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DES de Médecine Générale

par

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# EFFETS DE L'ARRÊT DES MÉDICAMENTS HYPOURICÉMIANTS: REVUE SYSTÉMATIQUE DE LA LITTÉRATURE

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| Président : | Madame le Doyen Pascale Jolliet |
| Directeur de thèse : | Monsieur le Docteur Jean-Pascal Fournier |
| Membres du jury : | Monsieur le Professeur Rémy Senand |
| | Monsieur le Docteur Benoît Le Goff |

« Rien n’est plus naturel pour les souffrants que de chercher des remèdes et du soulagement dans les tourments de leurs accès : rien n’est plus sage et plus prudent dans les intervalles, que de se précautionner contre leurs retours, et de mettre tout en usage pour s’en préserver. »

D. Diderot, 1772, *Encyclopédie ou Dictionnaire raisonné des sciences, des arts et des métiers*, tome 7 p 822

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**LISTE DES ABREVIATIONS**

ACR: American College of Rheumatology

ARHP: Association of Rheumatology Health Professionals

CCT: Clinical control trial

EULAR: European League against Rheumatism

RASI: Renin-angiotensin system inhibitor

RCT: Randomized control trial

SUL: Serum urate level

THU: Traitement hypouricémiant

ULT: Urate lowering therapy

## INTRODUCTION

La maladie goutteuse est une maladie chronique liée au métabolisme de l'acide urique. Elle se caractérise par la survenue d'arthrites récidivantes ou de lithiases urinaires, et est une des maladies rhumatismales les plus fréquentes chez l'adulte (0,9% des adultes en France, et 3,9 % aux États-Unis) (1,2). La prévalence de la goutte a augmenté ces dix dernières années en lien avec le vieillissement de la population, l'augmentation de la consommation d'alcool, de la fréquence de l'obésité et du syndrome métabolique, de l'hypertension, des maladies rénales chroniques et de l'utilisation des médicaments diurétiques (3).

Les traitements hypouricémiants (THU) sont recommandés (4,5) pour prévenir les crises de goutte en cas d'hyperuricémie symptomatique (accès répété d'arthrite goutteuse (≥2), tophus ou lithiase urique rénale) qu'elle soit primitive, ou secondaire (hémopathies, néphropathies, hyperuricémies iatrogènes). La mise à jour 2014 des recommandations EULAR stipule que le traitement est recommandé dès la première crise de goutte chez les patients jeunes (moins de 40 ans), ou ayant une uricémie très élevée (supérieure à 480 µmol/l ou 8 mg/dL) ou des comorbidités (insuffisance rénale, hypertension artérielle, insuffisance coronarienne, insuffisance cardiaque) (6). Le traitement médicamenteux de l'hyperuricémie asymptomatique n'est pas recommandé car, à l'heure actuelle, le lien entre hyperuricémie et cardiopathie ischémique ou élévation de la pression artérielle, n'a pas été démontré avec un niveau de preuve suffisant (4,7–9).

Deux classes de médicaments hypouricémiants sont utilisées : les inhibiteurs de la xanthine oxydase (allopurinol et febuxostat), qui inhibent la synthèse de l'acide urique; et les agents uricosuriques (probenecid, benzbromarone et sulfinpyrazone), qui diminuent la réabsorption tubulaire d'acide urique et augmentent sa sécrétion par les reins. Les plus prescrits sont l'allopurinol et le febuxostat, du fait de leur efficacité et de leur taux acceptable de survenue d'effets indésirables (4,5). Ces médicaments ont pour but de dissoudre les cristaux d'urate présents dans les tissus, et de prévenir la formation de nouveaux cristaux, en maintenant l'uricémie au dessous du seuil de saturation de l'urate de sodium, c'est à dire inférieur ou égal à 6,0 mg/dL (360 mmol/L) en l'absence de récidive *(niveau III*) (1,5). Les THU sont aujourd'hui instaurés à vie, sans que ce consensus ne s'appuie sur un niveau de preuve fort (10).

Il a été montré, dans la population générale, que l'allopurinol ainsi que les autres THU utilisés dans la maladie goutteuse présentaient le taux de compliance médicamenteuse le plus bas parmi sept maladies chroniques (36.8%) (11). Le même constat a été fait parmi plusieurs maladies chroniques rhumatismales (12) : 17 à 44% des patients seulement prenaient leur traitement au moins 80 % du temps (13–16). De plus, dans l'étude de Sarawate *et al.* (14), 24.7 % des patients ont arrêté définitivement leur traitement durant la première année. Dans la goutte l'inobservance semble plus importante chez l'homme jeune sans comorbidités, notamment sans facteurs de risque cardiovasculaire, et paraît favorisée par l'augmentation des doses d'allopurinol et/ou une durée courte de traitement (12–15,17). Ces données sont retrouvées dans les autres maladies chroniques rhumatismales (18). Aucune relation n'a été retrouvée entre l'observance et les effets indésirables liés aux traitements (18).

Les préoccupations soulevées par l'arrêt des traitements au long cours comprennent le risque de récidive clinique, le délai avant la récidive, les facteurs associés à la récidive, ou la possibilité d'effets indésirables (19,20). La réflexion peut également porter sur les conséquences biologiques de l'arrêt, ainsi que sur des stratégies d'interruption médicamenteuse (21–23). Les enjeux sont donc multiples, et exigent une évaluation globale. Ainsi, nous avons réalisé une revue systématique de littérature d'études cliniques s'intéressant aux conséquences de l'arrêt des médicaments hypouricémiants. Notre objectif principal fut d'identifier la récurrence de survenue d'arthrite goutteuse, de tophus ou de lithiases urinaires après l'arrêt d'un médicament hypouricémiant. Nos objectifs secondaires furent d'étudier les effets indésirables à l'arrêt, les taux de réintroduction des médicaments hypouricémiants, et les facteurs de risque liés à la récidive.

