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Flavoxate in the symptomatic treatment of overactive bladder: a meta-analysis

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Abstract. – OBJECTIVE: Overactive bladder is a syndrome of urinary frequency and urgency, with or without urge incontinence, in the absence of local pathological factors. Since multiple causes are responsible for OAB, it requires proper diagnosis and comprehensive management. For decades, flavoxate is a globally used and accepted molecule by the urologists and the general physicians for the symptomatic treatment of OAB. In spite of its extensive use in OAB, a meta-analysis of the available publications for efficacy, safety and tolerability of flavoxate has not been conducted. This paper evaluates the strength of evidence of clinical effectiveness of safety and tolerability of flavoxate in the symptomatic treatment of OAB.

METHODS: Review articles, original studies and case reports on MEDLINE, the Cochrane Library, Google Scholar, Scirus, internal repository, etc. were searched using the keyword "flavoxate". For the primary outcome, the comparative data of flavoxate versus comparator was extracted for following parameters – overall efficacy and its side effect profile. Similarly as for secondary outcome, data were extracted for flavoxate per se for overall efficacy, frequency, urinary incontinence, mixed incontinence, nocturia, unpleasant urination, stranguria and its side effect profile and were analyzed using Comprehensive Meta-Analysis (CMA) software version 2.0.

RESULTS: In the current meta-analysis, 43 relevant published studies were considered which clearly demonstrated that flavoxate had improved clinical efficacy than placebo, emepronium, propantheline, and phenazopyridine.

CONCLUSIONS: Amongst all the interventions studied, flavoxate was effective and well-tolerated, with almost negligible side effects, making it worthy of consideration for the treatment of OAB.

Key Words:
Clinical trial, Meta-analysis, Flavoxate, Placebo, Over active bladder, Detrusor overactivity, Efficacy, Side effects, Urinary Incontinence, Mixed Incontinence, Nocturia, Unpleasant urination, Stranguria.

Introduction

The International Continence Society defines overactive bladder (OAB) as a syndrome of urinary frequency and urgency, with or without urge incontinence, which appears in the absence of local pathological factors[1]. Incontinence, a bothersome symptom of OAB, increases with age[2]. Neurologic impairment, immobility, female gender, and history of hysterectomy are the risk factors for the development of OAB. Commonly urge incontinence coexists with stress incontinence, especially in women.

Detrusor overactivity is a predominant cause for the OAB. It may be either idiopathic or neurogenic in origin. The common symptoms complained by OAB patients are urinary urge incontinence, involuntary leakage accompanied by or immediately preceded by urgency[3,4].

Prompt diagnosis is crucial for the comprehensive management of OAB. Treatment is instituted according to the type of incontinence and includes behavioural training (prompted voiding, bladder training, pelvic muscle rehabilitation, pelvic floor exercises), transcutaneous electrical nerve stimulation, catheterization, use of absorbent pads or pharmacologic or surgical treatment[5].

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On the other hand, the pharmacological interventions for the treatment of OAB should focus on patient benefit and therefore patient perceived outcomes, rather than simple symptom resolution alone, should be taken into account[5]. Moreover, the efficacy of OAB therapy needs to be balanced against tolerability, since a low incidence of adverse events (AEs) improves compliance with treatment. This balance between efficacy and tolerability should provide palpable benefits from patient's perspective, and promote therapy persistence. Unfortunately, many older agents have modest clinical efficacy and are associated with unfavorable side effects, leading to poor persistence.

Among various pharmacological interventions for the treatment of OAB, flavoxate has been widely used and accepted among the urologists and the general physicians for decades globally[6]. We performed a meta-analysis on flavoxate to investigate, based on available evidence, its efficacy, side effects profile, and effects on frequency, urinary incontinence, mixed incontinence, nocturia, unpleasant urination and stranguria (defined as slow and painful urination or burning).

Methods

Database Search and Data Extraction

The search was performed between June and August 2015 by using the keyword "*flavoxate*" on various search engines like Google Scholar, Medline, Cochrane Database, and personal collection of literature No restrictions in terms of publication date were applied.

Inclusion and Exclusion Criteria

Publications on either flavoxate versus comparator (placebo, oxybutynin, emepronium, propantheline, phenazopyridine) or flavoxate *per se* in the treatment of OAB were included. Some publications that were in non-English language and could not be translated to English were excluded.

