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The Clinical Efficacy of Nitrofurantoin for Treating Uncomplicated Urinary Tract Infection in Adults: A Systematic Review of Randomized Control Trials

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Keywords
Urinary tract infection · Uncomplicated urinary tract infection · Cystitis

Abstract
Objective: To provide an updated systematic review of randomized control trials (RCTs) to investigate the clinical and microbiological efficacy of nitrofurantoin compared to other antibiotics or placebo for treatment of uncomplicated urinary tract infections (uUTI). A secondary aim is to assess whether nitrofurantoin use is associated with increased side effects compared to other treatment regimens. ***Summary:*** The review was performed according to PRISMA guidelines. We searched 4 databases for articles published from database inception to May 6, 2020: (1) PubMed electronic database of the National Library of Medicine, (2) Web of Science, (3) Embase, and (4) Cochrane Library. Nine RCTs were selected for the review. RCTs were a mixture of double-blind, single-blind, and open-label trials. The most common comparators were trimethoprim-sulfamethoxazole and fosfomycin tromethamine. Overall study quality was poor with a high risk of bias. The clinical cure rates in nitrofurantoin ranged from 51 to 94% depending on the length of follow-up, and bacteriological cure rates ranged from 61 to 92%. Overall the evidence suggests that nitrofurantoin is at least comparable with other uUTI treatments in terms of efficacy. Patients taking nitrofurantoin reported fewer side effects than other drugs and the most commonly reported were gastrointestinal and central nervous system symptoms. ***Key Messages:*** Evidence on the clinical and bacteriological efficacy of nitrofurantoin is sparse, with a lack of new data, and hampered by high risk of bias. Although no firm conclusions can be made on the current base of evidence, the studies generally suggest that nitrofurantoin is at least comparable to other common uUTI treatments in terms of clinical and bacteriological cure. More robust research with well-designed double-blinded RCTs is needed.

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Introduction

Urinary tract infection (UTI) is a common disorder; by the age of 32 years, half of all women report having at least 1 previous UTI [1]. Most UTIs are defined as uncomplicated (uUTI), defined as UTI in a person who is not pregnant, is not immunocompromised, has no anatomical and functional abnormalities of the urogenital tract, and does not exhibit signs of tissue invasion and systemic infection [2]. Treatment options for UTI are becoming more limited due to increasing resistance to UTI antibiotics [3]. According to the updated guidelines by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases [4], the first-line agents recommended for treating uUTI are nitrofurantoin monohydrate/macrocrystals and trimethoprim-sulfamethoxazole, although the latter was noted to have inferior efficacy compared with standard short-course regimens.

Nitrofurantoin has been used as a treatment for uUTI since the 1950s. However, the recommended regimen is 7 days, which has hampered its popularity in comparison to shorter or single-dose regimens, and there has been concern about resistance, but if given for only 3 days, nitrofurantoin's clinical efficacy diminishes [5]. Susceptibility to nitrofurantoin is reached if organisms' minimum inhibitory concentration is 32 μg/mL or less. Nitrofurantoin bioavailability is about 90% with 40% of urinary excretion. The drug is excreted in the urine achieving levels of 200 μg/mL or more. At a concentration >100 μg/mL, nitrofurantoin is a bactericide while it is bacteriostatic against organisms at concentrations <32 μg/mL [6].

A systematic review in 2015 [5] concluded that nitrofurantoin toxicity is mild and predominantly gastrointestinal with low resistance rates. In a large study in Canada and European countries [7] resistance to nitrofurantoin was low in *Escherichia coli* (E Coli), <3%, while rates were higher with ampicillin (30%), sulphonamides (29%), trimethoprim (15%), and trimethoprim/sulfamethoxazole (14%). Nitrofurantoin has also shown to be effective in the prevention of UTIs [8]. An earlier review concluded that nitrofurantoin has an overall equivalence to trimethoprim/sulfamethoxazole, ciprofloxacin, and amoxicillin [5] for the treatment of uUTI, but an update on the literature is needed. This is particularly important because there is low concordance with clinical guidelines for uUTI in primary care [9], with fluoroquinolones being the most commonly prescribed antibiotic in more than half of cases, and a significant trend toward increasing trimethoprim-sulfamethoxazole use and decreasing nitrofurantoin use.

