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Pharmacotherapy of urolithiasis: evidence from clinical trials

Orson W. Moe[1,2,3], **Margaret S. Pearle**[1,4], and **Khashayar Sakhaee**[1,2]

[1]Charles and Jane Pak Center of Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, Texas, USA

[2]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA

[3]Department of Physiology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

[4]Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Abstract

Urolithiasis is a worldwide problem with significant health and economic burdens. Medical therapy that alters the course of stone disease has enormous medical and financial impact. Urolithiasis is a final manifestation of a broad range of etiologies and pathogenesis. The modest progress in understanding the pathophysiology has hampered successful development of targeted therapy. Current regimens are based mostly on rational alteration of urinary biochemistry and physical chemistry to lower the risk of precipitation. In terms of pharmacotherapy, there are drugs to successfully improve hypercalciuria, hypocitraturia, aciduria, hyperuricosuria, and hypercystinuria. These agents have been proven to be effective in randomized controlled trials in improving urinary biochemical and physicochemical risk factors, as well as clinical outcomes. Although our current regimens have clearly improved the management and lives of stone formers, there are still clearly identifiable immense voids in the knowledge of pathophysiology of stone disease that can be filled with combined basic science and clinical studies.

Keywords

clinical trial; hypercalciuria; kidney disease: improving global outcomes; kidney stones; pathophysiology of renal disease and progression

Urolithiasis is a global problem spanning all geographic regions with an estimated annual incidence of 1%, prevalence of 3–5% and a lifetime risk of 15–25%. Once afflicted, urolithiasis tends to be recurrent in the majority of cases. According to data from the Urological Diseases in America Project, the total annual cost of nephrolithiasis in the United States in the year 2000 was about $5.3 billion. This underscores the toll taken by this disease on working-age individuals and society at large. Given the high cost of urgent medical treatment and/or surgical intervention, the attractiveness of a medical prophylactic program to reduce stone occurrences or increase the likelihood of successful conservative management of an acute-stone event is obvious. Indeed, simple medical management strategies utilizing inexpensive drug therapies have been shown to be efficacious and cost effective.[1] A retrospective study of patients followed for up to 20 years has shown sustained

Correspondence: Orson W. Moe, Charles and Jane Pak Center of Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75380, USA. orson.moe@utsouthwestern.edu.

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efficacy of medical therapy in the improvement of biochemical parameters and clinical events.[2]

Although there is steady improvement in therapy with shock-wave therapy and endourological techniques, the advance of medical therapy has been rather modest. From an etiological and pathophysiological point of view, it is important to emphasize that urolithiasis is a mere final manifestation of diverse and systemic etiological and pathogenic events. A major hurdle in this field in the past and present is the fact that the development of specific targeted therapy has been handicapped by the relative slow progress in unraveling pathophysiology. Current medical approaches are based on carefully constructed and rational modification of urinary biochemistry and physical chemistry to lower stone risk rather than etiology. This brief review is not meant to discuss the pathophysiology of urolithiasis, but rather provides a summary of the existing clinical data on medical therapy. Prospective randomized controlled trials will be highlighted, whereas uncontrolled and retrospective studies will be mentioned. Dietary and life style modifications and surgical therapy are not covered in this review. Because of the space limitation, complete and exhaustive citation is not possible.

Medical Expulsive Therapy (Met)

One area in which medical therapy alters the natural history of stone disease is on the spontaneous passage of ureteral calculi. The two most important factors in predicting the ureteral stone passage are stone size and location. A meta-analysis of observational studies showed spontaneous passage rates of 12, 22, and 45% for proximal, middle, and distal ureteral calculi, respectively, and 55, 35, and 8% for stones <4, 4–6, and >6 mm, respectively.[3] However, even stones that eventually pass may do so with debilitating pain over an unpredictable time interval. Consequently, agents that promote spontaneous stone passage and reduce the symptoms associated with passage are needed.

