What are the short-term benefits and potential harms of therapeutic modalities for the management of overactive bladder syndrome in women? A review of evidence under the auspices of the European Association of Urology, Female Non-Neurogenic LUTS Guidelines Panel

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ABSTRACT

Context
Overactive bladder syndrome (OAB) is highly prevalent among women and has negative impact on their quality of life. The current available treatments for OAB symptoms include conservative, pharmacological, or surgical modalities.

Objectives
To provide an updated contemporary evidence document regarding OAB treatment options and determine the short-term effectiveness, safety, and potential harms of the available treatment modalities for women with OAB syndrome.

Evidence Acquisition and methods
The Medline, Embase and Cochrane controlled trials databases and clinicaltrial.gov were searched for all relevant publications up to May 2022. Risk of bias assessment followed the recommended tool in the Cochrane Handbook for Systematic Reviews of Interventions and quality of evidence was assessed using modified GRADE criteria. Meta-analysis was performed where appropriate.

Evidence Synthesis

Antimuscarinics and Beta-3 agonists were significantly more effective than placebo across most outcomes, with beta-3 agonists more effective at reducing nocturia episodes and antimuscarinics causing significantly higher adverse events.

Onabotulinumtoxin-A was more effective than placebo across most outcomes, but with significantly higher rates of AUR/CISC (6-8 times) and UTIs (2-3 times). Onabot-A was also significantly better than antimuscarinics in cure of UUI but not in reduction of mean UUI episodes.

SNS success rate were significantly higher than antimuscarinics (61% vs. 42%, $p = 0.02$), with similar rates of adverse events. SNS and Onabot-A were not significantly different in efficacy outcomes. Satisfaction rates were higher with Onabot-A, but with a higher rate of recurrent UTIs (24% VS. 10%). SNS was associated with 9% removal rate and 3% revision rate.

Conclusions and Patient Summary

Overactive bladder is a manageable condition, with first line treatment options including antimuscarinics, beta-3 agonists and PTNS. Second-line options include onabotulinumtoxin-A bladder injections or sacral nerve stimulation. The choice of therapies should be guided by individual patient factors.

1. Introduction

Overactive bladder syndrome (OAB) is characterized by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, in the absence of proven infection or other obvious pathology [1]. Its overall prevalence in 5 western countries in the EPIC study was 13% [2]. Prevalence varies according to geographic distribution. It has been estimated at 8.1% in Japanese adult women based on OAB symptom score questionnaire (OABSS) [5], 16% in the USA [4], and 17% in Austria (10% OAB dry and 6.5% OAB wet) [67]. Approximately 67% of patients with OAB do not have urinary incontinence and are classified as OAB-dry [3].

The annual cost of OAB is estimated across Europe at seven billion euros, and 66 billion USD in the United States, including a significant amount of money spent on nursing home admissions for UUI [4].

Proposed risk factors associated with OAB syndrome are obesity, constipation, and ageing [5]. It has a negative impact on the quality of life of patients, being associated with depression and anxiety, loss of self-esteem, and impaired interpersonal interactions [6,7].

Current available treatment options for OAB symptoms start with conservative treatments - containment, lifestyle interventions and physical therapies such as pelvic floor muscle training (PFMT). Pharmacological treatments include antimuscarinics, beta-3 agonists, and topical estrogen. Surgical treatments include bladder wall injection of botulinum-A toxin, sacral nerve stimulation (SNS) or urinary diversion.

Previous reviews on OAB syndrome have focused on urgency incontinence, included mixed populations or included mixed study designs and heterogenous outcomes. The aim of this review is to provide a contemporary document, based on the highest quality available evidence and clinically relevant outcome measures, regarding OAB treatment options and to determine the effectiveness, safety and potential harms of the available treatment modalities for women with OAB syndrome.

2. Evidence Acquisition

2.1 Study Design

Included study designs were Randomised Controlled Trials (RCTs) or non-randomised prospective comparative studies evaluating women with OAB symptoms with at least one intervention. Trials with mixed populations were included if data from female participants could be extracted separately. Exclusion criteria were retrospective study designs, studies in paediatric populations and studies where a majority of participants had a neurological component to their symptoms. A detailed summary of the PICO characteristics for this review are given in table 1.

