The parent IRB protocol is PRO0010110 (titled: Brian control of voiding in women) which includes fMRI and UDS in neurogenic bladder individuals. Then there were several amendments (new uploaded version 6, please see pages 2-3) for a subset of individuals that underwent onabotulinumtoxinA injection as part of their neurogenic bladder management (routine clinical management) and had a repeat fMRI/UDS. Thus, this new analysis is entitled **"**Central Nervous System Changes Following BotulinumtoxinA Injection in the Bladder**"** as is this clincialtrials.gov registry.

# CLINICAL PROTOCOL: BRAIN CONTROL OF VOIDING IN WOMEN

Version 6 dated 7/20/2015

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**Background**

The lower urinary tract has two functions: storage and voluntary elimination of urine. Normal voluntary voiding in neurologically intact patients is triggered by the release of tonic inhibition from suprapontine centers, allowing the pontine micturition center to trigger the voiding reflex. Mediated through spinal centers, this reflex initiates the relaxation of the pelvic floor musculature and the urethral sphincter. The bladder then contracts and empties.

In the last two decades, the evolution of neuroimaging modalities in the field of neurourology has provided a new frontier of research. In 1998, Blok et al. studied normal female micturition in 10 subjects with CNS PET imaging. Increased blood flow was demonstrated in the right dorsal pontine tegmentum and the right inferior frontal gyrus. (1) Other investigators have incorporated the use of fMRI to examine brain region activation during bladder filling (2), and voluntary pelvic floor muscle contractions (3, 4). Furthermore, others have published fMRI evidence of cortical neuroplastic changes after pelvic floor muscle training and biofeedback therapy for stress urinary incontinence (5). Krhut et al. used fMRI to preliminarily examine brain activity during bladder emptying, localizing areas in the parahippocampal gyrus, anterior cingulate gyrus, inferior temporal gyrus and inferior frontal gyrus during micturition (6). Our project to evaluate the normal healthy female subjects with concurrent urodynamics and fMRI has yielded valuable information regarding anatomical locations neuronal control in micturition. We completed the first part of current project (IRB Pro00005508) in July of 2013 and have reported our results at multiple scientific meetings. The manuscript is in progress currently. This would be second report in the literature on micturition with simultaneous UDS and fMRI and higher number of subjects. In summary all of our ten subjects were able to void while supine. Each patient was able to void at least three complete voiding cycles within the fMRI scanning phase, with time to initiate voiding and cystometric capacity as factors in total number of voiding cycles.

Group analysis of the patients (since all were able to void) yielded consistent areas of activation during the initiation of voiding (asterisks, Figure 1). These included regions for motor control (cerebellum, thalamus, caudate, lentiform nucleus, red nucleus, supplementary motor area, postcentral gyrus), emotion (anterior and posterior cingulate gyrus and insula), executive function (left superior frontal gyrus), as well as the parahippocampal gyrus, precuneus, cuneus, occipital lobe (visual stimulus), and a focal region in the midbrain.

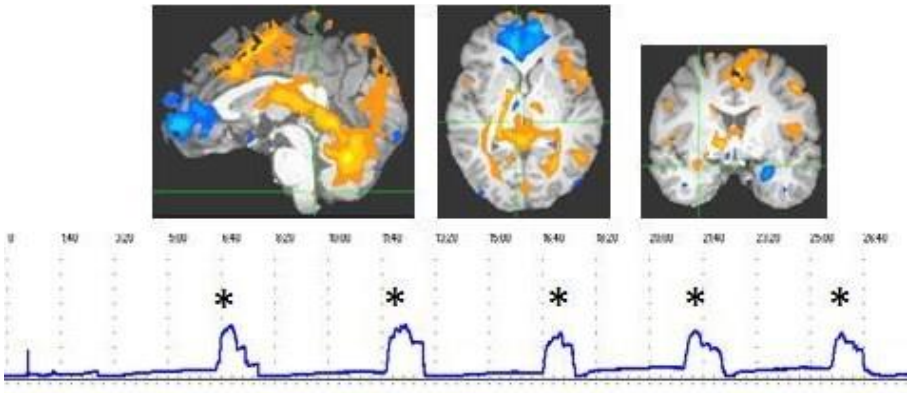


Figure 1.

