The benefits and harms of Botulinum toxin-A in the treatment of chronic pelvic pain: A systematic review.

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Abstract

Context:

Patients with chronic pelvic pain (CPP) may have pain refractory to conventional management strategies. Botulinum toxin A (BTX-A) is a potential therapeutic option.

Objective:

To evaluate benefits and harms of BTX-A injections in the treatment of CPP.

Evidence acquisition:

A systematic review of the use of BTX-A in the treatment of CPP syndromes was conducted (PROSPERO-ID:162416). Comprehensive searches of EMBASE, PUBMED, Medline and SCOPUS were performed for publications between January 1984 and May 2020. Identified studies were screened and selected studies assessed for quality prior to data extraction. The primary outcomes were improvement in pain and adverse events following treatment. Secondary outcomes included quality of life, global response assessment, sexual function, bowel function and bladder function.

Evidence synthesis:

After screening 1001 abstracts, 16 studies including 11 RCTs were identified, enrolling 858 patients and covering a range of CPP syndrome subtypes. Most studies showed high risks of bias and confounding across all domains. A narrative synthesis was performed as heterogeneity of included studies precluded a meta-analysis and calculation of pooled effect estimates of measured outcomes. BTX-A significantly reduced pain in patients with bladder pain syndrome in 2 studies and prostate pain syndrome in one study, but no included studies showed benefit for patients with gynaecological pelvic pain. Adverse event reporting was variable and generally poor, but no serious adverse events were described.

Conclusions:

Beneficial effects of BTX-A on pain, quality of life and functional symptoms were seen in patients with certain CPP subtypes, but the current evidence level is too weak to allow recommendations about BTX-A use for treating CPP.

Patient summary:

Botulinum toxin A is used to treat different pain disorders, but current studies are of insufficient quality to determine whether it reduces pain and improves quality of life in patients with chronic pelvic pain. Further research is needed.

Keywords: Chronic pelvic pain syndrome, bladder pain syndrome, prostate pain syndrome, gynaecological pain syndrome, myofascial pelvic pain, botulinum toxin A, chronic anal fissure

1. Introduction

Chronic pelvic pain (CPP) refers to chronic or persistent continuous, recurrent or cyclical pain perceived in structures related to the pelvis of men or women for at least six months [1]. This pain may be due to well-defined pathology such as infection or neoplasia, but is referred to as a CPP syndrome (CPPS) if it develops without identifiable disease. Animal and clinical research suggest that many mechanisms underlying CPPS are centrally mediated with central sensitisation and neural pathway modulation maintaining pain perception in the absence of an ongoing peripheral trigger or pathology [2].

CPPSs are associated with negative cognitive, behavioural, sexual, psychological and emotional consequences. Affected individuals can develop symptoms of lower urinary tract (LUT), sexual, bowel, gynaecological or pelvic floor dysfunction. The true prevalence of CPPS is not known due to variations in diagnostic criteria, evaluation tools and symptom overlap with other conditions, but has been reported at 5.7% in women and 2.7% in men [3].

CPP management is based on a biopsychosocial model with active patient involvement. Treatment options comprise physical therapies, psychological interventions, pharmacotherapy and surgery. Single interventions rarely work in isolation and multimodal approaches are needed within a broader personalised management strategy. Botulinum, a bacterial neurotoxin, has been used to treat a variety of pain disorders including CPP [4]. The toxin is a pre-synaptic neuromuscular blocking agent that inhibits release of the neurotransmitter acetylcholine from nerve endings. This causes temporary skeletal muscle relaxation and produces an indirect analgesic effect by reducing dysfunctional muscle hyperactivity. Botulinum toxin has also been shown to reduce pain directly by producing molecular changes in nociceptive fibre function and modulating the release of different neuropeptides involved in pain genesis [5-7]. There are eight serotypes of botulinum and seven are neurotoxins [8]. Botulinum neurotoxin type-A (BTX-A) is the most commonly produced for clinical use and there are three different formulations: onabotulinum-toxin-A (onaBTX-A; Botox®), incobotulinum-toxin-A (incoBTX-A; Xeomin® or Lantox ®) and abobotulinum-toxin-A (aboBTX-A; Dysport®) [9]. All formulations have a statistically significant therapeutic effect compared to placebo, but comparisons between formulations are rare in the published literature [10]. There are significant disparities amongst studies assessing the effects of BTX-A in the treatment of pain disorders. The objective of this systematic review (SR) was to determine the efficacy and safety of BTX-A injections in the treatment of CPPS.

2. Evidence acquisition

This SR was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [11] and followed the key steps and methodology set out by the European Association of Urology (EAU) Guidelines Group [12]; PROSPERO-ID:162416.

2.1 Data sources and searches

A comprehensive search of EMBASE, PUBMED, Medline, SCOPUS and the Cochrane Central Register of Controlled Trials was performed for papers published between January 1984 and May 2020. The search strategy and keywords used are available in the supplementary material. Titles and abstracts were retained for screening after search results were combined and deduplicated.

2.2 Study selection

Primary study design included randomised controlled trials (RCTs) and prospective or retrospective comparative non-randomised studies (NRSs) with a minimum of 3 months follow-up, as a shorter duration of clinical benefit would make repeat interventions impractical and difficult to justify. Comparative studies with ≤10 participants per arm or without at least one baseline measurement of interest were excluded. Single-arm case series were only included if no comparative studies were found. Case reports, editorial commentaries and narrative reviews were excluded. The reference lists of relevant SRs were searched for additional relevant studies. There was no language restriction.

The experimental intervention was BTX-A injections into any structures related to the pelvis for treating CPPS. Control groups comprised best clinical practice (including medication, bladder instillations, psychological interventions, physical therapy and surgery), no treatment, sham intervention or placebo. Additional inclusion criteria were adult participants (18 years and over) with CPPS; trials with assessment before and after treatment with BTX-A injections; and reporting primary outcomes of pain and treatment-related adverse events. All CPPS subtypes were included but studies with patients undergoing treatment for cancer (not excluding cancer survivors) and pelvic organ prolapse were excluded.

Two reviewers (SG and BP) independently screened titles and abstracts to identify potentially eligible studies, and then obtained and screened full text papers to determine the final included studies. A third reviewer (SD) was consulted for arbitration when needed. For studies with multiple publications, the main trial report was used.

2.3 Data extraction and risk of bias

Data was extracted using a standardised data extraction form. Collected data included year of publication, country of origin, number, sex and age of participants, type of CPPS, type and dose of BTX-A used, number and location of injections, duration of symptoms, type of medical therapy received prior to study participation and the outcome measures recorded. The primary outcomes were improvement in pain as defined by the trialist and treatment-related adverse effects. Secondary outcome measures were quality of life (QoL), global response assessment (GRA; not specific to pain), bladder, bowel and sexual function, and healthcare resource use.

The Cochrane Risk of Bias Assessment Tool was used for RCTs [13]. For non-RCT studies, a risk of confounding assessment was performed using an *a priori* list of confounders identified by clinical content experts (EAU CPP Guidelines Panel members). This enabled consideration of each confounder

and determination of whether it was controlled for. Identified confounders comprised gender, CPPS subtype, presence of bladder or bowel dysfunction and patient distress, depression or catastrophising.

2.4 Data synthesis

When continuous measurements were used to assess the intervention effect, the mean difference or standardised mean difference was calculated for each included study. The effect size and corresponding 95% confidence intervals were calculated for primary and secondary outcome measures. For dichotomous outcomes, the number of events in the control and intervention arms of each study were used to calculate Peto odds ratios. The clinical and methodological characteristics of included studies were considered and study heterogeneity assessed with the I-squared test. A value I^2>50% was taken to indicate significant heterogeneity. If included studies were sufficiently homogenous, their data was combined and an overall standard mean difference between treatment and control groups was calculated using a fixed effect model; otherwise a random effects model was used. Forest plots were generated to provide a visual representation of the results and illustrate the direction and magnitude of effects.

Analyses were performed using the OpenMeta[Analyst] software package (Centre for Evidence Synthesis in Health, Brown University, RI, USA). Risk of bias summary was generated using Cochrane Review Manager software version 5.3 (Informatics and Knowledge Management Department, Cochrane, London, UK).

3. Evidence synthesis

3.1 Search results

The PRISMA diagram illustrates the literature search and results (Figure 1). The search identified 1001 abstracts and following screening, 82 full text papers were retrieved and assessed for eligibility. The final 16 studies consisted of eleven RCTs and five comparative NRSs.

3.2 Study and patient characteristics

The characteristics of the included studies and their patient demographics are summarised in Table 1. Seven studies assessed use of BTX-A in bladder pain syndrome (BPS) [14-20], four in gynaecological pelvic pain (GPP) [21-24], three in prostate pain syndrome (PPS) [25-27], one in patients with chronic anal fissures [28] and one in patients with myofascial pelvic pain (MPP) [29]. Insufficient data was provided about funding sources and conflicts of interest. Two studies were funded by non-profit governmental agencies and two received unrestricted grants from a pharmaceutical company with interests in the trial (Allergan).

3.3 Risk of bias and confounding

There was a moderate to high risk of bias in both RCTs and NRSs (Figure 2). Power calculations were only undertaken in two studies [23, 29] so small population numbers were a frequent source of bias. In included RCTs, risk of bias was found for selection, attrition and reporting bias. Incomplete outcome data, selective reporting and failure to control for the *a priori* selected confounders were frequent in included NRSs.

