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PHARMACOLOGICAL MANAGEMENT OF PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS: A SYSTEMATIC REVIEW

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Abstract

Background— Over 180 different types of therapy have been used in the treatment and management of painful bladder syndrome/interstitial cystitis (PBS/IC), yet evidence from clinical trials remains inconclusive. This study aimed to evaluate the efficacy of pharmacological approaches to PBS/IC, quantify the effect size from randomized controlled trials, and begin to inform a clinical consensus of treatment efficacy for PBS/IC.

Methods— We identified randomized controlled trials for the pharmacological treatment of PBS/IC patients diagnosed on the basis of NIDDK or operational criteria. Study limitations include considerable patient heterogeneity as well as variability in the definition of symptoms and in outcome assessment.

Results— We included a total of 1470 adult patients from 21 randomized controlled trials. Only trials for pentosan polysulfate had sufficient numbers to allow a pooled analysis of effect. According to a random-effects model, the pooled estimate of the effect of pentosan polysulfate therapy suggested benefit, with a relative risk for patient-reported improvement in symptoms of 1.78 (95% confidence interval, 1.34 – 2.35). This result was not heterogeneous (p= 0.47) and was without evidence of publication bias (p= 0.18). Current evidence also suggests efficacy of DMSO and amitryptiline. Hydroxyzine, intravesical BCG and RTX failed to demonstrate efficacy, but evidence was inconclusive due to methodological limitations.

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Conclusions— Pentosan polysulfate may be modestly beneficial for symptoms of PBS/IC. There is insufficient evidence for other pharmacological treatments. A consensus on standardized outcome measures is urgently needed.

INTRODUCTION

Painful bladder syndrome/interstitial cystitis (PBS/IC) is a poorly defined clinical condition characterized by three key symptoms: pelvic pain, urinary urgency, and frequency.[1] These symptoms significantly overlap with those of other common conditions and are not associated with any known pathognomonic tissue, serum, or urine changes. PBS/IC is therefore primarily a diagnosis of exclusion.[2]

Further complicating diagnosis is a lack of a standard definition for the condition. In 1915, for example, Hunner described a form of bladder ulceration later designated as "classic IC".[3] In 1978, Messing and Stamey proposed that glomerulations apparent with bladder distension were diagnostic of IC in the absence of Hunner's ulcerations (*i.e.*, nonulcer IC).[4] Most recently, in 1987, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) attempted to unify these contrasting approaches by developing a list of criteria to define IC.[5] The NIDDK criteria, however, miss an estimated 60% of patients and, due to the criteria's restrictiveness, are currently recommended for research use only.[6] Moreover, Waxman[7] and others[8, 9] have called into question the specificity of the criteria by finding that 75% of healthy women show glomerulations even in the absence of symptoms. The term *Painful Bladder Syndrome* is now often used to describe the broader spectrum of patients who meet a more inclusive, symptom-based definition without the typical cystoscopic and histological features traditionally used to distinguish *interstitial cystitis*.[2, 10]

Prevalence estimates are highly variable, depending on what diagnostic criteria the epidemiologist is using. A number of surveys applying different methodologies have found IC incidence ranging from 1.6 per 100,000 women[11] to 158 per 100,000 women.[12] Self-reporting as part of the National Household Interview Survey found a rate of 450 per 100,000,[13] and three studies that used O'Leary-Sant scores found a prevalence of approximately 300 per 100,000.[14–16]

Treatment and management approaches vary widely. As of 1997, 183 different types of dietary, interventional, pharmacologic, and behavioral therapies had been used.[17] This diversity continues to be reflected within the broad range of pharmacologic agents currently applied to the condition.

Our aim was to synthesize and critically evaluate data from a wide range of current pharmacological approaches to PBS/IC, to quantify the effect size from randomized controlled trials, and begin to inform a clinical consensus of treatment efficacy for PBS/IC.

EVIDENCE ACQUISITION AND SYNTHESIS

Search strategy

A search strategy was developed for the purposes of the present review. The following databases were searched: PubMed (1966–2007), EMBASE (1988–2007), CINAHL (1982–2007), Healthstar (1975–2000), Current Contents (2000–2007), Web of Science (1980–2007), PsychInfo (1967–2007), Science Citation Indexes (1996–2007), and Cochrane Collaboration Reviews (1993–2007). The exploded Medical Subject Headings *interstitial cystitis* and *painful bladder syndrome* were combined with truncated keywords that described the type of publication, such as *random*, *double–blind*, *random allocation*, *placebo*, *clinical trial*, and *comparative study* and were limited to English–language studies in humans. Additional studies

were identified through a manual search of the bibliographies of retrieved articles, recent reviews, monographs, and the Interstitial Cystitis Task Force—an NIH/NIDDK initiative on the epidemiology and definition of PBS/IC.[1]

Inclusion criteria

Articles on clinical trials were included if they met all of the following six inclusion criteria:[18] a controlled clinical trial involving the pharmacologic treatment of PBS/IC; study population of adult patients; administration of a pharmacologic intervention to more than 10 patients; inclusion of a control group that received placebo therapy for PBS/IC; outcome measures of global status or individual PBS/IC symptoms (or both); and use of a randomized, double–blind, parallel–group or crossover design.

Data extraction

The study characteristics, patient demographic information, enrollment criteria, therapy allocation, adverse effects, outcomes, and reasons for dropout were extracted independently by two reviewers. We focused on the efficacy of treatment for PBS/IC compared with placebo or active controls. Continuous measures included assessment of specific symptoms (pain, frequency and urgency) as well as O'Leary-Sant Interstitial Cystitis Symptom and Problem Index scores (OLS-SI and OLS-PI).[19] Our dichotomous measure was patient-reported global improvement with treatment. Given the large placebo effect seen in IC trials, we provide only qualitative information about RCTs.