Outcomes

The primary outcome was represented by the comparative assessment of flavoxate versus comparator (placebo, phenazopyridine, oxybutynin, propantheline, emepronium) for the overall efficacy (defined as the global efficacy of treatment with intervention in the management of OAB) and side effects profile in the symptomatic treatment of OAB.

The secondary outcome was to assess the effect of flavoxate *per se* on overall efficacy, frequency, urinary incontinence, mixed incontinence, nocturia, unpleasant urination, stranguria, as well as its side effect profile in the symptomatic treatment of OAB.

Data Analysis

Meta-analysis was performed using Comprehensive Meta-Analysis (CMA) software version 2.0 procured from Biostat, Inc. USA. Mantel Haenszel risk ratio (MH risk ratio) was accessed for 'flavoxate versus comparator' (i.e., placebo, oxybutynin, phenazopyridine, emepronium, propantheline) and event rate for flavoxate *per se* in the symptomatic treatment of OAB. Heterogeneity between studies was accessed using Q value and I square statistics using both fixed and random effect model.

Results

The databases searches yielded 86 publications pooled from PubMed, Google Scholar, Medline, Cochrane Database and internal repository[7-49]. According to our inclusion and exclusion criteria, 43 relevant studies were identified (Figure 1).

Primary Efficacy Analysis

Flavoxate vs. Placebo

In total, eight studies included 262 patients on flavoxate and 233 patients on placebo. Of these studies, three showed a significant ($p < 0.05$) reduction in the risk with flavoxate as compared with placebo (Figure 2). The overall effect size favouring flavoxate was estimated to be 0.48 (95% CI: 0.38-0.62) and it was statistically significant (Z = -5.721; $p < 0.001$). The Q test for heterogeneity indicates that the studies were homogeneous [$p = 0.905$; Q Value (I^2) = 2.774 (0.00); df(Q) = 7].

Flavoxate vs. Oxybutynin

All the three studies that included oxybutynin (101 patients in both the flavoxate and oxybutynin group) show a similar efficacy of flavoxate and oxybutynin (Figure 2). The overall effect size favouring flavoxate was estimated to be 0.67 (95% C.I: 0.38-1.17), but it did not reach statisti-