3.4 Benefits and harms of botulinum toxin A injections

There was significant heterogeneity in design and outcome measures amongst the included studies so a narrative review of the evidence was undertaken. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was not used to assess the quality of the evidence because of the high risk of bias and confounding amongst included RCTs and comparative NRSs [30]. To facilitate comparison and interpretation of data, studies were grouped into major subtypes of CPPS.

3.4.1 Bladder pain syndrome

Seven of the 16 studies evaluated BTX-A use in BPS treatment [14-20], comprising five RCTs [14-18] and two comparative NRSs [19, 20], with a total of 374 participants (3% men). The median age ranged from 45 to 59 years. The type and dose of BTX-A used was variable with two studies using onaBTX-A, one using aboBTX-A, one using incoBTX-A and three not specifying the type. When recorded, the number of injections ranged from 10 to 40 sites. Injections were administered into either the detrusor muscle or suburothelium of the entire bladder, the bladder body (trigone sparing), or the trigone alone. Follow-up ranged from three to 30 months, but outcome measures were often only available for early time points during the follow-up period.

The intervention and control groups differed hugely. One RCT compared intradetrusor BTX-A injections with a 6 week course of intravesical Bacille Calmette-Guérin (BCG) [14], two compared BTX-A injections with hydrodistension (HD) [15, 16], one compared HD and saline injections against HD and BTX-A injections [17] and the most recent RCT compared trigone only BTX-A injections with a trigone-sparing template [18]. One comparative NRS compared the treatment effects (HD and suburothelial BTX-A) in patients with ulcer and non-ulcer BPS phenotypes [19]. The other NRS compared BTX-A against HD with intravesical cystistat [20]. For studies in which HD was carried out, the technique was either not described or the duration and magnitude of intravesical pressure delivered was variable.

3.4.1.1 Pain

The clinical and methodological diversity of included BPS studies meant it was not possible to determine a summary effect estimate for treatment-related improvement in pain (Figure 3A). Study outcomes were measured at time points ranging from one week to 12 months. The forest plot for change in pain scores measured at 3 to 12 months shows that half the studies reported benefits that did not achieve statistical significance. Two studies (96 participants) showed a significant benefit in favour of BTX-A [14, 20] and one study (53 participants) significantly favoured the control arm [17]. The Gao et al paper highlights the time-limited effects of BTX-A injections as it reported no effect on pain at 3 months, a reduction in

pain at 6 months that persisted at 12 months but to a lesser extent [20].The Lee et al study compared intervention in ulcer and non-ulcer BPS phenotypes and reported a lack of benefit of HD and BTX-A injections in patients with ulcer type disease, but the study had very small patient numbers [19].

3.4.1.2 Adverse events

Adverse events were reported in four of the seven BPS studies. Common side effects associated with intravesical BTX-A injections (dysuria, haematuria, urinary tract infection (UTI) and increases in post void residual (PVR)) were reported inconsistently. A forest plot of the four studies reporting UTI incidence following intervention does not suggest an increased infection risk following treatment with intravesical BTX-A (Figure 4A). The same applied for haematuria. Post-intervention dysuria was only reported in two studies, with a higher chance of dysuria in the control arm.

3.4.1.3 Quality of life

The impact of intervention on participant QoL was assessed in only two BPS studies [16, 20]; neither showed any lasting improvement.

3.4.1.4 Functional outcomes

The impact of intervention on the participants' storage symptoms was better assessed: five BPS studies reported on urinary frequency before and after treatment [14, 15, 17, 19, 20] and four studies recorded the effect on nocturia [14, 15, 17, 19]. The corresponding forest plots show a reduction in urinary frequency following BTX-A treatment compared to control, apart from one of the intervention arms of the Lee et al study that assessed the effect of BTX-A on the ulcer phenotype of BPS [19]. In contrast, no significant reduction in nocturia was seen. Different objective measures of LUT function were reported in five of the papers (see supplementary material). There was no significant change in maximum flow rate or PVR, and a small increase in functional bladder capacity that failed to achieve statistical significance. None of the BPS papers assessed bowel or sexual function. A large proportion of individuals in the treatment arm of two of the studies reported an improvement in GRA [14, 15].

3.4.2 Gynaecological pelvic pain syndrome

Four studies with 194 female participants assessed BTX-A injections in the treatment of GPP [21-24], comprising three RCTs comparing BTX-A and saline injections [21-23] and one comparative NRS comparing single and repeated BTX-A injections [24]. The median age ranged from 27 to 31 years. All four studies used onaBTX-A but the dose administered varied between 20 and 100 units injected at between two and five sites. In the Petersen et al study, onaBTX-A was injected into the bulbospongiosus muscle under EMG guidance [22], whereas in the other two studies injections were aimed at the puborectalis and pubococcygeus muscles without a specific targeting technique. In the Diomande et al study, sub-epithelial BTX-A was injected into the dorsal vestibule of the vagina [23]. Patients were followed-up for a median of 3 to 8 months.

3.4.2.1 Pain

Differences in the dose and method of drug administration precluded calculation of a summary effect estimate for treatment-related improvement in pain. Study outcomes were measured at time points ranging from 4 weeks to 6 months following intervention. Pain scores at 6 months follow-up showed no benefit of BTX-A injections on GPP (Figure 3B).

3.4.2.2 Adverse events

Adverse events were reported in all the GPP studies but were inconsistent in time and metric. Abbott et al reported that the occurrence of urinary and/or faecal incontinence in two out of the 30 women in the onaBTX-A treatment group (7%) was not statistically significant (p=0.492), despite no similar event occurring in the control arm [21]. The other three papers reported only mild adverse events, including injection site pain and flu-like symptoms during the follow-up period [22-24].

3.4.2.3 Quality of life

Participant QoL was only assessed and reported in one GPPS study, with an improvement in favour of BTX-A [21]. The Petersen et al paper reported no QoL improvement for women with vestibulodynia, despite a reduction in pain and better sexual functioning, but did not publish this data [22].

3.4.2.4 Functional outcomes

None of the GPP papers published data on the impact of BTX-A injections on participants' urinary symptoms or LUT function. Abbott et al reported no significant difference in uroflowmetry parameters, PVR and bladder function questionnaire scores between the saline and onaBTX-A injection arms at baseline or at subsequent assessments following intervention, but did not publish this data [21]. Bowel function was assessed at three months in two papers, but no statistically significant improvement in dyschezia was reported [21, 24]. There was no significant change in Female Sexual Function Index scores following intervention in the Petersen et al study ($p>0.05$) [22]. Despite a reduction in dyspareunia following BTX-A injections in the other three studies [21, 23, 24], this was not statistically significant as symptom reduction in the corresponding control arms was similar. There was also no record of GRA in any of the GPP papers.

3.4.3 Prostate pain syndrome

Three studies with 180 male participants assessed the use of BTX-A injections for PPS treatment [25-27] and comprised two RCTs [25, 26] and one comparative NRS [27]. The median age ranged from 36 to 42 years. All three studies used onaBTX-A, with doses varying between 100 and 200 units, delivered at 4 sites bilaterally (eight injections) in Falahatkar et al [25] and three sites bilaterally (six injections) in the other two studies [26, 27]. One RCT compared transurethral onaBTX-A injections with saline placebo [25], while the other compared transurethral vs transrectal drug administration [26]. The NRS compared onaBTX-A injections with cystoscopy (no intervention). Follow-up ranged from 6 to 12 months.

3.4.3.1 Pain

All three PPS papers used the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) to score pain, but incomplete data and differences in the dose and study methodology precluded calculation of a summary effect estimate for treatment-related improvement in pain (Figure 3C). Outcomes were measured at three to 12 months following intervention. The Falahatkar et al [25] and Abdel-Meguid et al papers [27] both reported a significant reduction in pain in the BTX-A intervention group compared to baseline, but pooling of results was not possible as the latter paper did not provide control arm data. Reduction in pain scores following BTX-A injections did not reach statistical significance in the El-Enen study [26], but this paper compared the route of drug administration and not BTX-A against placebo.

3.4.3.2 Adverse events

Adverse events were inconsistently reported in all the PPS studies, so direct comparisons were not possible. All three papers reported haematuria, but El-Enen et al also described haematospermia [26]. When reported, dysuria affected a large proportion of participants (29-72%), but surprisingly no infections were documented.

3.4.3.3 Quality of life

All three PPS studies assessed QoL using the NIH-CPSI QoL domain, but the Abdel-Meguid et al study failed to provide baseline and post-intervention data for the control arm [27]. An improvement in QoL in favour of the BTX-A intervention arm failed to reach statistical significance at the different time points assessed (three, six and 12 months).

3.4.3.4 Functional outcomes

Assessment of urinary symptoms and LUT function was inconsistent and incomplete, so summary effect estimates were not possible. Only Falahatkar et al reported a statistically significant reduction in urinary frequency and nocturia in the BTX-A arm compared to control [25]. There was no assessment of bowel or sexual function in any of the studies. GRA was only reported by Abdel-Meguid et al, showing a significant improvement in the BTX-A arm of the study, but the paper did not include the baseline and post-treatment data [27].

