What is the risk of peripheral neuropathy with nitrofurantoin (MACROBID)?

BOTTOMLINE

- **Nitrofurantoin-associated peripheral neuropathy** is rare & has been reported in both cystitis tx and prophylaxis settings. Majority of cases are reported in patients receiving therapy for longer than 5 days (recommended duration for cystitis tx[IDSA]).
- The absolute incidence of nitrofurantoin-associated peripheral toxicity is unknown due to limited data (e.g., reporting of exposure, comorbidities). Based on **health region/authority-level cohort data** the risk of peripheral neuropathy is **neutral to 1 case in 200** nitrofurantoin courses (average duration 7-9 days). Based on **population-level pharmacovigilance data** the risk of peripheral neuropathy is **1 case in ~150,000** nitrofurantoin courses (average duration not reported). Risk appears greater as age increases.
- **If Rxing nitrofurantoin for acute cystitis treatment:** Instruct patient to report tingling, prickling, numbness or abnormal sensations in the extremities.
- Nitrofurantoin is **not recommended** as 1st line therapy for recurrent cystitis prophylaxis due to the risk of adverse events, including peripheral neuropathy, which can lead to permanent impairment in chronic users (see also: RxFiles Risk of Pulmonary Toxicity with Nitrofurantoin Q&A). **If prescribing nitrofurantoin for recurrent cystitis prophylaxis:** Instruct patient to report tingling, prickling, numbness or abnormal sensations in the extremities. Reassess nitrofurantoin's indication at **6**-12 month. Stop nitrofurantoin if the patient develops a UTI while on prophylaxis.
- **If you suspect neuropathy**: Discontinue nitrofurantoin. May trial neuropathic pain agents to treat symptoms.

BACKGROUND[1-17]

- While there is extensive clinical experience with nitrofurantoin, its overall safety profile is somewhat unclear, as it was approved by the FDA in 1953 prior to robust drug development requirements. Safety data is largely observational with limitations of confounding & selection bias.
- Nitrofurantoin's monograph includes a serious warning regarding the potential risk of **peripheral neuropathy**.[1]
- **Clinical presentation**: variable; however, generally paresthesia (tingling, pricking, or numbness) and dysesthesia (abnormal sensation), usually bilateral and affecting the extremities (glove & stocking distribution) which progresses proximally with eventual muscle weakness and wasting; patients may also have decreased deep tendon reflexes and motor/sensory deficits.
    - In severe cases, there may be interstitial tissue edema, demyelination of peripheral nerve fibers, and changes in the spinal cord.
- **Prognosis**: resolution of symptoms more likely if non-severe muscle weakness symptoms.[1]
    - If severe symptoms, resolution of symptoms may be partial; however, if nitrofurantoin is stopped before symptoms become severe some patients may experience complete resolution.[2]
- **Mechanism of toxicity**: primarily axonal loss; however, the exact mechanism unknown. Theories include:[3]
    - Nitrofurantoin inhibition of acetyl coenzyme A synthesis.
    - Accumulation of nitrofurantoin metabolites (e.g., semicarbazides [produces polyneuropathy in rats]).
- **Risk factors for toxicity**: largely unknown due to small number of reported cases.
    - ? Renal impairment: patients with a low CrCl are at a theoretical ↑ risk of peripheral neuropathy due to decreased renal clearance (and tx failure due to decreased nitrofurantoin urine concentration); however, there are reports of peripheral neuropathy in patients with both normal AND abnormal renal function.[4,5]
        - Previously, nitrofurantoin was contraindicated in patients with < CrCl <60 mL/min; however, updated Beers Criteria for potentially inappropriate medication use have **revised this threshold to <30** mL/min based on efficacy & safety data of n=2 retrospective studies (see Geerts & Bains et al. in literature review section-cystitis treatment). AGS 2015 (strong recommendation, low quality of evidence)
    - ? Others: electrolyte imbalance, anemia, diabetes mellitus, vitamin B deficiency, or debilitating disease.[1]
- Nitrofurantoin is recommended 1st line for treatment of acute uncomplicated cystitis (MACROBID 100 mg PO BID x 5 days or nitrofurantoin 50 mg PO QID x 5 days).[IDSA 2011 (A-I, strong recommendation based on high quality evidence)]
    - Uncomplicated cystitis is typically defined as cystitis in premenopausal, non-pregnant ♀ with no known urological abnormalities or comorbidities.
- In recurrent cystitis (≥2 UTIs in 6 months or ≥3 UTIs in 12 months), reserve nitrofurantoin prophylaxis due to risk of AEs.
    - The Beers Criteria for potentially inappropriate medication use recommends avoiding long-term nitrofurantoin for cystitis prophylaxis in patients ≥ 65 yrs due to potentially irreversible peripheral neuropathy concerns.[AGS 2015 (strong recommendation, low quality of evidence)]
    - TMP/SMX or TMP are 1st line tx options for recurrent cystitis (other options include cephalexin, FQs, or fosfomycin).

