Mindfulness + tDCS to reduce urgency incontinence in women

NCT# 04652869

Study Protocol 9/13/2022

Scientific background

Urinary incontinence, particularly urinary urge incontinence (UUI), is a highly prevalent and costly ($83 billion/year) disorder among older women. Greater than 50% of UUI-related urgency and leakage may be due to situational incontinence provoked by confrontation with specific contextual triggers or cues (e.g., seeing one's front/garage door, doing dishes). We recently found that women with UUI experience increased urgency and actual leakage when exposed to personal "urge" versus "safe" photographic cues taken from their daily lives. Decades of cue-based research across other disorders has shown that such conditioned responses are rarely attenuated with pharmacologic methods and require cognitive and behavioral retraining. Therefore, new methods are needed to specifically target conditioned factors contributing to UUI, in order to effectively combat this persistent contributor to urgency and leakage and augment the efficacy of current UUI treatments.

We propose to test two new intervention methods to attenuate UUI symptomatology and reactivity to urgency cues among women with situational UUI. These methods include brief mindfulness (MI) and transcranial direct current stimulation (tDCS). Employing our well-tested method to personalize cues, women with situational UUI will create photographic personal "urge" cues, which capture their strongest urgency, and "safe" cues, in which they do not experience urge. Then, we will examine the feasibility, acceptability, participant compliance, and efficacy of using MI and/or tDCS to reduce cue-provoked urgency and/or leakage to these salient personal cues, reduce reaction time on a urinary Stroop test, and decrease multiple UUI outcomes.

Study Objectives:

Aim 1: Assess intervention feasibility, acceptability, and compliance. H1: Feasibility: 85% of all enrolled participants will complete the study, Acceptability: Moderate to high acceptability rating of ≥ 50 (0-100 scale) and Participant compliance: ≥ 75 (0-100 scale) for MI compliance on the self-reported post-study survey.

Aim 2: Examine UUI symptom reduction. H1: Each intervention will lead to a pre-post and pre-follow-up reduction in number of UUI episodes, self-report urgency, and bladder symptom severity (ICIQ-FLUTS). H2: MI + tDCS will lead to the greatest reduction in these UUI symptoms.

Aim 3: Examine attenuation of reactivity to urgency stimuli. H1**:** Each intervention will reduce cue-reactivity and urinary Stroop reaction time. H2: MI + tDCS will lead to greater reductions in these measures relative to either MI or tDCS alone.

Study Design and methods

We will examine the independent and combined effects of brief mindfulness (MI) and transcranial direct current stimulation (tDCS) across three group: 1) MI, 2) tDCS, 3) MI + tDCS. MI and / or tDCS will be employed during urgency-cue exposure to examine the efficacy of these methods to attenuate cue reactivity (cue-induced urgency, reaction time during a urinary Stroop test) and lead to reductions in self-reported bladder problem severity (ICIQ-FLUTS score), UUI episodes, and urgency ratings. Some participants will be trained in a brief mindfulness intervention (MI; 20-minute audio guide) to focus on body scan with acceptance language and will practice it out of session to use during cue exposure. Second, transcranial direct current stimulation (tDCS) targeting the dorsolateral prefrontal cortex (dlPFC) with be used to increase cortical excitability in the dlPFC, aimed at increasing cognitive control when confronted with personal urgency cues. tDCS has been shown to reduce cue reactivity on its own, and we will also test it as such, but research has also shown augmentation of its effectiveness when paired with tasks that engage brain regions being targeted for related behavior change. Past research has shown that mindfulness engages the PFC and that women with UUI who are not responsive to pharmacotherapy demonstrate down regulation of the PFC,

suggesting that tDCS combined with MI should further enhance cognitive control over reactivity to cue-provoked urgency and reduce UUI-related outcomes.

Procedures and Protocols

Sixty women will be recruited from the Pitt+Me online registry, local fliers and through collaboration with multiple community and university resources (see recruitment). Telephone screening will determine initial eligibility. Eligible participants will be invited to Dr. Conklin's laboratory for informed consent, further screening, and a semi-structured interview to identify personal urgency and safe cue environments, of which each participant will take pictures. Participants will then be randomized to one of 3 groups: 1) Mindfulness, 2) tDCS, 3) Mindfulness + tDCS. We will use the SAS® high quality pseudorandom deviate generator (SAS Institute, Cary, NC) to randomize subjects in a 1:1:1 ratio. We will use a blocked randomization scheme to force an approximate balance between the number of subjects in each arm at any point during recruitment. Participants will undergo 4 urgency cue exposure sessions with their assigned intervention. Cue-induced urgency and reaction time to modified Stroop will be assessed at baseline and post-training. Bladder diary and urgency survey will be completed daily throughout the study, and for one-week post-training.

Interventions:

1) Brief Mindfulness (Body Scan with awareness/acceptance language): Imaging studies have revealed enhanced activation of the PFC[1], and more specifically the dlPFC[2,3], during mindfulness practice, and while completing executive processing tasks after MI training. During mindfulness training, practitioners cultivate a nonjudgmental state of attention to experiences in the present moment[4], resulting in **active engagement of attentional control abilities**[5-7]. Recent work on MI-based stress reduction (MBSR) to attenuate UUI symptoms found significant reductions in UUI episodes post-treatment, with continued reduction over 6 months post-treatment, suggesting increased benefit over time[8,9]. Mindfulness has also been shown to reduce cue reactivity, with significant reductions in cue responding to food[10], anxiety[11], addiction[12-14], and mood regulation[15] cues following MI training, presumed to reflect increased cognitive control over salient disorder-related stimuli. Recently, less intensive brief mindfulness interventions (i.e., significantly less than 8-week MBSR) have been tested with positive results.[16-20] This work has shown immediate beneficial effects on anxiety[18], coping with social stressors[3], acute pain[20] and increasing self-control,[19] without requiring a full MBSR program[21]. Brief interventions are lower cost, less burdensome and more accessible at home, which is attractive for a self-management care model for chronic illness.[22,23] Given the success in reducing UUI episodes following the full 8-week MBSR program[8,9] UUI is a particularly good candidate for testing new brief mindfulness methods.

