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Review – Stone Disease

Medical Expulsive Therapy for Urinary Stones: Future Trends and Knowledge Gaps

Vincent De Coninck[a,*], *Jodi Antonelli*[b], *Ben Chew*[c], *Jacob M. Patterson*[d], *Andreas Skolarikos*[e], *Matthew Bultitude*[f]

[a] *Department of Urology, AZ Klina, Brasschaat, Belgium;* [b] *UT Southwestern Medical Center, Dallas, TX, USA;* [c] *Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada;* [d] *Department of Urology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK;* [e] *2nd Department of Urology, National and Kapodistiran University of Athens, Sismanogleio Hospital, Athens, Greece;* [f] *Urology Centre, Guy's and St. Thomas' NHS Foundation Trust, London, UK*

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Abstract

Context: Medical expulsive therapy (MET) for ureteral stones has become a controversial area due to the contradictory results of high-quality trials and meta-analyses.
Objective: We aimed to review the literature to evaluate the value of and future directions for MET for ureteral stone disease.
Evidence acquisition: A literature search of the MEDLINE database and the Cochrane Library was conducted to collect articles about MET for ureteral calculi published up to 28 October 2018. A total of 524 articles were screened. Sixty-nine publications that met the inclusion criteria for this review were chosen. Among the primary research articles on MET with stone clearance as the primary outcome, seven responded to high-quality requirements of Cochrane Collaboration's tool for assessing the risk of bias in randomised trials.
Evidence synthesis: The vast majority of randomised, double-blind, placebo-controlled trials without a high or an unclear risk of bias did not find a benefit of MET for increased ureteral stone passage rates. This is in contrast to results of meta-analyses that are skewed by low-quality trials.
Conclusions: The strength of evidence for the benefit of MET in ureteral stones is low, even for distal ureteral stones >5 mm. In the absence of further high-quality data, individual clinicians are required to decide for themselves whether to believe high-quality single trials or meta-analyses.
Patient summary: We evaluated the value of and future directions for medical expulsive therapy (MET) for ureteral stone disease. We found that outcomes varied between studies. Individual clinicians are required to decide for themselves which studies to believe. Alpha-blockers as MET may retain a role in a selective group of well-counselled patients with larger stones who understand the side effects and off-label use.
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* Corresponding author. Department of Urology, AZ Klina, Augustijnslei 100, Brasschaat 2930, Belgium.
E-mail address: vincent.de.coninck@klina.be (V. De Coninck).

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1. Introduction

Urolithiasis is a major health problem worldwide with increasing incidence and prevalence [1]. When ureteral stones are diagnosed, the management may consist of observation, drainage, shockwave lithotripsy (SWL), or ureteroscopy, depending on the clinical situation. The probability of spontaneous stone passage decreases with increasing stone size and location above the distal ureter [2,3].

If active treatment is not indicated, current international guidelines recommend medical expulsive therapy (MET) involving the administration of drugs to improve spontaneous stone passage and potentially avoid the need for surgical interventions [4–8]. MET for ureteral stones has become a controversial area due to the contradictory results of high-quality trials and meta-analyses [9–11]. Therefore, we aimed to review the literature to evaluate the value of and future directions for MET for ureteral stone disease.

2. Evidence acquisition

A literature search of the MEDLINE database (PubMed) and the Cochrane Library was conducted to collect articles about MET for ureteral calculi published up to 28 October 2018. The search terms "medical expulsive therapy", "urolithiasis", and "ureteral stones" were used, and the filters "English" and "humans" were applied. No time restriction was applied. For reviews and meta-analyses, priority was given to the latest publications as they include the most up-to-date individual studies. Older and additional articles identified through references lists were also included if they had genuine added value. After bibliographic search and removal of duplicates, a total of 524 articles were screened. Case reports and meeting abstracts were not considered eligible. Heterogeneity of outcomes in the primary research articles, reviews, and meta-analysis on MET was noticed. Additionally, unclear or high risks of selection, performance, detection, attrition, and reporting bias were noted in included trials. After full-text assessment of these articles (V.D.C.), and using the population, intervention, comparator, outcome (PICO) study design approach and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) standards, publications that met the inclusion criteria for this review were chosen (Fig. 1). Among the primary research articles on MET with stone clearance as the primary outcome, seven responded to high-quality requirements of Cochrane Collaboration's tool for assessing the risk of bias in randomised trials (Table 1) [12]. Placebo-controlled trials were considered of "high quality" if there were low risks of selection, performance, detection, attrition, and reporting bias. Meta-analyses were considered "recent" when published within the last 2 yr and included if genuine added value was provided. The coauthors agreed with the selection of included and excluded articles.

