The placebo and nocebo effects in functional urology

Hadi Mostafaei[1,2], *Sandra Jilch*[1], *Greta Lisa Carlin*[1], *Keiichiro Mori*[1,3], *Fahad Quhal*[1,4], *Benjamin Pradere*[1], *Ekaterina Laukhtina*[1,5], *Victor M. Schuettfort*[1,6], *Abdulmajeed Aydh*[1,7], *Reza Sari Motlagh*[1,8], *Claus G. Roehrborn*[9], *Shahrokh F. Shariat*[1,5,9,10,11,12,13,14] ✉ *and Sakineh Hajebrahimi*[2]

Abstract | A placebo is an inert substance normally used in clinical trials for comparison with an active substance. However, a placebo has been shown to have an effect on its own; commonly known as the placebo effect. A placebo is an essential component in the design of conclusive clinical trials but has itself become the focus of intense research. The placebo effect is partly the result of positive expectations of the recipient on the state of health. Conversely, a nocebo effect is when negative expectations from a substance lead to poor treatment outcomes and/or adverse events. Randomized controlled trials in functional urology have demonstrated the importance of the placebo and nocebo effects across different diseases such as overactive bladder, urinary incontinence, lower urinary tract symptoms and interstitial cystitis/painful bladder syndrome, as well as male and female sexual dysfunction. Understanding the true nature of the placebo–nocebo complex and the scope of its effect in functional urology could help urologists to maximize the positive effects of this phenomenon while minimizing its potentially negative effects.

Regression to the mean
Regression to the mean is a statistical term that indicates that if a variable from a population is extreme in the first measure it is likely that it will move to the mean (become less extreme) in the next measure.

Natural history
The natural history of a disease is the course of a disease from the beginning to resolution.

Symptom fluctuations
Symptom fluctuations are defined as a constantly changing symptom presentation between one level or another.

A placebo is a substance that looks like medical treatment but is not one as it does not have active ingredients that affect health[1]. The placebo effect is the therapeutic effect of a placebo[2] and is caused in part by the patients' positive expectations of the effect of treatment on their health[3]. The term 'placebo', which means "I shall please" in Latin, was first used to describe an ineffective intervention in the eighteenth century[4]. However, a placebo has been shown to be more than an inert treatment as it has an effect of its own[5]. Indeed, the placebo effect is more than positive thinking and/or believing a treatment or procedure will work. Symptoms of disease that are perceived by the brain, such as perception of pain and discomfort, are the main manifestations that are affected[3,6]. This effect is different from regression to the mean, natural history and symptom fluctuations[7,8]. The placebo effect has been shown to be difficult and variable in its presentation[9]. In clinical trials, researchers use placebos to help understand what effect a new drug or treatment has on a particular condition[10]. A reaction to placebo is not proof that the comparator (the treatment) does not work, but rather that another non-pharmacological mechanism might be present[9].

How a placebo works is still not understood, but it involves a complex neurobiological reaction that includes neurotransmitters, such as endorphins and dopamine, in certain brain regions linked to mood, emotions and self-awareness[5]. For instance, in a study on chronic pain, placebo responders had a higher concentration of endorphins in the cerebrospinal fluid than placebo non-responders[11]. In a another study in patients with Parkinson disease, the positive expectations of motor improvement in patients who received a placebo led to the activation of endogenous dopamine release in the striatum[12]. Thus, researchers recommend including a so-called no treatment arm in clinical trials, when possible, to differentiate between the random changes and the true placebo, which is presented as a 'sugar pill'[3,8,13]; however, blinding of patients is not possible in this scenario and response bias might occur as patients know that they are not receiving any medication[13]. The same problem can be observed owing to unblinded examiners[13,14].

The placebo effect has a great influence on functional ailments, including functional urological disorders. In uro-oncological conditions or objective outcomes such as biochemical tests and urodynamic data, the effect of placebos is uncertain[15,16]; however, in functional urology, patient-reported or subjective symptoms of the disease are remarkably improved by placebos[17,18]. Conversely, evidence shows that knowledge and expectations of having adverse events from a treatment can cause or facilitate them[19] — this phenomenon is called the nocebo effect[20]. The nocebo effect is a natural part of every clinical trial as the patients become aware of the

✉*e-mail: shahrokh.shariat@meduniwien.ac.at*

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Key points

- Placebo and nocebo effects have major roles in functional urological ailments.
- The mechanisms by which the placebo and nocebo effects function are not fully understood.
- The pontine micturition centre might be affected by positive and negative expectations through a cascade of events resulting in improvement or worsening of functional urological symptoms.
- Clinicians need to consider the placebo and nocebo phenomena when managing a patient with a functional urological ailment.
- Clinicians should be trained regarding the placebo and nocebo effects with the aim of maximizing the benefits of the placebo effect and minimizing the harms of the nocebo effect.
- An individualized approach and shared decision-making should be performed when dealing with placebo and nocebo effects, as each individual has different perceptions with regard to placebo and nocebo phenomena.

possible adverse events owing to the informed consent gained before the study[21]. Thus, understanding, assessing and using the placebo and nocebo effects are a challenge for health-care workers.

In this Review, we describe and discuss the placebo and nocebo effects in selected benign urological diseases, such as overactive bladder syndrome (OAB), stress urinary incontinence (SUI), female sexual dysfunction (FSD), erectile dysfunction (ED), interstitial cystitis/painful bladder syndrome (IC/BPS) and male lower urinary tract symptoms (LUTS).

Mechanisms of the placebo and nocebo effects

A common belief is that the placebo effect is caused by expectation — if one expects an effect from a drug, the biochemical mechanisms of the body might react to cause a similar effect to that of the drug[22]. The fact that the placebo effect is linked to expectation does not make it imaginary — evidence has shown that actual physical changes occur during placebo treatment[5]. For example, some studies have documented an increase in the body's production of endorphins[23,24]. A similar observation has been made for negative effects (that is, the nocebo effect). The observation that placebos can also cause harmful effects is currently called the nocebo effect and was first reported in 1955 (REF.[19]). In addition, when patients expect to experience adverse effects such as nausea and headache, these manifestations are more likely to happen[25]. The adverse effects that are experienced with placebo (the nocebo response) can be very similar to those observed in patients who receive active treatment, showing that the expectation of having an adverse event can lead to experiencing such adverse events even when no active treatment is received[26]. For example, in placebo arms of randomized controlled trials (RCTs) on medical treatment of OAB, 4.9% and 2.6% of patients experienced dry mouth and constipation, respectively, which were also the most common adverse events in the active treatment arms[25]. The placebo and nocebo effects are unpredictable and hard to measure even in the most efficiently conducted trials. The results of a Cochrane collaboration analysis of the placebo effect in various medical conditions showed that the most commonly reported placebo effects were those of improvement of pain (standardized mean difference (SMD) −0.28 (95% CI −0.36 to −0.19) and nausea (SMD −0.25 (−0.46 to −0.04))[27]. However, nocebo response was not evaluated in this study. Measuring the effect of the placebo and its extent is difficult owing to confounding factors[28]; for example, a patient might feel better after taking a placebo owing to regression to the mean, natural recovery or a change in symptoms[2,29]. Differentiating between the placebo effect and the effects of response bias, observer bias and changes in the outcomes are also difficult owing to methodological problems[30,31].

A number of explanations have been given for the placebo effect phenomenon[32,33]. The first is that after receiving drug treatment, patients assign all their improvements solely to the effects of that treatment[34]. For instance, if a patient uses medication for a condition and that condition improves, then that patient might assume that the effects were attributable to that medication. However, the patient's condition might have improved in its natural course without the use of medication, and the medication was designed only to increase the placebo effect. Thus, a self-limited illness could be the subject of medicalization and iatrogenic harm[34]. Second, the advice and suggestions provided by health practitioners can be argued to be damaging in some ways[35]. For example, if a practitioner provides unrealistic advice regarding drug-related adverse events, then the nocebo effect and, therefore, adverse events, could occur, which can broadly be an influencing factor for health anxiety[34,36]. The procedure of obtaining informed consent is the third triggering event that should be considered by caregivers; caregivers should provide good advice without exaggerating the minimum possible adverse events[37,38]. Some patients never read the list of adverse effects on the drug label and others read it every time; the ones who read it every time are the most vulnerable to the adverse effects and anxiety, which is a factor in the nocebo effect[34]. Thus, in this instance, adverse events during treatment cannot be assigned to the drug effect. In addition, in the Women's Health Initiative study of hormone replacement therapy for the

Author addresses

[1]Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria.
[2]Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
[3]Department of Urology, The Jikei University School of Medicine, Tokyo, Japan.
[4]King Fahad Specialist Hospital-Dammam, Dammam, Saudi Arabia.
[5]Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia.
[6]Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
[7]King Faisal Medical City, Abha, Saudi Arabia.
[8]Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[9]Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA.
[10]Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic.
[11]Department of Urology, Weill Cornell Medical College, New York, NY, USA.
[12]Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria.
[13]Hourani Center for Applied Scientific Research, Al-Ahliyya Amman University, Amman, Jordan.
[14]European Association of Urology research foundation, Arnhem, Netherlands.

treatment of menopausal symptoms, in an average of 5.7 years, 40% of those in the placebo arm compared with 63% of those in the treatment arm experienced withdrawal symptoms[39]. Thus, the nocebo effect might be the reason for withdrawal symptoms in patients who did not receive an active treatment.

To understand the concepts of the placebo and nocebo effects, differentiating the placebo and nocebo effects and the placebo and nocebo responses is important. The placebo effect and the nocebo effect are the mechanisms by which the effect is acting. In other words, the effects that are only attributable to the placebo and nocebo. The placebo response and the nocebo response in broad terms refer to all the changes that occur in a patient receiving an inert medication, including placebo effect, nocebo effect, regression to the mean, natural history and false positives[7]. Although several explanations exist for placebo and nocebo effects, expectation, including classical conditioning, is more extensively studied and supported by the literature[40–46]. These effects are induced by complex neuro-bio-behavioural mechanisms[47].