Quantitative assessment

Only trials for treatment of PBS/IC with pentosan polysulfate (PPS) had sufficient numbers to allow a pooled analysis of effect using a random-effects model.[20] Heterogeneity was assessed using the Q and I^2 statistic and publication bias was assessed using the Egger's test.[21] For the remaining treatment modalities, we decided not to attempt to pool the data because of the wide variety of designs; small sample sizes; many different treatments, with few studies on each specific treatment; broad classes of medications, raising the question of whether drugs within these broad classes can be pooled; different modes of drug administration (oral vs. intravesical); and considerable variation in the reporting of statistical details, such as exact *P* values and standard deviations.

For all trials, an attempt was made to abstract the data as a standardized mean difference. This produces measures of effect for each treatment trial on a similar metric. By convention, these standardized mean differences, also known as effect sizes, are considered small if less than 0.2, moderate if between 0.5 to 0.8 and large if greater than 0.8.[22] For many trials, this was not possible and the studies were classified simply as positive or negative, in terms of efficacy, for that outcome.

For some study-specific characteristics, such as duration of studies or number of patients included, the Student *t*–test was used to compare continuous variables, and the chi–square test to compare binary variables between certain study subgroups. The Mann-Whitney U-test was used to compare median sample sizes between positive and negative studies and between high and low quality studies as sample sizes were skewed.

RESULTS

Out of 278 trials identified using our search criteria, **21 RCTs** met the requirements for inclusion in our final analysis.. Those excluded (n = 257) did not address treatment of PBS/IC or did not report global or symptom–specific outcomes (n = 77); did not use a randomized, double–blind, placebo–controlled design (n = 55); included patients without a diagnosis of

PBS/IC (n = 57); were incomplete or duplicate publications (n = 7); were not published in English (n = 34); or involved fewer than 10 patients (n = 27).

The 21 randomized controlled trials (RCTs) we analyzed are shown in table 1. A single agent was evaluated in 18 RCTs, and a combination of two agents were evaluated in 3trials. The 21 trials spanned 1987 to 2006, reporting on a total of 1470 adult patients. The studies averaged 70 patients enrolled (range 16–265), with ages ranging from 18 to 80 years (mean, 46.87 years); 90% were women. Eleven RCTs (52%) were conducted in North America and 10 (48%) in Europe. All studies were conducted in urological settings, either single (63%) or multiple (37%) practices. Three trials (14%) were published before 1989, 6 (29%) between 1990 and 1999, and 12 (57%) between 2000 and 2007.

Patient population

Seventeen RCTs used the 1987 NIH/NIDDK Research Criteria for diagnosing IC **(**Table 1). Four studies based the diagnosis on operational criteria. All trials reported an adequate work–up to exclude organic disease, including history, physical examination, laboratory, radiologic, and cystoscopic evaluation.

Study design

Of the 21 RCTs, 17 employed parallel and 4 a crossover design. Length of the intervention ranged from a single treatment procedure to 36 weeks of treatment, with a mean of 15 and a median of 12 weeks. Symptom severity, as assessed within each individual trial, was similar at baseline between the intervention and control groups in all of the parallel RCTs. Treatment adherence was reported in only 4 RCTs and was measured by pill counts or patient interview. Adherence was similar between the intervention and control groups in these 4 trials, although actual adherence rates were not provided. Co–interventions, such as concurrent use of other medications to relieve IC symptoms and dietary changes during the intervention period, were assessed in 4 of the RCTs. In these 4 trials, patients were simply advised to avoid use of other medications. Despite relatively short trials with few patients enrolled, none of the trials with negative outcomes reported power analyses.

Outcome assessment

Both global as well as individual symptom improvement was reported in all of the studies. The definition of symptoms, such as pain, urgency and frequency, varied considerably across the trials. Data were collected by a daily voiding diary maintained by the patient. A standardized symptom questionnaire (OLS19) was used in 11 RCTs and was reportedly validated in 1 trial.[23]

Treatment efficacy

Table 1 shows the evidence for treatment efficacy of each pharmacologic agent in their respective RCT(s). Outcomes most frequently assessed—pain, urgency, frequency, and the OLS-SI—are itemized for each trial. The specific symptoms assessed and the measures used varied considerably among the different studies. Therefore, we viewed global improvement as the common metric across treatments which was usually reported as the number of patients reporting self-improvement in each group. The mean frequency of global improvement was 19% (range, 4% to 40%) among control groups and 49% (range, 28% to 89%) among treatment groups for all RCTs that reported this outcome. The effect size for the magnitude of improvement for pain, frequency, urgency and the OLS-SI among the studies reporting these outcomes was generally small **(**Figures 1–4).

Findings on specific agents

Six RCTs,[24–29] and one meta-analysis[30] examined treatment with oral **pentosan polysulfate (PPS) (**Table 1› Figs 1⁻5). The reported overall response rate varied between 15–67% at the 300 mg FDA-recommended dose. An industry-sponsored dose-ranging three-arm study comparing 300 mg, 600 mg and 900 mg failed to show dose-related efficacy; duration of administration was more important than dosage itself, although side-effects were dose-related.[31] The most rigorous NIDDK-supported trial by the Interstitial Cystitis Clinical Trials Group (ICCGT) failed to demonstrate superiority of PPS over placebo although the study was underpowered.[28] Our pooled analysis **(**Figure 5) suggested benefit, with a relative risk for patient-reported improvement in symptoms of 1.78 (95% CI: 1.34 – 2.35). This result was not heterogeneous (Q= 3.53, I^2 = 0%, p= 0.47) and was without evidence of publication bias (Egger's p= 0.18).