3. Evidence synthesis

3.1. *Modalities of MET*

3.1.1. *Alpha-blockers*

3.1.1.1. Scrutinisation of seven high-quality placebo-controlled trials. The first high-quality trial was reported by Hermanns et al [13] in 2009. They evaluated the expulsion rate of single distal ureteral stones ≤7 mm confirmed by computed tomography (CT). Ninety participants were randomised between tamsulosin and placebo groups. The mean stone size was 4.1 and 3.8 mm, respectively. The stone expulsion rate did not differ between the tamsulosin (86.7%) and placebo (88.9%) groups. The only reported advantage of

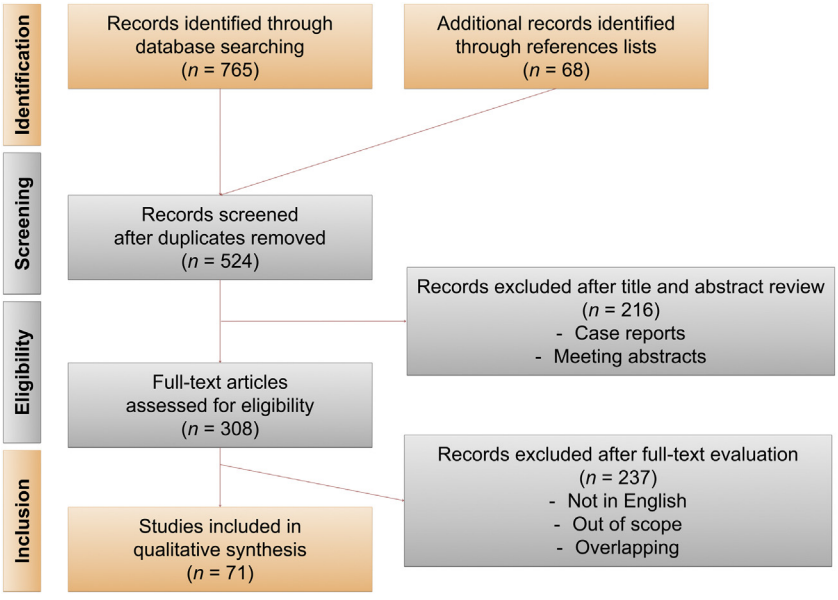

Fig. 1 – PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Table 1 – Risk of bias assessment of included studies.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdel-Meguid (2010) [33]	+	+	+	?	?	+	+
Agrawal (2009) [32]	?	?	?	?	+	+	+
Al-Ansari (2010) [30]	+	+	+	+	?	+	+
El-Gamal (2012) [34]	+	+	+	?	+	-	+
Furyk (2016) [17]	+	+	+	+	+	+	+
Hermanns (2009) [13]	+	+	+	+	+	+	+
Meltzer (2018) [10]	+	+	+	+	+	+	+
Ochoa-Gomez (2011) [26]	?	?	+	?	+	+	+
Pedro (2008) [27]	+	+	+	?	+	+	+
Pickard (2015) [15]	+	+	+	+	+	+	?
Sameer (2014) [29]	?	?	?	?	+	?	?
Sur (2015) [22]	+	+	+	+	+	+	+
Vincendeau (2010) [14]	+	+	+	+	+	+	+
Wang (2016) [28,42]	+	?	+	?	-	?	?
Ye (2011) [45]	+	+	-	+	+	+	+
Ye (2018) [18]	+	+	+	+	+	+	+

