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Lower urinary tract electrical sensory assessment: a systematic review and meta-analysis

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Objectives

To summarize the current literature on lower urinary tract electrical sensory assessment (LUTESA), with regard to current perception thresholds (CPTs) and sensory evoked potentials (SEPs), and to discuss the applied methods in terms of technical aspects, confounding factors, and potential for lower urinary tract (LUT) diagnostics.

Methods

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Medline (PubMed), Embase and Scopus were searched on 13 October 2020. Meta-analyses were performed and methodological qualities of the included studies were defined by assessing risk of bias (RoB) as well as confounding.

Results

After screening 9925 articles, 80 studies (five randomized controlled trials [RCTs] and 75 non-RCTs) were included, comprising a total of 3732 patients and 692 healthy subjects (HS). Of these studies, 61 investigated CPTs exclusively and 19 reported on SEPs, with or without corresponding CPTs. The recording of LUTCPTs and SEPs was shown to represent a safe and reliable assessment of LUT afferent nerve function in HS and patients. LUTESA demonstrated significant differences in LUT sensitivity between HS and neurological patients, as well as after interventions such as pelvic surgery or drug treatments. Pooled analyses showed that several stimulation variables (e.g. stimulation frequency, location) as well as patient characteristics might affect the main outcome measures of LUTESA (CPTs, SEP latencies, peak-to-peak amplitudes, responder rate). RoB and confounding was high in most studies.

Conclusions

Preliminary data show that CPT and SEP recordings are valuable tools to more objectively assess LUT afferent nerve function. LUTESA complements already established diagnostics such as urodynamics, allowing a more comprehensive patient evaluation. The high RoB and confounding rate was related to inconsistency and inaccuracy in reporting rather than the technique itself. LUTESA standardization and well-designed RCTs are crucial to implement LUTESA as a clinical assessment tool.

Keywords

current perception threshold, sensory evoked potential, afferent pathways, neuro-urology, sensation, lower urinary tract, sensory assessment, urinary bladder, urethra, afferent fibres

Introduction

Impairments of central and peripheral neurological pathways may result in lower urinary tract symptoms (LUTS) such as urgency, frequency, and urinary incontinence, as well as urinary retention or loss of bladder awareness. In the last years, several studies have provided evidence that the afferent nervous system is a key player in the regulation of lower urinary tract (LUT) function [1–3]. Besides being active during the storage phase, afferent nerve fibres are also involved in the micturition reflex during voiding [2]. So far, LUT sensory function is

semi-objectively assessable using urodynamic investigation (UDI), which is a clinically established method of obtaining information on filling-related sensations [4,5]. Nevertheless, UDI relies on the compliance and subjective feelings of the patients when characterizing LUT sensation and does not convey urethral afferent information. These may be reasons why UDI cannot explain all pathological mechanisms of different LUTS. LUT electrical sensory assessment (LUTESA) includes current perception threshold (CPT) recording, a semi-objective method for determining LUT electrical sensitivity, and sensory evoked potential (SEP) recording, a more objective technique, providing more detailed information on the functionality of the LUT afferent pathways. It implies repetitive electrical LUT stimulation, on the one hand, to detect the weakest current that can be identified by the investigated person (LUTCPTs) and, on the other hand, to evoke identifiable deflections (potentials) in cortical recordings near the vertex (LUTSEPs). The feasibility of LUTESA was shown in healthy subjects (HS) and patients with various forms of LUT dysfunction (LUTD) [6–8]. However, despite the considerably large number of articles reporting on LUTESA techniques and outcomes, and the relevant role LUT afferent pathways play in LUT function, LUTESA appears to be underrecognized and is not yet an established clinical tool. This may be at least partly attributable to the lack of a comprehensive overview on the achievements in this area of neurophysiological LUT evaluation, with critical discussion of the benefits and potential pitfalls of applied LUTESA techniques. Thus, the aim of the present systematic review was to summarize the literature on LUTESA, to highlight the different technical aspects and potential confounders of LUTESA, and to better understand the individual study findings and their meaning. Furthermore, we compared LUTESA outcome variables between subgroups (e.g. HS vs patients) and discussed the future potential of LUTESA for research and clinics.

Methods

Data Sources and Search Strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [9]. The protocol for the review can be accessed via PROSPERO (CRD42020047157; http://www.crd.york.ac.uk/PROSPERO). The literature search was performed in three databases (from 1 January 1946 to 13 October 2020): Medline (PubMed), Embase and Scopus (see Appendix S1 for detailed search strategy). While the PubMed database search was not limited, the Embase and Scopus database searches were restricted to articles in English or German language (additionally: only 'medicine' for the Scopus search). The reference lists of all included studies and any relevant review articles were screened for literature not discovered via the database search.

Study Selection and Data Extraction

The aim was to include randomized controlled trials (RCTs) and non-RCTs reporting LUTCPT and/or LUTSEP results. Duplicates, animal studies, studies not published as full text, non-original articles, and studies reporting on LUT electrical stimulation for treatment purposes only were excluded. The titles and abstracts of all identified studies, as well as the full texts of remaining articles, were reviewed by two independent authors (S.v.d.L. and U.M.). Discrepancies were resolved by a third reviewer (S.C.K.). The bibliography management software Endnote X7 (Thomson Reuters, Philadelphia, PA, USA) was used.

All extracted data are listed in Tables S1–S3. The main outcome variables of this review were: LUTCPTs, latencies, amplitudes, and responder rates of LUTSEP recordings.

Risk-of-Bias Assessment

The methodological qualities of the RCTs were assessed according to the Cochrane Reviewer's Handbook [10] with 'low', 'high', or 'unclear' risk of bias (RoB).
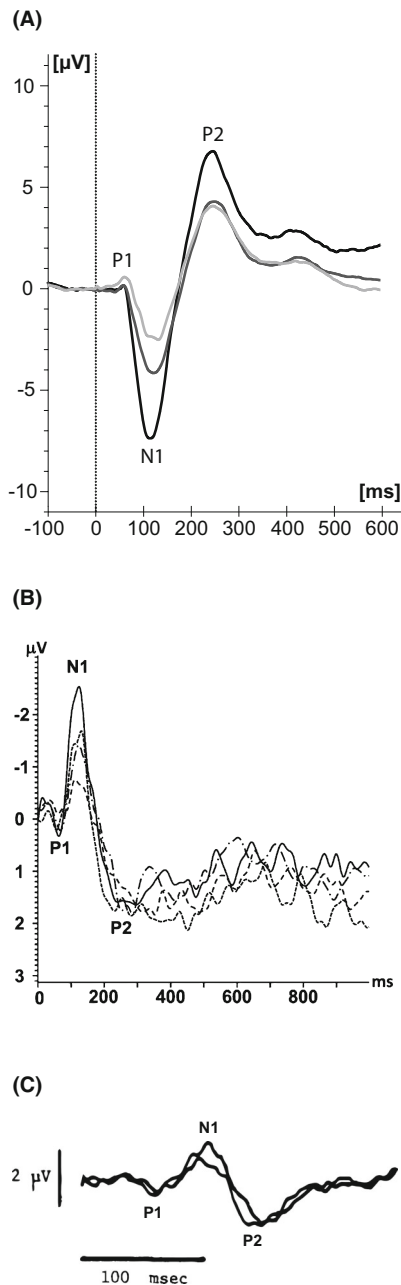
For the RoB assessment in non-RCTs, extra items were used to assess the risk of findings being explained by confounding. This is a pragmatic approach informed by methodological literature pertaining to evaluation of RoB in non-RCTs [10,11]. For each included study it was stated whether each confounder was taken into consideration and whether, if necessary, the confounder was controlled for in the respective analysis. The RoB assessment was performed independently by two authors (S.v.d.L. and U.M.) and discrepancies were discussed.