Ce travail de thèse présente notre rapport final, en anglais, en vue de publication.

# Effects of discontinuation of urate-lowering therapy: a systematic review

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**ABSTRACT**

**Background:** Gout is the most common rheumatic disease. Urate-lowering therapy (ULT) is recommended to decrease risk of acute attacks of gouty arthritis, in case of symptomatic hyperuricemia. Allopurinol and febuxostat are the most commonly used ULTs in gout, and are associated with low rates of adherence, with one out of four patients discontinuing their treatment during the first year of use.

**Objectives:** Our main aim was to identify the recurrence of gouty arthritis, tophi or urolithiasis after discontinuation of ULT. Secondary aims included the assessment of adverse events, ULT reintroduction rates, and factors associated with relapse.

**Methods:** We conducted a systematic literature review of clinical studies. We included all types of studies except case studies, investigating the effect of discontinuation of any ULT in adults with long-term therapy. We searched the following databases from inception to March 2016: The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Science Citation Index and ClinicalTrials.gov. Papers written in English or French were included.

**Results:** From 4639 studies, eight met the eligibility criteria and were included. Most of the studies predated 2000. Mean follow-up duration after discontinuation ranged from 12 months to 96 months. Five studies focused on ULT in gouty arthritis and tophi, two studies focused on ULT used in urolithiasis, and one in asymptomatic hyperuricemia. Relapse rate was high in gout (around 50%), and lower in urolithiasis (15%). These clinical effects occurred one to three years after ULT discontinuation, and a low serum urate level before and after ULT discontinuation was associated with fewer gout recurrences. ULT discontinuation was followed by an increase of serum urate level in most studies and had no consequences on creatinine levels in patients without renal dysfunction.

**Conclusions:** Discontinuation of ULT cannot be considered a globally advisable strategy for all patients in routine clinical practice yet. Further studies should be conducted to consider larger population in primary care, and discontinuation of other ULT, including febuxostat.

## INTRODUCTION

Gout is a chronic urate crystal deposition disease characterized by an excess burden of uric acid in the body. The most common symptoms are recurrent acute attacks of inflammatory arthritis and urinary tract stones. Gout is one of the most common rheumatic diseases in adults (3.9 % of adults in the US, 0.9% in France) (1,2). The prevalence of gout has increased in the last decade, in relation to the increasing age of population, and increasing incidence of obesity, alcohol consumption, metabolic syndrome, hypertension, diuretic use and chronic kidney disease (3).

Urate-lowering therapy (ULT) is recommended to decrease risk of acute attacks of gouty arthritis, in case of symptomatic hyperuricemia (intermittent gouty arthritis (≥2), chronic tophaceous gouty arthropathy, or urate urolithiasis), whether it is primary or secondary (hemopathy, nephropathy, iatrogenic hyperuricemia) (4,5). The 2016 update of EULAR recommendations state that ULT is recommended with the first incidence of gouty arthritis for young patients (less than 40 years), or in patients with very elevated serum urate levels (> 8.0 mg/dL), and/or comorbidities (renal insufficiency, high blood pressure, coronary insufficiency, heart failure) (6). Pharmacological management of asymptomatic hyperuricemia has not been addressed, since the association between hyperuricemia and ischemic heart disease, or high blood pressure, has not been established with a sufficient level of evidence (4,7–9).

Two classes of ULT are used: xanthine oxidase inhibitors (allopurinol and febuxostat), which reduce production of uric acid; and uricosuric agents (probecenid, benzbromarone and sulfinpyrazone), which decrease tubular reabsorption of uric acid, and promote renal excretion. Allopurinol and febuxostat are the most commonly used ULTs, owing to their effectiveness and safety (4,5). These drugs promote the dissolution of monosodium urate monohydrate crystals, and prevent formation of new crystals, by keeping SUL below the sodium urate saturation rate (6.0 mg/dL). ULTs are recommended for long-term use, although this consensus is based on a moderate level of evidence (10).

Allopurinol and other ULTs have been reported to be associated with the lowest drug adherence rate among chronic diseases (36.8%) (11). The same observation was made among selected chronic rheumatic conditions (12): 17 to 44% of patients use their medication at least 80% of the time one year after initiation (13–16). Furthermore, one out of four patients with

gout discontinue their ULT medications during the first year of treatment (14). In gout disease, noncompliance is more frequent in young male patients without comorbidities, such cardiovascular risk factor, and noncompliance increases over time and with increased dosage of allopurinol (12–15,17). These data are confirmed in other chronic rheumatic conditions (18). No relation between compliance and drug-related side effects has been observed (18).

Concerns related to discontinuation of life-long medications may include the risk of relapse, the time to relapse, the factors associated with relapse, and/or the possibility of adverse events (19,20). Other areas of interests include biological consequences of discontinuation, as well as discontinuation strategies (21–23). All of these topics require a comprehensive assessment. Thus, we conducted a systematic literature review of clinical studies addressing the issue of ULT discontinuation. Our main aim was to identify the recurrence of gouty arthritis, tophi or urolithiasis after discontinuation of ULT. Secondary aims included the assessment of adverse events, ULT reintroduction rates, and factors associated with relapse.

## METHODS

### Protocol and registration

The systematic reviews have been prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO): N°CRD42016042048.