The symbol + indicates a low risk of bias, ? indicates an unclear risk of bias, and - indicates a high risk of bias.

tamsulosin was the decreased analgesic requirement until stone expulsion. There was no difference between groups regarding time to stone passage, but the exact time was not available for 32% of participants. Additionally, there was no difference on subgroup analyses comparing stone passage rates according to size (≤5 vs >5 mm); however, the study was underpowered to draw conclusions on this because 80% of the stones were ≤5 mm. Other limitations were the small study population and single-centre study design.

In 2010, Vincendeau et al [14] studied expulsion rates of radiopaque distal ureteral stones between 2 and 7 mm. One hundred twenty-two patients were randomised to receive either tamsulosin or placebo in five French centres. No difference was found after 42 d between the groups for spontaneous stone passage (77.0% vs 70.5%), time to stone expulsion (9.1 vs 10.1 d), stone size (2–3 vs 4–7 mm), pain relapse, first morphine administration, or time to surgery. Shortcomings of this study are the small stone sizes (mean 2.9 and 3.2 mm, respectively) and the absence of CT in all patients.

The controversy was ignited in 2015 with the large, multicentre, placebo-controlled, randomised controlled trial by Pickard et al [15]. They evaluated the effectiveness of nifedipine and tamsulosin in the Spontaneous Urinary Stone Passage Enabled by Drugs (SUSPEND) trial. They included 1136 patients with single ureteral stones ≤10 mm localised by CT from 24 UK centres. The primary outcome was spontaneous stone passage, defined as the lack of need for further intervention to facilitate stone passage at 4 wk. At this time point, stone passage did not differ between tamsulosin (81%), nifedipine (80%), and placebo (80%) groups. This remained unchanged after adjusting for stone location (lower, mid, or upper ureter) or stone size (≤5 or >5 mm). There was no evidence of differences either in quality-adjusted life years gained or in the cost between the trial groups over 12 wk, or for secondary outcomes. Shortcomings were the lack of mandated imaging to confirm stone passage, since this study was designed to mimic the real life and the majority (75%) of stones were smaller than 5 mm. It could be argued that with such small stones, a difference may not have been realised between the two groups as smaller stones already have such high spontaneous passage rates. Response rates were only 63% and 49% for the 4- and 12-wk participant questionnaires, respectively, and the time to stone passage data were available only for 237 (21%) participants. Medication adherence was not monitored. Based on the SUSPEND trial, Portis et al [16] prospectively evaluated the impact of tamsulosin removal from standardised ureteral stone clinical protocols on the rate of stone surgery in 723 patients. They concluded that the removal of tamsulosin actually increased the stone passage rate and decreased the overall surgery rate.

In 2016, Furyk et al [17] assessed the efficacy and safety of tamsulosin compared with placebo. A total of 316 patients with distal ureteral stones ≤10 mm were enrolled in five emergency departments in Australia. The primary outcomes were stone expulsion on CT at 28 d and time to stone expulsion. Stone passage was not significantly different between the tamsulosin (87.0%) and placebo (81.9%) groups. The median stone diameters were 4.0 and 3.7 mm, respectively. In an underpowered subgroup analysis of stones ≥5 mm, stone passage occurred more frequently with tamsulosin (83.3%) than with placebo (61.0%). There was no difference in urological interventions, time to self-reported stone passage, pain, analgesia requirements, or adverse events. Limitations of this study were the small number of stones ≥5 mm (n = 77), poor self-reported compliance, and lack of follow-up CT for 17% participants.

