GYNECOLOGY

Hypnotherapy or medications: a randomized noninferiority trial in urgency urinary incontinent women

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BACKGROUND: Urgency urinary incontinence afflicts many adults, and most commonly affects women. Medications, a standard treatment, may be poorly tolerated, with poor adherence. This warrants investigation of alternative interventions. Mind—body therapies such as hypnotherapy may offer additional treatment options for individuals with urgency urinary incontinence.

OBJECTIVE: To evaluate hypnotherapy's efficacy compared to medications in treating women with urgency urinary incontinence.

MATERIALS AND METHODS: This investigator-masked, noninferiority trial compared hypnotherapy to medications at an academic center in the southwestern United States, and randomized women with nonneurogenic urgency urinary incontinence to weekly hypnotherapy sessions for 2 months (and continued self-hypnosis thereafter) or to medication and weekly counseling for 2 months (and medication alone thereafter). The primary outcome was the between-group comparison of percent change in urgency incontinence on a 3-day bladder diary at 2 months. Important secondary outcomes were between-group comparisons of percent change in urgency incontinence at 6 and 12 months. Outcomes were analyzed based on noninferiority margins of 5% for between group differences ($P < 0.025$) (that is, for between group difference in percentage change in urgency incontinence, if the lower bound of the 95% confidence interval was greater than −5%, noninferiority would be proved).

RESULTS: A total of 152 women were randomized to treatment between April 2013 and October 2016. Of these women, 142 (70 hypnotherapy, 72 medications) had 3-day diary information at 2 months and were included in the primary outcome analysis. Secondary outcomes were analyzed for women with diary data at the 6-month and then 12-month time points (138 women [67 hypnotherapy, 71 medications] at 6 months, 140 women [69 hypnotherapy, 71 medications] at 12 months. There were no differences between groups' urgency incontinence episodes at baseline: median (quartile 1, quartile 3) for hypnotherapy was 8 (4, 14) and medication was 7 (4, 11) ($P = .165$). For the primary outcome, although both interventions showed improvement, hypnotherapy did not prove noninferior to medication at 2 months. Hypnotherapy's median percent improvement was 73.0% (95% confidence interval, 60.0—88.9%), whereas medication's improvement was 88.6% (95% confidence interval, 78.6—100.0%). The median difference in percent change between groups was 0% (95% confidence interval, −16.7% to 0.0%); because the lower margin of the confidence interval did not meet the predetermined noninferiority margin of greater than −5%, hypnotherapy did not prove noninferior to medication. In contrast, hypnotherapy was noninferior to medication for the secondary outcomes at 6 months (hypnotherapy, 85.7% improvement, 95% confidence interval, 75.0—100%; medications, 83.3% improvement, 95% confidence interval, 64.7—100%; median difference in percent change between groups of 0%, 95% confidence interval, 0.0—6.7%) and 12 months (hypnotherapy, 85.7% improvement, 95% confidence interval, 66.7—94.4%; medications, 80% improvement, 95% confidence interval, 54.5—100%; median difference in percent change between groups of 0%, 95% confidence interval, −4.2% to −9.5%).

CONCLUSION: Both hypnotherapy and medications were associated with substantially improved urgency urinary incontinence at all follow-up. The study did not prove the noninferiority of hypnotherapy compared to medications at 2 months, the study's primary outcome. Hypnotherapy proved noninferior to medications at longer-term follow-up of 6 and 12 months. Hypnotherapy is a promising, alternative treatment for women with UUI.

Key words: hypnotherapy, mind-body therapy, pharmacotherapy, randomized trial in women, urgency urinary incontinence

Urinary urgency incontinence (UUI), that is, involuntary urine loss associated with a sudden, compelling desire to urinate,[1] is common and costly. Twice as prevalent in women as in men, UUI increases with age, afflicting 24% of women ≥40 years old.[2] Those affected by UUI may also experience depression, loss of work productivity, and loss of independence.[2,3] Pharmacotherapy, an accepted second-line UUI treatment, may have side effects limiting patient adherence and medication effectiveness. UUI medication continuation is as low as 45% at 1 month and 13% at 1 year.[4]

Increased awareness of UUI as a functional disorder suggests that therapy directed toward the brain rather than the bladder alone could serve as alternative treatment. Functional disorders, including irritable bowel syndrome (IBS) and UUI, exhibit increased visceral sensitivity to physiologic stimulation. Brain imaging studies have reported differences in brain activity in patients with functional disorders, including those with IBS[5] and UUI.[6–8] Women with UUI manifest abnormal activation of portions of the brain that govern interoception, the perception and interpretation of physiologic stimuli arising within the body. These abnormalities,

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AJOG at a Glance

Why was this study conducted?

Urgency urinary incontinence is common and emotionally distressing. Side effects and nonadherence may limit efficacy of medications, a standard treatment. Our study's objective was to study the use of hypnotherapy, an alternative mind-body intervention, in treating women with urgency urinary incontinence.

Key findings

This noninferiority trial compared the efficacy of hypnotherapy to medications in women with urgency urinary incontinence. Although both treatments improved urgency incontinence, the study did not prove hypnotherapy's noninferiority to medications at 2 months (study's primary outcome). Study findings did prove hypnotherapy's noninferiority to medications at 6 and 12 months.

What does this add to what is known?

Findings from this randomized trial, 1 of the first comparing hypnotherapy to pharmacotherapy, supports the use of hypnotherapy in women with urgency urinary incontinence. Hypnotherapy offers a potential alternative treatment for this condition.

and the effect that they have on other regions in the brain, likely influence bladder storage abnormalities.[9] Brain regions governing interoception can in turn be modulated by areas of the brain responsible for executive control. Mind–body therapies such as hypnotherapy likely affect these executive control networks.

Despite the US population's increasing reliance on mind–body therapies for chronic conditions,[10,11] few studies have focused on the use of alternative therapies, including hypnosis, for treatment of UUI. Freeman and Baxby's case series and a pilot study from our institution are 2 of the few reports supporting hypnotherapy's use in overactive bladder/UUI.[12,13] The American Psychological Association describes hypnosis as "…a therapeutic technique in which clinicians make suggestions to individuals who have undergone a procedure to relax… and focus their minds…for a wide range of conditions...."[14] Although hypnotherapy has been used to treat other visceral conditions such as IBS,[15,16] reports of its use in UUI are scarce.

The aim of the current randomized trial was to compare hypnotherapy to medications in UUI treatment. This noninferiority design, comparing a novel to a standard intervention, tested whether bladder-directed hypnotherapy was noninferior to medications. Our hypothesis was that bladder-directed hypnotherapy would be noninferior to medications for the primary outcome, namely, change in UUI episodes, at 2 months. Secondary outcomes included evaluation of the noninferiority of hypnotherapy based on other time points (6 and 12 months) as well as other exploratory measures.

Materials and Methods

Study design

Methodology for the Hypnotherapy Or Pharmacotherapy Trial has been described previously.[17] Briefly, this randomized, parallel-group, single-institution, noninferiority trial recruited women with UUI from an academic center in the southwestern United States. The study used a noninferiority design based on the rationale that, although medications are a standard UUI treatment, medication side effects limit effectiveness. The study was approved by the University of New Mexico Institutional Review Board (HRRC #09-314) and registered with ClinicalTrials.gov. #NCT01829425. All participants gave written consent.