Intravesical 50% DMSO, the only FDA-approved intravesical treatment for IC, proved beneficial in two crossover RCTs.[32, 33] One trial demonstrated a 93% objective improvement and 53% subjective improvement compared with 35% and 18%, respectively, for saline solution.[33] Symptom alleviation has been demonstrated in up to 80% of patients with the usual treatment schedule of 6 weekly bladder instillations of 50% DMSO, followed by maintenance therapy every 2–4 weeks and then every 2–3 months. One important caveat here is that saline cannot really be considered an appropriate "placebo" in DMSO trials since the latter possesses prominent side effects (taste and smell). Furthermore, in these early studies, DMSO was administered once every two weeks rather than weekly, as is usually the case today.

Amitriptyline, a tricyclic antidepressant, provided symptomatic relief for 15 out of 24 patients in one RCT, although the study did not provide details regarding the use of active or inactive placebo.[34] The median preferred dose was 75 mg in a range of 25 to 150 mg taken at dinner time rather than bedtime. As is the case with fibromyalgia and CFS, it is generally recommended that patients start at the lowest possible dose (10 mg) and titrate up to the dose which provides optimal symptom relief.[35–37]

The efficacy of **intravesical Bacillus Calmette-Guerin (BCG)** for the treatment of IC was evaluated in 3 RCTs.[32, 38, 39] Sixty percent of the BCG-treated and 27% of the placebo-treated patients reported at least moderate improvement in one trial (P=0.065).[38] The most recent NIDDK-sponsored RCT further supports those findings demonstrating benefit in 21% of the BCG-treated patients compared to 12% improvement in the placebo group (*P*=0.062).[40] In a crossover trial of BGC vs. DMSO, none of the patients improved on BCG as first treatment, whereas 7 improved on DMSO (two when DMSO was the first treatment, and five when DMSO followed BCG).[32] The findings from this study pose a special challenge to interpretation in light of the fact that there was no *a priori* outcome and, as a result, no estimated sample size for power calculation. Furthermore, the authors failed to observe an optimal washout period before crossing BCG patients over to DMSO. Thus, if BCG is followed by DMSO, the reported benefit might actually be a delayed BCG effect.

Hydroxyzine, an H1-blocker, failed to show efficacy as a single agent in the recent NIH/NIDDK study although the combination with PPS approached statistical significance (P=0.06).[28] However, the study lacked the power to detect significant differences.

DISCUSSION

Evaluation of treatment efficacy in PBS/IC is challenging due to short duration of trials, heterogeneity of disease, and the lack of knowledge of the natural history of disease.

The RCTs we analyzed have not taken into consideration the variability of symptoms over time and regression to the mean. Most trials were short, with a mean duration of 15 weeks, which might not be optimal given the chronic nature of PBS/IC symptoms. As reflected in results from the largest observational IC study to date, the Interstitial Cystitis Database (ICDB)—patients who began with the most severe symptoms demonstrated the greatest initial improvement (i.e., their symptom scores moved toward the population mean).[41] Conversely, patients who began with mild symptoms were more likely to worsen. Appropriately designed RCTs would have minimized such bias. Additionally, short duration of trials limits generalizability of findings.

Inadequate blinding (e.g., saline as placebo in DMSO trials[32, 33]), small number of patients (e.g., PPS[24–26], hydroxyzine[28], amitriptyline[34]), and nonstandardized outcome measures (e.g., bladder biopsy findings[42]) present additional challenges to analyzing treatment efficacy for PBS/IC. While most trials used the NIDDK diagnostic criteria for IC, very limited information was presented about participants who were ineligible or about symptomatic patients without bladder glomerulations (e.g. patients with painful bladder syndrome). It is well-known that strict use of NIDDK criteria would exclude 60% of patients with PBS/IC.[6] Therefore, it is difficult to extrapolate how the findings from IC trials might relate to the larger majority of patients across the spectrum of PBS/IC symptoms.

The definition of symptoms—such as pain, urgency and frequency—varied considerably across the trials. Symptoms were measured using several different scales, making it inappropriate to pool the data for specific pharmacologic interventions investigated in more than one trial and also making it difficult to compare the findings in a qualitative synthesis. Consequently, it is not clear whether a positive result based on the pain scale of the OLS-SI, for example, is as good as, better than, or worse than a positive result on a different scale. Outcomes such as “global improvement,” in which participants were asked to rate themselves as better or worse than they were before the intervention began, were frequently reported. However, as has been shown to be the case with CFS and other chronic pain syndromes, the person may feel better able to cope with symptoms because they have reduced their expectations of what they should achieve, rather than because they have made any recovery as a result of the intervention. A more objective measure of the effect of any intervention would be whether participants have increased their working or waking hours, returned to work or school, or increased their physical or sexual activities.

The appropriate duration and follow-up of interventions used in the management of PBS/IC remains unknown. Given fluctuation of symptoms and the relapsing nature of PBS/IC we suggest that follow-up should continue for at least an additional 6 to 12 months after the intervention period has ended to confirm that any improvement observed was due to the intervention itself and not just to a naturally occurring fluctuation in the course of the illness or regression to the mean.

High dropout rates may be important indicators of the unacceptability of an intervention. This appears to be the case with cyclosporine,[29] DMSO[32, 33] and antibiotics,[43] which had dropout rates of 55%, 19%, and 26%, respectively. High dropout rates may also indicate that the trial protocol is too rigid to accommodate any but a very specific group of participants, as might be the case with cyclosporine and DMSO. Again, this limits the generalizability of the findings.

