Critical Review Form
Therapy

Pickard R, Starr K, MacLennan G, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. Lancet. 2015 Jul 25;386(9991):341-9.

Objectives: **"to establish whether tamsulosin or nifedipine increased the likelihood of spontaneous stone passage measured by the absence of need for further intervention and, if so, which was the better drug." (p. 342)**

Methods: **This multicenter, randomized, placebo-controlled trial was conducted at 24 hospitals in the UK. Patients aged 18-65 years with a single ureteral stone of 10 mm in size of less on CT scan were eligible for inclusion. Exclusion criteria included need for immediate intervention, sepsis, an estimated GFR < 30 mL/min, coexisting use of or contraindication to alpha-blockers or calcium channel blockers.**

Participants were randomized in a 1:1:1 fashion to take tamsulosin (400 µg daily), nifedipine (30 mg daily), or placebo until stone passage or 28 days, whichever came first.

Patients were followed by patient questionnaire completed at home at 4 and 12 weeks, as well as case report forms completed during clinic visits or by telephone interview at 4 and 12 weeks. The primary outcome was spontaneous stone passage within 4 weeks of randomization. Other outcomes included pain, number of days of analgesic use, time to stone passage (evaluated by the date of imaging showing no stone), health status (assessed using the Short Form (SF)-36 questionnaire), serious adverse effects, and discontinuation of drug due to adverse effects.

During the study, 1167 patients were randomized (391 to tamsulosin, 387 to nifedipine, and 389 to placebo). Of these, 17 were excluded due to ineligibility and 14 were lost to follow-up, leaving 1136 in the final analysis (378 in the tamsulosin group, 379 in the nifedipine group, and 379 in the placebo group).

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. "Participants were allocated in a 1:1:1: ratio to oral tamsulosin , nifedipine , or placebo by a remote

		randomisation system...using an algorithm with centre, stone size (≤ 5 mm or > 5 mm), and stone location (upper, mid, or lower ureter) as minimisation covariates." (p. 342)
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Uncertain. While the authors specify that a remote randomization system was used system was used, they do not provide any information regarding how allocation was concealed.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "We analyzed data for the primary outcome from the modified intention-to-treat population, which included all randomly assigned participants apart from those with missing primary outcome data and those who were found to be ineligible after randomisation." (p. 343)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients in all 3 groups were similar with respect to age, gender, proportion of patients with a history of a previous stone, duration of pain at time of presentation, stone size (dichotomized at 5 mm), stone location, and pain score.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. Yes. "Each randomly assigned participant was given 28 capsules of trial medication (over-encapsulated tamsulosin or nifedipine, or placebo) supplied by an independent source...who had no further involvement in the trial, ensuring that participants, clinicians, and trial personnel remained unaware of the allocated group." (p. 342)
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of group allocation?	No. For the primary outcome, stone passage was essentially determined by the patient, who was blinded to group allocation. Most other outcomes (pain, analgesic use, and SF-36 questionnaire results, were also evaluated by the patients themselves.
4.	Was follow-up complete?	Mostly yes. There was very little loss to follow-up, with primary outcome data available for all but 5 patients in the tamsulosin group (1.3%), 4 patients in the nifedipine

		group (1.0%), and 5 patients in the placebo group (1.3%). The 4-week questionnaire was completed by only 62% of eligible patients, and the 12-week questionnaire was completed by only 49% of eligible patients. There was no difference in the proportion of patients in each group who returned their questionnaires.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• There was no difference between the groups with regards to the primary outcome. 307 (81%) of 378 patients in the tamsulosin group, 304 (80%) of 379 patients in the nifedipine group, and 303 (80%) of 379 patients in the placebo group required no further intervention. o Tamsulosin vs. placebo: unadjusted OR 1.08 (95% CI 0.76 to 1.56) o Nifedipine vs. placebo: unadjusted OR 1.02 (95% CI 0.71 to 1.45) o Any medical expulsive therapy vs. placebo: unadjusted OR 1.04 (95% CI 0.77 to 1.43). o There was still no difference in outcome when adjustments were made for stone location, stone size, and study center. • There was no difference between the groups with regards to analgesic use, time to stone passage, or health status. • Adverse events were reported in 3 patients allocated to receive nifedipine and 1 patient receiving placebo. None of these was life threatening.
2.	How precise was the estimate of the treatment effect?	See above. The 95% CI did not cross 1 for any of the primary outcome assessments.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Likely yes. While the study was conducted in the UK, these were emergency department patients diagnosed with ureteral colic, and could be expected to be similar in most regards to patients with ureteral colic in the US. While all patients were diagnosed by CT, and at least some of our patients are diagnosed by ultrasound, it seems likely that the results would apply to both groups.
2.	Were all clinically important outcomes considered?	Yes. While the authors did not assess cost or patient satisfaction, they did assess quality of life and pain scores.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This study certainly suggests that routine use of MET in ureteral colic is not beneficial. However, there is some suggestion (in Figure 2) that tamsulosin

		may provide benefit to patients with larger stones (> 5 mm) and those with more distal stones. As only one fourth of patients in this study had larger stones, it may be worth further research to determine if patients with large, distal stones would benefit from tamsulosin.

Limitations:

1. **There is no information regarding how allocation concealment was maintained (e.g. sequential opaque envelopes).**

2. **It is unclear how patients determined whether stone passage had occurred. There is no mention of the use of urine strainers.**

3. **Approximately three-quarters of patients in the study had stones less than or equal to 5 mm in diameter. The study was likely underpowered to detect a benefit in patients with larger stones, particularly those with distal stones (although there was a trend toward benefit with tamsulosin for both subsets). There is still a possibility that this group of patients would benefit from MET (external validity).**

4. **It is possible that some patients may have had persistent stones that did not require intervention within 4 weeks.**

5. **The authors make no discussion of the limitations of their study, instead boasting that based on their results, further research would be "futile." Very arrogant indeed.**

Bottom Line:

This large, methodologically sound, randomized controlled trial performed at multiple centers in the UK found no benefit to either nifedipine or tamsulosin in the management of ureteral stones. They claim that this study provides a definitive answer, and that further research would be "futile" seems extremely arrogant and unfounded. Figure 2 in the paper demonstrates a trend toward benefit in patients with larger, distal stones, and further research into this subset of patients should be undertaken. For patients with small stones, it seems unlikely that there is any benefit to medical expulsive therapy.