3.4.4 Other chronic pelvic pain syndromes

Two other studies assessing use of BTX-A for CPPS met our inclusion criteria: one NRS assessed the use of BTX-A in a form of chronic anal pain syndrome [28] and the other evaluated its use in MPP in women [29]. Massoud et al compared the effects of injecting 20 units of onaBTX-A into two sites on each side of the anal sphincter with surgical internal sphincterotomy for chronic anal fissure and followed patients up for six months [28]. Most participants were female (88%) with a similar mean age in both study arms.

Dessie at al completed an RCT comparing injection of 200 units of onaBTX-A with saline injections for treating MPP. Twenty injections were delivered bilaterally to areas of participant-reported pain rather

than using a reproducible standardised template. Both groups also had pelvic floor physical therapy for eight weeks, starting one month after the injections [29]. The baseline characteristics were similar in both groups and the last follow-up was at three months.

3.4.4.1 Pain

Massoud et al reported that internal anal sphincterotomy was more effective than BTX-A injections in treating chronic anal fissures with a significant improvement in pain at 6 months in favour of surgery ($p<0.05$).

Dessie at al reported that participants treated with BTX-A were more likely to describe an improved pain level, but at three months follow-up there was no statistically significant difference in pain score compared to the placebo ($p=0.16$) [29].

3.4.4.2 Adverse events

Massoud et al only reported bleeding as a complication at one and six months following intervention; there was a statistically greater risk of bleeding in the BTX-A group at 6 months, but this may have been related to a greater recurrence rate (20%). In Dessie et al adverse events were assessed two weeks after intervention: BTX-A participants had a higher number of UTIs and constipation, but this did not reach statistical significance [29].

3.4.4.3 Quality of life

Neither study assessed the impact of intervention on participant QoL.

3.4.4.4 Functional outcomes

Urinary, bowel or sexual function and GRA were not assessed in either study.

3.5 Discussion

This SR addressed the efficacy and safety of BTX-A in patients with various CPPS subtypes. Included studies were generally of poor quality with significant risks of bias and confounding, warranting results to be interpreted with caution. The heterogeneous nature of CPPS and the variable definitions used make it difficult for single centres to recruit enough individuals with phenotypically similar subtypes of the condition for meaningful treatment trials. Multicentre trials are needed as currently most CPPS treatment studies have small patient numbers so are underpowered. This limits the clinical generalisability of study findings. The Gao et al paper had the largest number of participants with 124, but significant attrition meant only 23 participants completed the 12-month follow-up period [20].

To facilitate comparison and interpretation of the data, included studies were separated according to the major subtypes of CPPS. Even within these groups there was considerable clinical and methodological diversity. Studies varied in the type, amount and method of BTX-A delivery. For the

BPS studies, BTX-A doses were based on those used to treat overactive bladder, but little justification was provided for the doses used in the GPP studies. Furthermore, identified RCTs had differing control arms and outcome measures. Most notably, the El-Bahnasy et al paper used intravesical BCG as a control [14], even though it is a rarely employed BPS treatment and is no longer recommended by urological guidelines. Even at the time of the study publication, the evidence for benefit of BCG in BPS patients was extremely limited [31, 32].

A summary estimate for an overall change in pain following BTX-A injections was not possible, but some individual studies reported a statistically significant reduction in pain for patients with BPS [14, 15, 20] and PPS [25-27]. In contrast, no study reported benefit for patients with GPP, so although pelvic floor dysfunction may co-exist, it does not appear to generate or perpetuate their pelvic pain.

Patient-centred secondary outcomes were poorly reported in the included studies. BTX-A reduced the storage symptoms associated with BPS, but to a lesser extent than would be expected if there was no associated pain. The impact that BTX-A injections had on the QoL of BPS patients could not be adequately assessed with the limited data from the included studies, but the reported short-lived improvement despite a reduction in pain and urinary frequency highlights the need to address outcomes that are important to the patient. Sexual and bowel function were poorly reported throughout the papers. The incidence and nature of adverse events was also poorly documented, a well-recognised problem in clinical trials [33]. Adequate reporting of adverse effects is important for establishing the safety profile of a potentially novel use for BTX-A, because a procedure-triggered infection may cause pain and symptoms that could mask its beneficial effects. Future studies need to standardise the reporting of adverse events and the time of their occurrence but small trials may still fail to reveal rare and potentially serious adverse effects.

Appropriately powered and well-designed RCTs with prolonged follow-up are needed to ascertain the efficacy and safety of BTX-A injections as a treatment for CPPS, but this is often difficult to achieve in non-cancer clinical trials. To reduce the deficiencies and biases of the current published literature, the outcome variables measured, the instruments used and the assessment time points need to be standardised. Core outcomes for CPPS trials should be identified by consensus of a panel of experts in collaboration with patient advocates using similar methodology to that set out by Core Outcome Measures in Effectiveness Trials (COMET) initiative [34-36]. A core outcome set would be an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population [34]. Their adoption would afford methodological robustness to studies and reduce the inconsistencies that hamper SRs and meta-analyses.

The Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) project published recommendations over 15 years ago about the core outcome domains that should be considered in chronic pain trials [37]. Despite this, a CPP-specific core outcome set has yet to be developed. Standardisation of pain assessment, adverse event reporting and QoL evaluation are key

domains that should be measured. Secondary outcomes would depend on the CPPS subtype but could include measures of LUT function (important in BPS and PPS), sexual function and bowel function. Despite the potential benefits of a core outcome set, the failure to develop one for CPP highlights the inherent difficulties in trying to standardise assessment of a heterogenous group of conditions that are poorly defined.

4. Conclusions

This review highlights the significant clinical and methodological heterogeneity of studies assessing treatments for CPPS. Clinical experience may show a beneficial effect of BTX-A on pain, quality of life and functional symptoms with an acceptable rate of complications in patients with certain subtypes of CPPS, but the current level of evidence is too weak for recommendations to be made about BTX-A use in the treatment of CPPS. Larger scale, multicentre, well designed and powered RCTs or prospective case-control studies with longer follow-up periods are needed. Systematic phenotyping of study participants, use of core outcomes sets and power calculations would reduce methodological heterogeneity, discourage underpowered studies and improve the level of evidence.

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Contributions of Authors:

All co-authors contributed to the SR study design, analysis of the results and drafting of the manuscript. EAU CPP Guidelines Panel provided expert input. The literature search was conducted by CY while screening, data extraction and outcomes summary were done by SG and BP with methodological input by SD.

Conflict of interest:

None to declare in relation to this current SR.

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Table 1 – Characteristics of included studies

Study ID; design; country; recruitment period; Type of CPPS	Interventions Experimental vs Control (last row of each study); Type of BTX used; substrate strength; number and location of injections	N	Age In years, mean +(±SD) OR median +[IQR]	Gender M/F (%)	Type of medical therapy prior to study participation	Duration of symptoms prior to study participation As defined by trialist	Duration of treatment before outcome assessment (Months), As defined by trialist	Outcomes measured
Bladder Pain Syndrome								
El-Bahnasy 2008 [14]; RCT; Egypt; Recruitment period NR; Bladder pain syndrome	BTX-A (type NR); 300 IU; Intra-detrusor, 30 sites, entire bladder	16	NR	0%/100%	NR	≥6 months (NR)	5.5 months	Pain (scale 0-9) Adverse events Voiding function (Qmax) Bladder diary (frequency and nocturia) GRA (7-point scale)
	Intravesical BCG weekly ($5x10^8$ CFU) for 6 weeks	16	NR	0%/100%	NR	≥6 months (NR)	5.75 months	
Kuo 2009 [15]; RCT; NR; Recruitment period NR; Bladder pain syndrome	onaBTX-A; 200 IU; suburothelial, 40 sites, trigone sparing, and HD (15 minutes, IVP 80cmH2O)	15	Mean 45.7 (±12.5)	16%/84%	Oral PS, intravesical instillation of heparin, hyaluronic acid, or tricyclic antidepressant for ≥6 month	Mean 96 (±60) months	24 months (outcome measures only available for 3-month follow-up)	Pain (VAS, 10-point scale) Adverse events Voiding function (Qmax, PVR, FBC, CC) Bladder diary (frequency, nocturia) GRA (7-point scale)
	onaBTX-A; 100 IU; suburothelial, 40 sites, trigone sparing, and HD (15 minutes, IVP 80cmH2O)	29	Mean 47.7 (±14.7)				24 months (outcome measures only available for 3-month follow-up)	
	HD (IVP 80cmH2O for 15 minutes)	23	Mean 52.5 (±15.3)				24 months (outcome measures only available for 3-month follow-up)	
Kasyan 2012 [16]; RCT (*Abstract only*); Russia Recruitment period NR;	BTX-A (type NR); 100 IU; number of injection sites NR, trigone only	15	NR	0%/100%	NR	NR	3 months	Pain (VAS, 10-point scale) QoL (Q8 IPSS, 0-6) Voiding function (Qmax, PVR)
	HD, specified only as 'standard' technique	17	NR		NR		3 months	