Preliminary correlation-interaction network analysis of 5 representative subjects were performed with the voxel-intensity time courses for a subject depicted (Figure 2A). This yielded spring-embedded network layouts that for each subject exhibited a small-world structure of focal clusters with short-range interactions connected by long-range edges (Figure 2B). A 3-D representation of cluster connectivity (Figure 2C) showed various clusters in the cerebellum connected to clusters in parietal, frontal and temporal lobes and to clusters in the limbic system mainly via the medial posterior brain regions (e.g. posterior cingulate).

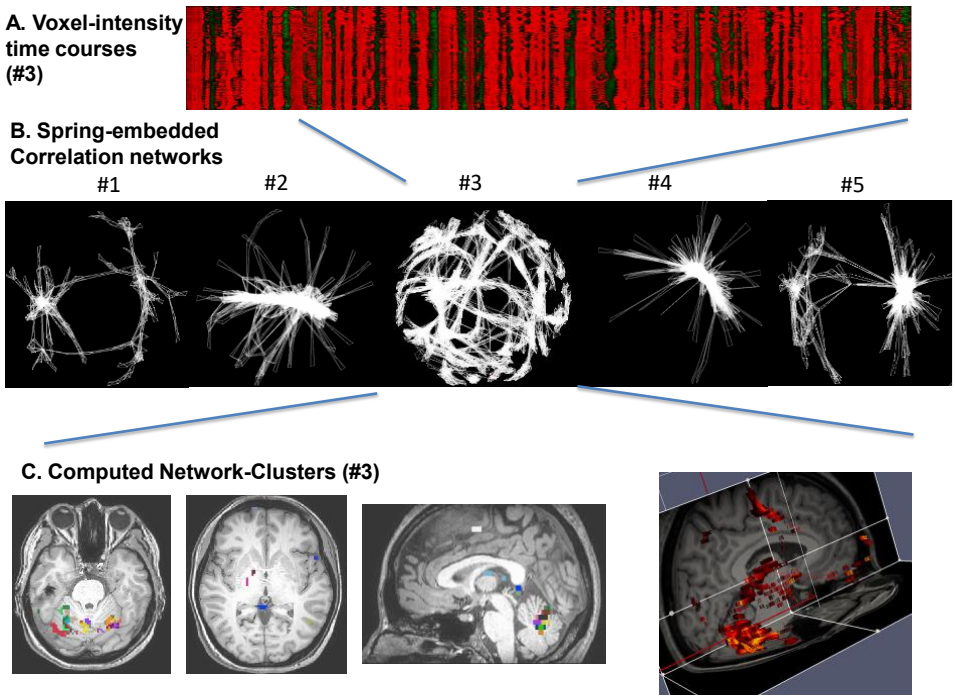


Figure 2

Now that we have a better understanding of normal healthy micturition we plan to study brain activity in patients with neurogenic bladder (such as patients with multiple sclerosis) and voiding dysfunction. There is no similar report in the literature. In patients with multiple sclerosis, urinary symptoms are common sequel: urgency, urge incontinence, frequency, urinary retention (7, 8). These patients often undergo urodynamic testing and abnormalities are seen in almost all symptomatic cases. Common findings include neurogenic detrusor over-activity, detrusor sphincter dyssynergia and detrusor hypocontractility.

Clinical correlation between women with these chronic urologic problems and new discoveries at the level of CNS activity will give a better understanding of this disorder, leading to the development of more effective diagnostic and treatment modalities.