Ye et al [18] evaluated the efficacy and safety of tamsulosin in a double-blind, placebo-controlled study of 3296 patients with distal ureteral stones between 4 and 7 mm. Patients were recruited from outpatient departments across 30 Chinese centres. The primary outcome was overall stone expulsion rate (assessed by weekly noncontrast CT) over 28 d. They reported a higher stone expulsion rate for tamsulosin (86.4%) than for placebo (78.6%). The mean stone size was 5.8 and 5.7 mm, respectively. Subgroup analysis showed a benefit only for distal stones >5 mm (85.6% vs 74.5%) and not for smaller stones. Considering secondary outcomes, tamsulosin-treated patients had shorter time to expulsion, lower use of analgesics, and better recurrent renal colic relief. There were no differences in adverse events. Limitations of this study were that the population did not represent the acute stone population seen in other studies since the majority of stones (66.2%) were >5 mm. As well, patients with severe hydronephrosis were excluded from the trial. Selection bias may have occurred since the number of larger stones seemed to be overenrolled, which is inconsistent with the protocol described in the pretrial registry and the study design. Finally, discrepancies in overall recruitment numbers from the pretrial registry and the actual trial remained unexplained [19–21].

A double-blind, placebo-controlled trial using tamsulosin was published in 2018 by Meltzer et al [10]. They evaluated stone passage based on visualisation or capture by the study participants (487 patients) by day 28 at six US emergency departments. They found no difference in stone passage rates between the tamsulosin (49.6%) and placebo (47.3%) groups. No benefit of MET was observed by stone size (<5 vs ≥5 mm) or location (upper vs lower ureter). Higher rates of abnormal ejaculation were reported by male participants in the tamsulosin group. Limitations of the study are the low mean stone size (3.7–3.8 mm), with a corresponding low number of stones ≥5 mm (24.9–27.0%). In addition, only 238/403 (59.1%) patients in the main trial (phase 2) had confirmatory CT scans of stone passage, although no difference was detected between the two groups.

The only high-quality placebo-controlled trial on MET using an alpha-blocker other than tamsulosin was published by Sur et al [22] in 2015. The primary endpoint was spontaneous unilateral ureteral stone passage (4–10 mm) with silodosin 8 mg after 4 wk. Analysing 232 participants from 27 locations in the USA, the authors found no difference in stone passage rates between the silodosin (52%) and placebo (44%) groups. However, silodosin achieved a greater expulsion rate for distal ureteral stones in an unplanned subgroup analysis. Silodosin neither demonstrated a benefit for proximal or midureteral stones nor showed a difference for differing stone size (4–6 vs >6–10 mm), time to stone passage, emergency room visits, hospital admission, or use of analgesics. Adverse events including retrograde ejaculation, nausea, dizziness, headache, and nasal congestion were more common with silodosin. Study limitations include that the number of patients in the intent-to-treat population was below the calculated sample size (232 vs 240 participants) and that the sample sizes were not powered for subgroup analyses. In addition, CT was not performed in all participants and patients with severe hydronephrosis were excluded. Their conclusions support the use of silodosin in distal ureteral stones.

3.1.1.2. Recent meta-analyses. The most recent high-quality meta-analysis on MET was performed by Campschroer et al [9]. In this Cochrane study including 67 trials, the authors assessed the effects of alpha-blockers compared with standard therapy for ureteral stones ≤10 mm. Overall, they found that alpha-blockers increased stone clearance (risk ratio [RR] 1.45, 95% confidence interval [CI] 1.36–1.55). No difference was found among stone locations or different types of alpha-blockers (tamsulosin, alfuzosin, terazosin, naftopidil, and silodosin), indicating that this is likely a class effect. After including only 15 studies that were placebo controlled, stone clearance remained significant for alpha-blockers, but the treatment effect decreased (RR 1.16, 95% CI 1.07–1.25). The gap further narrowed (RR 1.09, 95% CI 1.06–1.13) when excluding trials with a high or an unclear risk of bias, and only five studies were eligible for analysis [13,14,17,18,22]. Interestingly, this benefit was determined only by the findings of Ye et al [18], since the other four studies did not find a difference in stone clearance between alpha-blockers and placebo. Moreover, the SUSPEND trial [15] (incomplete stone passage data) and the trial by Meltzer et al [10] (only abstract was available at the time of publication) were excluded from the high-quality sensitivity analysis. In the subgroup analyses, they found better stone clearance only for stones >5 mm and those located at the distal ureter. Based on two high-quality studies [13,18], they concluded that the dose of diclofenac used was statistically lower among participants using MET than among those using placebo. Furthermore, they concluded that although the treatment with alpha-blockers appeared to reduce time to stone expulsion, number of pain episodes (except with silodosin), and need for hospitalisation, it increased the risk of major adverse events. Curiously, this conclusion was based on all included trials, while their sensitivity analyses of high-quality trials did not show a difference for the former three outcomes.