Bladder pain syndrome								
Manning 2014 [17]; RCT; Australia; Jan 2004 - Feb 2009; Bladder pain syndrome	AboBTX-A; 500 IU; 30 sites, trigone sparing and HD (4 minutes, IVP NR)	26	Mean 53 (NR)	0%/100%	Average of 7 prior treatments for BPS	Mean 192 (±112.8) months	3 months	Pain (OLS-PI Q4,0-5) Adverse events Voiding function (PVR, FBC, CC) Bladder diary (Frequency, nocturia)
	Saline injection; 30 sites, trigone sparing, and HD (4 minutes, IVP NR)	27	Mean 54 (NR)		Average of 4 prior treatments for BPS	Mean 132 (±49.2) months	3 months	
Evans 2020 [18]; RCT; USA; NR; Bladder pain syndrome	BTX-A (type NR); 100 IU; 10 sites (1ml per injection); trigone only	12	Mean 50.2 (13.1)	0%/100%	Failed conservative management including oral pharmacotherapy	NR	3 months	Adverse events Voiding function (PVR) Symptom questionnaires (O'Leary Sant questionnaire, pelvic pain and urgency/frequency symptom scale)
	BTX-A (type NR); 100 IU; 10 sites (1ml per injection); trigone sparing	14	Mean 46.5 (12.6)	0%/100%	Failed conservative management including oral pharmacotherapy	NR	3 months	
Lee 2013 [19]; Prospective comparative NRS; Taiwan; Jan 2008 to Jan 2012; Bladder pain syndrome	onaBTX-A in ulcer IC; 100 IU; Suburothelial, 40 sites, trigone sparing, and HD (15 minutes, IVP 80cmH2O)	10	Median 57.5 [IQR 53-66]	0%/100%	Failed treatment with 2 of the following: oral PS, tricyclic antidepressant and intravesical instillations	>12 months	30 months	Pain (VAS 0-10) Voiding function (Qmax, PVR, FBC, CC) Bladder diary (frequency, nocturia) GRA (7-point scale)
	onaBTX-A in non-ulcer IC with GRA ≥2 100 IU; suburothelial, 40 sites, trigone sparing, and HD (15 minutes, IVP 80cmH2O)	15	Median 45 [IQR 38-56]					
	onaBTX-A in non-ulcer IC with GRA<2; 100 IU; Suburothelial, 40 sites, trigone sparing, and HD (15 minutes, IVP 80cmH2O)	15	Median 45 [IQR 40-56]					

Gao 2015 [20]; Retrospective comparative NRS; China; Jan 2003- Jun 2013; Bladder pain syndrome	incoBTX-A; 100 IU; 20 sites, entire bladder, and HD (5 minutes, IVP 80cmH2O)	66	Mean 59 (NR)	0%/ 100%	Two out of oral PS, anticholinergics and tricyclic antidepressants for 1 year	>12 months	3 months (89%) 6 months (64%) 12 months (32%) (%= N% of patients assessed)	Pain (VAS 0-10) QOL (instrument used not recorded) Bladder diary (frequency)
	Sodium hyaluronate instillation; Strength/dosage NR, weekly for 1 month, then monthly for 5 months, and HD (5 minutes, IVP 80cmH2O)	58	Mean 57 (NR)	0%/100%	Two out of oral PS, anticholinergics and tricyclic antidepressants for 1 year	>12 months	3 months (81%) 6 months (38) 12 months (3.4%) (%= N% of patients assessed)	
Gynaecological Pelvic Pain								
Abbott 2006 [21]; RCT; Australia; Jan 2004 - Nov 2004; Gynaecological pelvic pain	onaBTX-A; 80 IU; 4 sites, pelvic floor	30	Mean 30.6 (±8.1)	N/A / 100%	NR	>24 months	6.5 months	Pain (VAS EQ-5D) Adverse events QoL (EQ-5D) Bladder diary (frequency) Bowel function (dyschezia) Sexual dysfunction (dyspareunia) Pelvic floor function
	Saline injection; 4 sites, pelvic floor	30	Mean 30.5 (±7.5)					
Petersen 2009 [22]; RCT; Denmark; Apr 2005 - Sep 2007; Gynaecological pelvic pain (Vulvodynia)	onaBTX-A: 20 IU; 5 sites, to bulbospongiosus using EMG	32	Mean 30.5 (±7.7)	N/A /100%	Use of analgesics within 1 month of inclusion	69 (±54.4) months	6 months	Pain (VAS 0-10) Adverse events QoL (SF-36, incomplete data) Sexual Dysfunction (FSFI)
	Saline injection; 5 sites, to bulbospongiosus using EMG	32	Mean 29.5 (±4.7)			79.1 (±47.9) months		
Diomande 2019 [23]; RCT; Switzerland; June 2008 to Sept 2014; Gynaecological pelvic pain (provoked vestibulodynia)	onaBTX-A; 50 IU; 2 sites (0.5ml each) in dorsal vestibule	12	Median 27 [IQR 25-28]	N/A /100%	NR	Median 42 months [IQR 17-92]	3 months	Pain (cotton swab provoked VAS 0-10) Tactile stimulation (Von Frey filaments) Adverse events Sexual function (Dyspareunia, Marinoff scale 0-3)
	onaBTX-A; 100 IU; 2 sites (0.5ml each) in dorsal vestibule	9	Median 28 [IQR 23-35]			Median 90 months [IQR 36-174]		
	Saline; 2 sites (0.5ml each) in dorsal vestibule	12	Median 27 [IQR 23-30]			Median 54 months [IQR 29-96]		

Nesbitt-Hawes 2013 [24]; Comparative NRS; Australia; Aug 2005 - Dec 2008; Gynaecological pelvic pain	onaBTX-A, repeat treatment in responders; 100 IU/treatment; 4 sites, pelvic floor	11	Median 31 [IQR 26-42]	N/A /100%	NR	≥24 months	Median 8.4 (NR) months	Pain (Non-menstrual, VAS 0-100) Adverse events Bowel function (dyschezia) Sexual function (dyspareunia) Pelvic floor pressure
	onaBTX-A, single treatment; 100 IU; 4 sites, pelvic floor	26	Median 30 [IQR 26-41]				Median 6.5 (NR) months	
Prostate Pain Syndrome								
Falahatkar 2015 [25]; RCT; Iran; Nov 2011 - Jan 2013; Prostate Pain Syndrome	onaBTX-A; 100 IU; 6 sites, transurethral intraprostatic injections	30	Mean 42.7 (±11.2)	100%/ N/A	Symptoms refractory to 4-6 weeks of treatment with fluoroquinolones, α-blockers, anti-inflammatory agents and muscle relaxants	NR	3 months 6 months	Pain (NIH-CPSI pain domain, 0-21) Adverse events QoL (modified NIH-CPSI QoL score, 0-6) Voiding dysfunction (PVR) Bladder diary (frequency, nocturia)
	Saline injections; 6 sites, transurethral intraprostatic injections	30	Mean 38.2 (±11.77)	100%/ N/A			3 months 6 months	
El-Enen 2015 [26]; RCT; Egypt; Jan 2008 - Dec 2013; Prostate Pain Syndrome	onaBTX-A; 100 IU; 6 sites, **transrectal** intraprostatic injections	35	Mean 41.4 (±5.0)	100%/ N/A	Failed response to antibiotics, a-blockers and anti-inflammatory agents	Mean 91.0 (±45.1) months	3, 6 and 12 months	Pain (NIH-CPSI pain domain, 0-21) Adverse events QoL (NIH-CPSI QoL domain, 0-12) Voiding function (Qmax) GRA (>4-point reduction in total CPSI)
	onaBTX-A; 100 IU; 6 sites, **transurethral** intraprostatic injections	28	Mean 42.0 (±5.2)			Mean 86.8 (±25.6) months	3, 6, and 12 months	
Abdel-Meguid 2018 [27]; prospective comparative NRS; Egypt; Feb 2011 - May 2015; Prostate Pain Syndrome	onaBTX-A; 200 IU; 8 sites, transurethral intraprostatic injection in template fashion	43	Mean 38.8 (±7.3)	100%/ N/A	CP/CPPS refractory to previous treatments (no further details described)	Mean 84 (±34.8) months	3, 6 and 12 months	Pain (NIH-CPSI pain domain 0-21 and VAS 0-10) Adverse events QoL (NIH-CPSI QoL domain, 0-12) Voiding function (Qmax, PVR) GRA (7-point scale)
	Cystoscopy alone	14	Mean 36.7 (±6.25)			Mean 97.2 (±44.4) months	3, 6 and 12 months	
Other types of Chronic Pelvic Pain Syndrome								

Massoud 2005 [28]; Comparative NRS; Australia; recruitment period NR; Chronic Anal Pain	onaBTX-A 20 IU; injection each side of anal sphincter (2 sites)	25	Mean 35.5 (±9.3)	4%/96%	NR	Mean 18.2 (±24.7) months	6 months	Pain (Yes vs No) Adverse events (Bleeding) Complete healing
	Internal anal sphincterotomy (procedure not detailed)	25	Mean 33.0 (±9.6)	20%/80%		Mean 10.1 (±8.5) months	6 months	
Dessie 2019 [29]; RCT; USA; Jan 2013 – Dec 2017; myofascial pelvic pain	onaBTX-A; 200IU in 20 x 1ml injections; number of sites NR and pelvic floor physical therapy for 8 weeks	30	Median 43 [IQR 30-55]	0%/100%	NR	Median 84 months [IQR 3-10]	3 months	Pain (overall pain, VAS 0-10) Adverse events QoL (NR) Symptom questionnaires (PFDI, pelvic pain and urgency/frequency symptom scale)
	Normal saline; 20 x 1ml injections and pelvic floor physical therapy for 8 weeks	30	Median 40 [IQR 31-54]	0%/100%		Median 60 months [IQR 3-10]	3 months	