In addition the literature lacks any data regarding sensory effects of bladder medications used for neurogenic detrusor overactivity(NDO) or overactive bladder(OAB). A common and FDA approved treatment for these patients include use of Botulinum toxin A injected in the bladder. This is a routine

management for urinary symptom control in these patients. Despite having knowledge and data that Botulinum toxin A decreases the bladder contractility we have no human data how it affects the sensory efferent fibers to the brain and decreasing urgency and frequency. Our platform is a perfect model to study the effects of botulinum toxin A on sensory efferent fibers of the bladder and correlate that to the centers in the brain that respond to urgency and frequency. Thus we propose that patients who based on their clinical needs and exams are candidates for intravesical botulinum toxin A and have been a candidate in our study to have another fMRI with concurrent UDS about 8 weeks following their intravesical botulinum toxin A injection.

**Purpose and Objectives**

To perform functional MRI neuroimaging and data analysis on female subjects diagnosed with voiding dysfunction or neurogenic bladder during the act of micturition. Our goal with this pilot study is to determine whether BOLD signal changes on fMRI during voiding are substantial for data analysis. If so, data analysis will yield specific regions of the brain that are activated and/or deactivated during voiding. The second objective of this study is to determine whether concurrent urodynamics data gathered in the scanner can be correlated to fMRI data in order to elucidate simultaneous bladder function measurements with BOLD signal measurements.

Second objective of this study is to evaluate the sensory effects of intravesical injection of botulinum toxin A used for neurogenic detrusor activity.

**Risk Category**

(45 CFR 46.406) Category 3: Research involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition.

**Research Design**

This is a pilot observational study in which brain activity will be observed via fMRI during simultaneous urodynamics testing. This study will examine the blood-oxygen-level-dependent (BOLD) signals during fMRI of the brain of subjects diagnosed with neurogenic bladder or dysfunctional voiding. BOLD signals are an indirect measure of neural activity that can be identified on fMRI. There are no known risks to a subject's fetus. There is no known teratogenic risk associated with urodynamics or fMRI. Patients will be screened with a urine pregnancy test at enrollment. Patients with a positive pregnancy test will be excluded from the study. As a pilot study, 50 subjects will be recruited to investigate the feasibility of the study. There is no control group because this study involving human subjects with both urodynamic and fMRI testing is complex, time-consuming, and expensive. In addition we can already use our data for the past two years on normal healthy females as our control. Furthermore, no investigator has published previously regarding simultaneous urodynamics and fMRI in patients with neurogenic bladder and dysfunctional voiding. Subjects diagnosed with neurogenic bladder (e.g. MS) and dysfunctional voiding would have already undergone baseline urodynamic studies as part of their routine care and will proceed to concurrent fMRI and urodynamics testing.

**Inclusion Criteria for subjects with voiding dysfunction and neurogenic bladder:**

- Women ages 18 years or older
- Primary language is English
- Presence of lower urinary tract symptoms (urinary frequency, urgency, urge incontinence or difficulty emptying)
- Presence or history of neurologic illness or injury (spinal cord injury, spina bifida, Parkinson's, major spine surgery, multiple sclerosis, or other neurological disorders) and dysfunctional voiding.
- Performed baseline clinic urodynamics testing as part of routine urologic evaluation of voiding dysfunction within 24 months of scanning (if not done, will be performed as part of the study).

**Exclusion Criteria for subjects with voiding dysfunction:**

- Male
- Patients without lower urinary tract symptoms (urinary frequency, urgency, urge incontinence or difficulty emptying, etc)
- Positive urine pregnancy test at enrollment (There are no known risks to a subject's fetus. There is no known teratogenic risk associated with urodynamics or fMRI)
- Presence of active and symptomatic urinary tract infection
- Exclusive use of indwelling urethral or suprapubic catheter or other methods of urinary diversion
- Severity of neurologic illness: severe immobility, severe dyscoordination, cognitive impairment

**STUDY PROCEDURE**

Subjects will be recruited via bulletin board advertisement, web site and word of mouth.