As a matter of convention for this review, 'early' or 'short-term' time points would include those up to 1 year post intervention, 'medium-term' or 'intermediate' time points between 1-5 years, and 'long-term' or 'late' time points beyond 5 years. Early time points have been further sub-divided for pharmacological studies as close as practically possible to 3 months (12 weeks), 6 months (24 weeks) and 1 year post intervention.

The GRADE approach was used for assessing the certainty of evidence (CoE) for outcomes within each comparison, with grades of very low, low, moderate and high certainty applied. This assessment is based on evaluation of risk of bias, indirectness, imprecision, inconsistency and publication bias across outcomes. The following outcomes were selected for the "Summary of Findings" table:

- Cure of OAB symptoms
- Improvement of OAB symptoms
- Adverse events as reported by trialist

2.2 Literature Search

The Medline, Embase and Cochrane controlled trials databases and clinicaltrial.gov were searched for all relevant publications (searched from 2000 to July 2021, limited to English language.) An updated search for high level evidence was conducted in May 2022. The literature search strategy is provided in Appendix 1. The study protocol was registered in PROSPERO in July 2020, registration number CRD42020192207. Reference lists of included studies and systematic reviews were also hand-searched to identify other possible studies for inclusion.

2.3 Data collection and analysis

Selection of studies and data extraction

Following de-duplication, four review authors (NS, VS, MK, SM) independently screened the titles and abstracts of identified records for eligibility. The full texts were retrieved and screened independently by two review authors using a standardised form, linking together multiple records of the same study in the process. Study characteristics were extracted by one review author and a second review author checked data extractions for accuracy. A standardised data extraction form was developed and piloted before use. This can be viewed in Appendix 2. Any disagreements were resolved by discussion or by consulting a third review author (FF).

Assessment of risk of bias in included studies

The 'risk of bias' of each included study was assessed by four review authors working independently (NS, VS, MK, SM). Any disagreements were resolved by discussion or by consulting a third review author (FF). Risk of bias in RCTs was assessed by using the recommended tool in the Cochrane Handbook for Systematic Reviews of Interventions [8,9]. This includes the assessment of:

- random sequence generation
- allocation concealment
- blinding of participants and personnel
- blinding of outcome assessment
- incomplete outcome data
- selective reporting
- other sources of bias.

As there were no non-randomised studies included in the final analysis, no other RoB assessment tools were utilised.

Unit of analysis issues

The primary analysis was per participant (randomised). For studies with more than two intervention groups, only the intervention groups relevant to the review were selected, or groups were combined to create a single pair-wise comparison where possible.

Dealing with missing data

Intention-to-treat analysis were performed when data were available. No imputation of missing data was carried out. For incompletely reported data, rigorous attempts were made to contact corresponding authors.

Assessment of publication bias

The review authors aimed to minimise potential publication bias by conducting a comprehensive literature search for eligible studies, including hand-searches of reference lists of included studies.

Data Synthesis

Meta-analysis was performed where there was more than one randomised controlled trial reporting the same outcome at similar time-points. For studies with multiple publications,

only the most up-to-date or complete data for each outcome was used. For cross-over study designs, data were extracted from only the first period of intervention. A fixed effects model was used to calculate pooled estimates of treatment effect across similar studies and their 95% CIs. Where clinical or methodological heterogeneity was expected, a random effects model was used.

Dichotomous outcomes were combined using the Mantel-Haenszel method for risk ratios (RR), 95% CI and p-values, where available. Continuous outcomes were combined using the inverse variance mean difference method using mean difference (MD) or weighted mean difference (WMD) with corresponding 95% confidence intervals (CIs). If studies use different scales to assess the same continuous outcome, the standardized mean difference was used instead of the weighted mean difference.