Participants

Study eligibility required women to have non-neurogenic UUI for at ≥3 months, Overactive Bladder–Awareness Tool scores ≥8,[18] and ≥3 UUI episodes (UUIEs) per week.[17] The inclusion criteria regarding UUI frequency were similar to those used in other medication trials.[19–21] Exclusions included untreated urinary tract infection, pelvic prolapse beyond the hymen, contraindications to study interventions, antimuscarinic medication use within 3 weeks of enrollment, or history of intravesical botulinum toxin or UUI neuromodulator treatment.

Randomization and masking

A computer-generated randomization sequence determined treatment group allocation in a 1:1 ratio. A research coordinator who was otherwise unaffiliated with the study placed group assignments in opaque, sequentially numbered, sealed envelopes. Randomization was stratified by UUI severity (≤3 or ≥4 UUIEs on a 3-day diary) in varying permuted block sizes of 4 to 8. Randomization envelopes were securely stored and, upon completion of baseline information, opened by study coordinators. Hypnotic susceptibility testing was performed prior to randomization. Hypnotherapists performing susceptibility testing, investigators performing data analysis/interpretation, and personnel performing data entry were masked to treatment assignment. Hypnotherapists providing treatment, medication counselors, and participants were not masked. The mask was broken when the final participant completed 12-month follow-up.

Procedures

Hypnotherapy and medications

At the baseline visit and prior to randomization, study coordinators educated all participants regarding first-line UUI behavioral interventions in a standard fashion. Education included urge suppression, bladder training, and pelvic floor exercise verbal instruction, supplemented with written handouts. All participants received instruction regarding voiding diaries; these were returned at baseline, 8 weeks, 6 months, and 12 months.

Hypnotherapy

Participants randomized to hypnotherapy received 8 weekly, 1-hour, one-on-one bladder-directed hypnotherapy sessions delivered by a board-certified hypnotherapist using a standardized format[17] (outlined in Supplemetary Table 1). The education in the first session mirrored that given by medication counselors. Thereafter, hypnotherapy, in contrast to medication counseling, primarily focused on the emotional issues (eg, anxiety, shame, fear) associated with UUI, including triggers and responses, identified by participants during hypnotherapy sessions. Hypnotherapists helped participants develop therapeutic suggestions to address UUI and its associated emotions. A board-certified hypnotherapist (R.E.S.) designed the hypnotherapy procedures manual in collaboration with a local hypnotherapy teaching institution, trained study hypnotherapists on the protocol, and monitored hypnotherapy quality, but did not personally administer the intervention. Procedures were reviewed with the 4 hypnotherapy interventionists in a 4-hour training prior to study initiation. All hypnotherapy sessions were audio recorded. Study personnel audited the recordings, confirming hypnotherapists' adherence to study procedures. Participants received 2 recordings to encourage self-hypnosis with an additional optional hypnotherapy session offered between 6- and 12-month follow-up.

Medications

Participants randomized to medications received 8 weekly, one-on-one medication counseling sessions delivered using a standardized format[17] (outlined in Supplementary Table 1). Medication counselors were trained on antimuscarinic use and side effects during a 4-hour session (Y.M.K.) and followed a medication procedures manual. Medication counselors reviewed medications and side effects during scheduled weekly telephone or in-person sessions. All sessions were audio recorded. Study personnel audited the recordings, confirming counselors' adherence to study procedures. Participants received long-acting UUI medications; extended-

TABLE 1
Baseline characteristics of participants

	Hypnotherapy (n = 70)	Pharmacotherapy (n = 72)
Age, y, mean (SD)	57.6 (12.77)	59.5 (10.30)
Body mass index, kg/m^2, mean (SD)	32.3 (8.04)	30.5 (7.87)
Ethnicity, n (%)		
Non-Hispanic	45 (64.29)	55 (76.39)
Hispanic/Latina	24 (34.29)	15 (20.83)
Unknown/not reported/ refused	1 (1.43)	2 (2.78)
Race n (%)		
American Indian/Alaskan Native	2 (2.86)	2 (2.78)
Asian	0 (0)	0 (0)
Hawaiian/Pacific Islander	1 (1.43)	0 (0)
Black/African American	3 (4.29)	1 (1.39)
White	52 (74.29)	61 (84.72)
Other	11 (15.71)	7 (9.72)
Unknown/not reported/ refused	1 (1.43)	1 (1.39)
Education (%)		
Less than high school	2 (2.86)	0 (0)
High school or equivalent	7 (10.00)	10 (13.89)
Some college	23 (32.86)	15 (20.83)
Associates degree	7 (10.00)	8 (11.11)
Bachelor's degree/graduate degree	31 (44.29)	39 (54.17)
Parity median (Q1, Q3)	2.00 (1, 3)	2.00 (1, 3)
Prior OAB treatment (%)		
none	34 (48.57)	28 (38.89)
Physical therapy	7 (10.00)	9 (11.11)
Medication	21 (30.0)	24 (33.33)
Bladder (voiding) diary	11 (15.71)	11 (15.28)
Pelvic floor exercise/kegels	24 (34.29)	26 (36.11)
Bladder drills/timed voids	3 (4.29)	6 (8.33)
Smoke cigarettes (%)	7 (10.0)	6 (8.33)
Require assistance walking (%)	4 (5.71)	3 (4.17)
Practice any of the following (%)		
None	49 (70.00)	45 (62.50)
Meditation	12 (17.14)	13 (18.06)
Yoga	8 (11.43)	16 (22.22)
Tai Chi	0 (0)	3 (4.17)
Acupuncture	5 (7.14)	6 (8.33)

Komesu et al. Hypnotherapy trial. Am J Obstet Gynecol 2020. *(continued)*

TABLE 1
Baseline characteristics of participants *(continued)*

	Hypnotherapy (n = 70)	Pharmacotherapy (n = 72)
Pelvic Organ Prolapse Quantitation stage		
Stage 0	17 (24.3)	8 (11.1)
Stage 1	22 (31.4)	23 (31.9)
Stage 2 (all points ≤0; prolapse does not extend past hymen)	31 (44.3)	41 (56.9)
Hypnotic susceptibility (%)		
Low	4 (5.7)	6 (8.3)
Medium	13 (18.6)	18 (25.0)
High	53 (75.7)	48 (66.7)
Pretreatment expectation: "I expect that my treatment will improve my urinary urgency incontinence." Range 1–5; 1 = strongly disagree, 5 = strongly agree (SD)	4.0 (0.87)	4.2 (0.87)
Overactive Bladder Questionnaire–Short Form (OABq-SF) symptom bother (SD)	66.88 (21.26)	66.99 (21.60)
Overactive Bladder Questionnaire–Short Form (OABq-SF) quality of life (SD)	47.11 (27.40)	50.38 (25.29)
Incontinence Severity Index (SD)	7.14 (3.11)	7.00 (3.18)
Patient perception of bladder condition (SD)	4.19 (1.20)	4.25 (0.92)
Prolapse Incontinence Sexual Questionnaire–12 (SD)	85.60 (18.35)	86.65 (15.10)

Komesu et al. Hypnotherapy trial. Am J Obstet Gynecol 2020.

release oxybutynin 10 mg/day initially or extended-release tolterodine 4 mg/day if oxybutynin had been previously ineffective or poorly tolerated. Participants could switch between these medications if one or the other's side effects or efficacy were unacceptable.