Data Synthesis and Analysis

Means and standard deviations (SDs) or means/medians and ranges (minimum–maximum or interquartile range [IQR]1–IQR3), where appropriate, were indicated for continuous variables, while percentages were used for dichotomous variables.

Because of the limited amount of available RCTs ($n = 5$), we pooled RCTs and observational studies during all exploratory analyses and partly ignored differences in study design.

Whenever enough data were available, meta-analyses were performed using a random-effect model. With the data of HS, meta-analyses on LUTESA outcomes (CPTs, SEP latencies [P1, N1, P2], SEP peak-to-peak amplitudes [P1N1, P2N1]; Fig. 1) were performed considering different confounders (e.g. stimulation frequency, location, gender, waveform, or stimulation algorithm). Since the stimulus waveform

(A)

(B)

(C)

Fig. 1 Representative examples of lower urinary tract sensory evoked potentials (SEPs) from different studies showing the three typical peaks, P1, N1, and P2. Please consider the varying scaling of the x- and y-axis and the different arrangement of the negative/positive scale of the y-axis. (**A**) Baseline-corrected SEP group averages across two visits after a constant stimulation duration of 300 s. SEPs were recorded from Cz-Fz during stimulation at the bladder dome (*n* = 20 subjects) with the three different stimulation frequencies: 0.5 Hz (black), 1.1 Hz (dark grey) and 1.6 Hz (light grey) [74]. Graph adapted from *van der Lely S. et al. Scientific Reports 2019, 20 (9): 19478* according to Creative Commons Attribution 4.0 International License: http://creativecommons.org/licenses/by/4.0/. (**B**) SEP group averages recorded from Cz-Fz during 0.5 Hz electrical stimulation in the lower urinary tract of 10 healthy female subjects. Black curves indicate the bladder dome. Dashed curves with square dots indicate the trigone. Dashed lines indicate the proximal urethra. Dashed lines with long dashes and dots indicate the distal urethra [85]. Graph adapted with permission from Wolters Kluwer Health, Inc.: *Gregorini F. et al., Sensory Evoked Potentials of the Human Lower Urinary Tract, The Journal of Urology 2013, 189 (6): 2179-2185*, https://www.auajournals.org/journal/juro. The Creative Commons license does not apply to this content. Use of the material in any format is prohibited withouit written permission from the publisher, Wolters Kluwer Health, Inc. Please contact permissions@lww.com. (**C**) Cortical evoked potential to bipolar stimulation of the vesico-urethral junction [8]. Reprinted from *Electroencephalography and clinical Neurophysiology, 65, Sarica Y. et al., Cerebral Responses Evoked by Stimulation of the Vesico-Urethral Junction in Normal Subjects, 440-446, 1986*, with permission from Elsevier. The Creative Commons license does not apply to this content. Use of the material in any format is prohibited withouit written permission from the publisher, Elsevier. Please contact https://service.elsevier.com/app/contact/supporthub/permissions-helpdesk/.

significantly impacts the character of the stimuli [12], the influence of stimulation frequencies and locations on LUTCPTs was analysed separately for sine (SiWS) and square wave stimulation (SqWS). In addition, meta-analyses were used to compare LUTESA data of HS groups to those of patient groups (mixed study populations were excluded) and to assess the impact of different interventions (baseline/pre intervention – post intervention) on LUTCPTs.

Forest plots were generated to supply visual representations of the results and to display the direction and magnitude of the effects. This was performed using the *metan* command in the Stata IC 16.0 software package (StataCorp, College Station, TX, USA).

Q–Q plots were used to assess data distribution optically. Data were assumed to be approximately normally distributed. Meta-regressions were performed to evaluate the effects of participants' age on the primary outcomes of interest (across all participants; only including HS). A significance level of $P < 0.05$ was used.

A RoB summary was generated using RStudio (Version 1.1.453; Boston, MA, USA) but in analogy to the Cochrane RevMan software v.5.3 (Informatics and Knowledge Management Department, Cochrane, London, UK), and edited using Adobe Illustrator CC 2017.

Results

Data Synthesis

The PRISMA flow diagram of the literature search is shown in Fig. 2. We identified 13 710 records and, overall, 80 reports (five RCTs, 75 non-RCTs) were included in the present review (Table S1; Fig. 2).

Fig. 2 PRISMA flow diagram [104].
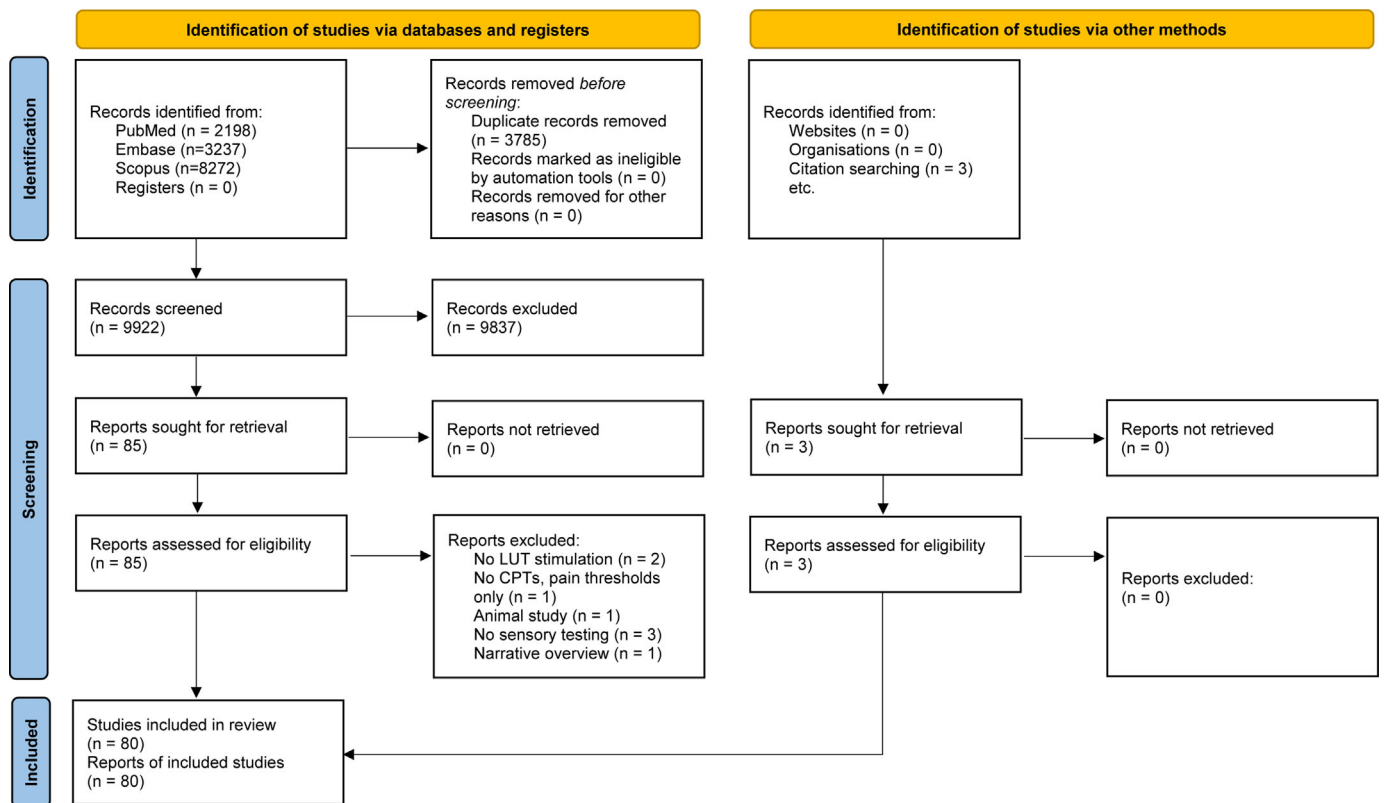
Out of 80 studies, 61 exclusively applied CPTs [6,7,13–71], but four reported incomplete or no CPT results [14,32,61,64] (Table S2).