Corticosteroids, hormones, nonsteroidal anti-inflammatory agents, calcium-channel blockers and α-adrenergic blockers have been evaluated. Calcium-channel blockers and α-blockers have emerged as the most promising agents for MET. Calcium-channel blockers suppress smooth muscle contraction and reduce ureteral spasm, whereas α-1 adrenergic receptor antagonists decrease ureteral smooth muscle tone and frequency and force of peristalsis.[4–5]

A meta-analysis of nine randomized clinical trials (RCTs) compared calcium-channel blockers or α-blockers, with or without corticosteroids, against placebo or no treatment.[6] Patients treated with MET had a 65% greater likelihood of spontaneous stone passage than the control group (pooled risk ratio 1.65, 95% confidence interval (CI) 1.45–1.88, $P<0.0001$). Efficacy was demonstrated for both calcium-channel blockers (risk ratio 1.90, 95% CI 1.51–2.40, $P<0.001$) and α-blockers (risk ratio 1.54, 95% CI 1.29–1.85, $P<0.001$). The additional benefit of corticosteroids with either calcium-channel blockers or α-blockers was modest. One small RCT directly compared tamsulosin vs tamsulosin plus corticosteroid and showed no difference in stone passage rates, but the corticosteroid group passed their stones on average 2 days sooner.[7]

A meta-analysis of 11 RCTs (911 patients) reported a 44% higher likelihood of spontaneous stone passage with α-blockers compared with no treatment (risk ratio 1.44, 95% CI 1.31–1.59, $P<0.001$).[8] The combined American Urological Association/European Urological Association 2007 Ureteral Stones Clinical Guidelines Panel evaluated all available MET trials and determined that α-blockers resulted in a 29% (95% CI 20–37) absolute increase in stone passage rate, whereas calcium-channel blockers showed only a statistically nonsignificant 9% (95% CI 7–25) improvement from no treatment.[9] The predominance of

α1D-receptor subtypes in the distal ureter and detrusor suggests selective antagonists may have superior efficacy, but there is no data to date to support this claim.[10–12]

The combined American Urological Association/European Urological Association Ureteral Stones Clinical Guidelines Panel recommended that for patients with newly diagnosed ureteral stone <10 mm and well-controlled symptoms MET should be prescribed.[9] There is good evidence to support the use of MET for patients with <10 mm distal ureteral calculi. Because of its low cost and high safety profile, prevention of even a single surgical intervention more than compensates for the cost of MET.

Some questions still remain. Most RCTs tested patients with distal ureteral calculi. It is not clear whether the results can be extrapolated to patients with proximal and middle ureter stones. The role of corticosteroids is still uncertain. Finally, the optimal MET regimen with regard to agent(s), dosage, duration, and patient selection await further large-scale multicenter randomized trials. A summary of the various MET treatments is shown in Table 1.

Hypercalciuria

At present, the only medical therapy directed at reducing urinary calcium is thiazide diuretics. The efficacy of thiazide on recurrent calcium-stone formation has been tested in six RCTs.[13–18] In four of these studies spanning a total of nearly 460 patient-years, thiazide diuretics significantly decreased stone recurrence.[15–18] The stone-forming populations studied were heterogeneous and hypercalciuria was reported in 20–100% of the study subjects in three studies.[15–16,18] Subgroup analyses were not made between hypercalciuric and normocalciuric kidney stone populations to discern whether the treatment is more beneficial in one group. In one study, a ‘non-selective’ approach was advocated in the prophylaxis of the renal stones as long as secondary causes, such as renal tubular acidosis, enteric hyperoxaluria, hypercalcemic disorders, and urinary tract infections, are excluded.[16] In studies in which pre-treatment data were available, stone events were decreased simply by enrollment into a trial highlighting the importance of general medical care.

In contrast, two RCTs conducted over a total of 75 patient-years concluded thiazide is ineffective in reducing kidney stone incidence.[13–14] The negative outcomes may in part be due to smaller sample size and shorter duration of treatment. Moreover, contrary to the studies cited above,[15–18] fluid intake and dietary restrictions were not controlled.[13–14] As thiazide-induced hypokalemia was not present, the negative response in these studies is unlikely due to hypokalemia-induced hypocitraturia.

