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Comparison of treatments for preventing lower urinary tract symptoms after BCG immunotherapy of bladder tumors : a systematic review and network meta-analysis

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Abstract

Background Bacillus Calmette-Guerin (BCG) immunotherapy is the standard adjuvant treatment for high-risk, non-muscle invasive bladder cancer (NMIBC). However, BCG immunotherapy is commonly accompanied by significant lower urinary tract symptoms (LUTS) including symptoms such as urinary urgency, frequency, dysuria and pelvic pain. These symptoms can undermine treatment adherence and clinical outcomes. In this study, the treatments for preventing LUTS after BCG instillations were compared through a systemic review and network meta-analysis (NMA).

Methods Eligible studies were obtained from the PubMed, Web of Science, Embase and Cochrane Library databases. We also searched the references of the included studies. Our protocol followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist. We performed NMA using Review Manager 5.3 and STATA MP 18.0.

Result The analysis included 6 studies with 556 participants. The results of the NMA revealed that celecoxib and prulifloxacin effectivelty reduce the incidence of LUTS including frequency, urgency and dysuria. Phenazopyridine showed the best performance in improving pelvic pain.

Conclusion The NMA indicated that medications such as celecoxib, prulifloxacin and phenazopyridine are effective in reducing the incidence of LUTS after BCG immunotherapy of bladder tumors.

Keywords BCG, Network meta-analysis, LUTS, Bladder cancer, Immunotherapy

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Introduction

Bladder cancer (BCa) is the tenth most commonly diagnosed cancer worldwide, and the age-standardized mortality rate (per 100 000 person-years) is 3.3 for men versus 0.86 for women. It continues to be the most prevalent malignancy of the urinary system [1]. On average, a patient's lifetime treatment costs for BCa are higher than those for any other malignancy [2].

Approximately 75% of patients with BCa present with disease confined to the mucosa (stage Ta or CIS) or submucosa (stage T1) [3], for younger patients, this percentage is even higher [4]. These tumours are grouped under the heading of NMIBC. In the treatment of NMIBC, surgical intervention such as transurethral resection of bladder tumor (TURBT) combined with intravesical instillation therapy is the current standard treatment principle [5].

Since BCG instillation was first used to treat patients with NMIBC in 1976 [6], BCG immunotherapy has become the most successful adjuvant therapy for reducing the rate of NMIBC recurrence and progression [7–9]. For patients with intermediate-risk or high-risk NMIBC, a 6-week course of intravesical BCG-based immunotherapy is the gold standard adjuvant therapy [10]. However, only 50% of patients with NMIBC received BCG maintenance therapy as recommended by the American Urological Association (AUA) and the European Association of Urology (EAU) guidelines [11], 19% of patients who accepted intravesical BCG had to stop the treatment because of complications, and only 16-29% of patients could complete three years immunotherapy [12, 13].

The substantial occurrence of complications was considered one of the main reasons for poor compliance with BCG immunotherapy. Mild and moderate local and systemic adverse events occur in more than 90% of patients [14]. LUTS are the most common complication after BCG instillation and are characterized by frequency, urgency, pelvic pain and dysuria [15]. Such LUTS are reported in 70–80% of patients in the initial 48 h following each infusion and can be debilitating [16]. Symtoms can last few days to few weeks, If adverse reactions persist over time or become intolerable, symptomatic treatment with spasmolytics, anticholinergics, analgesics and antiphlogistics are indicated, or, finally, a radical cystectomy in the case of contracted bladder or refractory symptoms [17]. To prevent such BCG-induced LUTS, potentially effective options include BCG dose reduction, BCG maintenance shortening, modifications of the BCG maintenance schedule and medical interventions [12, 13, 18]. Nanosized carriers were also developed to reduce the side effets of BCG immunotherapy [19].

Medical interventions are based on intravesical glycosaminoglycan substitution, oral antibacterial agents active against mycobacterium (fluoroquinolones or isoniazid) or oral anticholinergics. Although many studies have evaluated the efficacy of these medications, little is known about their relative efficacy. Therefore, a comparison of the effectiveness of all interventions is needed to review the current evidence and guide further clinical trials.

NMA is a statistical approach that compares different drugs that have not yet been directly compared via head-to-head randomized controlled trials (RCTs) [20]. On the basis of statistical inference, we can estimate its relative ranking [21]. Therefore, we performed a NMA on treatments for preventing LUTS after BCG immunotherapy, which included 6 studies published from 2000 to 2022 and compared the effectiveness of 7 interventions. These comparisons were performed using Review Manager 5.4 and STATA MP 18.0 software.

Materials and methods

Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [22]. The search was conducted in April 2024 without limiting the starting time of the literature. We searched multiple databases such as the PubMed, EMBASE, Web of Science and Cochrane Library databases. The search strategy involved the following keywords (MeSH terms and free text words) : "Urinary Bladder Neoplasms", "Administration, Intravesical", "BCG Vaccine", and "Lower Urinary Tract Symptoms". The reference lists of the included studies were examined to identify additional studies. The language was restricted to English. This study completed PROSPERO registration (CRD42024551912).

Study selection

The inclusion criteria were as follows: (1) the study design was RCTs; (2) patients were diagnosed with BCa and received 120 mg full-dose BCG immunotherapy; (3) the study included at least one drug or intervention with placebo control; and (4) the outcome of the study was the incidence of BCG-induced LUTS. The exclusion criteria were as follows: (1) the study was a case report, review or editorial comment; (2) the study included only one group; (3) the study was a repeated publication; (4) the data of the study were available or extractable.

Data extraction and quality assessment

Two investigators independently extracted the data via a standardized form. The following data were extracted: study information (title, authors, country, publication time, patient number), patient count, interventions, control and outcomes (the incidence or severity of LUTS). Quality assessment was performed via the risk of bias assessment tool from the Cochrane Handbook for

Systematic Reviews of Interventions [23]. Any discrepancy was resolved by discussion between the two reviewers or by a third reviewer.