Two other groups performed a meta-analysis of studies published before 2018 in which the efficacy of alpha-blockers for MET for ureteral stones ≤10 mm was investigated [23,24]. Despite substantial heterogeneity, both groups came to similar conclusions to those of Campschroer et al [9]. However, it is noteworthy that these groups were less strict when scrutinising studies with a low risk of bias and that they did not perform a sensitivity analysis of alpha-blockers versus placebo.

The meta-analysis on MET of Amer et al [25] deserves attention since they focused on trials with a low risk of bias. The authors found no benefit for calcium channel blockers in terms of stone clearance, stone size distribution, time to stone expulsion, or side effects. For alpha-blockers, a pooled analysis of 10 low-bias trials demonstrated a modest benefit in expulsion rate (RR 1.10, 95% CI 1.05–1.16). Interestingly, seven out of these 10 trials did not find a benefit in overall expulsion rates [13–15,17,22,26,27]. In their subanalyses, alpha-blockers increased the expulsion rate of distal stones and stones >5 mm, but not of smaller and more proximally located stones. Alpha-blockers were also associated with shorter time to expulsion and increased side effects. Since this literature search was performed in 2016, the studies of Meltzer et al [10] and Ye et al [18] were not included. Unfortunately, non–placebo-controlled trials and studies with unclear risks of selection bias [26,28,29], performance bias [28,29], detection bias [26–29], and attrition bias [28,30] were included.

Similarly, Wang et al [31] assessed the effect of tamsulosin on ureteral stones ≤10 mm by including only randomised, placebo-controlled, double-blind trials, assessing the effect of tamsulosin on stone passage. Evaluating eight trials, the pooled risk of stone passage favoured tamsulosin (85%) over placebo (66%). Subgroup analyses showed a benefit for larger but not smaller stones. Tamsulosin did not appear to increase the incidence of dizziness or orthostatic hypotension. Major limitations of this study were the substantial heterogeneity in the analysis and the inclusion of studies with unclear risks of selection bias [32], performance bias [32], detection bias [32–34], and attrition bias [30,33], and a high risk of reporting bias [34].

Sridharan and Sivaramakrishnan [35] performed a mixed treatment network meta-analysis and trial sequential analysis of randomised controlled clinical trials on alpha-blockers as MET for ureteral stones. They included 87 trials, and observed no publication bias for tamsulosin and alfuzosin for stone clearance and time to stone passage in comparison with the standard of care. They found that all the alpha-blockers improved stone clearance and all except naftopidil reduced stone expulsion time. Regarding stone size, no alpha-blocker improved the expulsion rate for stones <5 mm or in children. Interestingly, only four alpha-blockers (silodosin, terazosin, alfuzosin, and doxazosin) enhanced the clearance of stones ≥5 mm. A major limitation of this study was the absence of a sensitivity analysis. Conclusions were made on studies with an unclear or a high risk of bias in terms of randomisation, allocation concealment, and blinding. Dose variations were not taken into account.

Hsu et al [36] recently assessed the efficacy and safety of tamsulosin compared with silodosin as MET for ureteral stones <10 mm. Based on randomised controlled trials and observational studies with a high risk of bias, they concluded that silodosin achieved higher expulsion rates than tamsulosin (pooled risk difference 0.13; 95% CI 0.09–0.18). Silodosin was also associated with better expulsion rates for stones ≥5 mm and shorter expulsion time, but a higher incidence of retrograde ejaculation. They also noted a decreased number of pain episodes with silodosin, which is contrary to the findings of Campschroer et al [9]. The authors stated that their conclusions were robust based on a sensitivity analysis, despite mentioning that only four of 13 trials were free of an unclear or a high-grade bias. Their analysis could have been more stringent since these four studies also contain a selection, performance, or detection bias. These shortcomings were noted in former meta-analyses on silodosin as MET [37–41].