A component of MBSR commonly isolated for brief intervention is body scan[24]. This method involves focused attention on the present moment through observing one's breath and bodily sensations, while becoming aware of, and accepting without judgement, any thoughts and feelings that arise.[25] Body scans are used for brief mindfulness training in both clinical and research protocols, and typically last between 5 and 30 min[20,21]. We will test a novel MI presented and practiced with a 15-minute guided audio recording consisting of guidance to attend to physical sensations with a gentle, accepting attitude.

2) Transcranial Direct Current Stimulation (tDCS): tDCS is a safe, non-invasive method of brain stimulation that **can enhance cortical excitability and help attenuate cue-induced reactivity**. tDCS has become increasingly popular in clinical and neurocognitive research, showing promising efficacy for targeting cue-reactivity to stimuli related to a number of disorders (depression, addiction, anxiety), assisting physical and cognitive recovery secondary to stroke and spinal cord injury[26-28], and promoting cognitive enhancement in healthy subjects.[29-

[32] Addiction research incorporating tDCS has shown reductions in cue-induced craving in response to drug-related stimuli from baseline to re-test following a single session of tDCS,[33] as well as reductions in cue-induced craving and actual smoking after 3-5 tDCS sessions.[34]

In anxiety research, reductions in self-reported and physiological reactivity to fear stimuli have been noted after similar tDCS methods[35]. These effects have been characterized through consideration of the PFC's role in decision-making and cognitive control and are presumed to reflect increased control over cue reactivity following PFC-targeted tDCS Although effective as a standalone treatment to reduce reactivity, the effects of tDCS are greatly enhanced when stimulation is paired with behavioral training that engages the brain processes that underlie the targeted behavior.[36] Thus, we purport that brief mindfulness during urgency-cue exposure is a prime candidate for augmentation with dlPFC-targeted tDCS. Enhancement of excitability in the PFC during mindfulness, which has also been shown to increase dlPFC activation[3,37,38] and cognitive control[39] should lead to greater ability to dynamically recruit cognitive control systems during urgency situations, which will aid in retraining the salience of urgency-related cues.

Inclusion Criteria:

• Ambulatory women aged 40+ years

• Able to differentiate between stress symptoms (cough, laugh, exercise) and urgency symptoms (leakage following sudden strong urge to void that is difficult to defer), and history suggestive of UUI using our detailed incontinence history questionnaires and clinical expertise.

• self-report of 2 leaks/week,

• Self-report of 'sometimes' or 'often' experiencing urgency or leakage in at least 4 of 15 common urgency trigger scenarios

• A bother score ≥4 on a situational urgency questionnaire

• Subjects using OAB medication will be considered if they have used it consistently for 3 months and plan to keep using it throughout the duration of the study.

Exclusion criteria:

• Inability to reliably describe incontinence type (i.e. Inability to identify situational urgency trigger scenarios, differentiate between stress and urgency incontinence, describe leakage scenarios.)

• Cognitive impairment (inability to: accurately complete a bladder diary, identify and take appropriate photos of urge cue and safe cue scenarios, appropriately give incontinence history)

• Spinal cord injury; history of pelvic irradiation, advanced uterine or bladder cancer

• Urinary retention [PVR >200 ml]

• Interstitial cystitis; artificial sphincter implant

• Medical instability or expected change in medication during the study (e.g. change in anticholinergic, diuretic medication)

• Conditions that preclude tDCS including: Epilepsy or current seizure disorder, pregnant or lactating, implanted cardiac or brain medical device.

Primary Outcomes: Data Analysis Plan. Prior to hypothesis testing, descriptive statistics and graphic displays will be used to identify outliers, missing data, and patterns of attrition, and to guide transformations and appropriate tests. The primary analyses will be evaluated via mixed model regressions with Bonferroni post-hoc comparisons. Mixed model regression features advantages over traditional regression due to the ability to handle repeated assessments of both predictor variables and outcome variables. For **Aim 1**, We will assess feasibility as >85% study

completion, acceptability as a score ≥50 on 8-item post-study survey rating (scale 0-100), and mindfulness compliance as an average rating ≥75 on the compliance survey (scale 0-100). We will use chi-square to assess attrition differences between groups, and one-way ANOVA to assess differences in acceptability and compliance ratings. For **Aim 2**, mixed model regressions will test the main effects of experimental group (1=MI, 2=tDCS, and 3=MI+tDCS) on ICIQ-FLUTS score (pre, post, and follow-up), UUI episodes, and urgency survey scores (3-day mean score at baseline, last three days before re-test, and last 3-days of follow-up) as dependent variables. Pre-intervention (baseline) levels of each dependent variable will be entered as a covariate in respective regression models. This process will be repeated for **Aim 3**, with separate models evaluating treatment effects on Stroop RT and cue-provoked urgency. For Stroop RT, the primary dependent variable will be post-test minus pre-test change. For cue-provoked urgency, the primary dependent variable will represent a double-difference score of urgency minus safe cues, and post-test minus test.

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