The aim of the current paper is to provide an updated systematic review of randomized control trials (RCTs) to investigate the clinical and microbiological efficacy of nitrofurantoin compared to other antibiotics or placebo. A secondary aim is to assess whether nitrofurantoin use is associated with increased side effects compared to other treatment regimens.

Systematic Review Procedure and Inclusion Criteria

The review was carried out in accordance with the PRISMA recommendations [10]. PICOS was used to define the research question, as follows: (i) population – adults with uncomplicated UTI aged over 18; (ii) intervention – treatment with nitrofurantoin for UTI (monotherapy only); (iii) control/comparison – other antibiotics or placebo; (iv) outcomes – clinical efficacy and/or bacteriological cure (primary outcomes) and adverse effects (secondary outcome); (v) study design – RCT. Only studies in English were included.

Database Search

We searched 4 databases for articles published from database inception to May 6, 2020: (1) PubMed electronic database of the National Library of Medicine, (2) Web of Science, (3) Embase and, (4) Cochrane Library. MeSH terms and free words referring to the drug and uUTI were decided by 2 Urologists including the following key words: UTI, cystitis, bladder infection, urethritis, uUTI, urinary tract infection, acute cystitis, uncomplicated UTI, nitrofurantoin, Macrodantin, and Furadantin.

Two assessors independently screened the titles and abstracts of the selected studies according to the inclusion criteria defined in the PICOS, see above. The full texts of the articles selected by 1 or more of the assessors were retrieved for evaluation. Two assessors independently read the full texts and extracted the information from the selected studies. A third assessor reviewed the data extraction, and any disagreement was resolved through consensus. The numbers of abstracts screened, and studies assessed for eligibility, with reasons for exclusions at each stage, are presented in Figure 1.

Data Extraction

A data extraction form was designed to collect data relevant only to the aims of the current review, including study author and year, age and sex of participants, study design (open label, single or double blinded), identification of UTI at study inclusion (clinical symptoms and/or bacteriological confirmation), dosage of nitrofurantoin, comparator (placebo or other antibiotic) and dose, follow-up time(s), definition of 2 primary outcomes (symptomatic/clinical cure and bacteriological cure), and 1 secondary outcome (side/adverse effects), and results.

Risk of Bias

We used the Cochrane Collaboration's tool to assess risk of bias. Two authors independently assessed the quality of studies. Any disagreement was resolved via consensus discussion.

