Can we harness the placebo effect to improve care in lower urinary tract dysfunction? ICI-RS 2019

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Abstract
The proposal “Can we harness the placebo effect to improve care in lower urinary tract dysfunction?” was discussed at the International Consultation on Incontinence-Research Society (ICI-RS) 2019 meeting. The placebo effect can change the treatment outcome whether the treatment is an active treatment or placebo. The total active treatment outcome is a combination of the placebo and the active treatment effect which is seen in placebo-controlled trials. The placebo effect plays an important role in the treatment of lower urinary tract dysfunction in overactive bladder, bladder pain syndrome, and stress urinary incontinence. In clinical practice, a number of factors can be employed to use the placebo effect to maximize its effect on patients receiving an active treatment, such as having the same environment for review such as the same appointment time, same room, and same clinician. Clinicians should also be aware of the nocebo effect which is increased with an overemphasis on side effects or negative outcomes.

KEYWORDS
bladder pain syndrome, clinical trials, lower urinary tract symptoms, overactive bladder, placebo, stress urinary incontinence

1 | INTRODUCTION

The proposal “Can we harness the placebo effect to improve care in lower urinary tract dysfunction?” was discussed at the International Consultation on Incontinence-Research Society (ICI-RS) 2019 meeting. Placebo is defined as “any therapy or component of therapy used for the nonspecific, psychological, or pathophysiological effect or that is used for a presumed effect or that is used for an presumed specific effect but is not that specific activity for the condition being treated. The opposite effect of a placebo is the nocebo effect which is a negative effect of a pharmacological or nonpharmacological treatment that is induced by patients’ expectations but is unrelated to the physiological action of the treatment.1,2

When assessing the outcomes of a trial (according to the Oxford Classification by the Centre for Evidence-Based Medicine), the lack of a placebo arm is considered detrimental to the strength of the study.

The placebo effect has long been debated, and in 1955, Beecher3 first suggested satisfactory placebo effects in 35% of 1082 patients in 15 clinical trials of therapies for different diseases including angina, motion sickness, and mood changes.

Generally, the placebo effect has a multifactorial etiology consisting of a personal belief in the treatment,
leading to a perception of improvement, the brain’s role in illness and recovery, a physiological or psychological response that a patient applies to the placebo. The regression to the mean, that is, the natural progression of the disease toward what is the mean value as well as “meaning” or “expectancy” attributed to a treatment. In addition, enthusiasm of the treating clinician, differences in size and color of placebo pills, frequency of treatment regimen or by the use of more invasive placebo. There is now evidence that placebos influence patient outcomes after any treatment. In addition to the natural history of disease and regression to the mean, placebo effects can even result in high rates of good outcomes. There is little to lose and much to gain by subjecting new treatments to the vigorous scrutiny of placebo. “Improvement” may be expected in up to 35% of placebo-treated patients. However, the ethics of placebo-controlled trials have been questioned especially where an effective treatment exists and in situations where delaying a treatment has been shown to result in disease or disease progression. Such trials may be ethically justified, provided that stringent criteria for protecting research subjects are fulfilled. Some authors express concerns with equivalence and noninferiority trials, claiming the inability to determine whether treatments are equally good or bad. There is a possibility that successive noninferiority trials can lead to a gradual decrease in treatment efficacy. Another concern is that there is always some degree of unblinding as a result of somatic or psychological side effects of the active treatment or a slight edge of the active treatment over placebo. Unblinding may occur early in a study, which reflects poor placebo or study design, or late in a study where unblinding could be the result of side-effect profile or drug efficacy. Blinding needs to be ascertained throughout a trial because failure to recognize unblinding represents a major source of bias. The use of placebo has been key in the assessment of the treatment for lower urinary tract dysfunction, as the placebo effect can be large. An active substance has a placebo effect in addition to the pharmacological or absolute effect of the treatment. This placebo effect can be increased or decreased by environmental and psychological factors, which will add or detract from the active effect of a treatment in practice. In clinical trials, placebos are used to determine the true pharmacological effect of a drug and there are many factors which increase or decrease the placebo effect such as regression to the mean, expectations, environmental factors, methodological factors, and natural course of the disease. The true placebo effect is the difference between the treatment effect and the effect of being in a no-treatment group and varies with the condition being treated.