All procedures are investigational. None of the following are part of standard clinical care.

There are no known risks to a subject's fetus. There is no known teratogenic risk associated with urodynamics or fMRI. Patients will be screened with a urine pregnancy test at enrollment and before fMRI scanning. Patients with a positive pregnancy test will be excluded from the study.

**Procedure Visits:**

**1) Informed Consent and Enrollment**

Patients will be screened with a history and physical, urinalysis and urine culture, and urine pregnancy test. Subjects will also be asked to fill out the following questionnaires: Urogenital Distress Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7), and the Hamilton Anxiety Rating Scale (HAM-A). Patients will also be asked to fill out an fMRI safety screening questionnaire and demographics form.

After informed consent and enrollment, subjects will be scheduled for one or two visits:

**2) Clinic Urodynamics Visit**

Subjects diagnosed with neurogenic bladder or dysfunctional voiding have already undergone clinic urodynamics based on routine clinical care and will proceed to step 3. If there is a patient that would need a urodynamic study they will be instructed to arrive at The Methodist Hospital Department of Urology. This visit will consist of multichannel urodynamics in the clinic setting, so subjects can acclimate to the

catheters and the testing situation. This visit will be 100% research. However, the test performed is one used by the urology clinic in daily clinical care. While the data collected will be for study use only, there is nothing experimental about the urodynamics procedure. Prior to catheter insertion, a dip stick urinalysis is performed to exclude bacteriuria.

**3) fMRI Scanning Visit**

The second visit will be the fMRI scanning session at the Methodist Hospital. Subjects will be instructed to arrive 30 minutes prior to scanning. Subjects will have a dip stick urinalysis performed and a urine pregnancy test to confirm that they are not pregnant prior to the insertion of the catheters and the MRI. Urodynamics catheters will be inserted. After task instruction, subjects will be placed in the scanner. Task instruction consists of giving subjects directions to hold their urine, relax their pelvic muscles, and void will be conveyed to them via instructions printed on a screen they will see while in the scanner. Patients will also be instructed to squeeze a bulb in their hand if they experience claustrophobia or discomfort, and want to be removed from the scanner. Scanning will then begin.

After standard localizer and structural scans, the functional sequence and urodynamics will start. The bladder will be filled with sterile saline, as per urodynamics procedure. Subjects will be instructed (visually using a projection screen and mirror, standard procedure for the HNL) to hold their bladder, and then view a fixation cross for 30 seconds. They will be asked to indicate, via finger button, when their bladder is full. Subjects will then be instructed (again using a projection screen and mirror) to relax their pelvic floor muscles, and then to urinate. The experiment will conclude with the subject pressing the finger button to indicate they are finished urinating. At that point an instruction to relax will appear and then be replaced by a fixation cross that the subject will view it for 30 seconds and the experiment will be complete. The urodynamic and scanning cycle may be repeated up to 5 cycles.

**4) repeat fMRI scanning visit:**

This visit would only apply to the patients that clinically were a candidate for intravesical injection of botulinum toxin A and went on receiving it as a part of their routine care. If they agree, we would recruit them for a repeat fMRI scan just as detailed above about 8weeks (+/- 4 weeks) following their botox injection. Urogenital Distress Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7), and the Hamilton Anxiety Rating Scale (HAM-A) will be re-obtained at this visit.

**Sample Size**

How many subjects (or specimens, or charts) will be used in this study?
Local: 50 Worldwide: 50

Please indicate why you chose the sample size proposed:
This is a pilot study. These experiments are novel, as there is currently no similar study in the literature. There is no way to predict numbers required in order to find statistically variations between arms of each experiment. Pilot data from this study will aid in powering future studies on the same topic. This study involving human subjects with both urodynamic and fMRI testing is complex, time-consuming, and expensive. Furthermore, no investigator has published previously regarding simultaneous urodynamics

and fMRI. This protocol is for a feasibility study. Once the feasibility of our model is established, we can work on studying control groups.