Assessment of heterogeneity and sensitivity analyses

Heterogeneity between studies was assessed by visual inspection of plots of the data, the Chi^2 Q test for heterogeneity and I^2 statistics [10]. Substantial heterogeneity was considered present if I^2 was greater than 50%.

3. Evidence Synthesis

A total of 5434 abstracts were screened after removal of duplicates. A total of 466 full text articles were assessed for eligibility, and 45 RCTs [11–40, 51-66] were included in meta-analysis. Details of study selection process are depicted in PRISMA Flow diagram [41] (figure 1). Characteristics of the studies included in meta-analysis are summarised in table 2. Risk of bias in included studies is summarised in figure 2.

The question for this review is quite broad and consequently a large number of studies were identified. To align with our aim of synthesising only the highest quality available evidence, RCT data was prioritised. Non-RCT data was included in a qualitative synthesis but the certainty of evidence was too low to draw robust conclusions and is not presented in this manuscript. Good quality data allowing for meaningful comparisons could only be elicited for the following comparisons:

- Antimuscarinics vs Placebo;
- Antimuscarinics vs beta-3 agonists;
- Antimuscarinics vs Antimuscarinics + adjunct treatment;
- PTNS vs Antimuscarinics;
- Onabotulinum toxin-A vs placebo;
- Onabotulinum toxin-A vs Antimuscarinics;
- Sacral nerve stimulation vs other therapies; and
- Cyclical vs continuous sacral nerve stimulation.

Forest plots of all comparisons included in the metanalyses are presented in Appendix 3, Summary of Findings (SoF) tables in Appendix 4 and related GRADE forms are presented in Appendix 5.

3.1 Antimuscarinics vs. Placebo

Twelve studies on 11179 women were identified for this comparison. Antimuscarinics were significantly more effective than placebo in improving mean symptom score on OABq (MD -5.70, 95% CI -7.93 to -3.46, $p<0.001$, CoE is moderate) and in reducing daily frequency episodes (MD -1.30, 95% CI -1.77 to -0.84, $p<0.001$, CoE is low), daily urgency episodes (MD -

0.63, 95% CI -1.17 to 0.10, p= 0.019, CoE is low), urgency urinary incontinence (UUI) episodes (MD -0.48, 95% CI -0.71 to -0.24, p<0.001, CoE is moderate), and increase in bladder functional capacity (MD 14.31, 95% CI 9.93 to 18.68, p<0.001, CoE is moderate).

Antimuscarinics caused significantly higher adverse events than placebo including dry mouth (RR 3.20, 95% CI 1.54 to 6.67, p=0.002, CoE is low), cognitive impairment (RR 2.28, 95% CI 1.33 to 3.91, p=0.003, CoE is low), UTI (RR 1.91, 95% CI 1.03 to 3.57, p=0.037, CoE is low), and constipation (RR 1.72, 95% CI 1.1 to 2.69, P=0.018, CoE is low).

3.2 Antimuscarinics vs. Beta-3 Agonists

Four studies on 371 women were identified for this comparison. Beta-3 agonists were significantly more effective than antimuscarinics in reducing nocturia episodes (MD 0.38, 95% CI 0.16 to 0.61, p=0.001, CoE is low), but no significant differences were found between antimuscarinics and beta-3 agonists in reduction of mean symptoms score (SMD 0.16, 95% CI -0.26 to 0.58, p=0.4, CoE is very low), urgency episodes (SMD 0.06, 95% CI -0.21 to 0.32, p = 0.6, CoE is very low), frequency episodes (SMD 0.12, 95% CI -0.23 to 0.48, p=0.4, CoE is very low) or UUI episodes (SMD -0.13, 95% CI -0.39 to 0.13, p=0.3, CoE is very low) or voided volumes (SMD -0.05, 95% CI -0.32 to 0.21, p = 0.7, CoE is very low).

Antimuscarinics caused higher rates of dry mouth than beta-3 agonists (RR 6.44, 95% CI 1.97 to 21.01, p=0.002, CoE is low) but no significant difference was found in constipation rates (RR 2.11, 95% CI 0.49 to 9.04, p=0.3, CoE is very low).