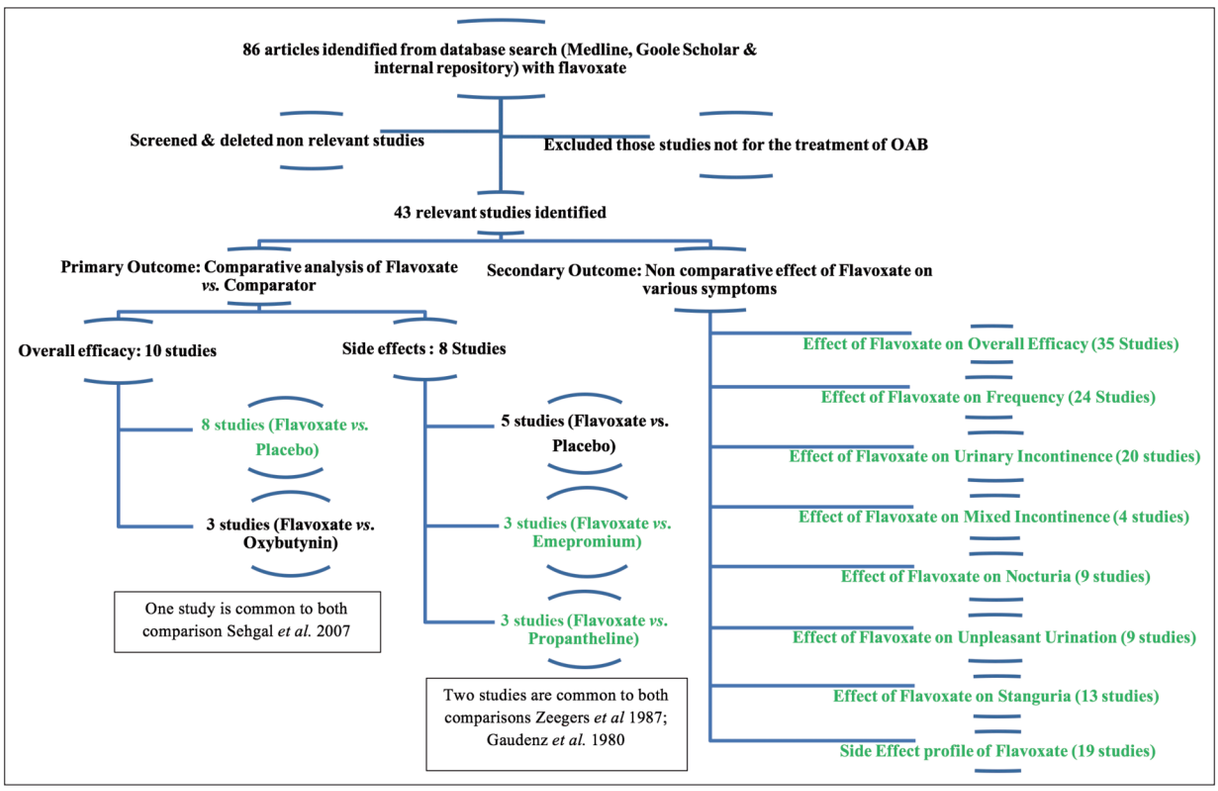

Figure 1. Flow Diagram of Meta-analysis.

cal significance (Z = -1.406; p = 0.160). The Q test for heterogeneity indicates that the studies were homogeneous [p = 0.477; Q Value (I^2) = 1.481 (0.00); df(Q) = 2].

Flavoxate vs. Others

Comparisons of flavoxate with emepronium or phenazopyridine or propantheline was not analyzed as the number of studies available were less than three. However, flavoxate showed higher efficacy than emepronium in two studies[7,21]. In other two studies [7,20], flavoxate was overall more effective than propantheline (in study[7], statistical significance was reached, $p < 0.05$). In another work[16] flavoxate was significantly more effective than phenazopyridine ($p < 0.05$).

Primary Safety Analysis

Flavoxate vs. Placebo

In all the five studies that compared the safety of flavoxate (n = 181) with that of placebo (n = 191), the incidence of adverse events was comparable in the two groups (Figure 3).

Flavoxate vs. Emepronium

Out of the three reports – involving 75 patients on flavoxate and 104 patients on emepronium – one study showed that flavoxate is associated with significantly ($p < 0.05$) fewer side effects as compared with emepronium (Figure 3). The overall effect size favouring flavoxate was estimated to be 0.32 (95% CI: 0.15-0.66) and was statistically significant (p = 0.002). The Q test for heterogeneity indicates that the studies were homogeneous [p = 0.989; Q Value (I^2) = 0.023 (0.00); df(Q) = 2].

Flavoxate vs. Propantheline

All the three papers comparing flavoxate with propantheline in terms of adverse effects showed a lower incidence of adverse effects with flavoxate (Figure 3). The overall effect size favouring flavoxate was estimated to be 0.194 (95% CI: 0.09-0.41) and it was statistically significant ($p < 0.001$). The Q test for heterogeneity indicates that the studies were homogeneous [p = 0.809; Q Value (I^2) = 0.425 (0.00); df(Q) = 2].