### Eligibility criteria

We included all types of studies [all randomized control trials (RCTs), clinical control trials (CCTs) and observational studies (case control, longitudinal study)] with the exception of case studies, investigating the effect of discontinuation of ULT in adults with long-term therapy (18 years of age and over). Trials and studies assessing discontinuation of any ULT were included: xanthine oxidase inhibitors (allopurinol, febuxostat) or uricosuric agents (probenecid, sulfinpyrazone, benzbromarone). Studies assessing switches between ULTs were not included. Studies were included regardless of the indication of ULT (acute gouty arthritis, tophi, urate nephropathy, uric acid nephrolithiasis, prophylaxis of chemotherapy-induced hyperuricemia, asymptomatic hyperuricemia, other). Studies assessing short-term effects (less than three months) of discontinuation of ULT were not included. If the same participants were assessed at different point in time or in multiple studies, we extracted and analyzed all the data of different follow-up periods, and those with the longest follow-up period for analysis were selected.

The search was limited by language (English and French), and only studies including human subjects were included.

### Information sources

The following databases were searched from inception to up to March 2016: the Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Library, Wiley InterScience, MEDLINE (1996 to present), EMBASE (1980 to present), Science Citation Index (web of science) and ClinicalTrials.gov (www.ClinicalTrials.gov). Reference lists of articles were inspected for supplemental relevant studies. Conference abstracts of the

American College of Rheumatology/ The Association of Rheumatology Health Professionals (ACR/ARHP) Annual Meetings (2006-2015) and European League Against Rheumatism (EULAR) Annual Congresses (2002-2015) were also manually searched.

**Search**

The search strategy for MEDLINE was developed in collaboration with two librarians and adapted for each database (Table 1).

**Study selection**

Three review authors [VB and PM and JPF] independently screened titles and abstracts for inclusion of all the potential studies using *Abtrackr*. (24). Any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant were obtained and the same three reviewers [VB, PM and JPF] independently assessed these for inclusion; any disagreements were resolved by consensus. Duplicates were identified and excluded, and multiple reports of the same study were collated so that each study, rather than each report, was the unit of interest in the review. The selection process was recorded in sufficient detail to complete a PRISMA flow diagram.

**Data collection process**

Two review authors (VB and PM) extracted data independently; discrepancies were identified and resolved by consulting another author (JPF). A standardized, pre-piloted form was used to extract data from the included studies, for assessment of study quality and evidence synthesis.

**Data items**

The following information was extracted: (i) methods (study design, total duration of study, number of study centers and location, study settings, mean follow-up after ULT discontinuation, and date of study); (ii) participants characteristics (number, mean age, age range, sex, disease duration, severity of condition, diagnostic criteria, baseline data; inclusion

criteria, and exclusion criteria); (iii) interventions (type of discontinuation: abrupt, titration), comparison (if applicable), concomitant medications, excluded medications; (iv) outcomes (recurrence of gouty arthritis, tophi, urate nephropathy, or urolithiasis, adverse events, ULT reintroduction, serum urate level, serum creatinine level, time of measurement); (v) notes (funding, and notable declarations of interest of authors)

**Quality of individual studies**

Two review authors (VB and PM) independently assessed the quality of non-comparative studies using the first eight items of the methodological index for non-randomized studies (MINORS) tool (25). Any disagreements were resolved by discussion, or by involving another author (JPF). MINORS tool identifies 12 items, including 8 specifically designed for non-comparison trials: a clearly stated aim, the inclusion of consecutive patients, a prospective collection of data, endpoints appropriate to the aim of the study, an unbiased assessment of the study endpoints, a follow-up period appropriate to the aim of the study, loss to follow-up less than 5%, a prospective calculation of the study size, an adequate control group, contemporary groups, baseline equivalence of groups and adequate statistical analysis. The items are scored 0 for not reported, 1 for reported but inadequate, or 2 for reported and adequate. The highest score possible was 16 for non-comparative studies, and 24 for comparative studies.

**Data synthesis**

After extracting data from each study, structured tables were used to summarize the main characteristics of included studies and a study-by-study narrative synthesis of the other findings was provided. It was anticipated that there would be limited scope for meta-analysis because of the range of different outcomes measured across the small number of existing studies.

## RESULTS

### Study selection

In the electronic search, a total of 4,639 articles were retrieved: 1,220 from MEDLINE, 573 from Web of science, 90 from CENTRAL, and 80 from ClinicalTrials.gov and 2,675 from EMBASE (Figure 1). The hand search through conference abstracts of the ACR/ARHP Annual Meetings (2006-2015) and EULAR Annual Congresses (2002-2015) retrieved one article.

A total of 557 duplicate publications were identified. After deleting duplicates and screening titles and abstracts, 4,082 articles were excluded leaving 21 articles for full-paper review. Among these, 13 were excluded, and eight were included in this review.

### Study characteristics

Eight studies assessing biological and clinical effects of discontinuation of ULT met eligibility criteria: design, methods, number of patients enrolled, discontinuation rates and other characteristics of included studies are listed in Table 2. All studies were observational. No RCTs have been identified. No ongoing studies were reported from ClinicalTrials.gov.

Most of the studies predated 2000. All studies were performed within a single country (Spain, England, Japan, Czech Republic, Egypt, Indonesia and the Netherlands). Most of the studies were conducted in hospital settings.

Mean duration of follow-up after discontinuation ranged from 12 to 96 months. Seven studies assessed the consequences of an abrupt discontinuation of ULT. A tapering strategy has been used in one study only, though strategies details were not reported (26). Five studies focused on ULT in gout (gouty arthritis or tophi), two studies focused on ULT used in urolithiasis, and one in asymptomatic hyperuricemia. Two studies (27,28) probably used data from similar patients: the authors of these two studies were contacted, and confirmed this possibility. However, they were not furthermore able to assess the ratio of patients that may have been included in both studies.