3.3 Antimuscarinics vs. antimuscarinics + adjunct treatment

Thirteen studies on 2805 women were identified for this comparison. Benefits and harms of antimuscarinic monotherapy were compared to benefits and harms of combinations of antimuscarinics plus a number of adjunct treatments including topical oestrogen, pregabalin, Stroller neurostimulation (SANS), PFMT, and behavioural therapy. Antimuscarinics alone were less effective than a combination of antimuscarinics plus another treatment modality in reducing urgency episodes (SMD 0.68 95% CI 0.04 to 1.32, p=0.038, CoE is low), UUI episodes (SMD 1.18 95% CI 0.18 to 2.17, p=0.019, CoE is low), frequency episodes (SMD 0.33 95% CI 0.10 to 0.55, p=0.004, CoE is low) and nocturia episodes (MD 0.44, 95% CI 0.04 to 0.84, p=0.027, CoE is low), and in improving the mean symptoms score (SMD 0.55 95% CI 0.16 to 0.95, p=0.006, CoE is low), but no significant differences were found in rates of dry mouth (RR 1.22, 95% CI 0.74 to 2.02, p=0.4, CoE is low), constipation (RR 1.38, 95% CI 0.58 to 3.27, p=0.4, CoE is low), or voiding dysfunction (RR 1.35, 95% CI 0.32 to 5.78, p=0.7, CoE is low).

3.4 Posterior Tibial Nerve Stimulation (PTNS) vs. Antimuscarinics

Five studies on 408 women were identified for this comparison. Posterior tibial nerve stimulation (PTNS) techniques were significantly more effective than antimuscarinics in reduction of UUI episodes (MD -0.67, 95% CI -1.31 to -0.02, p=0.037, CoE is very low) with no significant difference in reduction of mean symptoms score (MD -0.62, 95% CI -2.13 to 0.89, p=0.4, very low CoE) or frequency episodes (MD -0.55, 95% CI -2.01 to 0.90, p=0.4, CoE is very low) or urgency episodes (MD -0.43 95% CI -0.98 to 0.12, p=0.13, CoE is low).

3.5 Posterior Tibial Nerve Stimulation (PTNS) vs. Combination of PTNS plus antimuscarinics

Three studies on 185 women were identified for this comparison. The combination of PTNS plus antimuscarinics added no statistically significant difference to PTNS monotherapy in reduction of mean symptoms score (MD -1.78, 95% CI -4.66 to 1.11, p=0.2, very low CoE) or frequency episodes (SMD 0.37, 95% CI 0.01 to 0.74, p=0.048, moderate CoE), nocturia episodes (SMD 0.39, 95% CI -0.04 to 0.81, p=0.068. low CoE), or UUI episodes (SMD 0.57, 95% CI -1.05 to 2.19, p=0.4, very low CoE).

3.6 Intradetrusor injection of Onabotulinumtoxin-A vs. Placebo

Ten studies on 2055 patients were identified for this comparison. Onabotulinumtoxin-A was more effective than placebo in improvement of mean symptoms score (SMD -0.66, 95% CI -0.88 to -0.44, p<0.001, moderate CoE), reduction of mean urgency episodes (SMD -0.53, 95% CI -0.64 to -0.43, p<0.001, moderate CoE), mean UUI episodes (SMD -0.43, 95% CI -0.53 to -0.34, p<0.001, moderate CoE), mean frequency episodes (SMD -0.53, 95% CI -0.63 to -0.43, p<0.001, moderate CoE), mean nocturia episodes (SMD -0.25, 95% CI -0.35 to -0.15, p<0.001, moderate CoE). No statistically significant difference was found between ontabotulinumtoxin-A and placebo in change of mean voided volumes/maximum cystosmetric capacity (MCC) (SMD 0.08, 95% CI -0.05 to 0.2, p=0.2, very low CoE).