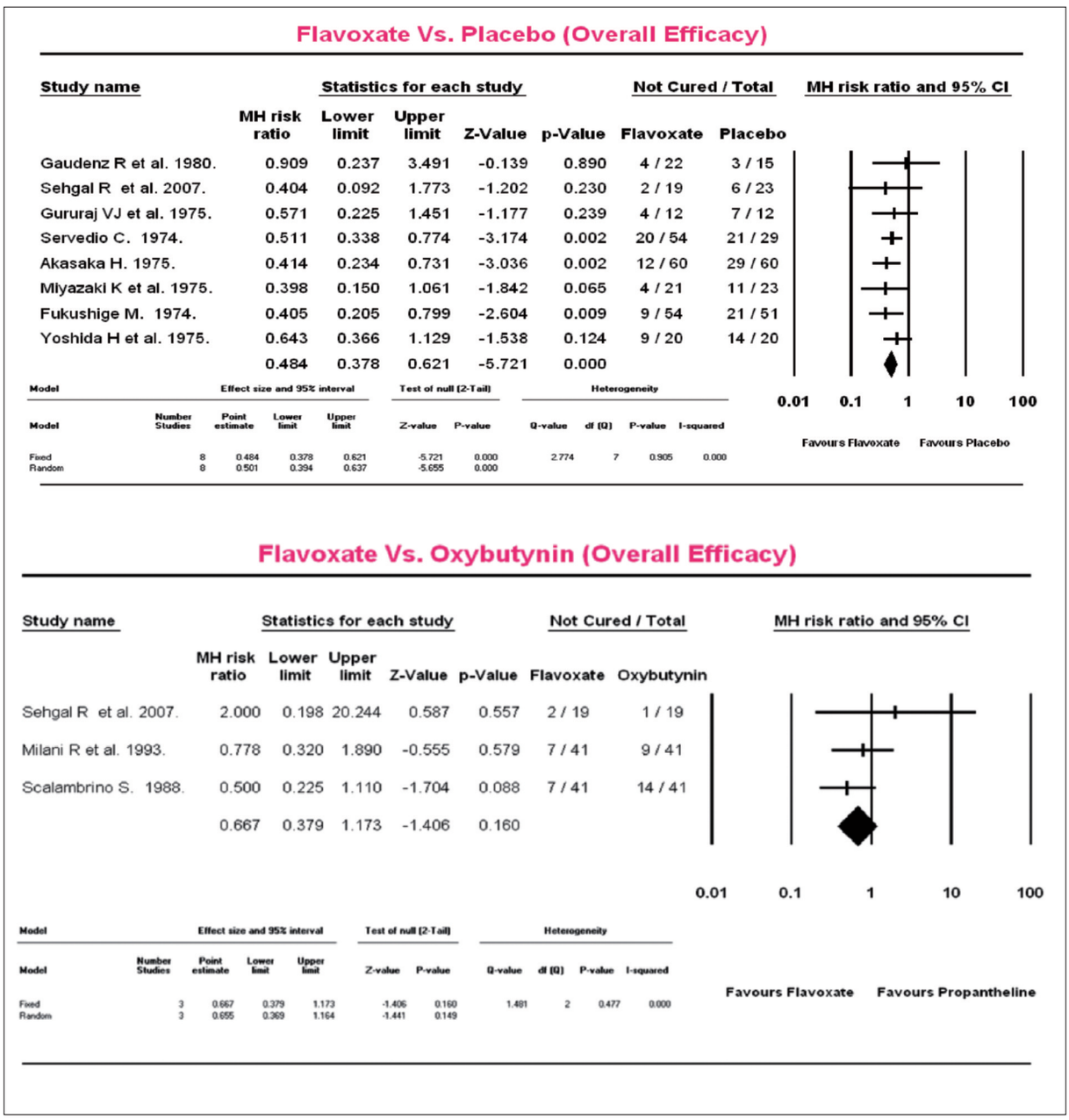

Figure 2. Comparison of overall efficacy of Flavoxate *vs*. Placebo/ Oxybutynin.

Flavoxate vs. Others

Comparison of flavoxate versus oxybutynin or phenazopyridine was not analyzed as the number of studies available were less than three. One study showed showed that side effect was significantly lower ($p < 0.05$) in flavoxate (26.8%) compared to oxybutynin (90.2%)[15]. Further, compared to phenazopyridine, side effects due to flavoxate were markedly less but not statistically significant[44].

Secondary Analysis

Supplementary Figures 1-8 summarize the results of the secondary analysis on flavoxate *per se*.

Of the 35 studies included in the efficacy analysis of flavoxate *per se* (n=2005), 19 showed significant results ($p < 0.05$). The overall effect size for efficacy favouring flavoxate was estimated to be 0.71 (95% CI: 0.70-0.74) and it was statistically significant (Z = -17.914; $p < 0.001$) (Supplementary Figure 1).

