal ideation, increased sleep and loss of appetite. Individuals may also experience fatigue and anxiety which is a common comorbid diagnosis.

Major Depressive Episode Criteria

The episode must last least two weeks and cause dysfunction. Psychosis may occur, such as delusions or hallucinations (Mayo Clinic, 2012). Other symptoms include being depressed for a majority of the day, insomnia or hypersomnia and sever weight loss. Additionally, individuals may also experience psychomotor agitation and feelings of worthlessness, coupled by incongruous feelings of guilt. Those experiencing this level of depression may experience an inability to concentrate and incessant thoughts of death. To be classified as a depressive episode, five (or more) symptoms must be present and persist in the aforementioned two week period in addition to altering the individual's functionality. An ongoing medical condition or substance abuse cannot be the source of these symptoms. The symptoms must be clinically significant meaning that they are debilitating and preclude the individual from performing everyday activities. The criterion for a mixed episode does not fit these symptoms.

Bipolar Types

Bipolar disorder is classified by severity of mood elevation, namely, Bipolar I, Bipolar II and not otherwise specified (NOS). A definitive number of subtypes of bipolar disorder have yet to be determined. However, the DSM-IV-TR recognizes four subtypes; three specified and one, not. The three specified subtypes are Bipolar I and II Disorder and NOS. The last subtype is referred to as "Bipolar Not Otherwise Specified (NOS)" (American Psychiatric Association, 2000).

Bipolar I

To be diagnosed with Bipolar Disorder I (BD I), one must experience one or more manic episodes. This subtype is characterized by severe, potentially perilous manic episodes and mood swings that may place strain on relationships, and require hospitalization. Such a severe manic episode may also result in psychosis. In addition, the individual cannot manage at school or work. Bipolar I is the most debilitating of the acknowledged subtypes on the continuum (Mayo Clinic, 2012). An episode of depression is not necessary for Bipolar I diagnosis, but usually occurs.

Bipolar II

Bipolar II (BD II) is characterized by the same symptoms as Bipolar I but the appearance of said symptoms are far more mild, and as such the individual with Bipolar II is able to carry on and function in daily life. One difference between Bipolar I (longer than one week) and II (more than four days) is the duration of episodes. Also, for a diagnosis of BD II, one needs to have experienced a major depressive episode. Those with BD II tend to experience longer periods of depression than hypomania (Mayo Clinic, 2012).

Table 1 the main mood and behavioral changes used to diagnose mania and depression. **Table 2** below shows the main neuropsychological profile of bipolar patients, especially the difference between depression (middle column) and mania (right column).

Bipolar Disorder Not Otherwise Specified (BD-NOS)

The diagnosis of bipolar disorder is not a simple task. When a diagnosis does not fit into one of the specified subtypes of bipolar disorder, the disorder falls into the category of NOS. Bipolar Disorder Not Otherwise Specified (NOS) is diagnosed when an individual exhibits symptoms of the subtypes of bipolar disorder. However, classification may not fall into a specific subtype because the symptoms not meet the subtype criteria fully. This may be a result of a preexisting medical condition or substance abuse (American Psychiatric Association, 2000).

Table 1: Diagnosis for Mania and Depression

Symptoms of mania or manic episode:	Symptoms of depression or a depressive episode:
Mood Changes: • A long period of feeling "high," or an overly happy or outgoing mood • Extremely irritable mood, agitation, feeling '"jumpy" or "wired" **Behavioral Changes** • Talking very fast, jumping from one idea to another , having racing thoughts • Being easily distracted • Increasing goal-directed activities, such as taking on new projects • Being restless • Sleeping little • Having an unrealistic belief in one's abilities • Behaving impulsively and taking part in a lot of pleasurable, high-risk behaviors, such as spending sprees, impulsive sex, and impulsive business investments	**Mood Changes:** • A long period of feeling worried or empty • Loss of interest in activities once enjoyed **Behavioral Changes** • Feeling slowed down • Having problems concentrating, remembering and making decisions • Being restless and irritable • Changing eating, sleeping or other habits • Thinking of death or suicide, or attempting suicide

Shown are the diagnostic symptoms for mood episodes of bipolar disorder (National Institute of Mental Health (NIMH), 2009).

Table 2: The Main Neuropsychological Profile of Bipolar Patients

Cognitive Domain	Bipolar Depression	Euthymia	Mania
Set-shifting and (or) concept formation	↓	↓↓	↓↓
Verbal fluency	↓	↓●	↓
Decision making	—	↓●	↓
Planning and (or) problem solving	↓	↓	↓↓
Nonverbal intelligence	↓	●●●	↓
Sustained attention	↓	↓↓↓	↓↓
Verbal memory–delayed recall	↓	↓	↓
Visual memory	↓	↓●	↓

↓●= Reduced and (or) impaired, compared with healthy control subjects; ● = no change, compared with healthy control subjects. Each symbol denotes the finding from one study.

Shown are the various cognitive functions altered in bipolar disorder (first column) and the extent each is affected in depression (middle column) and mania (right column) (Mahlo, 2004).

Bipolar Disorder, Menopause, and Dietary Supplements

The risk of unipolar depression increases during menopause. Potential relationships between BD I, BD II, and menopause together are relatively unstudied. Three reproductive phases, premenstrual, postpartum, and peri-menopause are characterized by a decline in estrogen and progesterone levels. These are associated with increased risk of depressive symptoms due to hormonal fluctuations. The hormone levels tend to decrease after the following occurrences: (i) the luteal phase of the regular menstrual cycle, (ii) labor, and (iii) the onset of irregular ovulation (actually menstruation) marking peri-menopause (Payne, 2007).

BD is a lifelong illness with no cure; however, recurrent symptomatic mood swings can be alleviated with proper treatment. It is hypothesized that bipolar disorders originate from an overactive cell-signaling pathway (Stoll, 1999). Suppression of the signal transduction pathways can in turn weaken the likelihood for bipolar disorders. Suppression may be achieved by medications which function to inhibit these neuronal membrane pathways, and are common treatments administered to individuals experiencing severe mood swings (Stoll, 1999). However, not enough evidence exists to prove or disprove this theory. Most treatments have to be administered on a long-term basis to reduce symptom severity. Treatments include mood stabilizing medications such as lithium, anticonvulsants for example valporic acid, or divalporex sodium (Depakote), or antipsychotics. Many anticonvulsants, which treat seizures, have FDA approval to be used as treatment for bipolar disorder, and as an alternative to lithium (National Institute of Mental Health, 2009).

Research suggests that omega three and six fatty acids exhibit a similar function of attenuating the signal transduction pathways overactive in BD (Stoll, 1999); thus, dietary supplements can serve as an adjunctive treatment for bipolar disorder. Additional studies revealed that when treatments are coupled with docosahexaenoic acid (DHA), the consumption of the omega three fatty acids are essential for neuronal development (Simopoulos, 1991). Omega three fatty acids reside within the brain in large concentrations, leading researchers to believe the fatty acids are associated with cognitive and behavioral function. However, the benefits of omega-three-fatty-acid-intake to improve bipolar disorder symptoms remain inconclusive (University of Maryland Medical Center (UMMC), 2011).

University of Massachusetts Medical School – Dr. Wendy Marsh's Study

Dr. Wendy Marsh at the University of Massachusetts Medical School (UMMS) is the principal investigator (PI) on a grant entitled "The Impact of Peri-menopause on Bipolar Disorder". The study is a five year career development award being conducted in the Department of Psychiatry. The research is designed to elucidate the course of bipolar disorder through peri-menopause in relation to menopausal phase and endocrinological status. The study is strictly observational.

Dr. Marsh targets a sample of 75 women, treated for bipolar disorder, who voluntarily participate in the study. Out of the sample, 25 will have experienced early peri-menopause, 25 will have experienced late-menopause, and another 25 will have experienced early post-menopause. Participants will record their mood symptoms for a total period of four months, equivalent to five clinical visits. Visits are completed on-site or through a phone interview (Marsh, 2008). To date, a total of 41 women have participated in the study. Of these 41 participants, 25 were peri-menopausal, and 14 were post-

menopausal. Of these subgroups, one peri-menopausal and another post-menopausal subject were lost to follow up.

Initial visits last two to three hours, and begin with a detailed informed consent. Mood and reproductive assessments (both administered self and by trained practitioner) are completed together with an endocrinological assessment (including an FSH and estradiol blood draw). The forms are discussed in the Methods section: Protected Health Information Form (PHI), Demographics Form, Clinical Monitoring Form (CMF), Montgomery-Aspberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Menstrual History Form, Greene Climacteric Scale, and Affective Disorders Evaluation (ADE). Subjects are also trained in the use of the daily mood tracking software ChronoRecord. At successful completion of the initial visit subjects are compensated with $20.00.

Follow-up visits are conducted either over 2 months between menstrual cycles, or at the time of a subject's menstrual cycle if less than 6 weeks form prior visit. If post-menopausal, visits are are completed on a monthly basis. The duration of the follow-up visits is roughly thirty minutes where participants only complete the CMF, MADRS, YMRS, the blood panel and return of the previous months ChronoRecord mood data. A total of $30.00 is received at completion of the fifth (final) visit.

Mood symptoms and hormonal data acquired for each subject are then reviewed and inputted into the REDCap database. Analysis of the information housed within the database will aid researchers' abilities to support or reject various hypotheses related to a correlation between menopause and BD. Specifically, researchers are investigating whether higher rates of depression are accompanied by a substantial increase in FSH levels present during late menopause (Marsh, 2008).

Forms Utilized and Their Significance

Protected Health Information (PHI)

The "Protected Health Information (PHI)" form contains the information that is to be separated from the subjects visit charts to de-identify the subjects. This information includes the subjects first and last name, date of birth, physical and e-mail addresses, and preferred phone numbers. This information is kept in a binder separate from the visit records and is used to contact the subjects about their appointments. This form is filled out only at the first visit.

Affective Disorders Evaluation (ADE)

The "Affective Disorders Evaluation (ADE)" form is filled out by the physician on the first visit. The ADE is a standardized assessment form based on DSM -IV criteria with which the physician determines the subjects' diagnosis.

Due to the complexity of mood disorders, it is necessary to glean as much information as possible to gain the clearest picture of the subjects' history and preset illnesses. This is important, as the uniqueness of the subjects' background may be crucial in determining the correct diagnosis and preset illnesses. The ADE will allow the physician or clinician to make these assessments about the subjects' disorders from a diagnostic standpoint (See Appendix B).

Demographics

Also completed at the first visit is the "Demographics Form" that contains information about the subject's socioeconomic status. This information includes the subject's marital status, occupation, annual income and other information. The possible selections for this form are predetermined and designated by numbers one through eight (Refer to Appendix C).

Greene Climacteric Scale

The "Greene Climacteric Scale" assesses menopausal symptoms, dividing them into three categories: mild, moderate and severe. The scale assesses the rate and force of the subjects' heartbeat. It assesses the subjects' tension and nervousness, whether they are experiencing difficulty sleeping or if they are excitable. The form inquires whether the subject is experiencing panic attacks, difficulty concentrating and level of lethargy. The scale also evaluates the subjects' level of interest in activities, depression levels, crying spells and irritability. Furthermore the form gauges whether the subject is feeling dizzy, faint, and tight in the head or body and numbness or tingling in the body. The scale also measures headache severity, muscle and joint pain and loss of feeling in extremities. Lastly, the Greene Climacteric Scale assesses the severity of the subjects' hot flushes, night sweats and potential loss of interest in sex (See Appendix D).

FSH and Estradiol Blood Panel

At each clinical visit the subjects' blood is drawn and sent to the lab where it is tested for FSH and Estradiol levels (See Appendix E).

Menstrual History

The "Menstrual and Medical History" form is a self-completed form filled out by the subjects at the first visit (See Appendix F and G).

Young Mania Rating Scale (YMRS)

Also completed at each subject visit is the "Young Mania Rating Scale (YMRS)". Both the YMRS and the MADRS assess mood. However, the YMRS was developed based on the central symptoms of mania associated with bipolar disorder. Specifically, the YMRS assesses the spectrum of mood elevation symptoms from mild to severe. As a result, this scale complements the MADRS (See Appendix H).

Montgomery-Aspberg Depression Rating Scale (MADRS)

Completed at all five visits is the "Montgomery-Aspberg Depression Rating Scale (MADRS)". Adopted in 1979, the MADRS is a depression scale created to measure incremental alterations in the subjects' mood. This scale is able to measure changes in mood over any time period. The MADRS is a highly focused and fine-tuned decedent of the Comprehensive Psychopathological Rating scale (CPRS). The CPRS was reduced from its 65 items down to the ten most essential items most relevant to the diagnosis of depression. These are the 10 symptoms assessed in the MADRS: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, inability to

feel, lassitude, and a propensity for both pessimistic and suicidal thought (Burns, Lawlor, & Craig, 2001)(See Appendix I).

Clinical Monitoring Form (CMF)

The "Clinical Monitoring Form" is a clinical evaluation and tracing instrument intended to make highly effectual the process of keeping record of differential diagnostic information, essential to making clinical assessments. There are four main purposes of the CMF. The primary goal of the CMF is to establish the subjects' present clinical status. The secondary goal of the CMF is to deliver a methodical follow-up to enable ongoing valuation.

ChronoRecord

Based on the ChronoSheet from the 1970's, the ChronoRecord is a longitudinal analysis software used to measure subjects' menstrual cycle sleep pattern and mood. This data can then be used to help clinicians treat mood disorders, such as bipolar disorder. In addition the software also keeps records of the medications that the subjects are taking to treat symptoms.

Methods

Biology students of Worcester Polytechnic Institute (WPI) approached physician Wendy Marsh M.D.M.S. of University of Massachusetts Medical School (UMMS) to inquire if there was ongoing research that she was involved in that the students could participate in. She had a grant to study the impact of peri-menopause on the clinical course of bipolar disorder.

Internal Review Board (IRB) Approval and Physical Examination

In order to begin research at the University, the students were required to receive Internal Review Board (IRB) approval at UMMS. To do this the students had to participate in human subject training since this project involves research with human subjects. The training involved a web based course and test (CITI website) that took approximately five hours to complete. Each student was required to read the modules associated with the test in order to answer pertinent questions. To pass the training and be qualified for IRB approval the students had to the pass the exams with an average of 80%. This training is required of volunteer in staff to teach them the fundamentals of research ethics and protocols outline CITI courses. This was important because the students would be working with highly sensitive information regarding the subjects, such as medical records, and additional information that would be entered into a database.

The other requirement for working with human subjects on the campus was to become volunteers of the Department of Psychiatry at UMMS. To do this the students had to have a physical examination to make sure that the students were free of tuberculosis, hepatitis and HIV. This type of physical examination is required by any employee of the medical staff at UMMS.

REDCap Database

REDCap stands for Research Electronic Data Capture. Developed by the University of Vanderbuilt, the database software is used by researchers at the University of Massachusetts Medical

School (Harris, 2009). The software is a web-based interface. The user interface is very simple and intuitive. The software lends itself nicely to producing forms with custom fields that allow the data collectors to collect` information specific and pertinent to their research. For security purposes, the subject's research records are de-identified by removing the protected health information like name and date of birth from the data and resolve to numbering the records. For further security measures, all of the data entry was completed on campus in a locked office, to maintain the privacy of the subjects as enforced by the protocols outlined in human subjects training and HIPPA.

The actual data base was a digital version of the medical records that were built upon each visit of the subjects. The forms in each patients chart included the following forms:

1. Protected Health Information (PHI)
2. Demographics
3. Menstrual and Medical History
4. Affective Disorders Evaluation (ADE)
5. Clinical Monitoring Form (CMF)
6. Young Mania Rating Scale (YMRS)
7. Montgomery-Aspberg Depression Rating Scale (MADRS)
8. Greene Climateric Scale
9. FSH and Estradiol blood panel data

Other data not included in the REDCap databases include:

1. Mood Attribution Answers (open ended questions answered by the patient and audio recorded by the physician)
2. ChronoRecord (a daily mood monitoring form software given to the subjects) add website address

Each subject participates in the study for a period of four to five months and completes a total of five visits. The first baseline visit is the longest, lasting for three to four hours. This visit encompasses all of the aforementioned forms. Subsequent visits last an approximate duration of twenty to thirty minutes; covering the CMF, YMRS, MADRS, and blood panel. Some of the postmenopausal subjects complete their subsequent visits via a telephone call as a blood panel is unnecessary. The blood panel is not necessary for postmenopausal subjects as women's hormones remain relatively constant after they have gone through menopause. Researchers Curry and Ortiz, entered medical records for subjects 304 through 341, each containing individual sub-folders for one to five subsequent visits. Below is a table of the data entered into the REDCap database.

There is a $50.00 compensation given to the subjects that participate in the study. They receive $20.00 at the first visit and $30.00 at the last visit. At UMass Medical University the IRB Board has strict policy regarding subject's compensation as to adhere to the protocols and mores outlined in the human subjects training. Therefore the subjects are not compensated handsomely, to avoid immoral instances such as coercion.

Results

Demographic Form Data

Data from the forms in the subjects' charts were collected over the duration of the study and inputted into the REDCap database.