Baseline assessment and follow-up

Baseline data obtained prior to randomization included participant characteristics (Table1), 3-day bladder diaries, validated questionnaire results, hypnotic susceptibility tests, and pretreatment expectations. The Stanford Hypnotic Susceptibility Scale[22] was administered in individualized sessions prior to randomization by a hypnotherapist other than the hypnotherapist administering the intervention. Participants were categorized into high, medium, and low hypnotic susceptibility groups post hoc for 1 of the exploratory secondary analyses.[23] Participants rated their pretreatment expectations following randomization and before treatment. Follow-up occurred after 2 months of the active intervention (hypnotherapy or medications/medication counseling) and at 6 and 12 months.

Primary outcome

The primary outcome was the difference between treatment groups' percent change in UUIEs on 3-day diaries at 2 months using a modified intention-to-treat analysis.

Secondary outcomes

Differences between groups' percent change in UUIEs at 6 and 12 months were important secondary outcomes. Validated questionnaire and other diary results at 2, 6, and 12 months were other secondary outcomes chosen to support or to counter UUIE diary outcome results. Questionnaires included the following: the Overactive Bladder Short Form questionnaire (OABq-SF),[18] Patient Perception of Bladder Condition (PPBC),[24] Incontinence Severity Index (ISI),[25] and Prolapse and Incontinence Sexual Questionnaire Short Form (PISQ-12).[26] Secondary diary outcomes included >70% change in UUIEs, number of voids and pads, and UUI cure.

Per protocol analysis of change in UUIEs between groups was also performed, comparing differences in UUIEs in those participants who were compliant with hypnotherapy or medications. At 2 months, hypnotherapy compliance was defined as ≥60% attendance of hypnotherapy sessions. At 6 and 12 months, hypnotherapy compliance was defined as answering "yes" to the question "Do you perform self-hypnosis or listen to your hypnotherapy recording?" Medication compliance was defined as answering "yes" to the question "Are you still taking your medication for urgency urinary incontinence?"

Coordinators reviewed adverse event (AE) occurrence at each study visit and by spontaneous participant report. Medication AEs included constipation, dyspepsia, dry eyes, dry mouth, and voiding difficulties. Hypnotherapy AEs included emotional upset attributable to hypnotherapy interfering with daily activities.

Statistical analysis

This study tested whether hypnotherapy was noninferior to medication. A sample size of 104 women (52 per group) provided 80% power with $\alpha = 0.025$ using a 1-sided, 2-sample t test, with a noninferiority margin of 5% to detect a between-group difference in percent

change in UUIEs of 9%, assuming standard deviations of 25% for each group.[21] Assuming 30% loss by 12-month follow-up, 152 participants (approximately 76 per group) were required for randomization.

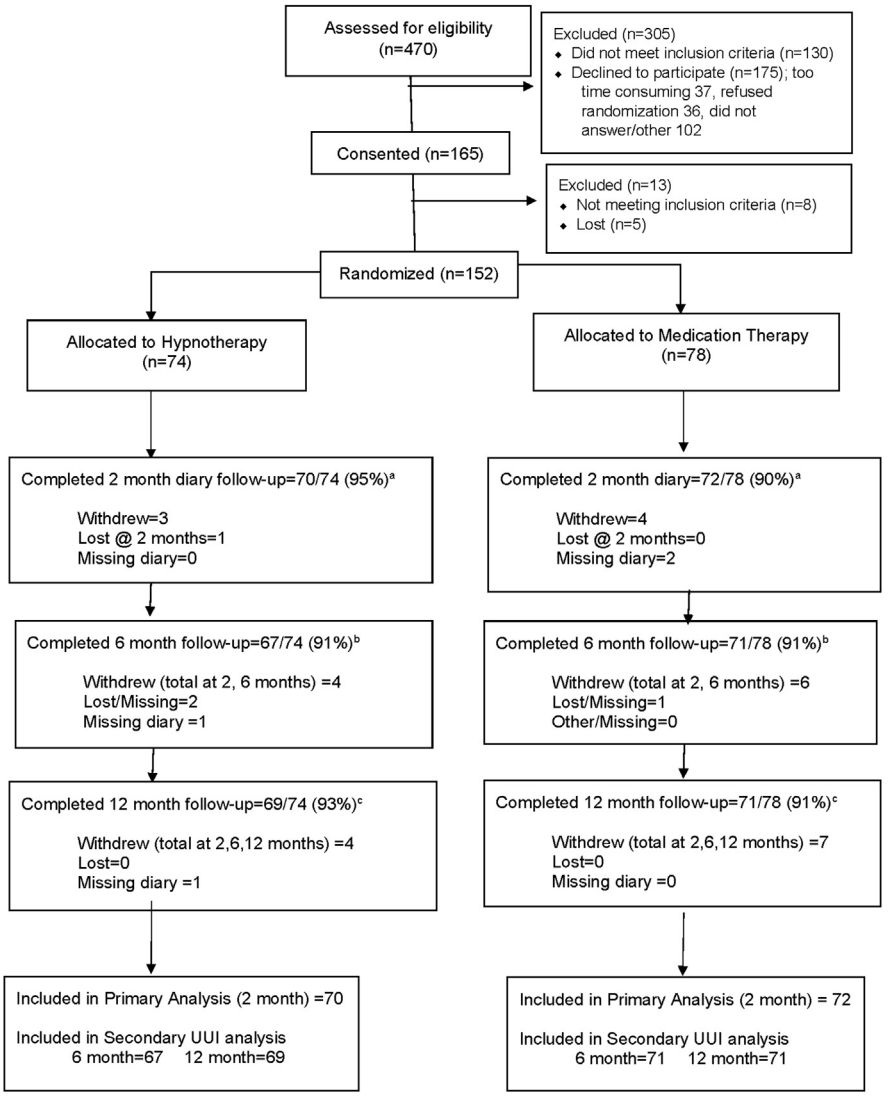
Analyses of differences between groups' percent change in UUIEs for the 2-month primary outcome and the 6- and 12-month secondary outcomes were performed based on a modified intention to treat. Women with complete diary information at 2-, 6-, and 12-month time points were included in the analyses. Analyses were based on participants' original group assignments. Because missing data were few, imputation was not performed at 6 or 12 months, precluding a strict intention-to-treat analysis.

Exploratory secondary outcomes compared questionnaire results and the other diary parameters using intention-to-treat analysis. Outcomes were evaluated using a linear mixed model with an unstructured covariance pattern. Binary diary parameters, >70% UUIE improvement, and restoration of continence were analyzed with the Fisher exact test. Per protocol analyses of group difference in percent change in UUIEs was also performed. The per protocol analyses included those participants who complied with treatment and had complete diary information.