Data analysis

Review Manager 5.4 and STATA MP 18.0 software were used for analysis (Cochrane Collaboration, Oxford, United Kingdom). A random-effects model was adopted for pooled analysis when statistical heterogeneity was found ($I2 \geq 50\%$, $P \leq 0.1$), whereas a fixed-effects model was adopted when no significant heterogeneity was detected ($I2 < 50\%$ and $P > 0.1$). Surface under the cumulative ranking curve (SUCRA) was used to rank the effectiveness of various medications.

Results

Literature search

The initial literature search identified a total of 630 articles: 96 from PubMed, 245 from Web of Science, 189 from the Cochrane Library and 101 from EMBASE. After removing 278 duplicates, we identified 352 citations. Through screening the titles and abstracts for eligibility, we retrieved 41 articles for full-text assessment. Of these, 12 articles were excluded because of unavailable data, 12 articles were excluded because different outcomes were assessed and 7 articles were conference abstracts or editorial comments. The research process is shown in Fig. 1. Finally, 6 studies met our review inclusion criteria and remained for qualitative synthesis and quantitative meta-analysis.

Characteristics and qualities of the included studies

All of the studies included 556 patients and compared 7 different medications, specifically levofloxacin [24], isoniazid [25], ofloxacin [26], prulifloxacin [27, 28], celecoxib [29], phenazopyridine [29] and oxybutynin [29]. We present a comprehensive explanation of the included studies in Table 1. All six studies were RCTs. We conducted a risk of bias assessment using the Cochrane risk of bias assessment tool for RCTs (Fig. 2). The effects of different interventions on the incidence of LUTS are shown in Fig. 3.

Network meta-analysis

A NMA was performed to assess indirect treatment comparisons. The network constructions for comparison are shown in Fig. 4. After the NMA was conducted, pairwise comparisons were obtained and are shown in Tables 2 and 3. On the basis of results of the pairwise comparisons, we further calculated the SUCRA values and ranked them. The outcomes of SUCRA are shown in Fig. 5. Smaller SUCRA values corresponded to a lower incidence of BCG-induced LUTS.

Frequency

The frequency analysis was based on six studies and the network construction was shown in Fig. 3a. Compared with the placebo, levofloxacin, ofloxacin, prulifloxacin, celecoxib, phenazopyridine and oxybutynin were effective in reducing the incidence. The outcomes of pairwise comparisons are shown at the bottom-left

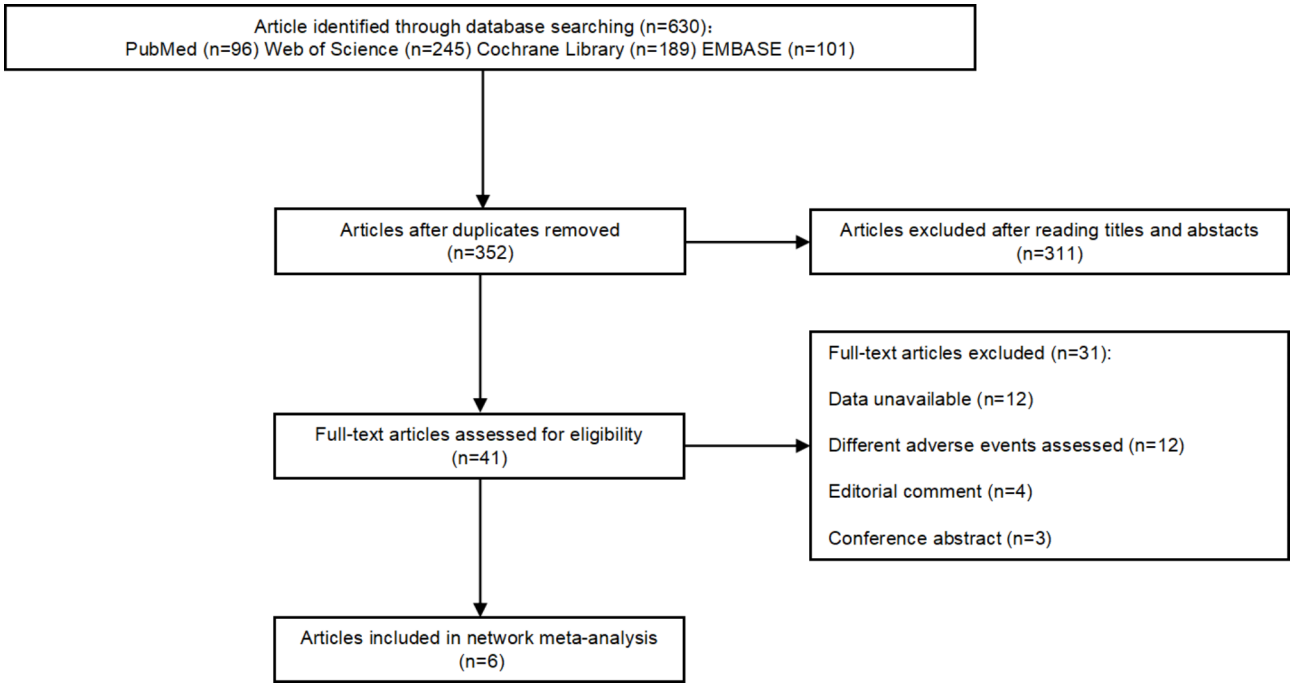

Fig. 1 Flow chart of the study search

Table 1 Characteristics of the studies included in the NMA

Study	Country	Published year	Study design	Treatment arms	Patient number	Discontinued patients	Intervention duration
Numakura [24]	Japan	2022	2-arm RCTs	1.Placebo	51	4	6 weeks
				2.Levofloxacin	55	5	
Kamali [29]	Iran	2020	4-arm RCTs	1.Placebo	30	0	6 weeks
				2.Celecoxib	30	0	
				3.Phenazopyridine	30	0	
				4.Oxybutynin	30	0	
Serretta [28]	Italy	2010	2-arm RCTs	1.Placebo	22	1	6 weeks
				2.Prulifloxacin	21	3	
Damiano [27]	America	2009	2-arm RCTs	1.Placebo	35	12	6 weeks
				2.Prulifloxacin	37	7	
Colombel [26]	France	2006	2-arm RCTs	1.Placebo	58	20	9 weeks
				2.Ofloxacin	57	9	
Al Khalifa [25]	Canada	2000	2-arm RCTs	1.Placebo	80	9	6 weeks
				2.Isoniazid	80	7	