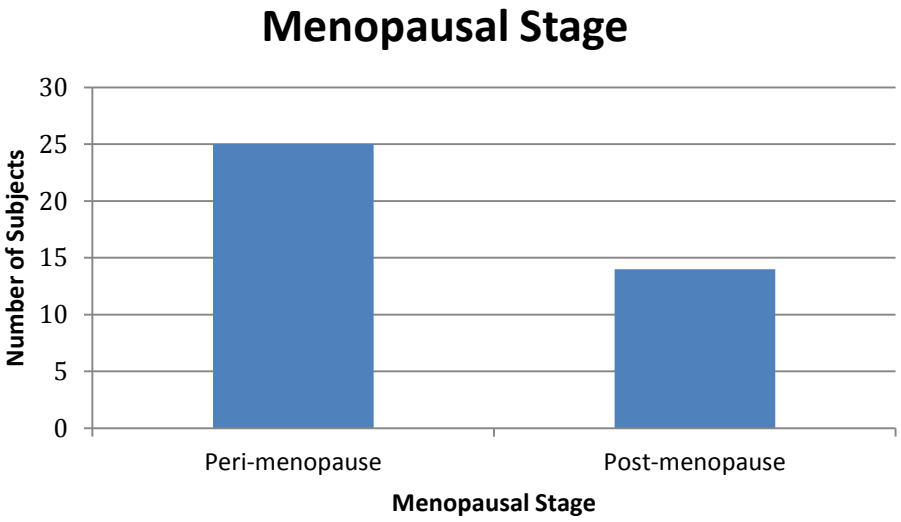

Figure 5: Bar Chart of the Subjects' Menopausal Stage

Presented is the menopausal stage distribution of the subjects participating in the study.

Figure 5 above shows 25 subjects were peri-menopausal (early and late combined) and 14 subjects were post-menopausal (See Appendix A).

The figures below display data from the fields found on the Demographics Form. The first field on the demographics form is the highest level of education completed by each subject in the study and the data is shown in **Figure 6** below.

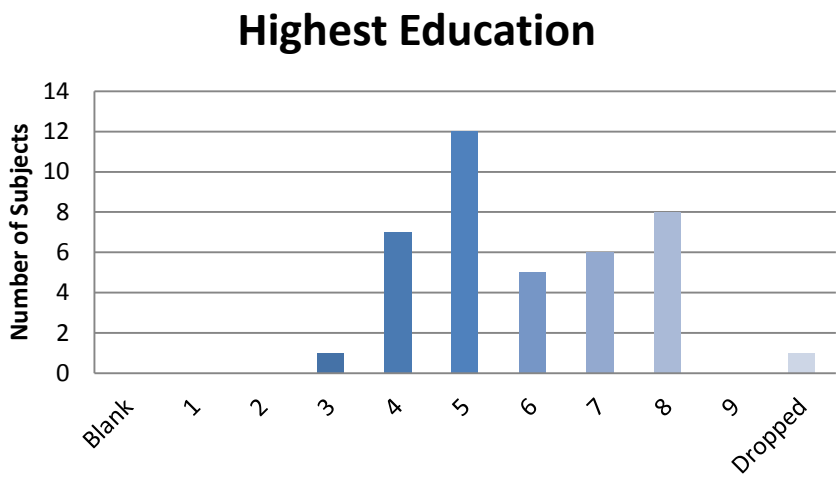

Figure 6: Bar Chart of the Levels of Education Completed by Subjects

Shown are the levels of education completed by the subjects of the study. Above each bar is the number of subjects that completed the respective level of education shown according to the scale.

Each of the numerical value on the scale represents a level of education:

1. Less than the seventh grade
2. Seventh grade – ninth grade
3. Partial High School
4. High School Diploma or GED
5. Some college (at least one year)
6. Technical School or Associates Degree
7. College Diploma (Bachelor's Degree)
8. Graduate or Professional Degree

As seen in the **Figure 7** below, there one subject that partially completed their high school education. Seven of the subjects earned a high school diploma, or equivalent such as a GED. Twelve of the subjects completed at least one year of college. Five of the subjects attained either a technical certification or an associate's degree. Six of the subjects earned a college diploma. None of the subjects completed graduate or professional education. One subject dropped.

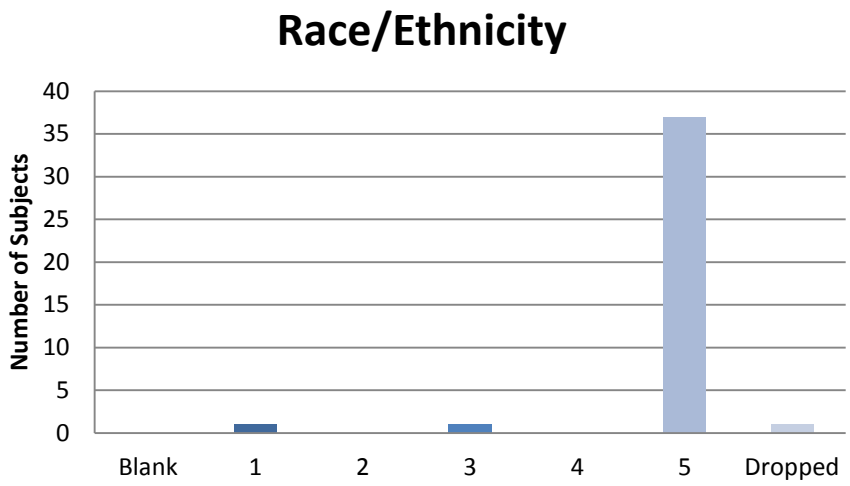

Figure 7: Bar Chart of Race/Ethnicity of Subjects

Shown is the ethnicity of the subjects participating in the study. Numerical values on the x-axis denote the subjects' given ethnicity.

Each of the numerical value on the scale represents a race or ethnicity:

1. American Indian or Alaska Native
2. Asian
3. Hispanic or Latino
4. Black or African American
5. White, Non-Hispanic
6. Native Hawaiian or Pacific Islander

There was one american indian subject, one hispanic subject and thirty-seven white, non-hispanic subjects. One of the subjects as aforementioned was lost to follow-up.

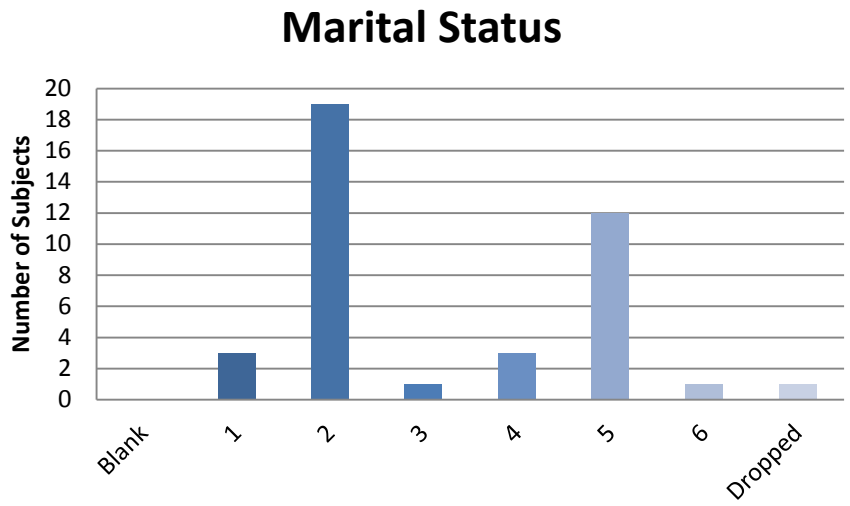

Figure 8: Bar Chart of the Marital Status by Subjects

Presented is the employment status of the subjects participating in the study.

Each of the numerical value on the scale represents a marital status:

1. Never Married (Never lived as Married)
2. Married
3. Living as Married
4. Separated/No longer living as married
5. Divorced
6. Widowed

As presented in **Figure 8** above, there were three subjects that had never been married. Nineteen of the subjects were married. One of the subjects was living as married. Three more of the subjects had been seperated from there significant other. Twelve of the subjects were divorced. One of the subjects had been widowed.

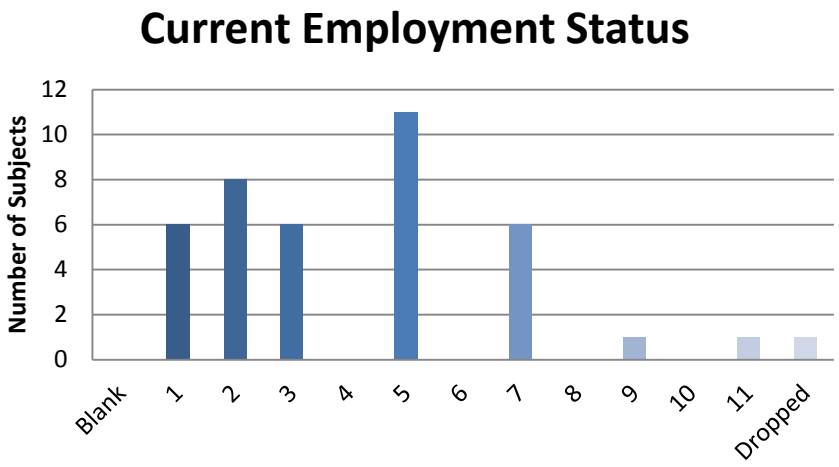

Figure 9: Bar Chart of the Current Employment Status Subjects

Shown is the employment status of the subjects participating in the study. The majority of the subjects identified themselves as volunteers or as individuals working for part-time pay.

Each of the numerical value on the scale represents an employment status:

1. Full-time
2. Part-time for pay
3. Homemaker
4. Student
5. Volunteer
6. Incarcerated

7. Disabled
8. Leave of Absence
9. Unemployed
10. Retired
11. Other

As presented in **Figure 9** above, six of the cadidates were emplyed full time. Eight of the subjects worked part-time for pay. Six other subjects were homemakers. None of the subjects were students at the time of the study. Six of the subjects qualified for disability. One of the subjects was unemployed.

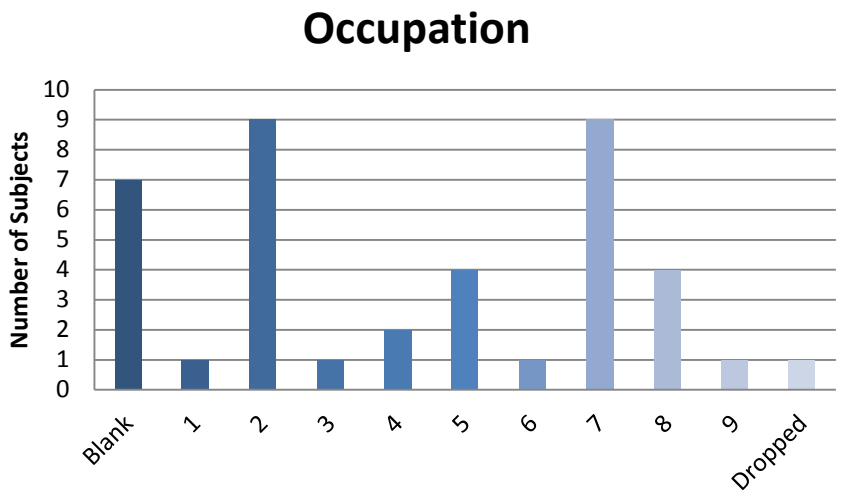

Figure 10: Bar Chart of the Occupation of the Subjects

Displayed is the occupation of the subjects participating in the study. Most subjects partook in a professional or clerical occupation.

Each of the numerical value on the scale represents an occupation type:

1. Executive manager
2. Professional
3. Business/Tech Manager
4. Arts or Entertainment
5. Administrative Personnel
6. Technical Personnel
7. Clerical
8. Skilled Manual

As displayed in **Figure 10** above, seven of the of the subjects left the occupation field blank. One was an executive professional. Nine of the subjects were professionals. Another subject was a business/tech manager. Two of the subjects were in the arts or entertainement industry. Four of the subjects were administrative personnel. One of the subjects was a technical personnel. Another nine of the subjects held clerical positions. Lastly eight of the subjects were skilled laborers.

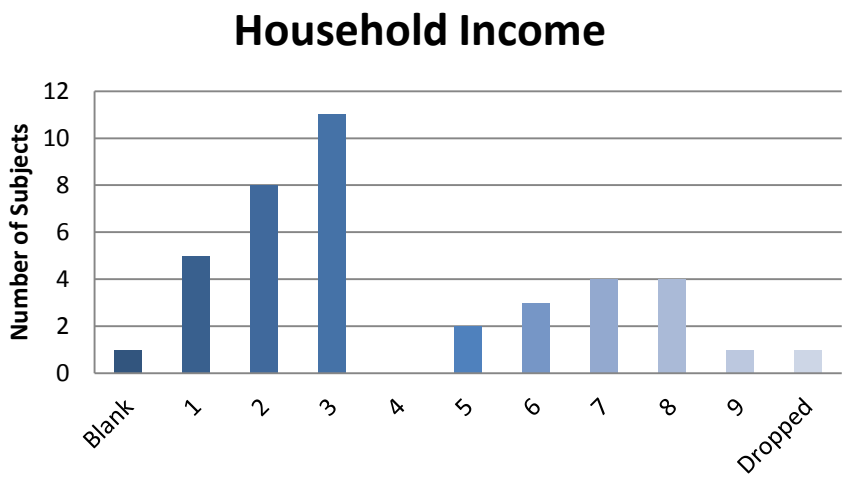

Figure 11: Bar Chart of the Household Income Received by Subjects

Exhibited is the household income of the subjects participating in the study. A good portion of the subjects received $20,000-$29,999.

Each of the numerical value on the scale represents a household income range:

1. Less than $10,000
2. $10,000-$19,999
3. $20,000-$29,999
4. $30,000-$39,999
5. $40,000-$49,999
6. $50,000-$74,999
7. $75,000-$99,999
8. $100,000-$149,999
9. $150,000-$199,999
10. $200,000 or more

As displayed in **Figure 11** above, one subject left the income field blank. Five subjects enjoyed a household income of lest than $10,000 per anum. Eleven of the subjects enjoyed a household income range beween $20,000 and $29,999. Two subjects had a household income range of $40,000-$49,999. Three enjoyed a household income range between $50,000 and $74,999. Four subjects had household incomes of $75,000-$99,999 while another four enjoyed household incomes between $100,000 and $149,999. Lastly, one of the subjects enjoyed a household income range beween $150,000 and $199,999.

Correlations and Data Analysis

Taking the empirical data from the REDCap database, correlations were made in an effort to validate findings found in literature. Correlations were made using the Microsoft Excel Data Analysis ToolPak. Using this software, regressions were produced. In a regression analysis correlation, when an intercept p-value is less than .01, this shows that the data is statistically significant. If the data is statistically significant, the line of best fit uses the empirical data points to give a forecast of future data. In the plots below, the blue data points represent the empirical data points, while the red points represent the forecast of future data. An example of the intercept p-value and other regression statistics can be seen below in.

Table 3: Regression Statistics for Age &Menopausal Stage Correlation

	Coefficients	*Standard Error*	*t Stat*	***P-value***	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	40.72444	2.382142	17.09572	**1.45E-18**	35.88843	45.56045	35.88843	45.56045
Menopausal Stage	3.619701	1.027169	3.523957	0.001206	1.534436	5.704965	1.534436	5.704965

Below is a correlation plot made between the menopausal stage of the subjects in the study and their reported age.

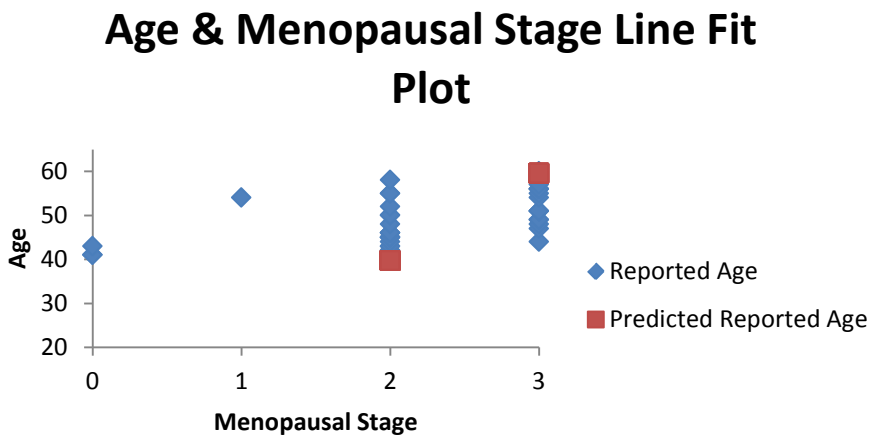

Figure 12: Scatter Plot of Reported Age and Menopausal Stage

Shown is the reported age of the subjects participating in the study (y-axis) correlated with the subjects' menopausal stage (x-axis). The numbers 0, 1, 2, and 3 are ordinal values that indicate that the subject is pre-menopausal, menopausal, peri-menopausal and post-menopausal respectively.

In **Figure 12** it can be seen that peri-menopausal and the post-menopauasl subjects are in their mid-fifties to sixties as literature states. Likewise, the menstruating to pre-menopausal subjects are in their

mid-fifties or below. There was an intercept p-value of 1.45E-18 suggesting that the correlation between the subjects reported age and menopausal stage is statistically significant.