In two studies (27,28), the 1977 American Rheumatism Association (ARA) preliminary criteria for primary gout (29) were used. Darmawan *et al.* used also these criteria if the diagnostic by identification of crystals of monosodium urate in the synovial fluid was not possible. Perez-Ruiz *et al.* definite gouty arthritis on the basis of monosodium urate crystal identification from a tophus or synovial fluid aspiration. Loebl *et al.* did not report any used diagnostic criteria.

No studies reported any adverse event.

**Quality of studies**

The results of the quality assessment using the MINORS tool are reported in Table 2. Quality scores ranged from 5 to 14 out of a possible 16.

**Result of individual studies**

*Clinical and biological effects of discontinuation in gouty arthritis and tophi*

The first study by Loebl *et al.* (30) included 33 patients with a diagnosis of gouty arthritis. Patients had a mean age of 58 years (33-75 years) and 97% of them were male. All patients had a normal renal function and none were over-producers of uric acid. The mean length of history of gout before starting therapy was 15 years (0.5-42 years), with an average of 4-5 attacks per year before treatment. Included patients were treated with allopurinol with a mean daily dose of 378 mg. In five patients, the drug had to be discontinued because of a side effect (skin rash or malaise probably attributable to the drug). In other cases, the drug was stopped after full discussion with patients. Twelve (36.4%) patients had a recurrence of arthritis and twenty-one (63.6%) remained free of symptoms after a mean follow-up of 19.8 months. Thirteen (39.4%) patients restarted the drug after a mean duration off treatment of 55 weeks because of recurrence of gouty arthritis, or because of the patient's or his physician's preference. One patient restarted because of acid uric cristalluria and one restarted to avoid a risk of post-operative gout. Final discontinuation rate of allopurinol at the end of the study was 61% after a mean follow of 19.8 months. Patients who had no recurrence tended to have lower plasma uric level while on ULT, than those who had a recurrence of gouty arthritis.

In the Dutch study by Gast *et al.* (28), 10 patients were included. All patients had tophaceous gout. Included patients were all males with a mean age at onset of gout of 46.1 years (25-54 years), and a mean body mass index (BMI) of 22.6 $kg/m^2$. Patients were supervised every 3 to 6 months, during a mean time of 30.8 months (5 to 52 months). Three patients were treated with benzbromarone (mean dose: 100 mg/day), six with allopurinol (mean dose 300 mg/day) and one patient was treated with both allopurinol and benzbromarone. Five (50%) patients remained free of gout attacks or tophi. Five (50%) patients had recurrence of arthritis, and two of them redeveloped tophi. Recurrence of arthritis occurred after a period without ULT from 5 to 29 months (mean 15.8 months). The final ULT discontinuation rate was 80%: two patients restarted the drug because of a tophus attack. Lower BMI, early onset age of gout, serum urate level before discontinuation and duration of ULT before discontinuation tended to be associated with fewer recurrences of arthritis.

In a second Dutch study conducted by Van Lieshout-Zuidema *et al*. (27), 21 patients were included by retrospective investigation. All patients had chosen to discontinue their ULT. All patients were men with a mean age of 45.1 years (25-63 years), and had tophaceous gout. They had a mean history of gout of 5.9 years (1-20 years), and took ULT for a mean period of 6.4 years (1-19 years). Twelve (57.1%) patients used allopurinol and nine (42.9%) a uricosuric agent (specific agent name was not reported). Patients were met every three months. Among them, 17 (81%) had recurrence of arthritis after 19 months (4-52 months) of follow-up, and nine (42.9%) who also developed tophi. ULT was reintroduced in twelve (57.1%) patients (nine because of tophi, three because arthritis was not controlled by colchicine alone). No significant differences were observed between patients with or without recurrence of tophi. No patient presented any urolithiasis during the study.

In the 2002 Indonesian study by Darmawan *et al.* (26), a group of 206 patients discontinued their ULTs. All were Malayo-Polynesian men, and were treated with either allopurinol alone, or allopurinol and probenecid. ULT was discontinued when a patient was free from acute attack for at least two years, with a serum urate level below 5 mg/dL. After 8 years, 176 patients remained in the cohort: 84 (40.8%) patients were free of gout without treatment, 86 (41.7%) were treated again with allopurinol, and six (2.9%) were treated again with allopurinol and probenecid. Overall, 122 (59.2 %) patients had a recurrence of gout after eight years. No urolithiasis and no deterioration of renal function were recorded during the eight years in those who had discontinued ULT.

In the most recent study by Perez-Ruiz *et al*. (31), 211 patients were included, with a mean age at onset of clinical gout of 59.9 years (±11.6 years). Among these, 202 (95.7%) were males, and the time from onset of gout to the beginning of the study was 6.7 years (±6.3 years). All have been treated for a mean time of 66 months (±5.5 years) before study. Eighty-two patients (38.9%) had a recurrence of gout during the follow-up period after discontinuation (mean time before clinical effects: 56 months). However, none of the 27 patients with serum urate lower than 7 mg/dL level after ULT discontinuation had any recurrence of gout. The only variables independently associated with gout recurrence were a higher serum urate level during treatment, and during follow-up after ULT discontinuation (Cox multivariate survival analysis, $p<0.05$). In addition, factors associated with serum urate level <7 mg/dL after ULT discontinuation were reduction of weight ($p<0.01$), treatment with losartan ($p=0.02$) and treatment with fenofibrate ($p=0.02$). Additional data were presented at the 2010 ACR meeting. In this analysis, 179 patients were included with a follow-up of 34 ±23 months (1-124). Lower renal function at discontinuation, presence of proteinuria and the highest quartiles of serum urate levels after discontinuation were independently and significantly associated with renal dysfunction (renal function <60 ml/min) after ULT discontinuation (32).