List of Abbreviations: AboBTX-A = abobotulinum toxin A (Dysport ®, Galderma Laboratories), BCG = Bacille Calmette-Guérin, BPS = bladder pain syndrome, BTX-A = botulinum toxin A, CC = cystometric capacity, CFU = colony forming units, CP = chronic prostatitis, CPPS = chronic pelvic pain syndrome, CPSI = chronic prostatitis symptom index, EMG = electromyographic, EQ-5D = EuroQOL-5D, FBC = functional bladder capacity, FSFI = Female Sexual Function Index, GRA = Global Response Assessment, HD = hydrodistension, IC = interstitial cystitis, incoBTX-A = Incobotulinum toxin A (Xeomin® or Lantox ®, Lanzhou Institute of Biological Products in China), IQR = interquartile range, IU = International Unit, IVP = intravesical pressure, N/A = not applicable, NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index, NR = not reported, NRS = non randomised study, onaBTX-A = onabotulinum toxin A (BOTOX ®, Allergan), PFDI = pelvic floor distress index, PS = pentosan polysulphate, PVR = post void residual volume, Qmax = maximum flow rate, QoL = quality of life, Q8 IPSS = International prostate symptom score, question 8, RCT = randomised controlled trial, SD = standard deviation, VAS = visual analogue scale

Table 2 – Primary benefit outcome for included studies – reduction in pain score

Study ID					Pain Scores												
	CPPS type, Study Design	N	Group	Type and scale of Pain Score assessment	Pain before	SD	Pain after	SD	p value	Mean diff before vs after	95% CI or SD of mean diff	p value of mean diff	Mean NIH-CPSI pain domain index before	SD	Mean NIH-CPSI pain domain index after	SD	p value
El-Bahnasy 2008 [14]	BPS, RCT	16	Interv	Likert Scale 0 to 9	5.83	1.39	0.22	0.40	<0.001	NR	NR	NR	NR	NR	NR	NR	NR
		16	Control		5.44	1.26	1.06	0.77	<.0.005	NR	NR	NR	NR	NR	NR	NR	NR
Kuo 2009 [15]	BPS, RCT	15	Interv	VAS 1 to 10	5.47	2.1	2.47	2.1	<0.05	NR	NR	NR	NR	NR	NR	NR	NR
		29	Interv2		4.83	2.21	2.97	1.99	<0.05	NR	NR	NR	NR	NR	NR	NR	NR
		23	Control		4.30	2.60	3.52	3.07	>0.05	NR	NR	NR	NR	NR	NR	NR	NR
Kasyan 2012 [16]	BPS, RCT	15	Interv	VAS 1 to 10	9.3	0.9	5.8	2.4	>0.05	NR	NR	NR	NR	NR	NR	NR	NR
		17	Control		8.7	1.2	6.1	2.8	>0.05	NR	NR	NR	NR	NR	NR	NR	NR
Manning 2014 [17]	BPS, RCT	26	Interv	OLS-PI Q4 0 to 5	NR	NR	NR	NR	NR	0.89	(0.29 to 1.4)	0.02 (Interv vs control)	NR	NR	NR	NR	NR
		27	Control		NR	NR	NR	NR	NR	-0.16	−0.74 to 0.42)		NR	NR	NR	NR	NR
Evans 2020 [18]	BPS, RCT	12	Interv	Pain score NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		14	Control		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lee 2013 [19]	BPS, NRS	10	Interv	VAS 1 to 10	7.5 (est)	NR	6 (est)	NR	0.472 (Interv vs control)	NR	NR	NR	NR	NR	NR	NR	NR
		15	Interv2		6 (est)	NR	2 (est)	NR	0.136 (Interv vs control)	NR	NR	NR	NR	NR	NR	NR	NR
		15	Control		5 (est)	NR	2	NR		NR	NR	NR	NR	NR	NR	NR	NR
Gao 2015 [20]	BPS, NRS	56/66	Interv	VAS 1 to 10 3 months	9.4	0.9	8.1	1.3	<0.05	NR	NR	NR	NR	NR	NR	NR	NR
		47/58	Control		9.2	0.8	7.9	1.3	<0.05	NR	NR	NR	NR	NR	NR	NR	NR
		42/66	Interv	VAS 1 to 10 6 months	9.4	0.9	8.9	1.0	<0.05	NR	NR	NR	NR	NR	NR	NR	NR
		22/58	Control		9.2	0.8	9.6	0.8	>0.05	NR	NR	NR	NR	NR	NR	NR	NR

		21/66	Interv	VAS 1 to 10	9.4	0.9	9.3	0.7	>0.05	NR	NR	NR	NR	NR	NR	NR	NR
		2/58	Control	12 months	9.2	0.8	9.5	0.7	>0.05	NR	NR	NR	NR	NR	NR	NR	NR
Abbott 2006 [21]	GPP, RCT	30	Interv	EQ-5D VAS 100 to 0	55.8 (est)	6.1 (est)	71.3 (est)	7.23 (est)	0.01	NR	NR	NR	NR	NR	NR	NR	NR
		30	Control	3 months	53.3 (est)	6.1 (est)	64 (est)	5.22 (est)	0.14	NR	NR	NR	NR	NR	NR	NR	NR
		30	Interv	EQ-5D VAS 100 to 0	55.8 (est)	6.1 (est)	67.8 (est)	8.36 (est)	0.01	NR	NR	NR	NR	NR	NR	NR	NR
		30	Control	6 months	53.3 (est)	6.1 (est)	65 (est)	11.5 (est)	0.14	NR	NR	NR	NR	NR	NR	NR	NR
Petersen 2009 [22]	GPP, RCT	32	Interv	VAS 0 to 10	7.44	NR	5.14	NR	<0.001	NR	NR	NR	NR	NR	NR	NR	NR
		32	Control		7.63	NR	5.13	NR	<0.001	NR	NR	NR	NR	NR	NR	NR	NR
Diomande 2019 [23]	GPP, RCT	12	Interv	VAS 0 to 10	6.6	2.01	6.2	2.60	0.41	NR	NR	NR	NR	NR	NR	NR	NR
		8/9	Interv2		7.4	1.85	6.0	1.77	0.239	NR	NR	NR	NR	NR	NR	NR	NR
		11/12	Control		7	2.22	6.5	1.31	0.623	NR	NR	NR	NR	NR	NR	NR	NR
Nesbitt-Hawes 2013 [24]	GPP, NRS	11	Interv	VAS 0 to 100	39.0 (est)	9.25 (est)	24.3 (est)	13.6 (est)	0.008	NR	NR	NR	NR	NR	NR	NR	NR
		26	Control		41.5 (est)	7.48 (est)	19.0 (est)	10.4 (est)	<0.001	NR	NR	NR	NR	NR	NR	NR	NR
Falahatkar 2015 [25]	PPS, RCT	30	Interv	NIH-CPSI 0 to 21	NR	NR	NR	NR	NR	12.73	0.10	<0.001	16.83	2.27	4.10	5.31	<0.001
		30	Control	3 months	NR	NR	NR	NR	NR	-0.37	0.36	1.00	17.17	2.08	17.53	2.17	1.000
		30	Interv	NIH-CPSI 0 to 21	NR	NR	NR	NR	NR	13.47	0.98	<0.001	16.83	2.27	3.37	5.61	<0.001
		30	Control	6 months	NR	NR	NR	NR	NR	-0.83	0.27	0.28	17.17	2.08	18.00	1.95	0.028
El-Enen 2015 [26]	PPS, RCT	35	Interv	NIH-CPSI 0 to 21	NR	NR	NR	NR	NR	NR	NR	NR	11 (est)	3 (est)	8 (est)	3 (est)	<0.05
		28	Control	3 months	NR	NR	NR	NR	NR	NR	NR	NR	12 (est)	2.7 (est)	11 (est)	2.7 (est)	>0.05
		35	Interv	NIH-CPSI 0 to 21	NR	NR	NR	NR	NR	NR	NR	NR	11 (est)	3 (est)	9 (est)	3 (est)	<0.05
		28	Control	6 months	NR	NR	NR	NR	NR	NR	NR	NR	12 (est)	2.7 (est)	9 (est)	4 (est)	<0.05
		35	Interv	NIH-CPSI 0 to 21	NR	NR	NR	NR	NR	NR	NR	NR	11 (est)	3.0 (est)	10 (est)	3.0 (est)	>0.05
		28	Control	12 months	NR	NR	NR	NR	NR	NR	NR	NR	12 (est)	2.7 (est)	9.5 (est)	2.4 (est)	>0.05