**Data Analysis**

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

The data analysis will be similar to other data analytic strategies carried out in the laboratory. It requires fairly complex analysis techniques and is thus difficult to summarize without going into lengthy details. Briefly, our data analysis will be as follows: We have made extensive use of a general linear model in analyzing and designing our fMRI experiments. To compare data from different subjects, the scan data from each subject must be transformed into a standard anatomical framework. We follow the approach of Frackowiak et al (1997), which analyzes the brain into small local volumes or "voxels". The fMRI signal from each voxell is then subjected to the following transformation steps:

Analysis Step 1: Spatio-temporal normalization to a standard brain map, and smoothing to improve the signal-to-noise ratio.

Analysis Step 2: Statistical analysis to determine the significance of the activity measured at each voxel. We use an established statistical framework [K.J. Friston, et al., Human Brain Mapping 2, 189-210 (1995); K.J. Friston, A.P. Holmes, K.J. Worsely, Neuroimage 10, 1-5 (1999)] in terms of a general linear model, which incorporates and formalizes the independent explanatory variables in our experiment. Given the variance of each parameter, we can construct a t-statistic as a measure of the significance of differences in the parameters estimated from the different experiments, at different voxels, or in different subjects. In practice, we construct a statistic out of a particular linear combination of the parameters that describes a quantity of interest. To express this mathematically, we define a contrast vector that specifies a linear combination of parameters. Then the t-statistic is the quantity of interest divided by its standard error. When we calculate a t-statistic at each voxel in an imaged brain, measuring the significance of a difference between parameters from different subjects or different experimental conditions, the resulting set is called a statistical parametric map. We use such maps to determine areas of significant activation in the brain during presentation of stimuli or performance of the task.

A linear regression analysis will also be employed to look for covariance of behavioral variables with observed brain activity. For instance, the degree of preference for an image or the amount of prior exposure to the stimulus can be entered into the analysis as explanatory variables for the brain activation. In this case, the degree to which behavioral variables cause linear changes in brain activity can be illustrated by fitting the estimated response to the observed time series of dynamic blood flow in the brain. The regions identified in this type of analysis will be used to generate "regions of interest", smaller areas of voxels that can be analyzed without making assumptions regarding the underlying hemodynamics. In this analysis, the raw change in magnetic signal can be read out and compared across any variable of interest.

**Potential Risks/Discomforts**

**Risks with Pregnancy:**
There are no known risks to a fetus associated with urodynamics or fMRI. Regardless, pregnancy is an exclusion criterion. Every subject will be screened with a urine pregnancy test at enrollment. Subjects with a positive pregnancy test will be excluded from the study.

**Urodynamics Testing:**
Urodynamics studies involve invasive catheterization of the urethra and the rectum. The risks and discomforts of urodynamics testing include: discomfort in the bladder, urethra and rectum at the time of testing. The subject may also experience dysuria for 12 hours after testing. Another risk is that of urinary tract infection (UTI). All subjects undergoing urodynamic testing will be screened for UTI prior to testing. Patients will be given information regarding the symptoms and signs of UTI and asked to call the urology investigator's office if they have any of the symptoms after testing. If a UTI is present, it will be treated.