LITERATURE REVIEW [2,3,18-29]

There are **no** reports of nitrofurantoin-associated peripheral toxicity for cystitis treatment or prophylaxis in controlled trials.[18,19] Below is a sampling of observational trials reporting nitrofurantoin-associated peripheral toxicity cases (priority given to larger studies & those reporting renal function or prognosis).

Cystitis Treatment

Synopsis: Nitrofurantoin is recommended 1st line for cystitis treatment. No cases in controlled trials and minimal cases reported in observational trials when used for ≤ 5 days (range 3-28 days), including patients with reduced renal function and elderly patients.

Hutter et al. 2015: meta-analysis of controlled trials (N=27 trials [N=24 RCTs], n=4807) assessing lower UTI treatment
- nitrofurantoin (≤ 14 days) for vs. active comparator/placebo: no peripheral toxicity events

Comments: majority of trials were conducted 1970-90s & poor quality (Cochrane risk of bias tool); AMSTAR score 5/11.

Author	Methodology	Results
Ingalsbe et al. 2015	Design: single-arm cohort Case definition: **males** with cystitis Rxed nitrofurantoin (pyelonephritis and prostatitis excluded) Data source: VA Western New York Healthcare System; 2004-13; 7 d follow up after tx completion	n=801 patients treated with MACROBID 100 mg PO BID x ~9 d -73 yr; **0%** ♀ ; CrCl 66 ±27 mL/min; neuropathy 18%; n=4 (0.5%) cases of peripheral neuropathy -**n=2 CrCl <40; n=1 CrCl 40-59; n=1 CrCl ≥60** mL/min **Prognosis**: NR Note: study is **not** reflective of acute, uncomplicated cystitis as **males** were studied.
Geerts et al. 2013	Design: population-level, cohort Case definition: adult ♀ with UTI txed with nitrofurantoin for 3-9 d Data source: Dutch database (community pharmacy, GP, hospital); 2005-10	n=21,317 patients treated with nitrofurantoin for 3-9 days -48 yr (18-103 yr); 100% ♀; 4% DM; 80% tx duration 4-5 days; **eGFR 83** mL/min/1.73m^2 (**9-200** mL/min/1.73m^2); **0.9% eGFR <50** mL/min/1.73m^2; **82% unknown eGFR** n=0 cases of peripheral neuropathy
Bains et al. 2009	Design: single-arm cohort Case definition: patients with cystitis treated with nitrofurantoin Setting: Vancouver Island Health Authority; 2004-08; 7 d follow up after tx completion	n=356 patients treated with MACROBID 100 mg PO BID x ~7 d - ~75 yr (4-103 yr); 75% ♀; 12% previous neuralgia; 9% DM; **36% impaired renal function 40** mL/min (**15-50** mL/min) n=0 cases of peripheral neuropathy
Rubenstein et al. 1964	Design: case series Case definition: peripheral neuropathy associated with nitrofurantoin Setting: Duke University Medical Center; 1959-63	n=5 cases of peripheral neuropathy -41 to 68 yr; 60% ♀; nitrofurantoin 300-400 mg/d; tx duration 10-28 d; **n=4 "history of CKD" (CrCl/SCr NR)** **Prognosis**: n=1 complete recovery at 6 mos; n=2 improvement in muscle strength/sensory; n=1 persistent weakness of lower extremities; n=1 fatal (reason NR)