Abdel-Meguid 2018 [27]	PPS, NRS	35/43	Interv	VAS 0 to 10 NIH-CPSI 0 to 21 3 months	7.63	1.59	1.60	1.52	<0.0001	-6.03	−7.20 to -4.85	<0.0001	15.51	3.08	3.14	3.77	<0.01
		14	Control		NR	NR	NR	NR	>0.05	NR	NR	>0.05	NR	NR	NR	NR	>0.05
		35/43	Interv	VAS 0 to 10 NIH-CPSI 0 to 21 6 months	7.63	1.59	2.10	1.59	<0.0001	-5.53	-6.72 to -4.34	<0.0001	15.51	3.08	4.64	3.23	<0.01
		14	Control		NR	NR	NR	NR	>0.05	NR	NR	>0.05	NR	NR	NR	NR	>0.05
		35/43	Interv	VAS 0 to 10 NIH-CPSI 0 to 21 12 months	7.63	1.59	5.54	1.57	<0.0001	-2.09	-2.98 to -1.12	<0.0001	15.51	3.08	13.23	2.91	<0.01
		14	Control		NR	NR	NR	NR	>0.05	NR	NR	>0.05	NR	NR	NR	NR	>0.05
Massoud 2005 [28]	CAP, NRS	25	Interv	Pain YES vs NO 0 or 1	Yes 25/25	NR	YES 6/25	NR	<0.05 (Interv vs Control	NR	NR	NR	NR	NR	NR	NR	NR
		25	Control		Yes 25/25	NR	YES 1/25	NR		NR	NR	NR	NR	NR	NR	NR	NR
Dessie 2019 [29]	MPP, RCT	30	Interv	VAS 0 to 10	7	NR	4	NR		NR	NR	NR	NR	NR	NR	NR	NR
		29/30	Control		6	NR	5.5	NR		NR	NR	NR	NR	NR	NR	NR	NR

List of abbreviations: BPS = bladder pain syndrome, CAP = chronic abdominal pain, CI = confidence interval, CPPS = chronic pelvic pain syndrome, Diff = difference, EQ-5D = EuroQOL-5D, Est = estimated value, GPP = gynae pelvic pain, Interv = intervention, Interv2 = second intervention, NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index, NR = not reported, NRS = Non randomised study, OLS-PI Q4 = O'Leary Sant Problem Index Question 4, PPS = prostate pain syndrome, RCT = randomised control trial, SD = standard deviation, VAS = visual analogue scale

Table 3 – Primary harm outcome for included studies – adverse events

Study ID				**Adverse events**								
	CPPS type, Study Design	N	Group	Bleeding because of treatment	UTI	Dysuria	Post void residual	Urinary retention Acute	Urinary retention Chronic	Other adverse effect	P value (Interv Vs Control)	Time point of assessment
El-Bahnasy 2008 [14]	BPS, RCT	16	Interv	0/16 (0%)	1/16 (6%)	3/16 (19%)	NR	NR	NR	NR	NR	NR
		16	Control	1/16 (6%)	2/16 (13%)	5/16 (31%)	NR	NR	NR	NR	NR	NR
Kuo 2009 [15]	BPS, RCT	15	Interv	2/15 (13%)	3/15 (20%)	7/15 (47%)	5/15 (33%)	2/15 (13%)	2/15 (13%)	NR	Greater PVR 0.041 (Interv vs control)	NR
		29	Interv2	0/29 (0%)	0/29 (0%)	3/29 (10%)	3/29 (10%)	1/29 (3%)	0/29 (0%)	NR		NR
		23	Control	0/23 (0%)	0/23 (0%)	1/23 (4%)	0/23 (0%)	0/23 (0%)	0/23 (0%)	NR		NR
Kasyan 2012 [16]	BPS, RCT	15	Interv	NR	NR	NR	NR	NR	NR	NR	NR	NR
		17	Control	NR	NR	NR	NR	NR	NR	NR	NR	NR
Manning 2014 [17]	BPS, RCT	26	Interv	NR	7/26 (27%)	NR	2/26 (8%) >200mls	NR	NR	NR	NR	NR
		27	Control	NR	5/27 (19%)	NR	0/27 (0%)	NR	NR	NR	NR	NR
Evans 2020 [18]	BPS, RCT	12	Interv	NR	1/12 (8%)	NR	NR	2/12 (17%)	NR	NR	>0.05 (Interv vs control)	NR
		14	Control	NR	3/14 (21%)	NR	NR	2/14 (14%)	NR	NR		NR
Lee 2013 [19]	BPS, NRS	10	Interv	NR	NR	NR	NR	NR	NR	NR	NR	NR
		15	Interv2	NR	NR	NR	NR	NR	NR	NR	NR	NR
		15	Control	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gao 2015 [20]	BPS, NRS	56/66	Interv	NR	NR	NR	NR	NR	NR	NR	NR	NR
		47/58	Control	NR	NR	NR	NR	NR	NR	NR	NR	NR
Abbott 2006 [21]	GPP, RCT	30	Interv	NR	NR	NR	NR	NR	NR	Urinary/faecal incontinence 2/30 (7%)	0.492 for incontinence (faecal or urinary)	NR
		30	Control	NR	NR	NR	NR	NR	NR	No serious complication 0/30 (0%)		NR
Petersen 2009 [22]	GPP, RCT	32	Interv	NR	NR	NR	NR	NR	NR	Mild AE including injection site pain 4/32 (12.5%)	NR	Variable
		32	Control	NR	NR	NR	NR	NR	NR	Mild AE	NR	Variable

										2/32 (6.25%)		
Diomande 2019 [23]	GPP, RCT	12	Interv	NR	NR	NR	NR	NR	NR	88% reported some pain immediately after injection	NR	NR
		8/9	Interv2	NR	NR	NR	NR	NR	NR		NR	NR
		11/ 12	Control	NR	NR	NR	NR	NR	NR		NR	NR
Nesbitt-Hawes 2013 [24]	GPP, NRS	11	Interv	NR	NR	NR	NR	NR	NR	Cold like symptoms within 26 weeks of injection	NR	NR
		26	Control	NR	NR	NR	NR	NR	NR	23/66 (35%)	NR	NR
Falahatkar 2015 [25]	PPS, RCT	30	Interv	2/30 (7%)	NR	NR	NR	NR	NR	NR	NR	NR
		30	Control	0/30	NR	NR	NR	NR	NR	NR	NR	NR
El-Enen 2015 [26]	PPS, RCT	35	Interv	3/35 (9%)	NR	17/35 (29%)	NR	NR	NR	Haematospermia 5/35 (14%)	NR	NR
		28	Control	6/28 (21%)	NR	12/28 (43%)	NR	NR	NR	Haematospermia 2/28 (7%)	NR	NR
Abdel-Meguid 2018 [27]	PPS, NRS	35/ 43	Interv	29/43 (67%)	NR	31/43 (72%)	NR	NR	NR	NR	NR	Variable
		14	Control	NR	NR	NR	NR	NR	NR	NR	NR	NR
Massoud 2005 [28]	CAP, NRS	25	Interv	9/25 (36%)	NR	NR	NR	NR	NR	NR	0.02 (interv vs control)	1 month
		25	Control	1/25 (4%)	NR	NR	NR	NR	NR	NR		
Dessie 2019 [29]	MPP, RCT	30	Interv	NR	4/30 (13%)	NR	NR	<4 participants	NR	Constipation 4/30 (13%)	1.0 (interv vs control)	2 weeks post injection
		29/ 30	Control	NR	1/29 (3%)	NR	NR		NR	Constipation 2/29 (7%)		

List of abbreviations: AE = adverse effect, BPS = bladder pain syndrome, CAP = chronic abdominal pain, CPPS = chronic pelvic pain syndrome, GPP = gynae pelvic pain, Interv = intervention, Interv2 = second intervention, NR = not reported, NRS = Non randomised study, PPS = prostate pain syndrome, PVR = post void residual, RCT = randomised control trial, UTI = urinary tract infection

Figure legends

Figure 1 – PRISMA Flow diagram for systematic review of the benefit and harms of Botulinum toxin in the treatment of CPPS. BPS = bladder pain syndrome, CPPS = chronic pelvic pain syndrome, GPP = gynaecological pelvic pain, PPS = prostate pain syndrome. *Other types of CPPS include chronic anal pain (CAP) and myofascial pelvic pain (MPP)

Figure 2 – Risk of bias and confounding assessment of included studies presented by type of CPPS. For randomised controlled trials (RCTs), a risk of bias assessment was performed while for comparative non-randomised studies (NRSs), an additional risk of confounding assessment was added (last four columns in figure). Small population bias was the primary "other bias" assessed. BPS = bladder pain syndrome, CAP = chronic anal pain, CPPS = chronic pelvic pain syndrome, GPP = gynaecological pelvic pain, PPS = prostate pain syndrome.

Figure 3:
Forest plot illustrating the primary benefit of reduction in pain in studies with BPS (3A), GPP (3B) and PPS (3C) were comparative mean differences and corresponding standard deviations in pain reduction scores were available. Fixed effect model was used. As shown, some studies compared multiple study arms whilst other studies provided outcome measures at different time points following intervention BCG = Bacille Calmette-Guérin instillation into bladder, BPS = bladder pain syndrome, BTX = Botulinum toxin A (any subtype), HD = hydrodistension, IU = international units, GPP = gynaecological pelvic pain, PPS = prostate pain syndrome.