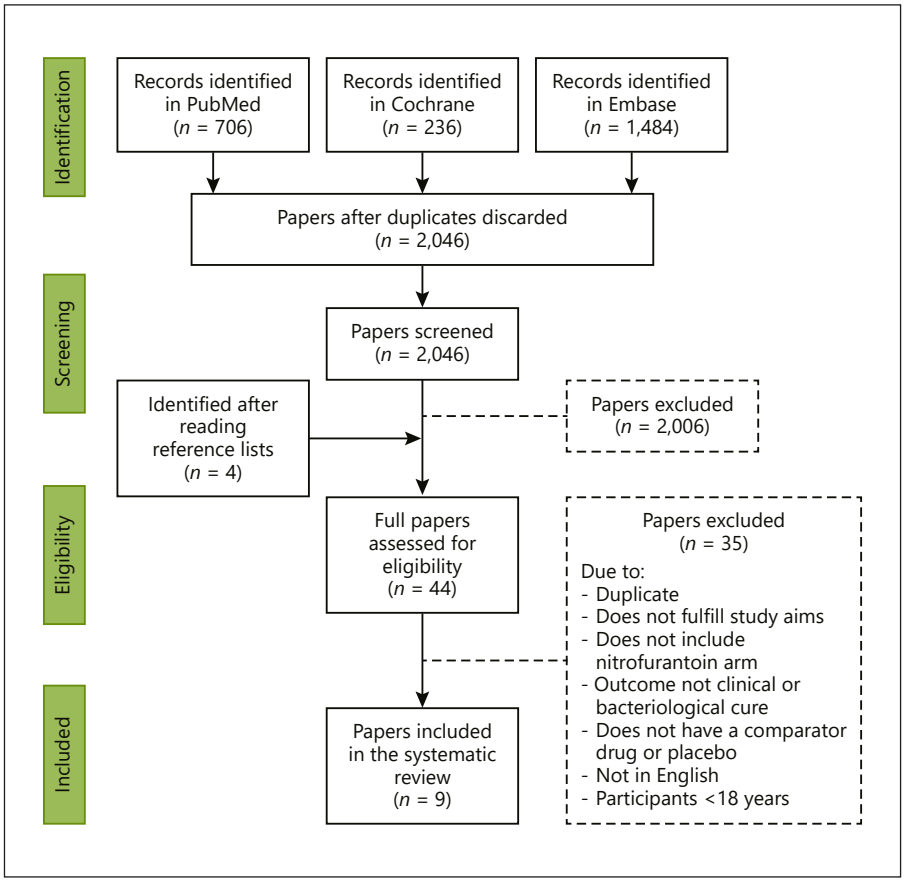

Fig. 1. PRISMA flowchart.

Results

Search Results

Figure 1 shows the PRISMA flowchart, including the key words used in the search strategies, the number of papers identified in the 4 databases, and the number and reason for exclusion. After removing duplicates, 2,046 titles and abstracts were screened; 44 were selected for full-text reading and 35 were excluded because they did not match the aims of the current review.

Study Characteristics

Nine RCTs were selected for the review. Characteristics of the studies are detailed in Table 1. All the studies included only women. Four were double-blind RCTs [11–14], 1 observer blinded [15], and 3 open labels [16–18], while 1 [19] did not state blinding status. Two studies [16, 19] included bacteriological resolution as an outcome (with or without symptomatic improvement), whereas the remaining studies all included 2 outcomes measures (clinical cure and bacteriological resolution). There were differences in the threshold for defining bacteriological cure, with 3 studies using $<10^5$ CFU/mL as a cutoff [11, 13, 14], 1 using $<10^7$ CFU/mL [18], and 4 using either $<10^3$ CFU/mL or $<10^2$ CFU/mL [12, 16, 17, 19]. Ludwig and Pauthner [15] did not specify the threshold. Follow-up times differed between studies, from 3 days to 6 weeks, with most studies having >1 follow-up points. All studies reported data on adverse effects and side effects.

One study [11] compared nitrofurantoin with a placebo while 5 had 1 comparator drug [12–16], and 3 compared with 2 or more other antibiotics [12, 18, 19]. The most common comparator was trimethoprim-sulfamethoxazole (co-trimoxazole) which was investigated in 4 studies [12, 16, 18, 19] and fosfomycin tromethamine, which was the comparator in 3 studies [13, 14, 17]. Oral ciprofloxacin [12], trimethoprim [18], cefadroxil [19], amoxicillin [19], and ofloxacin [15] were investigated in 1 study each.

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Table 1. Characteristics of the 9 RCTs included in the systematic review