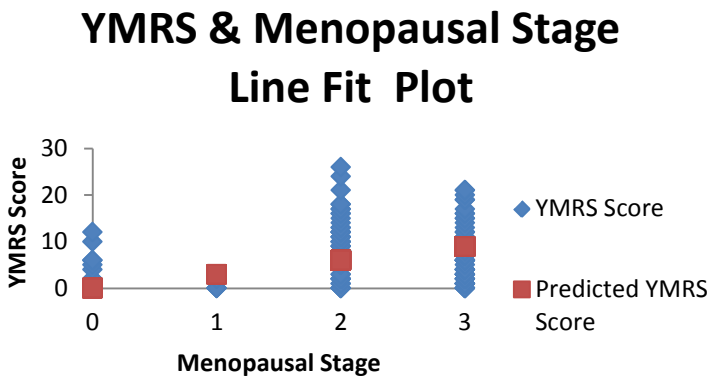

Figure 13: Scatter Plot of YMRS Total Score and Menopausal Stage

Shown is the total YMRS score of the subjects participating in the study (y-axis) correlated with the subjects' menopausal stage (x-axis). The numbers 0, 1, 2, and 3 are ordinal values that indicate that the subject is pre-menopausal, menopausal, peri-menopausal and post-menopausal respectively.

Figure 13 shows the correlation plot for the subjects' YMRS total scores and their menopausal stages. The empirical data consists of a data plot for each visit and subsequent YMRS evaluation. It is apparent from the data that the peri-menopausal and post-menopausal subjects display the highest YMRS scores meaning that they experience more intense manic episodes. An intercept p-value was inconclusive as to the correlation between the YMRS score and the subjects' menopausal stage. As such no statistical correlation between menopausal stage and manic episodes was found. However, visually the graphical data suggests that bipolar symptoms may increase during menopausal transitioning, giving rise to a high YMRS score.

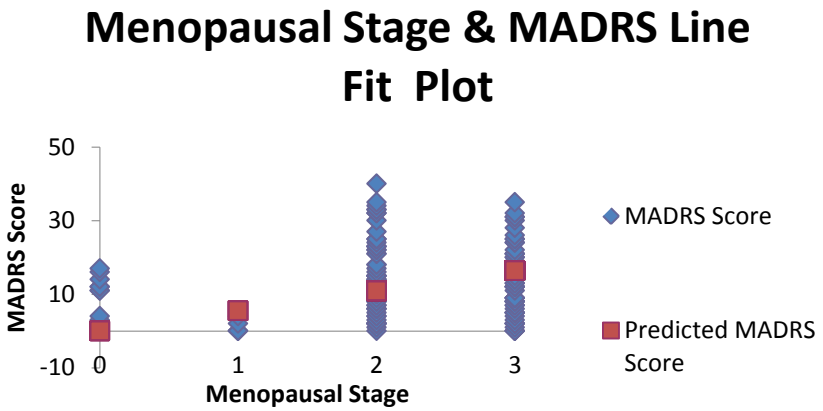

Figure 14: Scatter Plot of MADRS Total Score and Menopausal Sage

Shown is the reported MADRS score of the subjects participating in the study (y-axis) correlated with the subjects' menopausal stage (x-axis). The numbers 0, 1, 2, and 3 are ordinal values that indicate that the subject is pre-menopausal, menopausal, peri-menopausal and post-menopausal respectively.

Figure 14 shows the correlation plot for the subjects' MADRS total scores and their menopausal stage. The empirical data consists of a data plot for each visit and subsequent MADRS evaluation. It is apparent from the data that the peri-menopause and post-menopause subjects display the highest MADRS scores meaning that they experience more intense depressive episodes. An intercept p-value was inconclusive as to the correlation between the MADRS score and the subjects' menopausal stage. As such no statistical correlation between menopausal stage and depressive episodes was found.

Correlation between FSH Levels to Bipolarity Index Score

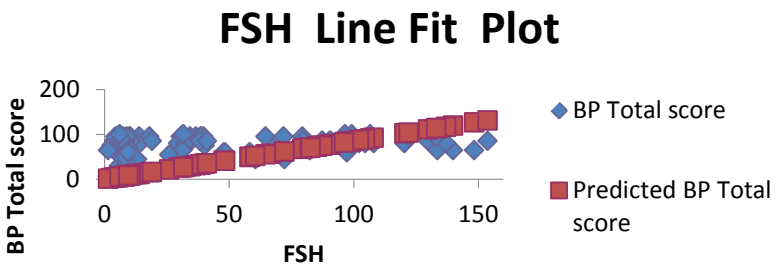

Figure 15: Scatter Plot of Bipolarity Index and FSH Levels

Shown is the subjects' bipolarity index total score (y-axis) correlated with the subjects' FSH levels (x-axis).

Figure 15 shows the correlation plot for the subjects' bipolarity index total scores and follicular stimulating hormone (FSH) levels. The empirical data consists of a bipolarity index value and subsequent FSH level per visit. The bipolarity index score is comprised of five scored categories, on a spectrum that add together, from which a subtype diagnosis is made. The categories from which the score is derived, include, the subjects' family history, response to medicinal treatment, course of illness, age of onset of first mood episode and mania symptomology. It can be seen that the empirical data fits the line of best fit somewhat. However, an intercept p-value was inconclusive as to the correlation between the bipolarity index score and the subjects' FSH levels. As such no statistical correlation between menopausal stage and depressive episodes was found.

Conclusion

The data from the "Demographics Form" was visually displayed as bar graphs representing the makeup of the subjects in the study. On preliminary demographic examination we found that the majority of the subjects were white, non-Hispanic individuals who were married and had some college background. Most received a household income of $20,000-$29,999 and held either a professional or clerical occupation. In the future, variables in the "Demographics Form", such as, household income and marital status, can be correlated with bipolar disorder symptoms in order to see if demographics have an effect on symptom severity.

As shown in the correlations section of the data analysis, no strong statistical correlations were found using a regression analysis. However, background research suggested a correlation may exist between menopause and bipolar disorder due to severe hormonal fluctuations in endocrine levels. Literature suggests that the menopausal transition may be associated with greater mood flux for those diagnosed with bipolar disorder (Kukopulos, Reginaldi, Laddomada, & Floris, 1980). Despite these correlations, regression analysis failed to validate all literature-based relationships. For instance, it is known that there is a correlation between a woman's age and her menopausal stage. This relationship was confirmed. However, when making correlations between the MADRS total scores, YMRS total scores and the subjects' menopausal stage, the data failed to lend itself to the establishment of a statistically significant correlation as indicated by the p-value. . Nevertheless biological correlations have been underlined in previous studies on the basis that elevated endocrine levels during menstrual transitions alter the mood severity of both manic and depressive episodes, thus exacerbating a subjects' bipolar disorder at its foundation (Steiner, Dunn, & Born, 2001). Furthermore, some research points to similar mood and in turn symptom elevation as a result of postpartum states (Payne, 2007).

Despite the statistical inconclusiveness, the empirical data as seen in **Figures 15** and **16** shows that peri-menopausal and post-menopausal subjects may in fact have a tendency to experience more intense manic and depressive episodes. There may be a relationship between the line of best fit and the empirical data in **Figure 17**. The failure to come up with statistically significant intercept p-values from the regressions in **Figures 15-17**, may be due to the current small sample size of the study. There are currently only 39 participants in the study, while the goal for participants is set at approximately 70 subjects. Despite the current sample size, a better way to analyze the data of this study is to use a repeated measures design. This design model lends itself well to longitudinal studies in which the same subjects are evaluated for different measures over a period of time (Toutenburg, 2009). This type of model will allow for stronger correlations to be made with smaller sample sizes. At this time in the study however, there is simply not enough data per menstrual phase to draw conclusions.

The other possible issue with making statistical correlations between numerical representations of symptom severity is that, to date, individuals are diagnosed on a continuum divided by Bipolar I, Bipolar II, and Bipolar NOS. With the specific symptoms of the disorder falling into such broad categories, especially the heterogeneous NOS classification, it may be difficult to make conclusive correlations between subjects' menopausal stage and bipolar symptoms.

This MQP endeavored to consider alternative options that may be associated with mood stability in bipolar disorder. To accomplish this, researchers drafted a questionnaire, which would result in a matrix of prescription treatments coupled with hypothesized dietary supplements associated with

mood stability. These dietary supplements included omega-3 fatty acids and vitamins, such as vitamin B complex. Said supplements were chosen because they have been associated clinically with mood stability. Vitamins, like B6, are known to contribute to serotonin precursor development, which could aid a treatment such as an SSRI to combat depressive symptoms more effectively, for instance (Bernstein, 2006).

Due to time constraints and pending IRB approvals, this questionnaire was finalized, but data collection from study participants never came to fruition. Even further research in other subsequent studies could lead to the development of animal models to examine bipolar disorder. For instance, there already exists a mouse model for depression. The effectiveness of antidepressants has been tested on this model, which houses genes associated with depression-syndrome (Urani, Chourbaji, & Gass, 2005). However if a model displaying both manic and depressive symptoms was developed, the study of bipolar disorder could take great strides.

Herein we learned the criteria for bipolar disorders and menopausal staging and its application in clinical research. We gained experience in the execution of clinical research in an outpatient setting on an observational study examining the clinical course of bipolar disorder during the menaopausal transition. In particular, we mastered REDCap software for data entry and learned basic analytical techniques. On preliminary analysis, while age was associated with menopausal stage, neither severity of mood elevations nor depression was associated with menopausal stage of FSH levels. While our initial report does not reveal significant associations and it may be that menopausal stage and hormonal levels are not associated with mood, further more thorough analysis with a larger study sample will be performed by the primary investigator.

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Study Improvements

After completing data entry into the REDCap database, a series of recommendations were made regarding computer-based data and paper-form data. The following list consists of possible improvements that can be made to facilitate the data entry process, as well as maintaining consistency.

Data Collection – Databases and Forms

General

- The text fields are inconsistent in accepting the entry for blank vs. 0. During certain cases, if age is left blank, sometimes the database allows one to enter **blank** and sometimes it requires the age **0** as a numerical digit.

PHI

- Under **Preferred Contact Number** there is an option for **other** but it does not correspond to an optional field in the database.

Menstrual History

- If the time period of **last period** is less than 1 month (i.e. 4 days) the equation will return -1 months.
- In page 2, **in the past month, have you had hot flashes that awakened you at night or caused night sweats?** is indented, so it appears to be part of the **In the past month, have you had hot flashes that occur during the day?** section. If the patient answers no to the latter, then they assume to skip the aforementioned question.
- Under **would you describe yourself as currently…** it may be assumed that a portion of the question **was your menopause…** only pertains to post-menopausal.
- Under the amount of time that the subject exercised, on REDCap it asks for the exercise duration in minutes; however, on the actual form there is no specification and therefore the subject just gives a general period of time. (i.e. every day, twice a week, etc.).

CMF

- If **Yes** is not marked for **Alcohol Abuse**, the number of drinks that the subject has per week cannot be entered. If the value is like 4 drinks per week, that is not necessarily abuse.
- When the subject is not currently abusing alcohol, but has in the past (i.e. subject #313) there is no way to indicate that they have and that they are sober for x-period of time.
- On the CMF paper form, under **Onset of Menses** it gives the option for early, late and unavailable if the subject is still menstruating; however, these options do not appear on the database form.

The Greene Climacteric Scale

- The word “Climacteric” in the title of the Greene Climacteric Scale form is misspelled.

MADRS

- While the physician is checking off the boxes based upon subject’s response, there is no actual place on the REDCap database to add the physician’s comments that are written (i.e. answers to the guided questions).

ADE1-5

- In REDCap, it asks for a **+/- value** for **Alcohol Abuse** and does not give a place to enter the number of drinks written on the physical sheet. So if the subject has 2 drinks per day as shown on the sheet, that is not necessarily alcohol abuse.
- Under **Past Depression** the program asks to rate (**no, probable** or **definite**) and then a field appears for comments even though there is no actual field on the actual form.
- Under **If either of above answers is "definite," answer the following questions. If not, skip to next section** under **SI** the actual form has LNWL, Active and Passive as choices but REDCap has those 3 in addition to refused, don't know and blank.
- Under **Perimenstrual exacerbation** on REDCap there is a comment section even though there is none on the actual form.
- Under **Past psychiatric history** on the actual form there is a Comments Section that does not appear in REDCap.
- Under **Other current symptoms** the physician is able to choose between: euthymic, depressed, elevated, mixed and fill in, however you can only choose one on the online form even though multiple may be selected on the actual form.
- Under **Have you ever had a time...when you were feeling so good or hyper that other PEOPLE THOUGHT YOU WERE NOT YOUR NORMAL SELF?** the fields for the date should only appear if the user selects **yes** as a response. This should not happen when they select **probable** as a response.
- It is often forgotten to circle **yes** or **no** under **abuse or trauma** on the Past Psychiatric History form.
- On page 3 for **Number of Phases**, the field for **past 12 months** should have a **0** as an option.

ADE6-8

- In the **Treatment History** section, there should be a **blank** option as opposed to **don't know** or **didn't ask**.
- Under **Psychoactive Substance Use History** from Nicotine on, for those substances if the current use is marked as **yes** the additional fields for the **age last use, age peak use, age onset** and **abuse treatment** do not generate.
- Under **Psychoactive Substance Use History:** All fields appear for **EtOH only**, while the rest concentrate only on current use and history of abuse.
- Under **Neuro-endocrine** what is the purpose of having **Other entry in review of systems? Followed by Indicate yes, no, didn't ask**? Is there a difference between the two?

ADE9

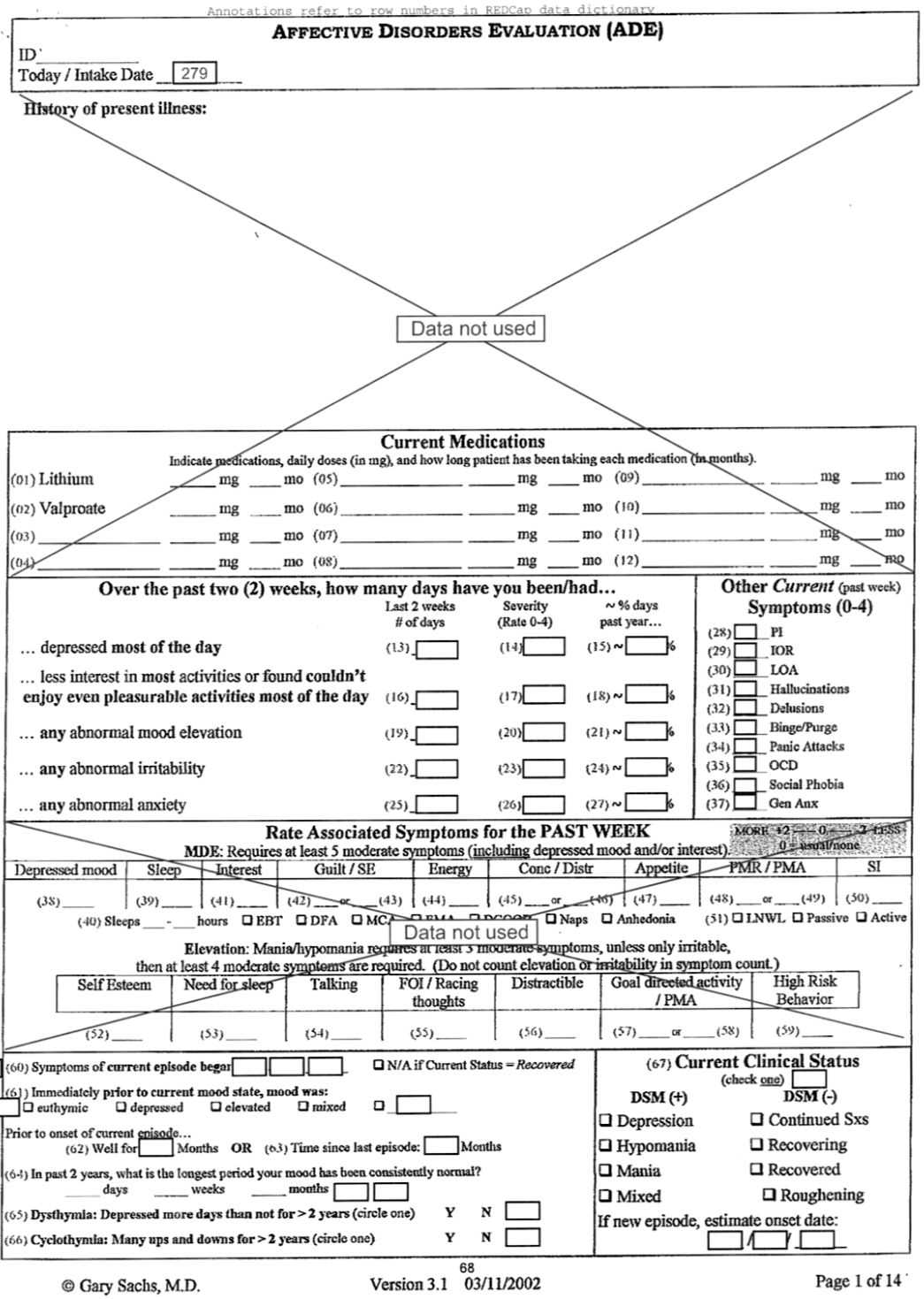
- Under **Family History** if the user checks **yes** in the dropdown field, then there is no corresponding checkbox for **nieces**, and **nephews**. This is a common write-in on the actual form.