2 PLACEBO EFFECT

The placebo effect can be altered by trial design, patients’ own beliefs about the treatment, as well as the selection and behavior of individuals in the studies. Inherently, the active treatment in any trial will have a placebo response. It has been reported that the factors leading to the placebo and nocebo are psychological or neurobiological, particularly in studies of the pain treatment. Key psychological factors appear to be anxiety, body focus, learning, memory, condition, expectations, and effects of others on the participants in the trial, such as clinicians or family members. Expectation is a key factor in the placebo effect where the patient’s own expectation of receiving a placebo can be altered by the chances of receiving a placebo by altering randomization ratios. In addition, the clinician can change patient expectations easily during the initial counseling. Therefore, the use of a new drug class may induce excitement in the investigator, and this can lead to a change in the patient’s perception of the active drug or expectation of receiving the active drug. These increased expectations of a medication can produce less adverse symptoms with improved patient well-being and increased adherence to the medication with a positive treatment outcome.

The placebo effect includes both neurobiological and psychological mechanisms. For pain, the placebo effects are accompanied by a reduction in neural activation in brain areas known to produce anxiety and pain. The magnitude of the reduction is proportional to the reduction in pain ratings. These effects on pain are reversed by naloxone, a µ-opioid antagonist. Conditioned responses can also lead to a placebo effect such as previous exposure to medication for the overactive bladder (OAB) leading to a placebo effect on urinary symptoms which may be similar to a patient’s previous experiences. This means that antecedent successful treatment leads to an increased placebo response and previous unsuccessful treatment response may reduce the patient’s placebo response, depending on the patient’s expectations of the new treatment. The combination of patient’s expectation and a conditioned response produces a large placebo response in pain studies. Placebo improvements and deterioration in urinary symptoms may also be due to the natural variation in disease severity or regression to the mean.

The placebo response varies according to the patient’s ability to learn, which has an impact on expectations. This means in studies of patients with Alzheimer’s disease and pain, deteriorating cognitive function leads to a reduced placebo and nocebo response. Placebo responses have also been positively related to intelligence quotient in intellectual disability.
Prescribing placebo relies on some degree of patient deception and is, therefore, not recommended without consent. However, informing a patient that an inactive placebo is given reduces its efficacy. This is called the “placebo paradox.” It may be considered unethical to deceive a patient by using a placebo, but the question remains as to whether clinicians should withhold a treatment that has the potential to heal.

3 | PLACEBO EFFECT IN OAB TREATMENT

The common reasons for a placebo effect in OAB are expectations of both patients and assessors, experimental design, a response to the additional attention, and concern afforded by trial protocols, the effect of bladder training resulting from the use of bladder diaries in OAB trials.

There are numerous studies that have investigated antimuscarinic agents for OAB, of which 62 included a placebo arm. A total number of 7810 patients received placebo in the 62 trials, of whom 17% were men.

Five commonly reported parameters from the placebo arm of the OAB clinical trials are incontinence episodes per day, micturition episodes per day, urgency episodes per day, mean volume per micturition, and maximum cystometric capacity.

The placebo effect produces reductions in incontinence episodes ranging from 32% to 65%. Whereas active drugs decrease incontinence episodes by 45% to 77% and symptom scores by 22% to 45%. Placebo responses are much lower when objective changes in mean voided volume (5%-6% placebo, 11%-22% active or peak flow rate are assessed). Stress urinary incontinence (SUI) is reduced by the placebo effect in 33% compared with the active drug effect of 53%. Nocturia episodes when comparing placebo and drug effects have been cited in the drug information for Nocdurna (desmopressin acetate) sublingual compared with placebo where a 58% had one void per night or less in the active arm compared with 45% in the placebo group.