Nineteen studies assessed LUTSEPs [8,72-89] (five studies showed corresponding CPT results [73–75,78,82]; 14 studies reported incomplete or no CPT data [8,72,76,77,79–81,83–89], Table S3).

Data pooling for meta-analysis was limited because of the large variability and heterogeneity of study designs and methods. Where applicable, outcomes of LUTCPT meta-analyses are mentioned in the subsections below. The outcomes of the meta-analyses regarding LUTSEPs are summarized in Appendix S1.

Characteristics of Study Participants

Overall, 4450 participants (+ an unclear number of participants from two studies [6,14]) were investigated (Table S1): 2239 female subjects (50.3%), 1363 male subjects (30.6%), and 848 (19.1%) without reported gender. Age ranged from 1 to 89 years (the mean age of the majority of the studies ranged between 40 and 60 years; 28 studies insufficiently reported age). A total of 692 HS and 3732 patients were included (+ an unclear number and/or
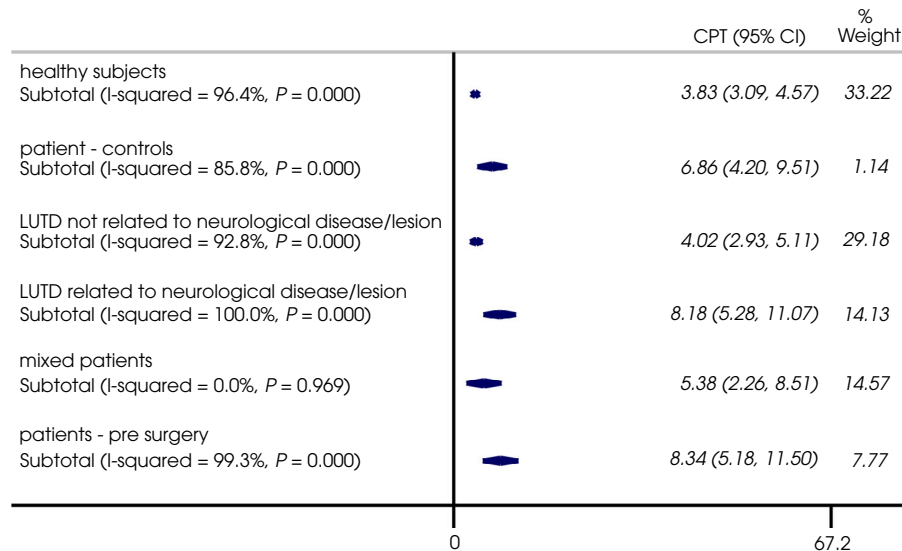
classification of participants from three studies [6,14,15]). Of 3732 patients, 1067 (28.6%) had LUTS/LUTD related to neurological disease/lesion, 1636 (43.8%) had LUTS/LUTD not related to neurological disease/lesion, 327 (8.8%) had pelvic surgery, and 260 (7.0%) served as controls (e.g. patients planned for oncological surgery, patients without obvious clinical signs of LUTD/LUTS or urodynamically 'normal' patients). The number of participants and/or classification of LUTS/LUTD aetiology were unclear in six studies [6,14,15,16,17,18].

Influence of Subject Characteristics

Of 80 studies, 13 (16.3%) reported the impact of age on LUTESA, but with conflicting results [15,19,20,21,22,23,24,25,72,73,74,75,76]. Pooling the data of all available studies in a univariate model, increasing age was significantly correlated with higher LUTCPTs ($r = 0.03$, $P = 0.011$; only HS: $r = 0.04$, $P = 0.079$ [trend]).

Gender-specific LUTESA results were shown by six studies, but only five of 80 studies (6.3%) statistically assessed the influence of gender on LUTESA. While these studies revealed conflicting results [22,26,27,74,75,77], the meta-analyses of this review indicated no influence of gender on LUTCPTs.

Fig. 3 Effect of study population on lower urinary tract current perception thresholds. Average current perception thresholds for each panel are shown as diamonds. The category 'mixed patients' includes studies where the investigated population consisted of different patient groups and studies with unknown group allocation. All data have been analysed using a random-effect model. For more details see Fig. S1. LUTD, lower urinary tract dysfunction.

	CPT (95% CI)	% Weight
healthy subjects Subtotal (I-squared = 96.4%, P = 0.000)	3.83 (3.09, 4.57)	33.22
patient - controls Subtotal (I-squared = 85.8%, P = 0.000)	6.86 (4.20, 9.51)	1.14
LUTD not related to neurological disease/lesion Subtotal (I-squared = 92.8%, P = 0.000)	4.02 (2.93, 5.11)	29.18
LUTD related to neurological disease/lesion Subtotal (I-squared = 100.0%, P = 0.000)	8.18 (5.28, 11.07)	14.13
mixed patients Subtotal (I-squared = 0.0%, P = 0.969)	5.38 (2.26, 8.51)	14.57
patients - pre surgery Subtotal (I-squared = 99.3%, P = 0.000)	8.34 (5.18, 11.50)	7.77

Body height was positively associated with LUTCPTs [21]. For LUTSEPs, one study reported that increasing body heights resulted in longer latencies and unaffected amplitudes [74], whereas another study revealed no impact on latencies [72].