Author	Study design and identification of UTI	Comparators, doses, and patient numbers	Sex, age, and follow-up	Outcomes	Results Cure in patients prescribed nitrofurantoin versus comparator	Side effects
Christiaens et al. [11]	Double blind Women with symptoms suggestive of uUTI, bacteriological confirmation at inclusion (data shown here only for confirmed cases)	Capsules of nitrofurantoin (macrocrystalin formulation) 100 mg ($n = 29$) versus placebo capsules with the same appearance ($n = 27$) Treatment duration: 3 days	Women Age: 15–54 Follow-up: 3 and 10 days	Clinical: symptomatic cure or improvement (diary) Bacteriological: negative culture test $<10^5$ CFU/mL ITT and CCA performed	Day 3 **Symptomatic cure:** Nitrofurantoin 80% Placebo 44% ITT: $p = 0.0$; CCA: $p = 0.02$ **Bacteriological cure:** Nitrofurantoin 81% Placebo 20% ITT: $p < 0.001$; CCA: $p < 0.001$ Day 7 **Symptomatic cure:** Nitrofurantoin 88% Placebo 54% ITT: $p = 0.1$; CCA: $p = 0.03$ **Bacteriological cure:** Nitrofurantoin 74% Placebo 41% ITT: $p = 0.1$; CCA: $p = 0.05$	9 (nitrofurantoin) versus 10 (placebo) reported side effects; no significant difference between treatment and placebo groups Most reported side effects: Gastrointestinal Headache Dizziness/fatigue Sleep disturbances, vaginal itching, dermatological
Gupta et al. [16]	Open label Clinical symptoms plus uropathogen 10^2 CFU/mL	Nitrofurantoin, 100 mg twice daily for 5 days ($n = 160$) versus trimethoprim-sulfamethoxazole 1 double-strength tablet twice daily for 3 days ($n = 148$) Treatment duration: 3 and 5 days	Women Age: 18–45 Overall follow-up: 30 days Early follow-up: 5–9 days	Clinical cure after 30 days Microbiological cure In asymptomatic women $<10^5$ CFU/mL of all uropathogens and at least a 1-log decrease in colony count of the causative uropathogen compared with the urine culture at enrollment In symptomatic women $<10^2$ CFU/mL of a uropathogen	**Overall clinical cure rate:** Nitrofurantoin 84% Trimethoprim-sulfamethoxazole 79% Nonsignificant difference of −5% (95% CI −13 to 4) ITT analysis confirmed no significant difference **Early microbiological cure:** Nitrofurantoin 92% Trimethoprim-sulfamethoxazole 91% Nonsignificant difference of −1% (95% CI −7 to 6) **Early clinical cure:** Nitrofurantoin 90% Trimethoprim-sulfamethoxazole 90% Nonsignificant difference of −0.1% (95% CI −7 to 7)	Similar proportions of women reported adverse effects 28% (nitrofurantoin) 31% (trimethoprim-sulfamethoxazole) No significant difference between treatment and placebo groups Most reported side effects Gastrointestinal system (nausea or diarrhea) Central nervous system (headache or lightheadedness) Urogenital system (vaginal itching)
Hooton et al. [19]	Symptoms of acute UTI at inclusion Blinding not stated	Nitrofurantoin 100 mg ×4 daily ($n = 38$) Trimethoprim-sulfamethoxazole ($n = 40$) Cefadroxil ($n = 37$) Amoxicillin ($n = 43$) Treatment duration: 3 days	Women Age: ≥18 Follow-up: 6 weeks	10^2 uropathogens per mL with or without symptoms on 2+ consecutive cultures	**Bacteriological cure rates:** Nitrofurantoin 61% Trimethoprim-sulfamethoxazole 82% Cefadroxil 66% Amoxicillin 67% No significant difference between nitrofurantoin versus trimethoprim-sulfamethoxazole $p = 0.4$	Side effects reported in: Nitrofurantoin (43%) Trimethoprim-sulfamethoxazole (35%) Cefadroxil (30%) Amoxicillin (25%) The most reported side effects in nitrofurantoin arm were: Symptomatic yeast vaginitis warranting treatment ($n = 7$) Nausea ($n = 10$) Headache ($n = 3$) Diarrhea ($n = 3$)

Table 1 (continued)