3.1.2. Calcium channel blockers

Wang et al [42] compared the efficacy of tamsulosin versus nifedipine for distal ureteral stones in a meta-analysis. Comparable with other meta-analyses [43,44], they found that tamsulosin was superior to nifedipine for distal ureteral stones <10 mm in terms of expulsion rate, expulsion time, and safety. However, only four of 12 studies found a benefit for tamsulosin. A limitation was the lack of patient blinding. This was overcome in the study by Pickard et al [15], where the trial medication was over-encapsulated and no benefit of calcium channel blockers was found. Other shortcomings were the use of different medication dosages, inclusion of patients following SWL in several trials, and inclusion of a study with a high risk of performance bias [45].

3.1.3. Phosphodiesterase type 5 inhibitors

It is hypothesised that elevation of cyclic guanosine monophosphate in ureteral smooth muscle by phosphodiesterase type 5 (PDE5) inhibitors may lead to ureteral relaxation and enhanced stone clearance. This has been studied further in meta-analyses [46,47] that concluded that tadalafil facilitated distal ureteral stone expulsion and decreased the time to stone expulsion, but the majority of included studies had an unclear risk of selection or performance bias; therefore, high-quality placebo-controlled trials are necessary before any conclusions can be drawn about the role of PDE5 inhibitors as MET.

3.1.4. Corticosteroids

Sridharan and Sivaramakrishnan [48] stated in their meta-analysis that alpha-blockers combined with corticosteroids performed better than alpha-blockers alone in terms of stone clearance. The authors hypothesised that corticosteroids may facilitate ureteral stone expulsion by reducing ureteral wall oedema. Owing to the unclear risk of bias of included studies and significant side effects, more high-quality prospective randomised trials should be performed before corticosteroid administrations could be recommended for MET.

3.1.5. Other treatments

Palmisano et al [49] found that the association of bromelain and tamsulosin increased stone clearance of symptomatic distal ureteral stones. Bromelain is hypothesised to reduce oedema at the site of stone impaction in the ureteral wall by downregulating COX-2 and PGE-2 expression levels and activating inflammatory mediators. The authors recorded no bromelain-related side effects. Solakhan et al [50] hypothesised that mirabegron could be used as MET by inducing ureteral relaxation through beta-3 adrenoceptor stimulation. In their retrospective study, stone expulsion rates increased and pain episodes decreased in the mirabegron group. Again, prospective randomised trials should be performed to validate these findings.

3.2. MET after extracorporeal SWL

In 2017, Yang et al [43] published their network meta-analysis evaluating the expulsive effect of tamsulosin, doxazosin, nifedipine, terazosin, and Rowatinex after SWL. They included 26 studies and subdivided data into three groups according to the duration of follow-up. After 15 and 90 d of follow-up, doxazosin was found to be the medication with the highest stone expulsion rate. After 45 d of follow-up, better results were found for tamsulosin, followed by nifedipine and Rowatinex. Doxazosin could not be assessed for this time point due to the lack of available data. The authors suggested that doxazosin can improve the stone-free rates following SWL, while tamsulosin may accelerate the expulsion. In an older meta-analysis on MET following SWL, alpha-blockers, nifedipine, Rowatinex, and Uriston also increased stone clearance [51].