Appendix

Appendix A: Table of Subject Visits and Menstrual Status

Subject Identifier	Visits Completed	Status	Menopausal Stage
304	5	Complete	Post-menopausal
305	5	Complete	Post-menopausal
306	5	Complete	Post-menopausal
307	4	Dropped	Peri-menopausal
308	4	Still Participating	Peri-menopausal
309	5	Complete	Post-menopausal
310	5	Complete	Post-menopausal
311	5	Complete	Peri-menopausal
312	2	Lost to Follow-up	Peri-menopausal
313	5	Complete	Post-menopausal
314	5	Complete	Post-menopausal
315	5	Complete	Peri-menopausal
316	5	Complete	Peri-menopausal
317	1	Lost to Follow-up	Peri-menopausal
318	5	Complete	Post-menopausal
319	5	Complete	Post-menopausal
320	3	Lost to Follow-up	Menstruating
321	5	Complete	Menstruating
322	5	Complete	Menstruating
323	5	Complete	Peri-menopausal
324	1	Lost to Follow-up	Peri-menopausal
325	5	Complete	Post-menopausal
326	1	Lost to Follow-up	Peri-menopausal
327	2	Lost to Follow-up	Peri-menopausal
328	5	Complete	Peri-menopausal
329	1	Lost to Follow-up	Peri-menopausal
330	1	Lost to Follow-up	Peri-menopausal
331	5	Complete	Pre-menopausal
332	3	Still Participating	Post-menopausal
333	1	Lost to Follow-up	Peri-menopausal
334	4	Still Participating	Peri-menopausal
335	4	Still Participating	Peri-menopausal (late)
336	2	Still Participating	Post-menopausal
337	3	Still Participating	Peri-menopausal (late)
338	1	Lost to Follow-up	Peri-menopausal
339	2	Still Participating	Peri-menopausal (early)
340	1	Still Participating	Peri-menopausal
341	1	Still Participating	Post-menopausal

Appendix B: Affective Disorders Evaluation (ADE) Form



Annotations refer to row numbers in REDCap data dictionary

AFFECTIVE DISORDERS EVALUATION (ADE)

ID _____

Today / Intake Date 279

History of present illness:

Data not used

Current Medications

Indicate medications, daily doses (in mg), and how long patient has been taking each medication (in months).

(01) Lithium	____	mg	____	mo	(05) _____	____	mg	____	mo	(09) _____	____ mg ____ mo
(02) Valproate	____	mg	____	mo	(06) _____	____	mg	____	mo	(10) _____	____ mg ____ mo
(03) _____	____	mg	____	mo	(07) _____	____	mg	____	mo	(11) _____	____ mg ____ mo
(04) _____	____	mg	____	mo	(08) _____	____	mg	____	mo	(12) _____	____ mg ____ mo

Over the past two (2) weeks, how many days have you been/had…

	Last 2 weeks # of days	Severity (Rate 0-4)	~ % days past year…
… depressed **most of the day**	(13)	(14)	(15) ~ %
… less interest in **most** activities or found **couldn't enjoy even pleasurable activities most of the day**	(16)	(17)	(18) ~ %
… **any** abnormal mood elevation	(19)	(20)	(21) ~ %
… **any** abnormal irritability	(22)	(23)	(24) ~ %
… **any** abnormal anxiety	(25)	(26)	(27) ~ %

Other *Current* (past week) Symptoms (0-4)

(28) PI
(29) IOR
(30) LOA
(31) Hallucinations
(32) Delusions
(33) Binge/Purge
(34) Panic Attacks
(35) OCD
(36) Social Phobia
(37) Gen Anx

Rate Associated Symptoms for the PAST WEEK

MORE +2 ___ 0 ___ -2 LESS
0 = usual/none

MDE: Requires at least 5 moderate symptoms (including depressed mood and/or interest).

Depressed mood	Sleep	Interest	Guilt / SE	Energy	Conc / Distr	Appetite	PMR / PMA	SI
(38) ____	(39) ____	(41) ____	(42) ____ or ____ (43)	(44) ____	(45) ____ or ____ (46)	(47) ____	(48) ____ or ____ (49)	(50) ____

(40) Sleeps ___ - ___ hours ☐ EBT ☐ DFA ☐ MCA ☐ PMA ☐ DSCOPE ☐ Naps ☐ Anhedonia (51) ☐ LNWL ☐ Passive ☐ Active

Data not used

Elevation: Mania/hypomania requires at least 3 moderate symptoms, unless only irritable, then at least 4 moderate symptoms are required. (Do not count elevation or irritability in symptom count.)

Self Esteem	Need for sleep	Talking	FOI / Racing thoughts	Distractible	Goal directed activity / PMA	High Risk Behavior
(52) ____	(53) ____	(54) ____	(55) ____	(56) ____	(57) ____ or ____ (58)	(59) ____

☐ (60) Symptoms of **current episode began** ☐☐☐ ☐ N/A if Current Status = *Recovered*

(61) Immediately **prior to current mood state, mood was:**
☐ ☐ euthymic ☐ depressed ☐ elevated ☐ *mixed* ☐ ☐

Prior to onset of current episode…
(62) Well for ☐ Months **OR** (63) Time since last episode: ☐ Months

(64) **In past 2 years, what is the longest period your mood has been consistently normal?**
_____ days _____ weeks _____ months ☐☐

(65) **Dysthymia: Depressed more days than not for > 2 years** (circle one) Y N ☐

(66) **Cyclothymia: Many ups and downs for > 2 years** (circle one) Y N ☐

(67) **Current Clinical Status** (check one) ☐

DSM (+)	DSM (-)
☐ Depression	☐ Continued Sxs
☐ Hypomania	☐ Recovering
☐ Mania	☐ Recovered
☐ Mixed	☐ Roughening

If new episode, estimate onset date: ☐☐/☐☐/☐☐☐☐

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Annotations refer to row numbers in REDCap data dictionary

ABNORMAL MOOD ELEVATION (LIFETIME)

Have you ever had a time…

	No	Probable	Yes	
…when you were feeling so good or so hyper that other people thought you were not your normal self?	☐	☐	☐	If yes, when was that? ☐☐/☐☐/☐☐ Age: ☐☐
…or you were so hyper you got into trouble?	☐	☐	☐	If yes, when was that? ☐☐/☐☐/☐☐ Age: ☐☐
…did anyone say you were manic?	☐	☐	☐	If yes, when was that? ☐☐/☐☐/☐☐ Age: ☐☐
…when you felt like you could do much more than ordinarily capable of?	☐	☐	☐	If yes, when was that? ☐☐/☐☐/☐☐ Age: ☐☐
…when you were so irritable that you shouted at people or started fights or arguments? Did you find yourself yelling at people you didn't really know?	☐	☐	☐	If yes, when was that? ☐☐/☐☐/☐☐ Age: ☐☐

For the most severe episode identified above, determine:

During that time, were there ***any times*** when your mood was: ☐ ☐ euphoric ☐ expansive ☐ irritable ☐ dysphoric

(Was it really too _____, or just better than the times you felt down?)

Were you admitted to the hospital during this time? ☐ ☐ hospitalized ☐ not hospitalized

Altogether, how long did this period last? ☐☐ ____ hours ____ days ____ weeks ____ months

Symptoms present to a significant degree during most severe episode identified above

During that time… (Much less) -2 -1 0 +1 +2 (Much more)	
…were you feeling more self-confident than usual or like you were special, more talented, more attractive, or smarter than usual? Were there any times when your thoughts were grandiose?	☐ Self-esteem
…were there nights you got less sleep than usual and found you didn't really miss it?	☐ Need for sleep
…were there any times you were more talkative than usual, or you found you said much more than you intended? Were there any times you spoke faster than usual?	☐ Talking
…did you find that you had more ideas than usual? Were there times when your thoughts seemed to be racing through your head?	☐ FOI/Racing
…did you find you were easily distracted?	☐ Distractible
…did you experience difficulties due to making new plans or getting new projects started? Were you so active that people worried about you taking on so much? Were there times when you were so energized or agitated you couldn't sit still?	☐☐ Goal-directed activity/PMA
…did you do anything that was unusual for you or that other people might think was excessive, foolish or risky? Did you do anything that would have caused a problem if you were caught?	☐ High-risk behavior

Other features of past episodes of mood elevation ("+" indicates symptom present to a significant degree in any week, "-" indicates absent.)

☐ ↑ Risky pleasure: ☐ _____ ☐ Extraordinary accomplishment

☐ Sudden onset ☐ Easily annoyed ☐ PI ☐ Delusions

☐ Hallucinations: ☐ _____

Associated stressor: ☐ _____

Organic factors:

☐ Alcohol abuse ☐ Substance abuse

☐ Onset <12 wks after ↑ antidepressant

☐ Other: ☐ _____

During worst week of episode: Rate: 0 = none, 1 = mild, 2 = moderate, 3 = severe

☐ Marital discord ☐ Occupational dysfunction ☐ Social dysfunction ☐ Violence ☐ Legal problems

(68) **Mania?** ☐ (69) If no, **Hypomania?** ☐ If neither, is mood elevation sufficient for BP NOS? ☐

Determine number of (hypo)manic episodes

The time we've been talking about is what we would call (hypo)mania.

Using that time as a guide, how many times have you been like that for as long as 1 wk?

(70) Number of phases (circle one) ☐ 0 1 2 3-4 5-9 10-20 20-50 Too many to count Indeterminate

(71) When was the last episode of (hypo)mania? (Do not consider current episode.) Estimated onset ☐☐/☐☐/☐☐ Estimated offset ☐☐/☐☐/☐☐

How many times have you felt like that in the past year? Mania: ☐ Hypomania: ☐ Mixed: ☐ (72) **Total:** ☐

(If the total is >1): How were you feeling between those times? ☐ _____

Earliest episode: When was the first time your mood was like that for a week or more? (73) Age: ☐ Date onset ☐☐/☐☐/☐☐

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Annotations refer to row numbers in REDCap data dictionary

PAST DEPRESSION

	No	Probable	Definite
Has there ever been a period when you were feeling down or depressed most of the day, nearly every day, for as long as two weeks?	☐	☐	☐
What about being a lot less interested in things or unable to enjoy things you usually would enjoy nearly every day for as long as two weeks?	☐	☐	☐

If either is "Defininte":

Symptoms present to a significant degree during most severe episode

During that time… (Much less) -2 -1 0 +1 +2 (Much more)

…did you have a change in sleep pattern? ☐	Sleep ☐☐ hours)
…were you down on yourself? Did you feel as if you were a bad person or that you deserved to suffer? ☐/☐	Guilt / Self-esteem
…how was your energy level? Were there things that you should have done and didn't because you didn't have enough energy or were simply too tired? ☐	Energy
…how was your concentration? Were you able to read the newspaper or watch TV? Did you find that you were easily distracted? ☐/☐	Concentration / Distractibility
…how was your appetite? Did your weight change? ☐	Appetite
…were there times when you were so fidgety or agitated it was hard for you to stay still? What about the opposite, thinking or moving more slowly than usual (or feeling like molasses in January)? If I had been there, would I have noticed that something was wrong? ☐/☐	PMR / PMA
…were there times when you were feeling so bad that you felt life was not worth living? What about actually thinking about suicide or harming yourself? ☐	SI ☐ ☐ LNWL ☐ Passive ☐ Active

Other features of past episodes of depression ("+" indicates symptom present to a significant degree in any week, "-" indicates absent.)

(79 ☐ PI (80 ☐ Delusions (8 ☐ Hallucinations

Associated stressor: ☐

Organic factors:
☐ Alcohol abuse
☐ Substance abuse
☐ Other: ☐

Determine number of depressive episodes

The time we've been talking about is what we'd call an episode of depression. Using that time as a guide, how many times have you been like that for as long as 2 weeks?

(82) Number of phases (circle one ☐ 0 1 2 3-4 5-9 10-20 20-50 Too many to count Indeterminate

(83) When was last episode of depression? (Do not consider current episode.) Estimated onset ☐☐/☐☐ Estimated offset: ☐☐/☐☐

(84) How many times have you felt like that in the past year? ☐
(If the total is >1): How were you feeling between those times? ☐

Earliest episode: When was the first time your mood was like that for a week or more? (85) Age: ☐ Date onset ☐☐/☐☐

PATTERN OF MOOD SYMPTOMS: ☐ NONE APPARENT USUAL ONSET: ____-____ USUAL OFFSET ____-____

(86) Hx Antidepressant induced (hypo)mania ☐ Yes ☐ No ☐ Unknown/not done
↘ If yes, drug: ☐☐, date ☐☐/☐☐

(87) Perimenstrual Exacerbation: ☐ ☐ Yes ☐ No ☐ Unknown/not done ☐ N/A ☐

75 Mood Sxs associated with Pregnancy: ☐ ☐ Yes ☐ No ☐ N/A

(88) Postpartum ☐ ☐ Yes ☐ No ☐ N/A

NUMBER OF PHASES: (SEPARATED BY 4 WEEKS OF EUTHYMIA OR AN EPISODE OF OPPOSITE POLARITY)	No RELIABLE INFO	0	1	2	3	4	5-12	13-52	≥53
(89) LIFETIME ☐									
(90) PAST 12 MONTHS ☐									
(91) MOST EVER IN 12 MONTHS ☐									

(92) Episode pattern ☐ ☐ DEM ☐ DME ☐ MED ☐ MDE ☐ MDMDMD ☐ Inconsistent ☐ Unclear

IS SEASONAL PATTERN SUSPECTED ☐ ☐ YES ☐ NO ☐ UNKNOWN/NOT DONE
↘ If yes, comment: ☐

CYCLOTHYMIA, DYSTHYMIA, AND SUBSYNDROMAL MOOD ELEVATION

CYCLOTHYMIA (Optional, determine whether patient has/had current or past cyclothymia)

Other than the times we talked about when you met criteria for depression…

…have you ever had a period when you had lots of ups and downs, that is, some days you felt too good or even a little high, and other days you felt down and depressed?	Y	N
(If yes)Were the good days really too good, or just better than the bad days?	Y	N
Did the ups and downs follow any pattern?	Y	N
Was there a period of time like that for as long as two years during which you were never without those ups and downs for as long as two months?	Y	N
During that time, what's the longest period that you felt normal?	____ weeks	
Well interval / - /		

Note: DSM-IV does not specify the number of symptoms of mood elevation required for cyclothymia. Use script to screen for occult periods of mood elevation.

During those period when you were high, did you find that you…

…needed less sleep than usual?	Y	N
…felt particularly full of energy?	Y	N
…felt especially self confident?	Y	N
…get a lot more done than usual?	Y	N
…felt physically restless?	Y	N
…talked more than usual?	Y	N
…had unusually good ideas or think especially clearly?	Y	N
…did things that could have caused trouble for you o Data not used ish spending sprees, reckless driving)?	Y	N
…laugh or joke about things that other people don't find funny (or think are in poor taste)?	Y	N
Cyclothymia	Y	N

DYSTHYMIA (Optional, or if unclear whether patient has mood disorder)

Have you ever felt down/depressed more often than not for 1-2 years and were never without those feelings for as long as 2 months?	Y	N
During that time, what was the longest period of time that you felt normal? _____ weeks		

During this period of feeling depressed most of the time…

…did your appetite change significantly?	Y	N
…did you have trouble sleeping or sleep excessively?	Y	N
…did you feel tired or without energy?	Y	N
…did you lose your self-confidence?	Y	N
…did you have trouble concentrating or making decisions?	Y	N
…did you feel hopeless?	Y	N
Are two or more answers coded yes?	Y	N
Did these symptoms cause significant distress or impair your ability to function at work, socially, or in some other way?	Y	N
Dysthymia	Y	N

SUBSYNDROMAL MOOD ELEVATION (Optional, or if unclear whether patient has bipolar disorder)

Have you ever had even brief periods when your mood was abnormally high or when you were very easily annoyed?	Y	N
In the past 2 months how many weeks have you had without even one day like that? _____ weeks		

Annotations refer to row numbers in REDCap data dictionary

CHILDHOOD HISTORY

Use DSM criteria and code: "No," "Probable," or "Definite." If uncertain of criteria, indicate "Probable" and check DSM. If patient is short of criteria, indicate "No."