Expectations of the patient. In the clinical setting, the expectations of a patient refer to what they can encounter during a consultation and the mental picture that patients have of the outcomes of their medical interventions[48]. The patient should be the focus during the management of their illness, meaning that they should be provided with complete information about the treatment effects and adverse events to encourage trust in their physician and to assure them that they will receive quality health care. Determining the best way to secure informed consent for intervention is crucial. For example, when the clinician provides patients with realistically positive expectations instead of highlighting information about the possible harms, the positive results could be increased and the nocebo effect reduced[37,48]. However, a history of failed interventions could lead to negative expectations from new interventions[45,49]. Thus, many investigators prefer to choose participants without any negative treatment history for inclusion in trials[50], but this preference might harm the representativeness of the trial. Such restricted target populations lead to biases, such as selection bias. For example, in most trials, older individuals with comorbidities and co-prescriptions are excluded[51]. In a trial in which treatment of social anxiety disorder was investigated, both arms received a selective serotonin reuptake inhibitor (SSRI); however, one of the arms received SSRI with a normal label whereas the other group received an SSRI without a label and were deceptively told that they had received an active placebo. Active placebos commonly refer to control group interventions that have the adverse effects of the experimental interventions in RCTs and are used to reduce the risks of unblinding and nocebo effects[52]. Thus, the latter group was told that this medication would have no benefit in improving the treatment outcomes, although adverse events might occur[53]. Telling patients they were being treated with an SSRI doubled its effectiveness according to a continuous measure of anxiety, and tripled the response rate compared with the other group, who were told that they would only receive an active placebo[53]. Interestingly, overt administration of analgesics is more effective than non-overt administration[54], highlighting the possible additive effect of expectations in the efficacy of analgesics[54]. This observation indicates how expectations shape the way in which the body reacts to a certain medication.

Patients can have different expectations about treatment owing to their treatment history, socioeconomic levels and comorbidities[55]. In daily practice, some patients expect to be totally cured after any intervention, meaning that, for example, even minor urine leakage after incontinence surgery could be considered a negative result by these patients. In addition, many patients think that SUI or ED is part of the natural ageing process[56]. Some patients are more prone to nocebo effects and could even relate the slightest changes in their health status to adverse events (whether specific or non-specific) caused by the received treatment[49]. Thus, the placebo and nocebo effects could have a strong behavioural component in functional urological ailments. Most RCTs in functional urology have assessed outcomes by using bladder diaries, which might increase patients' awareness of their voiding behaviour. In addition, interactions between clinicians and patients can have a potential influence on their expectations. Interactions in which the clinician does not convey a message of empathy, acceptance and understanding to the patient can lead to the nocebo effect[57,58]. Patients with negative expectations should be screened before treatment and undergo an expectation modification process[59]. Physicians can also promote social learning by encouraging the patients to meet other patients who have had previous positive experiences from the same medication to modify patient expectations[60]. Patients can talk with the other patients with positive experiences or watch videos of them describing their experiences[59]. This will increase the positive expectations of patients, improving the placebo effect (FIG. 1). A similar effect can be observed regarding negative expectations. For example, among 107 patients with benign prostatic hyperplasia (BPH) treated with finasteride, the rate of sexual dysfunction was threefold higher in patients who were informed about the potential adverse events of finasteride than those who were not ($P = 0.03$)[61]. When patients are informed about the chance of experiencing adverse events such as ED, decreased libido or ejaculation problems, the patient expects to have these adverse events. This false-positive response might occur because of the patient's expectations, history of previous unsuccessful treatments, or conditions such as depression and anxiety[62]. Thus, a realistic consultation could have an important role in managing patients' expectations.

Avicenna, one of the most important physicians of the Islamic golden age, stated, "Often the confidence of the patient in his physician does more for the cure of his disease than the physician with all his remedies"[63]. The balance of the influence might have changed owing to advances in effective therapeutics for many diseases, but this observation still holds true today. Expectations of the patients still have a major role in improving the treatment outcomes (placebo effect) and/or increasing the adverse events (nocebo effect).

Classical conditioning
Classical conditioning is a behavioural process in which an unconditioned stimulus (such as food) is paired with a conditioned stimulus (such as a bell).

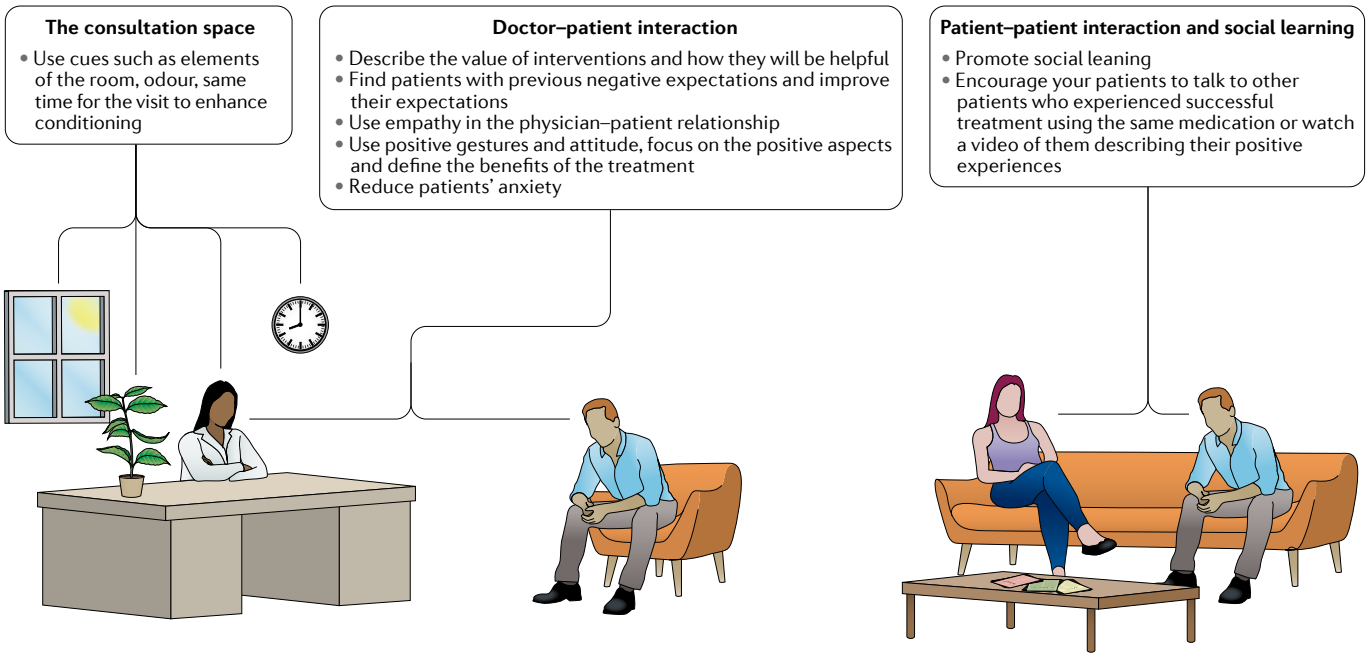

Fig. 1 | **Methods to harness the placebo effect in daily practice based on a model by Enck and colleagues[59].** The patients refer to the doctor's clinic with previous positive or negative expectations. This figure depicts a summary of the steps that the doctor should take to maximize the placebo effect and minimize the nocebo effect. The consultation space: doctors can use elements of the consultation room, the same visiting time, odours and colours as cues to promote conditioning. Doctor–patient interaction: doctors should identify patients who are prone to experiencing the nocebo effect and modify their expectations. Doctors should use positive gestures, focusing on the positive aspects of the treatment and they should convey the message of understanding and empathy. Doctors should calm the patient and reduce their anxiety. Doctors should describe the value of the intervention and the treatment to the patients and focus on its positive aspects. Patient–patient interaction and social learning: patients should be encouraged to talk to other patients who have had similar experiences with positive outcomes or watch a video of them describing their positive experiences.

Conditioning. Early studies on the placebo effect independently addressed classical conditioning as a contributing mechanism to the placebo effect[64,65]. These studies were published just 2 years after Beecher's seminal paper that attracted attention to the scientific evaluation of the placebo effect[19]. The idea was supported by previous studies on the use of drugs as unconditioned stimuli to reach a conditioned response in laboratory animals[66]. In one study, the role of conditioning in placebo response in humans was investigated[67]. Glyceryl trinitrate was given to three women and a minimum increase of 15 beats per minute was considered to be an unconditioned response. In the process of conditioning a placebo was given to the patients. In two of three patients, the heart rate noticeably increased but in the other patient a much smaller change occurred. The latter patient then admitted that she knew she was receiving a placebo[67]. They reported classical conditioning as the main mechanism of the placebo response, but expectancy was one of the major components of their findings[68]. One hypothesis presented by Kirsch[69] suggests that expectancies mediate classical conditioning, in other words, classical conditioning is just another way by which expectancies lead to placebo effects[69]. In a 1988 study, the role of response expectancy in receiving placebo caffeine was explored. In a sample of 31 men and 69 women, one group of the participants was deceptively told that they would receive caffeinated coffee, the other group was told that they would either get a caffeinated or a non-caffeinated coffee (double-blinded administration) and the last group did not receive any coffee. The deceived group had a significantly higher increase in the pulse rate than the double-blinded administration group ($P < 0.05$)[70]. In the double-blind administration group, the change was in the other direction, meaning that only the deceived group experienced changes in the direction of the desired outcome[70]. This finding highlights the role of expectancies in placebo response. Hence, in this circumstance, conditioning occurs in a conscious state and is mediated by expectations[46]. By contrast, Bąbel[46] argued that conditioning can also occur without a conscious stimulus (that is, hidden conditioning)[46]. In hidden conditioning, unlike open conditioning, the participants are not aware of the relationship between placebo (that is, conditioned stimulus) and the active drug (that is, unconditioned stimulus)[46]. In one study, the effects of open versus hidden conditioning in placebo analgesia were compared[71]. In this study, 90 volunteers were randomly assigned to three groups (open conditioning, hidden conditioning and control) to receive painful stimuli after a cue (orange or blue light). In the conditioning phase, in both the hidden and open conditioning groups, one of the colours was coupled with a painful stimulus (control stimulus) and the other with a non-painful stimulus (conditioned stimulus). However, only in the open conditioning group were the patients informed regarding

Hidden conditioning
Hidden conditioning is when the process of classical conditioning proceeds without the target individual noticing.

Open conditioning
Open conditioning is when the target of conditioning is aware of the process of classical conditioning.

this connection. In the control group, both colours were coupled with painful stimuli. In the testing phase, both of the lights were associated with painful stimuli. The evaluated outcomes were pain intensity, the expectancy of pain intensity, fear and fear of pain. Placebo analgesia only occurred in the hidden conditioning group[71]. In a similar study, 42 volunteers were randomly assigned to three groups (placebo, nocebo and control) to receive a cue (orange or blue light) followed by a painful stimulus. In a hidden conditioning procedure, one light was associated with a moderate-intensity painful stimulus (control stimulus) and the other colour was associated with a non-painful stimulus (placebo group) and a high-intensity stimulus (nocebo group). Both lights in the control group were coupled with a moderate-intensity painful stimulus. In the testing phase, both colours were coupled with a moderate-intensity painful stimulus. A significant analgesic effect in the placebo group ($P < 0.001$) and a hyperalgesic effect in the nocebo group ($P < 0.001$) was observed[72]. Thus, although expectations have a major role in mediating conditioning, conditioning itself can be a distinct mechanism of placebo and nocebo effects[46]. Despite the advances in the field of conditioning research, most of the studies are focused on placebo and nocebo effects in pain[46]; more studies are needed to elucidate the role of classical conditioning in other aspects of the placebo and nocebo effects.