Ontabotulinumtoxin-A was associated with significantly higher rates of voiding dysfunction (defined as AUR or need for CISC) compared to placebo at both 100 units dose (RR 8.89, 95% CI 4.39 to 17.6, p< 0.001, moderate CoE) and 200 units dose (RR 6.4, 95% CI 3.11 to 13.2, p< 0.001, moderate CoE), and significantly higher rates of UTI both at 100 units dose

(RR 2.72, 95% CI 2.06 to 3.59, p< 0.001, moderate CoE) and 200 units dose (RR 3.84, 95% CI 2.37 to 6.21, p< 0.001, moderate CoE).

3.7 Intradetrusor injection of Onabotulinumtoxin-A vs. Antimuscarinics

Two RCTs on 545 patients were identified for this comparison. Onabotulinumtoxin-A was significantly more effective than antimuscarinics in the cure of UUI symptoms (2 RCTS, RR 1.56, 95% CI 1.16 to 2.11, p=0.004, high CoE). Onabotulinumtoxin-A showed no significant difference compared to antimuscarinics in reduction of mean UUI episodes (MD -0.01, 95% CI -0.3 to 0.28, p>0.9, CoE low). However, it was associated with significantly higher rates of voiding dysfunction than antimuscarinics (RR 18.5, 95% CI 2.45 to 140, p=0.005, moderate CoE), and UTIs (RR 4.07 95% CI 2.23 to 7.45, p<0.001, high CoE).

3.8 Sacral Neurostimulation (SNS) vs. Other Interventions

Meta-analysis was not possible for this comparison, but due to the clinical importance we present a narrative review here. Amundsen et al reported the two-year outcomes of the ROSETTA Trial [42]. A total of 386 women with refractory UUI were randomised to SNS (n=194 women) or intradetrusor injection of onabotulinumtoxin-A (BTX) (n=192 women) across 9 centres in an open label setting. The authors found no statistically significant difference between SNS and BTX in improvement of mean symptoms score on OABq-SF (-36.2 (SE 2.2) vs. -33.9 (SE 2.1), p=0.4) or in reducing the mean UUI daily episodes (-3.8 for BTX vs. -3.5, 95%CI -0.1 to -0.9, p=0.11). While patients reported significantly higher

satisfaction with BTX, this modality was associated with significantly higher rates of recurrent UTIs than SNS (24% VS. 10% respectively, p=0.012). On the other hand, SNS was associated with 9% removal rate and 3% revision rate at 2 years follow-up.

Siegel et al compared SNS with antimuscarinics in a multicentre randomised trial (INSITE) [43]. A total of 70 (94% women) patients underwent SNS implantation while 77 patients (92% women) received antimuscarinics. At 6 months follow-up, Intention to treat (ITT) analysis revealed statistically significant higher success rate for SNS compared to antimuscarinics (61% vs. 42%, respectively, p = 0.018) with success defined as >50% improvement in daily UUI or frequency episodes. Adverse events occurred in 30% and 27% of SNS and antimuscarinics trial arms respectively, none were serious. SNS was associated with higher rates of UTIs (p=0.011) and was associated with implant site infection and lead migration in 3.4% of cases each.

3.9 Sacral neurostimulation – cyclic vs. continuous settings.

Two cross-over RCTs were identified including 61 women with OAB symptoms where trialists compared different cyclic stimulation settings with continuous stimulation setting in women with refractory OAB symptoms. Siegel et al [44] applied 4 different stimulation settings: continuous, 16 s. on/ 8 s. off, 10min on / 10 min off, and 30 min on / 23.5 hrs off) in women with UUI with mean age 64 yrs and mean implant duration of 2.8 yr. In the first period of this cross-over trial, the 10 min on/off setting was associated with significantly less episodes of UUI than the 16 s. on / 8 s. off setting (p = 0.002), while 54% of women found that 10 min on/off setting was associated with improvement in their UI symptoms as per

the Global Response Assessment (GRA) compared to 42% improvement with the 30 min on / 23 hrs off pattern.

Price and Noblett et al [45] found that both modalities were associated with significant improvement in all voiding diary parameters when compared to baseline, however, no modality proven to be statistically superior to another in terms of mean score on UDI or change in mean daily episodes of frequency, urgency, nocturia or voided volumes.