	No	Probable	Definite	Comment	Age / Onset
(122) ADD/ADHD					(123)
(124) Oppositional/Defiant					(125)
(126) Conduct Disorder					(127)
(128) Learning Disorders					(129)
(130) Overanxious/GAD					(131)
				Data not used	

Compared to average classmate/peer: Much worse = -2 — 0 — +2 = Much better (0 = average)	Best term	Worst term
Academic function:		
Data not used		
	Best year	Worst year
Social function:		

PSYCHOACTIVE SUBSTANCE USE HISTORY

	Current use	Age last use	Age peak use	Hx Abuse?	Age onset	Abuse Treatment
EtOH	(148) ___ hr/d			Y N	(149)	(150) Y N if yes, age:
Caffeine	(151) ___ /d	___	___	Y N	(152) __ __	(153) Y N if yes, age: __ __
Nicotine	(154) ___ /d	___	___	Y N	(155) __ __	(156) Y N if yes, age: __ __
MJ	(157) Y N	___	___	Y N	(158) __ __	(159) Y N if yes, age: __ __
Amphtetamine	(160) Y N	___	___	Y N	(161) __ __	(162) Y N if yes, age: __ __
Cocaine	(163) Y N	___	___	Y N	(164) __ __	(165) Y N if yes, age: __ __
PCP	(166) Y N	___	___	Y N	(167) __ __	(168) Y N if yes, age: __ __
LSD	(169) Y N	___	___	Y N	(170) __ __	(171) Y N if yes, age: __ __
Opiates	(172) Y N	___	___	Y N	(173) __ __	(174) Y N if yes, age: __ __
	Y N	___	___	Y N	__ __	Y N if yes, age: __ __
	Y N	___	___	Y N	__ __	Y N if yes, age: __ __

Data not used

Data not used

How old were you when you were first treated for…	Age	Treatment
…any psychiatric (emotional, psychological, behavioral) problem? (Dx:)		
…depression?		
Data not used		
…depression with medication or ECT? (if first tx did not include antidepressant meds or ECT)		
…mood elevation (irritability)?		
…mood elevation (irritability) with medication or ECT? (if first tx did not include antimanic meds or ECT)		

TREATMENT HISTORY

Treatment	Date	Wks of tx	Max dose (mg/d)	Response	Affective switch* in 1st 12 weeks (circle one)	Comments / adverse effects
Mood stabilizing agents						
❑ (175) Lithium ☐					Y N ?	
❑ (176) Valproate ☐					Y N ?	
❑ (177) Carbamazep ☐					Y N ?	
❑ (178) Lamotrigine ☐					Y N ?	
❑ (179) Gabapentin ☐					Y N ?	
❑ (180) Clonazepam ☐					Y N ?	
❑ (181) Omega-3 ☐					Y N ?	
❑ (182) Ca blocker ☐					Y N ?	
Antidepressants						
❑ (183) Buproprion ☐					(184) Y N ?	
❑ (185) Mirtazapine ☐					(186) Y N ?	
❑ (187) MAOI ☐					(188) Y N ?	
❑ (189) Citalopram ☐					(190) Y N ?	
❑ (191) Fluoxetine ☐					(192) Y N ?	
❑ (193) Sertralinė ☐					(194) Y N ?	
❑ (195) Paroxetine ☐					(196) Y N ?	
❑ (197) Fluvoxamine ☐					(198) Y N ?	
❑ (199) Venlafaxine ☐					(200) Y N ?	
❑ (201) Nefazodone ☐					(202) Y N ?	
❑ (203) Heterocyclic ☐					Y N ?	
❑ (205) ECT Uni Bi ☐ ☐					(206) Y N ?	
Stimulants						
					Y N ?	
					Y N ?	
Anxiolytics						
❑ (207) Benzodiazepine ☐					Y N ?	
❑ (208) Buspirone ☐					Y N ?	
❑ (209) Beta blocker ☐					Y N ?	
Antipsychotic						
❑ (210) Risperidone ☐					(211) Y N ?	
❑ (212) Clozapine ☐					(213) Y N ?	
❑ (214) Olanzapine ☐					(215) Y N ?	
❑ (216) Quetiapine ☐					(217) Y N ?	
❑ (218) Ziprasidone ☐					(219) Y N ?	
❑ (220) Haloperidol ☐					(221) Y N ?	
❑ (222) Other ☐ ☐					(223) Y N ?	
❑ (224) Other ☐ ☐					(225) Y N ?	
Other						
❑ (226) Thyroid ☐					(227) Y N ?	
❑ (228) Light ☐					(229) Y N ?	
❑ (230) Verbal tx ☐					(231) Y N ?	

Data not used

* *Affective switch* is defined as a switch to a new episode of opposite polarity.

Annotations refer to row numbers in REDCap data dictionary

MEDICAL HISTORY

Major Illnesses/Surgeries/Admissions

Childhood: _____

Adulthood: _____

Data not used

Date of Last Physical Exam: __ / __ / ____ PCP: _____ Phone: _____

Data not used

Menstrual History	❑ N/A (Check if male)
(236) Menarche, age:	
Cycles: ____ days	Current ❑ Regular ❑ Irregular
Became irregula	Range: ____ - ____ days
Last menstrual period:	
(237) **Parity:** ____ Conception ____ Miscarriages ____ Abortions ____ Live Births	
(238) **Current contraceptive method:** ❑ None ❑ OBC ❑ Barrier ❑ Abstinence ❑ Other ____	
____ Hysterectomy Age ____	
____ Oopharectomy Age ____	

Review of Systems

	No	Yes
(239) Allergies		
(240) HT with LOC		
(241) Other LOC		
(242) Seizure		
(243) Migraine		
(244) Multiple Sclerosis		
CVA (Stroke)		
(245) Peptic Ulcer Disease		
(246) Hepatitis		
(247) Asthma		
(248) Eczema		
(249) Raynauds		
(250) Stevens Johnson		
(251) Diabetes		
(252) Thyroid		
Lupus		
Traumatic injury		
Rheumatoid Arthritis		
Osteoarthritis		

Abdomen

Thorax

Skin

Neuro-Endocrine

Extremities/ Joints

Physical Examination

Vital signs

(253) Blood pressure: _____ Data not used) Pulse: _____

(255) Height: ____ in (256) Weight: ____ lb.

(257) Handedne ❑ Left ❑ Right ❑ Ambidextrous

(258) **Clinically Significant Abnormalities?** ____

❑ No ❑ Yes ❑ Unclear

If yes, specify clinically significant findings: ____

Annotations refer to row numbers in REDCap data dictionary

FAMILY HISTORY

Siblings: ☐ F (ages: Data not used) ☐ M (ages: Data not used)
Children: ☐ F (ages:) ☐ M (ages:)

Code: 3= Professionally dx or treated 2= Likely by description 1= Negative ?= No info available		Any Blood relative	Mother	Father	Sister	Brother	Daughter	Son	Maternal: GM	Maternal: GF	Maternal: Aunt	Maternal: Uncle	Maternal: Cousin	Paternal: GM	Paternal: GF	Paternal: Aunt	Paternal: Uncle	Paternal: Cousin
Psychiatric hospitalization																		
Bipolar disorder																		
Other Mood Disorder																		
ADD/ADHD																		
Alcohol abuse																		
Substance abuse																		
Schizophrenia																		
Schizoaffective																		
Panic																		
Suicide																		
Suicide Attempt																		

Social History

Lives is _____ with _____

Occupation _____

Education _____ Military Service _____

Monetary support _____

Data not used

Involvement in role Rate -2—0—+2

__ Gainful employment __ Student __ Parenting __ Home chores __ Recreation __ Unemployed Impairment ___ % of normal

Notes/comments:

Annotations refer to row numbers in REDCap data dictionary

BIPOLARITY INDEX

For each of the items below, circle the score next to the characteristic that best describes the patient.
Characteristics' scores range from 0 (no evidence of bipolar disorder) to 20 (most convincing characteristic of bipolar disorder).

I. Episode Characteristics	
20	▪ Documented acute mania or mixed episode with prominent euphoria, grandiosity, or expansiveness and no significant general medical or known secondary etiology.
15	▪ Clear-cut acute mixed episode or dysphoric or irritable mania with no significant general medical or known secondary etiology.
10	▪ Clear-cut hypomania with no significant general medical or known secondary etiology. ▪ Clear-cut cyclothymia with no significant general medical or known secondary etiology. ▪ Clear-cut mania secondary to antidepressant use.
5	▪ Clear-cut hypomania secondary to antidepressant use. ▪ Episodes with characteristic sxs of hypomania, but sxs, duration, or intensity are subthreshold for hypomania or cyclothymia. ▪ A single MDE with psychotic or atypical features (Atypical is 2 of the following sxs: hypersomnia, hyperphagia, leaden paralysis of limbs) ▪ Any postpartum depression.
2	▪ Any recurrent typical unipolar major depressive disorder. ▪ History of any kind of psychotic disorder (i.e., presence of delusions, hallucinations, ideas of reference, magical thinking).
0	▪ No history of significant mood elevation, recurrent depression, or psychosis.
II. Age of Onset (1st affective episode/syndrome)	
20	▪ 15 to 19 years
15	▪ before age 15 or between 20 and 30
10	▪ 30 to 45 years
5	▪ after age 45
0	▪ No history of affective illness (no episodes, cyclothymia, dysthymia, or BP NOS).
III. Course of Illness / Associated Features	
20	▪ Recurrent, distinct manic episodes separated by periods of full recovery.
15	▪ Recurrent, distinct manic episodes with incomplete inter-episode recovery. ▪ Recurrent, distinct hypomanic episodes with full inter-episode recovery.
10	▪ Comorbid substance abuse. ▪ Psychotic features only during acute mood episodes. ▪ Incarceration or repeated legal offenses related to manic behavior (e.g., shoplifting, reckless driving, bankruptcy).
5	▪ Recurrent unipolar MDD with 3 or more major depressive episodes. ▪ Recurrent, distinct hypomanic episodes without full inter-episode recovery. ▪ Recurrent medication non-compliance. ▪ Comorbid borderline personality disorder, anxiety disorders, or eating disorders, or history of ADHD. ▪ Engagement in risky behaviors that pose a problem for patient, family, or friends. ▪ Behavioral evidence of perimenstrual exacerbation of mood symptoms.
2	▪ Baseline hyperthymic personality (when not manic or depressed. ▪ Marriage 3 or more times (including remarriage to the same individual. ▪ In two or more years,, has started a new job and changed jobs after less than a year. ▪ Has more than two advanced degrees.
0	▪ None of the above.
IV. Response to Treatment	
20	▪ Full recovery within 4 weeks of therapeutic treatment with mood stabilizing medication.
15	▪ Full recovery within 12 weeks of therapeutic treatment with mood stabilizing medication or relapse within 12 weeks of discontinuing tx. ▪ Affective switch to mania (pure or mixed) within 12 weeks of starting a new antidepressant or increasing dose.
10	▪ Worsening dysphoria or mixed symptoms during antidepressant treatment subthreshold for mania. ▪ Partial response to one or two mood stabilizers within 12 weeks of therapeutic treatment. ▪ Antidepressant-induced new or worsening rapid-cycling course.
5	▪ Treatment resistance: lack of response to complete trials of 3 or more antidepressants. ▪ Affective switch to mania or hypomania with antidepressant withdrawal.
2	▪ Immediate near complete response to antidepressant withdrawal.
0	▪ None of the above, or no treatment.
V. Family History	
20	▪ At least one first degree relative with documented bipolar illness.
15	▪ At least one second degree relative with documented bipolar illness. ▪ At least one first degree relative with documented, recurrent unipolar MDD and behavioral evidence suggesting bipolar illness.
10	▪ First degree relative with documented, recurrent unipolar MDD or schizoaffective disorder. ▪ Any relative with documented bipolar illness or recurrent unipolar MDD and behavioral evidence suggesting bipolar illness.
5	▪ First degree relative with documented substance abuse. ▪ And relative with possible bipolar illness.
2	▪ First degree relative with possible recurrent unipolar MDD. ▪ First degree relative with diagnosed related illness: anxiety disorders, eating disorders, ADD/ADHD.
0	▪ None of the above, or no family psychiatric illness.
	← **Total score (0 – 100)** (273)

Annotations refer to row numbers in REDCap data dictionary

Axis I Mood Disorder Dx: *(Use DSM-IV Codes)*

Current (or most recent) episode: ☐ 296.4 ☐ 296.5 ☐ 296.6 ☐ 296.7 ☐ 296.8 ☐ 296.2 ☐ 296.3 ☐ 295.7 ☐ Other ____

Lifetime: ☐ BP I ☐ BP II ☐ BP NOS ☐ Unipolar MDD ☐ Schizoaffective BP ☐ Schizoaffective UP ☐ Other ____

Lifetime: ☐ Cyclothymia ☐ Dysthymia ☐ Neither

(277) Other Axis I: ____

(278) Axis II: ____

(279) Axis III: ____

(280) Axis IV (stressors): ____

(281) Axis V (GAF): Current Month = ____ Past Year: Best = Data not used Worst = ____

~~CGI (current month): (282) CGI-BP-Depression = ____ (283) CGI-BP-Elevation = ____ (284) CGI-BP-Overall = ____~~

GAF Scale (frequently used definitions)

71-80:	• No more than slight impairment in functioning, varying degree of every day worry and problems that sometimes get out of hand. Minimal symptoms may or may not be present.
61-70:	• Some mild symptoms (e.g., depressed mood and mild insomnia) OR some difficulty in several areas of functioning, but generally functioning pretty well, has some meaningful interpersonal relationships, and most untrained people would not consider him "sick."
51-60:	• Moderate symptoms OR generally functioning with some difficulty (e.g., few friends and flat affect, depressed mood and pathological self-doubt, euphoric mood and pressured speech, moderately severe antisocial behavior).
41-50:	• Any serious symptomatology or impairment in functioning that most clinicians would think obviously requires treatment or attention (e.g., suicidal preoccupation or gesture, severe OC rituals, frequent anxiety attacks, serious antisocial behavior, compulsive drinking, mild but definite manic syndrome).
31-40:	• Major impairment in several areas, such as work, family relationships, judgement, thinking or mood (e.g., depressed woman avoids friend, neglects family, unable to do housework), OR some impairment in reality testing or communication (e.g., speech is sometimes obscure, irrelevant), OR single suicide attempt.
21-30:	• Unable to function in almost all areas (e.g., stays in bed all day) OR behavior is considerably influenced by either delusion or hallucinations OR serious impairment in communication (e.g., sometimes incoherent or unresponsive) or judgement (e.g., acts grossly inappropriately)

Recommendations / Plan:

Data not used

Physician's signature: _____ Date: __/__/____

Appendix C: Demographics Form

Annotations refer to row numbers in REDCap data dictionary

Demographic Form

Subject ID _____ Date ___/___/___

Age ___

Highest Education Achieved (c___) :

1	Less than seventh grade
2	Seventh grade - ninth grade
3	Partial High School
4	High School Diploma or GED
5	Some college (at least one year)
6	Technical School or Associates Degree
7	College Diploma (Bachelors Degree)
8	Graduate or Professional Degree

Race (c___)

1	American Indian or Alaska Native
2	Asian
3	Hispanic or Latino
4	Black or African American
5	White, Non-Hispanic
6	Native Hawaiian or Pacific Islander

Marital Status (c___):

1	Never Married, (Never lived as Married)
2	Married
3	Living as Married
4	Separated/No longer living as married
5	Divorced
6	Widowed

Current Employment status___

1	Full-time
2	Part-time for pay
3	Homemaker
10	Student
11	Volunteer
4	Incarcerated
5	Disabled
6	Leave of Absence
7	Unemployed
8	Retired
9	Other ___

Occupation (c___):

1	Executive manager
2	Professional
3	Business Tech/ Manager
4	Arts or Entertainment
5	Administrative Personnel
6	Technical Personnel
7	Clerical
8	Skilled Manual

Annotations refer to row numbers in REDCap data dictionary

Household Income (c[ ]):

1	less than $10,000
2	$10,000 - $19,999
3	$20,000 - $29,999
4	$30,000 - $39,999
5	$40,000 - $49,999
6	$50,000 - $74,999
7	$75,000 - $99,999
8	$100,000 - $149,999
9	$150,000 - $199,999
10	$200,000 or more

Appendix D: Greene Climacteric Scale

Annotations refer to row numbers in REDCap data dictionary

ID _____ Intake/today's Date ___/___

The Greene Climateric Scale.

Reproduced with kind permission from Dr Greene.

The Greene Scale provides a brief measure of menopause symptoms.
It can be used to assess changes in different symptoms, before and after menopause treatment.