The results of the RCTs were consistent with open studies totaling over 6600 patient-years of thiazide treatment for calcium nephrolithiasis.[19–25] Hydrochlorothiazide at 50 mg twice a day lowered stone incidence in normocalciuric kidney stone formers.[26] Coe *et al.* reported new stone formation in only 2 out of 37 patients with idiopathic hypercalciuria on trichlormethiazide (4 mg/day) over a total of 740 patient months of treatment[24] and showed that thiazide and/or allopurinol drastically reduced new stone formation in recurrent calcium-stone formers with hypercalciuria and/or hyperuricosuria over 625 patient-years.[20] Over 88 patient-years, bendroflumethiazide (2.5 mg/day) reduced new stone formation compared with the pre-treatment phase.[25] Pak *et al.* segregated hypercalciuria into predominantly intestinal hyperabsorption or renal leak and noted a decline in stone formation rate from 2.1 to 0.40 in both groups of patients.[23] In a 5-year experience with hydrochlorothiazide (50 mg/day) and amiloride (5 mg/day) in 519 patients with recurrent calcium nephrolithiasis, where 65% of which were classified as hypercalciuric, 53 new stones were formed in the treated group in contrast to the predicted 916 stones.[22] A summary of these trials are illustrated in Table 2.

The incidence of side effects on thiazide diuretics is approximately 30% although side effects necessitating discontinuation are much less frequent.[19] Whether long-term thiazide has harmful effects remains to be examined in stone formers. A meta-analysis of clinical trials in hypertensive subjects revealed an relationship between changes in serum glucose and potassium concentrations.[27] The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial also showed increased incidence of new-onset diabetes mellitus in patients treated with chlorthalidone compared with amlodipine or lisinopril. The potential pathophysiological link between thiazides and glucose intolerance is of an unknown nature and is of concern[28] and has not been prospectively tested in kidney stone populations. Part of the hypocalciuric effect of thiazide is due to mere volume contraction-induced increased proximal tubule calcium absorption. If this were true, the thiazide effect can be achieved equally well with dietary sodium restriction without exposure to the risk of glucose intolerance. A summary of drug used in the treatment of hypercalciuric nephrolithiasis is detailed in Table 3.

In a short term trial, bisphosphonates were shown to lower urinary calcium excretion.[29–30] However, no long-term RCTs have been performed displaying the efficacy if these agents on recurrent calcium stone-forming population.

Hypocitraturia

Three randomized trials were performed in recurrent calcium-stone formers.[31–33] These were heterogeneous populations with respect to urinary citrate excretion with normal or low normal urinary citrate reported in two studies,[31,32] and low urinary citrate in half of the patients in the third study.[33] In two of these studies, treatment with potassium citrate or potassium-magnesium-citrate at 30–60 mEq base/day over a total of 129 patient-years reduced recurrent calcium-oxalate-stone formation.[31,32] However, one RCT in 25 patients over 3 years using oral sodium-potassium-citrate (90 mEq/day) did not show efficacy compared with high fluid intake and dietary restrictions.[33] The differences between these studies may be due to the small size and higher dosages of alkali treatment in the latter study.

A rather dramatic result was seen in one controlled study using 60mEq potassium citrate/day in 34 patients with residual stones 4 weeks and 56 patients free of residual stones after shockwave lithotripsy, potassium citrate was shown to significantly decrease the stone recurrence rate to zero at 12 months in treated subjects compared with 28.5 stone recurrence in untreated subjects (P =<0.05).[34] In the study by Kang *et al.* of 503 subjects treated for a mean duration of 41 months (range 6–168), there was significant and durable increase in urinary pH (5.90–6.46, P<0.0001) and citrate (470–700 mg a day, P<0.0001), and decrease in stone formation rate from 1.89 to 0.46 stones per year (P<0.0001).[35]

This effect is compatible with results from non-randomized studies. In hypocitraturic calcium or uric acid urolithiasis, potassium citrate (1–4.33 years) corrected physicochemical profiles and reduced stone formation in 98% of patients, and the need for surgical intervention for new stone formation was totally abrogated.[36] In recurrent stone formers with hypocitraturia alone, potassium citrate treatment increased urinary citrate and decreased the rate of total stone formation from 0.7/year 0.13/year (P<0.005).[37] In patients with hypocitraturia plus other metabolic abnormalities, there was a more dramatic decline in total stone formation rate from 1.2/year compared with 0.08/year following the treatment (P<0.05). A summary of these trials is illustrated in Table 2.

Alkali treatment is relatively safe with minor gastrointestinal side effects. One potential concern is that the overtreatment with alkali may increase the risk of calcium-phosphate-stone formation by increasing the abundance of monohydrogen phosphate. Although this

pathophysiological link has been proposed, it has never been studied. It is interesting that the potassium citrate treatment in patients with distal renal tubular acidosis and pre-existing high urinary pH has been shown to considerably lower rather than increase kidney stone recurrence rate.[38] It is interesting that, if one uses the JESS instead of the EQUIL program to predict supersaturation,[39] the rise in brushite saturation is not marked upon rise in pH and that of calcium oxalate actually falls. Although both sodium and potassium alkali treatment are equally effective in raising urinary pH, potassium citrate is more effective in preventing the formation of calcium stones by attenuating urinary calcium excretion.[40] Currently, there is no data comparing pharmacological alkali therapy against dietary manipulation of urinary citrate.