Limitations of the study by Yang et al [43] were the huge heterogeneity in terms of stone size (3–24 mm), stone location (kidney to distal ureter), and the number of SWL sessions (1–3, or unknown). This heterogeneity resulted in stone-free rates varying between 15% and 97%. The majority of studies were small, single-centred, unblinded, non–placebo-controlled trials and had no head-to-head comparisons between medications. This led to biased estimates of treatment effects. Most studies investigated tamsulosin, and no data were available for doxazosin at 45 d, for terazosin at 45 and 90 d, and for nifedipine at 90 d. Most trials also had a high or an unclear risk of selection, performance, or detection bias. Only one study by Vicentini et al [52] was deemed to be free of a high or an unclear risk of bias. These authors found higher stone-free rates after SWL with adjuvant tamsulosin or nifedipine for non–lower pole renal stones between 10 and 20 mm compared with placebo.

3.3. MET in children

Few studies have focused on MET in children. In a subanalysis of a recent meta-analysis by Sridharan and Sivaramakrishnan [35], they found no benefit of tamsulosin or doxazosin in terms of stone expulsion rate. These findings are in contrast to the meta-analysis of Tian et al [53] reporting that alpha-blockers are effective for ureteral stones in paediatric patients. The latter was limited by the inclusion of studies with an unclear risk of bias and the absence of a sensitivity analysis. Another meta-analysis on MET in children also included calcium channel blockers and other adjuvant medications (eg, steroids or tolterodine) [54]. It found that MET significantly increased the odds of spontaneous stone passage, but all studies were characterised by a selection, performance, detection, or reporting bias, and even some retrospective studies were included.

3.4. Current guidelines

The European Association of Urology guidelines recommend the off-label use of alpha-blockers for (distal) ureteral stones >5 mm. The guidelines also conclude that there is insufficient evidence of PDE5 inhibitors or corticosteroids in combination with alpha-blockers as an accelerating adjunct [5]. The guidelines of the American Urological Association [6] and Canadian Urological Association [7] recommend that MET with alpha-blockers should be offered to patients with distal ureteral stones <10 mm. Further recent guidance by the National Institute for Health and Care Excellence in the UK has suggested to "consider alpha-blockers for adults, children, and young people" for distal ureteral stones <10 mm [8]. They also suggest that alpha-blockers could be offered as adjunctive therapy for adults having SWL for ureteric stones <10 mm.

3.5. Discussion

The current evidence is very mixed, with the majority of individual high-quality studies showing no benefit to MET [10,13–15,17], with the exception of the trials by Sur et al [22] and Ye et al [18]. However, pooled data in meta-analyses tend to show some limited benefit, especially for the larger stones in the distal ureter [9]. Guidelines seem to follow these meta-analyses and consequently recommend MET. These findings are based on the results of the large trial of Ye et al [18] and a subanalysis of Furyk et al [17], which overshadow the results of other high-quality placebo-controlled trials in which no benefit was found for larger stones [10,13–15,22].

Most of the meta-analyses state that there is "sufficient but low quality of evidence" that alpha-blockers improve ureteral stone clearance. Shortcomings of most meta-analyses are that they mainly included trials with an unclear or a high risk of bias. The vast majority of these trials were limited by poorly defined primary outcomes of stone passage, absence of a placebo, inadequate generation of a randomised sequence, inadequate concealment of allocations prior to assignment, lack of blinding of participants, personnel or outcome assessment, incomplete outcome data, and selective reporting or other bias that bring the validity of the results into question. Most of the trials included in meta-analyses were small and were enrolled from a single centre, which led to biased estimates of treatment effects. Even when the authors recognised these methodological limitations, they concluded a benefit for MET [44,51,54–64]. This has been a criticism of multiple

reviews and meta-analyses, but continues to be repeated in further analyses [23,35,38,39,41–43,46–48,53,65,66]. In the rare case that sensitivity analyses were performed, findings were not taken into account fully in the conclusions [9].

For secondary outcomes, scientific evidence of meta-analyses is even lower since unclear and high risks of bias still remain, there was substantial heterogeneity, and the trials were seldom powered for these outcomes. Therefore, statements that alpha-blockers shorten the time to stone expulsion reduce the number of pain episodes, use of diclofenac, and the need for hospitalisation ("very low– to moderate-quality evidence"), and slightly increase the risk of major adverse events should be questioned [9,48]. These conclusions are also in contrast to the results of most high-quality trials in which no benefit was found for these secondary outcomes.