Finally, many of the treatment response differences in IC clinical trials may be related to the heterogeneity of this illness. Identifying patient subsets based on response to specific treatments and biologic variables is one of the most challenging tasks in IC research. Patients with Hunner’s ulcer on cystoscopy form one such subgroup. This group, however, is relatively

small since an ulcer is present in only about 15% of patients with IC. Hunner's ulcer patients, therefore, should probably be enrolled as an isolated subset of IC patients.

Scant data are available from RCTs to confirm the efficacy of current pharmacological approaches to PBS/IC. What data do exist emerge from inadequately designed trials characterized by high dropout rates, restrictive protocols, variation in outcomes measures and definitional vagueness. Moreover, PBS/IC is a multifactorial and heterogeneous clinical symptom complex, yet RCTs designed to test pharmacologic agents have not taken into consideration the variability of symptoms over time or regression to the mean. Determining the optimal treatment strategy therefore remains elusive. Future treatments for PBS/IC will certainly be better informed by further unraveling the pathophysiologic mechanisms underlying the disease. Meanwhile, the key to developing evidence-based therapies is in establishing a consensus on standardized outcome measures and then designing and conducting appropriate RCTs that employ those standards.

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ABBREVIATIONS

BCG

Bacillus Calmette-Guerin

CFS

chronic fatigue syndrome

CI

CI
: confidence interval

DMSO
: dimethylsulfoxide

IBS
: irritable bowel syndrome

ICCTG
: interstitial cystitis clinical trials group

ICDB
: interstitial cystitis database

ITT
: intention–to–treat

NIH/NIDDK
: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases

OLS
: O’Leary-Sant questionnaire

OLS-SI
: O’Leary-Sant Symtpom Index

PBS/IC
: painful bladder syndrome/interstitial cystitis

PPS
: pentosan polysulfate

RR
: risk ratio

RCT
: randomized controlled trial

RTX
: resiniferatoxin

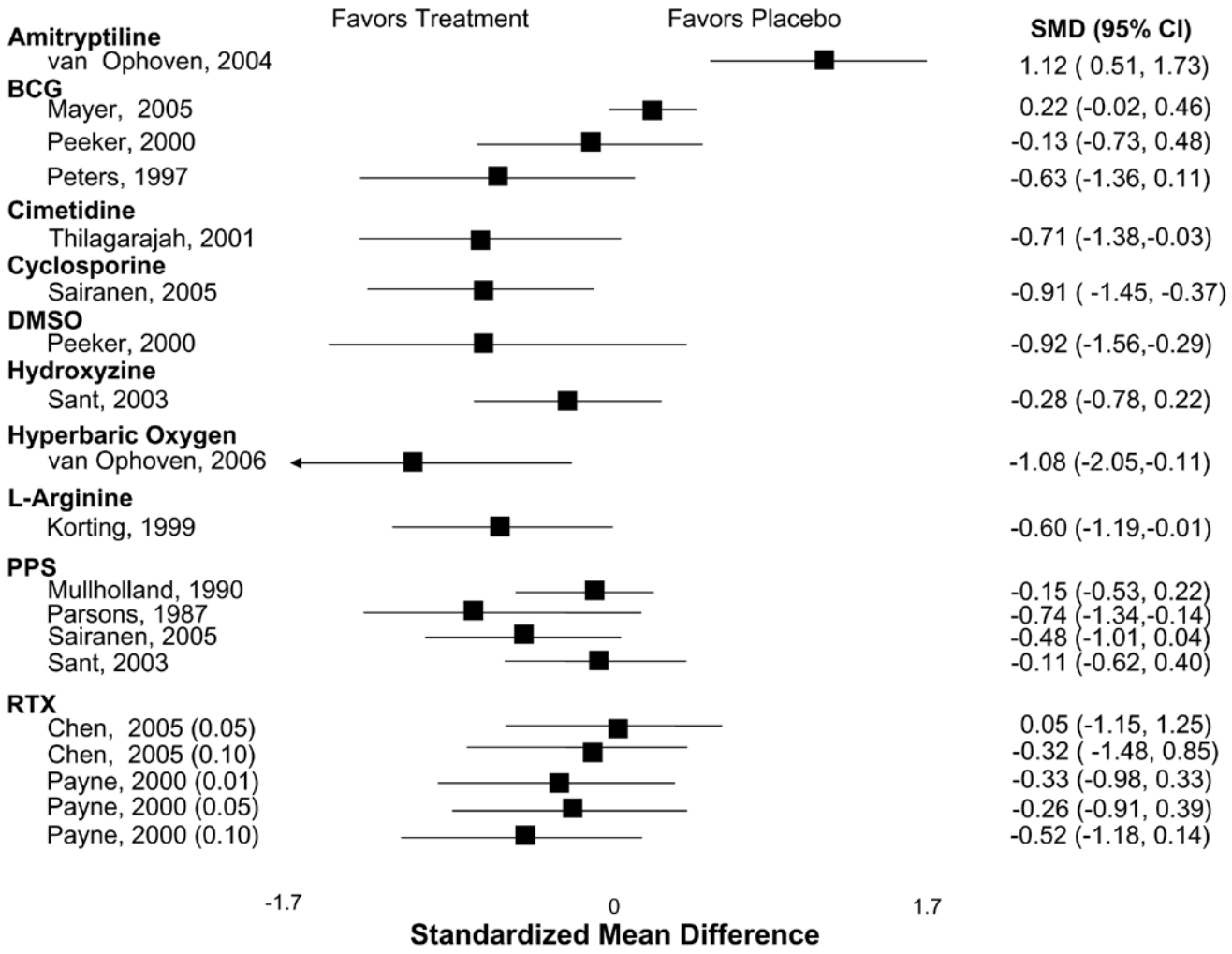

Figure 1.
Effect on Patient-Reported Pain

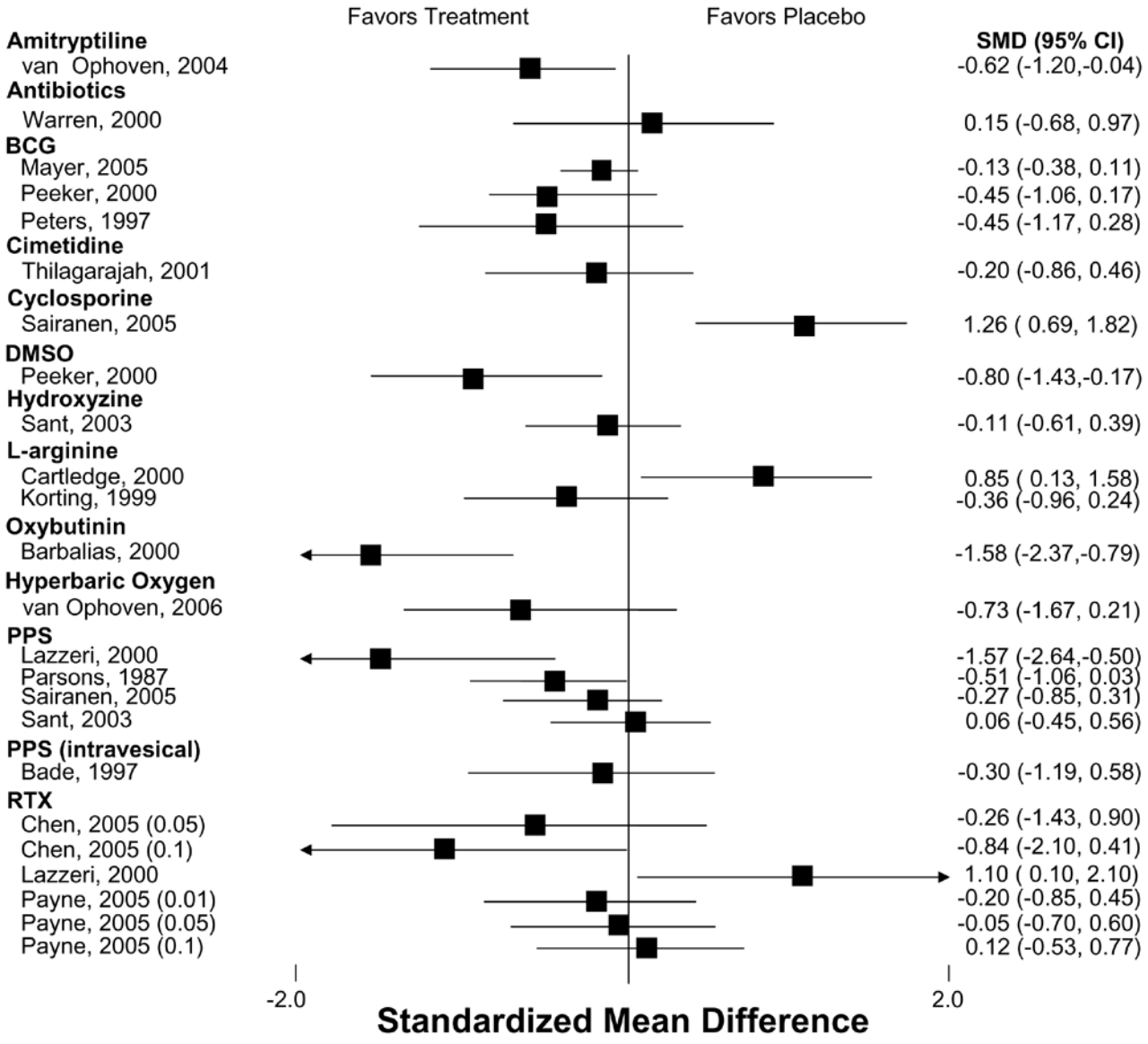

Figure 2.
Effect on Patient-Reported Frequency

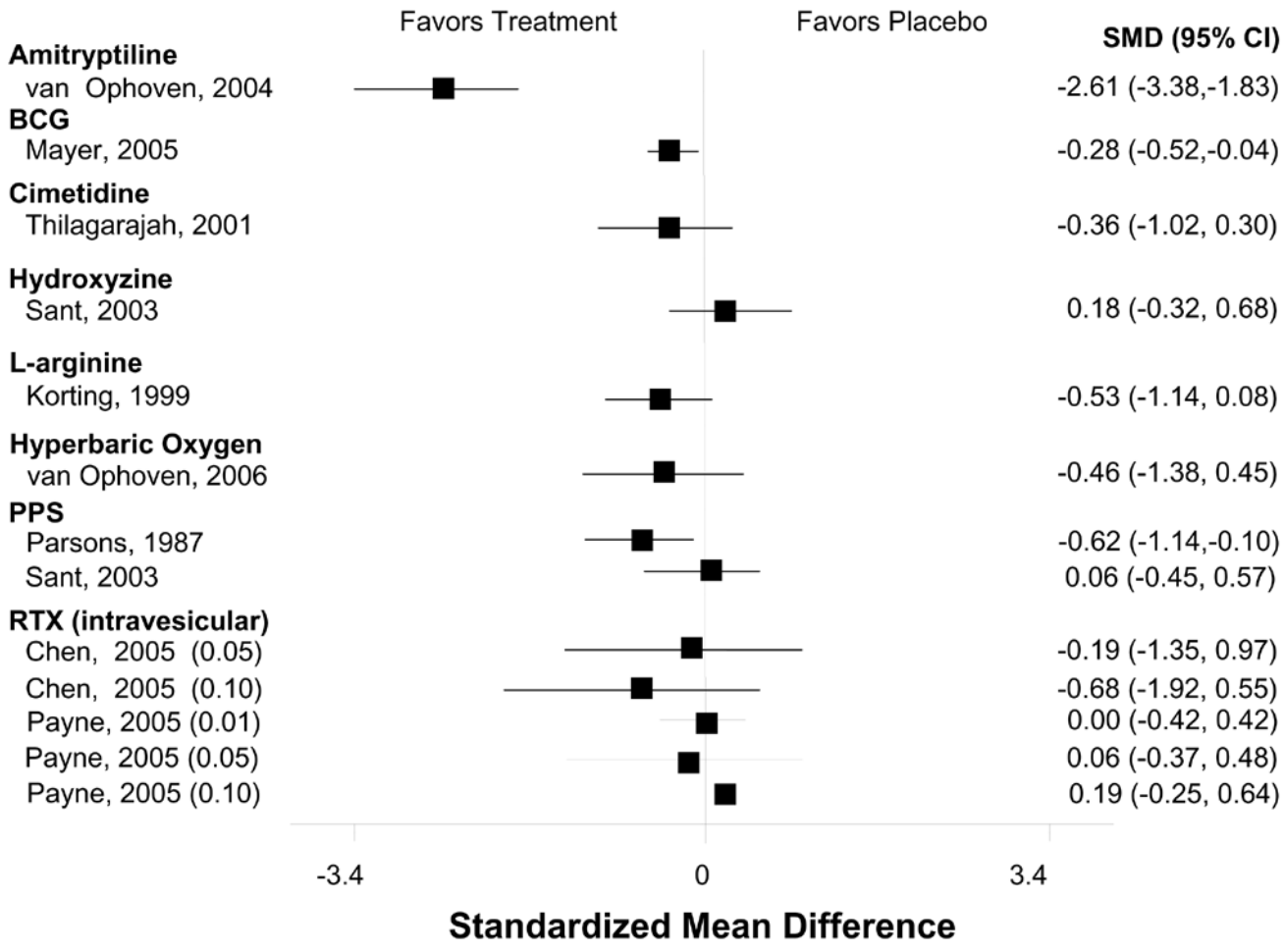

Figure 3.
Effect on Patient-Reported Urgency

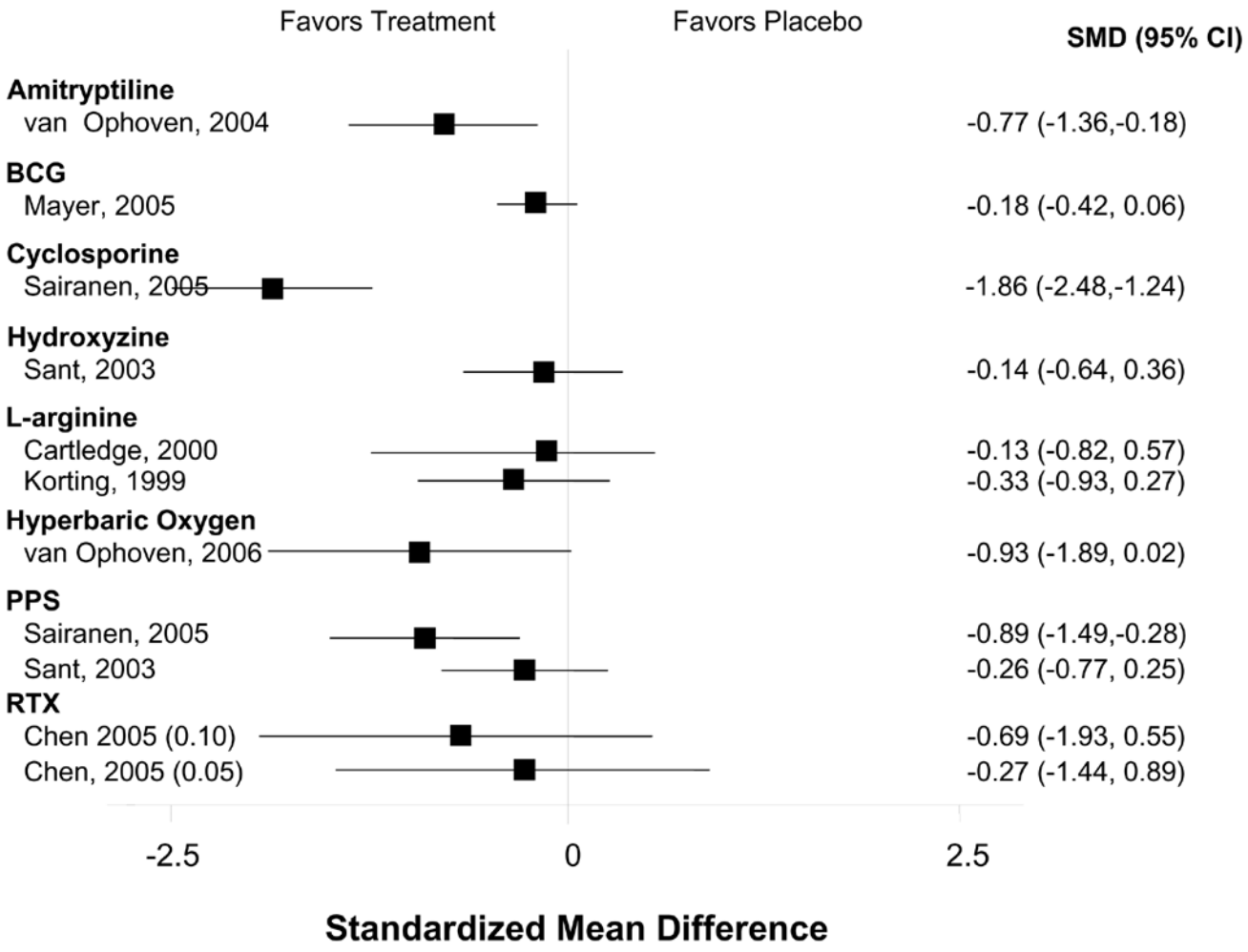

Figure 4.
Effect on Patient-Reported O'Leary IC Symptom Index

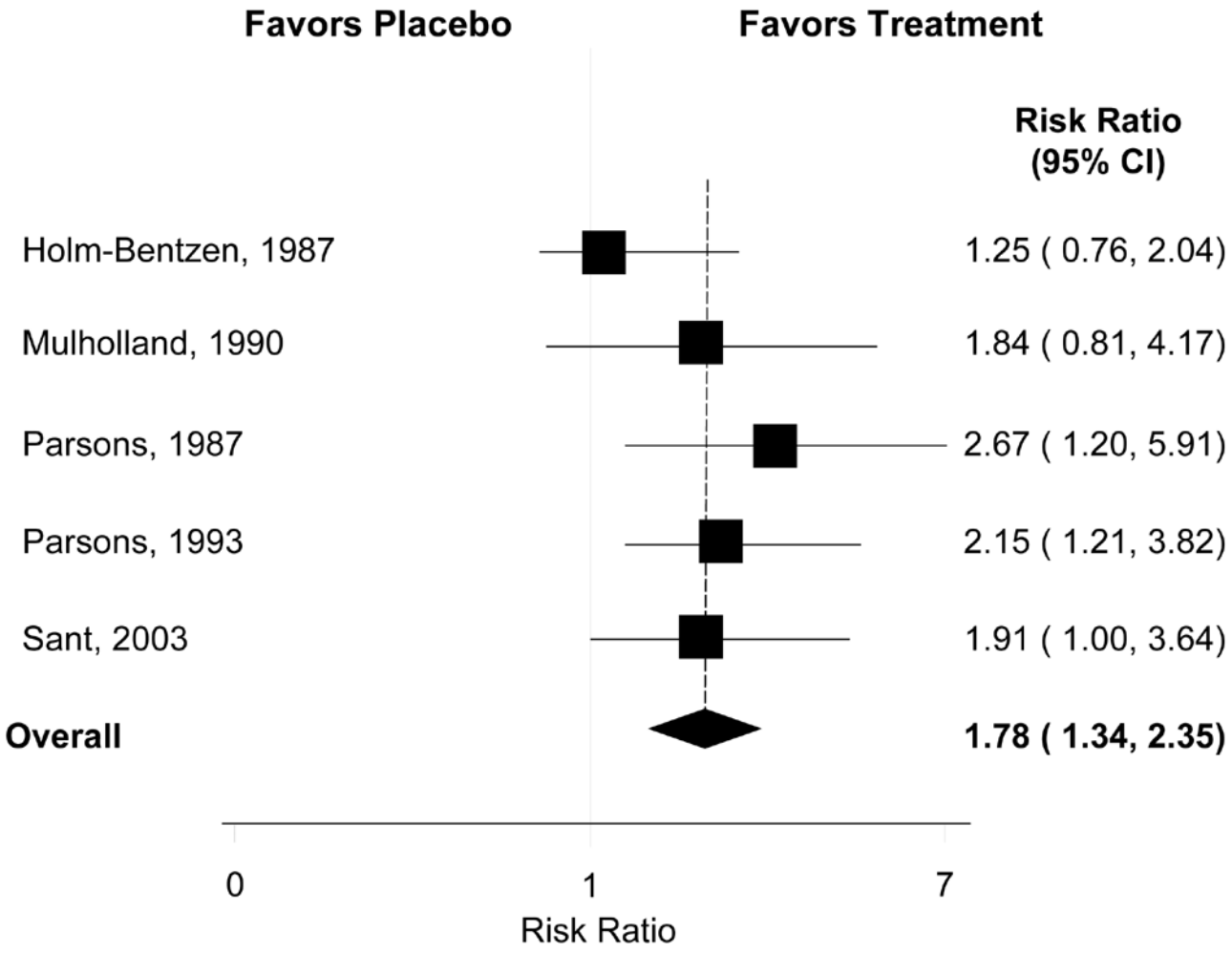

Figure 5.
Relative Risk of Overall Improvement with PPS treatment

Table 1

RCTs for the Treatment of Painful Bladder Syndrome/Interstitial Cystitis*