The noninferiority analyses for both the primary UUIE intention-to-treat and the secondary UUIE per protocol outcomes were based on 2-sample *t* tests. The data demonstrated skewed distributions with large singularity at 100% change in UUIE. With this distribution, the 2-sample *t* test was not appropriate for analysis; we analyzed these results (between-group differences in percent change in UUIEs) using the exact Mann–Whitney test, reporting within group median, first quartile (Q1), and third quartile (Q3). Because of the skewed distribution of UUIE following treatment, confidence intervals (CIs) are reported as medians. The difference in medians between the 2 groups, however, does not correspond to the median difference between individuals in the 2 groups, which was calculated by the Hodges–Lehmann estimator. The resulting Hodges–Lehman median difference measured the expected benefit associated with membership in the superior group.[27] Hypnotherapy was considered noninferior to medication if the lower bound of the 95% CI for the difference in UUIE percent change compared to medication was greater than −5% ($P < .025$). If the lower bound of the 95% CI was −4.9% or higher (meaning more positive), noninferiority would be proved; if it was −5.1% or lower (meaning more negative), noninferiority would not be proved. Hypnotherapy was superior if the confidence limit lower bound was >0.

Exploratory investigation of covariates identified a priori in the study protocol (pretreatment expectations and hypnotic susceptibility) was performed. UUIE outcomes were count variables with repeated measures (baseline, 2, 6, 12 months). Count data models using log

FIGURE 1
CONSORT diagram. Participant flow through the study



Komesu et al. Hypnotherapy trial. Am J Obstet Gynecol 2020.

TABLE 2
Intention-to-treat comparisons

UUI episodes on 3-day diary and % change between groups	Hypnotherapy group: median UUI episodes on 3-day diary (Q1,Q3); median % change (95% CI)[a] at follow-up	Pharmacotherapy group: median UUI episodes on 3-day diary (Q1,Q3); median % change (95% CI)[a] at follow-up	Median difference in % change between groups[b,c] (95% CI)	Meets noninferiority criteria[d] (95% CI lower bound greater than −5%)
Baseline UUI (n = 142) Median UUI episodes (Q1,Q3)	n = 70 8 (4–14)	n = 72 7 (4–11)	Not applicable	Not applicable
2 mo UUI (n = 142) Median UUI episodes (Q1,Q3) Median % change UUI episodes (95% CI)	n = 70 2 (0–6) 73.0% (60.0–88.9%)	n = 72 1 (0–3) 88.6% (78.6–100.0%)	0% (−16.7% to 0.0%)	No
6 mo UUI (n = 138) Median UUI episodes (Q1,Q3) Median % change UUI episodes (95% CI)	n = 67 1 (0–4) 85.7% (75.0–100.0%)	n = 71 1 (0–4) 83.3% (64.7–100.0%)	0% (0.0–6.7%)	Yes
12 mo UUI (n = 140) Median UUI episodes (Q1,Q3) median % change UUI episodes (95% CI)	n = 69 1 (0–3) 85.7% (66.7–94.4%)	n = 71 1 (0–6) 80.0% (54.5–100.0%)	0% (−4.7% to 9.5%)	Yes

CI, confidence interval; *UUI*, urgency urinary incontinence.

[a] Exact Mann–Whitney test used to account for skewed data with many tied values; [b] All within-group changes relative to baseline for exact test confidence intervals. Hodges–Lehmann estimate of differences between groups can differ from differences between group medians; [c] Median difference in % change = hypnotherapy % change − medication % change; [d] The lower bound (ie, smaller number noted in 95% CI) of the difference in hypnotherapy % change − medication % change must be greater than −5% to meet the noninferiority criteria. For example, −5.1% for the lower bound would mean that hypnotherapy did not meet the noninferiority criteria; −4.9% would mean that hypnotherapy did meet the noninferiority criteria.

Komesu et al. Hypnotherapy trial. Am J Obstet Gynecol 2020.

link were evaluated using the Akaike Information Criterion to deal with zero-inflation and overdispersion. The negative binomial was superior by that criterion. Repeated measures were managed using generalized estimating equations (GEEs), with the negative binomial regressions fit using PROC GENMOD in SAS (version 9.4; SAS Institute, Cary, NC). This linear mixed model assessed changes from baseline to 2, 6, and 12 months; 95% CIs are reported for the least-squares mean (LSM), or adjusted means, and their ratios.

Results

A total of 470 women were screened for eligibility, and 152 were randomized (74 hypnotherapy, 78 medications) during April 2013 to October 2016. Of these, 142 women (70 hypnotherapy, 72 medications) completed treatment and had UUIE primary outcome information at 2 months; ≥90% had UUIE information at 6 and 12 months (Figure 1). Baseline participant characteristics did not differ (Table 1). The average participant was in her sixth decade and obese, had undergone some prior overactive bladder (OAB) therapy, had received some college education, and was of non-Hispanic white ethnicity (Table 1).

The intention-to-treat UUIE outcomes at 2, 6, and 12 months are summarized in Table 2 and Supplementary Figure 1. Baseline UUIE medians on 3-day diary were similar for hypnotherapy (8 [Q1=4, Q3=14]) and medications (7 [Q1=4, Q3=14]). UUIEs for both groups improved at all time points. For the 2-month primary outcome, the noninferiority of hypnotherapy was not proved. Although the median percent change from baseline comparing hypnotherapy and medications was 0% (95% CI, −16.7% to 0.0%), the lower bound of the 95% CI was less than −5.0%. Supplementary Figure 2 illustrates individual participants' percent change in UUIEs by treatment group. The UUIE secondary outcomes at 6 and 12 months showed hypnotherapy to be noninferior to medications (Table 2, Supplementary Figure 1).

Exploratory secondary outcomes included the questionnaire (Table 3) and UUIE per protocol (Supplementary Table 1) results. The per protocol analysis found hypnotherapy to be noninferior in reduction of UUIEs at 2, 6, and 12 months. There were no differences between groups regarding questionnaire results when adjusted for baseline.

We also explored the impact of baseline UUIEs and hypnotic susceptibility on outcomes. Repeated-measures regression analysis indicated that follow-up UUIEs were associated with number of UUIEs at baseline ($P < .0001$), and that a group by time by hypnotic susceptibility 3-way interaction existed ($P < .0001$). UUIE counts