Uric Acid Stones

As acidic urine pH is the most predominant factor in the development of uric acid stones, alkalinization of the urine is the most effective way to treat patients with uric acid nephrolithiasis. [40,41] In patients with uric acid nephrolithiasis (pure uric acid and mixed uric acid and calcium oxalate stones) treated with potassium citrate at 30–80 mEq/day, urinary pH and undissociated uric acid increased and new stone formation decreased from 1.20 to 0.01 stones/year,[40,42] Stone remission was experienced in 94% of the patients, and group stone formation diminished by 99%. A summary of these trials is illustrated in Table 2. Although it has not been tested in long-term randomized trials, sodium bicarbonate may also offer the same alkalinizing effect although this treatment may confer an increased risk of calcium stone formation due to sodium-induced hypercalciuria, promotion of monosodium urate-induced calcium oxalate crystallization, and high pH-induced calcium phosphate precipitation. Although urinary alkalinization does not get at the root of the pathophysiology of aciduria in uric acid stones, it is a pragmatic and effective therapy. The initial recommended alkali dosage is 30–40 mEq/day. A common practice is to frequently measure 24-h urine pH and to titrate the alkaline dose to maintain a urine pH above 6.1 but less than 7.0 to avoid complications of calcium phosphate stones. However, urine pH from a 24-h urine collection may not adequately reflect the diurnal variation in urine pH during periods of extreme acidity. Although direct urinary pH measurements throughout the day would be impractical, pH measurements may be performed by urinary dip-stick analysis.[43,44] This may allow for the adjustment of medication dosage as needed throughout the day. Allopurinol at the dosage of 300 mg/day is used when urinary uric acid excretion is higher than 600 mg/day in women and 700 mg/day in men. This treatment should be invariably considered in patients with hyperuricemia, including primary gout, those with inborn errors in metabolism, myeloproliferative disorders, hemolytic anemia, and in tumor lysis syndrome.

Hyperuricosuric Calcium Nephrolithiasis

Although hyperuricosura is not usually the cause of uric acid stones in the absence of aciduria, there is the condition of hyperuricosuric calcium oxalate urolithiasis in which sodium urate or uric acid contributes to the formation of calcium oxalate stones.[45,46] Calcium oxalate stone-formers with hyperuricosuria, but not hypercalcemia, hypercalciuria, hyperoxaluria, or hypocitraturia will benefit from reduction of the hyperuricosuria. Two studies have shown that for hyperuricosuric calcium oxalate stone-formers without other metabolic abnormalities, allopurinol is effective in reducing urinary uric acid and stone recurrence compared with no treatment (Table 2).[20,47] In hyperuricosuric calcium oxalate-stone formers with multiple metabolic abnormalities, the benefit of reduction of hyperuricosura alone by allopurinol is less evident.[48] This underscores the importance of pathophysiological and metabolic evaluation with complete blood and urinary profiles.

A non-purine analog xanthine oxidase inhibitor was recently approved for treating hyperuricemia associated with gouty arthritis. Although shown to be effective in reducing hyperuricemia and arthritis attacks, the effect on uricosuria was not reported. On the basis of its mechanism of action, one would expect hypouricosuric effects, so for patients who cannot tolerate allopurinol, febuxostat is a plausible consideration without supportive data. The use of recombinant uricase has no proven role in the chronic management of hyperuricosuria.