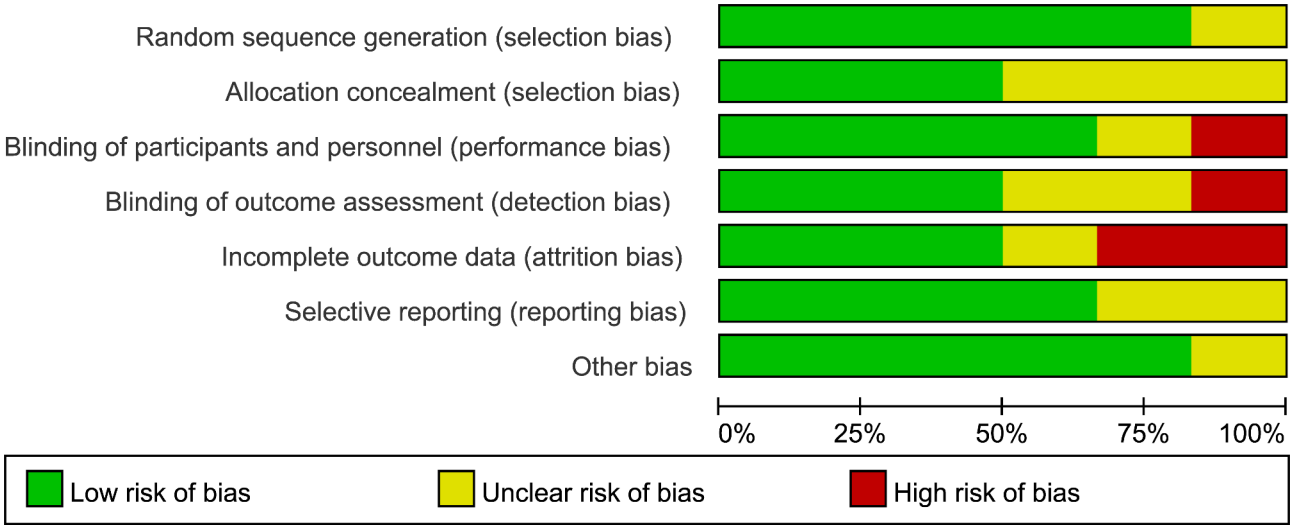

Fig. 2 Risk of bias for all RCTs included in this study

of Table 2. According to the SUCRA results (Fig. 5a), celecoxib was considered to be the most effective choice (SUCRA = 12.5%), followed by prulifloxacin (SUCRA = 29.6%), ofloxacin (SUCRA = 32.9%), levofloxacin (SUCRA = 33.8%), oxybutynin (SUCRA = 49.2%) and phenazopyridine (SUCRA = 75.7%). Isoniazid (SUCRA = 83.5%) did not significantly improve the therapeutic effect compared with placebo (SUCRA = 82.9%).

Urgency

The urgency analysis was based on three studies and the network construction is shown in Fig. 3b. Compared with placebo, prulifloxacin and celecoxib were more effective in reducing urgency. The outcomes of pairwise comparisons are shown at the top-right of Table 2. However, oxybutynin and phenazopyridine showed no significant improvement. According to the SUCRA results (Fig. 5b), celecoxib was the highest-ranked treatment for urgency (SUCRA = 8.1%) and prulifloxacin ranked the second (SUCRA = 18.9%). Oxybutynin (SUCRA = 83.8%) and phenazopyridine (SUCRA = 83.7%) did not have significant advantages in terms of therapeutic effects over the placebo (SUCRA = 55.4%).

Pelvic pain

The pelvic pain analysis was based on four studies and the network construction is shown in Fig. 3c. Compared with the placebo, oxybutynin, prulifloxacin, phenazopyridine and celecoxib were effective in reducing pelvic pain. The outcomes of pairwise comparisons are shown at the bottom-left of Table 3. According to the SUCRA results (Fig. 5c), phenazopyridine was the highest-ranked treatment for urgency (SUCRA = 24.5%), followed by prulifloxacin (SUCRA = 33.8%), celecoxib (SUCRA = 41.1%) and oxybutynin (SUCRA = 52.0%). Compared with the placebo (SUCRA = 66.8%), levofloxacin (SUCRA = 81.9%) did not significantly improve the therapeutic effect.