Patients with LUTS/LUTD

Patients with neurological diseases or lesions such as diabetic neuropathy or spinal cord injury generally demonstrated higher CPTs compared to controls [7,26,28,29,30,31,32,78].

In non-neurogenic overactive bladder (OAB) patients, results were more conflicting, as some studies demonstrated higher LUTCPTs in patients with OAB compared to controls [19,33], while other studies showed no difference [25,34] or decreased LUTCPTs [35]. Patients with stress urinary incontinence have been reported to show elevated CPTs compared to controls [36], with no difference compared to patients with OAB [25]. In addition, decreased urethral sensitivity was shown in girls with bed-wetting [37].

Our meta-analyses demonstrated that LUTCTPs were significantly lower in HS and patients with LUTD not related to neurological disease/lesions compared to patients with LUTD related to neurological disease/lesions and patients before pelvic surgery (reconstructive or cancer; Figs 3,S1 for more details). LUTSEPs were shown to be absent or protracted in neurological patients compared to HS or non-neurogenic patients [76,78,79,80]. In patients with complete spinal cord injury, no LUTSEPs could be recorded [78,81].

Effect of Interventions

Twenty-nine studies listed CPTs before and/or after an intervention (Table S2). Of these, one study additionally evaluated changes in LUTSEPs after surgery.

Drug Treatment

Antimuscarinics Three of six studies reported increased CPTs after treatment with antimuscarinic drugs (i.e. tolterodine, oxybutynin) in HS as well as in patients with idiopathic or neurogenic LUTD [38–40]. However, three other studies showed either unaltered or decreased CPTs after antimuscarinic treatment (solifenacin, tolterodine) in HS and non-neurogenic LUTD (urgency urinary incontinence) patients [41–43].

Bethanechol In HS it was shown that bladder CPTs decreased with bethanechol [44]. The same was observed in patients with voiding difficulties, but only in those with positive response to bethanechol [45].

Resiniferatoxin Two studies investigated the effect of intravesical resiniferatoxin therapy on bladder CPTs, with a special focus on the responsiveness of C-fibre afferents, which are supposed to be mainly affected by this neurotoxin. Resiniferatoxin treatment seems to increase 5 Hz CPTs in patients with idiopathic LUTD [46] and spinal cord injury (single case study) [31]. However, there was no significant change at group level [46].

Different drug treatments The effect of pseudoephedrine extended release 120 mg, imipramine 25 mg, cyclobenzaprine 10 mg, tamsulosin 0.4 mg, solifenacin 5 mg, and placebo on urethral CPTs was investigated in a cohort of HS. A trend towards increased sensation, i.e. decreased CPTs, was demonstrated after treatment with pseudoephedrine (only 5 Hz), while sensation was not changed by the other medications or placebo [42].

Pelvic/Abdominal Surgery

Thirteen studies compared LUTCPTs of pelvic surgery patients to (preoperative) controls. Most studies reported decreased LUT sensitivity after pelvic surgery [24,30,47,48,49,50,51,82], however, some studies indicated location-specific differences [7,20,52,53].

In addition, the LUTSEP responder rate was strongly reduced after radical retropubic prostatectomy [82].

Sacral Neuromodulation

The two available studies on sacral neuromodulation demonstrated contradictory effects of such therapy on bladder CPTs, but no effect on urethral CPTs [16,18]. The relevant changes in bladder CPTs, however, were only observed when CPT assessment was performed with frequencies intended to activate A-beta and A-delta fibres [16].

Other Interventions

Rectal distension Trigonal CPTs were shown to be significantly higher when the rectum was distended compared to an empty rectum [54].

Ice water test Patients with a negative ice water test seemed to have lower CPTs compared to patients with a positive ice water test (IWT). In patients with a positive IWT, no significant differences in CPTs were demonstrated between neurological and non-neurological patients (except after the third instillation). In those with a negative IWT, the CPTs were significantly higher in neurological patients [28].

Lidocaine jelly instillation in urethra Lidocaine jelly considerably increased penile and bulbar urethral thresholds compared to a lubricant without lidocaine [55].

Intramuscular administration of opiate analgesic drugs While opiate analgesics caused a significant decrease in urethral sensitivity, opiate/opioid antagonists caused a significant increase [56].

The meta-analysis indicated the largest changes in LUTCPT values after pelvic surgery (increased CPTs after intervention) as well as the application of bethanechol (decreased CPTs after intervention, Fig. 4).

Technical Aspects of LUTESA

In principle, LUTESA uses the electrical field generated between two electrodes to stimulate afferent nerve fibres. Various technical approaches have been applied.

Electrode Configuration and Positioning in the LUT

Most studies (85.0%) reported the use of ring electrodes mounted on a transurethral catheter (exceptions: one study used the suprapubic route [30] and two studies used a cystoscope to introduce the electrodes [81,83]). The electrode diameter and width as well as the distance between electrodes were only partly reported and varied among studies (Table S1).

For LUTESA, predominantly bipolar stimulation (78.8%, current flows between two electrodes that are placed in the LUT within a distance of a few millimeters) was used, while monopolar stimulation (current flows between an electrode in the LUT and a remote reference electrode elsewhere [i.e. thigh]) was reported by 12.9% of studies (stimulation type unclear for 8.2% of the studies). Bipolar stimulation led to significantly lower LUTCPTs [34], lower LUTSEP amplitudes and fewer SEP deflections at shorter latencies [79,81,83,84] compared to monopolar stimulation.

When the catheter-mounted stimulation electrodes were positioned in the trigone or urethra, lower CPTs were reported by several studies compared to a positioning at the bladder dome [20,22,26,27,57,58,73]. Accordingly, the conducted meta-analysis showed increased sensitivity at the vesicourethral junction (including also bladder neck, proximal urethra [pUR]), distal urethra (dUR) and female urethra compared to the bladder area, but only when using SqWS (Fig. S2a,b).

Although LUTSEP studies reported variable effects of stimulation locations on latencies [8,72,73,77,85,86], amplitudes rather consistently decreased from bladder to distal urethral locations [72,73,85].

Character of Electrical Stimulus

Although most LUTESA studies (79.3%) used SqWS, some studies (20.7%) applied supposedly neuroselective SiWS (Table S1). The meta-analyses indicated lower LUTCPT values for SiWS compared to SqWS. For LUTSEP recording, only SqWS was used.

With increasing stimulation frequencies, the meta-analysis with HS data indicated a trend towards rising CPTs for SiWS

(Fig. S3a). When using SqWS, higher stimulation frequencies led to decreased CPTs, but only when comparing 250 Hz to lower stimulation frequencies (0.5–3 Hz; Fig. S3b).

Studies on LUTSEP showed higher amplitudes and responder rates when using slow frequencies (i.e. 0.5 Hz) as compared to higher stimulation frequencies [72,73,74,85].