Cystinuria

As the pH dependency of urinary cystine solubility was shown over half a century ago, alkali treatment has been widely used in the management of cystinuric subjects. However, alkali therapy alone has limited effectiveness, as a large dose is necessary because of the high pKa of cystine (8.5). Such highly alkaline urine can predispose the patient to calcium phosphate stone formation thus a urinary pH of 6.5–7.0 has been recommended to achieve dissolution of cystine. In patients with severe cystinuria (>1000 mg/day), other agents are usually required which are thiol derivatives that split a single cystine molecule into two cysteines and create a highly soluble disulfide compound of the drug and a cysteine molecule.[49] Dahlberg *et al.* first showed that new stone recurrence, stone passage, and stone growth were lowered when D-penicillamine (dimethyl-cysteine) was added to conservative treatment.[50] These agents do not affect the underlying defect in cystinuria, but their use is based on rich biochemical and physicochemical action α-mercaptopropionylglycine (tiopronin) is currently the most commonly prescribed agent for cystinuric patients. Chow *et al.* compared the effect of conservative treatment of hydration and alkalinization with drug treatment using D-penicillamine or tiopronin and showed reduction of stone events from 1.6 to 0.452 per years.[51] One study showed tiopronin-induced stone remission in 63% of patients who received previous treatment with D-penicillamine and in 71% of patients who were naive to treatment. Stone formation rate was reduced by 81 and 94%, respectively, by tiopronin.[52] Treatment with either D-penicillamine or tiopronin significantly decreased stone event by 32–65% when compared with conservative management with hydration and alkali treatment.[51,53] A summary of these trials is illustrated in Table 2. However, to date no RCTs have been performed demonstrating the superiority of medical treatment over placebo in this population.

α-Mercaptopropionylglycine may have lower incidence of side effects compared with D-penicillamine[52] and, therefore, is sometimes preferred, although both drugs are effective in reducing kidney stone incidence. The thiol-containing compound captopril has been suggested to function similarly to reduce urinary cystine excretion,[54,55] but this finding was not reproduced by others.[53,56] In summary, in mild cases of cystinuria, judicious urinary alkalinization and fluid may suffice but in more severe cases, a thiol agent, such as tiopronin or D-penicillamine, should be added.

Hyperoxaluria

Hyperoxaluria is an equally important contributor to calcium oxalate supersaturation as hypercalciuria. Hyperoxaluria can result from rare monogenetic causes (primary hyperoxaluria type 1: alanine-glyoxylate aminotransferase deficiency; type 2: glyoxylate reductase-hydroxypyruvate reductase deficiency). Type 1 patients can be managed with pyridoxine. In one study over 250 patient-years, pyridoxine reduced hyperoxaluria, but effect on stone events were not reported.[57] Patients with type 2 are unlikely to respond to pyridoxine.[58] Because of its rarity, there have been no RCTs for this condition. Unfortunately, there is currently no proven pharmacotherapy to effectively treat the more common form of ‘idiopathic’ hyperoxaluria present in up to 40% of stone formers. The

probiotic approach of *Oxalobacter formigenes* or direct administration of recombinant oxalate decarboxylase is still in the experimental phase with mixed results in both humans and rodents. Although luminal oxalate degradation will certainly lower stool oxalate, it is still unclear whether this will lower urinary oxalate. In another short-term study, patients with enteric hyperoxaluria were treated with increasing dosages of a lactic acid bacteria mixture. This study demonstrated lowered calcium oxalate supersaturation during this treatment, mainly due to decreased urinary oxalate excretion. However, the degree of change was not statistically significant.[59]

Current Status and Direction of Further Clinical Studies

Despite some clear and encouraging successes we have witnessed over the last few decades, we are poised at a juncture where there is a dire need for development of novel medical pharmacotherapeutics in urolithiasis both in depth and in lateral scope. The approach of developing a universal treatment protocol regardless of underlying pathophysiology or even urinary chemical parameters, may have its pragmatic attractions because of sheer simplicity, obviation of investigations, and initial cost reduction. This really is not in the best interest of the patient as potential for ineffective or even harmful therapy is substantial. Future efforts should be directed to refine therapy based on underlying etiology and pathophysiology so eventually therapy can be tailored for the individual stone former rather than population of stone formers. This will require coordinated and simultaneous investigations at the levels of the laboratory bench, human metabolic investigations, and population-based clinical research. The majority of breakthrough discoveries will no doubt originate from the former two categories. At the present moment and with the current database, certain clinical trials can be very informative and will clearly improve our existing treatment protocols. These efforts should be multi-center-based to ensure power and shorten the duration to completion. For such a common disease, this really should be an achievable goal provided support is available.