*Clinical effect of discontinuation in urolithiasis*

The Japanese study by Kenjiro Kohri *et al.* (33) included 87 patients with idiopathic calcium oxalate or calcium phosphate urinary stones. They had a mean age of 41.8 years (33-75 years), and all of them were male. They were randomized with allopurinol, or allopurinol and trichlormethiazide. Among them, 53 discontinued their ULT for at least twelve months and were studied. The mean duration of ULT was 4.8 years. Mean study follow-up after discontinuation was two years. Nine patients (15.1%) had a recurrence of urolithiasis after allopurinol discontinuation (mean time to relapse: 9.5 months). Urolithiasis relapse rate after ULT discontinuation was lower than that during treatment (48.3%)**.** The number of new stones/year/patient after ULT discontinuation decreased by around 50% compared with the treatment period (paired t-test, $p<0.05$). Urinary calcium, uric acid excretion, oxalate and citrate increased again in the two groups after discontinuation, but stayed lower than pretreatment levels in group 1 ($p<0.05$). Phosphate and magnesium levels showed no significant difference.

Jabor *et al.* (34) have followed 508 calcium-oxalate urolithiasis formers, in the Kladno hospital, Czech Republic, during ten years. The effect of allopurinol on uric acid parameters was studied by conducting a retrospective analysis: allopurinol (100 mg/day) was first introduced, and then discontinued in 24 patients. A decrease of serum urate level and the output of urate (daily output of urate, ratio of urine urate to urine creatinine, and ratio of the daily urate to the patient mass) were observed after introduction of allopurinol. All the parameters reincreased after discontinuation of allopurinol.

*Clinical effects of discontinuation in asymptomatic hyperuricemia*

In the Egyptian study conducted by Talaat *et al.* (35), chronic allopurinol therapy was discontinued in patients with asymptomatic hyperuricemia. There were 50 patients (19 females, 31 males) with stage 3 and 4 chronic kidney disease related to hypertension. The authors assessed the impact of the discontinuation of the drug on the control of hypertension, and progression of chronic kidney disease. Patients were treated with allopurinol during a mean time of 17±3.4 months before discontinuation. Patients were further classified according to their antihypertensive regimen (with or without renin-angiotensin system inhibitors, RASIs). Serum urate levels, blood pressure and kidney function were regularly measured one year before and one year after discontinuation of allopurinol. In all patients, serum urate levels increased again after allopurinol discontinuation (11.5 mg/dL at 2 weeks, 12.4 mg/dL at twelve months). No associations were observed between antihypertensive regimens and serum urate levels before and after allopurinol discontinuation. No significant modifications of blood pressure were observed in patients with RASIs. Significant rises in both systolic blood pressure (unpaired 2-tailed Student test, $p<0.05$) and diastolic blood pressure (unpaired 2-tailed Student test, $p<0.05$) were observed two weeks after allopurinol discontinuation in patients with antihypertensive regimens without RASIs. Also, kidney function decreased faster in the group of patients without RASIs (unpaired 2-tailed Student test $p<0.05$).

**Additional analyses**

In the majority of studies, serum uric acid level increased again one to three weeks after ULT discontinuation (Table 2).

## DISCUSSION

This systematic review examined the literature on the clinical and biological effects of the discontinuation of ULT. Relapse rate was high in gout (around 50%), and was lower in urolithiasis (15%). These clinical effects occurred one to three years after ULT discontinuation, and few predictive factors have been identified. From a biological perspective, ULT discontinuation was followed by a rapid reincrease of serum urate level. ULT discontinuation had no consequences on creatinine levels in patients with normal renal function, however renal function of patients with kidney disease tended to deteriorate. These results should be balanced with important limitations relative to internal and external validity of the studies included (design, power, and representativeness of participants).

### Clinical effects after discontinuation of urate-lowering therapy

*Relapse rate and time to relapse*

Results of this review suggest an important rate of relapse of gout after ULT discontinuation. The highest gout recurrence rate (81%) was observed in one study only, and could be explained by the inclusion of patients with more severe gout (all patients had a tophaceous gout before treatment with ULT). Relapse of tophus was less frequent than gouty arthritis in this review, and appeared only in patients who had tophi before ULT. Gout relapse rate after ULT discontinuation should be balanced with the relapse rates reported in patients still maintained with ULT. In their 253 gouty patients study, Becker *et al.* showed that there was a 64% rate of recurrence of gout flares between nine and 52 weeks of allopurinol treatment (11% between 49 and 52 weeks) *(36)*. In Sohji *et al.* study, 29.7% of patients treated with allopurinol, benzbromarone or both, experienced gout flares during a three year period of follow-up (37). Further studies should consider the comparison of discontinuation versus maintenance of ULT, with randomized designs, in order to assess to what extent relapse of gout is associated with ULT discontinuation.

Gout flare recurrences occurred several months after ULT discontinuation (15.8 to 56 months). However, only three studies reported this information. The two studies that reported a shorter time to relapse (15.8 and 19 months), were those with the smallest cohort size, and probably used data from similar patients with tophi. The third study has the largest cohort and

reported the longest time to relapse (56 months before gout recurrence). Therefore, although relapse of gout flare may seem high, it does not occur before a mean of one year, in the most severe patients.

Few studies were identified with limited sample size and shorter follow-up duration that have assessed the effects of ULT discontinuation in alternative conditions. In patient with urolithiasis, only one study reported a low relapse rate of urolithiasis (approximately 15%), two years after allopurinol discontinuation. Two randomized studies showed 17.2% and 42.9% of recurrence of urolithiasis during allopurinol therapy, but stones recurrences appeared after a longer time period (around 33 months) (38,39). A longer follow-up duration should be considered to determine the risk of relapse of urolithiasis after ULT discontinuation.