Placebo and nocebo effects as neurophysiological responses. Interventional studies have shown that placebos can have observable biological effects, especially when enhanced through psychophysiological mediators such as conditioning and expectation management[73]. Anticipation of pain could also have a role in the changes observed on functional magnetic resonance imaging (fMRI) of the brain and electroencephalography. In one trial, the possible role of placebo in alleviating pain in 24 patients receiving an electric shock in their right wrist was evaluated[74]. The study was done in 5 blocks of 15 trials, each trial lasting about 30 s beginning with a 3-s warning cue indicating whether the patient would receive an intense shock (red spiral icon) or mild shock (blue spiral icon). After a 3- to 12-s anticipation phase, 6 s of mild or intense shock was administered. The patients were then asked to rate the intensity of shock on a ten-point scale (1: just painful to 10: unbearable pain) and a 3-s to 12-s rest phase followed. In the first block of the trial, shocks were given to the patients without any medication. In this phase, the examiner applied an inert skin cream to the right wrist. In blocks 2 and 3, half of the patients were told that this cream could alleviate pain (placebo condition). After the completion of blocks 2 and 3, the cream was removed and the same cream was applied. This time, patients were told that it was an ineffective cream used as a control (control condition). For the other half of the patients, the control and the placebo condition were reversed. fMRI studies were performed across the whole process beginning from the cue to the shock. A significant reduction in the activity of pain-related areas of the brain on fMRI after the administration of the placebo ($P < 0.005$) together with significantly reduced patient-reported pain ($P < 0.05$) in the participants who received placebo were observed[74].

A meta-analysis of brain imaging studies illustrated that placebo analgesia might increase activity in the left anterior cingulate, right precentral cortex, lateral prefrontal cortex and left periaqueductal grey (PAG) matter[75]. These regions are likely to be involved in a pain inhibitory system that inhibits the brain regions that have roles in the processing of pain[76]. Placebo analgesia in pain, to certain degrees, is mediated by endogenous opioid release, which can also reduce the nociception at the spinal cord. Spinal afferent inhibitions might have this role throughout the pain matrix; but, such reductions might be involved only in a few regions[74]. The prefrontal cortex has a central role in the micturition permission phase in humans[77]; thus, these observations could help to explain the strong role of placebos in expected outcomes and adverse events in functional urological disorders as the prefrontal cortex is involved in pain perception[78,79]. When the bladder is full, sacral chords receive a message from the A-d fibres in the bladder and send this message to the PAG. The PAG then excites the pontine micturition centre (PMC), which induces micturition through the sacral pathway[80]. However, the prefrontal cortex and the limbic system could interact with this function through their pathways to the PAG, which probably has control over the PMC[81]. Several cortical structures, such as medial and lateral prefrontal cortex and insula, in the brain have projections to the PAG; thus, the PAG can be influenced by serotoninergic, dopaminergic and noradrenergic pathways. Positive or negative expectations that are processed in higher brain centres (such as the prefrontal cortex), could interrupt or initiate the micturition process through the PAG, resulting in placebo and nocebo effects (FIG. 2).

The placebo effect is well reported in some neurogenic disorders such as pain, Parkinson disease, anxiety and depression. These disorders are related to the function of certain neuropeptides and/or neurotransmitters in the central nervous system[82]. Nicotinic, muscarinic and β-adrenergic receptors in the lower urinary tract system can be modulated by a number of neurotransmitters such as glutamic acid, enkephalin, glycine, 5-hydroxytryptamine and γ-aminobutyric acid[82]. Thus, the placebo effect observed in neurogenic disorders might be related to neurotransmitter modulation, in a similar manner, the placebo effect might occur owing to neurotransmitter modulation in neural pathways of the lower urinary tract. Thus, the role of neurotransmitters can partially explain the important effect of placebos in LUTS and OAB[82]. Additionally, the central dopaminergic pathway can modulate the micturition cycle[83]. The role of the dopaminergic pathway in the placebo effect has been established in Parkinson disease, as positron emission tomography studies have shown considerable endogenous release of dopamine in the striatum of patients with Parkinson disease in response to placebo (a saline injection)[84]. In some patients with Parkinson disease, dopaminergic medication can improve their lower urinary tract storage symptoms, suggesting that placebo-induced dopaminergic activity in the central nervous system might also have a role in improving LUTS[85].

Placebo administration can activate the endogenic opioid network. Enkephalin (an endogenous opioid)-containing nerve terminals are present in the sacral parasympathetic nuclei, pontine micturition centre and Onuf nucleus in the spinal cord, which all have important roles in micturition control[83]. The release of endogenous opioids in response to placebo administration might have a remarkable effect in the treatment of LUTS[83]. Furthermore, cannabinoid systems can be activated in conjunction with the opioid network. Interestingly, neurotransmitter studies indicated that the release of endogenous opioids with coactivation of cannabinoid systems might mediate placebo-driven analgesic effects[86–89]. The presence of cannabinoid CB_1 receptors in the rodent bladder has been demonstrated[90] and the results of the Cannabinoids in Multiple Sclerosis study, a randomized, controlled, multicentre trial, has indicated the possibility of the presence of cannabinoid receptors in the urothelium and detrusor muscle[91]. Results of an isolated bladder strip study suggested that these receptors are located in the prejunctional neuron. These studies indicate a possible role of cannabinoid receptors in the process of micturition. Thus, a placebo response similar to the one to opioids can be expected in the case of the cannabinoid system. However, the data in this regard are scarce. Most studies on placebo effects have involved healthy volunteers with experimental or acute pain. With chronic pain, such as that occurring with irritable bowel syndrome, migraine, low back pain, and BPS, the same expectations, emotions and brain structures are involved; however, previous studies could not specifically elucidate the role of neurotransmitters in the placebo effect[92].

The neurobiological mechanism of the nocebo effect is less well investigated than the placebo effect. In addition to the role of the endogenic opioids in analgesic or hyperalgesic reactions in pain, evidence shows that modulation of anxiety and hyperalgesia by the cholecystokininergic (CCKnergic) system is considered a mechanism of the nocebo effect[93]. In one study, post-operative patients with mild pain were told that they would receive a medication that would increase their pain for 30 min. Patients were asked to report the pain intensity on a scale of 0 (no pain) to 10 (unbearable) pain before the injection and 30 min after the injection. All the outcomes were compared with a group that had received hidden saline and no instructions regarding pain increase (the no treatment group). In the group that were told that they would receive medication, a nocebo effect was observed as the patients reported an increase in pain compared with the no treatment group ($P < 0.005$). However, in the groups that received 0.5 or 5 mg proglumide (a cholecystokinin antagonist) injection, the nocebo effect was blocked. Administration of naloxone had no effect on the blockade of nocebo effect, which was induced by proglumide, meaning that the opioid system was not involved in the cholecystokininergic mechanism of nocebo hyperalgesia[94].

In summary, several neurobiological mechanisms have been reported for placebo and nocebo effects. Neurotransmitter signalling, the dopaminergic pathway, endogenic opioid activation, cannabinoid systems and the CCKnergic system can have a role in placebo and nocebo effects in general and in functional urological ailments.

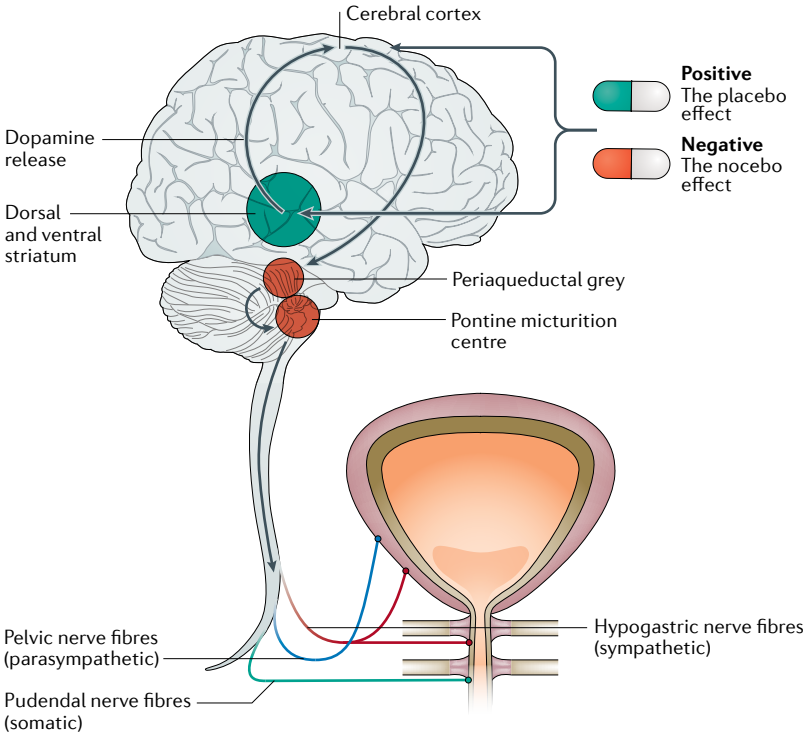

Fig. 2 | **The placebo effect as a psychophysiological response.** Brain imaging studies show that placebo analgesia might increase activity in the left anterior cingulate, right precentral cortex and lateral prefrontal cortex, as well as reducing nociception at the spinal cord. The prefrontal cortex has a central role in the micturition permission phase in humans; thus, these observations could help to explain the strong role of placebos in expected outcomes in functional urological disorders. In the micturition process, the brain cortex sends this message through its arrays to the periaqueductal grey (PAG). The PAG then excites the pontine micturition centre (PMC), which induces micturition through the sacral pathway. The positive or negative expectations that are processed in higher brain centres (such as the prefrontal cortex), could interrupt or initiate the micturition process through PAG, resulting in placebo and nocebo effects. The central dopaminergic pathway can modulate the micturition cycle. In some patients with Parkinson disease, dopaminergic medication can improve their lower urinary tract storage symptoms. The expectation of motor improvement can result in activation of endogenous dopamine release in these patients meaning that placebo-induced dopaminergic activity in the central nervous system might also have a role in improving lower urinary tract symptoms.

Regression to the mean. Regression to the mean is one of the oldest statistical concepts, first described by Galton[95], who said that every statistical measurement is prone to random error and natural variations in repeated measurements might look like actual change[29]. In clinical trials, regression to the mean is when trial participants show improvement regardless of what the clinician does[96]; this improvement can probably be explained by the phenomenon of natural intraindividual variability and random error[29,96].