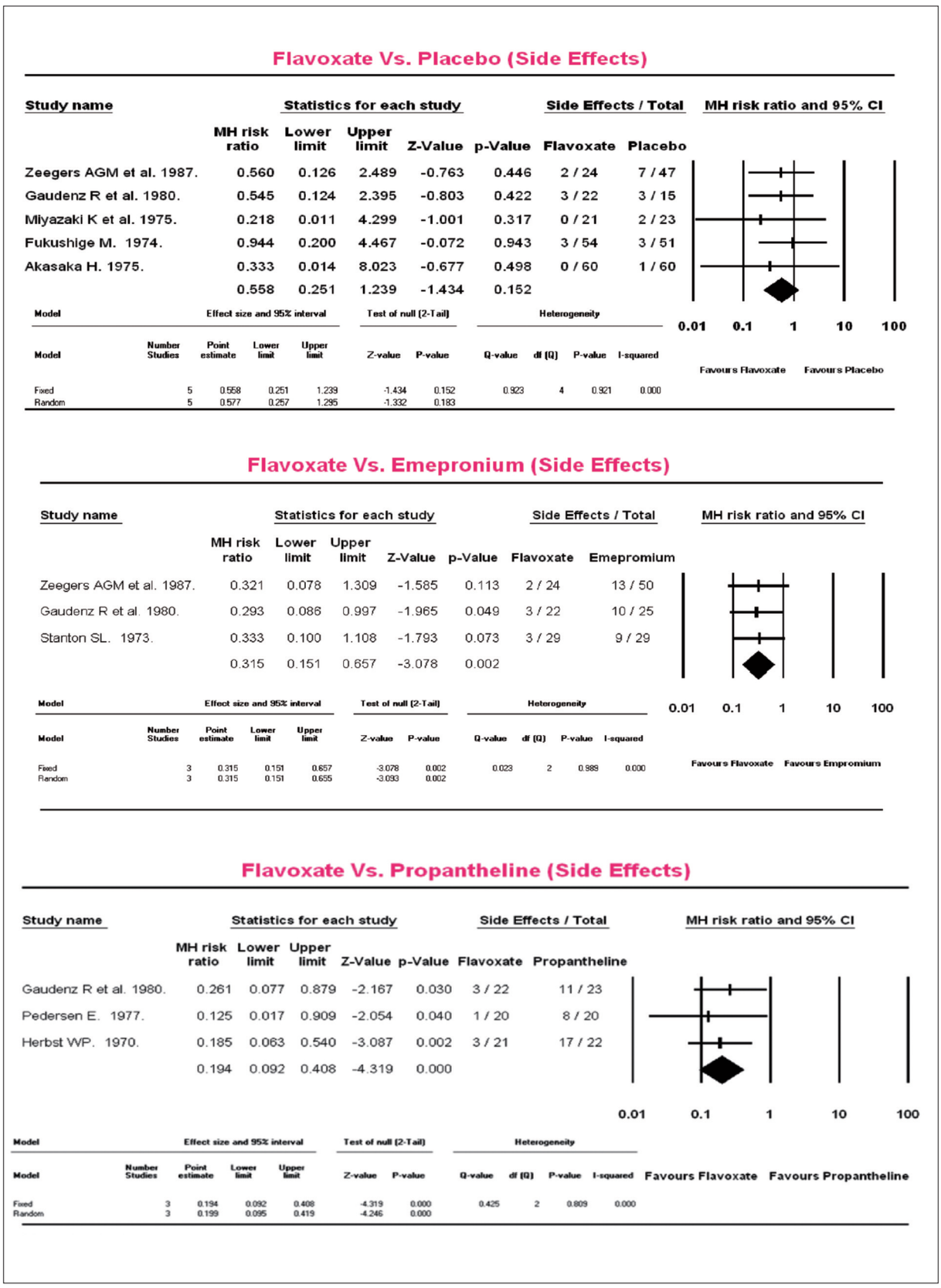

Figure 3. Comparison of overall safety of Flavoxate *vs*. Placebo/Emepromium/Propantheline.

The analysis of flavoxate on frequency (24 studies involving 989 patients) showed that in all individual studies frequency was decreased, reaching statistical significance in 11 individual studies ($p < 0.05$). The overall effect size for decreasing frequency in favouring flavoxate was estimated to be 0.69 (95% CI: 0.66-0.72) and it was statistically significant ($p < 0.001$) (Supplementary Figure 2).