In addition, LUTSEP potentials became clearer and more prominent with increasing intensity [8,75,77]. Intensities of 1.5–3 times the CPT were needed to constitute SEPs with amplitudes that allow clear peak detection of all SEP components [8,77].

In these studies, 80–2000 electrical stimuli were applied with at least one repetition (Table S3). An increasing number of consecutive stimuli, however, decreased SEP amplitudes,

responder rates and signal-to-noise ratio [74]. In HS, two runs of 100 stimuli at a frequency of 0.5 Hz were needed to achieve robust responses [74].

Bladder Filling

While the catheters were on constant drainage in 12.5% of all 80 studies, the bladder was often prefilled (36.3%) with a certain amount of saline or contrast agent, to provide a conductive medium for the electrical stimulation and/or to verify positioning of the stimulation electrodes (Table S1). Increasing levels of bladder filling seem to increase LUT electrical sensitivity if the different filling levels were a deliberate part of the investigation and constant contact of the stimulation electrodes to the LUT mucosa was assured

Fig. 4 Effect of different interventions on lower urinary tract current perception thresholds (CPTs changes: pre–post intervention). Size of the grey boxes is proportional to study weight and black lines represent 95% CIs. Summary estimates for each panel are shown as diamonds. Negative values indicate an increase in CPTs, positive values indicate a decrease in CPTs. All data have been analysed using a random-effect model. Some studies are listed multiple times because the same study populations were investigated with several parameters. * incontinent patients (after surgery), ** continent patients (after surgery). IWT, ice water test; LUTD, lower urinary tract dysfunction; m. of levels, method of levels; m. of limits, method of limits; mUR, membranous urethra; NOS, not otherwise specified; pw, pulse width; SMD, standardized mean difference; VUJ, vesicourethral junction.
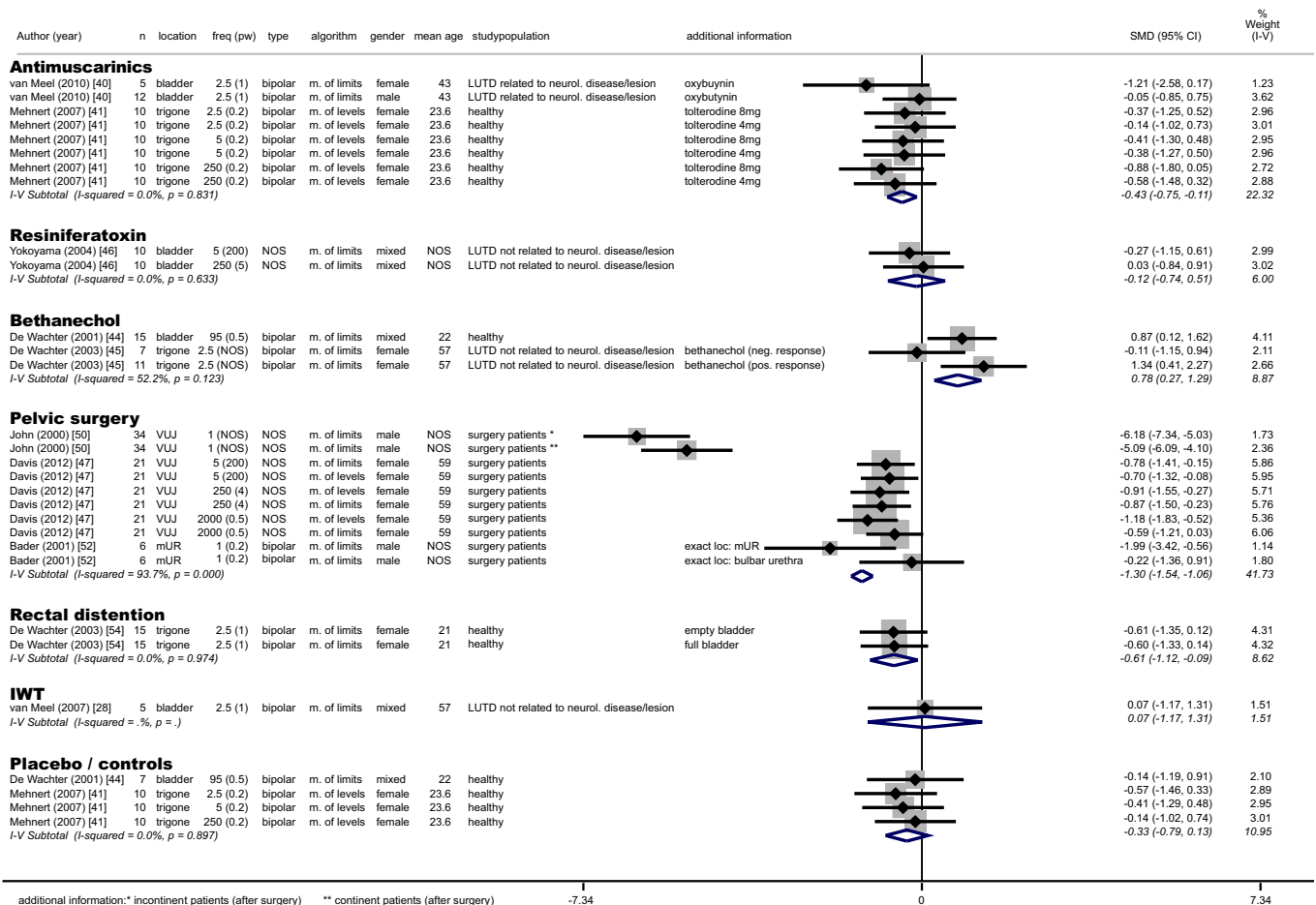
[59,60]. However, one study illustrated that bladder volumes can significantly increase during LUT stimulation [90], even unnoticed. This may cause unintentional displacement of the mucosa from the electrodes, resulting in higher CPTs [59].

Current Perception Threshold Detection

For CPT detection, two stimulation algorithms were used: method of limits (70.4%) and method of levels [91]. Although the methods of limits was more timesaving [47], it led to significantly higher CPT values [47]. The latter finding was supported by our current meta-analysis.

Sensory Evoked Potential Recording and Processing

The LUTSEPs were recorded with highest amplitudes when the scalp electrodes were placed at Cz, Cz-2 cm or Cz-2.5 cm referenced to Fz, FPz or the midpoint between Fz and FPz [8,77,79,81,85].

Three research groups reported LUTSEP sampling rates (500–5000 Hz) [8,72,73,74,79,81,84,85,86], but no comparative studies are available.

Previous studies used a wide variation of band-pass filters (Table S3). One study comparing two low-pass filters (70 Hz vs 200 Hz) revealed similar curve shapes without significant differences in latencies and amplitudes [74]. Nevertheless, manual marker setting was easier using the 70 Hz low-pass filter due to the smoother SEP curve [74].

Reliability of LUTESA

Reliability across visits was assessed by 10 studies (12.5%; interval: 7 days to 12 weeks). In general, LUTCPT reliability across visits was shown to be good to excellent [25,27,45], but reliability differed between locations [22,58]. In addition, a better reliability was shown for slow compared to faster stimulation frequencies (i.e. 3 Hz) [58] and for SqWS compared to SiWS [34].