Figure 4:
Forest plot illustrating the primary harm with adverse events comprising UTI (4A), dysuria (4B) and post-procedure bleeding (4C) in studies comparing BTX to any other treatment for BPS. Fixed effect model was used. As shown, one study compared multiple study arms. BCG = Bacille Calmette-Guérin instillation into bladder, BPS = bladder pain syndrome, BTX = Botulinum toxin A (any subtype), HD = hydrodistension, IU = international units, UTI = urinary tract infection.

Figure 5:
Forest plot illustrating the secondary outcomes of change in daytime voiding frequency (5A) and nocturia (5B) as assessed by a bladder diary in studies comparing BTX to any other treatment for BPS. Fixed effect model was used. As shown, some studies compared multiple study arms whilst other studies provided outcome measures at different time points following intervention. BCG = Bacille Calmette-Guérin instillation into bladder, BPS = bladder pain syndrome, BTX = Botulinum toxin A, any subtype, HD = hydrodistension, IU = international units.

Figure 1 – PRISMA flow diagram

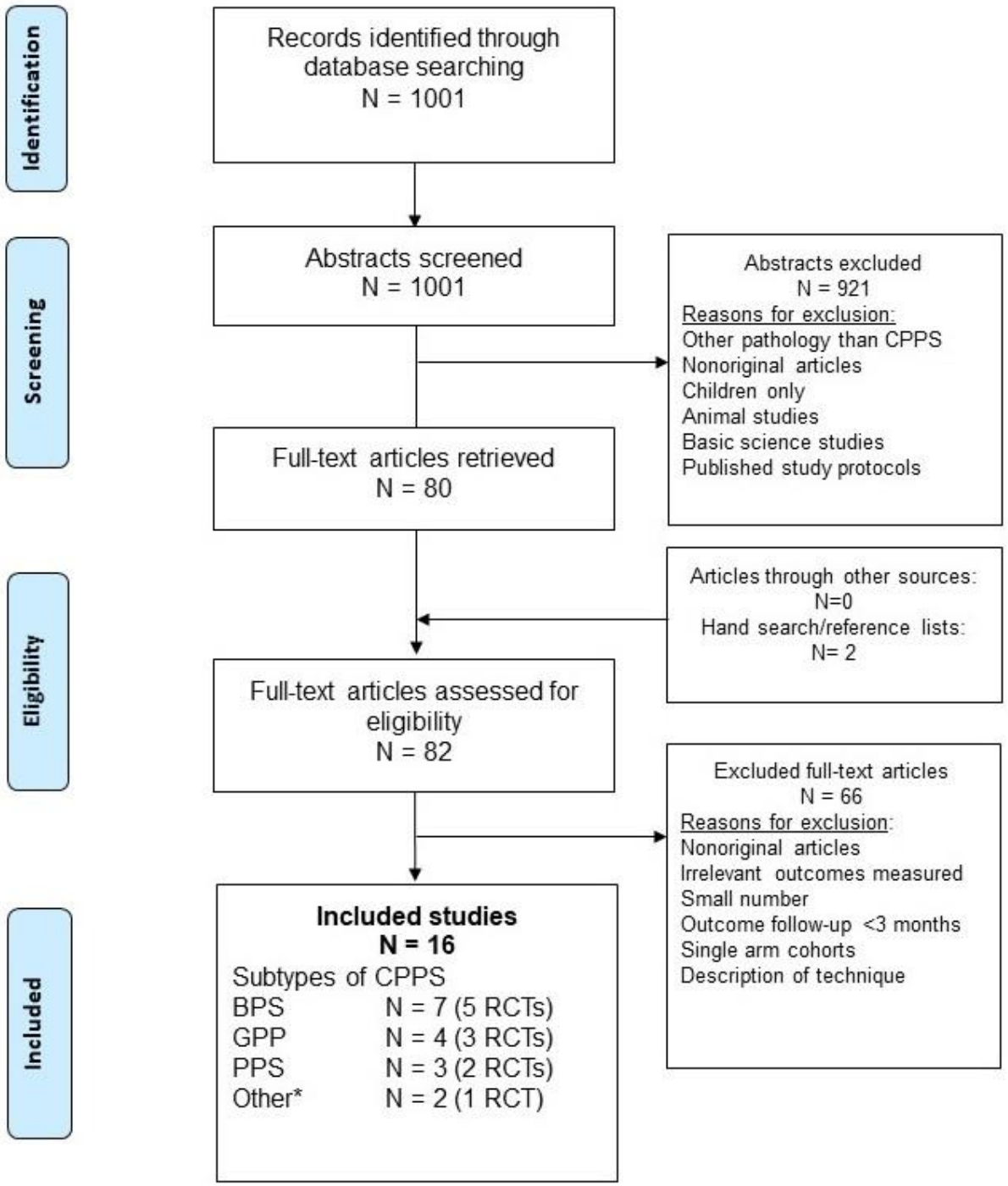


Figure 2 – Risk of bias and confounding summary

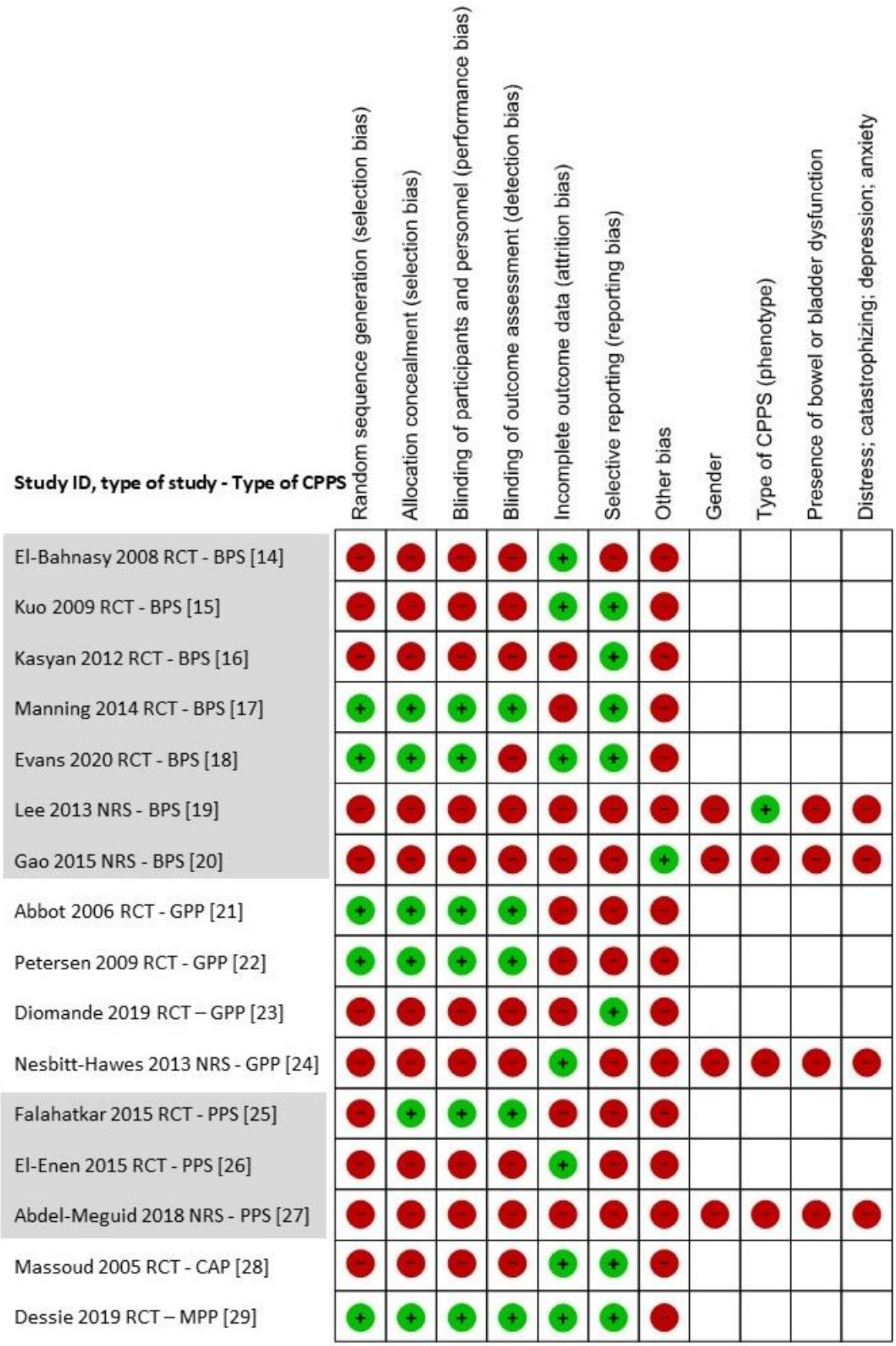


Figure 3 – Forest plot of primary benefit – Reduction in pain

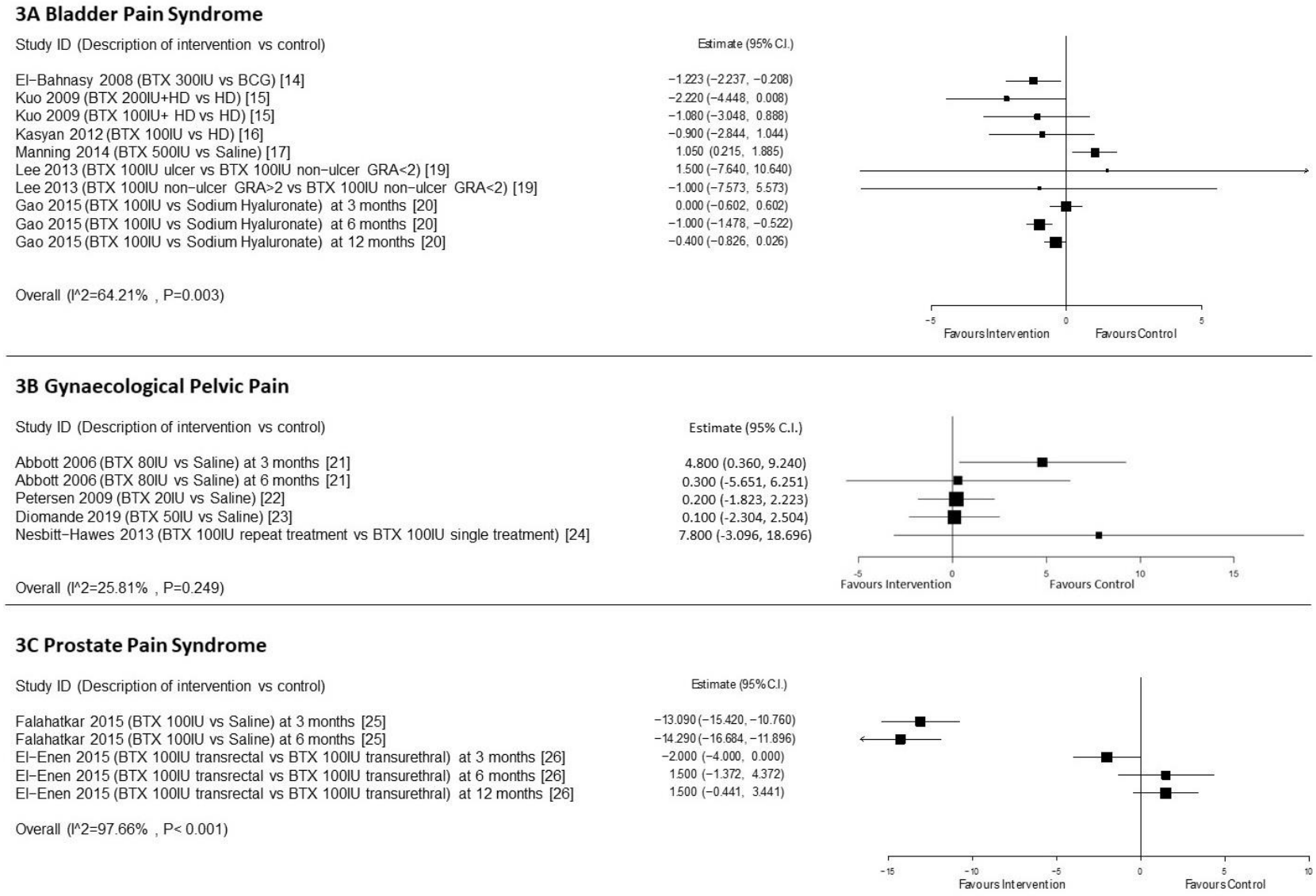


Figure 4 – Forest plot of adverse events in studies treating bladder pain syndrome

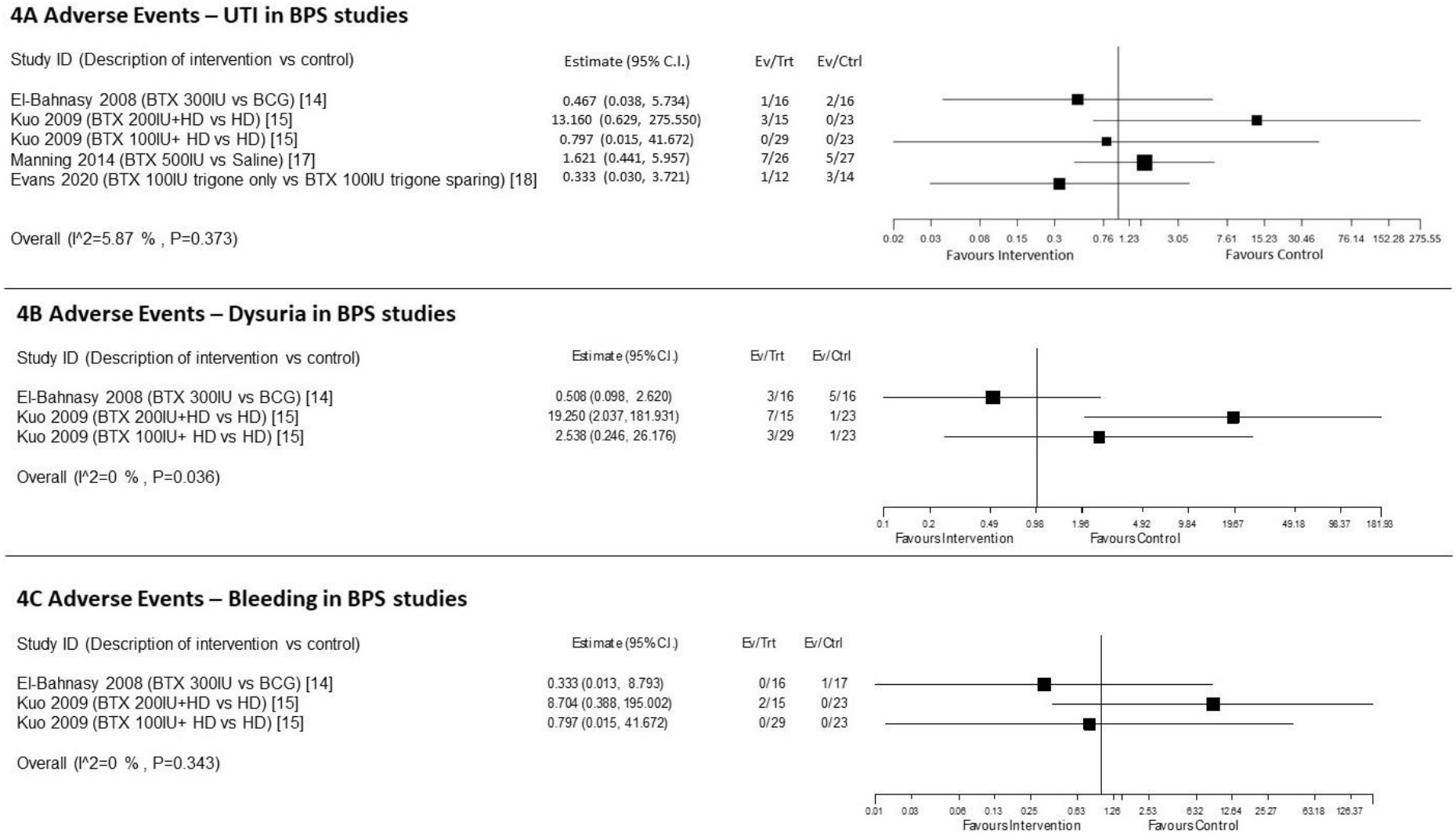
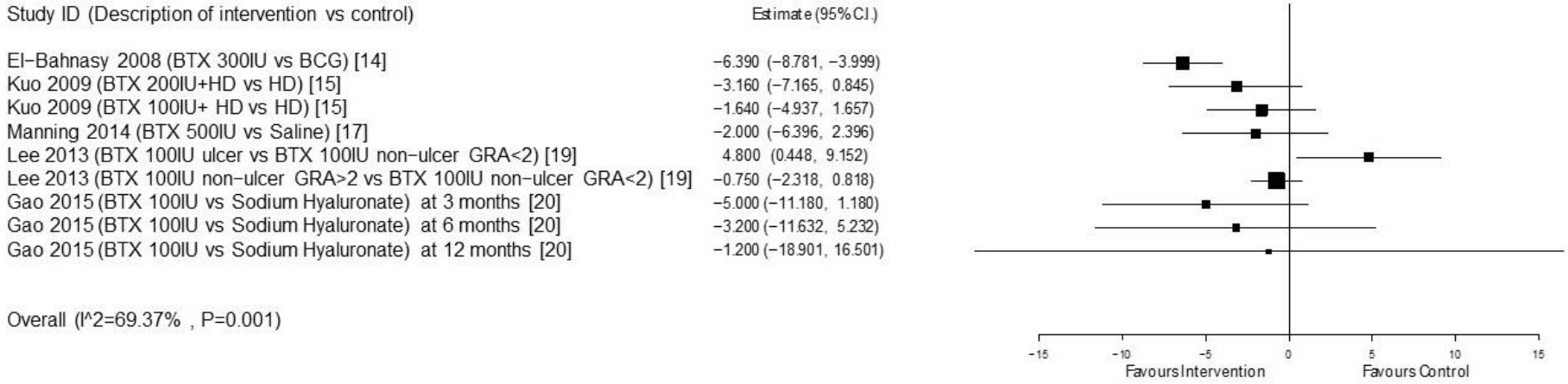


Figure 5 – Forest plot of bladder diary in studies treating bladder pain syndrome

5A Daily voiding Frequency



5B Nocturia