**fMRI:**
Movement or heating of metallic implants is a potential risk, and so subjects will be screened to exclude people with metallic implants. Some individuals experience claustrophobic reactions in the scanner. Subjects will be informed of this prior to the study, but because it is difficult to predict who will have such a reaction, this is not a specific exclusion criterion. Any subject experiencing claustrophobia will be removed from the scanner immediately. There is no invasive component to this study, such as IV catheters. Therefore, bruising or infection are not risks.. The Siemens 3 T scanner has been approved by the FDA. However, there may be additional risks associated with scanning at 3 T compared to the conventional clinical scanners in the 1.5-2.0 T range. These include: 1) Effect of the static field. There is no conclusive evidence for irreversible or hazardous bioeffects to acute, short term exposures of humans up to 2.0 T (Shellock and Kanal, 1996). Studies have indicated some side-effects at 4.0 T, namely unusual sensations including nausea, vertigo, and metallic taste (Schenk 1991). However, there is no evidence that this is either irreversible or harmful. If subjects experience unusual sensations, they will be withdrawn. 2) Effect of the gradient field. MRI operates by rapidly changing small additional fields, called gradients. This will induce small electrical currents in any conductor, and this could theoretically induce mild peripheral nerve stimulation. However, this is not substantially different at higher magnetic fields since the gradients are separate from the main magnet. There is no evidence that the effect of the gradients is any different at 3 T than at 1.5 T. However, if subjects experience peripheral nerve stimulation, e.g. tingling or twitching, they will be withdrawn. 3) Effect of the RF electromagnetic field. The higher magnetic field strength requires that higher RF frequency pulses are used to excite the protons in the subject's brain.

**QUESTIONNAIRES:**
Completing the questionnaires may cause you to have or to experience some level of emotional discomfort due to the personal nature of the questions. The study doctor and staff will maintain a professional and caring attitude while administering the questionnaires.

**REFERNCES**


1. Blok BF, Sturms LM and Holstege G: Brain activation during micturition in women. Brain. 121 ( Pt 11): 2033-42, 1998.
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7. De Seze M, Ruffion A, Denys P, Joseph PA, Perrouin-Verbe B: The neurogenic bladder in multiple sclerosis: review of the literature and proposal of management guidelines. Mult Scler. 13: 915-928, 2007.
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## APPENDICIES

Appendix A: UDI-6 Questionnaire
Appendix B: IIQ-7 Questionnaire
Appendix C: HAM-A rating scale
Appendix D: Schedule of Events
Appendix E: Patient Demographics Questionnaire

**Appendix A: UDI-6 Questionnaire**

**BRAIN CONTROL OF NORMAL VOIDING IN WOMEN** **PI: Rose Khavari, MD**

**SUBJECT INITIALS/ID#:** _____ **DATE:** _____

| *Urogenital Distress Inventory UDI-6* | Does not happen (0) | Present, but not at all bothersome (1) | Somewhat bothersome (2) | Moderately bothersome (3) | Quite a bit bothersome (4) |
|---|---|---|---|---|---|
| 1. Do you usually experience frequent urination? | | | | | |
| 2. Do you usually experience urine leakage associated with a feeling of urgency; that is, a strong sense of needing to go to the bathroom? | | | | | |
| 3. Do you usually experience urine leakage associated with coughing, sneezing, laughing? | | | | | |
| 4. Do you experience small amounts of leakage (that is, drops)?? | | | | | |
| 5. Do you experience difficulty emptying your bladder? | | | | | |
| 6. Do you experience pain or discomfort in the lower abdomen or genital region? | | | | | |
| *TOTAL* | | | | | |

**Appendix B: IIQ-7 Questionnaire**

**BRAIN CONTROL OF NORMAL VOIDING IN WOMEN** **PI: Rose Khavari, MD**

**SUBJECT INITIALS/ID#:** _____ **DATE:** _____

| *Incontinence Impact Questionnaire (IIQ-7)* | Not at all (0) | Slightly (1) | Moderately (2) | Greatly (3) |
|---|---|---|---|---|
| **Has urine leakage affected your:** | | | | |
| 1. Household chores? | | | | |
| 2. Physical recreation activities? | | | | |
| 3. Entertainment activities? | | | | |
| 4. Travel for distances greater than 30 minutes away from home? | | | | |
| 5. Social activities? | | | | |
| 6. Emotional health (nervousness, depression, etc)? | | | | |
| 7. Feeling frustrated? | | | | |
| ***TOTAL*** | | | | |