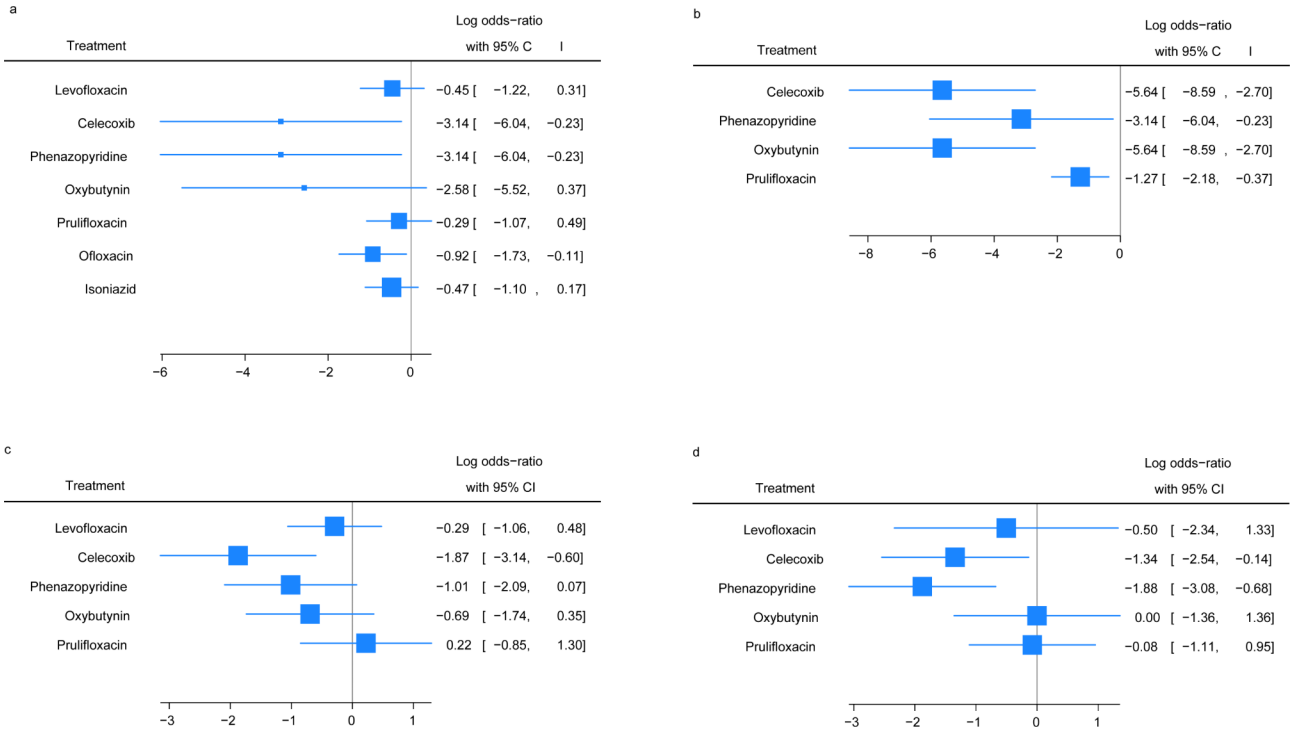

Fig. 3 Summary of the effects of different interventions on the incidence of LUTS, frequency (**a**), urgency (**b**), pelvic pain (**c**), and dysuria (**d**)

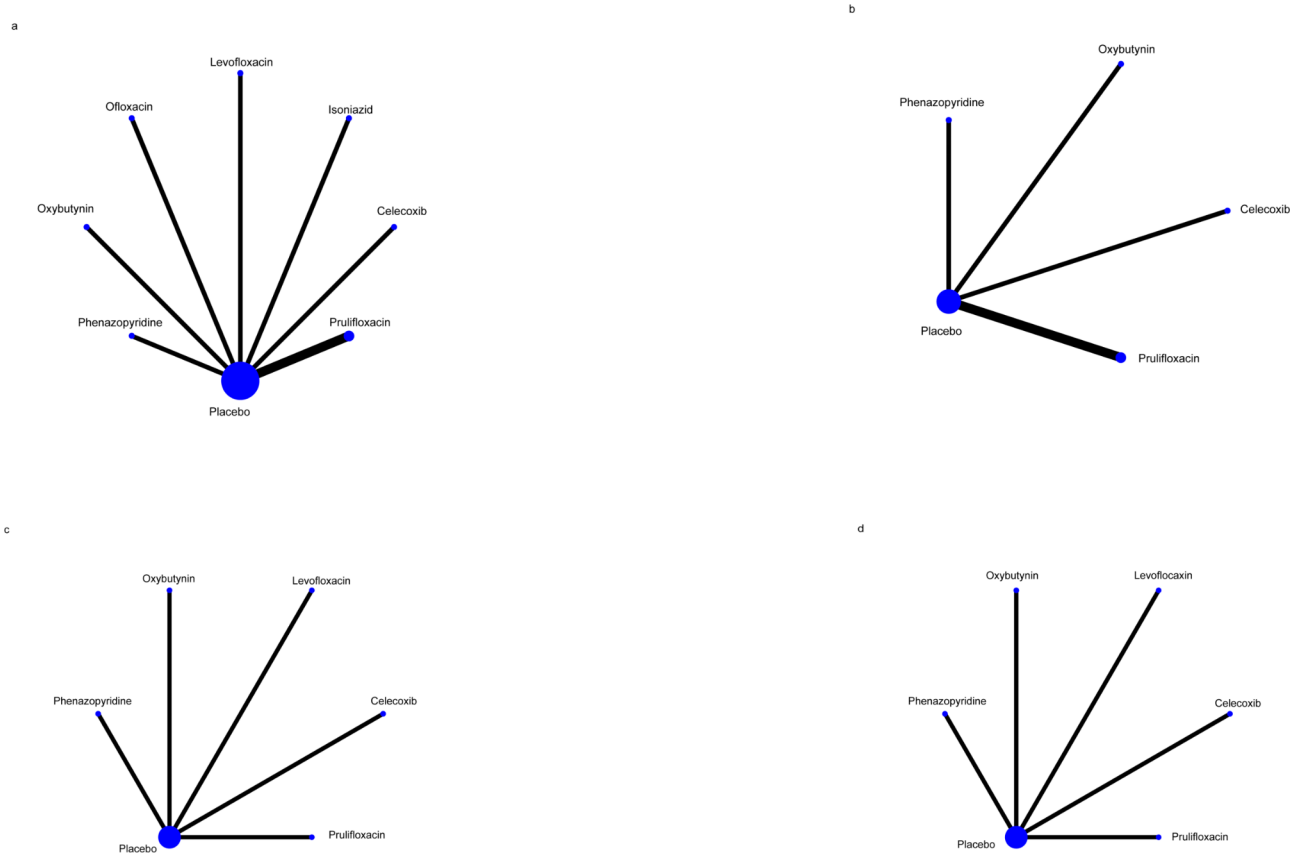

Fig. 4 Network constructions for comparison of the incidence of LUTS, frequency (**a**), urgency (**b**), pelvic pain (**c**), and dysuria (**d**)