In one study, the effect of inclusion criteria-based censoring of patients during screening for BPH treatment trials on the outcome of subsequent tests was investigated[96]. In total, 145 men without known prostatic diseases aged between 23 and 85 years were enrolled in a trial. In the first test, all participants filled in the

American Urological Association (AUA) Symptom Index (SI), BPH Impact Index as well as the Quality of Life (QOL) questionnaires, and the urine flow rate was recorded. After 2 weeks, in the second test, all questionnaires were re-evaluated without any health-care interventions. Taking into account the typical BPH trial inclusion and/or exclusion criteria, the patients who were not qualified were censored in a stepwise manner considering multiple thresholds from the analysis. The first tests and the second tests were compared using a *t* test. Censoring the patients resulted in considerably improved scores on the questionnaires and even the flow rate was improved. Increasingly strict inclusion criteria increased the improvement in outcomes. Mean differences between the first and second tests ranged from 1.4 to 1.7 ml/s for the peak flow rate ($P = 0.002$), from −1.0 to −1.4 for the AUA SI, and from −0.4 to −0.8 for the BPH Impact Index (95% CI −2 to 0.08)[96].

The conclusion drawn from this study was that censoring a group of patients based on inclusion and exclusion criteria for the treatment of BPH could induce a regression-to-the-mean phenomenon, resulting in artificial improvement in outcome parameters. However, this cannot be caused by the placebo effect itself, because patients did not receive any medical advice or consultations; thus, it can be counted as a part of the overall placebo response. A meta-analysis of the placebo effect in LUTS showed a 32–65% reduction in incontinence episodes[58]. However, the observed changes were reduced (9–34%) when prostate or urinary incontinence symptom scores were applied. Furthermore, incontinence episodes experienced by active treatment groups were reduced by 45–77% and symptom scores were reduced by 22–45% when related questionnaires were applied. The placebo response was dramatically low when objective changes in the voided volume or Q_{max} were measured[58]. The voided volume per micturition (recorded in a bladder diary) increased 5–6% in the placebo group but 10–22% in the active treatment group. For objective outcomes, conditioning and expectation might not have an effective role and the placebo response might be a result of regression to the mean and the natural history of the diseases. The placebo effect has been widely reported in trials on different diseases and conditions, but some studies have indicated that the placebo effect is different from the placebo response[13], meaning that the placebo itself does not seem to have a major role in the improvement of patient outcomes and regression to the mean and conditioning might have the main roles.

The natural history of the condition or disease and regression to the mean are also a part of the placebo response observed in the placebo arm of clinical trials. Thus, determining the actual magnitude of the placebo effect involves subtracting the effect of regression to the mean and natural history from the total placebo response. Several strategies, such as the classification of patient characteristics and disease severity, increasing the sample size, and adding no-treatment groups or co-interventions can reduce the effect attributable to regression to the mean and natural history of the disease and improve the estimate of the true placebo effect[13]. This phenomenon might not be relevant for the nocebo response; however, factors such as observations and social interactions can influence the overall nocebo response. In order to calculate the nocebo effect in clinical trials, comparing the placebo arm, in which the participants have received information regarding possible drug-related adverse events, with a no-treatment arm that has received the same information is necessary and can be achieved by subtracting the number of adverse events observed in the no-treatment arm from the adverse events observed in the placebo arm.

The placebo effect in urological disorders

Functional urology is a part of urological practice that deals with functional disorders of the lower urinary tract. LUTS have many diagnostic terms, such as BPH, IC/BPS and OAB. These functional disorders could be caused by conditions such as spina bifida, spinal cord injury (SCI), pelvic organ prolapse and urethral strictures. LUTS are the reason why most patients consult a functional urologist. LUTS are categorized as storage, voiding and/or postmicturition in nature, but various clinical labels are available to categorize a patient's problem and these often affect the initial intervention. Results of RCTs assessing medications for functional urological disorders have shown considerable placebo responses. Improved definition, assessments and insight into the true needs of the patient are needed[97].

Overactive bladder syndrome. OAB is defined by the International Continence Society as "urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence (OAB-wet) or without (OAB-dry), in the absence of urinary tract infection or other detectable diseases"[98]. This condition is prevalent (with an overall prevalence ranging from 11.8% to 35.6%)[99–102] and greatly affects patients' QOL[103]. In a prevalence study involving 16,776 patients, 65% reported that OAB negatively affected their QOL[102]. OAB symptoms are mainly caused by overactivity of the detrusor muscle during the filling phase of the urinary bladder[98]. The consequent detrusor muscle contractions are induced by acetylcholine-based stimulation of the muscarinic receptors[104]. The management of patients with OAB is initially behavioural therapy. If patients do not respond to behavioural therapy, medical therapy is given[105]. For the patients with refractory symptoms, switching the drug class or combination therapy is recommended[105]. If these strategies fail, patients might benefit from intravesical botulinum toxin injection or neuromodulation[105].

Many reliable RCTs have been conducted in the field of medical therapy for OAB that indicate the role of the placebo in the defined outcomes. In a multicentre RCT, 2,049 men and women >20 years old with OAB syndrome for at least 6 months were randomized to four groups — solifenacin 5 mg ($n = 400$), solifenacin 10 mg ($n = 385$), propiverine 20 mg ($n = 402$) and placebo ($n = 406$) — but 1,584 were treated overall. All treatments were more effective than placebo, but considerable improvements from baseline (mean change, s.d.) were observed in the placebo group in all outcomes, including

the number of voids/24 h (−0.94, 2.29), urgency (−1.28, 2.90), urgency incontinence (−0.69, 2.00) and nocturia episodes (−30, 0.91), as well as volume voided per micturition (11.67, 33.74). These results showed that, although the active treatment groups had an almost twofold increased response rate compared with the placebo arm, the changes from baseline in the placebo arm were considerable. For example, the mean changes in the number of voids in the placebo group and solifenacin 5 mg group were −0.94 and −1.87, respectively. Such changes can be statistically significant but, in reality, a decrease of one or two episodes in the number of voids is not very different clinically. Volume voided per void increased dramatically in the active treatment group but not too much in the placebo arm, which shows the difference in placebo response in subjective and objective outcomes[106]. Furthermore, in the MIRACLE trial, in which the efficacy and safety of mirabegron were evaluated for treating patients with OAB from 14 institutes, 464 men were randomized to receive mirabegron 50 mg ($n = 310$) or placebo ($n = 154$). The results showed a significant change from baseline OAB symptom score in both active treatment and placebo groups. At 12 weeks, this change was superior in the mirabegron arm ((mean, s.d.) −2.56, 2.71) to placebo (−1.90, 1.78; $P = 0.01$). However, this difference was not sustained at the 26-week follow-up point (−2.61, 2.77) and (−2.79, 3.03) for active and placebo arms, respectively ($P = 0.65$). Such variation can be related to regression to mean over time[107]. Surprisingly, adverse events and treatment-emergent adverse events (TEAEs) were similar in the placebo and mirabegron groups, indicating the role of nocebo effect in the treatment of patients with OAB. At the start of the trial, all possible adverse events were explained to the participants in both groups. Adverse events occurred in 48 (15.48%, 59 events) patients in the active treatment group ($n = 310$) and 18 (11.69%, 22 events) patients in the placebo group ($n = 154$). TEAEs, such as allergic reaction, gastrointestinal problems and cardiovascular events were reported in 13 patients (4.19%, 13 events) in the mirabegron group and in 4 patients (2.60%, 5 events) in the placebo group. There were no statistically significant differences in the number of adverse events and TEAEs between the two groups in the first 12 weeks of the trial ($P = 0.27$ and $P = 0.39$, respectively). In addition, in the period between the 12th and 26th weeks, the rate of adverse events and TEAEs between the two groups were not statistically different ($P = 0.46$ and $P = 1.00$, respectively). This study is a good example of the nocebo effect and the roles of expectations and conditioning in this regard[107].

In a study on the use of intradetrusor injection of onabotulinum toxin A for patients with urinary incontinence caused by neurogenic detrusor overactivity, 275 participants were randomized 1:1:1 to three groups to receive placebo, onabotulinum toxin A 200 IU, or onabotulinum toxin A 300 IU. The proportions of patients with multiple sclerosis (MS) in the study who experienced a 100% reduction in UI episodes at week 6 (intent-to-treat population) were 12.0%, 43.4% and 41.2% in the placebo, onabotulinum toxin A 200 U and 300 U groups, respectively ($P < 0.001$); the proportions of patients with SCI who experienced 100% reduction in UI episodes were 2.4%, 30.8% and 37.5%, respectively ($P < 0.001$; among groups comparison). The placebo effect was more prominent in patients with multiple sclerosis than in those with SCI. These results suggest that high cerebral centres are important in the placebo response[108]. A main adverse event in this study was the increased post-void residual urine in patients without a history of clean intermittent catheterization (CIC); surprisingly, 12% of the placebo group needed CIC as a nocebo response of the intervention compared with 30% and 42% of patients in the 200 U and 300 U groups, respectively. In a systematic review on the placebo effect in the medical treatment of OAB, statistically significant changes in the outcomes of patients in the placebo groups were observed[15]. Apart from the urgency episodes per day (weighted mean difference (WMD) = −1.15; $P = 0.37$), other outcome measures including the changes in micturition episodes per day (WMD = −1.04; $P = 0.0016$), incontinence episodes per day (WMD = −1.12; $P < 0.001$), micturition episodes per day, mean micturition volume (WMD = 10.61 ml; $P = 0.02$) and maximum cystometric capacity (WMD = −16.87, $P = 0.009$) were statistically significantly improved over time in the placebo groups[15]. The reason for placebo having no significant effect on urgency episodes is not clear, but it had a remarkable effect on improving the other defined outcomes. In a meta-analysis of the placebo arms from RCTs assessing medical treatments for OAB, multiple statistically significant improvements were reported in clinically relevant outcomes including micturition episodes per 24 h (SMD = −0.45; $P < 0.001$), incontinence episodes per 24 h (SMD = −0.517; $P < 0.001$), urgency urinary incontinence episodes per 24 h (SMD = −0.46; $P < 0.001$), urgency episodes per 24 h (SMD = −0.50; $P < 0.001$), volume voided per micturition (SMD = 0.251; $P < 0.001$) and nocturia (SMD = −0.33; $P < 0.001$)[109]. However, both of the studies evaluated the overall change in the placebo group (the placebo response) rather than the change solely caused by the mechanism of the placebo (the placebo effect). The change in the placebo arms of these studies also includes the natural history and regression to the mean; indicating the importance of designing trials that also include no-treatment arms in order to improve understanding of the placebo effect.