Author	Study design and identification of UTI	Comparators, doses, and patient numbers	Sex, age, and follow-up	Outcomes	Results Cure in patients prescribed nitrofurantoin versus comparator	Side effects
Huttner et al. [17]	Open label Symptoms of lower UTI plus a positive urine dipstick result (with detection of nitrites or leukocyte esterase) ($\geq 10^3$ CFU/mL)	Oral nitrofurantoin, 100 mg 3 times a day for 5 days ($n = 255$) versus single 3-g dose of oral fosfomycin ($n = 258$) Treatment duration: 5 days and 1 day	Women Age: ≥18 Follow-up: 14 and 28 days	Clinical resolution: complete resolution of symptoms and signs of UTI without prior failure Bacteriologic response: eradication of the infecting strain with no recurrence of bacteriuria ($<10^3$ CFU/mL)	14 days **Clinical resolution:** Nitrofurantoin 75% Fosfomycin 66% (difference 9%, 95% CI 1–17%; $p = 0.03$) **Bacteriologic response:** Nitrofurantoin 82% Fosfomycin 73% (difference 9%, 95% CI 0.4–18%; $p = 0.04$) 28 days **Clinical resolution:** Nitrofurantoin 70% Fosfomycin 58% (difference 12%, 95% CI 4–21%; $p = 0.004$) **Bacteriologic response:** Nitrofurantoin 74% Fosfomycin 63% (difference 11%, 95% CI 1–20%; $p = 0.04$)	Few adverse events reported Nausea: Nitrofurantoin (3%) Fosfomycin (2%) Diarrhea Nitrofurantoin (1%) Fosfomycin (15)
Iravani et al. [12]	Double blind Symptomatic patients with positive urine culture (i.e., single organism with a colony count $>10^3$ CFU/mL of urine) accompanied by signs and symptoms of pyuria (positive dipstick or >10 WBC/mm^3 uncentrifuged urine)	Nitrofurantoin (100 mg bd) for 7 days ($n = 179$) Oral ciprofloxacin (100 mg bd) for 3 days ($n = 168$) Co-trimoxazole (160/800 mg bd) ($n = 174$) Treatment duration: 3 and 7 days	Women Age: ≥18 Follow-up: 9–15 days	Clinical resolution: absence of all signs and symptoms related to infection Bacteriological eradication: causative organism $<10^3$ CFU/mL	**Clinical resolution:** 4–10 days after therapy and at the 4–6 weeks follow-up was similar among the 3 treatment groups **Bacteriological eradication:** Nitrofurantoin 86% Ciprofloxacin 88% Co-trimoxazole 93% At the 4–6 weeks follow-up, ciprofloxacin had statistically significantly higher eradication rates (91%) than nitrofurantoin (82%)	Overall incidence of treatment-emergent adverse events was not significantly different ($p = 0.093$)
Ludwig and Pauthner [15]	Observer blind Lower UTI	Nitrofurantoin 100 mg 3 times daily for 7 days ($n = 39$) versus ofloxacin 100 mg twice daily for 3 days ($n = 41$) Treatment duration: 7 and 3 days	Women Age: not stated Follow-up: 4 weeks	Clinical cure (disappearance of frequent and painful micturition) Bacterial eradication: not specified	**Clinical cure:** Nitrofurantoin 51% Ofloxacin 82% **Bacterial eradication rate:** Nitrofurantoin 66% Ofloxacin = 81%	Of the 39 patients administered nitrofurantoin 6 dropped out because of nausea and vomiting (4 of these also had fever) The frequency of side effects in the 2 comparison groups was similar ∼15%
Spencer et al. [18]	Open label Symptoms of uUTI and with blood and leukocytes in the urine	Nitrofurantoin modified release 100 mg bd ×7 days ($n = 178$) Trimethoprim 200 mg bd × 7 days ($n = 179$) Co-trimoxazole 960 mg bd × 7 days ($n = 181$) Treatment duration: various	Women Age: ≥18 Follow-up: 9–15 days	Clinical cure: relief from symptoms (diary) Bacteriological cure: absence of causative pathogens $<10^7$ CFU/L of urine	**Clinical cure:** Nitrofurantoin 87.2% Co-trimoxazole 84.5% Trimethoprim 86.5% **Bacteriological cure rate:** Nitrofurantoin 82.3% Co-trimoxazole 83.2% Trimethoprim 76.8% No significant differences between the 3 treatment groups	Adverse events reported Nitrofurantoin 15.7% Co-trimoxazole 15.5% Trimethoprim 15.6% Nitrofurantoin showed fewer patients with drug-related adverse events as judged by the investigator Nitrofurantoin 5.6% Co-trimoxazole 8.8% Trimethoprim 7.3%

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Table 1 (continued)