It has been hypothesized that reduced fluid intake could partially be the cause of the placebo effect seen in OAB trials. Pooled analysis using patient-level data from 3011 patients and accounting for the studies within the models showed that all patients voided progressively less total urine per 24 hours during treatment than at baseline. However, reduction in total urine volume voided per 24 hours was larger in patients receiving placebo vs those on solifenacin. Hence, assuming volume voided is a good surrogate measure for fluid intake, it could be concluded that fluid restriction almost completely explains the reduction in micturition frequency in the placebo group. In contrast, patients receiving active treatment adopt more normal drinking patterns once they start to perceive improvement in their OAB symptoms.

There have been no published trials on the placebo effect of sacral neuromodulation as none of the studies have included a sham operation or stimulation. However, a protocol for a randomized, placebo-controlled, double-blind clinical trial investigating sacral neuromodulation for neurogenic lower urinary tract dysfunction was published.

A randomized, double-blind, controlled study on 20 children with OAB that were treated with tibial nerve stimulation included a sham arm which reported that placebo leads to statistically significant improvements in 4 out of 5 commonly reported OAB parameters in clinical trials of adults with OAB.

4 | BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

For many diseases, there are valid arguments against placebo-controlled trials including a gold standard treatment of accepted value. This is not the case for bladder pain syndrome/interstitial cystitis (BPS/IC) given that, to date, there is no consensus about a generally effective standard therapy for BPS/IC. Placebo double-blind studies are ideal in this disorder which is characterized by strong variations in its natural history, limited symptom severity progression over time, and close to zero mortality. However, unblinding is of specific concern in BPS/IC because primary outcomes may be subject to patient-specific psychological and physiological factors.

Surprisingly, only a few treatments for BPS/IC have been subjected to a placebo-controlled trial. In contrast, although many patients would probably volunteer having already tried frustrating therapies that will alter their expectations and placebo response, proof of efficacy may be difficult considering the spontaneous remission rate for BPS 11% to 50% when combined with placebo. Previously published placebo-controlled trials on sodium pentosan polysulfate, hyaluronic acid in differing concentrations, the vanilloid receptor 1 activator resiniferatoxin, or the opioid antagonist nalmefene have failed to establish efficacy. As a consequence, numerous pharmaceutical manufacturers have not pursued FDA approval in the United States for seemingly promising intravesical therapies. Several medications for BPS/IC, such as amitriptyline, hydroxyzine, cimetidine, heparin, and lidocaine are therefore currently used off-label. Most of these medications may not show any success if tested in the stringent manner of a placebo-controlled trial.
However, recent studies have assessed antibodies targeting various proteins which are thought to play a role in the development of BPS/IC within a placebo-controlled setting. Wang et al have randomized 31 BPS/IC patients to a placebo group and an intervention group applying fulranumab (9 mg), a human monoclonal antibody directed against nerve growth factor (NGF). As a primary efficacy endpoint, they defined the change from baseline to study endpoint in an average daily pain intensity score. The trial was terminated prematurely before reaching the target number of 70 patients because of concerns about rapidly progressing osteoarthritis or osteonecrosis in the fulranumab group.

Bosch et al performed a randomized, double-blind, placebo-controlled pilot study on 39 patients with refractory BPS/IC, comparing certolizumab, a fragment of a monoclonal antibody blocking specifically tumor necrosis factor-alpha (TNF-α), to placebo. The authors reported significant improvement in the certolizumab group compared with placebo at 18 weeks (global response assessment, \( P = .002 \)). However, the small sample size and the lack of a long-term follow-up within the margin of expected spontaneous disease remission represent strong limitations of this study.

In another phase III, randomized, double-blind, placebo-controlled study assessing an antibody against TNF-α, Bosch et al focused on adalimumab, including a total of 43 BPS/IC patients. The authors reported improvement after adalimumab was associated with no significant adverse events. However, adalimumab failed to demonstrate positive proof of concept compared with placebo.