4. Discussion

This review presents a contemporaneous high-level search on the treatment of OAB symptoms in adult women. It evaluates the highest quality available evidence with strict methodological rigour and, as such, it has helped inform the development of the EAU non-neurogenic female LUTS guideline [66].

466 full-text articles were assessed and 134 included in the qualitative synthesis, across multiple interventions, comparisons, outcome measures and time-points. This makes quantitative synthesis difficult, hence the authors strived to maintain stringent quality standards for inclusion in the final analysis, restricting to RCTs (45) and guided by consistent risk of bias assessment and a GRADE system of evaluation of data across outcomes to arrive at certainty ratings from very low to high. These certainty ratings are an important component of the overall results and hence we have included them with the forest plots to make interpretation easier for the reader.

Clinical significance of outcome measures has also been taken into account. The authors acknowledge that true effectiveness of an intervention relates to much more than statistical

significance. Fragility of p-values and minimum clinically important difference in outcome measures must be considered, and we attempt to do so in our discussion.

Heterogeneity of definitions and outcome measures is also the primary reason why studies on PFMT and other physical therapies have not been evaluated in this review. To avoid long narrative sections with no scope for data synthesis, and to keep the review succinct and methodologically robust, these comparisons were removed. However, the evidence was used to underpin the EAU non-neurogenic female LUTS guideline recommendations.

Overall, the results show that antimuscarinics are more effective than placebo for improving OAB symptom scores, frequency episodes, urgency episodes, UUI episodes and voided volumes, but at the cost of higher risk of side effects. These results will be unsurprising to most healthcare practitioners familiar with OAB, as antimuscarinics have been a staple treatment option for many years. This review also reinforces the findings that there is a significant placebo effect in the treatment of OAB (as high as 30%), and the added benefit with active intervention may, though statistically significant, be clinically small (mean reduction of 1.3 frequency episodes per day, 0.6 urgency episodes per day, and mean 14ml increase in functional bladder capacity).

The comparison between antimuscarinics and beta-3 agonists are perhaps more interesting, showing no significant difference in efficacy parameters except in terms of reduction in nocturia episodes (where beta-3 agonists are significantly better). Overall certainty of this outcome is low, but one high quality RCT [14] suggests that the result holds for the comparison between solifenacin and mirabegron. Beta-3 agonists have the advantage of causing fewer side effects and therefore tolerability may be improved.

The comparison of antimuscarinics vs antimuscarinics + adjuncts is plagued by heterogeneity of interventions. Although grouping is technically possible, the heterogeneity becomes clear with a cursory review of the forest plot, and the most likely reason is apparent. The adjunct intervention for each trial was significantly different, so we would not recommend drawing any hard conclusions from the pooled estimates, but rather stick to data from the individual studies for specific comparisons. As such, statistical analysis supports the addition of stoller afferent neurostimulatiuon to trospium, and PFMT to trospium, in reduction of frequency episodes, urgency/UUI episodes without significantly increasing the rate of adverse events, but the clinical significance of these differences should be weighed carefully against the economic cost of these adjuncts. The minimal clinically important difference (MCID) across outcome measures for OAB studies has not been established satisfactorily and, along with a core outcome set (COS) would be a very useful tool for SR's of the topic in future.

Perhaps the most surprising results were in the comparison of PTNS to antimuscarinics. PTNS was shown to be more effective than antimuscarinics in reducing UUI episodes, although closer inspection reveals that this comparison only just reaches significance and is mainly driven by the PTNS vs tolterodine study [15], while comparisons against oxybutynin and solifenacin did not show the same difference. Total number of participants in this analysis was also low, and certainty of evidence here is very low. Combination therapy did not seem to profer any additional benefit.