Study (Year)	N	Design	Mean Age	Women,%	Duration in weeks	NIDDK Criteria	Symptom Outcomes SMD (95% CI)			
							Symptom Index	Pain	Urgency	Frequency
Amitriptyline										
van Ophoven[34] (2004)	50	Parallel	55	88%	16	Yes	−0.77 (−1.36, −0.18)	1.12 (0.51, 1.73)	−2.61 (−3.38, −1.83)	−0.62 (−1.2, −0.04)
Antibiotics										
Warren[43](2000)	50	Parallel	52	90%	18	Yes	NR	–	–	0.15 (−0.68, 0.97)
Bacillus Calmette-Guerin (BCG) – Intravesical										
Peters[38] (1997)	33	Parallel	42	100%	6	Yes	NR	−0.63 (−1.36, 0.11)	–	−0.4 (−1.17, 0.28)
Peeker[32] (2000)	21	Cross over	51	95%	12	Yes	NR	−0.13 (−0.74, 0.48)	–	−0.45 (−1.1, 0.17)
Mayer[39] (2005)	265	Parallel	48	82%	6	No†	−0.18 (−0.42, 0.07)	0.22 (−0.02, 0.46)	−0.28 (−0.52, −0.04)	−0.13 (−0.38, 0.11)
Cimetidine										
Thilagarajah[42] (1998)	36	Parallel	42	97%	12	No‡	NR	−0.71 (−1.38,−0.03)	−0.35 (−1.02, 0.3)	−0.20 (−0.86, 0.46)
Cyclosporine										
Sairanen[29] (2005)	64	Parallel	59	83%	24	Yes	−1.87 (−2.48, −1.25)	−1.34 (−1.92, −0.77)	+	−1.42 (−2.0, −0.85)
Dimethylsulfoxide (DMSO) – intravesical										
Perez– Marrero[33] (1988)	33	Cross Over	48	91%	8	Yes	NR	+	+	–
Peeker[32] (2000)	21	Cross Over	51	95%	12	Yes	NR	−0.92 (−1.56, −0.29)	NR	−0.80 (−1.43, −0.17)
Hydroxyzine										
Sant[28] (2003)	121	Parallel	45	89%	24	No†	−0.14 (−0.64, 0.36)	−0.28 (−0.78, 0.22)	0.18 (−0.32, 0.68)	−0.11 (−0.61, 0.39)