Agreement between visits with regard to LUTSEPs was demonstrated to be good for mean LUTSEP waveforms [72], with higher reliability for lower compared to higher stimulation frequencies [73,74,85]. In addition, greater reliability was reported for latencies compared to peak-to-peak amplitudes [74,85]. Intraclass correlation coefficients of N1 and P2 LUTSEP latencies were shown to be comparable to intraclass correlation coefficients of latencies of clinically established pudendal SEPs when stimulating with lower stimulation frequencies [74].

Moreover, good inter-rater agreement was reported for manual LUTSEP peak detection [72].

Safety of LUTESA

Out of 80 studies, 15 (18.8%) reported adverse events (AEs; Table S1): dysuria ($n = 123$ + unclear number from one study [73]); haematuria ($n = 13$); fatigue and headache (one study not indicating exact number [41]*); nausea and vomiting ($n = 1$); irritating tickling in the meatus ($n = 1$); discontinued medication due to side effects ($n = 4$*); constipation ($n = 2$*); dry mouth ($n = 4$*); severe urgency during resiniferatoxin instillation ($n = 6$*); catheterization problems ($n = 34$ + unclear number from three studies [37,61,74]); and uncomfortable feeling caused by catheter/stimulation ($n = 7$ + unclear number from one study [74]). However, several AEs were obviously related to the applied drug treatment (marked by *) rather than LUTESA. All reported AEs were self-limited and did not require medical therapy. In 14 studies (17.5%), oral antibiotics were given post measurement to prevent urinary tract infections [19,20,21,27,28,29,34,35,36,40,44,57,62,63,64].

Risk of Bias and Confounding

Risk of bias and confounding was relevant in both RCTs and non-RCTs (Fig. 5). In particular a high risk of selection (allocation concealment) and performance bias was found.

Discussion

Consistent with our aim, the present review compiles important knowledge on LUTESA as a diagnostic tool to assess LUT afferent function. In addition, methodological details of applied LUTESA techniques and also potential confounders were summarized, categorized and, where possible, analysed on a meta-level to allow a conclusive overview. The extracted studies show that LUTESA is a feasible and safe approach to evaluating the sensitivity and integrity of LUT afferent pathways in HS and patients [86,92]. LUTESA is sensitive enough to detect differences between HS and patients with known or expectable neurological diseases/lesions. CPTs are generally elevated in patients with neurogenic LUTD compared to HS, which can be attributed to the neurological impairment. Correspondingly, LUTSEP studies demonstrated reduced responder rates and protracted SEPs in patients with neurogenic lower urinary tract dysfunction compared to HS. In populations without overt neurological diseases/lesions, however, the difference compared to HS becomes less clear. Yet, patients with LUT cancer (prostate, bladder) had higher LUTCPTs compared to HS, which may be indicative of localized cancer-related impairment of nerve conduction.

In addition, LUTESA was used to assess the effect of different interventions on LUT afferent function. Pelvic surgery decreased afferent sensibility, indicating surgery-related

Fig. 5 Risk-of-bias summary for randomized controlled trials (RCTs) (**A**) and non-RCTs (**B**). RCTs: $n = 5$; non-RCTs: $n = 75$. Note: 'description of study population': required complete information on the study group including the underlying diseases, lower urinary tract symptoms/lower urinary tract dysfunction; 'age of study population': required information on mean age ± SD or median (range); 'age-/gender matching': NA if only one group or if the same participants were included in the different groups; 'stimulation parameters': required information on frequency, pulse width and waveform; 'electrode specifications': required information on electrode size, area of electrodes and distance between electrodes; 'positioning of electrodes at stimulation location': required information on the exact placement of the two electrodes in the LUT; 'randomized order of stimulation frequencies/ locations': NA if only one frequency/one location, other sensory evoked potential recordings (i.e. pudendal sensory evoked potentials [SEPs]) were considered for the evaluation of location order; 'impedance recording electrodes, position of active/reference recording electrode, data assessment filter, number of averaged segments, segment length, latencies and amplitudes, description of peak finding': NA was added for current perception threshold (CPT) studies.
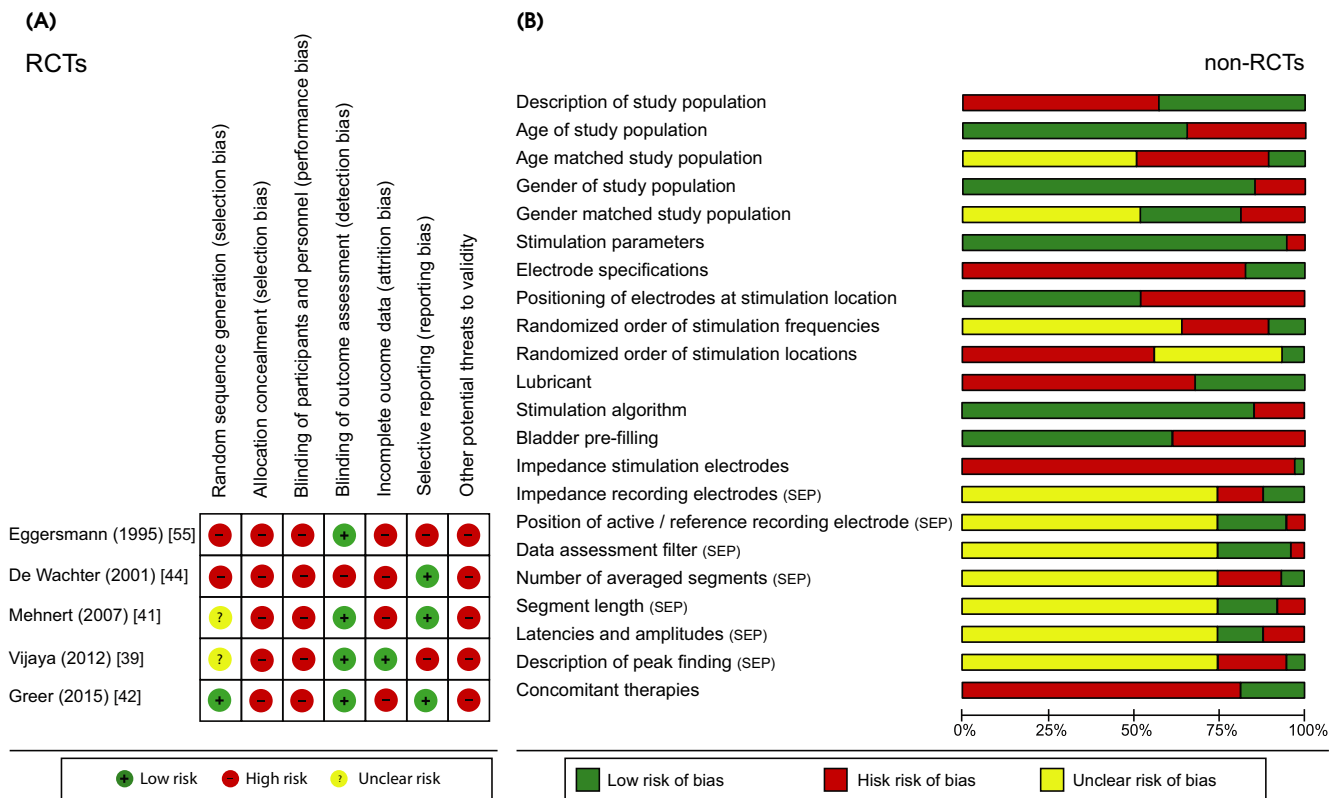
lesions of peripheral LUT nerves. The observed variations in location-specific LUTCPT changes following surgery may be attributed to the different surgical approaches and extent of surgery [7,20,52,53].