As indicated above, one can systematically test therapy targeted to known underlying pathophysiology using individualized regimens vs non-selective blanket treatment for stone formers. Although targeted therapy is intuitively correct, its practical utility has not been definitively documented in the form of a trial. One would predict that the results will favor tailored therapy but this needs to be shown at the population level. Such clinical evidence will provide the justification and motivation for metabolic evaluation of all patients with urolithiasis. Sometimes when the ideal is not possible and realizing that there may be circumstances in some practices in which metabolic evaluation is not realistic, which empiric pharmacological agent(s) should one use for calcareous stones-alkali, thiazides, or both?

There is a need for comparison between pharmacotherapy vs dietary therapy vs both. As discussed earlier, the hypocalciuric effect of thiazides alone needs to be compared with dietary sodium restriction alone, and to both salt restriction plus thiazide. Although most experts will agree that thiazide therapy alone without sodium restriction is unwise, it is not clear whether thiazides when added to sodium restriction, have additional direct benefits either in hypocalciuria and/or bone health. If the effect of thiazides is really due solely to volume contraction, one may consider using it as an alternative or adjuncts to dietary sodium restriction. The long-term side effects of thiazides, particular regarding glucose intolerance, in stone formers should also be prospectively evaluated. It is not known whether thiazides have a direct effect on glucose metabolism or potassium deficiency may be the mediating culprit. Another pharmacological vs dietary treatment is potassium citrate vs low protein/ acid diet. One may find comparable efficacy of pharmacological and dietary therapy in a strictly controlled clinical trial, but adherence may be difficult to achieve with chronic

dietary changes leaving potassium alkali as the preferred choice. Protein restriction may also be quite different from acid neutralization because there may be non-acid components of protein that are lithogenic.

Another study will be to test single vs combination therapy. An empirical approach used by practitioners is that when one therapy does not suffice, often a second drug is tried or added. Are two drugs better than one? The intuitive answer appears to be yes, but we really do not have clinical data to support whether combination therapy is indeed superior. As none of the current regimens are completely effective, there is clearly room for further reduction of stone events. A combination therapy of thiazide and potassium citrate is logical from a pathophysiological viewpoint and not necessarily contrived.

Another kind of study will be to prospectively examine the response of stone formers who have never undergone procedures vs those who have. Retrospective data seem to indicate much better result with medical treatment in patients post lithotripsy or percutaneous procedures than those without medical treatment following non-invasive surgical intervention. This is a most intriguing finding lending one to wonder whether there is a fundamental difference in the pathobiology after surgical intervention or simply patients become much more compliant and motivated to avoid further procedures. As urolithiasis is a systemic disease, there is a dire need to understand the long-term effects of pharmacotherapy on parameters other than urinary chemistry and stone events, such as bone health.

As current markers of kidney stone formation relies on computer-based analysis of urine chemistry as surrogates or stones events as long-term gold standard outcomes. One may consider an intermediate form of physical chemical surrogate such as crystal agglomeration and growth as an additional read-out to improve prediction. Finally, as urolithiasis is a systemic disease, outcomes such as insulin resistance, and hypertension should also be targeted and examined in the course of intervention.

There is no doubt that these efforts are costly as with all multi-center clinical trials and should be prioritized when resources are limiting. It is also apparent that we need further multi-level efforts at the basic science bench, metabolic research units, and population studies to unravel and discover pathophysiology-directed intervention strategies. Although urolithiasis rarely carries the grave curse of mortality of end stage renal failure, cardiovascular disease, or neoplasm, it does have profound impact on quality of life and unlike the aforementioned conditions; cure of urolithiasis is not too far in the horizon if the proper efforts are executed.

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Table 1
| Commonly used drugs in medical expulsive therapy

	Drug		
Type	**Generic name**	**Trade name**	**Recommended dosage**
Calcium-channel blocker	Nifedipine	Adalat Adalat CC Procardia Procardia XL	30 mg/day
α_1-Selective α-blocker	Tamsulosin	Flomax Flomaxtra Urimax	0.4 mg/day
α_1-Selective α-blocker	Terazosin	Hytrin	5 mg/day
α_1-Selective α-blocker	Doxazosin	Cardura	4 mg/day
Corticosteroid	Deflazacort	Calcort Cortax Decortil Deflanil	30 mg/day
Glucocorticoid	Methylprednisolone	Medrol A-methaPred Depo-Medrol Medrol DosePak Solu-Medrol	16 mg/day