Author	Study design and identification of UTI	Comparators, doses, and patient numbers	Sex, age, and follow-up	Outcomes	Results Cure in patients prescribed nitrofurantoin versus comparator	Side effects
Stein [13]	Double blind 10^5 CFU/mL per milliliter of a uropathogen	7-day course of nitrofurantoin ($n = 374$) versus single-dose fosfomycin tromethamine ($n = 375$) Treatment duration: 1 and 7 days	Women Age: ≥12 years Follow-up: 7 and 32 days	Clinical efficacy: improvement or absence of symptoms Clinical efficacy ≥10^5 CFU/mL ITT analysis also performed	**Clinical cure:** Fosfomycin 80% and nitrofurantoin 80% ITT population, % receiving additional antibiotic therapy Nitrofurantoin 29.8% Fosfomycin 25.5% ($p = 0.3$) **Bacteriologic cure rate:** Nitrofurantoin 59% Fosfomycin 60% The number of reinfections (7 vs. 10) in the 2 groups was not statistically different	Adverse effects reported: Nitrofurantoin 5.6% Fosfomycin 5.3% Most frequent side effects for nitrofurantoin: Nausea 1.6% Vaginitis 1.6% Dizziness 0.8% Diarrhea 0.8%
Van Pienbroek et al. [14]	Double blind Symptomatic patients	Nitrofurantoin 50 mg 4 times daily for 7 days ($n = 115$) Single dose of 3-g fosfomycin trometamol ($n = 116$) Treatment duration: 1 and 7 days	Women Age: ≥12 years Follow-up: 4, 9, and 42 days	Clinical cure: Patient's judgment of cure or improvement Bacteriological cure rates: Negative culture <10^5 CFU/mL Overall efficacy GP opinion on day 42	The clinical cure rates and bacteriological cure rates were not significantly different between the treatment groups **Clinical cure:** Days 4 and 9 Nitrofurantoin 94% Fosfomycin trometamol 95% Day 42 Nitrofurantoin 80% Fosfomycin trometamol 82% **Bacteriological cure day 9:** Nitrofurantoin 90% Fosfomycin trometamol 81% **Overall efficacy cure:** Nitrofurantoin 82% Fosfomycin trometamol 85% **Reinfection rate at day 42:** Nitrofurantoin 11% Fosfomycin trometamol 6% $p = 0.24$	Patient reported side effects reported at day 4: Nitrofurantoin 25% Fosfomycin trometamol 43% $p < 0.05$ GP reported side effects reported at day 4: Nitrofurantoin 12% Fosfomycin trometamol 33% Patient reported side effects reported at day 9: Nitrofurantoin 16% Fosfomycin trometamol 20% GP reported side effects reported at day 9: Nitrofurantoin 8% Fosfomycin trometamol 15% Most of the side effects were gastrointestinal, mainly nausea and diarrhea

CCA, complete case analysis; CFU, colony-forming units; ITT, intention-to-treat analysis; uUTI, uncomplicated urinary tract infection; WBC, white blood cell; RCT, randomized control trial.

Table 2. Risk of bias ratings

Author	Random sequence (selection bias)	Generation allocation Concealment (selection bias)	Blinding of participants/ personnel (performance bias)	Blinding of outcomes Assessment (detection bias)	Incomplete outcome Data (attrition bias)	Selective reporting (reporting bias)	Other sources of bias
Christiaens et al. [11]	+	+	+	+	–	+	na
Gupta et al. [16]	+	+	–	+	+	+	na
Hooton et al. [19]	+	?	–	+	–	+	na
Huttner et al. [17]	+	+	–	+	+	+	na
Iravani et al. [12]	+	+	+	+	+	+	na
Ludwig and Pauthner [15]	+	?	–	?	–	?	na
Spencer et al. [18]	+	?	–	+	+	+	na
Stein [13]	+	?	+	+	–	+	na
Van Pienbroek et al. [14]	+	–	+	+	+	+	na

– High risk of bias; + low risk of bias; ? unclear risk of boas.

Symptomatic/Clinical Cure

The clinical cure rates in nitrofurantoin ranged from 51 [15] to 94% [14] depending on the length of follow-up. The placebo-controlled trial showed a significantly higher clinical cure rate in patients treated with nitrofurantoin [11]. Two studies demonstrated a significantly higher clinical cure rate in patients treated with nitrofurantoin versus fosfomycin [13, 17] whereas 1 found no difference [14]. Two studies reported no significant difference between nitrofurantoin and trimethoprim-sulfamethoxazole [12, 16]. No significant difference between nitrofurantoin and oral ciprofloxacin was found [12]. Ludwig and Pauthner [15] reported that ofloxacin was superior to nitrofurantoin though no statistical test was performed, and it was noted that many nitrofurantoin patients discontinued because of side effects.

Bacteriological Cure

The bacteriological cure rates ranged from 61 [19] to 92% [16] depending on the length of follow-up. The placebo-controlled trial showed a significantly higher bacteriological cure rate in patients treated with nitrofurantoin [11]. Huttner et al. [17] demonstrated a significantly higher bacteriological cure rate in patients treated with nitrofurantoin versus fosfomycin (both at 14 and 28 days), whereas 2 found no significant difference [13, 14]. Three studies found no significant difference between nitrofurantoin and trimethoprim-sulfamethoxazole [16, 18, 19]. There were no differences between nitrofurantoin and cefadroxil [19], amoxicillin [19], or trimethoprim [18] in terms of bacteriological cure. At a 4–6 week follow-up, Iravani et al. [12] reported that ciprofloxacin had statistically significantly higher eradication rates than nitrofurantoin.