Table 2 Pairwise comparisons of each intervention for the LUTS (bottom-left for frequency and top-right for urgency)

Celecoxib	**NA**	**NA**	**NA**	**282.82 (10.94.,7213.64)**	**0.00 (0.00,0.09)**	**0.04 (0.04,1.08)**	**0.71 (0.20,2.50)**
23.04 (1.08,489.72)	**Isoniazid**	NA	NA	NA	NA	NA	NA
1.60 (0.51,5.03)	0.07 (0.00,1.81)	**Levofloxacin**	NA	NA	NA	NA	NA
1.57 (0.46,5.35)	0.07 (0.00,1.84)	0.98 (0.18,5.26)	**Ofloxacin**	NA	NA	NA	NA
2.52 (0.72,8.80)	0.11 (0.00,2.97)	1.58 (0.29,8.60)	1.60 (0.28,9.22)	**Oxybutynin**	1.00 (0.01,99.47)	12.27 (0.13,1190.95)	201.07 (6.15,6574.61)
13.16 (0.60,290.09)	0.57 (0.01,44.17)	8.23 (0.30,222.97)	8.37 (0.30,232.98)	5.23 (0.19,147.04)	**Phenazopyridine**	12.27 (0.13,1190.95)	201.07 (6.15,6574.61)
23.04 (1.08,489.72)	1.00 (0.01,75.37)	14.42 (0.55,377.30)	14.65 (0.54,394.34)	9.15 (0.34,248.91)	1.75 (0.02,135.51)	**Placebo**	16.38 (0.52,518.52)
1.41 (0.47,4.28)	0.06 (0.00,1.58)	0.88 (0.18,4.36)	0.90 (0.17,4.68)	0.56 (0.11,2.99)	0.11 (0.00,2.87)	0.06 (0.00,1.58)	**Prulifloxacin**

Table 3 Pairwise comparisons of each intervention for the LUTS (bottom-left for pelvic pain and top-right for dysuria)

Celecoxib	**0.15 (0.01,2.80)**	**0.75 (0.07,7.68)**	**1.73 (0.23,13.20)**	**0.36 (0.02,5.38)**	**1.25 (0.29,5.47)**
6.50 (0.36,118.33)	**Levofloxacin**	4.86 (0.09,275.01)	11.23 (0.23,537.29)	2.36 (0.03,199.27)	8.12 (0.27,246.61)
1.34 (0.13,13.74)	0.21 (0.00,11.65)	**Oxybutynin**	2.31(0.27,19.57)	0.49 (0.01,20.01)	1.67 (0.13,21.37)
0.58 (0.08,4.43)	0.09 (0.00,4.26)	0.43 (0.05,3.66)	**Phenazopyridine**	0.21 (0.01,7.23)	0.72 (0.07,7.11)
2.75 (0.19,40.68)	0.42 (0.01,35.67)	2.06 (0.05,84.55)	4.75 (0.14,163.19)	**Placebo**	3.44 (0.15,80.24)
0.80 (0.18,3.50)	0.12 (0.00,3.74)	0.60 (0.05,7.64)	1.38 (0.14,13.58)	0.29 (0.01,6.79)	**Prulifloxacin**

Dysuria

The dysuria analysis was based on four studies and the network construction is shown in Fig. 3d. All the interventions were effective in reducing dysuria. The outcomes of pairwise comparisons are shown at top-right of Table 3. According to the SUCRA results (Fig. 5d), prulifloxacin was the highest-ranked treatment for urgency (SUCRA = 34.2%), followed by celecoxib (SUCRA = 34.9%), phenazopyridine (SUCRA = 35.9%), oxybutynin (SUCRA = 50.2%) and levofloxacin (SUCRA = 67.0%). The SUCRA of placebo was 77.7%.

Discussion

BCG-induced LUTS are both common and debilitating. In some cases, the severity of these symptoms could lead to the discontinuation of the planned treatment, thus worsening the oncological outcomes of patients [30]. Moreover, BCG-induced LUTS seems to be an important factor associated with the impaired quality of life (QoL) in these patients [31].

The mechanisms underlying BCG-induced LUTS have yet to be determined and multiple elements are likely to be present. Mechanisms such as the sensitization of bladder afferents, direct interactions between BCG and sensory afferents, urothelial permeability and inflammation are considered to be involved [16]. Among these mechanisms, exaggerated sensory signaling from the bladder is considered to be a major contributing factor, which is caused by subsequent peripheral afferent sensitization [16]. The other three mechanisms ultimately lead to varying degrees of sensitization of the afferent nerves [32–34]. During pathophysiological states, bladder afferents generate increased input into the central nervous system for lower bladder volumes, leading to exaggerated bladder sensations and bladder dysfunction, which ultimately leads to the LUTS [35]. The management of BCG-induced LUTS is key aspect for ensuring treatment compliance and improving bladder cancer survivorship. However, there are no specific guidelines for the management of BCG-induced LUTS outlined by the AUA. The EAU recommended the use of anticholinergics including oxybutynin, paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) [3]. However, there is limited clinical evidence to support these guidelines and no obvious clinical consensus on which intervention offers the best outcomes.