TABLE 3
Questionnaires, diary, compliance results

	Hypnotherapy patients	Pharmacotherapy patients	*P*	Estimated group difference (95% CI)[a]
Overactive Bladder Questionnaire—Short Form Symptom Bother[b] Scores				
Baseline mean (CI)	66.88 (61.81—71.94)	66.99 (62.92—72.07)	.97	−0.11 (−7.23 to 7.00)
2-mo Means[c] (CI)	38.17 (30.19-46.14)	35.33 (28.64-42.02)	.59	2.84 (−7.58 to 13.25)
6-mo Means[c] (CI)	34.61 (26.26—42.96)	27.93 (20.66—35.20)	.24	6.68 (−4.39 to 17.76)
12-mo Means[c] (CI)	32.27 (22.89—41.66)	30.74 (22.53—38.95)	.81	1.53 (−10.94 to 14.00)
Overactive Bladder Questionnaire—Short Form Quality of Life[d] Scores				
Baseline mean (CI)	47.11 (40.58—53.65)	50.38 (44.39—56.36)	.46	−3.26 (−12.04 to 5.52)
2-mo Means[c] (CI)	73.96 (66.93—81.00)	74.86 (68.96—80.76)	.85	−0.90 (−10.08 to 8.28)
6-mo Means[c] (CI)	75.85 (68.24—83.46)	80.19 (73.63—86.75)	.40	−4.34 (−14.39 to 5.72)
12-mo Means[c] (CI)	75.71 (68.07—83.35)	81.57 (74.91—88.23)	.26	−5.86 (−16.00 to 4.28)
Incontinence Severity Index[e] scores				
Baseline mean (CI)	7.14 (6.40—7.88)	7.00 (6.25—7.75)	.79	0.14 (2.82 to 3.56)
2-mo Means[c] (CI)	4.74 (3.54—5.94)	5.18 (4.17—6.19)	.58	−0.44 (−2.01 to 1.12)
6-mo Means[c] (CI)	4.87 (3.60—6.13)	4.69 (3.58—5.79)	.83	0.18 (−1.50 to 1.86)
12-mo Means[c] (CI)	3.64 (2.52—4.76)	3.33 (2.34—4.31)	.67	0.32 (−1.17 to 1.81)
Patient Perception Bladder Conditions[f] scores				
Baseline mean (CI)	4.19 (3.90—4.47)	4.25 (4.03—4.47)	.72	−0.06 (−0.42 to 0.29)
2-mo Means[c] (CI)	3.19 (2.75—3.64)	3.35 (2.98—3.72)	.59	−0.16 (−0.74 to 0.42)
6-mo Means[c] (CI)	3.12 (2.67—3.58)	2.71 (2.31—3.10)	.17	0.42 (−0.19 to 1.02)
12-mo Means[c] (CI)	2.93 (2.46—3.40)	2.65 (2.24—3.06)	.37	0.29 (−0.34 to 0.91)
Prolapse and Incontinence Sexual Questionnaire—12[g] scores				
Baseline mean (CI)	85.60 (79.57—91.62)	86.65 (81.69—91.62)	.99	0.065 (−7.71 to 7.84)
2-mo Means[c] (CI)	93.08 (85.29—100.86)	91.58 (84.58—98.59)	.77	1.50 (−6.48 to 14.64)
6-mo Means[c] (CI)	92.73 (84.33—101.13)	89.00 (81.92—96.08)	.50	3.73 (−7.29 to 14.75)
12-mo Means[c] (CI)	93.74 (86.45—101.05)	92.36 (85.84—98.89)	.78	1.39 (−8.43 to 11.22)
No.of pads on 3-day diary				
Baseline mean (CI)	5.52 (4.06—6.98)	4.63 (3.57—5.70)	.33	0.89 (−0.89 to 2.67)
2-mo Means[c] (CI)	3.57 (2.37—4.77)	2.74 (1.82—3.66)	.28	0.83 (−0.67 to 2.33)
6-mo Means[c] (CI)	3.01 (1.87—4.16)	2.63 (1.85—3.40)	.58	0.38 (−0.99 to 1.76)
12-mo Means[c] (CI)	3.46 (2.07—4.84)	3.07 (2.13—4.01)	.65	0.39 (−1.28 to 2.05)
No. of voids on 3-day diary				
Baseline mean (CI)	29.07 (27.06—31.08)	29.19 (27.14—31.24)	.94	−0.12 (−2.97 to 2.73)
2-mo Means[c] (CI)	26.4 (24.29—28.59)	25.35 (23.59—27.12)	.44	1.08 (−1.67 to 3.85)
6-mo Means[c] (CI)	25.58 (23.48—27.68)	24.28 (22.69—25.87)	.32	1.30 (−1.31 to 3.91)
12-mo Means[c] (CI)	25.74 (23.69—27.79)	25.37 (23.71—27.02)	.78	0.37 (−2.24 to 2.99)
>70% Improvement of UUI				
2 mo n (%) (CI)	60 (86%)(CI 75—93%)	59 (82%; CI 71%—90%)	.65	OR 0.76 (0.27—2.04)[h]
6 mo n (%) (CI)	55 (82%)(CI 71—90%)	58 (82%; CI 71%—90%)	1.00	OR 1.05 (0.40—2.81)[h]
12 mo n (%) (CI)	54 (78%)(CI 67—87%)	53 (75%; CI 63%—84%	.69	OR 0.81 (0.33—1.94)[h]

Komesu et al. Hypnotherapy trial. Am J Obstet Gynecol 2020.

(continued)

TABLE 3
Questionnaires, diary, compliance results *(continued)*

	Hypnotherapy patients	Pharmacotherapy patients	*P*	Estimated group difference (95% CI)[a]
Continent (no UUI on diary)				
At 2 mo n (%) (CI)	24 (34%)(CI 23−47%)	30 (42%; CI 30−54%)	.39	OR 1.4 (0.66−2.86)[h]
At 6 mo n (%) (CI)	29 (43%)(CI 31−56%)	28 (39%; CI 28−52%)	.73	OR 0.85 (0.41−1.78)[h]
At 12 mo n (%) (CI)	25 (36%)(CI 25−49%)	30 (42%; CI 31−55%)	.49	OR 1.3 (0.62−2.69)[h]
No UUI at all follow−up, n (%;CI)	11 (16%)(CI 8−27%)	16 (23%; CI 14−34%)	.39	OR 1.5 (0.60−4.00)[h]
Treatment compliance				
At 2 mo n (%) (CI)	67/70 (96%)	61/72 (85%)	.63	OR 1.13 (0.68−1.87)[h]
At 6 mo n (%) (CI)	54/67 (81%)	55/71 (77%)	.90	OR 1.04 (0.61−1.77)[h]
At 12 mo n (%) (CI)	53/69 (77%)	47/71 (66%)	.60	OR 1.16 (0.67−2.00)[h]

CI, confidence interval; *OR,* odds ratio; *UUI,* urgency urinary incontinence.

[a] Estimated group differences and 95% CIs were derived using linear mixed models; [b] Validated questionnaire reflecting symptoms. Higher scores indicate more symptoms; higher scores are worse. Score range 0−100. <2% Missing data; [c] Adjusted means; [d] Validated questionnaire reflecting quality of life. Higher scores indicate better quality of life: higher scores are better. Score range, 0−100. <1% Missing data; [e] Validated index. Higher scores indicate greater incontinence severity. Score range, 1−12. 2% Missing data; [f] Validated global scale regarding patients' perception of the severity of their bladder condition. Lower scores are better, higher scores are worse. Score range, 1−6. No missing data; [g] Validated sexual function questionnaire in women with prolapse or incontinence. Higher scores are better. Range, 0−123. Only administered to women having heterosexual relations in the last 6 months (33 women in each group: met criteria and answered these questions); [h] ORs and 95% CIs based on Fisher exact test.

Komesu et al. Hypnotherapy trial. Am J Obstet Gynecol 2020.

at all time points were integrated into the regression model. UUIE adjusted means, controlling for baseline UUIE, were calculated for the 9 levels representing time (2, 6, and 12 months) by hypnotic susceptibility (low, medium, and high). Adjusted results suggested that change in UUIE between groups differed at various time points and depended on participants' hypnotic susceptibility (Supplementary Table 2, Supplementary Figure 3). In this model at 6 months, among medium−hypnotic susceptibility participants, hypnotherapy was superior to medication. At 12 months, among high−hypnotic susceptibility participants, hypnotherapy was superior to medication. In these participants, UUIE improved between 2 and 12 months in the hypnotherapy group (LSM decreased from 2.35 to 2.10) but worsened in the medication group (LSM increased from 1.61 to 3.74). The difference in these trends was significant ($P = .0002$; point estimate, 2.60; 95% CI, 1.56−4.34).