The problem with the meta-analyses is that they can be as strong as the included trials only. Retrospective trials, including the vast majority of studies evaluating MET, should be excluded. For prospective trials, an unclear or a high risk of selection bias in terms of unclear allocation concealment and lack of blinding should be recognised, because this results in a performance and a detection bias, and possibly in an attrition bias with selective reporting. This may lead to an overestimation of the effectiveness of treatment effects. It has been suggested that when this conflict exists between high-quality randomised trials and meta-analyses, readers should analyse the evidence themselves to decide which offers the best-quality evidence [11]. Readers of meta-analyses should bear in mind that more than one-third of meta-analyses are later discredited after the publication of high-quality randomised controlled trials. Therefore, in case there are many low-quality trials among a limited number of high-quality randomised controlled trials, the latter and not the meta-analyses are considered as the gold standard in the evaluation of therapies [67].

Given the number of high-quality studies published in the past few years, it seems unlikely that we will get better evidence than is currently available, and we have to make the most of the available evidence. We seem to be at an impasse with most high-quality trials being negative, most meta-analyses being positive, and guideline panels choosing to recommend MET on the basis of those meta-analyses and low cost to the medication. It should be remembered that these drugs have side effects and are prescribed off label for this indication.

Future research areas might analyse the value of MET for asymptomatic ureteral stones, multiple ureteral stones <10 mm, and single stones >10 mm. Concerning the stone size, volume as well as largest diameter should be reported in trials, since this may decrease the reported variability in stone clearance [68]. Standardised outcome measures would also improve the quality of the data available. The influence of gender, age (including children) and ethnicity, anatomical considerations, history of ipsilateral stenting or surgery, presence of hydronephrosis, and stone composition should also be studied, as these are often not reported or are exclusion criteria in current trials.

Given the low cost and favourable side-effect profile, perhaps prospective randomised controlled trials powered to detect even a small difference between drug and placebo groups are warranted. Taking a short course of well-tolerated medication may be preferred if it is associated with even a small decrease in the chance of needing intervention. For trials focusing on MET following SWL, it would be interesting to study the influence of ureteral wall oedema and the average size of fragments following this procedure. Additionally, recent early data have suggested that passage of the ureteroscope or access sheath may be made easier by preoperative administration of MET [69,70]. This is an interesting new concept and needs to be confirmed in proper large randomised controlled trials. If confirmed, then this may highlight the difference between the importance of relaxation for retrograde access and the importance of maintaining ureteral coaptation as well as relaxation to allow antegrade passage of calculi. Recent laboratory studies have also assessed the properties of topical medications given intraoperatively into the ureter to induce relaxation (Lee CX, Cheah JH, Soule CK, et al. Local drug delivery for relaxation of the ureter. Nat Biomed Eng [in revision 2019]. Verbal communication). This is a potential new exciting avenue with clinical promise.

4. Conclusions

The strength of evidence for the benefit of MET in ureteral stones is low, even for distal ureteral stones >5 mm. The vast majority of randomised, double-blind, placebo-controlled trials without a high or an unclear risk of bias did not find a benefit of MET for increased ureteral stone passage rates. This is in contrast to results of meta-analyses that are skewed by low-quality trials. It seems likely that there is a weak effect of MET in the distal ureter, but that this benefit in terms of improved stone passage is far weaker than originally thought. In the absence of further high-quality data, individual clinicians are required to decide for themselves whether to believe high-quality single trials or meta-analyses. It is likely that selective use of alpha-blockers as MET may retain a role, in those with larger stones and only in well-counselled patients who understand the side effects and off-label use, but the era of MET for all comers is over.

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Study concept and design: De Coninck, Bultitude.
Acquisition of data: De Coninck.
Analysis and interpretation of data: De Coninck, Bultitude.
Drafting of the manuscript: De Coninck, Bultitude.
Critical revision of the manuscript for important intellectual content: De Coninck, Antonelli, Chew, Patterson, Skolarikos, Bultitude.
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