A profound placebo effect has been reported in trials assessing treatments for nocturia[15]. In one study in women >20 years old with nocturia (>2 times voiding per night), 261 patients were randomized to receive low-dose (25 μg) desmopressin (133), or placebo (128). The number of nocturnal voids was significantly reduced by 1.24 episodes at the end of the treatment in the group receiving placebo and by 1.46 episodes in the group receiving desmopressin ($P = 0.02$)[110]. Importantly, a dramatic change from baseline was seen, but, also, the frequency of adverse events was similar in the active treatment and placebo groups (44% versus 45%, respectively), meaning that the nocebo response rate was 45% in this study. In addition, two serious adverse events occurred in the placebo group but there was none in the desmopressin arm[110]. In a secondary analysis of

data from a 12-month trial of 1,078 men with prostatic symptoms receiving terazosin, finasteride, combination or placebo, improvements in nocturia were evaluated. Overall, nocturia decreased from a baseline mean of 2.5 episodes to 1.8, 2.1, 2.0 and 2.1 episodes in the terazosin, finasteride, combination and placebo groups, respectively, which showed no clinically important results. Thus, the net advantage of terazosin over placebo was a reduction of 0.3 nocturia episodes[111]. This response could be a result of the fluid restriction instructions given to the patient before starting the trial. Furthermore, certain habits such as using voiding diaries can affect the patients' fluid intake behaviours[110], especially when fluid restriction is advised at the starting point of the trial. Thus, additive benefits can be observed in the placebo arm, which can make it difficult to estimate the placebo effect. However, more studies are needed to elucidate the nature of this response.

Being a multifactorial disease, OAB can be triggered or influenced by other health conditions. Different phenotypes for OAB have been defined, including metabolic disorders (such as diabetes), neurogenic, urothelial, urethral, myogenic or microbiota[112].

In a pooled analysis of 3,011 patients, fluid intake habits and the voided volumes per 24 h from patients receiving active treatment (solifenacin 5 mg or solifenacin 10 mg) were compared with those of patients receiving placebo. A statistically significant decrease in the voided volume per 24 h was observed in the placebo arm ($P < 0.0001$); however, after statistically adjusting the voided volumes based on water intake, the total effect in the placebo arm decreased dramatically. The explanation was that the patients in the placebo groups tended to restrict their water intake owing to a lack of improvement, whereas the patients in the treatment groups continued their previous water intake habits[113]. This reduction in fluid intake in the placebo group might also have a role in the placebo effect in OAB trials because it is hypothesized that when patients in both of the arms are advised to restrict fluid intake, patients in the placebo arm might show more improvement as they experience less dry mouth than those in the active treatment group[113]. Bladder diaries can also contribute to the placebo effect by functioning as a form of behaviour therapy[114].

The role of the nocebo effect in OAB has been evaluated in a systematic review and meta-analysis addressing adverse events reported in the placebo arms of 57 OAB clinical trials comprising 15,446 patients[25]. The calculated adverse event rate does not show the actual nocebo effect, but it represents all the adverse events reported in the placebo arm during the period of the trials (nocebo response). The results suggested that considerable rates of adverse events are present in the placebo arms and that the nocebo effect might have a major role in this occurrence. This meta-analysis showed that of 13 commonly reported adverse events, dry mouth (4.9%; 95% CI 0.042–0.057; $P < 0.001$), headache (3.1%; 95% CI 0.026–0.037; $P < 0.001$) and constipation (2.6%; 95% CI 0.022–0.031; $P < 0.001$) were the most common[25].

Statistically significant outcomes have been reported in the case of both the placebo and the nocebo responses. Further investigations and well-designed trials are required to improve understanding of the true placebo effect. Understanding the benefits of the placebo effect and the harms of the nocebo effect could help to improve the treatment outcomes and patient satisfaction.

OAB is a multifactorial condition and the placebo response is widely studied in trials for different interventions. The placebo response can be reduced in large trials and can be increased when patients are not informed that one arm of the study is a placebo. Regression analyses have determined that a physical placebo intervention, such as sham or acupuncture, causes increased placebo response. Additionally, trials with patient-reported or patient-observed outcomes might have increased placebo responses[27]. Current data show that conditioning, expectation and regression to the mean have a role in the placebo response of OAB trials. However, it seems that the main reasons for placebo response in patients with nocturia are regression to the mean and/or restriction of fluid intake.

Stress urinary incontinence. Urinary incontinence is a prevalent condition, with results of most studies showing a prevalence of 25–45%, and affects patients' QOL[115–118]. It affects health-care systems owing to its immense economic burden. In the USA alone, the total cost of SUI was estimated to be $13.12 billion, 82% of the total budget for urinary incontinence in 1995 (REF.[119]). In 2007, the total indirect cost of UUI was estimated to be $66 billion in the USA[120]. In a study on the prevalence of female urinary incontinence in developing countries, SUI was the most common type of urinary incontinence (12.6%; 95% CI 10.3–15.4) and the total prevalence of urinary incontinence was 25.7% (95% CI 22.3–29.5)[118]. SUI is defined as episodes of incontinence (that is, the involuntary voiding of urine) occurring when intra-abdominal pressure and, therefore, bladder pressure, supersede the total urethral resistance[121]. Initial management of SUI is with conservative treatments such as lifestyle modification and pelvic floor muscle training (PFMT), as well as drug therapies (such as duloxetine). In patients who do not respond to primary treatments, surgical interventions (such as Burch colposuspension, mid-urethral sling placement, bulking agents and artificial sphincter) are recommended[122].

A multicentre trial in 16 countries across Africa, Australia, Europe, North America and South America was conducted to evaluate whether having had previous SUI treatment or having severe baseline urinary incontinence can change the effect of placebo. Women with SUI ($n = 921$) were included in four 12-week-long RCTs comparing duloxetine with placebo[123]. At baseline, patients were asked about their previous surgical treatment and their current PFMT. Incontinence episode frequency (IEF) was measured at the baseline and at the end of the trials. The median decrease in IEF in the placebo arms was 33%. This change was reduced in patients with severe SUI (29.6% versus 36.4%, $P = 0.07$), with a history of surgical treatment for incontinence (25.0% versus 33.3%, $P = 0.26$), and in those doing PFMT (23.6% versus 33.3%, $P = 0.02$). These results suggested that treatment-naive and/or less severe forms of SUI might

be important predictors of increased placebo response, whereas a history of surgical treatment for incontinence and PFMT might lead to a reduced placebo response[123]. These findings indicate the prominent role of previous experiences in the level of observed placebo response in patients with SUI. No statistically significant differences were found in a study in which fesoterodine 4 mg, fesoterodine 8 mg and placebo were compared for treating SUI[124]. The outcome measures were urethral pressure reflectometry (UPR) and self-reported bladder diary. A placebo effect was observed in the self-reported SUI episodes collected in a bladder diary; however, no effect was found in the end points measured with urethral pressure reflectometry (UPR), calling into question the objectivity and accuracy of the self-reported bladder diary[124]. This observation suggests that objective measures are less influenced by the placebo effect than subjective measures. In addition, SUI, similar to most benign urological ailments, is a disease that profoundly affects QOL and the subjective perception of the patient is the most important end point. In 2018, a total of 114 premenopausal parous women with SUI were randomized in two groups of 57 patients (Er:YAG laser therapy and sham) to evaluate the effect of non-ablative Er:YAG laser therapy on SUI. The results demonstrated a statistically significant change in the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) scores in the sham group (−2.86, −4.34 to −1.35, $P=0.03$)[125]. A systematic review comprising ten trials including 5,738 women was conducted to assess the efficacy of duloxetine in the management of SUI[126]. Response was defined as having a minimum decrease of 50% in the episodes of SUI after active or placebo treatment. Overall, an improvement of 52.5% was observed in the treatment arms and 33.7% in the placebo arms (RR 1.56; 95% CI 1.46–1.66; $P<0.001$). Thus, approximately one-third of the women responded to the placebo. However, 45.3% of the women who were receiving the placebo, surprisingly, experienced drug-related adverse events (a nocebo response) compared with 62.7% in the duloxetine group. These results suggest that negative expectations of having adverse events might result in their occurrence in all patients in the placebo arm receiving an inert substance. Thus, the placebo had positive and negative effects on these women with SUI[126].

In conclusion, the placebo effect in SUI is real and considerable but is also variable and unpredictable. However, data regarding the nocebo effect in SUI are limited. Further investigations are needed to understand the role of nocebo effect in the management of SUI. One of the best strategies for gaining this understanding is to design placebo-controlled trials that also include a no-treatment arm.

Female sexual dysfunction. FSD is defined as distressing sexual conditions, such as persistent genital arousal disorder and pleasure dissociative orgasm disorder, and sexual health problems, such as scars in the vaginal opening (from injury, surgery, childbirth, or pelvic infections), chronic pelvic pain syndrome and dermatological conditions (such as lichen sclerosis or lichen planus), that can be experienced by women[127]. FSD is a common clinical condition that affects the QOL of up to 50% of women[128]; however, understanding of its multifactorial causes and how to deliver the best treatment is still quite limited. Pharmaceutical treatment strategies such as oestrogen therapy, androgen therapy and bremelanotide have, to date, failed to provide the expected results[128–131].

In order to assess FSD, the female sexual function index (FSFI) has been developed, which is a score based on a questionnaire spanning the sexual function domains of arousal, lubrication, orgasm, desire, pain and satisfaction to validate diagnostic cut-off scores. A five-point Likert scale from 1 to 5 (higher score indicating more severe) was used in the 19 items of the FSFI. Of these items, 15 also had a zero option on the Likert scale, mostly for women who are not sexually active or who did not have active intercourse during the previous 4 weeks before the interview. Having no intercourse did not mean FSD, but the total FSFI becomes affected and dramatically reduced in these patients. Thus, applying routine clinical cut-off values might overestimate the initial evaluation of the patients when using the FSFI. For this reason, validated cut-off points should be used to eliminate such problems[132,133].

The placebo effect has been reported and studied frequently with regard to the treatment of FSD[130]. A secondary analysis of 50 patients in the placebo arm of a trial on the use of tadalafil in female sexual arousal dysfunction showed that the mean FSFI scores in the placebo arm were 17.98 (s.d. 6.44) at baseline, 24.05 (s.d. 5.83) at week 4, 22.84 (s.d. 6.44) at week 8 and 23.8 (s.d. 6.6) at week 12. An overall significant change in FSFI score over time in the placebo arm was seen in a repeated measure ANOVA (F 32.65, degrees of freedom 3, $P<0.001$)[134]. The statistically significant improvement in the patients receiving placebo indicates a non-negligible placebo effect in FSD.

In a meta-analysis of placebo arms of 24 RCTs assessing various pharmacological modalities for FSD that included 1,723 women who received placebo for FSD, the placebo effect accounted for 67.7% of the treatment effect[132]. In addition, the cohorts of the analysed RCTs were pooled for statistical calculations; in this analysis, the placebo effect did not account for 67.7% of all treatments. However, in 7 out of the 8 analysed studies, it did account for more than 50% of the treatment effect[132].

In conclusion, methodological factors might be effective in generating a placebo response; therefore, additional well-designed research is needed to understand the mechanisms and minimize misconceptions[135]. Data regarding the role of nocebo effect in FSD are limited. One reason might be the complex nature of FSD, making it difficult to assess the role of placebo effect in its management. However, evaluation of the drug-related adverse events observed in the placebo-controlled FSD trials could be the first step to gaining understanding.