**Appendix C: HAM-A Rating Scale**

# Hamilton Anxiety Rating Scale (HAM-A)

***Reference:*** **Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55.**

*Rating* Clinician-rated

*Administration time* 10–15 minutes

*Main purpose* To assess the severity of symptoms of anxiety

*Population* Adults, adolescents and children

## Commentary

The HAM-A was one of the first rating scales developed to measure the severity of anxiety symptoms, and is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Although the HAM-A remains widely used as an outcome measure in clinical trials, it has been criticized for its sometimes poor ability to discriminate between anxiolytic and antidepressant effects, and somatic anxiety versus somatic side effects. The HAM-A does not provide any standardized probe questions. Despite this, the reported levels of inter-rater reliability for the scale appear to be acceptable.

## Scoring

Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe.

## Versions

The scale has been translated into: Cantonese for China, French and Spanish. An IVR version of the scale is available from Healthcare Technology Systems.

## Additional references

Maier W, Buller R, Philipp M, Heuser I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord 1988;14(1):61–8.

Borkovec T and Costello E. Efficacy of applied relaxation and cognitive behavioral therapy in the treatment of generalized anxiety disorder. J Clin Consult Psychol 1993; 61(4):611–19

## Address for correspondence

The HAM-A is in the public domain.

## Hamilton Anxiety Rating Scale (HAM-A)

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

**1 Anxious mood** [0] [1] [2] [3] [4]

Worries, anticipation of the worst, fearful anticipation, irritability.

**2 Tension** [0] [1] [2] [3] [4]

Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.

**3 Fears** [0] [1] [2] [3] [4]

Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.

**4 Insomnia** [0] [1] [2] [3] [4]

Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.

**5 Intellectual** [0] [1] [2] [3] [4]

Difficulty in concentration, poor memory.

**6 Depressed mood** [0] [1] [2] [3] [4]

Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.

**7 Somatic (muscular)** [0] [1] [2] [3] [4]

Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.

**8 Somatic (sensory)** [0] [1] [2] [3] [4]

Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.

**9 Cardiovascular symptoms** [0] [1] [2] [3] [4]

Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.

**10 Respiratory symptoms** [0] [1] [2] [3] [4]

Pressure or constriction in chest, choking feelings, sighing, dyspnea.

**11 Gastrointestinal symptoms** [0] [1] [2] [3] [4]

Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.

**12 Genitourinary symptoms** [0] [1] [2] [3] [4]

Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.

**13 Autonomic symptoms** [0] [1] [2] [3] [4]

Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.

**14 Behavior at interview** [0] [1] [2] [3] [4]

Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.

## Appendix D: Schedule of Events

| Activity** | Screening Phase | Study Phase | | Only if indicated 8 weeks after BOTOX inj. |
|---|---|---|---|---|
| | Screen and Enroll Visit 1 | Visit 2 | Visit 3 | Visit 4 |
| Patient History | X | | | |
| Physical Exam | X | | | |
| Medication Review | X | | | |
| Consent for Study | X | | | X |
| UA and UC+S | X | X[1] | X[1] | X |
| Urine Pregnancy Test | X | | X[2] | X |
| UDI-6 questionnaire* | X | | | X |
| IIQ-7 questionnaire† | X | | | X |
| HAM-A rating scale‡ | X | | | X |
| fMRI Screening Form | X | | | |
| Urodynamics Testing (part of routine care in this population) | | X[3] | X | X |
| fMRI Scanning | | | X | X |

**NOTE: All activities are RESEARCH Related.

1 – The urine analysis done at visit 2 and visit 3 are dipstick analysis only and no culture is performed

2 – The urine pregnancy test done at visit 3 is a kit that shows immediate results of positive or negative

3 -- Only for the patients who have not had a UDS in the preceding 24 months

UA: urine analysis. UC: Urine culture & Sensitivity. *UDI-6: Urogenital Distress Inventory questionnaire. † IIQ-7: Incontinence Impact questionnaire. ‡HAM-A : Hamilton Anxiety rating scale.