*Factors associated with relapse after discontinuation of ULT*

Serum urate level before ULT discontinuation consistently tended to be associated with fewer gout recurrences in initial studies (27,28,30). However, Perez-Ruiz et al only statistically confirmed this association in the largest study. A second factor identified was mean serum urate level after ULT discontinuation. Perez-Ruiz *et al.* suggested a potency for intermittent use of ULT(31). They proposed to maintain the serum urate level just below the saturation level (6-7 mg/dl) to avoid new crystal formation, after a period of crystal depletion (far below 6 mg/dL) of 5 years of ULT after tophi, if present, had resolved. Indeed, in another study, the time required for disappearance of urate crystals in synovial fluid in non tophaceous patients was 3 to 33 months (40). Such regimen could be used in patients without tophus, who would be discouraged by a life-long therapy, in order to improve compliance and frame ULT discontinuation.

Several others factors have been explored across studies. Among them, reduction of weight, treatment with fenofibrate and treatment with losartan seemed to be associated with lower serum urate levels (<7 mg/dl) (31). These factors were not directly associated with less recurrence of gout, but the topic could be studied further with a larger sample size. These data are supported by previous studies which noted that appropriate lifestyle such as low animal purine food, lower level of seafood consumption, weight loss, decrease in alcohol consumption, including beer, keep an important place in the management of gout (41–44).

Identification of other predictive factors of recurrence of gout is still necessary to design advisable strategies for ULT discontinuation in daily practice.

## Biological effects after discontinuation of Urate-Lowering Therapy

*Serum urate level*

All study results revealed that serum urate levels increased rapidly (1-2 weeks) after discontinuation of ULT. Post-discontinuation serum urate levels were similar to pre-treatment levels in most studies. Only one study reported a significant association between mean serum urate level after ULT discontinuation and relapse. Further studies are necessary to assess the potential benefits of serum urate level monitoring after ULT discontinuation.

*Creatinine serum level*

Discontinuation of ULT had no consequences on creatinine serum level in patients without renal dysfunction. In one study, conducted by Talaat *et al.,* patients with chronic kidney insufficiency (stages 3 and 4) and hypertension, who were not treated with RASIs experienced a more rapid increase in creatinine serum level than other patients. This result is consistent with those observed in rat model of mild hyperuricemia, that showed an amplification of the noxious effects of the angiotensin 2 mediated by uric acid. This physiopathological pathway leads to intrarenal inflammation, contributing to the deterioration of kidney function. Similarly, in the largest cohort study included in this review, lower clearance of creatinine at withdrawal and presence of proteinuria were independently and significantly associated with decrease of clearance of creatinine after ULT withdrawal. Discontinuation of ULT should thus be cautious in patients with kidney function impairment, especially in those with hypertension who are not treated with RASIs.

## Strengths and limitations

The strengths of this study include an exhaustive search strategy that identified more studies than the recent systematic review of Choi *et al.* that focused on gout, and did not retrieve some of the studies identified in the present systematic review (10). Also, the

systematic review was extended to studies that explored indications other than gout, which brought consistent results (such as reincrease of serum urate level after ULT discontinuation), and also raise complementary issues (such as possible blood pressure increase in patients who are not treated with RASIs).

The present review also has limitations. Despite an extensive search strategy, a limitation of this review is the possibility of incomplete retrieval of identified research. Also, this review is mainly limited by the quantity and quality of published manuscripts. No randomized control trials were identified, only observational longitudinal studies. In such studies, the main limitation was associated with the lack of a control group, for the normal evolution of the condition under medication, and would determine the clinical effects truly associated with the discontinuation of ULT. A possible overlap of patients across two studies is also possible. Information was missing in some studies, in particular details about setting and time to relapse or symptoms. Moreover, several studies had limited sample size: more than half of the studies included 50 patients or less. Such figures reduce the statistical power, and the ability to provide precise estimates of relapse rates. The study conducted in patients with asymptomatic mild hyperuricemia had the shortest follow-up (12 months): a longer follow-up would be necessary to ascertain the results in this specific population, in which use of ULT is still considered off-label, although highly frequent (25 to 91 %) (45–48).

Selection criteria of participants in the majority of included studies made it difficult to generalize of the results to a greater population and no studies conducted in primary care were identified. It would be interesting, however, to conduct such a study, considering the importance of the ULT prescription in larger, unstudied populations: 95% of allopurinol was prescribed outside of the hospital in 2013 (49). Also, primary care patients often have a less severe form of gout, with fewer tophi and refractory gout. (50). It is likely that if a study assessing ULT discontinuation were conducted in primary care, the relapse rate of gout would be lower than those identified in the present review. Furthermore, the effects of discontinuation of febuxostat has not been studied, although this is a frequently used ULT: 16% of ULT prescription in France (49), 6% of ULT market share (51) and 14,4% of new ULT users in the United-States (52).

## CONCLUSION

This systematic review demonstrates that relapse of gout after ULT discontinuation is frequent: one out of two patients experiences recurrence of gout. Relapses of gout are delayed (33 months after discontinuation), and short-term prognosis after ULT discontinuation seems favorable if serum urate level was low during ULT. Alternatively, relapses of urolithiasis were rare (around 15%) after ULT discontinuation.

Discontinuation of ULT cannot be considered a globally advisable strategy for all patients in routine clinical practice. Certain factors may facilitate a framed ULT discontinuation. These factors include: a sustained low serum urate level during ULT, a low serum urate level after ULT discontinuation, and the absence of kidney impairment. Further studies should be conducted to consider larger population in primary care, or discontinuation of other ULT, including febuxostat.