With respect to urinary incontinence, the effect of flavoxate as derived from 21 reports involving 2104 patients, was evident in all cases, reaching statistical significance in 10 studies ($p < 0.05$). The overall effect size for decreasing urinary incontinence with flavoxate was estimated to be 0.67 (95% CI: 0.65-0.69) and it was statistically significant ($p < 0.000$) (Supplementary Figure 3).

Similar findings were observed for mixed incontinence (4 studies on 490 patients). This symptom was decreased in all studies, reaching statistical significance in one ($p < 0.05$). The overall effect size for decreasing mixed incontinence with flavoxate was estimated to be 0.71 (95% CI: 0.67-0.75) and it was statistically significant ($p < 0.001$) (Supplementary Figure 4).

The effect of flavoxate on nocturia was investigated in 9 researches involving 1186 patients. In all studies, nocturia was decreased, and it was significantly decreased in three ($p < 0.05$). The overall effect size for decreasing nocturia with flavoxate was estimated to be 0.63 (95% CI: 0.60-0.66), reaching statistical significance ($p < 0.001$) (Supplementary Figure 5).

Nine reports (n = 92) have assessed the effect of flavoxate on unpleasant urination, and all showed some effect of this molecule – reaching statistical significance in two ($p < 0.05$). The overall effect size was 0.74 (95% CI: 0.64-0.88), and it was statistically significant ($p < 0.001$) (Supplementary Figure 6).

The effect of flavoxate on stranguria - from 13 studies involving 1300 patients - showed that in all individual papers stranguria was decreased and it was significantly decreased in 8 studies ($p < 0.05$). The overall effect size for decreasing stranguria with flavoxate was estimated to be 0.56 (95% CI: 0.53-0.59), reaching statistical significance ($p < 0.001$) (Supplementary Figure 7).

Lastly, 19 work (n = 3039) were included in side effects profile analysis of flavoxate *per se* (Supplementary Figure 8). Actual occurrence of side effects due to flavoxate given in the forest plot ranged from 0.8 to 26.8% with an overall incidence of 5.3% (95% CI: 0.04-0.06). However, incidence due to each comparator *per se* may not be discussed as all the reports were not included in the analysis.

Discussion

Overall, the results of the current meta-analysis demonstrate clinically-relevant improvements in all evaluated parameters with flavoxate as compared with all the comparators tested (Figure 4). Of note, the prevalence of adverse events with

<table>
<tr><td colspan="6">Primary Outcomes
Matrix of Flavoxate Vs. Comparators
Number of Studies (Total Number of Patients) (P Value)</td><td colspan="2">Secondary Outcomes
Matrix of Flavoxate Per Se
Number of Studies (Total Number of Patients)
(P Value)</td></tr>
<tr><td>Primary Outcomes (Parameters)</td><td>Flavoxate Vs. Placebo</td><td>Flavoxate Vs. Emepromium</td><td>Flavoxate Vs. Oxybutynin</td><td>Flavoxate Vs. Phenazopyridine</td><td>Flavoxate Vs. Propantheline</td><td>Flavoxate Per Se</td><td>Secondary Outcomes (Parameters)</td></tr>
<tr><td rowspan="4">Overall Efficacy</td><td rowspan="4">8 (495)
(P Value < 0.001)</td><td rowspan="4">Studies Less Than Three
(Not Analysed)</td><td rowspan="4">3 (495)
P Value < 0.160)</td><td rowspan="4">Studies Less Than Three
(Not Analysed)</td><td rowspan="4">Studies Less Than Three
(Not Analysed)</td><td>35 (2005)
(P Value < 0.001)</td><td>Overall Efficacy</td></tr>
<tr><td>19 (3039)
(P Value < 0.001)</td><td>Side Effects</td></tr>
<tr><td>24 (989)
(P Value < 0.001)</td><td>Frequency</td></tr>
<tr><td>20 (2104)
(P Value < 0.001)</td><td>Urinary Incontinence (UI)</td></tr>
<tr><td rowspan="4">Side Effects</td><td rowspan="4">5 (377)
(P Value <0.152)</td><td rowspan="4">3 (179)
(P Value <0.002)</td><td rowspan="4">Studies Less Than Three
(Not Analysed)</td><td rowspan="4">Studies Less Than Three
(Not Analysed)</td><td rowspan="4">3 (128)
(P Value <0.001)</td><td>4 (490)
(P Value < 0.001)</td><td>Mixed Incontinenece</td></tr>
<tr><td>9 (1186)
(P Value < 0.001)</td><td>Nocturia</td></tr>
<tr><td>9 (92)
(P Value < 0.001)</td><td>Unpleasant Urination (UU)</td></tr>
<tr><td>13 (1300)
(P Value < 0.001)</td><td>Stanguria (Burning or Painful Urination)</td></tr>
<tr><td>Results (Colour Code)</td><td colspan="2">Significant</td><td colspan="3">Not Significant</td><td colspan="2">Studies Less Than Three (Not Analysed)</td></tr>
</table>