Of 152 randomized women, 62 (40.8%) reported at least 1 AE (25 hypnotherapy, 34 medications). Medication participants reported anticipated AEs 12 times. No hypnotherapy participant reported the anticipated AE of severe emotional upset. Both groups reported the following AEs: urinary tract infection (6 medications, 5 hypnotherapy), falls (5 medications, 3 hypnotherapy), headache (3 medications, 3 hypnotherapy), and back pain (4 medications, 3 hypnotherapy). Four serious AEs (3 medications, 1 hypnotherapy) occurred, likely unrelated to treatment (hospitalizations for pre-existing disease, 3; and a fall while horseback riding, 1.

Comment

Main findings

This study found that hypnotherapy and medications were both associated with markedly reduced UUIEs, although when comparing hypnotherapy to medications, hypnotherapy was not found to be noninferior to medications at the 2-month, primary end point. Hypnotherapy did attain noninferiority at the secondary 6- and 12-month end points. Thus, hypnotherapy and medications were both associated with substantially decreased UUIEs and these decreases were sustained over time.

Clinical implications

Hypnotherapy and medications were both associated with decreased UUIEs. Notably, both groups were associated with a >70% decrease in UUIEs, a previously identified point at which women report enhanced quality of life and treatment satisfaction.[10] More than three-fourths of women maintained this meaningful change for 12 months. Secondary outcomes (questionnaires, other diary data, and the per protocol analysis) further supported the comparative effectiveness of the treatments; participants in both groups experienced similar improvement at all time points.

Exploratory repeated-measures regression analysis suggested that hypnotic susceptibility affected the results for both interventions. Both treatments were associated with improved UUIEs in medium− and high−hypnotic susceptibility participants (>90% of participants). Among low−hypnotic susceptibility participants (7% of participants), trends in UUI improvement favored medications, suggesting that hypnotherapy may be less efficacious in this subgroup.

Both groups' high treatment continuation rates were unexpected. Individualized UUI education and 2 months of weekly contact may have improved continuation. Although for UUI, patient education and individualized follow-up are routinely recommended,[28] the attention provided to study participants may have exceeded that provided in clinical practice, enhancing treatment continuation. Approximately 75% of hypnotherapy and 66% of medication participants continued treatment at 1 year. In contrast, database studies have reported 1-year medication continuation rates of 10−25%.[29,30] Implications for routine UUI care with medications seem clear; augmenting medications with education and individualized follow-up likely improves medication continuation and efficacy.[29,31] Hypnotherapy continuation was also high. Audio recordings encouraging self-hypnosis practice may have improved this behavioral intervention's continuation. The importance of personal contact and follow-up in UUI, albeit difficult to measure, conceivably contributed to the success of both treatments.

Scant literature exists regarding hypnotherapy's efficacy in OAB and/or UUI. A pilot study compared hypnotherapy to behavioral therapy in women with OAB (with or without incontinence); hypnotherapy had greater global improvement in OAB symptoms.[13] The sole report describing hypnotherapy in women with UUI (ie, OAB with incontinence), to our knowledge, has been that of Freeman and Baxby.[12] That case series of 50 women found that following UUI-directed hypnotherapy, 60% were cured, 28% were improved, and 14% were unchanged.[12] At 6 months, 86% continued to be cured or improved. The current trial further strengthens existing evidence that hypnotherapy is associated with UUI improvement, and that these associations are durable. Similar to Freeman and Baxby's study, this trial found that hypnotherapy was associated with a 73% median improvement in UUIEs at 2 months. However, its noninferiority to medications was not proved, as medications were associated with 88.3% improvement. At 6 and 12 months, hypnotherapy was noninferior to medications, and both treatments maintained ≥80% improvement. Hypnotherapy's UUIE improvement, compared to that of medications, occurred later and remained stable at 1 year.

This study indicates that UUI-directed hypnotherapy is associated with improved UUI despite its uncertain mechanism of action. Emotional distress frequently accompanies UUI,[2] potentially manifesting as enhanced sensory sensitivity.[32,33] Whether hypnotherapy affects UUI's emotional distress, tempers UUI's enhanced sensory sensitivity, or acts by other means, remains unknown. Functional magnetic resonance imaging (fMRI) during hypnotic induction has suggested increased interaction between the attentional component of the executive network and the salience, or interoceptive, network [34,36] Interestingly, fMRI of UUI patients suggests that interaction between the executive and interoceptive areas of the brain (responsible for interpretation of physiologic stimuli within the body) may underlie the response of UUI to physical therapy.[37,38] Although little is known about hypnotherapy's brain-related effects outside the hypnotic state, we postulate that hypnotherapy modulates output received from afferents via central brain mechanisms.

This study did not prove the noninferiority of hypnotherapy to medications at 2 months, but did prove noninferiority at 6 and 12 months. This may reflect an association between hypnotherapy and UUI improvement that increases over time. Other mind−body studies have also shown a similar trend. A randomized trial of patients with chronic back pain compared 2 mind−body therapies, namely, mindfulness-based stress reduction (MBSR) and cognitive-behavioral therapy (CBT), to usual care.[39] Groups did not differ in pain reduction at 2 months, but both mind−body treatment groups demonstrated greater improvement at 6 and 12 months compared to controls. An IBS trial randomized women to 8 weeks of mindfulness training or to a control group with follow-up at 2 and 3 months.[15] Not only were mindfulness group findings superior to those of controls, improvement within the mindfulness group increased between 2 and 3 months. Repeated-measures regression analysis performed in the current hypnotherapy study also demonstrated a group by time difference in UUIEs. In patients with moderate-to-high hypnotic susceptibility (94% of the cohort), UUI improvement increased between 2 and 6−12 months, a pattern not demonstrated by medications. This supports the supposition that symptom improvement associated with hypnotherapy increases over time. Perhaps brain remodeling potentially associated with mind−body therapies requires additional time to exert its effect. In aggregate, both prior work and our data suggest that these therapies may be associated with continued symptom improvement over longer duration. This may have resulted in hypnotherapy's comparative noninferiority at longer-term, but not initial, follow-up.

Study strengths and weaknesses

This study is 1 of few studies evaluating hypnotherapy in UUI, and its results support its use as an alternative UUI treatment. This study's novelty notwithstanding, its limitations warrant acknowledgement. First, participants were not masked to treatment, potentially biasing treatment results. However, as both groups had high pretreatment expectations, this potential bias did not favor 1 treatment over another. In addition, participants willing to engage in a 1-year trial may be more committed to treatment success than typical patients. Study strengths include its innovative use of a mind−body therapy compared to accepted therapy in treating UUI, treatment standardization, treatment fidelity monitoring, and high participant retention at 1 year.