L–Arginine										
Korting[44] (1999)	53	Parallel	49	100%	12	Yes	−0.33 (−0.93, 0.27)	−0.60 (−1.19, −0.01)	−0.52 (−1.14, 0.08)	−0.36 (−0.96, 0.24)
Cartledge[45] (2000)	16	Parallel	51	75%	4	Yes	−0.13 (−0.82, 0.57)	NR	NR	0.85 (0.13, 1.58)
Oxybutynin – intravesical										
Barbalias[46] (2000)	36	Parallel	45	100%	18	NR	+	NR	NR	−1.59 (−2.4, −0.80)
Oxygen, hyperbaric										
van Ophoven[47] (2006)	21	Parallel	65	100%	36	Yes	−0.93 (−1.89, 0.02)	−1.08 (−2.05, −0.11)	−0.47 (−1.38, 0.46)	−0.73 (−1.67, 0.21)
Pentosan Polysulfate										
Holm– Bentzen[24] (1987)	115	Parallel	57	90%	16	Yes	NR	–	–	NR
Parsons[26] (1987)	75	Cross Over	NR	75%	16	Yes	NR	−0.74 (−1.3, −0.14)	−0.62 (−1.14, −0.10)	−0.51 (−1.06, 0.03)
Mulholland [25] (1990)	110	Parallel	44	NR	12	No‖	NR	−0.15 (−0.53, 0.22)	–	NR
Parsons[27] (1993)	148	Parallel	43	97%	12	No‖	NR	+	+	NR
Sant[28] (2003)	121	Parallel	45	89%	18	No†	−0.26 (−0.77, 0.25)	−0.11 (−0.62, 0.40)	0.06 (−0.45, 0.56)	0.06 (−0.45, 0.57)
Sairanen [29] (2005)	64	Parallel	59	83%	24	Yes	−0.89 (−1.50, −0.28)	−0.49 (−1.01, 0.04)	NR	−0.27 (−0.85, 0.31)
Pentosan Polysulfate – Intravesical										
Bade[48] (1997)	20	Parallel	51	100%	12	Yes	NR	NR	–	−0.30 (−1.19, 0.58)
Resiniferatoxin (RTX)– intravesical										