In a further proof-of-concept study, the same authors concluded that improvement occurred because the patients were more conscientious about following physician’s advice and feeling less stressed while in the study. These are factors known to increase the placebo effect.

In summary, superiority of hyaluronic acid, TNF-antibodies, and NGF-antibodies over placebo could not be demonstrated in the current literature. More placebo-controlled trials about BPS/IC are needed which consider “unblinding” as a potential source of bias.

5 STRESS URINARY INCONTINENCE

SUI is primarily due to mechanical dysfunction of pelvic floor structures and subsequent urinary leakage when an increase in bladder pressures over urethral pressures in the absence of detrusor overactivity occurs. Its primary treatment includes either conservative methods such as pelvic floor muscle training (PFMT), drug therapy such as duloxetine or surgery (midurethral sling placement, Burch colposuspension, or bulking agents), there can be high success rates at follow-up. Placebo-controlled studies would involve sham procedures, such as a faked surgical intervention that omits the step thought to be therapeutically necessary.

Numerous alternative treatments for SUI have been tested in placebo-controlled trials. Yamanishi et al have assessed pelvic floor electrical stimulation. They found that maximum urethral closure pressure significantly increased \( (P = .0275) \) during stimulation, that patient impressions were good in 60% of the active group compared with only 8% in a dummy group \( (P = .0051) \). There were significant improvements in pad test results and a cure rate was higher in the active device group (45% vs 7.7%).

Jackson et al assessed estrogen supplementation in postmenopausal SUI patients and found no significant effect of estrogen over placebo for any subjective or objective clinical outcome measures after a 6-month therapy with estradiol.

In a review, Alhasso et al summarized the results of a total of 22 studies assessing adrenergic drugs for the treatment of urinary incontinence. The included substances were phenylpropanolamine, midodrine, norepinephrine, clenbuterol, terbutaline, eskornade, and Ro-115-1240. Eleven studies showed some crossover and there is limited evidence that drugs are better than placebo with regard to a reduction of SUI episodes and number of pad changes. Two small trials showed the superiority of drugs over PFMT with more withdrawals in the pelvic floor exercise group. In 4% of cases, adrenergic treatment was ceased due to insomnia, restlessness, and vasomotor stimulation.

Numerous placebo-controlled trials assessed the efficacy of duloxetine, a serotonin-norepinephrine reuptake inhibitor. Two phase II/III studies in the United States and one Canadian-European study including duloxetine doses ranging from 20 to 80 mg found a placebo effect of up to 41% compared with a duloxetine effect ranging from 50% to 64%. An Australian phase III study reported a greater median decrease in incontinence with duloxetine (54% vs 40%; \( P = .05 \)), significant improvements in quality of life (incontinence quality-of-life questionnaire [I-QOL] score increases of 10.3 vs 6.4; \( P = .007 \)) and increases in voiding intervals (20.4 vs 8.5 minutes; \( P < .001 \)). The placebo response was 10.7% and 12.5%, discontinuation rates were 1.7% vs 17.2%, mainly for nausea, dizziness, insomnia, and anxiety with duloxetine. Yalctin et al assessed the relationship between previous treatment experience and baseline SUI severity with the placebo response. The placebo response in women with SUI was variable with a reduction in incontinence episode frequency ranging between 27% and 40% for placebo. They also performed a secondary analysis, nearly 1000 women with SUI who received placebo during duloxetine trials and described the effects of previous treatment for SUI (both PFMT and continence surgery). They concluded that treatment naïvetiness and less severe incontinence are
associated with an increased placebo response in sham- and placebo-controlled groups, although this difference was statistically significant only for PFMT.52

In a post hoc analysis from a phase III study of a novel SUI therapy (SUCCESS Trial), Dmochowski et al pointed out that individual endpoints may not demonstrate a significant treatment effect as standalone SUI measures but may do so as components of a composite endpoint including the placebo effect.53

In summary, most previously described drug treatments for SUI are not more effective than placebo. However, duloxetine does appear to be effective. There are high rates of discontinuations due to side effects, particularly nausea and fatigue. In numerous studies, it is difficult to assess the component of the composite endpoint separately when including placebo effect. Only a few studies consider the effects of previous treatment for SUI.