Cystitis Prophylaxis

Synopsis: Nitrofurantoin in NOT currently recommended 1st line for cystitis prophylaxis due to risk of harms, which may be non-reversible. No cases in controlled trials and minimal cases reported in the following observational trials, including patients with reduced renal function and elderly patients.

Muller et al. 2016: systematic review of trials assessing nitrofurantoin for UTI prophylaxis
- controlled trials (N=17, n=511 patients); average prophylaxis duration 6 mos (3-24 mos): no peripheral neuropathy cases
- observational trials (N=16, n=NR); population-level, single-arm cohort studies; while peripheral neuropathy was noted, this AE was comined with with other AEs to determine estimated frequency.

Comments nitrofurantoin duration NR; majority included trials actually studied potentially both tx & prophylaxis population (e.g., D'Arcy below).

- Not included in Muller et al.: population-level cohort (single arm) based on national (Finland), pharmacovigilance data; 1976-85; no serious life-threatening reactions (peripheral neuropathy not specifically repoted) in n=1,023 patients <16 yrs with 3 UTIs previous 6 months receiving nitrofurantoin prophylaxis (avg 2 courses/patient; mean course duration was 316 d).[23]

Price et al. 2016: meta-analysis of RCTs (N=12, n=1063) assessing UTI prophylaxis
- nitrofurantoin (≥ 6 mos) for vs. active comparator: no peripheral neuropathy cases

Comments: majority of trials were conducted 1977-2007; 3/12 studies were rated as poor-fair quality; publication bias present (? presence of unpublished negative studies); AMSTAR score 9/11.

Author	Methodology	Results
Penn & Griffin 1982	Design: population level, single-arm cohort Case definition: AEs associated with nitrofurantoin Data source: voluntary, national (UK, 1964-80; Holland 1975-80) pharmacovigilance database	UK: n=455 total reports; n=64 (14%) reports of peripheral neuropathy Holland: n=88 total reports; n=8 (9%) reports of peripheral neuropathy Note: characteristics of cases were not reported