Side Effects

Only one study reported higher side effects in patients taking nitrofurantoin compared to cefadroxil, amoxicillin, and trimethoprim-sulfamethoxazole [19]. Patients taking nitrofurantoin reported fewer side effects that those prescribed trimethoprim [18] or co-trimoxazole [18], or fosfomycin [14]. In the remaining studies, no differences in adverse events were reported between nitrofurantoin and placebo [11], trimethoprim-sulfamethoxazole [12, 16], ofloxacin [15], ciprofloxacin [12], or fosfomycin [13, 17]. The most commonly reported side effects in patients taking nitrofurantoin were gastrointestinal (e.g., nausea or diarrhea) and central nervous system (e.g., headache) symptoms.

Risk of Bias

Table 2 shows results of the risk of bias assessment. Five studies were rated as having a high risk of bias due to lack of blinding, and general allocation (concealment) was unclear in 4 studies. For the bacteriological cure outcome, the detection bias was rated as low for all studies because they used objective measures from urine tests.

Conclusion

Our systematic review found only a limited number of RCTs comparing the clinical and bacteriological cure rates of nitrofurantoin with placebo or other antibiotic agents.

Most were old: 6 were conducted in the 1980s and 1990s, with only one study published in the last 10 years. Results were heterogeneous but overall, the studies suggest that nitrofurantoin is at least equivalent to other antibiotics for the clinical and bacteriological cure of uUTI, and in some studies, it was demonstrated to be superior to trimethoprim-sulfamethoxazole. The only agent demonstrated to have higher bacteriological cure rates than nitrofurantoin was ciprofloxacin, which was reported in 1 study. Most studies reported no significant differences in side effects between nitrofurantoin and other antibiotic agents. Generally, the studies had a high risk of bias, mostly due to lack of blinding or unclear concealment methods.

There were large differences in the methodology of the studies. In particular, the threshold for defining bacteriological cure varied enormously from $<10^2$ to $<10^7$ CFU/mL. FDA guidelines for patient eligibility for enrollment in uUTI trials state a threshold of $\geq 10^5$ CFU/mL in symptomatic adult and adolescent females [20]. Further, less than half of the studies were double-blind RCTs. It is also likely that there were variations in the definition of clinical cure although such a parameter was more difficult to determine as many studies did not specifically state their methodology for assessing this outcome.

The evidence suggested that nitrofurantoin is at least equivalent to other antibiotics for the clinical and bacteriological cure of uUTI in women, confirming results of previous meta-analyses [5, 21] Our review suggested that nitrofurantoin was not associated with a higher risk of side effects than other antibiotic agents. However, previous case reports have documented adverse effects in individual patients, including lung injuries such as organizing pneumonia [22], interstitial lung disease [23], respiratory arrest [24], and pleural effusion [25]. Another report highlighted a case of systemic inflammatory response syndrome in a 74-year-old woman [26]. Only one study in our review reported higher adverse effects of nitrofurantoin compared to cefadroxil, amoxicillin, and trimethoprim-sulfamethoxazole, and in remaining studies rates were equivalent, the most common being, nausea, headache, and diarrhea. The clinical efficacy and equivalence in adverse effects to other antibiotics provide support to the guidelines [4] that recommend nitrofurantoin as the first-line agent for treating uUTI.