Conclusion

In summary, although both hypnotherapy and medications were associated with markedly improved symptoms in women with non-neurogenic UUI, at 2 months, the noninferiority of hypnotherapy compared to medications was

unproved. Hypnotherapy did compare favorably to medications at longer-term follow-up. This study, which we believe is the first randomized trial evaluating bladder-directed hypnotherapy vs standard pharmacotherapy, provides evidence that hypnotherapy offers an alternative, underutilized treatment for UUI. The findings also suggest that hypnotherapy's comparative efficacy in treating UUI may improve over time. ■

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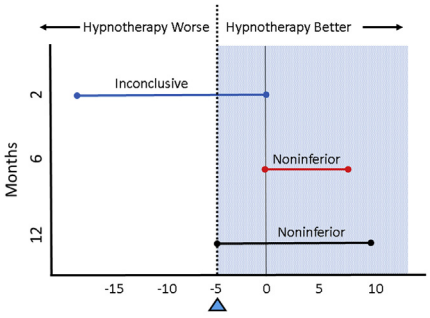
SUPPLEMENTARY FIGURE 1
Differences in hypnotherapy versus pharmacotherapy at 2, 6, and 12 months



Error bars indicate 95% confidence intervals. Dashed line indicates the noninferiority margin. Treatments the error bars for which lie wholly to the right of the dashed line, within the blue-tinted area, are noninferior. Only treatments the error bars for which are wholly to the right of the dashed line and do not include zero can be considered superior. Difference between treatments is nonsignificant if error bars include both the noninferiority margin and zero, but result is inconclusive regarding noninferiority. At 2 months, hypnotherapy was not noninferior to pharmacotherapy, and findings were in the inconclusive range. At 6 and 12 months, hypnotherapy was found to be noninferior to pharmacotherapy.

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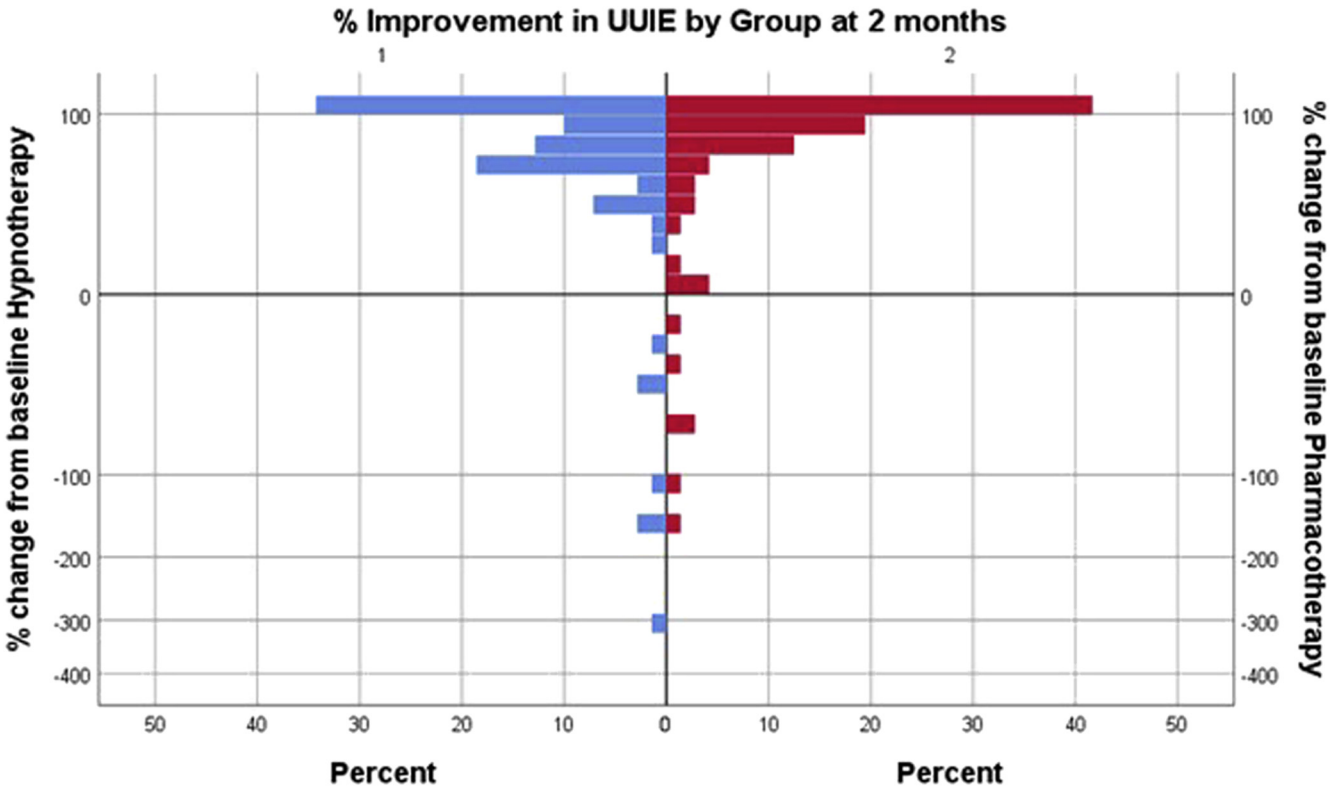
SUPPLEMENTARY FIGURE 2
Percent change in urinary urgency incontinence episodes (UUIEs) for individual participants



Histogram of percent UUIE change on 3-day diary from baseline to 2 months using an exponent transformed (square root) scale. Hypnotherapy results are represented in blue, and medications in red. Top bar represents patients with UUI cure, 100% reduction in UUIE from baseline. Histogram bars below zero represent patients whose UUIE worsened. (One patient in each group had less than −500% improvement, and are not represented on this graph.)

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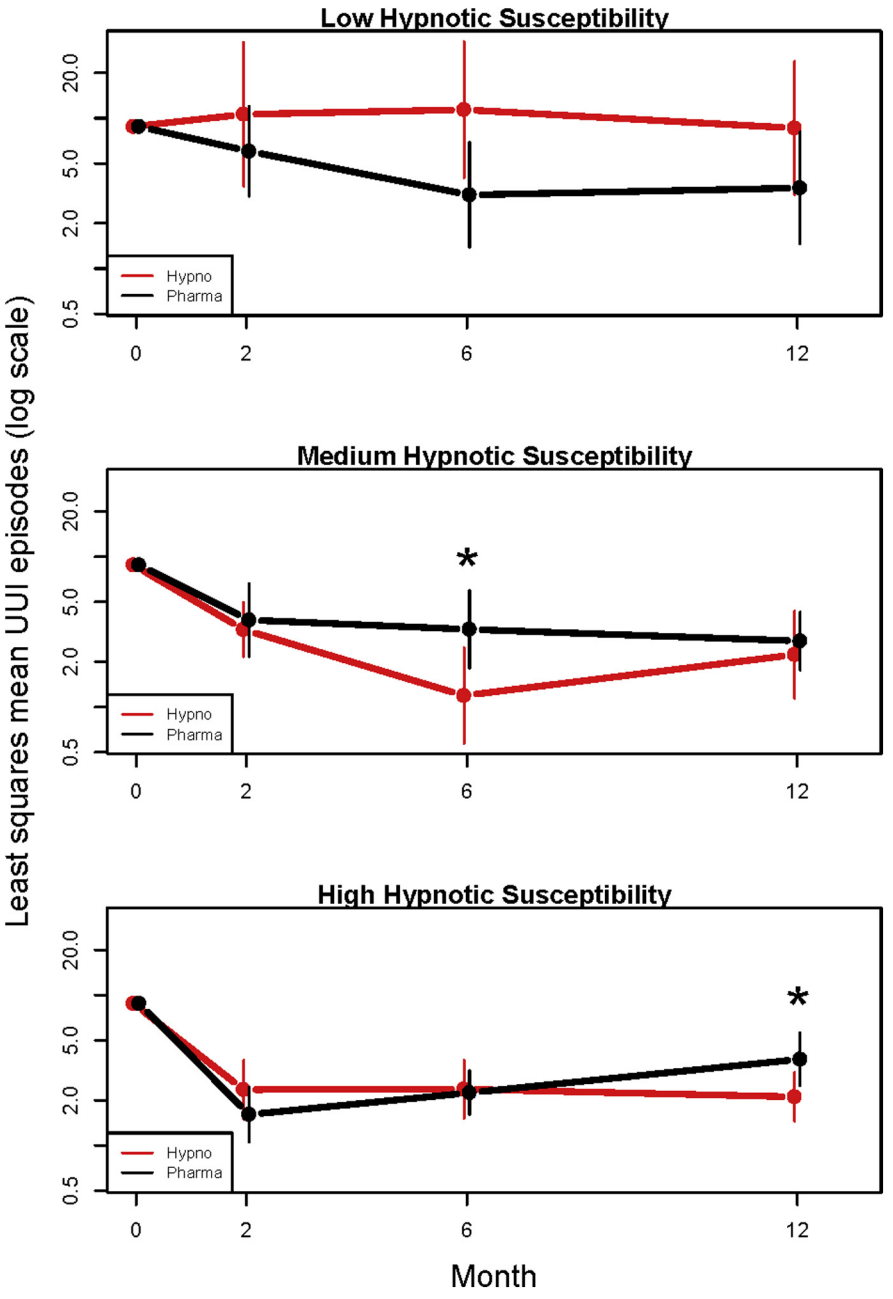
SUPPLEMENTARY FIGURE 3
Regression analysis 2, 6, and 12 months