Cystitis Treatment & Prophylaxis

Author	Methodology	Results
Tan et al. 2012	Design: case series Case definition: peripheral neuropathy associated with nitrofurantoin Data source: Baltimore, Maryland; date of reports NR	n=2 cases of nitrofurantoin-associated peripheral neuropathy -53 to 59 yr; 100% ♀; **100% normal renal function (SCr/CrCl NR)**; n=1 cystitis treatment, nitrofurantoin x 1 week (dose NR); n=1 cystitis prophylaxis, nitrofurantoin 100 mg daily x 4 weeks **Prognosis**: n=1 partial resolution of sx at 3 y (treated with prednisolone & then gabapentin & duloxetine); n=1 significant improvement of sx, time of assessment NR (txed with duloxetine & transdermal fentanyl)
D'Arcy et al. 1985	Design: population level, single-arm cohort Case definition: nitrofurantoin courses associated with AEs Data source: manufacturer database (literature, clinical studies, & voluntary reports from practitioners/ regulatory authorities); 1953-84	n=121,430,000 nitrofurantoin courses n=847 cases of nitrofurantoin related neurological AEs -neurological reaction incidence: 1 in 143,365 *courses (~0.0007%)* Note 1: characteristics of cases were NR; incidence may be overestimated as study compared worldwide cases to US courses; however, may also be underestimated as some reliance on voluntary reports. Note 2: prevalence of peripheral neuropathy in general population is ~2,384 cases per 100,000 *people* (~2.4%).
Yiannikas et al. 1981	Design: case series Case definition: peripheral neuropathy associated with nitrofurantoin Data source: Australia	n=4 cases of nitrofurantoin-associated peripheral neuropathy -63 to 82 yr; 100% ♀; 100% recurrent UTI; duration of tx 7-336 d; total exposure 1.4-67 g; **SCr 20-230** umol/L **(n=2 cases abnormal renal function** [**SCr 150, 230** umol/L]); n=1 case with rxn onset after tx D/C **Prognosis**: n=1 fatal (pneumonia, sepsis); n=3 disability at 12 months
Holmberg et al. 1980	Design: case series Case definition: adverse events associated with nitrofurantoin Data source: voluntary, national (Sweden) pharmacovigilance database; 1966-76	n=921 reports of nitrofurantoin related adverse events -62 yr (range 0-95 yr); 86% ♀; 19% had previously received nitrofurantoin of which 55% had a previous nitrofurantoin related adverse event [type not reported]); 30% chronic/recurrent UTI, 2% asymptomatic bacteriuria; 68% indication not reported n=20 reports of nitrofurantoin-associated peripheral neuropathy -median dose 150 mg/d (20-200 mg/d); < 1 mon tx 45%; 1-12 mons tx 35% > 12 mons tx 5%; **n=4/12 patients had SCr** (**>106** umol/L) **Prognosis**: n=13 (65%) hospitalized; n=0 fatal cases
Tool & Parish 1973	Design: review of case series Case definition: peripheral neuropathy associated with nitrofurantoin Note: full text not available	n=137 cases of nitrofurantoin-associated peripheral neuropathy described in 58 reports **Prognosis**: (n=100 cases follow up, time of assessment N/A): n=45 partial regression of symptoms; n=34 total regression of symptoms; n=13 no change; n=8 fatal

Koch-Weser et al. 1971	Design: single-arm cohort Case definition: nitrofurantoin associated AEs in hospitalized pts Data source: Massachusetts General Hospital; 1967-68; 3 d follow up after tx completion	N= 757 cases of nitrofurantoin associated AEs -majority 45-64 yr (but included <15 to >74 yr); 80% cystitis treatment; **renal function not reported** n= 1 (0.13%) case of polyneuropathy **Prognosis**: not reported

UNCERTAINTIES

- **Diagnosis is challenging**, as clinical presentation is variable. Nitrofurantoin-associated peripheral neuropathy is considered a diagnosis of exclusion.
    - There may be a potential role for skin biopsy to aid in diagnosis as nitrofurantoin-associated peripheral neuropathy; however, further study is required.[3] Characteristic morphologic changes on biopsy include: clustered terminal nerve swelling without nerve fiber degeneration in n=2 cases.[3]
- **Monitor patients** for numbness, tingling, numbness or abnormal sensations.
- **If nitrofurantoin-associated peripheral toxicity is suspected, discontinue nitrofurantoin immediately.**
    - Unknown if corticosteroids are beneficial; conflicting reports & one case of sx rebound after steroid taper.[3,32]
    - Case reports of symptomatic benefit with the following agents: gabapentin, duloxetine, fentanyl.[3]

AE adverse event **BID** twice daily **CrCl** Creatinine Clearance **CKD**=chronic kidney disease **d**=days **eGFR** estimated glomerular filtration rate **DM** diabetes mellitus **FDA** Food and Drug Act **GP** general practitioner **h** hour **mon(s)** month(s) **NA** not available **NR** not reported **PO** oral **pts** patients **QID** four times daily **Rx** prescription **rxn** reaction **SCr** serum creatinine **sx** symptoms **TMP/SMX** cotrimoxazole or sulfamethoxazole/trimethoprim **tx** treatment **UK** United Kingdom **US** United States **UTI** urinary tract infection **VA** Veterans Affairs **Yr** year

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