The available data on the relative efficacy of various interventions are scarce because of the lack of published

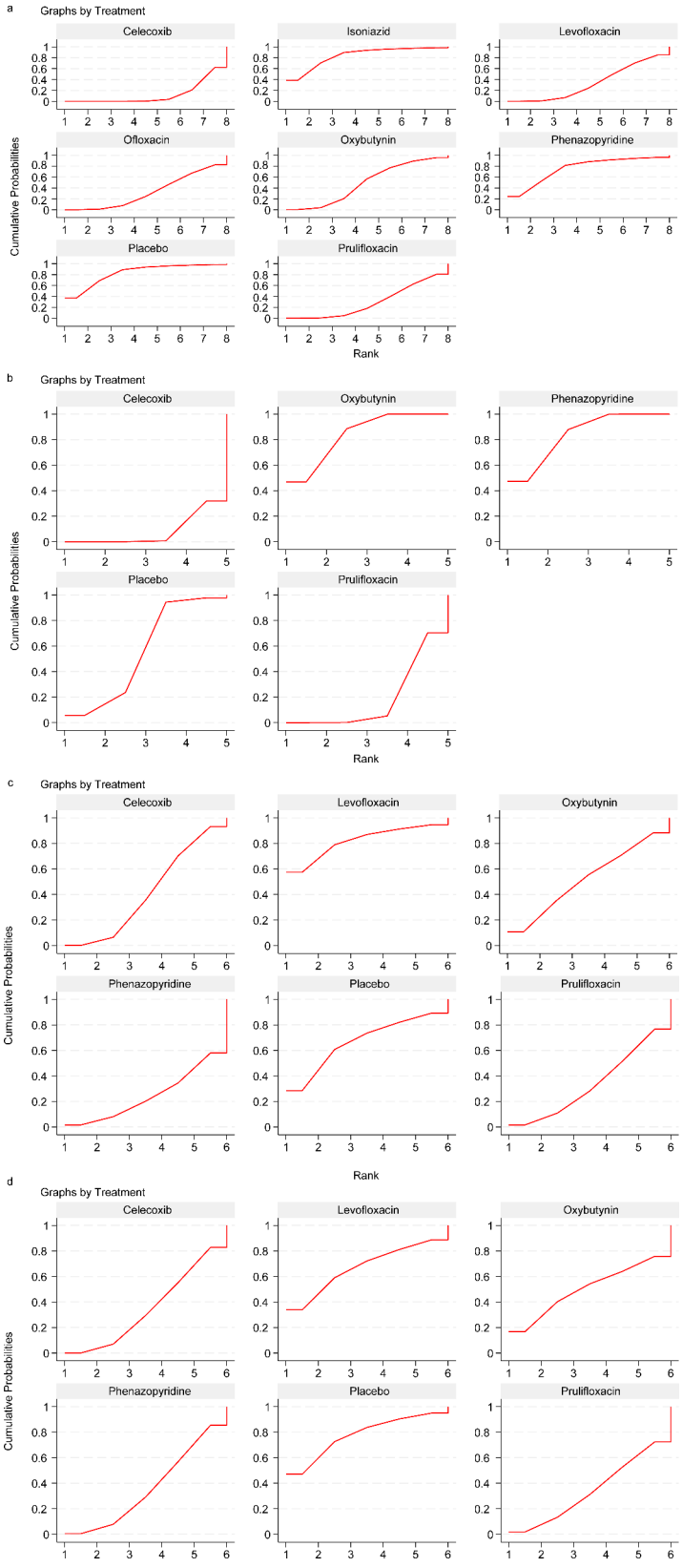

Fig. 5 Cumulative ranking probability for the incidence of LUTS, frequency (**a**), urgency (**b**), pelvic pain (**c**), and dysuria (**d**)

studies that directly compare them. To compare multiple interventions, NMA was developed using direct comparisons of interventions among trials and indirect comparisons across RCTs [36, 37]. Hence, this systematic review and NMA assessed the efficacy of a range of medications for BCG-induced LUTS.

In our analysis, we found that for various aspects of LUTS, the effects of the intervention measures were not the same. In terms of improving symptoms of frequency and urgency, celecoxib ranked first on the basis of the SUCRA and caused a significant reduction in the odds of fever compared with the placebo group [29]. As a class of COX-2 selective NSAIDs, celecoxib is widely used in clinical practice because of its 3 A properties (Analgesic-Antipyretic-Anti-inflammatory) [38]. In addition, celecoxib have been identified as a potential player in the cellular dynamics of cancer treatment [39], and research has gradually revealed that celecoxib has therapeutic effects on some malignant tumors including bladder cancer and prostate cancer [40, 41]. However, the antitumor effect of celecoxib in bladder instillation therapy still needs further research.

Prulifloxacin ranked second accroding to the SUCRA in terms of improving symptoms of frequency and urgency. Prulifloxacin is a new fluoroquinolone antibacterial agent with a broad spectrum of activity. Fluoroquinolones are presently considered an important tools in the management of BCG-related toxicity. In our study, levofloxacin and ofloxacin also had therapeutic effects on BCG-induced LUTS. It was previously reported that in a mouse model, fluoroquinolones had a beneficial effect on primary systemic BCG infections and that administering fluoroquinolones during an intravesical treatment course did not affect the antitumour efficacy of BCG [42]. Moreover, it was reported that commonly used antibiotics exhibit significant dose-dependent toxicity against bladder cancer cells at concentrations achievable in the urine after oral administration [43]. Thus, antibiotics might prove beneficial in preventing the seeding of exfoliated cancer cells after TURBT, thereby decreasing tumor recurrence rates. However, whether fluoroquinolone drugs will affect the antitumor effect of BCG instillation still requires further research.

Phenazopyridine showed the best performance in improving pelvic pain. Celecoxib and prulifloxacin also had good therapeutic effects. Phenazopyridine is an over-the-counter available urinary analgesic that provides symptomatic relief of pain caused by LUTS [44]. It is now generally accepted that phenazopyridine has no significant bactericidal activity. Despite the long and extensive use of phenazopyridine, the mechanisms underlying its analgesic effects of phenazopyridine are largely elusive and its molecular targets in the LUTS remain unknown [45]. TRPM8 inhibition may underlie the analgesic activity of phenazopyridine according to the latest research [46]. Although long-term follow-up results are lacking, phenazopyridine, owing to its mechanism of action not involving antimicrobial activity, should theoretically not affect the antitumor effects of the BCG bladder instillation. As the efficacy of BCG is tied to the development of inflammation, and the LUTS side effects of BCG are sensory, directly targeting the peripheral ends of bladder-innervating sensory nerves without impacting the critical components of BCG-induced inflammation is an attractive target for preventing BCG-induced LUTS. Nevertheless, there is a significant shortage of precisely managed studies that have examined the specific targeting of sensory nerves innervating the bladder, which become hyperresponsive during BCG-induced LUTS. The most extensively studied related drug at present is phenazopyridine exactly.