Adjusted means results for months 2, 6, and 12, stratified by hypnotic susceptibility. Least-squares means calculated by negative binomial regression adjusting for baseline urinary urgency incontinence episodes and hypnotic susceptibility. Vertical lines represent 95% confidence intervals. Each least-squares mean is calculated using an overall average baseline value of 8.8 UUI episodes on 3-day voiding diary. Asterisk (*) indicates significant group difference ($P < .05$); because of the correlation structure, the individual confidence intervals may overlap slightly while the test for difference is significant.

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SUPPLEMENTARY TABLE 1
Overview of interventions

Weeks 1–8	Hypnotherapy	Pharmacotherapy
Week 1	Give study overview, explain bladder physiology, UUI pathophysiology, hypnotherapy principles. Participants discuss any fears/concerns regarding interventions. Patients set goals for this session. Perform hypnosis; induction and progressive relaxation/deepening/ therapeutic suggestions/terminate hypnosis. Debrief.	Give study overview, explain bladder physiology, UUI pathophysiology, discuss medications and mechanism of action. Participants discuss any fears/concerns regarding interventions. Medication instructions given and medication dispensed.
Week 2	Review change/persistence in UUI symptoms and prior week's experiences, address UUI- associated emotions/life impact, introduce self-hypnosis. Proceed with hypnosis/debrief (see week 1).	Review change/persistence in UUI symptoms and prior week's experiences, tolerability of medications discussed. Coping mechanisms regarding side effects discussed. If needed, arrangements made for medication change.
Week 3	Identify emotional triggers or responses associated based on self-discovery of emotional/physical connection with UUI and develop positive actions to deal with these emotions. Proceed with hypnosis/ debrief (see week 1).	Review change/persistence in UUI symptoms and prior week's experiences, discuss tolerability of medications. Coping mechanisms regarding side effects discussed. If needed, arrangements made for medication change.
Week 4	Assist participant to develop therapeutic suggestions and imagery to cope with UUI. Proceed with hypnosis/ debrief (see week 1).	Same as above. Medication instructions given and medication dispensed.
Week 5	Provide digital recording for participant specifically prepared for patient and for hypnotherapy home practice (based on work from week 4; emphasizes ego strengthening). Patients develop own therapeutic suggestions to reverse UUI after identifying beliefs that limit their bladder health. Proceed with hypnosis/ debrief (see week 1).	Same as week 3.
Week 6	Have participant reflect on their past (including responses resulting in current UUI-associated behavior; consider how to alter this behavior). Proceed with hypnosis/debrief (see week 1).	Discuss urgency incontinence triggers, and encourage participant to develop coping mechanisms. Same as above.
Week 7	Focus on integration of resources developed through hypnotherapy to improve UUI and overall health, countering negative emotions/responses related to emotional and physical connections. Proceed with hypnosis/debrief (see week 1).	Same as above.
Week 8	Focus on healing imagery and continuation of self-hypnosis. Proceed with hypnosis/debrief (see week 1).	Same as above. Interventionist discusses potential setbacks and emphasizes that these are temporary. Medication side effects and coping mechanisms reviewed. Medications dispensed.

UUI, urinary urgency incontinence.

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SUPPLEMENTARY TABLE 2

Per protocol between-group comparisons: median UUI episodes on 3-day diary and percent change between groups

	Hypnotherapy group: median UUI episodes on 3-day diary (Q1, Q3) Median % change (95% CI)[a]	Pharmacotherapy group: median UUI episodes on 3-day diary (Q1, Q3) Median % change (95% CI)[a]	Median difference in % change between groups[b,c] (95% CI)	Meets noninferiority criteria (95% CI lower bound greater than −5%)[d]
Baseline UUI (n = 142) Median UUI episodes (Q1, Q3)	n = 67 8 (4, 12.5)	n = 61 7 (4, 11)	NA	NA
2 mo UUI (n = 128) Median UUI episodes (Q1,Q3) Median % change UUI episodes (95% CI)	n = 67 1 (0, 5) 75.0% (62.5–88.9%)	n = 61 1 (0, 3) 88.9% (83.3–100.0%)	0% (−2.0% to 1.0%)	Yes
6 mo UUI (n = 109) Median UUI episodes (Q1,Q3) Median % change UUI episodes (95% CI)	n = 54 1 (0, 3) 93.7% (81.8–100.0%)	n = 55 1 (0, 4) 83.3% (64.7–100.0%)	−2.0% (−4.0% to 0.0%)	Yes
12 mo UUI (n = 100) Median UUI episodes (Q1,Q3) Median % change UUI episodes (95% CI)	n = 53 1 (0, 3) 85.7% (66.7–93.8%)	n = 47 1 (0, 5.5) 87.5% (54.5–100.0%)	−2.0% (−4.0% to 1.0%)	Yes

CI, confidence interval; *NA,* not available; *Q,* quartile; *UUI,* urgency urinary incontinence.

[a] Exact Mann–Whitney test used to account for skewed data with many tied values; [b] All within-group changes relative to baseline for exact test confidence intervals. Hodges–Lehmann estimate of differences between groups can differ from differences between group medians; [c] Median difference in % change = hypnotherapy % change − medication % change; [d] Lower bound (ie, smaller number of 95% CI) of difference in hypnotherapy % change − medication % change must be greater than −5% to meet the noninferiority criteria. For example, −6% for the lower bound would mean that hypnotherapy did not meet the noninferiority criteria; −4.9% would mean that hypnotherapy did meet the noninferiority criteria.

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