Lazzeri[49] (2000)	18	Parallel	41	37%	Single application	Yes	NR	−4.01 (−5.67, −2.34)	1.10 (0.10, 2.10)	−1.57 (−2.64, −0.50)
Chen[50] (2005)	22	Parallel	44	77%	Single application	Yes	**0.05 ugm** −0.27(−1.44, 0.89) **0.10 ugm** −0.69 (−1.93, 0.55)	**0.05 ugm** 0.05 (−1.15, 1.25) **0.10 ugm** −0.32 (−1.48, 0.85)	**0.05 ugm** −0.26 (−1.43, 0.90) **0.10 ugm** −0.84 (−2.10, 0.41)	**0.05 ugm** −0.19 (−1.35, 0.97) **0.10 ugm** −0.68 (−1.92, 0.56)
Payne[51] (2005)	163	Parallel	47	86	Single application	Yes	–	**0.01 ugm**	**0.01 ugm**	**0.01 ugm**

Study (Year)	N	Design	Mean Age	Women,%	Duration in weeks	NIDDK Criteria	Symptom Outcomes SMD (95% CI)			
							Symptom Index	Pain	Urgency	Frequency
								−0.33 (−0.98, 0.33) **0.05 ugm** : −0.26 (−0.91, 0.39) **0.10 ugm** −0.52, −1.18,0.39)	−0.20(−0.85, 0.45) **0.05 ugm** −0.05 (−0.70, 0.60) **0.10 ugm** 0.12 (−0.53, 0.77)	0.00 (−0.42, 0.42) **0.05 ugm** 0.06 (−0.37, 0.48) **0.10 ugm** 0.19 (−0.25, 0.64)

*Abbreviations:

NR: Not Collected,

–Reported as not effective, data not extractable,

+Reported as effective, data not extractable

†urodynamics not required,

‡urodynamics not required, chronic inflammation on bladder biopsy required, which is not part of the NIDDK criteria,

§cystoscopy and urodynamics not required,

||urodynamics not required, capacity under anesthesia <800 ml required, which is not part of the NIDDK criteria.