Subcutaneous application of the muscarinic receptor agonist bethanechol led to increased LUT sensitivity [44,45], which is in line with the finding that LUT afferents express muscarinic receptors that can be excited by agonists and inhibited by antagonists, respectively [93]. As expected, lidocaine jelly applied into the urethra significantly reduced urethral CPTs [55]. However, other interventions on LUT afferent nerve function, such as oral antimuscarinics, sacral neuromodulation, and resiniferatoxin bladder instillation showed somewhat inconclusive results (Fig. 4). This may be attributable to different reasons such as patient/subject selection, but also varying technical approaches with regard to

electrode configuration, stimulation location, stimulation algorithm, stimulation waveform and frequency.

Regarding electrode configuration, bipolar stimulation has been preferred since it enables a more location-specific stimulation, whereas monopolar stimulation can unintentionally excite multiple structures between anode and cathode [34,79,81,83,84]. To reach LUT stimulation locations, electrodes were mainly mounted on a transurethral catheter that was positioned at the required location (Table S1). A location-specific effect was demonstrated for CPTs using SqWS, which corresponds well to the known unequal distribution of the sensory nerve plexus that has its highest density around the trigone [94,95]. Another aspect in this regard is the distance of the stimulation electrodes to the LUT mucosa as it could be demonstrated that the current decreases to almost 1% of the actual output current within a

radius of 10 mm [59]. This is important, as conditions in the LUT do not remain stable due to diuresis and consequently changes in bladder filling [90], which can affect electrode position, particularly in the bladder, and potentially also afferent activity, e.g. increased urethral CPTs [59]. Therefore, some studies performed LUTESA with constant bladder drainage through the catheter (Table S1) to avoid any influence from bladder filling.

Despite the less stable and thus more challenging conditions in the LUT compared to standard neurophysiological assessments at cutaneous sites, a good test-retest reliability can be achieved when ensuring constant bladder pre-filling and equal placement of stimulation electrodes across visits [58,74].

To assess LUTCPTs, two main stimulation algorithms were applied: the 'method of limits' and the 'method of levels'. The shorter investigation time but higher CPTs using the method of limits [47] has to be regarded with caution, since the method of limits was mainly performed manually, whereas the method of levels was applied semi-automatically. Hence, the type of applied stimulation algorithm may be less relevant compared to the execution, whereas semi-automated application seems to be more accurate as the investigator-related bias is excluded.

In regard to the waveform of the stimuli, LUTSEP studies used SqWS only, probably because it is the standard in neurophysiological testing [92,96]. Some LUTCPT studies also used SiWS with the aim of neuroselectively stimulating C-, A-delta and A-beta fibres using five, 250 and 2000 frequencies, respectively [20,27]. This neuroselectivity, however, has never been proven for the LUT. The skepticism is supported by a study lacking to demonstrate a significant difference in 5 Hz CPTs before and after resiniferatoxin instillation into the bladder [46], although resiniferatoxin should desensitize afferent C-fibres [46,97]. Furthermore, CPT studies persistently reported CPT values after 2000 Hz stimulation of the bladder mucosa, which would indicate the presence of A-beta fibres [16,19,20,27,31,35,39,42,43,47,48,65]. However, A-beta fibres have never been described in the LUT [3].

The lower CPTs with SiWS compared to SqWS could be explained by the larger energy input due to the continuous wave form. With increasing frequency, however, this may revert, as the sine waves become narrower and the area under curve decreases, while with square waves the single stimuli accumulate. Figure S3a shows this frequency effect on LUTCPTs for SiWS, although this was nonsignificant (only two studies available for meta-analysis [27,31]). For SqWS, the frequency effect becomes significant for frequencies below 5 Hz vs 250 Hz but the overall picture is less clear (Fig. S3b) due to a larger and inhomogeneous amount of studies and the fact that different pulse widths were used.

A location-specific effect as described for SqWS could not be observed for SiWS (Fig. S2a,b). Whether this makes SqWS the more physiological method remains to be elucidated.

In regard to stimulation frequency, various parameters have been applied (0.5–2000 Hz), mainly without a clear rationale, except for the sine wave neuroselectivity hypothesis. From a neurophysiological view point, lower frequencies appear more suitable for the LUT slow-conducting fibres due to a more synchronous excitation and less refractoriness of these fibres. This is supported by the findings of increased LUTSEP reliability, responder rate and amplitudes (especially P2N1) for lower stimulation frequencies [72,73,74,85].

For successful LUTSEP assessment, additional aspects have to be considered: stimulation intensity, stimulation duration, and recording set-up. Selecting the stimulation intensity in relation to the CPT is an approach used in clinical neurophysiology that has also been suggested for LUTSEPs using 1.5–3 times the CPT to allow recording of clear cortical potentials [8,77]. In addition, reliable SEP recording requires a certain number of repeated stimuli. Too few (no clear extraction of SEP from brain signals not time-locked to the stimuli) but also too many stimuli (habituation, decreasing subject attention, longer investigation with higher likelihood of changes in bladder volume) may impede adequate recording. While for HS, 200 stimuli have been suggested as the optimal choice with good SEP peak-to-peak amplitudes [74], it remains to be investigated if this is also true for patients. For LUTSEPs, recording parameters are equally important as stimulation parameters. Inappropriate settings (e.g. wrong cortical recording position, too low sampling rates or band-pass filters removing important frequency components of the signal), could alter SEP characterization and/or lead to the disappearance of particular components.

Two patient/subject characteristics that could be particularly relevant for LUTESA are age and gender. Despite the fact that some studies reported possible age and gender effects on LUTESA, a systematic evaluation is still lacking and results between studies are controversial, e.g. previous human and animal studies showed that aging was associated with loss of afferent nerve function [19,98,99,100], but also increased afferent excitability [73,101]. Hence, a conclusion is currently pending.

Another influencing factor that is often associated with gender is body size. Urethral CPTs were shown to increase with participants' height [21] and a positive correlation was also indicated for LUTSEP latencies [74]. Consequently, body height should not be neglected, especially when comparing the LUTESA data obtained in males, who are on average taller, with those of females [102].