SEVERITY OF PROBLEM IS SCORED AS FOLLOWS:

SCORE
0.....None
1.....Mild
2.....Moderate
3.....Severe

Heart beating quickly and strongly		1	2	3	Feeling dizzy or faint		1	2	3
Feeling tense or nervous		1	2	3	Pressure or tightness in head or body		1	2	3
Difficulty in sleeping		1	2	3	Parts of body feeling numb or tingling		1	2	3
Excitable		1	2	3	Headaches		1	2	3
Attacks of panic		1	2	3	Muscle or joint pains		1	2	3
Difficulty in concentrating		1	2	3	Loss of feeling in hands or feet		1	2	3
Feeling tired or lacking in energy		1	2	3	Breathing difficulties		1	2	3
Loss of interest in most things		1	2	3	Hot flushes		1	2	3
Feeling unhappy or depressed		1	2	3	Sweating at night		1	2	3
Crying spells		1	2	3	Loss of interest in sex		1	2	3
Irritability		1	2	3	SUM				

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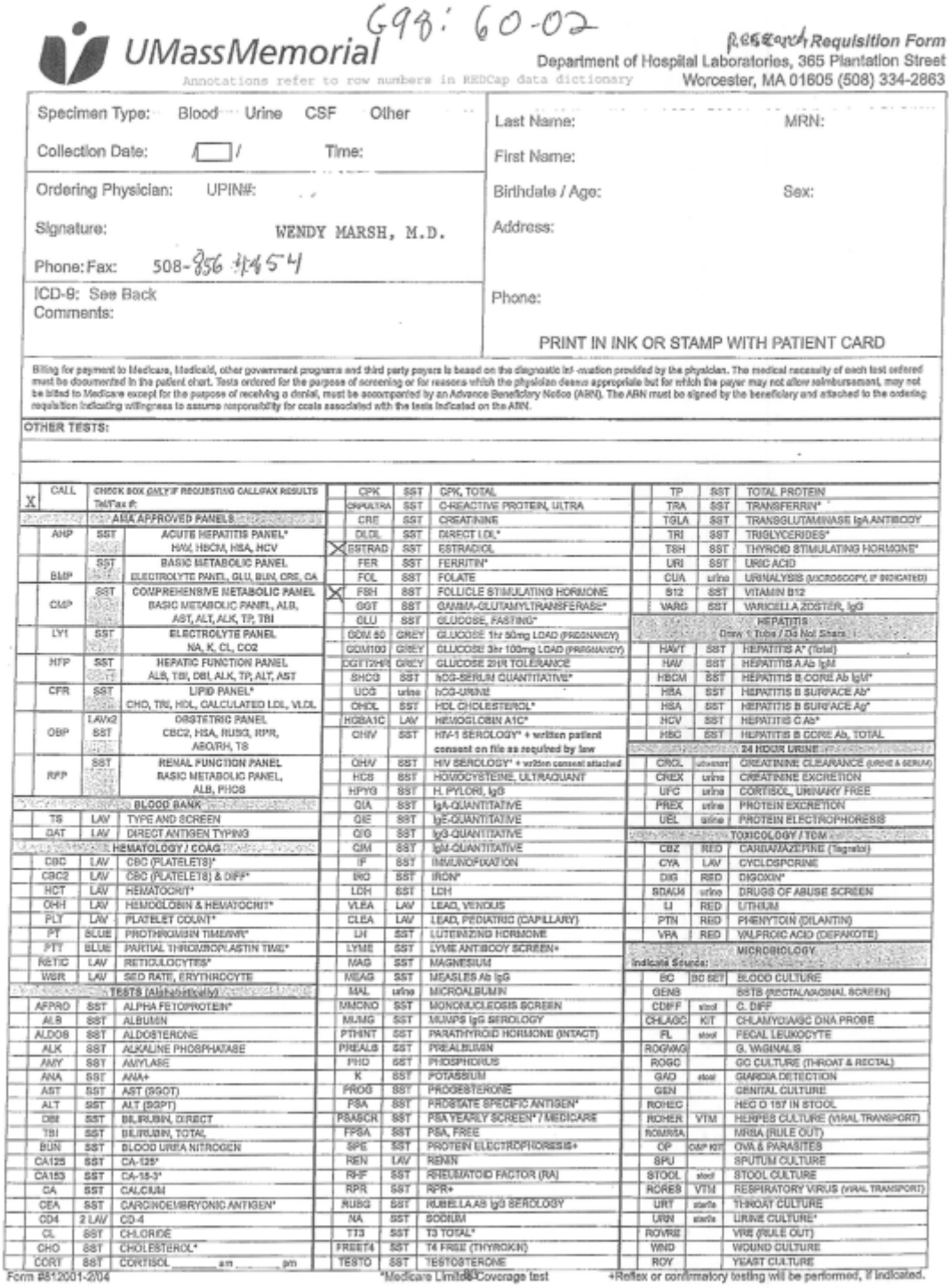
Appendix E: FSH and Estradiol Blood Panel



UMassMemorial

G98: 60-02

Research Requisition Form

Department of Hospital Laboratories, 365 Plantation Street
Worcester, MA 01605 (508) 334-2863

Annotations refer to row numbers in REDCap data dictionary

Specimen Type: Blood Urine CSF Other

Collection Date: / / Time:

Ordering Physician: UPIN#:

Signature: WENDY MARSH, M.D.

Phone: Fax: 508-856-1454

ICD-9: See Back
Comments:

Last Name: MRN:

First Name:

Birthdate / Age: Sex:

Address:

Phone:

PRINT IN INK OR STAMP WITH PATIENT CARD

Billing for payment to Medicare, Medicaid, other government programs and third party payers is based on the diagnostic information provided by the physician. The medical necessity of each test ordered must be documented in the patient chart. Tests ordered for the purpose of screening or for reasons which the physician deems appropriate but for which the payer may not allow reimbursement, may not be billed to Medicare except for the purpose of receiving a denial, must be accompanied by an Advance Beneficiary Notice (ABN). The ABN must be signed by the beneficiary and attached to the ordering requisition indicating willingness to assume responsibility for costs associated with the tests indicated on the ABN.

OTHER TESTS:

X	CALL	CHECK BOX ONLY IF REQUESTING CALL/FAX RESULTS	Tel/Fax #:
		AMA APPROVED PANELS	
	AHP	SST	ACUTE HEPATITIS PANEL* HAV, HBCM, HBA, HCV
	BMP	SST	BASIC METABOLIC PANEL ELECTROLYTE PANEL, GLU, BUN, CRE, CA
	CMP	SST	COMPREHENSIVE METABOLIC PANEL BASIC METABOLIC PANEL, ALB, AST, ALT, ALK, TP, TBI
	LYT	SST	ELECTROLYTE PANEL NA, K, CL, CO2
	HFP	SST	HEPATIC FUNCTION PANEL ALB, TBI, DBI, ALK, TP, ALT, AST
	CFR	SST	LIPID PANEL* CHO, TRI, HDL, CALCULATED LDL, VLDL
	OBP	LAV/2 SST	OBSTETRIC PANEL CBC2, HBA, RUBG, RPR, ABO/RH, TS
	RFP	SST	RENAL FUNCTION PANEL BASIC METABOLIC PANEL, ALB, PHOS
		BLOOD BANK	
	TS	LAV	TYPE AND SCREEN
	DAT	LAV	DIRECT ANTIGEN TYPING
		HEMATOLOGY / COAG	
	CBC	LAV	CBC (PLATELETS)*
	CBC2	LAV	CBC (PLATELETS) & DIFF*
	HCT	LAV	HEMATOCRIT*
	OHH	LAV	HEMOGLOBIN & HEMATOCRIT*
	PLT	LAV	PLATELET COUNT*
	PT	BLUE	PROTHROMBIN TIME/INR*
	PTT	BLUE	PARTIAL THROMBOPLASTIN TIME*
	RETIC	LAV	RETICULOCYTES*
	WBR	LAV	SED RATE, ERYTHROCYTE
		TESTS (Alphabetically)	
	AFPRO	SST	ALPHA FETOPROTEIN*
	ALB	SST	ALBUMIN
	ALDOB	SST	ALDOSTERONE
	ALK	SST	ALKALINE PHOSPHATASE
	AMY	SST	AMYLASE
	ANA	SST	ANA+
	AST	SST	AST (SGOT)
	ALT	SST	ALT (SGPT)
	DBI	SST	BILIRUBIN, DIRECT
	TBI	SST	BILIRUBIN, TOTAL
	BUN	SST	BLOOD UREA NITROGEN
	CA125	SST	CA-125*
	CA153	SST	CA-15-3*
	CA	SST	CALCIUM
	CEA	SST	CARCINOEMBRYONIC ANTIGEN*
	CD4	2 LAV	CD-4
	CL	SST	CHLORIDE
	CHO	SST	CHOLESTEROL*
	CORT	SST	CORTISOL ____ am ____ pm
	CPK	SST	CPK, TOTAL
	CRPULTRA	SST	C-REACTIVE PROTEIN, ULTRA
	CRE	SST	CREATININE
	DLDL	SST	DIRECT LDL*
X	ESTRAD	SST	ESTRADIOL
	FER	SST	FERRITIN*
	FOL	SST	FOLATE
X	FSH	SST	FOLLICLE STIMULATING HORMONE
	GGT	SST	GAMMA-GLUTAMYLTRANSFERASE*
	GLU	SST	GLUCOSE, FASTING*
	GDM 50	GREY	GLUCOSE 1hr 50mg LOAD (PREGNANCY)
	GDM100	GREY	GLUCOSE 3hr 100mg LOAD (PREGNANCY)
	DGTT2HR	GREY	GLUCOSE 2HR TOLERANCE
	SHCG	SST	hCG-SERUM QUANTITATIVE*
	UCG	urine	hCG-URINE
	OHDL	SST	HDL CHOLESTEROL*
	HGBA1C	LAV	HEMOGLOBIN A1C*
	OHIV	SST	HIV-1 SEROLOGY* + written patient consent on file as required by law
	OHV	SST	HIV SEROLOGY* + written consent attached
	HCS	SST	HOMOCYSTEINE, ULTRAQUANT
	HPYG	SST	H. PYLORI, IgG
	GIA	SST	IgA-QUANTITATIVE
	GIE	SST	IgE-QUANTITATIVE
	GIG	SST	IgG-QUANTITATIVE
	GIM	SST	IgM-QUANTITATIVE
	IF	SST	IMMUNOFIXATION
	IRO	SST	IRON*
	LDH	SST	LDH
	VLEA	LAV	LEAD, VENOUS
	CLEA	LAV	LEAD, PEDIATRIC (CAPILLARY)
	LH	SST	LUTEINIZING HORMONE
	LYME	SST	LYME ANTIBODY SCREEN+
	MAG	SST	MAGNESIUM
	MEAG	SST	MEASLES Ab IgG
	MAL	urine	MICROALBUMIN
	MMONO	SST	MONONUCLEOSIS SCREEN
	MUMG	SST	MUMPS IgG SEROLOGY
	PTHINT	SST	PARATHYROID HORMONE (INTACT)
	PREALB	SST	PREALBUMIN
	PHO	SST	PHOSPHORUS
	K	SST	POTASSIUM
	PROG	SST	PROGESTERONE
	PSA	SST	PROSTATE SPECIFIC ANTIGEN*
	PSASCR	SST	PSA YEARLY SCREEN* / MEDICARE
	FPSA	SST	PSA, FREE
	SPE	SST	PROTEIN ELECTROPHORESIS+
	REN	LAV	RENIN
	RHF	SST	RHEUMATOID FACTOR (RA)
	RPR	SST	RPR+
	RUBG	SST	RUBELLA AB IgG SEROLOGY
	NA	SST	SODIUM
	TT3	SST	T3 TOTAL*
	FREET4	SST	T4 FREE (THYROXIN)
	TESTO	SST	TESTOSTERONE
	TP	SST	TOTAL PROTEIN
	TRA	SST	TRANSFERRIN*
	TGLA	SST	TRANSGLUTAMINASE IgA ANTIBODY
	TRI	SST	TRIGLYCERIDES*
	TSH	SST	THYROID STIMULATING HORMONE*
	URI	SST	URIC ACID
	CUA	urine	URINALYSIS (MICROSCOPY, IF INDICATED)
	B12	SST	VITAMIN B12
	VARG	SST	VARICELLA ZOSTER, IgG
		HEPATITIS Draw 1 Tube / Do Not Share	
	HAVT	SST	HEPATITIS A* (Total)
	HAV	SST	HEPATITIS A Ab IgM
	HBCM	SST	HEPATITIS B CORE Ab IgM*
	HBA	SST	HEPATITIS B SURFACE Ab*
	HSA	SST	HEPATITIS B SURFACE Ag*
	HCV	SST	HEPATITIS C Ab*
	HBC	SST	HEPATITIS B CORE Ab, TOTAL
		24 HOUR URINE	
	CRCL	urine/SST	CREATININE CLEARANCE (URINE & SERUM)
	CREX	urine	CREATININE EXCRETION
	UFC	urine	CORTISOL, URINARY FREE
	PREX	urine	PROTEIN EXCRETION
	UEL	urine	PROTEIN ELECTROPHORESIS
		TOXICOLOGY / TDM	
	CBZ	RED	CARBAMAZEPINE (Tegretol)
	CYA	LAV	CYCLOSPORINE
	DIG	RED	DIGOXIN*
	SDAUM	urine	DRUGS OF ABUSE SCREEN
	LI	RED	LITHIUM
	PTN	RED	PHENYTOIN (DILANTIN)
	VPA	RED	VALPROIC ACID (DEPAKOTE)
		MICROBIOLOGY Indicate Source:	
	BC	BD SET	BLOOD CULTURE
	GENB		SSTB (RECTAL/VAGINAL SCREEN)
	CDFF	stool	C. DIFF
	CHLAGC	KIT	CHLAMYDIAGC DNA PROBE
	FL	stool	FECAL LEUKOCYTE
	ROGWG		G. VAGINALIS
	ROGC		GC CULTURE (THROAT & RECTAL)
	GAD	stool	GIARDIA DETECTION
	GEN		GENITAL CULTURE
	ROHEC		HEC O 157 IN STOOL
	ROHER	VTM	HERPES CULTURE (VIRAL TRANSPORT)
	ROMRSA		MRSA (RULE OUT)
	OP	O&P KIT	OVA & PARASITES
	SPU		SPUTUM CULTURE
	STOOL	stool	STOOL CULTURE
	RORES	VTM	RESPIRATORY VIRUS (VIRAL TRANSPORT)
	URT	sterile	THROAT CULTURE
	URN	sterile	URINE CULTURE*
	ROVRE		VRE (RULE OUT)
	WND		WOUND CULTURE
	ROY		YEAST CULTURE

Form #812001-2/04 *Medicare Limited Coverage test +Reflex or confirmatory testing will be performed, if indicated.

Appendix F: Menstrual History Form

Annotations refer to row numbers in REDCap data dictionary

ID _____ intake/today's Date ___/___/____

MENSTRUAL HISTORY

Would you describe yourself as currently

____ premenopausal with no change in your periods
____ perimenopausal/menopause transition (changes in periods but have menstruated in last 12mo)
____ post menopausal (over 12months since last period)
Was your menopause
___ spontaneous / natural
___ surgical (removal of both ovaries = oophorectomy)
When? ___/___(mo/yr)
___ due to chemo- or radiation therapy
When complete? ___/___
____ Other ___

Do you have your uterus? ___
If no, when was the surgery to remove it (hysterectomy)? ___/___

At what age did you get your period? ___
In your 20s and 30s were periods regular (over 22days and less than 35days)? ___
Have you ever been diagnosed with polycystic ovarian syndrome or PCOS? ___
Have you taken birth control pills? ___
Did birth control pills make you feel (more) depressed? ___ ___
Did birth control pills make you feel manic or hypomanic? ___ ___

Have you been pregnant ___
If yes, how many times? ___
How many live births? ___
When was your last period? ___/___/___(if >12mo to *)

When was your second to last period? If known ___/___/___
Compared to a year ago, has the number of days between the start of one menstrual period and the start of your next menstrual period become less predictable? ___

If less than 1year since your last period, how many times in the last twelve months have you had your period? ___
Have you gone 60 days without having a period, or have you missed a period? ___
If yes, when did you first miss a period or go sixty days without one? answr ~ ___/___ two months and year (ex mar and apr 08)

How many days does your period last? ___
Are your periods painful? ___ if yes: ___ moderate severe
Do you have spotting between periods? ___
Is there a change to how often you have periods compared to a year ago? ___

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Appendix G: Medical History Form

Annotations refer to row numbers in REDCap data dictionary 3

ID _____ intake/today's Date ___/___/____

MEDICAL HISTORY

	Have you had:	if yes, at what age?
	Y N Hypothyroid/ *under*-active thyroid	
	Y N Hyperthyroid/ *over*-active thyroid	
	Y N Prolactinoma / pituitary tumor producing too much prolactin	
	Y N Congenital adrenal hyperplasia	
	Y N Ovarian cancer	
	Y N Chemo or radiation therapy that stopped your periods	
	Y N Anorexia nervosa where your periods stopped	
	Y N Surgical removal of the left ovary	
	Y N Surgical removal of the right ovary	
	Y N Removal of your uterus (hysterectomy)	
	Y N Diabetes mellitus	
	Y N Periods stopped because of weight loss, excessive exercise or stress	
	Y N Endometriosis	
	Y N Fibroids	
	Y N High blood pressure	
	Y N Stroke	
	Y N High cholesterol	
	Y N Heart Attack	
	Y N Blood Clots	
	Y N Anemia	
	Y N Migraines	
	Y N Hepatitis	
	Y N Cancer (which type ____)	
	Y N Seizures	
	Y N Problem with Broken bones	

PERSONAL HABITS

Do you consider your health: ☐ cellent good fair poor

Exercise:

How often do you exercise? ☐

6-7days/week 3-5days/week 1-2 days/ week 1-2days/month never

What do you do? ☐

For how long? ☐

Diet:

How many servings of fruits and vegetables do you eat a day? ☐

How many dairy (milk, cheese, yogurt) servings do you eat a day? ☐

How many servings of soy foods (tofu, edamame/soy beans, soy milk) do you eat a week? ☐

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Appendix H: Young Mania Rating Scale

Entered: __/__/____ Initials: _____ Subject ID: _____

Verified: __/__/____ Initials: _____ Date __/__/____

Young Mania Rating Scale (YMRS)

For each item below begin inquiry using script. Ask additional questions if necessary to assign ratings. Rate each item using your judgment rather than patient self report, *check one box to the left of the number* that best rates each question.

The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be the exception rather than the rule. **Use whole point rating only.**

I will now be asking you questions to rate symptoms you may have had during the past week.

1. Elevated Mood

This past (week) how has your mood been?

Did you feel optimistic about the future? (Was there reason to feel that way?)

Did you feel especially self confident (especially good about yourself)?

Were there any times you felt too good or even a little high? [If yes] Were the good days really too good, or just better than the bad days?

Were there times when you laughed about things you ordinarily wouldn't find funny? Or did you laugh or joke about things that other people don't find funny (or thought in poor taste)?