Table 2

| Major clinical trial in pharmacotherapy of urolithiasis

	Author (ref.)	Drug	*N*	Design	Finding
Renal colic	Hollingsworth *et al.*[6]	α-Blocker or calcium-channel blockers vs placebo or no Rx		Meta-analysis	Improved likelihood of stone passage
	Parsons *et al.*[8]	α-Blocker vs no Rx	911	Meta-analysis	Improved likelihood of stone passage
Hypercalciuria	Brocks *et al.*[13]	Bendroflumethiazide vs placebo	62	RCT	Both groups showed decrease in stone formation
	Scholz *et al.*[14]	Hydrochlorothiazide vs placebo	51	RCT	Thiazides decreased calciuria but not stone events
	Laerum and Larsen[15]	Hydrochlorothiazide vs placebo	50	RCT	Decreased new stone formation Prolonged stone-free interval
	Ettinger *et al.*[16]	Chlorthalidone vs Mg hydroxide vs placebo	124	RCT	Chlorthalidone more effective than Mg hydroxide or placebo in reducing stone events
	Ohkawa *et al.*[17]	Trichlormethiazide vs no treatment	175	RCT	Decreased calciuria and stone formation rate
	Borghi *et al.*[18]	Diet vs diet+indapamide vs diet+indapamide+allopurinol	75	RCT	Diet + pharmacotherapy better than diet alone.
Hypocitraturia	Barcelo *et al.*[31]	Potassium citrate vs placebo	57	RCT	Decreased stone formation and increased urinary citrate
	Ettinger *et al.*[32]	Potassium magnesium citrate vs placebo	64	RCT	Decreased stone formation
	Hofbauer *et al.*[33]	Diet+sodium potassium citrate vs diet	50	RCT	No difference in stone formation
	Soygür *et al.*[34]	Potassium citrate vs no treatment after shockwave lithotripsy	110	RCT	Decreased stone recurrence
	Kang *et al.*[35]	Mix of potassium citrate, thiazide, allopurinol vs no treatment after percutaneous nephrolithotomy	226	NCT	Decreased stone recurrence
	Pak *et al.*[36]	Potassium citrate vs pretreatment in calcium and uric acid stone formers	89	NNT	Decreased stone events
Aciduria (uric acid stones)	Pak *et al.*[42]	Potassium citrate	18	NNT	Decreased stone events
Hyperuricosuria (calcium stones)	Ettinger *et al.*[47]	Allopurinol vs placebo	60	RCT	Decreased stone events
	Coe[20]	Thiazide vs allopurinol vs both	202	RCT	Decreased stone events vs pretreatment
Cystinuria	Dahlberg *et al.*[50]	D-penicillamine	89	Retrospective	Decreased stone event and dissolution of stones
	Chow *et al.*[51]	D-penicillamine or α-mercaptopropionylglycine vs conservative Rx	16	NNT	Decreased stone event
	Pak *et al.*[52]	D-penicillamine or α-mercaptopropionylglycine vs conservative Rx	66	Retrospective	Both drugs equally effective in reducing stone events

	Author (ref.)	Drug	*N*	Design	Finding
	Barbey *et al.*[53]	D-penicillamine or α-mercaptopropionylglycine vs conservative Rx	27	Retrospective	Decreased stone events

Abbreviations: N, number of patients; NCT, non-randomized controlled trial; NNT, non-randomized non-placebo controlled trial; RCT, randomized controlled trial; Rx, treatment.

Table 3
| Commonly used drugs in the treatment of hypercalciuric calcium nephrolithiasis

Drug	Recommended dosage(s)	Comments
Hydrochlorothiazide	50 mg/day 25mg twice/day	A single dosage is preferred since the twice a day dosage may cause frequent nocturia and consequent patient discomfort.
Chlorthalidone	25 mg/day 50 mg/day	Both dosages lower urinary calcium by the same degree. Because of its long action, this treatment may cause hypokalemia and hypocitraturia.
Indapamide	1.2 mg/day 2.5 mg/day	This treatment may have fewer side effects that hydrochlorothiazide, including the rare occurrence of hypokalemia and hypotension.
Amiloride	5 mg/day	This treatment is a potassium sparing diuretic that lowers urinary calcium, but to a lesser degree than hydrochlorothiazide.
Amiloride/Hydrochlorothiazide	5 mg/50 mg/day	Maintains the hypocalciuric effect of thiazide, whereas averting the development of severe hypokalemia.
Trichlormethiazide	2 mg/day 4 mg/day	This drug is not marketed in the United States.