**Appendix E: Patient Demographic Form**

# Demographics Form

## Brain Control of Normal Voiding in Women

Dear Subject:

Please take a few minutes to complete this form. This information is completely confidential. The information is needed for the study, Brain Control of Normal Voiding in Women, in order to match your data with other subjects.

**Subject ID Number:** _____ **Date:** _____

**Age**: _____ **Date of Birth** ____/____/____ Occupation: _____

| List any **medical illnesses** you have had and the approximate year of treatment: | |
|---|---|
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |

| List all **surgical procedures** you have had and the approximate year of treatment: | |
|---|---|
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |

| List all **medications** you are taking (Include non-prescription drugs): | |
|---|---|
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |

| List all **medication allergies**: | | | |
|---|---|---|---|
| Medication | Type of Reaction | Medication | Type of Reaction |
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |

## OB/GYN History

| | |
|---|---|
| How many times have you been pregnant? _____ | Date of last menstrual period _____ |
| Number of vaginal deliveries _____ C-sections _____ | How many days does period last _____ |
| Weight of largest child at birth _____ | Do you have severe menstrual cramping? Yes ___ No ____ |
| Any deliveries with an episiotomy or tear into the rectum? | Date of last PAP smear _____ |
| Yes ___ No ___ | Was last PAP normal? Yes ___ No ____ |

**Subject ID Number:** _____

## Social History

| | |
|---|---|
| Do you smoke now or in the past? No _____ Yes _____ | Do you drink alcoholic beverages? No _____ Yes _____ |
| Packs per day? _____ Years smoked? _____ | Explain: _____ |
| If you have quit, please indicate year _____ | How much coffee, tea and/or soda do you drink in one day? |
| | Explain: _____ |
| | _____ |

## Review of Systems

***Do you now or have you had problems with any of the following?***

| | Y | N | Please explain any Yes answers. |
|---|---|---|---|
| **General:** Recent weight changes, fever, weakness, fatigue, headaches | | | |
| **Integumentary:** Rashes, eruptions, dryness, jaundice, changes in skin, hair or nails, discoloration of skin | | | |
| **Eyes:** Blurred vision, double vision, pain | | | |
| **Ears, Nose, Mouth & Throat:** Soreness and/or redness of gums, hoarseness, difficulty in swallowing, head colds, discharges, obstruction, postnasal drip, sinus pain, earaches | | | |
| **Musculoskeletal:** Joint pain, neck pain, back pain | | | |
| **Respiratory:** Chest pain, wheezing, cough, difficulty breathing, asthma, bronchitis, pneumonia, tuberculosis, shortness of breath, emphysema | | | |
| **Neurologic:** Fainting, blackouts, seizures, paralysis, tingling, tremors, memory loss, dizzy spells, stroke | | | |

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| **CARDIOVASCULAR:** Chest pain, rheumatic fever, rapid heart beat, high blood pressure, swelling, dizziness, faintness, varicose veins, heart valve problems | | | |
| **ENDOCRINE:** Thyroid trouble, fatigue, heat or cold intolerance, excessive sweating, thirst, hunger | | | |
| **GASTROINTESTINAL:** Appetite, nausea, vomiting, diarrhea, constipation, indigestion, food intolerance, hemorrhoids, jaundice, heartburn, diabetes, hepatitis | | | |
| **GENITOURINARY – MALE:** Hernias, testicular or penile problems, impotency, (erectile dysfunction), infertility, frequency or painful urination, blood in urine, urinary retention | | | |
| **GENITOURINARY – FEMALE:** Vaginal pain, pain with sexual intercourse, low sexual desire, frequency or painful urination, blood in urine, urinary retention | | | |
| **HEMATOLOGIC/LYMPHATIC:** Anemia, easy bruising or bleeding, past transfusions, swollen glands, blood clotting problems | | | |
| **PSYCHOLOGIC:** Nervousness, insomnia, headache, depression | | | |
| **ALLERGIES:** Plant, food, environmental | | | |