- ☐ **0** Absent
- ☐ **1** Mildly or possibly increased on questioning
- ☐ **2** Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
- ☐ **3** Elevated, inappropriate to content; humorous
- ☐ **4** Euphoric; inappropriate laughter; singing

2. Increased Motor Activity/Energy

This week:

What's your energy been like?
Were there times you felt particularly full of energy?

[If yes] Was it hard to calm down?

Did you feel physically restless? (have trouble sitting still?)

Have you been more active than usually? Did you Get a lot more done than usual?

- ☐ **0** Absent
- ☐ **1** Subjectively increased
- ☐ **2** Animated; gestures increased
- ☐ **3** Excessive energy; hyperactive at times; restless (can be calmed)
- ☐ **4** Motor excitement; continuous (cannot be calmed)

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3. Sexual Interest

Was sex more interesting to you than usual?

Did you do anything sexual that is unusual for you?

Were you talking or joking about sex more than you normally do?

- ☐ 0 Normal, not increased
- ☐ 1 Mildly or possibly increased
- ☐ 2 Definite subjective increase on questioning
- ☐ 3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
- ☐ 4 Overt sexual acts (towards patients, staff, or interviewer)

4. Sleep

How many hours of sleep are you getting?

Did you need less sleep than usual (and still feel rested?)

- ☐ 0 Reports no decrease in sleep
- ☐ 1 Sleeping less than normal amount by up to one hour
- ☐ 2 Sleeping less than normal by more than one hour
- ☐ 3 Reports decreased need for sleep
- ☐ 4 Denies need for sleep

5. Irritability

Were you annoyed about things that happened or how people treated you?

Did you notice these things bothered you more than they usually do?

Were you often irritable?

How did you show your anger?

- ☐ 0 Absent
- ☐ 1
- ☐ 2 Subjectively increased
- ☐ 3
- ☐ 4 Irritable at times during interview; recent episodes of anger or annoyance on ward
- ☐ 5
- ☐ 6 Frequently irritable during interview; short, curt throughout
- ☐ 7
- ☐ 8 Hostile, uncooperative; interview impossible

6. Speech (Rate and Amount)

Have you been more talkative than usual?

Did anyone complain that they couldn't get a word in?

Did you find it hard to stop talking once you got started?

Were there times you spoke so fast people had trouble understanding you?

- ☐ 0 No increase
- ☐ 1
- ☐ 2 Feels talkative
- ☐ 3
- ☐ 4 Increased rate or amount at times, verbose at times
- ☐ 5
- ☐ 6 Push; consistently increased rate and amount; difficult to interrupt
- ☐ 7
- ☐ 8 Pressured; uninterruptible continuous speech

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Subject ID: _____

7. Language – Thought Disorder

Have you had more ideas than usual or any particularly good ideas?

Was your thinking especially keen or clear this week?

Did you often get distracted?

Has you mind seemed to be going very fast?

Did you sometimes have so many ideas that you lost track of what you were saying?

Were you getting lost in the details?

- ☐ **0** Absent
- ☐ **1** Circumstantial; mild distractibility; quick thoughts
- ☐ **2** Distractible; loses goal of thoughts; changes topic frequently; racing thoughts
- ☐ **3** Flight of ideas; tangentiality; difficult to follow; rhyming; echolalia
- ☐ **4** Incoherent; communication impossible

8. Content

Did you make any new plans or get new projects started?

Did you accomplish anything special? Were you more capable than usual?

Did you find you could understand things more deeply than usual?

Did you have any religious insight?

Did you find you were more aware of coincidences?

Did you find special significance in things that happened or the way things were arranged around you?

Did you notice things that other people missed, or have the sense that people were talking about you, or even trying to hurt you?

Did you have any thoughts that didn't make sense to other people?

Did you have any hallucinations?

- ☐ **0** Normal
- ☐ **1**
- ☐ **2** Questionable plans, new interests
- ☐ **3**
- ☐ **4** Special project(s); hyperreligious
- ☐ **5**
- ☐ **6** Grandiose or paranoid ideas; ideas of reference
- ☐ **7**
- ☐ **8** Delusions; hallucinations

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9. Disruptive – Aggressive Behavior

How have you gotten along with other people? (Have you been cooperative?)

Were there times when you were loud, demanding, or sarcastic?

Have you had any confrontations with people? (What happened?)

Did you find yourself shouting, throwing things, or doing anything destructive?

- ☐ 0 Absent, cooperative
- ☐ 1
- ☐ 2 Sarcastic, loud at times, guarded
- ☐ 3
- ☐ 4 Demanding, threats on ward
- ☐ 5
- ☐ 6 Threatens interviewer; shouting; interview difficult
- ☐ 7
- ☐ 8 Assaultive; destructive; interview impossible

10. Appearance

How well did you keep up your appearance and grooming?

Was it hard to do?

Were there occasions when people thought you were over-dressed or under-dressed?

Did you choose to wear different colors than usual this week?

What about wearing more jewelry or makeup than usual?

Were there times when you neglected your grooming?

- ☐ 0 Appropriate dress and grooming
- ☐ 1 Minimally unkempt
- ☐ 2 Poorly groomed; moderately disheveled; overdressed
- ☐ 3 Disheveled; partly clothed; garish make-up
- ☐ 4 Completely unkempt; decorated; bizarre garb

11. Insight

As you look back on the week, were there things you did that stand out as unusual behavior for you? [If yes] Was that because your mood was high?

How do you understand: _____

(example patient's possible behavioral symptoms)?

- ☐ 0 Present; admits illness; agrees with need for treatment
- ☐ 1 Possibly ill
- ☐ 2 Admits behavior change, but denies illness
- ☐ 3 Admits possible change in behavior, but denies illness
- ☐ 4 Denies any behavior change

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Appendix I: Montgomery-Aspberg Depression Rating Scale (MADRS)

Entered: __/__/____ Initials: _____ Patient ID _____-_____-_____
Date ___/___/____

Verified: __/__/____ Initials: _____ For office use only. #Visit ____/4

Montgomery-Asberg Depression Rating Scale (MADRS)

STEP-BD Certification Code: _____

Overview: I'd like to ask you some questions about the past week. How have you been feeling since last (day of week)? Have you been working? Why not?

MADRS 2. Reported Sadness

Do you feel better when pleasant things happen (often, occasionally, never)?

Can a good joke brighten your mood?

Is there anything that can make you feel better even briefly?

- ☐ 0 Occasional sadness in keeping with the circumstances.
- ☐ 1
- ☐ 2 Sad or low but brightens up without difficulty.
- ☐ 3
- ☐ 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
- ☐ 5
- ☐ 6 Continuous or unvarying sadness.

MADRS 9. Pessimistic Thoughts

Are you pessimistic about the future?

How often do you feel this way?

- ☐ 0 No pessimistic thoughts.
- ☐ 1
- ☐ 2 Fluctuating ideas of failure, self-reproach or self-deprecation.
- ☐ 3
- ☐ 4 Persistent self-accusations, or definite but still rational ideas of guilt or sin, increasingly pessimistic about the future.
- ☐ 5
- ☐ 6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd or unshakable.

Gary Sachs, M.D. & Paul Desan, M.D., Ph.D., Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114

Patient ID ___-___-____

MADRS 10. Suicidal Thoughts

How often do you think about suicide?

- ☐ **0** Enjoys life or takes it as it comes.
- ☐ **1**
- ☐ **2** Weary of life. Only fleeting suicidal thoughts.
- ☐ **3**
- ☐ **4** Probably better off dead. Suicidal thoughts are common and suicide is considered as a possible solution, but without specific plans or intention.
- ☐ **5**
- ☐ **6** Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

MADRS 4. Reduced Sleep

Do you sleep at least two hours less than usual?

Do you sleep at least three hours per night?

- ☐ **0** Sleeps as usual.
- ☐ **1**
- ☐ **2** Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ **3**
- ☐ **4** Sleep reduced or broken by at least 2 hours.
- ☐ **5**
- ☐ **6** Less than 2 or 3 hours of sleep.

MADRS 8. Inability to Feel

Have you lost your feelings for friends and acquaintances?

- ☐ **0** Normal interest in the surroundings and in other people.
- ☐ **1**
- ☐ **2** Reduced ability to enjoy usual interests.
- ☐ **3**
- ☐ **4** Loss of interest in surroundings. Loss of feelings for friends and acquaintances.
- ☐ **5**
- ☐ **6** The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

Patient ID ____-____-_____

MADRS 7. Lassitude

Do you have difficulty starting things?

Do you have difficulty starting even simple activities?

- ☐ **0** Hardly any difficulty getting started. No sluggishness.
- ☐ **1**
- ☐ **2** Difficulties starting activities.
- ☐ **3**
- ☐ **4** Difficulties in starting simple routines which are carried out with effort.
- ☐ **5**
- ☐ **6** Complete lassitude. Unable to do anything without help.

MADRS 6. Concentration Difficulties

Do you have difficulty concentrating or collecting your thoughts?

Do you have difficulty concentrating when holding a conversation or reading?

- ☐ **0** No difficulties in concentrating.
- ☐ **1**
- ☐ **2** Occasional difficulties in collecting one's thoughts.
- ☐ **3**
- ☐ **4** Difficulties in concentrating and sustaining thought which reduces the ability to read or hold a conversation.
- ☐ **5**
- ☐ **6** Unable to read or converse without great difficulty.

MADRS 3. Inner Tension

Do you feel tension or edginess only some of the time?

Have you been able to handle this tension?

- ☐ **0** Placid. Only feeling inner tension.
- ☐ **1**
- ☐ **2** Occasional feelings of edginess and ill-defined discomfort.
- ☐ **3**
- ☐ **4** Continuous feelings of inner tension or intermittent panic, which patient can master only with some difficulty.
- ☐ **5**
- ☐ **6** Unrelenting dread or anguish. Overwhelming panic.

Patient ID ___-___-____

MADRS 5. Reduced Appetite

How has your appetite been this past week?
What about compare to your usual appetite?

Have you forced yourself to eat?

Have other people had to urge you to eat?

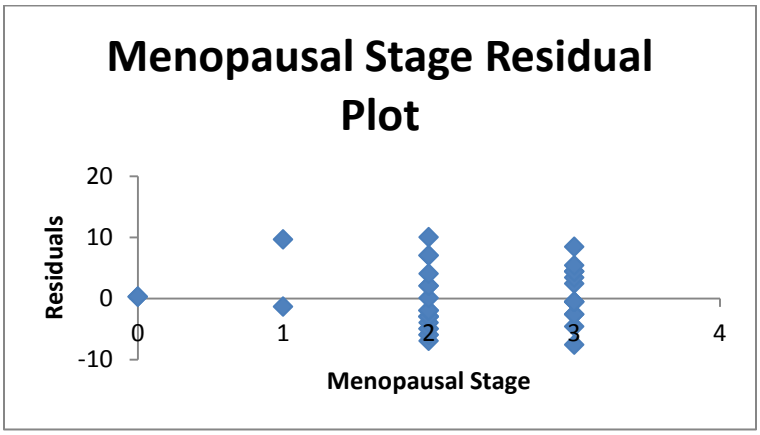
- ☐ **0** Normal or increased appetite.
- ☐ **1**
- ☐ **2** Slightly reduced appetite.
- ☐ **3**
- ☐ **4** No appetite.
- ☐ **5**
- ☐ **6** Needs persuasion to eat at all.

MADRS 1. Apparent Sadness
Rating Based on Observation During Interview

- ☐ **0** No sadness.
- ☐ **1**
- ☐ **2** Looks dispirited.
- ☐ **3**
- ☐ **4** Appears sad and unhappy most of the time.
- ☐ **5**
- ☐ **6** Looks miserable at the time. Extremely despondent.

Appendix J: Correlations

Correlation between Menopausal Stage and Age



Regression Statistics	
Multiple R	0.434473
R Square	0.188767
Adjusted R Square	0.164907
Standard Error	2.852284
Observations	36

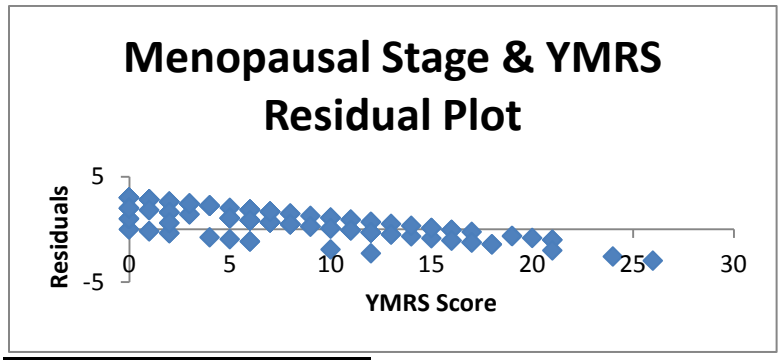
	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	64.36435	64.36435	7.911517	0.008102
Residual	34	276.6079	8.135526		
Total	35	340.9722			

	Coefficients	*Standard Error*	*t Stat*	***P-value***	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	40.72444	2.382142	17.09572	**1.45E-18**	35.88843	45.56045	35.88843	45.56045
Menopausal Stage	3.619701	1.027169	3.523957	0.001206	1.534436	5.704965	1.534436	5.704965

Observation	*Predicted Age of onset (1st affective episode/syndrome)*	*Residuals*	*Standard Residuals*
1	16.51717	-6.51717	-2.31825
2	15.75307	-5.75307	-2.04645
3	14.98898	-4.98898	-1.77465
4	16.51717	-1.51717	-0.53968
5	15.37102	-0.37102	-0.13198
6	15.75307	-0.75307	-0.26788
7	17.28126	-2.28126	-0.81148

8	14.22488	0.775118	0.275721
9	18.04535	-3.04535	-1.08328
10	16.89921	-1.89921	-0.67558
11	16.89921	-1.89921	-0.67558
12	13.07874	1.92126	0.68342
13	16.51717	-1.51717	-0.53968
14	17.28126	-2.28126	-0.81148
15	17.28126	-2.28126	-0.81148
16	17.28126	-2.28126	-0.81148
17	14.60693	0.393071	0.139821
18	15.75307	-0.75307	-0.26788
19	16.89921	-1.89921	-0.67558
20	14.22488	0.775118	0.275721
21	15.37102	-0.37102	-0.13198
22	16.51717	-1.51717	-0.53968
23	16.51717	3.482835	1.238895
24	18.04535	1.954646	0.695296
25	18.4274	1.572598	0.559396
26	17.28126	2.71874	0.967096
27	18.04535	1.954646	0.695296
28	15.37102	4.628976	1.646595
29	18.04535	1.954646	0.695296
30	16.13512	3.864882	1.374795
31	14.60693	5.393071	1.918394
32	18.04535	1.954646	0.695296
33	17.28126	2.71874	0.967096
34	18.04535	1.954646	0.695296
35	17.66331	2.336693	0.831196
36	18.4274	1.572598	0.559396

Correlation of Menopausal Stage to YMRS Sum



Regression Statistics	
Multiple R	0.756118
R Square	0.571715
Adjusted R Square	0.564362
Standard Error	1.577287

Observations	137

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	451.6546	451.6546	181.5453	9.39E-27
Residual	136	338.3454	2.487834		
Total	137	790			

	Coefficients	*Standard Error*	*t Stat*	***P-value***	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	0	#N/A	#N/A	**#N/A**	#N/A	#N/A	#N/A	#N/A
YMRS Score	0.191298	0.014198	13.47388	**8.15E-27**	0.163221	0.219375	0.163221	0.219375

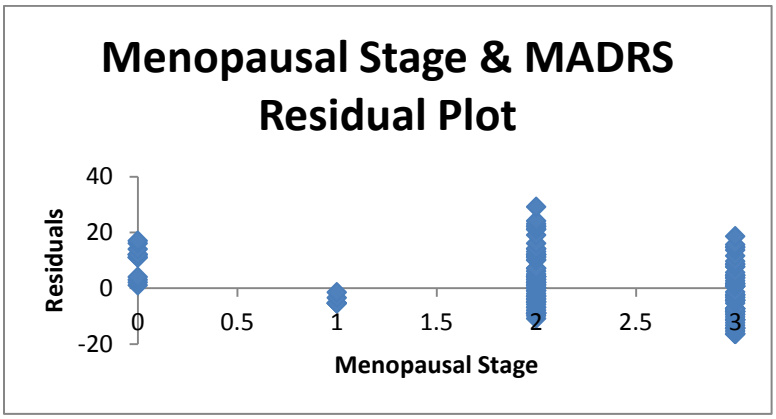
Observation	*Predicted Menopausal Stage*	*Residuals*	*Standard Residuals*
1	0	3	1.90898
2	0	3	1.90898
3	0	3	1.90898
4	0	3	1.90898
5	0	0	0
6	0	0	0
7	0	1	0.636327
8	0	1	0.636327
9	0	1	0.636327
10	0	3	1.90898
11	0	2	1.272653
12	0	2	1.272653
13	0	2	1.272653
14	0	2	1.272653
15	0.191298	2.808702	1.787252
16	0.191298	2.808702	1.787252
17	0.191298	2.808702	1.787252
18	0.191298	1.808702	1.150925
19	0.191298	2.808702	1.787252
20	0.191298	-0.1913	-0.12173
21	0.191298	-0.1913	-0.12173
22	0.191298	2.808702	1.787252
23	0.191298	2.808702	1.787252
24	0.191298	2.808702	1.787252
25	0.191298	1.808702	1.150925
26	0.382596	2.617404	1.665524
27	0.382596	2.617404	1.665524
28	0.382596	2.617404	1.665524