Prulifloxacin ranked first and celecoxib ranked second based on the basis of he SUCRA in terms of improving symptoms of dysuria. Although they have different mechanisms of action, celecoxib and prulifloxacin both effectively improve symptoms including frequency, urgency and dysuria. This means that the routine application of these two drugs may yield benefits.

Our study had certain limitations. First, a relatively small number of patients were included in the study. We will continue to follow the latest RCTs, allowing us to comprehensively address this limitation comprehensively in the future. Second, the included studies exhibited heterogeneity, with differing assessments of outcome measures, and the treatment times and dosages of various drugs were also not uniform. On the one hand, the mechanisms underlying BCG-induced LUTS have yet to be determined and multiple elements are likely to be present, therefore, drugs with various mechanisms of action may all have potential therapeutic benefits. On the other hand, and most importantly, current research on this issue is relatively fragmented, with only a small number of studies existing for any single mechanism of action, thus making it impossible to conduct a more precise comparison. When the mechanisms of related complications are further elucidated in the future, or when a sufficient number of studies on any drug have been accumulated, further research can then be conducted. Third, many studies lacked long-term follow-up data, resulting in the prognostic impact of the medications on BCa remaining unclear.

Conclusion

In conclusion, BCG immunotherapy remains the gold standard treatment for high-risk NMIBC after TURBT, and the resulting irritation symptoms are presently the primary factor influencing patient compliance and therapeutic effects. The NMA results indicated that

celecoxib and prulifloxacin effectively improved BCG-induced LUTS including frequency, urgency and dysuria. Phenazopyridine showed the best performance in improving pelvic pain. Whether fluoroquinolone drugs like prulifloxacin will affect the antitumor effect of BCG instillation still requires further research.

Abbreviations

BCG	Bacillus Calmette-Guerin
NMIBC	Non-muscle invasive bladder cancer
LUTS	Lower urinary tract symptoms
BCa	Bladder cancer
TURBT	Transurethral resection of bladder tumor
NMA	Network meta-analysis
RCTs	Randomized controlled trials
SUCRA	Surface under cumulative ranking curves
AUA	American urological association
EAU	European association of urology

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Author contributions
Conception: CZH and LDC; study design: YC and CX; data collection: CZH and CX; data analysis: CZH and JJG; manuscript editing: All authors.The author(s) read and approved the final manuscript.

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Data availability
The datasets analyzed during the current study are available in the public databases PubMed, Embase, Cochrane Library, and Web of Science.The data from the 6 studies included can be traced and accessed via the DOIs provided in the references section of our manuscript.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All the authors agreed to publish the article.

Competing interests
The authors declare no competing interests.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209–49.
2. Halaseh SA, Halaseh S, Alali Y, Ashour ME, Alharayzah MJ. A Review of the Etiology and Epidemiology of Bladder Cancer: All You Need To Know. Cureus. 2022;14:e27330.
3. Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). Eur Urol. 2022;81:75–94.
4. Compérat E, Larré S, Roupret M, Neuzillet Y, Pignot G, Quintens H, et al. Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. Virchows Arch. 2015;466:589–94.
5. Lenis AT, Lec PM, Chamie K, Mshs MD. Bladder Cancer: Rev JAMA. 2020;324:1980–91.
6. Morales A, Eidinger D, Bruce AW. Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol. 1976;116:180–3.
7. Jiang S, Redelman-Sidi G. BCG in Bladder Cancer Immunotherapy. Cancers. 2022;14:3073.
8. Kamat AM, Flaig TW, Grossman HB, Konety B, Lamm D, O'Donnell MA, et al. Consensus statement on best practice management regarding the use of intravesical immunotherapy with BCG for bladder cancer. Nat Rev Urol. 2015;12:225–35.
9. Unsworth-White SR, Kitchen MO, Bryan RT. Immunotherapy for non-muscle-invasive bladder cancer: from the origins of BCG to novel therapies. Future Oncol. 2022;18:105–15.
10. Nargund VH, Tanabalan CK, Kabir MN. Management of Non–Muscle-Invasive (Superficial) Bladder Cancer. Semin Oncol. 2012;39:559–72.
11. Witjes JA, Palou J, Soloway M, Lamm D, Kamat AM, Brausi M, et al. Current clinical practice gaps in the treatment of intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC) with emphasis on the use of bacillus Calmette-Guérin (BCG): results of an international individual patient data survey (IPDS). BJU Int. 2013;112:742–50.
12. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol. 2000;163:1124–9.
13. Sylvester RJ, Brausi MA, Kirkels WJ, Hoeltl W, Calais Da Silva F, Powell PH, et al. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guérin, and bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol. 2010;57:766–73.
14. Akaza H, Koiso K, Ozono S, Kuroda M, Kameyama S, Okajima E, et al. A clinical study of PMCJ-9 (Bacillus Calmette-Guérin Connaught strain) treatment of superficial bladder cancer and carcinoma in situ of the bladder. Jpn J Clin Oncol. 2003;33:382–90.
15. Macleod LC, Ngo TC, Gonzalgo ML. Complications of intravesical bacillus calmette-guérin. Can Urol Assoc J J Assoc Urol Can. 2014;8:E540–544.
16. Bourlotos G, Baigent W, Hong M, Plagakis S, Grundy L. BCG induced lower urinary tract symptoms during treatment for NMIBC-Mechanisms and management strategies. Front Neurosci. 2023;17:1327053.
17. Pichler R, Stäblein J, Mari A, Afferi L, D'Andrea D, Marcq G, et al. Treating BCG-Induced Cystitis with Combined Chondroitin and Hyaluronic Acid Instillations in Bladder Cancer. J Clin Med. 2024;13:2031.
18. Zeng S, Yu X, Ma C, Zhang Z, Song R, Chen X, et al. Low-Dose Versus Standard Dose of Bacillus Calmette-Guerin in the Treatment of Nonmuscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. Med (Baltim). 2015;94:e2176.
19. Erdoğar N, Iskit AB, Eroğlu H, Sargon MF, Mungan NA, Bilensoy E. Antitumor Efficacy of Bacillus Calmette-Guerin Loaded Cationic Nanoparticles for Intravesical Immunotherapy of Bladder Tumor Induced Rat Model. J Nanosci Nanotechnol. 2015;15:10156–64.
20. Watt J, Del Giovane C. Network Meta-Analysis. Methods Mol Biol Clifton NJ. 2022;2345:187–201.
21. Daly C, Soobiah C. Software to Conduct a Meta-Analysis and Network Meta-Analysis. Methods Mol Biol Clifton NJ. 2022;2345:223–44.
22. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.
23. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:ED000142.
24. Numakura K, Kobayashi M, Ishida T, Okane K, Suzuki K, Shimoda N, et al. Effect of Levofloxacin on the Efficacy and Adverse Events in Intravesical Bacillus Calmette-Guerin Treatment for Bladder Cancer: Results of a Randomized, Prospective, Multicenter Study. Eur Urol Focus. 2022;8:1666–72.
25. Al Khalifa M, Elfving P, Månsson W, Colleen S, Hellsten S, Duchek M, et al. The effect of isoniazid on BCG-induced toxicity in patients with superficial bladder cancer. Eur Urol. 2000;37(Suppl 1):26–30.
26. Colombel M, Saint F, Chopin D, Malavaud B, Nicolas L, Rischmann P. The effect of ofloxacin on bacillus calmette-guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. J Urol. 2006;176:935–9.