Intradetrusor injections of botulinum toxin-A (BoNT-A) is a widely used second-line treatment for refractory OAB and the evidence strongly supports its efficacy vs placebo injections across all parameters with moderate certainty, but with 2-3 times increased risk

of UTI, and 6-8 times increased risk of urinary retention or the need to self-catheterise. The risk of AUR/CISC appears to be higher with the 100U dose (RR 8.8) compared to 200U (RR 6.4), but this is likely related to the smaller number of participants and studies in the latter comparison. Compared to antimuscarinics, BoNT-A injections are significantly better for cure of UUI (moderate certainty) but not for reduction of UUI episodes (low certainty). Once again BoNT-A causes higher rates of urinary retention/need for CIC and UTI.

Sacral nerve stimulation could not be evaluated in a meta-analysis because there were only single trials for each comparison, but a high quality randomised study found improved efficacy compared to antimuscarinics [43], and no difference between SNS and BoNT-A in improvement of symptom scores or reduction in mean daily UUI episodes, although treatment satisfaction rates overall were higher with BoNT-A [42]. Wound infection rates and lead migration rates were around 3%, and at 2 years the removal and revision rates were 9% and 3% respectively.

There are no other reviews encompassing the gamut of treatments for OAB, however reviews on pharmacological management and BoNT-A have been carried out. A 2014 systematic review by Maman et al [49] assessed the efficacy and tolerability of OAB medications, specifically mirabegron 50 mg versus antimuscarinics in patients with OAB. They concluded that mirabegron 50mg had similar efficacy to most antimuscarinics, with a lower incidence of dry mouth - a finding that is corroborated by our review, as well as a 2021 SR by Mostafaei et al [50]. A 2015 systematic review by Henriet et al [47] on intradetrusor botulinum toxin injections for refractory detrusor overactivity reported that it reduces frequency, urgency, nocturia and incontinence episodes at the cost of increased risk of voiding dysfunction and UTI, again similar to our own findings. Drake et al [48] conducted

a network meta-analysis on the efficacy of BoNT-A and oral therapies for overactive bladder at 12-week follow-up. They included 56 RCT's across all comparisons and concluded that BoNT-A produced the average greatest reductions in urinary incontinence episodes (UIE), urgency episodes, and micturition frequency, and the highest odds of achieving decreases of 100% and ≥50% from baseline in UIE/day. It is to be noted that SNS was not a comparator in this review, and network meta-analysis allows for more indirect comparisons than standard meta-anlaysis. However, the results are still largely consistent, though we could not make strong conclusions in relation to BoNT-A vs antimuscarinics due to the small number of included studies and heterogeneity in outcomes.

A drawback of this review may be the strict inclusion criteria in terms of study designs, definition of interventions and outcome heterogeneity. The justification here is two-fold: firstly, the broad topic area was inevitably going to result in a very large number of identified studies, hence a degree of pragmatism was required to keep the numbers manageable without sacrificing quality. Secondly, the aim was to evaluate the highest quality available evidence while keeping comparators as pure as possible. Heterogeneity is always a major issue in reviews of OAB therapy, and the principal cause is usually difference in mode or delivery of intervention. We have therefore tried to keep the comparators and outcomes as similar as possible. A few larger studies also had to be excluded because data was not available for female subjects separately. This was despite multiple attempts to contact corresponding authors, and although most of the studies included predominantly women, on balance the integrity of the data was considered paramount.

Overall, our results are consistent with other, more focused, reviews in the topic area and therefore adds to the evidence base. It is reassuring that a review with strict methodological criteria focusing on high quality studies draws broadly similar conclusions to more focused reviews in the topic area. It will also help inform upcoming versions of the EAU non-neurogenic female LUTS guideline and current good practice relating to OAB.

5. Conclusions

Overall, this review provides high quality contemporary evidence on the management of overactive bladder that will help inform treatment decisions and guideline development. It supports the use of antimuscarinics and beta-3 agonists as first line therapy, with beta-3 agonists perhaps causing less side effects overall and more useful for nocturia symptoms. Botulinum toxin injections and sacral nerve stimulation are equivalent second line options in terms of efficacy but have a different adverse event profile and their suitability should be discussed based on patients' individual circumstances. The evidence for PTNS is still uncertain.

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