29	0.382596	2.617404	1.665524
30	0.382596	1.617404	1.029197
31	0.382596	-0.3826	-0.24346
32	0.382596	-0.3826	-0.24346
33	0.382596	1.617404	1.029197
34	0.382596	1.617404	1.029197
35	0.382596	1.617404	1.029197
36	0.382596	0.617404	0.392871
37	0.382596	0.617404	0.392871
38	0.573894	2.426106	1.543796
39	0.573894	2.426106	1.543796
40	0.573894	2.426106	1.543796
41	0.573894	1.426106	0.907469
42	0.573894	1.426106	0.907469
43	0.573894	2.426106	1.543796
44	0.573894	2.426106	1.543796
45	0.765192	2.234808	1.422068
46	0.765192	2.234808	1.422068
47	0.765192	2.234808	1.422068
48	0.765192	2.234808	1.422068
49	0.765192	-0.76519	-0.48691
50	0.765192	2.234808	1.422068
51	0.95649	1.04351	0.664013
52	0.95649	2.04351	1.30034
53	0.95649	-0.95649	-0.60864
54	0.95649	1.04351	0.664013
55	0.95649	1.04351	0.664013
56	0.95649	1.04351	0.664013
57	1.147788	0.852212	0.542285
58	1.147788	1.852212	1.178612
59	1.147788	1.852212	1.178612
60	1.147788	0.852212	0.542285
61	1.147788	1.852212	1.178612
62	1.147788	0.852212	0.542285
63	1.147788	0.852212	0.542285
64	1.147788	1.852212	1.178612
65	1.147788	1.852212	1.178612
66	1.147788	-1.14779	-0.73037
67	1.147788	-1.14779	-0.73037
68	1.147788	1.852212	1.178612
69	1.147788	0.852212	0.542285
70	1.147788	1.852212	1.178612
71	1.147788	0.852212	0.542285
72	1.339086	1.660914	1.056884
73	1.339086	1.660914	1.056884
74	1.339086	0.660914	0.420557
75	1.339086	1.660914	1.056884

76	1.339086	0.660914	0.420557
77	1.339086	1.660914	1.056884
78	1.339086	0.660914	0.420557
79	1.339086	0.660914	0.420557
80	1.339086	0.660914	0.420557
81	1.339086	0.660914	0.420557
82	1.339086	1.660914	1.056884
83	1.530384	1.469616	0.935156
84	1.530384	0.469616	0.298829
85	1.530384	0.469616	0.298829
86	1.530384	0.469616	0.298829
87	1.530384	1.469616	0.935156
88	1.530384	0.469616	0.298829
89	1.530384	0.469616	0.298829
90	1.721682	0.278318	0.177101
91	1.721682	1.278318	0.813428
92	1.721682	0.278318	0.177101
93	1.721682	0.278318	0.177101
94	1.91298	1.08702	0.6917
95	1.91298	1.08702	0.6917
96	1.91298	0.08702	0.055373
97	1.91298	1.08702	0.6917
98	1.91298	-1.91298	-1.21728
99	1.91298	0.08702	0.055373
100	1.91298	0.08702	0.055373
101	2.104278	0.895722	0.569972
102	2.104278	0.895722	0.569972
103	2.104278	-0.10428	-0.06635
104	2.104278	-0.10428	-0.06635
105	2.104278	-0.10428	-0.06635
106	2.295576	0.704424	0.448244
107	2.295576	-0.29558	-0.18808
108	2.295576	-0.29558	-0.18808
109	2.295576	0.704424	0.448244
110	2.295576	-2.29558	-1.46074
111	2.295576	-0.29558	-0.18808
112	2.295576	-0.29558	-0.18808
113	2.486874	0.513126	0.326516
114	2.486874	-0.48687	-0.30981
115	2.486874	-0.48687	-0.30981
116	2.678172	-0.67817	-0.43154
117	2.678172	0.321828	0.204788
118	2.86947	0.13053	0.08306
119	2.86947	-0.86947	-0.55327
120	2.86947	0.13053	0.08306
121	3.060768	-0.06077	-0.03867
122	3.060768	-0.06077	-0.03867

123	3.060768	-1.06077	-0.675
124	3.060768	-1.06077	-0.675
125	3.252066	-0.25207	-0.1604
126	3.252066	-1.25207	-0.79672
127	3.252066	-1.25207	-0.79672
128	3.443364	-1.44336	-0.91845
129	3.443364	-1.44336	-0.91845
130	3.634662	-0.63466	-0.40385
131	3.634662	-0.63466	-0.40385
132	3.82596	-0.82596	-0.52558
133	4.017258	-1.01726	-0.64731
134	4.017258	-1.01726	-0.64731
135	4.017258	-2.01726	-1.28364
136	4.591152	-2.59115	-1.64882
137	4.973748	-2.97375	-1.89228

Correlation of Menopausal Stage to MADRS Sum – Residual Output



Regression Statistics	
Multiple R	0.792878
R Square	0.628656
Adjusted R Square	0.621303
Standard Error	10.14359
Observations	137

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	23689.63	23689.63	230.237	5.73E-31
Residual	136	13993.37	102.8924		
Total	137	37683			

Coefficients	*Standard Error*	*t Stat*	***P-value***	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
0	#N/A	#N/A	**#N/A**	#N/A	#N/A	#N/A	#N/A

5.462216625	0.359982509	15.17356112	**4.76589E-31**	4.750329336	6.174103914	4.750329336	6.174103914

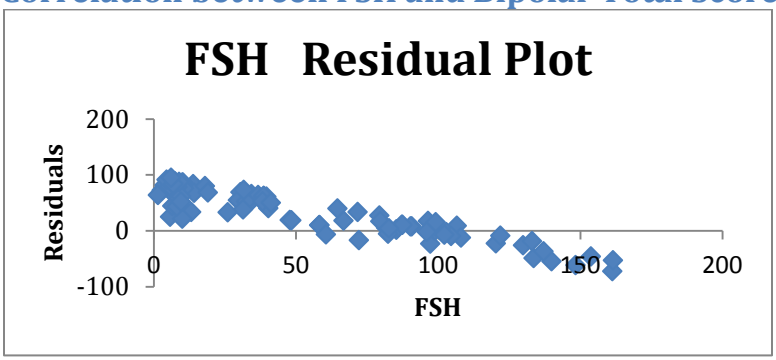
Observation	*Predicted MADRS Score*	*Residuals*	*Standard Residuals*
1	16.38665	-16.3866	-1.6214
2	16.38665	-16.3866	-1.6214
3	5.462217	-5.46222	-0.54047
4	5.462217	-5.46222	-0.54047
5	5.462217	-5.46222	-0.54047
6	16.38665	-16.3866	-1.6214
7	10.92443	-10.9244	-1.08093
8	0	1	0.098946
9	16.38665	-15.3866	-1.52245
10	10.92443	-9.92443	-0.98199
11	16.38665	-14.3866	-1.4235
12	16.38665	-14.3866	-1.4235
13	16.38665	-14.3866	-1.4235
14	10.92443	-8.92443	-0.88304
15	16.38665	-14.3866	-1.4235
16	10.92443	-8.92443	-0.88304
17	0	2	0.197892
18	5.462217	-3.46222	-0.34257
19	10.92443	-8.92443	-0.88304
20	10.92443	-8.92443	-0.88304
21	10.92443	-8.92443	-0.88304
22	16.38665	-13.3866	-1.32456
23	10.92443	-7.92443	-0.78409
24	0	3	0.296839
25	16.38665	-12.3866	-1.22561
26	10.92443	-6.92443	-0.68515
27	10.92443	-6.92443	-0.68515
28	0	4	0.395785
29	5.462217	-1.46222	-0.14468
30	10.92443	-5.92443	-0.5862
31	16.38665	-11.3866	-1.12667
32	16.38665	-11.3866	-1.12667
33	16.38665	-11.3866	-1.12667
34	16.38665	-11.3866	-1.12667
35	16.38665	-10.3866	-1.02772
36	10.92443	-4.92443	-0.48725
37	10.92443	-4.92443	-0.48725
38	10.92443	-4.92443	-0.48725
39	16.38665	-9.38665	-0.92877
40	10.92443	-3.92443	-0.38831
41	16.38665	-9.38665	-0.92877

42	10.92443	-3.92443	-0.38831
43	16.38665	-8.38665	-0.82983
44	16.38665	-8.38665	-0.82983
45	16.38665	-8.38665	-0.82983
46	16.38665	-8.38665	-0.82983
47	10.92443	-2.92443	-0.28936
48	10.92443	-2.92443	-0.28936
49	10.92443	-2.92443	-0.28936
50	16.38665	-7.38665	-0.73088
51	16.38665	-7.38665	-0.73088
52	16.38665	-7.38665	-0.73088
53	16.38665	-7.38665	-0.73088
54	10.92443	-1.92443	-0.19042
55	10.92443	-0.92443	-0.09147
56	10.92443	-0.92443	-0.09147
57	16.38665	-5.38665	-0.53299
58	10.92443	0.075567	0.007477
59	0	11	1.088408
60	0	11	1.088408
61	10.92443	0.075567	0.007477
62	10.92443	0.075567	0.007477
63	10.92443	0.075567	0.007477
64	16.38665	-4.38665	-0.43404
65	16.38665	-4.38665	-0.43404
66	16.38665	-4.38665	-0.43404
67	10.92443	1.075567	0.106423
68	16.38665	-4.38665	-0.43404
69	0	12	1.187355
70	0	12	1.187355
71	10.92443	1.075567	0.106423
72	16.38665	-3.38665	-0.3351
73	16.38665	-3.38665	-0.3351
74	10.92443	2.075567	0.205369
75	10.92443	2.075567	0.205369
76	10.92443	2.075567	0.205369
77	16.38665	-2.38665	-0.23615
78	16.38665	-2.38665	-0.23615
79	16.38665	-2.38665	-0.23615
80	10.92443	3.075567	0.304316
81	10.92443	3.075567	0.304316
82	0	14	1.385247
83	16.38665	-1.38665	-0.1372
84	10.92443	4.075567	0.403262
85	10.92443	4.075567	0.403262
86	10.92443	4.075567	0.403262
87	10.92443	4.075567	0.403262
88	0	16	1.583139

89	10.92443	5.075567	0.502208
90	16.38665	0.61335	0.060689
91	16.38665	0.61335	0.060689
92	16.38665	0.61335	0.060689
93	0	17	1.682086
94	10.92443	6.075567	0.601154
95	16.38665	0.61335	0.060689
96	16.38665	1.61335	0.159635
97	10.92443	7.075567	0.700101
98	16.38665	1.61335	0.159635
99	10.92443	7.075567	0.700101
100	16.38665	1.61335	0.159635
101	16.38665	2.61335	0.258581
102	16.38665	3.61335	0.357527
103	16.38665	3.61335	0.357527
104	16.38665	4.61335	0.456474
105	10.92443	10.07557	0.996939
106	16.38665	4.61335	0.456474
107	16.38665	4.61335	0.456474
108	10.92443	10.07557	0.996939
109	16.38665	5.61335	0.55542
110	10.92443	11.07557	1.095885
111	10.92443	11.07557	1.095885
112	10.92443	12.07557	1.194832
113	10.92443	12.07557	1.194832
114	10.92443	12.07557	1.194832
115	10.92443	13.07557	1.293778
116	16.38665	7.61335	0.753312
117	16.38665	7.61335	0.753312
118	16.38665	8.61335	0.852258
119	10.92443	14.07557	1.392724
120	10.92443	14.07557	1.392724
121	16.38665	8.61335	0.852258
122	16.38665	9.61335	0.951205
123	10.92443	16.07557	1.590616
124	16.38665	11.61335	1.149097
125	10.92443	19.07557	1.887455
126	16.38665	13.61335	1.346989
127	16.38665	14.61335	1.445936
128	16.38665	14.61335	1.445936
129	10.92443	21.07557	2.085348
130	10.92443	21.07557	2.085348
131	16.38665	15.61335	1.544882
132	10.92443	22.07557	2.184294
133	10.92443	22.07557	2.184294
134	10.92443	23.07557	2.28324
135	10.92443	24.07557	2.382186

136	16.38665	18.61335	1.841721
137	10.92443	29.07557	2.876917

Correlation between FSH and Bipolar Total Score



Regression Statistics	
Multiple R	0.736215
R Square	0.542013
Adjusted R Square	0.531374
Standard Error	54.59239
Observations	95

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	331549	331549.0472	111.2458	1.44E-17
Residual	94	280151	2980.329285		
Total	95	611700			

	Coefficients	*Standard Error*	*t Stat*	***P-value***	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	0	#N/A	#N/A	**#N/A**	#N/A	#N/A	#N/A	#N/A
FSH	0.852761	0.080851	10.54731137	**1.27E-17**	0.692229	1.013293	0.692229	1.013293

Observation	*Predicted BP Total score*	*Residuals*	*Standard Residuals*
1	34.36627	40.63373	0.748259789
2	72.8258	2.1742	0.040037346
3	72.8258	2.1742	0.040037346
4	69.75586	5.24414	0.096569514
5	82.97366	-22.9737	-0.423054079
6	40.84726	19.15274	0.352692898
7	49.6307	10.3693	0.190948083
8	49.80125	10.19875	0.187807407
9	41.35891	18.64109	0.34327087
10	56.96444	18.03556	0.332120216

11	126.5498	-61.5498	-1.133423069
12	119.3013	-54.3013	-0.999944338
13	113.9289	-48.9289	-0.901013043
14	137.5504	-72.5504	-1.335996672
15	77.43071	7.56929	0.139386561
16	77.00433	7.995671	0.147238251
17	84.42335	0.576649	0.010618844
18	11.85338	83.14662	1.531123959
19	4.60491	90.39509	1.664602689
20	8.78344	86.21656	1.587656127
21	8.612887	86.38711	1.590796803
22	5.372395	89.6276	1.650469647
23	9.636201	35.3638	0.651215409
24	11.25645	33.74355	0.621378987
25	90.90434	9.095664	0.167494356
26	82.29145	17.70855	0.326098495
27	84.5939	15.4061	0.283699369
28	67.70923	27.29077	0.502552562
29	61.22825	33.77175	0.62189825
30	55.08837	39.91163	0.734962587
31	29.59081	55.40919	1.020346185
32	87.74912	-2.74912	-0.050624339
33	67.96506	17.03494	0.31369408
34	74.44605	10.55395	0.194348391
35	74.6166	10.3834	0.191207715
36	29.33498	65.66502	1.209204666
37	31.29633	63.70367	1.173086892
38	33.85462	61.14538	1.125976752
39	26.09449	68.90551	1.268877511
40	2.473007	72.52699	1.335566205
41	92.18348	-12.1835	-0.224355649
42	89.19881	-9.19881	-0.169393819
43	87.15219	-7.15219	-0.131705706
44	25.24173	54.75827	1.008359689
45	27.80001	52.19999	0.961249549
46	12.10921	67.89079	1.250191743
47	4.946015	25.05399	0.461362798
48	8.612887	21.38711	0.393838264
49	5.457671	69.54233	1.280604374
50	5.884052	69.11595	1.272752684
51	6.054604	68.9454	1.269612008
52	5.201843	69.79816	1.285315388
53	6.736813	68.26319	1.257049304
54	9.039268	75.96073	1.398797645
55	5.287119	79.71288	1.467892518
56	5.884052	79.11595	1.456900152
57	6.736813	78.26319	1.441196772
58	6.395708	78.60429	1.447478124
59	3.325768	81.67423	1.504010292

60	4.860738	80.13926	1.475744208
61	7.077917	77.92208	1.43491542
62	7.077917	77.92208	1.43491542
63	7.24847	52.75153	0.971406075
64	131.1547	-46.1547	-0.849926386
65	110.7737	-25.7737	-0.474615601
66	137.8062	-52.8062	-0.972412751
67	6.395708	88.60429	1.631625591
68	5.628223	44.37178	0.817095029
69	6.907365	43.09263	0.793539959
70	7.589574	57.41043	1.057198456
71	26.7767	38.2233	0.703872404
72	8.186507	61.81349	1.138279824
73	32.91658	62.08342	1.14325047
74	15.3497	79.6503	1.4667401
75	7.589574	87.41043	1.609640859
76	3.837425	91.16257	1.678735732
77	33.08713	61.91287	1.140109794
78	70.26752	-5.26752	-0.096999982
79	1.32178	63.67822	1.1726183
80	22.17179	32.82821	0.604523189
81	32.66075	52.33925	0.963814016
82	35.13376	49.86624	0.918274214
83	16.28774	68.71226	1.265318914
84	116.9135	-36.9135	-0.679753672
85	81.95034	-1.95034	-0.035915088
86	102.6724	-22.6724	-0.417507224
87	61.56935	-16.5694	-0.30512044
88	51.67732	-6.67732	-0.12296123
89	113.5025	-18.5025	-0.34071895
90	104.0369	-9.03686	-0.166411431
91	5.884052	84.11595	1.548973885
92	5.201843	94.79816	1.745684057
93	27.03253	72.96747	1.343677526
94	8.186507	51.81349	0.954132356
95	70.60862	4.391379	0.080866134