5.1 | Genetic association with the placebo response

Anxiety is associated with BPS/IC54 as well as OAB.55 In the treatment of anxiety, patients with a serotonin gene-related polymorphism (tryptophan hydroxylase-2) have a significant placebo response to treatment for anxiety.56 It is not clear if the same polymorphism is associated with the placebo response in the treatment of the OAB.

The catechol-O-methyltransferase val158-met polymorphism is a G to A mutation causing an amino acid change at codon 158 in a transmembrane enzyme.57 This mutation has been found to be associated with the placebo response in irritable bowel syndrome (IBS) treatment.58 IBS is found in 50% of women with OAB59 and this mutation may be associated with the placebo response in the OAB.

5.2 | Increasing the placebo response

Increasing the placebo response is applicable to the use of an active substance. This means that the placebo effect can be useful in daily practice to improve the effect of all active treatments including conservative, surgical, and pharmacological treatments for lower urinary tract dysfunction. A number of strategies have been proposed to increase the placebo effect such as screening out individuals who have negative attitudes that can occur in clinical practice when discussing the options of surgical treatments and specifically avoiding a superior efficacious treatment which has increased adverse outcomes. An example would be fascial sling surgery, which has an increased rate of voiding difficulty and intermittent self-catheterization may not be encouraged for women with certain personality traits. This may be the subconscious thoughts behind the “appropriate selection of patients for invasive treatments” and the reason why it is difficult to predict outcome.60 Other factors that can increase the placebo response including reduce anxiety or have contact with successfully treated patients.15 The environment can increase the placebo response such as a good doctor-patient relationship, more patient contact time, explaining the treatment plan in detail, keeping the time, room, and other sensory clues constant.

5.3 | Using placebo to improve care

Placebos are prescribed by 17% to 80% of doctors in routine clinical practice.61-67 Improving expectations plays a key role in increasing the placebo response for many treatments.15 Unfortunately, there are ethical issues in prescribing placebos68,69 and this leads to difficulty with consent and autonomy, if the patient is not informed that a placebo has been or may have been

| TABLE 1 | Maximizing the placebo effect (Ench et al15) |
|---------------------------------|-------------------------------------------------|
| Managing expectations                  | Conditioning                                      |
| Screen out patients with negative outlook | Reduced chance of having a placebo in randomization |
| Hidden applications when discontinuing a drug expected to cause withdrawal symptoms | Use salient stimuli and constant context when administering treatment including sensorial cues, same room, and time of day when giving treatment |
| Promote social contact with successful patients | Use effective pretreatments |
| Reduce anxiety of the patient        | Avoid stopping long-term treatments |
|                                      | Motivation strategies |
|                                      | Having a good physician-patient relationship |
|                                      | Empathic style, more time of contact of the health care professional |
|                                      | Describe the treatment in detail to improve attention |
prescribed. However, by prescribing an active treatment and then optimizing all the factors which lead to a maximized placebo response, patients in clinical practice could have the optimal response. These are summarized in Table 1.

It is also important to minimize the nocebo response as this impacts the benefit from a treatment. Conditioned responses can lead to a nocebo, such as a dry mouth in a patient previously exposed to an anticholinergic which increases the expectation of a dry mouth with other OAB medications. The effect of nocebo has been reported in pain studies and these need to be minimized to optimize treatment effect.

6 | CONCLUSION

The placebo effect can substantially alter treatment outcome whether the treatment is active or placebo. It can be argued that the total active treatment outcome is a combination of the placebo and the active treatment effect, which is seen in placebo-controlled trials. In clinical practice, a number of factors can be employed to use the placebo effect to maximize its effect on patients receiving active treatment, such as having the same environment for reviews such as the same appointment time, same room, and same clinician. Clinicians should also be aware of the nocebo effect which is increased with an overemphasis on side effects or negative outcomes.

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