Figure 4. Meta-analysis Outcomes Matrix.

flavoxate was similar to what observed with placebo. The effect of flavoxate was also evident when this drug was evaluated *per se* with respect to a number of bothersome symptoms of OAB including frequency, urinary incontinence, mixed incontinence, nocturia, unpleasant urination and stranguria.

However, some limitations should be taken into account when evaluating the above-mentioned findings. First, the urodynamic parameters evaluated (e.g., residual volume and bladder volume at first urge) are continuous quantitative data and require raw data to generate standard deviations; moreover, *p*-values were not available in most of the publications. Therefore, the authors of all researches should have been contacted to collect raw data, which was not feasible. Moreover, there were no head to head clinical trials of flavoxate with antimuscarinics like darifenacin, solifenacin, tolterodine, *etc*. used in practice. Since pharmacodynamics was not considered for meta-analysis, some individual studies and their results are discussed for the interest of clinicians.

In the study[7], the average bladder capacity increase was 83 ml in patients on flavoxate, 39 ml on emepronium and 28 ml on propantheline.

In the study[12], nineteen cases of nervous pollakiuria or female vesicopathy were treated with flavoxate 600 mg per day or placebo for one week. Cystometry was performed before and after the administration. Administration of flavoxate gave rise to increase of both at minimum and maximum desire to void, particularly that at the minimum desire. Resting intravesical pressure both at the minimum and maximum desire to void did not change significantly. Namely, the pressure curve showed a decline. It was speculated that flavoxate might have some action on the center controlling desire to void besides its relaxing action on the vesical detrusor. Highly significant correlation was proved between the bladder volume at the minimum desire to void and the vesical capacity. The desire to void seemed to be activated by intravesical pressure rather than by vesical distention.

In the study[15], 41 patients (20 affected by sensory urgency and 21 by motor urgency) completed both courses of treatment (Flavoxate *vs.* Oxybutynin) and were evaluated for urodynamic parameters. A statistically significant improvement in all urodynamic parameters was present at the end of both treatment courses. The effect on the urodynamic parameters of the two treatments was comparable. According to the patients, flavoxate cured or greatly improved the syndrome in 81.6% of cases, while oxybutynin produced the same effects in 78.9%.

In the study[22], with respect to uninhibited detrusor contractions, 1200 mg/day was significantly superior to 600 mg/day. Assessment of urodynamic variables showed volume at first urge increased significantly ($p < 0.01$) compared with baseline by both the 600 and 1200 mg daily dosages.

In the study[25], improvement of first desire volume, bladder capacity and pressure at capacity were clinically and statistically superior with 1200 mg/day compared with 600 mg/day flavoxate hydrochloride.

In the study[10], the results of cystometrography in 7 patients on flavoxate and 7 on placebo showed that the increase in bladder capacity and the reduction in pressure after flavoxate treatment were statistically significant ($p < 0.01$) but not so in the case of placebo.

In the study[14], 66.67% (12 out of 18 patients) of patients had decreased residual urine.

In the study[48], 618 patients without urinary tract infections or benign prostatic hyperplasia were treated with flavoxate only. Bladder volume at first urge sensation increased by 55.1 ± 58.8 ml (36%), which was comparable to data from the entire group (1800 patients). In 89.2% of all patients, the residual urine volume was stable or decreased. This work confirms that bladder volume at first urge tends to increase, in this instance by an average of 60 ml (30%), an effect that tended to favour patients suffering from sensory urge incontinence. Average residual urine volumes decreased from 16.7 ± 25.7 ml to 13.0 ± 20.7 ml in those patients treated for no longer than 15 days, and the decrease for those treated longer than 15 days was similar: from 17.0 ± 29.4 ml to 12.0 ± 23.9 ml. For the entire group, a reduction from 21.8 ± 31.7 ml to 15.9 ± 25.4 ml was observed. In all patients, 57.2% were reported to show no change in residual urine volumes, 32.0% showed a decrease and 10.8% showed an increase. There are practically no differences between the various forms of urge incontinence, whether reported as sensory, motor urge, or in combination with a stress component.