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## CONTRIBUTIONS

1. Draft the protocol: VB, PM, AM, HM, BG, JPF

2. Study selection: VB, PM, JPF

3. Extract data from studies: VB, PM, JPF

4. Carry out the analysis: VB, PM, JPF

5. Interpret the analysis: VB, PM, JPF

6. Draft the final review: VB, PM, JPF

7. Critical revision of the review for important intellectual content: VB, PM, JPF

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**FIGURES**

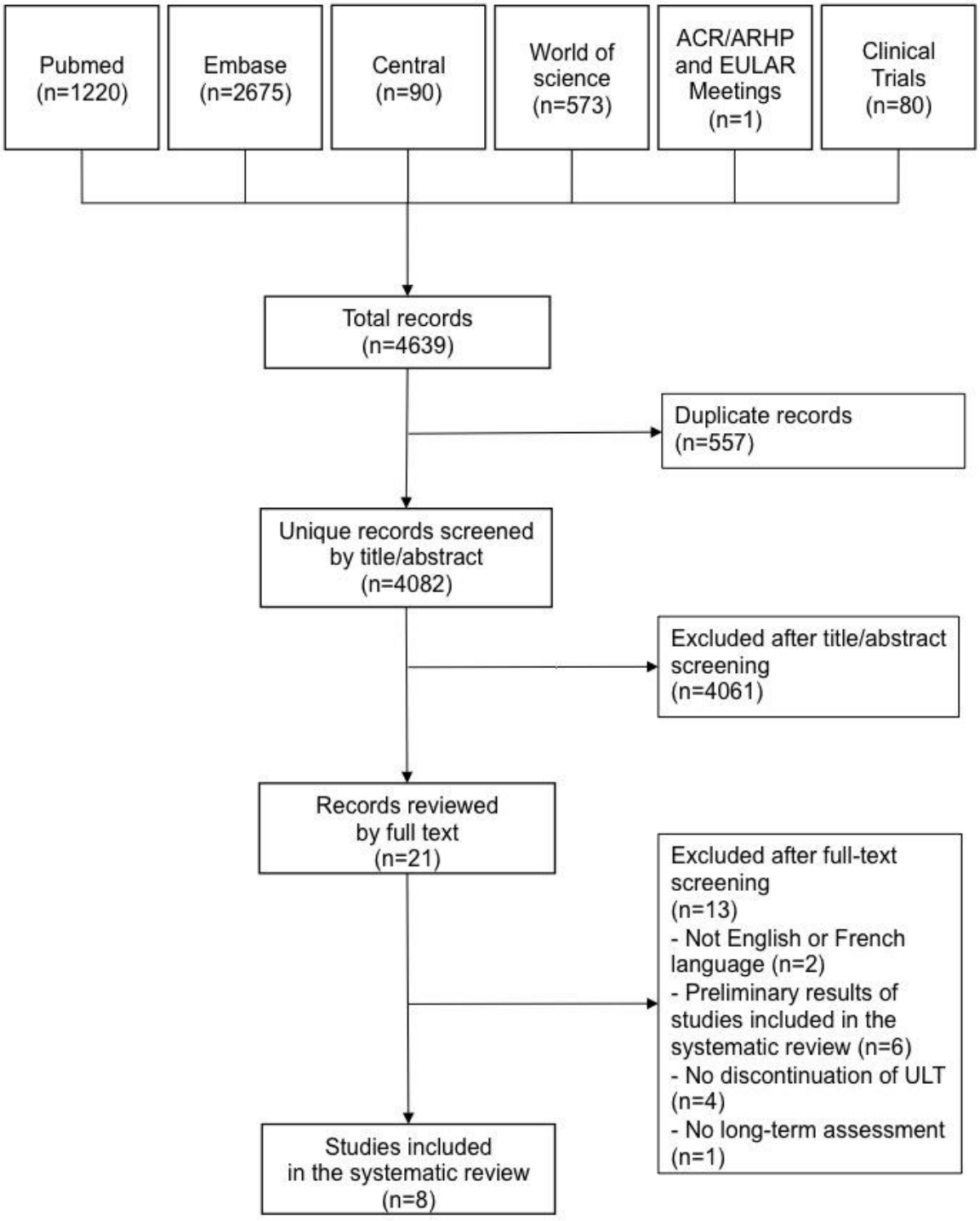


**Figure 1.** Flowchart of study selection

**TABLES**

**Table 1.** Defined search strategy for the extraction of pertinent studies from Medline

| **Outcome** | **Descriptor** |
|---|---|
| Search for urate-lowering drug | 1. allopurinol |
| | 2. febuxostat |
| | 3. probenecid |
| | 4. benzbromarone |
| | 5. urate lowering |
| | 6. xanthine oxidase inhibitor |
| | 7. antihyperuricemic |
| | 8. anti-hyperuricemic |
| | 9. gout suppressants |
| | 10. OR/1-9 |
| Search for discontinuation | 11. stop* |
| | 12. withdraw* |
| | 13. cess* |
| | 14. discontinu* |
| | 15. withhold* |
| | 16. step-down |
| | 17. deprescri* |
| | 18. OR/11-17 |
| Search for humans studies | 19. animals (Mesh) |
| | 20. not humans (Mesh) |
| | 21. NOT 19-21 |
| Search for combinations | 22. 10 AND 18 AND 21 |