27. Damiano R, De Sio M, Quarto G, Di Lorenzo G, Perdonà S, Palumbo IM, et al. Short-term administration of prulifloxacin in patients with nonmuscle-invasive bladder cancer: an effective option for the prevention of bacillus Calmette-Guérin-induced toxicity? BJU Int. 2009;104:633–9.
28. Serretta V, Ruggirello A, Giaimo R, Sommatino F, Billone V, Allegro R, et al. [Prevention of topic toxicity of BCG with single-dose prulifloxacin. Preliminary results of a randomized pilot study]. Urologia. 2010;77:240–7.
29. Kamali K, Nikbakht J, Ayubi E, Nabizadeh M, Sarhadi S. Comparison of the Efficacy of Oxybutynin, Phenazopyridine, Celecoxib, and Placebo in the Treatment of Urinary Tract Symptoms after BCG Therapy in Patients with Bladder Tumors. Urol J. 2020;18:439–44.
30. Petca R-C, Popescu R-I, Toma C, Dumitrascu MC, Petca A, Sandru F, et al. Chemical hemorrhagic cystitis: Diagnostic and therapeutic pitfalls (Review). Exp Ther Med. 2021;21:624.
31. Wei L, Li Q, Liang H, Jianbo L. The quality of life in patients during intravesical treatment and correlation with local symptoms. J Chemother Florence Italy. 2014;26:165–8.
32. Simons MP, O'Donnell MA, Griffith TS. Role of neutrophils in BCG immunotherapy for bladder cancer. Urol Oncol. 2008;26:341–5.
33. Grundy L, Caldwell A, Lumsden A, Mohammadi E, Hannig G, Greenwood Van-Meervald B, et al. Experimentally Induced Bladder Permeability Evokes Bladder Afferent Hypersensitivity in the Absence of Inflammation. Front Neurosci. 2020;14:590871.
34. Ruhl CR, Pasko BL, Khan HS, Kindt LM, Stamm CE, Franco LH, et al. Mycobacterium tuberculosis Sulfolipid-1 Activates Nociceptive Neurons and Induces Cough. Cell. 2020;181:293–e30511.
35. Yoshimura N, Oguchi T, Yokoyama H, Funahashi Y, Yoshikawa S, Sugino Y, et al. Bladder afferent hyperexcitability in bladder pain syndrome/interstitial cystitis. Int J Urol Off J Jpn Urol Assoc. 2014;21(Suppl 1 0 1):18–25.
36. Li T, Puhan MA, Vedula SS, Singh S, Dickersin K. Ad Hoc Network Meta-analysis Methods Meeting Working Group. Network meta-analysis-highly attractive but more methodological research is needed. BMC Med. 2011;9:79.
37. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004;23:3105–24.
38. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol. 2020;180:114147.
39. Cao Y, Prescott SM. Many actions of cyclooxygenase-2 in cellular dynamics and in cancer. J Cell Physiol. 2002;190:279–86.
40. Woolbright BL, Pilbeam CC, Taylor JA. Prostaglandin E2 as a therapeutic target in bladder cancer: From basic science to clinical trials. Prostaglandins Other Lipid Mediat. 2020;148:106409.
41. Saxena P, Sharma PK, Purohit P. A journey of celecoxib from pain to cancer. Prostaglandins Other Lipid Mediat. 2020;147:106379.
42. Durek C, Jurczok A, Werner H, Jocham D, Bohle A. Optimal treatment of systemic bacillus Calmette-Guérin infection: investigations in an animal model. J Urol. 2002;168:826–31.
43. Kamat AM, Lamm DL. Antitumor activity of common antibiotics against superficial bladder cancer. Urology. 2004;63:457–60.
44. Hill JR, Isom-Batz G, Panagopoulos G, Zakariasen K, Kavaler E. Patient perceived outcomes of treatments used for interstitial cystitis. Urology. 2008;71:62–6.
45. Amábile-Cuevas CF, Arredondo-García JL. Nitrofurantoin, phenazopyridine, and the superoxide-response regulon soxRS of Escherichia coli. J Infect Chemother Off J Jpn Soc Chemother. 2013;19:1135–40.
46. Luyts N, Daniluk J, Freitas ACN, Bazeli B, Janssens A, Mulier M, et al. Inhibition of TRPM8 by the urinary tract analgesic drug phenazopyridine. Eur J Pharmacol. 2023;942:175512.

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