The aim of our review was to investigate the overall clinical and bacteriological efficacy of nitrofurantoin, but it is worth noting that the efficacy can differ depending on the organism causing the uUTI. The most common causative organisms are *E. coli* [16], others include *S. saprophyticus, Enterococci, Klebsiella species*, and *Proteus mirabilis,* etc. Evidence from the studies included in the current review also revealed some differences in the efficacy of nitrofurantoin for curing the different uropathogens. For example, in Huttner et al.'s [17] study, 57–56% of uUTIs were due to *E. coli*. When looking in this subgroup of patients, they found that the clinical response to nitrofurantoin was significantly higher than fosfomycin, and more pronounced when all uUTIs, irrespectively of the uropathogen involved were analyzed. In Ludwig and Pauthner [15] trial, ofloxacin was better than nitrofurantoin at eliminating *E. coli,* whereas nitrofurantoin had better eradication rates for *Enterococci*. In Spencer et al.'s [18] RCT, co-trimoxazole, trimethoprim, and nitrofurantoin had equivalent efficacy against *E. coli*, but against all other organisms (including *Staphylococcus pluralis, Klebsiella pluralis, Enterococci,* etc.) nitrofurantoin and co-trimoxazole were almost 15% better than trimethoprim. However, in all studies *E. coli* accounted for the majority of uUTIs and, therefore, numbers were low for comparing the efficacy of different antibiotics for other uropathogens.

In the current review, we focused on 2 main outcomes: symptomatic cure and microbiological cure. However, there are many other endpoints that have clinical relevance to patients and health-care providers, for example, quality of life, or cost-effectiveness. An open-label RCT [27] suggested that patients experiencing a clinical cure had significantly better QoL than patients with failed treatment, but this was not dependent on the drug prescribed. Hooton et al. [19] included a cost analysis in their study based in USA and reported higher costs for nitrofurantoin (USD 155 per patient) compared to trimethoprim-sulfamethoxazole (USD 114), which were mainly due to higher drug and pharmacy charges (3–4 times as high) and costs associated with more frequent return visits to the clinic for treatment of recurrent UTI and/or yeast vaginitis. However, another study reported that cost-effectiveness differed depending on resistance rates. For example, when the threshold for resistance is set at <30% trimethoprim is more cost-effective than nitrofurantoin, but at ≥35% nitrofurantoin has the higher cost-efficiency. Last update of the German clinical guideline on epidemiology, diagnostics, therapy, prevention, and management of uUTI reports as resistance is a growing global problem that leads to significant challenges and costs in the health-care system. An international reevaluation of therapeutic recommendations in uUTI is guided by the resistance level of pathogens against commonly used antibiotics and by cost increase [28, 29].

Our review highlighted some gaps in current knowledge. First, all of the trials included in our review were

restricted to female participants. Generally, UTIs in men are considered to be complicated because the prostate is often involved [30], although in some rare circumstances they could be considered uncomplicated in young men with a UTI without systemic symptoms, where the patient's medical history and physical examination do not suggest a causative factor [2]. Our search did not find any RCTs on the efficacy of nitrofurantoin for treating uUTI in men. Second, most studies were old (conducted in the 1980s and 1990s), and few had a robust methodology with double blinding and adequate concealment methods. Third, most of the studies were not powered to investigate efficacy according to less common causative uropathogens, and therefore, most drug comparisons could only provide sufficiently powered results related to *E. coli*. Fourth, the comparator drugs differed hugely between studies, making difficult to perform a methodologically sound meta-analysis. The most common comparator was trimethoprim-sulfamethoxazole. Fifth, no association with compounds and dietary supplement was included as comparator or in association with antibiotics [31].

In conclusion, the current systematic review highlighted the need for more RCTs to investigate the efficacy of nitrofurantoin for treating uUTI. Studies are old, and risk of bias is generally high. Although no firm conclusions can be made based on the current base of evidence, the studies generally suggest that nitrofurantoin is at least comparable to other common uUTI treatments in terms of clinical and bacteriological cure. Furthermore, recent fluoroquinolone warning on side effects represents another reason to prefer other molecules to treat uUTI.

Conflict of Interest Statement

The authors have nothing to disclose.

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Author Contributions

Conception or design of the work: Matteo Ferro, Gian Maria Busetto, Katie Palmer, and Angelo Porreca. Acquisition of data: Gian Maria Busetto, Francesco Del Giudice, Martina Maggi, Daniele Romagnoli. Interpretation of data for the work: Angelo Porreca, Ettore De Berardinis, Alessandro Sciarra, Katie Palmer, and Daniele D'Agostino. Drafting the paper: Gian Maria Busetto, Daniele D'Agostino, Daniele Romagnoli, and Angelo Porreca. Paper critically revising: Ettore De Berardinis, Alessandro Sciarra, Vincenzo Mirone, Matteo Ferro, Walter Artibni, Roberto Falabelle, and Daniele D'Agostino.

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