Erectile dysfunction. Almost one in five men is affected by ED, with the rate increasing steadily with advancing age[136]. In addition to vascular risk factors, many pathophysiological factors and organic disorders are associated with this condition. First-line therapy, when no absolute

contraindication is apparent (such as patients using any form of nitrate (such as nitroglycerine) or NO donors (such as amyl nitrite))[137,138], is oral phosphodiesterase type 5 inhibitors (PDE5is).

In some RCTs on PDE5is, the placebo effect resulted in a low-to-moderate improvement in erection[139]. A prospective controlled trial was performed on 123 patients with ED to evaluate the efficacy of placebo alone in improvement of ED by measuring the mean change in scores on the International Index of Erectile Function and quality of erection questionnaire[139]. The participants were randomized to three groups including group 1, who were told that they would receive an active treatment (31.7%, $P=0.039$); group 2, who were told that they would receive placebo or an active treatment (36.8%, $P=0.028$) and group 3, who were informed that they would receive placebo (36.8%, $P=0.002$). The aim of giving certain information was to eliminate the benefit that might arise from learning and conditioning phenomena. Despite the fact that all of these groups only received placebo, ED severity improved in all groups and there were no significant differences in the final scores between the groups[139]. Sexual function in men is probably like an on and off switch, but in women it is very complex; probably like a fuse box with many switches. The reason is that the definition, scoring index and effective intervention are not well defined; thus, placebo and nocebo responses can differ between men and women. In a randomized placebo-controlled study, 152 men with ED and mild-to-moderate depression were randomly assigned to flexible-dose sildenafil ($n=74$) or matching placebo ($n=78$). Improvement in erection was reported by 11.4% of men receiving placebo and 12.9% reported improvement in their ability to have sexual intercourse. Nocebo response was reported in 10 out of 78 patients who received placebo. Headache was the most common nocebo response reported in 6.4% of men receiving placebo[140].

In a retrospective analysis of 42 placebo-controlled RCTs on sildenafil for treatment of ED including 4,360 men, predictors of the placebo response were investigated[141]. The results showed that Black men <45 years of age with mild ED and without diabetes were most receptive to the placebo effect. The reason for the increased placebo effect in this population was not clear and requires a larger data set to understand this correlation. The placebo effect was inversely proportional to ED severity[141]; thus, men with the most mild ED exhibited the biggest placebo response. This phenomenon might be caused by conditioning or the increased rates of psychological problems experienced by men with ED. In a systematic review and meta-analysis of trials that included >12,000 men diagnosed with ED in total, placebo improved erectile function significantly, with a small-to-moderate effect size ($P<0.001$). However, participants who had ED associated with post-traumatic stress disorder (PTSD) had an increased effect size with placebo[142]. This improvement suggests a role for psychological factors in the development of ED in the case of PTSD[142,143]. The study did not find a significant difference between treatment with placebo and PDE5is ($P=0.08$) following prostate cancer surgery or radiotherapy, possibly because of severe neural inflammation and/or damage in cancer surgery and radiotherapy[142]. The authors suggest that response to therapy might change considering the characteristics of medical or surgical interventions. For example, specific brand names and labelling of interventions might have psychological effects on the reported outcomes[144]. Thus, clinical practice for ED should reflect these limitations.

Taken together, contextual factors are important in the delivery of care to patients with ED, and the lack of difference in response between placebo and PDE5Is in certain patient subgroups suggests that clinical practice should change in a way to reduce non-evidence-based treatments such as prescription of long-term daily PDE5Is after prostate cancer treatment.

Data concerning the nocebo effect in ED are limited; however, ED has been reported to be caused by the nocebo effect in trials of other conditions[61]. Conducting randomized placebo-controlled trials on treatment of ED that also include a no-treatment arm should be included in future investigations of placebo and nocebo effects in ED. The magnitude of placebo response in ED can be evaluated through analysis of adverse events observed in the placebo arms of related RCTs.

Interstitial cystitis/bladder pain syndrome. IC/BPS is a debilitating condition with an estimated prevalence between 2.7% and 6.5% in women in the USA[145]. IC/BPS is characterized by chronic pain and/or inflammation leading to pain, tenderness and discomfort in the bladder and pelvis accompanied by some LUTS such as frequency, urgency and nocturia[146–148]. Dr. Guy Hunner was the first to describe the classical form of IC as bladder pain caused by specific lesions, subsequently known as Hunner lesions[149]. The term bladder pain syndrome was added to interstitial cystitis to explain the conditions in which bladder pain exists without macroscopic findings in cystoscopic evaluations resulting in the term IC/BPS[150]. The International Continence Society standardized additive terms, but BPS and IC are still used interchangeably[145,151]. The prevalence of IC/BPS can be underestimated owing to the lack of strict guidelines and criteria for diagnosis as well as the multifaceted nature of its symptoms[152–154].

Different interventional modalities exist for the management of IC/BPS, from behavioural therapy and medical treatment to surgical interventions. The role of placebo in urinary symptom improvement and pain relief in IC/BPS has been evaluated in several studies.

Amitriptyline is used for the treatment of IC, although it is not licensed, with doses from 10 to 70 mg. In a multicentre RCT on the efficacy and adverse events of amitriptyline compared with placebo, a remarkable placebo effect was observed[155]. In this study, considering the intention-to-treat analysis, 45% (61/136) of patients showed moderate-to-marked symptom improvement. This result was 55% for the active treatment group and no statistically or clinically significant difference was seen when comparing amitriptyline with placebo ($P=0.12$). The overall adverse event rate was 88% in the active treatment arm and 72% in the placebo arm, which shows a remarkable nocebo response. Constitutional

symptoms (for example, primarily fatigue and malaise) were observed in 31% of patients (42) and gastrointestinal adverse events (primarily dry mouth and constipation) were observed in 24% of patients (32) in the placebo arm[155].

In addition, in a meta-analysis, six randomized placebo-controlled studies in which the participants received either 300–400 mg per day of pentosan polysulphate (PPS) or placebo for IC/BPS were assessed[156]. The primary results of this meta-analysis showed only a 12.5% (95% CI 6.4–18.3) difference in symptom improvement between the active treatment and placebo groups. Overall placebo response was >50%, and when only considering the patients who completed the study, it was increased to 75%[156]. The high placebo response rate in this meta-analysis was partly because of not including patients lost to analysis in the final analyses. Other influencing factors could be patient selection criteria, regression to the mean, conditioning and learning from other trials[157].

In one RCT, 43 patients with IC/BPS were randomized to receive adalimumab ($n = 21$) or placebo ($n = 22$). Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index were considerably reduced after placebo treatment at week 12 compared with baseline. Substantial improvement was observed in the O'Leary–Sant Interstitial Cystitis Symptom and Problem Indices in patients treated with placebo (−8.1, 95% CI 3.0–13.2)[158].

Improvements in patients receiving sham interventions have also been reported[158]. For example, in a double-blind study including 60 patients with refractory IC/BPS, patients were randomized to receive botulinum toxin ($n = 40$) or saline intravesical injection ($n = 20$). The treatment outcome (success rate) was assessed using the global response assessment. The assessment was successful if one or more points from the global response assessment were filled and the primary end point was a decrease in pain assessed using a visual analogue scale. At week 8, two or more pain visual analogue scale reductions were reported by 24 patients (60%) in the botulinum toxin group and by 9 patients (45%) in the normal saline group. However, the overall success rate in the normal saline group was 3/20 patients (15%) compared with 25/40 (62%) in the botulinum toxin injection group ($P = 0.028$)[159]. This result means that 15% of patients improved by receiving saline injection to the bladder wall. The improvement in the botulinum toxin injection arm was statistically significant when compared with the placebo arm; however, only two patients in the placebo group experienced adverse events such as dysuria or urinary infection. A low nocebo response was recorded in the placebo arm despite the fact that, based on IC/BPS guidelines, all patients should be told about the chances of urinary retention and/or infection before intravesical botulinum toxin injection. In a phase II trial of patients with refractory IC/BPS in which injection of 100 IU botulinum toxin into the bladder trigone in 10 patients was compared with injection of saline into the bladder trigone of 9 patients, a reduction in O'Leary–Sant score was observed in the active treatment and placebo arms (-3.8 ± 2.5 versus -1.6 ± 2.1, $P < 0.05$). The symptoms improved statistically significantly in both arms, but the clinical relevance was doubtful[160] owing to the small sample size and small amount of change in O'Leary–Sant score. Urinary retention and infection are two known adverse events that can occur as a result of intravesical botulinum toxin injection; in this study, although no urinary retention was reported in the placebo arm, 2 of 9 patients had urinary infection at 2-week follow-up monitoring[160], which can be interpreted as a nocebo response.

The placebo effect could be harnessed effectively in IC/BPS because it is a pain-related disease; however, only the two RCTs described[159,160], including a total of 79 patients with refractory IC/BPS, have been conducted that evaluate the efficacy and adverse events of the active treatment versus placebo arms. Thus, studies with increased populations are needed to help to understand the amplitude and duration of placebo and nocebo response in IC/BPS[161].

Lower urinary tract symptoms. LUTS comprise a complex of symptoms that are subdivided into voiding, storage and post-voiding symptoms. Based on the results of EpiLUTS, in which the epidemiology of LUTS in the USA, UK and Sweden was evaluated, the prevalence of at least one LUTS was sometimes 72.3% for men and 76.3% for women[162]. In addition to the high prevalence, LUTS affect QOL greatly[163,164]. Previously, LUTS in men were generally accepted as manifestations of bladder outlet obstruction owing to benign prostatic enlargement with a pathological background of BPH[165]. Currently, factors such as bladder overactivity, nocturnal polyuria and other urological and/or non-urological conditions are also known to contribute to LUTS[166]. Prostatic tissue growth that leads to LUTS, also called clinical BPH, is often treated with pharmacological therapies such as α-blockers and 5α reductase inhibitors[167]. Race, age, environment and hormones (such as oestrogens and androgens) influence prostate growth[168]. BPH has an incidence rate of 14% in men <50 years old and increases to >50% in men over the age of 60 years[168], reaching >80% in patients over 80 years of age[169]. Patients under the age of 30 years very rarely have symptoms[170].

Placebo has a strong influence on LUTS, affecting both subjective symptom scores and objective measurements[171]. Comparing placebo with α-blockers is difficult, as α-blockers show a statistically significant difference from placebo, but the placebo effect is also notable in these patients[171]. In most RCTs, the placebo has an American Urological Association Symptom Score (AUASS) change of a maximum of three points[171]. This change was not clinically significant because a clinically significant change is defined as an AUASS score of at least 3 points[172] (≥3), but it is not negligible and is only an agreed cutoff point considering expert opinion. When the net drug effect (which is calculated by subtracting the placebo effect from the drug effect) is measured for α-blockers, the average AUASS is 2.2 and only in a limited number of trials is the net drug effect clinically significant (≥3)[171].