**Table 2.** Characteristics of included studies

| Study details | | | | | | | | Intervention details | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Authors Year of publication Country** | **MINORS** | **Study design Settings** | **N *** | **ULT Agent** | **ULT treatment duration before ULT discontinuation (months), mean (range)** | **ULT indication** | **Follow-up after discontinuation (months), mean (range)** | **Serum urate level pre-ULT, during ULT, and after ULT discontinuation (mg/100mL), mean** | | | **Clinical effects (relapse)** | **Time to relapse (months), mean (range)** | **Final discontinuation rate#** |
| Loebl *et al.* (30)<br>1974<br>England | 5 | Prospective | 33 | Allopurinol | 21.4<br>(4.4-54.3) | Acute arthritis | 19.8 (3.2-48.3) | 8.4 | 5.5 | 8.8 | 36.4% (gout) | NR | 61% |
| Gast *et al.* (28)<br>1986<br>The Netherlands | 12 | Prospective<br>University hospital | 10 | Allopurinol, Benzbromarone or Allopurinol+ Benzbromarone | 86.4 | Tophus and acute arthritis | 30.8 (5-52) | 9.58 | 5.55<br>5.04 (group without recurrence)<br>6.05 (group with recurrence) | 9.92 | 50%<br>(gout: 50%, tophus: 20%) | 15.8 (5-29) | 80% |
| Van Lieshout-Zuidema *et al.* (27)<br>1992<br>The Netherlands | 11 | Prospective<br>University hospital | 21 | Allopurinol or uricosuric agent | 76.8<br>(12- 228) | Tophus and acute arthritis | 37.7 (4-107) | 9.58 | 5.72 | 9.41 | 81% (tophus: 42.9 %, gout: 81% ) | 19 (4-52) | NR |
| Darmawan *et al.* (26)<br>2002<br>Indonesia | 11 | Prospective<br>Hospital | 206 | Allopurinol±Probenecid | ≥24 | Acute arthritis ±tophus | 96 | NR | NR | NR | 59.2% gout | NR | 40.8% |
| Perez-Ruiz *et al.* (31)<br>2011<br>Spain | 14 | Prospective<br>University hospital | 211 | Allopurinol, Benzbromarone or Allopurinol+ Benzbromarone | 66 (NR) | Acute arthritis ±tophus | 33.1 (NR) | 8.8 | 4.9 | 8.5 | 38.9% gout | 56 (NR) | NR |
| Kohri*et al.* (33)<br>1990<br>Japan | 13 | Prospective | 53 | Allopurinol | 57.6 (16-96) | Calcium oxalate or calcium phosphate urolithiasis | 24 (7- 45.6) | NR | NR | NR | 15.1 % urolithiasis | 9.5 | NR |
| Jabor (34)<br>1996<br>Czech republic | 6 | Prospective<br>Hospital | 24 | Allopurinol | NR | Calcium oxalate urolithiasis | NR | NR | 5.04 | 5.58 | NR | NR | NR |
| Talaat *et al.* (35)<br>2007<br>Egypt | 12 | Prospective | 50 | Allopurinol | 17 (13-20) | Asymptomatic hyperuricemia | 12† | 9.6 | 7.5 | 12.4 | NA | NA | NA |

ULT: Urate-lowering therapy

NR: not reported

NA: not applicable

* patients who discontinued ULT within the study

# at the end of the follow up

† except 6 patients: 6 months only

Vu, le Président du Jury,

Vu, le Directeur de Thèse,

Vu, le Doyen de la Faculté,

BESLON Virginie

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# EFFETS DE L'ARRÊT DES MÉDICAMENTS HYPOURICÉMANTS: REVUE SYSTÉMATIQUE DE LA LITTÉRATURE

## RÉSUMÉ

**Introduction**: La goutte est la maladie rhumatismale la plus fréquente. Les traitements hypouricémiants (THU) sont recommandés pour prévenir les crises de goutte en cas d'hyperuricémie symptomatique. L'allopurinol et le febuxostat sont les THU les plus utilisés dans la goutte. Ils ont un faible taux de compliance: 24% des patients arrêtent définitivement leur traitement après un an d'utilisation. Notre objectif principal fut d'identifier la récurrence de survenue d'arthrite goutteuse, de tophus ou de lithiases urinaires après l'arrêt d'un THU. Nos objectifs secondaires étaient d'étudier les effets indésirables à l'arrêt, les taux de réintroduction des THU et les facteurs de risques liés à la récidive.

**Méthode:** Nous avons réalisé une revue systématique de la littérature. Nous avons inclus tous les types d'études, excepté les études de cas, étudiant les effets de l'arrêt d'un THU chez l'adulte ayant ce traitement au long cours. Nous avons recherché dans les bases de données suivantes jusqu'en Mars 2016: The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Science Citation Index and ClinicalTrials.gov. Les études écrites en français ou anglais ont été incluses.

**Résultats:** Sur 4639, 8 articles étaient éligibles et ont été inclus. La plupart des études étaient antérieures aux années 2000. La durée de suivie moyenne après l'arrêt était de 12 à 96 mois. Cinq études abordaient les THU dans l'arthrite goutteuse et le tophus, deux études abordaient les THU dans les lithiases urinaires et une dans l'hyperuricémie asymptomatique. Le taux de récurrence était élevé dans l'arthrite goutteuse (environ 50%) et faible dans les lithiases urinaires (15%). Ces effets cliniques sont survenus, en moyenne, un à trois ans après l'arrêt des THU et un taux bas d'uricémie avant et après l'arrêt était associé à la diminution des récurrences d'arthrite goutteuse. L'arrêt des THU était suivi par l'augmentation rapide du taux d'acide urique dans le sang. Le taux de créatinine n'était pas modifié après l'arrêt des THU chez les patients avec une fonction rénale normale.

**Conclusion:** L'arrêt des THU ne peut, à l'heure actuelle, être considéré comme une stratégie recommandable en routine. D'autres études devraient être menées, notamment en soins primaires, ou étendues à d'autres THU comme le febuxostat.

## MOTS-CLÉS:

Traitement hypouricémiant, goutte, lithiase urinaire, allopurinol, febuxostat, acide urique