In the study[38], the urodynamic data showed a diminishing of the mean pressure during uninhibited detrusor contraction by almost 50% and the delay of the onset by 80% of bladder capacity. However, average bladder capacity increase was only 19%.

In study[23], treatment with flavoxate did not increase the end residual urine volume.

In the study[24], an increased bladder capacity in the standing position and a decreased frequency of detrusor contractions was found in the urodynamic investigations. The residual urine remained constant.

In the study[26], 12 out of 15 diagnosed motor urge incontinence patients, there was a decreased detrusor contraction at average bladder capacity 213 ml. In a sensory urge incontinence patients, there was a statistically significantly reduction in vesical pressure.

In the study[18], improvement occurred with flavoxate in 75% of the patients with detrusor instability and 50% of those with sphincter dysfunction as compared to 25% detrusor and 36% sphincter improvement with emepronium. Neither drug produced any significant increase in residual urine. However, both drugs reduced intravesical pressure in the sphincter dysfunction and detrusor instability groups. Flavoxate was more effective than emepronium. In patients with mixed pathology, flavoxate produced a decrease ($p = 0.05$) in pressure while emepronium produced an increase. Both drugs caused a delayed first sensation and strong desire in the patients and increased overall bladder capacity (Flavoxate more than emepronium, $p < 0.02$). Flavoxate was significantly more effective in the sphincter dysfunction group ($p < 0.05$) and in the mixed groups.

In the study[19], both flavoxate and propantheline increased bladder capacity significantly, but flavoxate did not increase residual urine in contrast to propantheline.

In the study[50], in one group both flavoxate and propantheline produced increase in bladder capacity. Male patients appeared to be more responsive to flavoxate than propantheline while female patients showed a comparable increase in capacity after both drugs. All changes were statistically significant ($p < 0.05$) when compared to controlled values. Resting bladder pressure decreased significantly in female patients after administration of either drug. In another group, flavoxate produced a significant increase in bladder capacity in 13 of 21 patients while propantheline caused a similar change in 8 of 21 patients. Flavoxate also produced a slightly greater increase in average bladder capacity when compared to controlled bladder measurements.

In the study[51], of the 40 patients with uninhibited contractions (UC), 18 patients reported positive responses to flavoxate.

Flavoxate, a flavone derivative, was the first drug to be approved in 1970 by the Food and Drug Administration for the symptomatic treatment of OAB and it has been widely used for more than four decades[6]. Flavoxate is available in tablets and it readily absorbed from the gastrointestinal tract and metabolized (peak blood levels within 20 minutes from administration; plasma half-life: 3.5 hours). It is widely distributed in tissues, liver, kidney and bladder. The identified principle metabolite is 3-methylflavone-8-carboxylic acid (MFCA) with urinary and faecal excretion practically completing within 24 h[52]. Flavoxate exerts direct smooth muscle relaxant activity, specific to urinary bladder by the inhibition of phosphodiesterase (PDE) activity and inhibition of L-type Ca^{2+} channels in human detrusor[53-55]. It also has some local analgesic and anesthetic activity, without exerting any anticholinergic activity[56].

According to the Japanese Urological Association the level of recommendation for flavoxate is grade C (supported by level II clinical studies). Moreover, the Japanese Urological Association underlined the optimal safety profile of flavoxate, as this drug is almost associated with no adverse events: this finding may have great importance in the chronic treatment of OAB, as it is potentially associated with improved compliance[56].

Conclusions

We believe that the results of the present meta-analysis, which suggest the efficacy and safety of flavoxate in the treatment of OAB also when compared with some other molecules used in the same setting lend further support to the position of the Japanese Urological Association. In particular, the excellent tolerability makes flavoxate worthy of consideration as a choice in the symptomatic treatment of dysuria, urgency, frequency and incontinence in OAB patients.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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