Several trials have been conducted in which 5α reductase inhibitors for male LUTS showed a symptom

score decrease of >2 points. For example, four trials in which finasteride for the treatment of LUTS was investigated and that included a placebo arm have been conducted. In these studies, symptom score reductions of 4.8, 3.2, 6.6 and 5.6 were seen in the treatment arms and 3.4, 2.6, 5.7 and 4.9 were seen in the placebo arms[173–176]; however, the change in the net drug effect was <2 points in each trial. These long-term (1–4 years) studies of finasteride showed a strong placebo effect[173,174]. However, the duration of response and amplitude change over time needs to be further assessed[171]. A 2-year study on the efficacy and safety of finasteride therapy for BPH (the PROSPECT trial[177,178]) showed that the effect of placebo diminished over time but plateaued for a long period. Prostate volume was increased at the end of the study in the placebo group (+8.4%), but maximum urinary flow rate (Q_{max}) improved +1.4 ml/s over baseline in the first 5 months and remained 1 ml/s over the baseline at the end of the study. Furthermore, the total symptom score decreased by 2.3 points from the baseline at the end of the study in the placebo group. A correlation with the prostate size was also observed — patients with smaller prostates and more bothersome baseline symptoms had a better placebo response than those with larger prostate volumes and fewer bothersome symptoms. Furthermore, 246 patients (81.2%) reported adverse events (nocebo response) in the placebo arm. The most common adverse events were urogenital (40.3%) including impotence (6.3%) and decreased libido (6.3%); surprisingly, 13.2% of patients in the placebo arm discontinued the intervention owing to adverse events. In addition, adverse events were seen in 81.2% of all patients receiving placebo therapy[177,178].

An analysis of the MTOPS trial, a multicentre RCT that included 2,931 men >50 years old with AUASS of 8–35 who were randomly assigned to receive placebo, doxazosin, finasteride or combination therapy, showed a mean reduction of 4.9 in AUASS in the placebo group, 6.6 in the doxazosin group, 5.6 in the finasteride group, and 7.4 in the combination therapy group[173]. All arms showed a clinically significant decrease in the score (>3 points); however, a statistically significant difference was seen between placebo and the three active treatment arms ($P = 0.002$, $P < 0.001$, $P < 0.001$), when comparing doxazosin, finasteride or combination therapy with placebo, respectively. The MTOPS trial showed a median decrease of 4 points in the AUASS score at the 1-year follow-up point, which was not statistically significant ($P = 0.77$)[173]. However, at the 4-year follow-up point, a median decrease of 4 points for placebo and 5 points for finasteride was observed, which was statistically significant ($P = 0.04$) The most common adverse events that occurred more frequently in the doxazosin group than in the placebo group were dizziness (4.41 versus 2.29 rate/100 persons/year), postural hypotension (4.03 versus 2.29 rate/100 persons/year), and asthenia (4.08 versus 2.06 rate/100 persons/year). The most common adverse events that occurred more frequently in the finasteride group than in the placebo group were ED (4.53 versus 3.32 rate/100 persons/year), decreased libido (2.36 versus 1.4 rate/100 persons/year), or abnormal ejaculation (1.78 versus 0.83 rate/100 persons/year) with a statistical significance of $P < 0.05$. These active TEAEs manifest as nocebo response in the placebo group.

The results of a study in which a sham surgery group ($n = 66$) was compared with prostatic urethral lift ($n = 140$) for BPH showed that the placebo group had a change of 5.9 points on the AUASS compared with an AUASS of 11.1 for the prostatic urethral lift group[179], suggesting a clinically significant (≥3) placebo response in the sham surgery group. No active intervention was performed in the sham group, and patient symptom score improved clinically. Thus, the placebo effect is not specific to non-surgical interventions and it might be seen in minimally invasive treatments for BPH.

PDE5Is, which are generally used to treat male sexual dysfunction, entered some trials owing to their effects on LUTS caused by BPH. A pooled analysis of RCTs from four centres showed a 1.7 reduction in AUSS in the placebo arm, which included 746 men. The result for active treatment groups was −2.9. Thus, a fair decrease in symptom scores was seen in both arms. In a study on the efficacy and safety of tadalafil for BPH, TEAEs were reported in 36 of 164 (22%) men of the placebo arm versus 42 of 161 (26.1%) patients in the tadalafil arm, showing a notable nocebo response[180]. In a placebo-controlled study on the treatment of LUTS secondary to BPH, one group ($n = 20$) received tadalafil and tamsulosin in combination and the other group ($n = 20$) received a combination of tamsulosin and placebo. A urodynamic study was performed before and after the treatment. The primary outcome was change in the voiding cystometry parameters. Q_{max} improved in both groups (mean (s.d.), 1.0 (2.4) in the treatment arm and 1.4 (2.4) in the placebo arm, $P = 0.6$) but no statistically significant difference was observed between the two groups. However, the AUASS improved In the treatment group when compared with the control group, meaning that placebo can also, partly, result in the improvement of objective outcomes such as flow rate[181]. A systematic review of the placebo or sham effects of different modalities in the treatment of LUTS in patients with at least 12 months of follow-up monitoring after intervention included 10,587 patients from 25 RCTs. Placebo and sham arms from trials of phytoextracts, medical treatments, intraprostatic botulinum toxin injection and transurethral microwave thermotherapy for the treatment of LUTS were included[182]. The results showed a mean 4.4 IPSS score improvement for placebo or sham treatments, with a range between 0.7 and 6.8 (REF.[182]). The mean maximum flow rate changes for placebo or sham at the end of 12 months were not relevant (+0.8 ml/s) owing to the high range of the heterogeneity in the results across the trials[182]. These results highlight the fact that the placebo effect is more commonly observed in subjective and patient-reported outcomes than in objective measurements. This observation can be related to expectation and conditioning that result in a subjective improvement rather than an objective one.

Data regarding the nocebo response in LUTS are limited; however, they have been reported. For example, during a trial of finasteride treatment for BPH, the rate of sexual adverse effects (a nocebo response) was

threefold higher in the group of individuals who were informed of the related adverse effects than those who were not[61]. In a 1-year trial including patients with BPH, patients were divided into two groups, with the first group receiving finasteride and information regarding its possible adverse events, and the second group receiving the same finasteride (same dose) without any information on adverse events. ED was reported in 30.9% of the informed patients compared with 9.6% in non-informed patients[61].

From these data, it seems evident that treatment with placebo does not stop the natural progression of BPH; placebo does not seem to change the growth or the size of the prostate and whether it affects the incidence of urinary retention or the switch to surgical treatments is questionable[171,183]. However, in this condition, which has a large effect on QOL, placebo statistically and clinically significantly improves symptoms and some objective measures (such as Q_{max}).

Factors affecting the placebo and nocebo effects

Demographic factors have been shown to affect the placebo effect. For example, the placebo response in patients receiving oral therapy for OAB increased with advancing age for nocturia but the effect of the placebo response on daily micturition episodes was reduced with advancing age[109].

For many years, biological sex was hypothesized to be a predictor of the placebo and nocebo effects, but the relevance of this potential predictive power has not been investigated. However, research suggests that the placebo effect in women is a result of conditioning and that the effect in men is a result of manipulation of expectations[184]. In addition, the placebo response is more common in men than in women and the nocebo response is more common in women than in men[185]. One of the explanations for the observed sex differences in the placebo response is that the response to stress-related endogenous pain modulatory processes (such as endogenous opioid systems) is greater in men than in women, and an increased nocebo response in women can be related to the effect of increased negative emotions on induced symptoms such as pain[185]. In one study, adverse events in women receiving oral placebo who had previous experience of adverse events to other medications were more than those of men (30% versus 19%; $P=0.01$)[186]. Vasopressin has been shown to enhance the magnitude of the placebo effect and decrease stress levels in women but not in men[187], which means that observed sex differences in stress and related neurobiological mechanisms support the hypothesis of sex differences in the placebo effect. Women have been shown to respond more often and more strongly to nocebo hyperalgesic treatment than men, suggesting that the relationship between high levels of anxiety and high levels of pain is increased in women compared with men. Finally, nocebo responses can be a form of compensatory conditioned response, but evidence does not show that this mechanism is increased in women[188].

The sex of the experimenter might also contribute to the observed difference between the sexes in outcome reports[185]. Hence, reporting sex differences in the placebo and nocebo effect, together with the sex of the experimenter, has been suggested[185].

The conclusions of a study on placebo responses in major medical areas known for high placebo responses suggested that the placebo response is mostly influenced by the severity of the symptoms at baseline rather than age and sex[189]. Thus, no single trend is evident for the change direction in the placebo response within different age and/or sex groups[184,189]. This observation highlights the need for more high-quality trials with reduced confounding variables to further elucidate the role of age and sex in placebo and nocebo responses.

In conclusion, data supporting the relationship of age and sex with the placebo and nocebo effects are limited and generally focused on pain and neuropsychological conditions.

Statistical significance and clinical importance

When reporting a research study, whether the results are real needs to be demonstrated; that is, significant results are required. When the term significant is used in publications, clarifying the type of significance being considered is reasonable (such as statistical significance, practical significance and clinical significance)[190]. This clarification also implies statistically significant placebo and nocebo responses in different trials.

Statistical significance is easily reported by calculating the *P* value. Many trials on pain management, depression, anxiety and functional urological disorders have reported statistically significant results; however, identifying the level of change that is clinically acceptable and that results in tangible change in the patients is more important than statistical significance.

Practical significance indicates the magnitude of different effect sizes[191], which is the extent of change that is acceptable to the researchers or practitioners for answering a particular research question. For example, some researchers and practitioners indicate a relative risk ratio of 2 as a practically significant result and a relative risk ratio of 5 as a very significant result[191]. Moreover, various measurements, including the standard error, standard deviation, effect size, minimal detectable change, reliable change index, and standardized response mean, could provide good estimations of practical significance[192] (FIG. 3). However, in many fields of functional urology, the importance of practical significance for the patients is still unclear. For instance, an improvement in the outcomes could be statistically and practically significant, but whether this can remarkably change the level of patient satisfaction is unclear.