Limitations

The present review has some limitations. The extracted studies report on various methodological approaches and study populations, which, on the one hand, offers a broad perspective on this kind of investigation but, on the other hand, results in a substantial variability and heterogeneity among studies. This hampers summary presentation and in particular meta-analysis. Consequently, further stratification during meta-analysis was often not possible and differences in study design had to be partly ignored. In addition, the five identified RCTs reported exclusively CPT results with a high RoB and low statistical power. Hence, conclusions can only be drawn to a limited extent because most studies were observational without comparators and due to insufficient reporting of important information on study design (e.g. assessment order, exact number of applied stimuli for SEP recording), study population (often mixed populations, LUTS or LUTD not clarified), methods and outcome measures (e.g. CPT unit not clearly stated, only LUTSEP latencies reported, without information on amplitudes).

Furthermore, only half of the available studies were eligible for the meta-analyses on LUTSEP data (e.g. 10 of 19 studies when comparing N1 latency data of HS (five studies) to patients (five studies; Appendix S1).

In addition, the current LUTSEP meta-analyses results (see Appendix S1) should be interpreted with caution due to presentation of deviant SEP configurations observed in earlier studies (multiphasic configurations with shorter SEP latencies [8,76,80,82,83,84,86]) compared to more recent studies (triphasic P1, N1, P2 configurations with latencies corresponding to the transmission of A-delta fibres [72,73,85]). This resulted in unbalanced data pooling (e.g. most patient data from earlier studies vs HS data from recent studies), creating significant differences that do not correspond to the current neurophysiological understanding of SEPs. Possible explanations for the different LUTSEP morphologies in the older studies are as follows:

- Nearby faster conducting fibres, i.e. branches of the pudendal nerve, were recruited (e.g. when applying urethral stimulation, monopolar stimulation and/or increased stimulation intensities).
- In consequence, markers in those studies were placed on the earlier SEP peaks potentially originating from the pudendal nerve. This is supported by the example figures of the potentials in these studies and the lower amplitudes of these early potentials.
- Varying filter settings (higher low- and high-pass filters in earlier studies, Table S3) that largely impacted SEP morphology and marker setting (Fig. S4).

LUTESA itself covers only part of the innervation at spinal cord level, similar to somatosensory evoked potentials, which are tract-specific. Furthermore, the cortical LUTSEP recording approach does only provide information on signal transduction of the whole neuroaxis (from the site of stimulation to the cortical recording site) without differentiating between different levels. A more precise localization of the lesions/problems and an approximation of spinal transit time could, however, be achieved by a segmental evaluation, including simultaneous recordings of spinal and cortical SEPs.

Finally, the LUTESA technique requires specific equipment and knowledge that may not be readily available everywhere. However, this is typical for many diagnostic tools in their initial phase. Actually, considering LUTESA, all neurophysiological stimulation and recording material and devices are commercially available and there are even catheters for urethral and bladder mucosa stimulation commercially available (e.g. Neurotron). In this context, it may be relevant for the future to also estimate the cost/benefit ratio once this diagnostic tool is to be further considered for implementation into clinical practice.

Value of this Review and Future Potential of LUTESA

This review provides the first overview of the current status of research and development of LUTESA. It provides a picture of the methodological variables and their potential impact on the outcome parameters. Further investigations can build from here to optimize protocols and to better control for confounders. This would allow standards regarding the procedure and outcome reporting to be defined, which is a prerequisite for integration of LUTESA in clinical LUTS assessment. Despite the above-mentioned limitations, LUTESA could help to correctly classify pathological findings and complement the limited assessment of LUT afferent function (i.e. perineal sensation with light digital touch, filling sensations during UDIs) towards a more comprehensive neurophysiological evaluation of the whole LUT, i.e. bladder and urethra [29,64,66].

Furthermore, LUTESA could serve as an instrument to monitor the effect of drug and surgical treatments on LUT sensory pathways [103] in research and clinics. SEP recording may even serve to perform intra-operative monitoring during pelvic surgery.

CONCLUSIONS

Although LUTESA techniques and outcome measures differed widely among studies, this review summarizes relevant information on LUTESA and shows that LUTCPT and LUTSEP assessments are feasible and safe approaches to reliably evaluate bladder and urethral afferent pathways in HS and patients with LUTS/LUTD. Such tools complement already established, diagnostic methods such as UDIs and thereby improve qualitative assessment of LUT afferent

function. Whether LUTESA can finally fill, at least partly, the postulated gap in LUT diagnostics needs to be further elucidated. However, standardization on LUTESA conduction and reporting is necessary to exploit the full potential of this promising methodology.

Acknowledgements

Conflict of Interest

A. Sartori is an associate member of the European Association of Urology (EAU) Guidelines on Neuro-Urology panel. T. M. Kessler received funding and is chief investigator or co-investigator on multiple current and previous research grants funded by SNSF, Swiss Paraplegic Foundation, Swiss Continence Foundation, Balgrist Foundation, and University Medicine Zurich (HMZ). He holds a patent (number: 16172056.0 – 1657), and is a member of the EAU Guidelines on Neuro-Urology panel, a treasurer of the International Neuro-Urology Society (INUS), chairman of the Swiss Continence Foundation (SCF), the president of the Swiss Society for Sacral Neuromodulation (SSSNM), and a section editor of the *British Journal of Urology International*. U. Mehnert received funding and is principle investigator or co-investigator on multiple current and previous research grants funded by the Swiss National Science Foundation (SNSF), SCF, Swiss Life Foundation, and Balgrist Foundation. He is vice-chairman of the SCF. All other authors declare no other relationships or activities that could appear to have influenced the submitted work.

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Abbreviations: AE, adverse event; CPT, current perception threshold; HS, healthy subjects; IQR, interquartile range; LUTD, lower urinary tract dysfunction; LUT, lower urinary tract; LUTESA, lower urinary tract electrical sensory assessment; OAB, overactive bladder; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; RoB, risk of bias; SEP,

sensory evoked potential; SiWS, sine wave stimulation; SqWS, square wave stimulation; UDI, urodynamic investigation.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Effect of study population on lower urinary tract current perception thresholds.

Fig. S2a. Effect of stimulation location on lower urinary tract current perception thresholds in healthy subjects using sine wave stimulation.

Fig S2b. Effect of stimulation location on lower urinary tract current perception thresholds in healthy subjects using square wave stimulation.

Fig. S3a. Effect of stimulation frequency on lower urinary tract current perception thresholds in healthy subjects using sine wave stimulation.

Fig. S3b. Effect of stimulation frequency on lower urinary tract current perception thresholds in healthy subjects using square wave stimulation.

Fig. S4. Example for the effect of different filters applied on LUTSEP data.

Table S1. Characteristics of the included LUTESA studies.

Table S2. Outcomes of the studies evaluating lower urinary tract current perception thresholds (LUTCPTs) at baseline/pre intervention and/or post intervention.

Table S3. Stimulation- and recording parameters of the lower urinary tract sensory evoked potential (LUTSEP) studies and outcome parameters.

Appendix S1. Search strategy, meta-analysis results for LUTSEP data.