Clinical significance is defined as the benefit perceived by the patients to have meaningful effects on their lives[191]. Hence, a statistically significant change in an outcome might not be as important for the patient and might not improve their life. Without a no-treatment group in RCTs, which is common in RCTs in functional urology, providing a real and clinically meaningful estimation is difficult. For instance, in studies on the treatment of OAB, the researchers might have calculated any reductions in incontinence episodes as positive results; however, a reduction of one or two incontinence episodes in patients who experience 10 incontinence

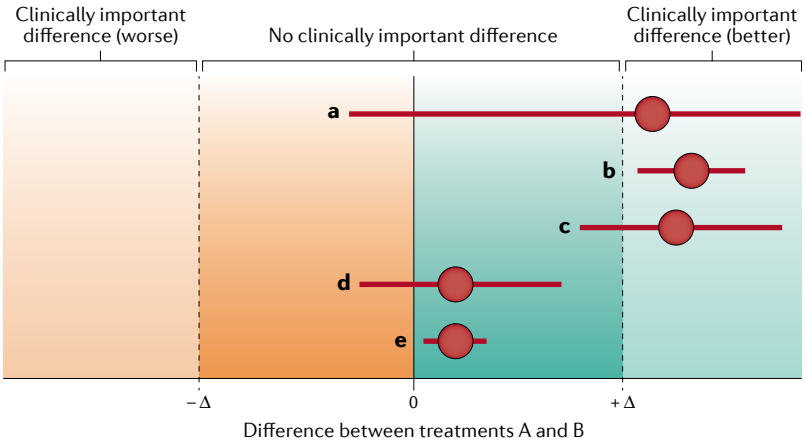

Fig. 3 | **Understanding clinical importance.** Statistical significance represents the reliability of study results and is used for hypothesis testing. However, not all statistically significant results are clinically important for the patient and the caregiver. Sample size has a huge effect on statistical significance; for example, in studies with large sample sizes, some unimportant outcomes turn out to be statistically significant. Clinical significance represents the treatment effect size, which is an important change for the patients and the caregivers. The cut-off value for clinical significance (the minimum clinically important difference) varies from study to study and is influenced by the investigators' opinions. The minimum clinically important difference is presented as Δ in this figure. **a** | This result can occur when a clinically important change is expected from a certain drug, but the result is not statistically significant. In these cases, repeating the trial with an increased sample size might lead to a statistically significant result. **b** | The result is both clinically important and statistically significant (with a high precision). **c** | The result is clinically important and statistically significant (with low precision). **d** | The result is neither statistically nor clinically significant. **e** | The result is statistically significant but not clinically important. Such statistically significant yet not clinically important results can occur in trials with large sample sizes.

episodes per day might not be an important response. The anchor-based method, distribution-based method, or Delphi technique can be applied as an adjunct to the trial design to define a clinically important difference[192]. The distribution-based method is a collection of statistical measures (such as standard error of measurement (SEM), effect size and standard deviation) that are related to the statistical characteristics of the sample population. For example, an SEM is defined as the variation in patient-reported outcomes owing to the unreliability of the measurement instrument; thus, a change smaller than the SEM can be attributable to random measurement variation rather than a real change[193]. In order to assess the clinically meaningful change, some thresholds for SEM (1 SEM[194], 1.96 SEM[195] and 2.77 SEM[196]) have been recommended. Thus, a change larger than the SEM threshold can be considered clinically meaningful. In the anchor-based method, the patient-reported outcomes are compared with a more commonly known external measure such as a global assessment, which is known as the anchor. Finally, the Delphi method is a method in which individuals share their opinions and argue to develop a formal consensus[197]. In this method, a panel of experts in a specific field are given a questionnaire or interview to reach a consensus[198]. The anchor-based method and distribution-based method were applied to estimate the clinical importance of changes in the ICIQ-UI SF and the International Consultation on Incontinence Questionnaire-Lower Urinary Tract Symptoms Quality of Life[199]. Reductions of 4 points and 6 points in the ICIQ-UI SF score and International Consultation on Incontinence Questionnaire-Lower Urinary Tract Symptoms Quality of Life score, respectively, represented clinically meaningful changes in patients with urinary incontinence receiving non-surgical therapies[199].

Regarding the American Urological Association Symptom Index (AUA-SI), patients who reported a slight improvement in their symptoms had a mean decrease of 3.1 in the AUA-SI[172]. In a cohort comprising 494 patients, the global perception of changes in patients with LUTS was compared with their AUA-SI scores to evaluate the clinical meaningfulness of the changes in the AUA-SI score. The AUA-SI scores of patients with global improvement in symptoms being slightly better, the same, slightly worse and much worse scores were −2 (interquartile range (IQR) −6 to 0), −1 (IQR −5 to 1), 0 (IQR −2 to 2), 5 (IQR 0–9) and 11 (IQR 5–18), respectively[200]. Interestingly, with small decreases in the AUA-SI score, the patients reported their status as slightly better or much better. Conversely, a large increase in the AUA-SI score is needed for them to report worsening of their symptoms[200]. This observation indicates that there is no one-size-fits-all measure of significance. As statistically and practically significant ranges are defined by the statistician, researcher or practitioner, they might or might not be clinically important or meaningful to the patients. Moreover, the individual viewpoint of patients regarding a particular condition varies and should be assessed in this context. Thus, the placebo and nocebo effects must be studied in a personalized manner based on patient characteristics, perspectives and natural history of the disease. For example, the perception of improvement might be different in two patients in the placebo arm of an RCT with statistically significant improvements in their outcomes. One might argue that his or her situation has not changed, whereas another might be satisfied with the slightest improvements. The same can be true for the perception of adverse events and the nocebo effect.

Clinical implications and ethical issues

The challenge is to make use of the placebo effect. A placebo-controlled trial might provide information about the effectiveness of a treatment, but it denies some patients what could be the best available, yet unproven, treatment; the practice of doctors prescribing placebos that are disguised as a real medication is even more controversial than denying patients active medication. The chief concern is that this practice is deceptive and could harm the doctor–patient relationship in the long term. Furthermore, legitimate doctors and pharmacies could be subject to accusations of fraud or malpractice by using a placebo. Using a placebo can also delay the proper diagnosis and treatment of serious medical conditions. This area is a hotly debated part of bioethics. Shared decision-making and individualized medicine should also be considered because some patients might be prone to the nocebo effect[49,201].

Considering all the benefits of the placebo effect, the harms of the nocebo effect and the clinical

Anchor-based method
The anchor-based method compares changes in scores with an 'anchor' as a reference. An anchor establishes whether the patient is better after treatment than baseline according to the patient's own experience.

Distribution-based method
The distribution-based approach is a method of determining minimal clinically important changes. It relies on the variability of data and the statistical characteristics of estimates of magnitudes of change.

Delphi technique
The Delphi method is a process used to reach an agreement or decision by surveying a panel of experts.

meaningfulness of the effects, whether a placebo could be prescribed as an individual treatment option is a pertinent question. The answer is complex, but it can be argued that the placebo itself should not have any medical effect. In this scenario, a placebo could not be used to improve patient outcomes. Several strategies have been recommended for optimizing the placebo and nocebo effects to improve clinical outcomes[59]. Before the treatment, an expectation modification should be performed in patients with negative expectations regarding a certain medication or intervention[202]. Positive gestures and giving positive instructions regarding the benefits of a certain drug can improve positive treatment outcomes[54]. Hearing the positive experiences of other patients as a form of social learning should be promoted[60]. Having an empathic encounter with the patients[203] and reducing their anxiety[204] could also increase the placebo effect and minimize the nocebo effect. Combining the medications with a certain cue (such as colour or odour) and in a certain context (for example, a certain time of the day or in the daylight) could improve the outcomes through the conditioning pathway[205]. Another strategy is to identify patients who are susceptible to nocebo effects at an early stage, such as patients with previous negative experiences regarding the treatment and patients with anxiety or depression[201]. These patients should be educated regarding non-specific side effects of the medication and the nocebo phenomenon[201] (FIG. 1). However, if the efficacy of the active treatment and that of the placebo are almost similar, then logically the safer option would be preferred. If the placebo is chosen as a treatment with fewer adverse effects than the active treatment, then the ethical aspects of its prescription must be addressed.

Knowingly administering placebo to someone when effective treatment options are available is a bioethically complex issue. A major concern is that the trust of the patient in the physician might be damaged owing to the violation in informed consent[206]. Maintaining a balance between a patient's right to receive transparent information and the fact that this information would not lead to harm owing to the nocebo phenomenon is important[7].

No clear statement in clinical guidelines regarding the application of a clinically effective placebo with reduced adverse events for the treatment of functional disorders is available. Instructions on the ways in which to optimize placebo and nocebo effects should be given for the clinicians in clinical guidelines to improve positive clinical outcomes and to reduce adverse events and the nocebo effect. However, more studies are needed to elucidate the role of training of the clinicians regarding the nocebo effect in the improvement of patients' clinical outcomes[7]. The effects of open-label placebos are always reduced owing to the treatment not being blinded to the participants and clinicians[207]. However, they might have fewer ethical problems as most patients find this type of intervention ethically acceptable[208]. The effects of open-label placebos were compared with those of no treatment in a systematic review and meta-analysis[209]. The results of this study showed that patients receiving placebos experienced improvements compared with those who received no treatments[209]. The studies discussed were small in scale, and the overall evidence was not strong enough to reach a robust conclusion; however, suggestions made by physicians and the placebo might have major roles in the overall outcomes. Clearly, larger and better-powered studies than have previously been conducted are required. Finding ways to distinguish the placebo effect from the pure effect of the treatment might also help to improve treatment and reduce the cost of drug testing while developing strategies to use the power of the placebo in disease treatment. Understanding the individual differences in placebo and nocebo responders is crucial[7]. This knowledge could be obtained by performing multifaceted studies to further clarify the underlying mechanisms of placebo and nocebo effects. Finally, considering these individual differences in the context of shared decision-making and understanding patient preferences could potentially improve the success rate of treatment.

Conclusions

The placebo and nocebo effects have major roles in several aspects of functional ailments, one of them being functional urology. The true mechanism of the placebo and nocebo effects is unclear, but the scope of their effect in functional urology is prominent and unharnessed. Urologists should realize the difference between statistical significance and what is actually important for the patient (clinical significance). Furthermore, clinicians should be educated regarding the placebo and nocebo responses as a strategy to optimize the placebo effect and limit the possible adverse events related to the nocebo effect. An individualized approach should be taken in the management of patients with regard to the placebo and nocebo effects and patients prone to experiencing nocebo effects should be identified. A thorough consultation and shared decision-making should be part of this process, which shall include a clear discussion regarding the placebo and nocebo effects. Further dedicated research in this enigmatic but important part of everyday life in medical care should be performed to help harness the power of placebo and avoid the harms of nocebo for patients.

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Author contributions

H.M., S.J. and E.L. researched data for the article. H.M., K.M., F.Q., V.M.S., A.A., C.G.R., S.F.S. and S.H. made substantial contributions to discussions of content. H.M., G.L.C. and R.S.M. wrote the article. H.M., B.P., C.G.R., S.F.S. and S.H. reviewed and edited the manuscript before submission.

Competing interests

S.F.S. is an advisory board member and/or speaker for Astellas, AstraZeneca, Bayer, BMS, Cepheid, Ferring, Ipsen, Jansen, Lissy, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Sanochemia, Sanofi and Wolff. C.G.R. is a consultant for GSK, Lilly, Procept, NxThera, Neotract and Sophiris and has previously received grants or research support from NxThera, Neotract, Procept and Astellas. The other authors declare no competing interests.

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