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Evidence-based management of gout - A systematic search and review

Md Abu Bakar Siddiq

Abstract

Gout is the most common form of inflammatory arthritis. Hyperuricaemia is the pre-requisite for gout and is influenced by variable modifiable and non-modifiable risk factors. Clinical features unique for gout are due to deposition of monosodium urate (MSU) crystal in articular and extra-articular tissues. Among various treating agents, anti-inflammatory drugs and urate lowering therapies (ULT) are used widely and successfully, however, non-medicinal means are also effective in the disorder. In their updated guidelines, ACR (2012) and EULAR (2016) recommended both medicinal and non-medicinal approaches that could be used in treating gout, though some of the recommendations are based on lower level of evidence. Moreover, researchers' continued effort in finding new gout managing agents appear promising, for example, role of Lesinurad in gout management (CLEAR1, CLEAR2). In this new synthesis the author is aimed to provide updated information on gout management based on a systematic review including published work within last ten years between 2008 and 2018 and for this purpose, using 'clinical trials in gout management' string, published worked searched in PubMed database from 1st September 2018 to 30 October 2018. Besides the recent ACR and EULAR-evidence based management guidelines, the author reviewed another 91 (total 93) articles to make this new draft – 39 articles describe role of pharmacological agents and 54 describe different gout risks, pharmacokinetics/pharmacodynamics of ULT, association between raised sUA level and renal impairment, efficacy of non-pharmacological agents in reducing sUA. According to published work, anti-inflammatory agent is the most appropriate drug group in mitigating inflammatory symptoms of gout, though they often adversely affect over other vital

organs with impaired function. Besides ULT, uricase analogues are also found useful in non-refractory gout. Since anti-inflammatory agents and ULT contraindicate in some clinical conditions, intra-articular steroid and or adrenocorticotropic hormone (ACTH) are appropriate alternatives instead. However, head-to-head comparison between different NSAIDs, NSAID and prednisolone, NSAID and colchicine are yet to perform. Use of combined anti-inflammatory preparations in gout is also based on lower level of evidence. Regarding effective maximum dose and long-standing impact of ULT on vital organs we are yet to reach a conclusion. Likewise, non-medicinal approaches are widely using in achieving target sUA level, though some of them are based on biased study outcomes and or study with inadequate power, requiring further analysis. Among non-pharmacological approaches, life-style modification, restriction of purine rich diets, avoidance of gout inciting agents are important, but inconclusive. Educating patients' about diseases, risk factors, available treatment options and side effects from them are also important in terms of achieving sUA level, nevertheless too much counseling sometimes could be worthless.

Keywords: Gout, Hyperuricemia, Lesinurad, Life style, Prednisolone, Uric Acid, Urate Oxidase

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1. Introduction

Gout is a form of acute inflammatory arthritis of metabolic origin that causes severe pain and swelling in peripheral joints and soft tissues. It most commonly affects the big toe, but heel, ankle, hand, wrist, or elbow are also involved. Hyperuricaemia is the pre-requisite of gout and resultant clinical manifestation is due to urate crystal deposition in articular and non-articular soft tissues. Uric acid is the end product of purine metabolism and hyperuricaemia signifies serum urate (sUA) level beyond normal level, greater than either 5.0 or 6.0 mg/dl *(Richette et al., 2017)* or 6.8 or 7.0 mg/dl *(Khanna et al., 2012).* When sUA level past the normal level of saturation, urate crystal starts to form and deposit in both intra-articular and or extra-articular soft tissues, with resultant detrimental clinical manifestations, called gout and is of two types: podagra (acute) and tophous (chronic) *(Khanna et al., 2012).* Hyperuricaemia (HU) is the result of either increased uric acid production or decreased excretion of uric acid; in case of increased uric acid production some intrinsic (for example, myelo-proliferative disorders, psoriasis) and extrinsic (like, consumption of red meat, seafood, purine-rich vegetables) factors contribute, however, in the millieu of renal impairment and concomitant ingestion of gout triggering diet and drugs could result in secondary HU, due to decreased excretion of uric acid *(Khanna et al., 2012).*

Hyperuricaemia (HU) doesn't always require drug management and sometimes non-pharmacological approaches appear sufficient. Persistent asymptomatic HU could lead to renal impairment and could develop unwanted cardiovascular events, for example atherosclerosis, requires timely judicial pharmacological interventions *(Khanna et al., 2012; Mallat, Kattar, Tanios & Jurjus 2016).* Furthermore, as incidental HU is a

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component of metabolic syndrome, further screening for other components of metabolic syndrome in asymptomatic HU could be a great help for both patients and treating physicians as well.

1.1 History of Gout

The Dominican monk, Randolphus of Bocking was the first person using the term gout, which was rooted from gutta, a Latin word meaning drop, and it was believed that the disorder was due to excessive flow of one of the four "humors" (????) that are essential for maintaining optimal health causing joint inflammation and pain as a consequence *(Deshpande 2014)*. However, nowadays, this belief doesn't exist in reality, as researchers' continuous effort over the last few years unveil exact pathophysiology behind hyperuricaemia and gout. Now it is well established that gout is a metabolic disorder, where accumulating negatively charged birefringent needle shaped monosodium urate (MSU) crystal in and around joint is required to proliferate features characteristic for gouty arthritis *(Zhang, Lee, Zhang, Furst, Fitzgerald & Ozcan 2016)*. Ultrasonographic appearance of 'double contour sign' over the hypoechoic aricular hyaline cartilage also favors gout diagnosis *(Thiele & Schlesinger 2007)*. Before crystallization of soluble urate, persistent hyperuricaemia is a pre-requisite and now we are well informed about factors responsible for HU and that triggers gout and more importantly how to treat them. Hippocrates remarks about gout is ubiquitous (aphorisms of gout) and many of them are still alive today - 'Eunuchs do not take gout', 'women does not take gout before their menopause', 'young men do not experience gout unless they indulge in coitus', 'an un-walkable disease', 'related to affluent community', etc. *(Deshpande 2014)*. However, regarding Hippocrates remark – 'Eunuchs do not take gout', study is lacking.

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1.2. Prevalence of gout

Across the world gout is becoming more prevalent. In the USA, the prevalence of gout based on managed-care administrative claims database, successive National Health Interview Surveys has shown an increasing trend. Same was true for epidemiological surveys from the UK. In a random population surveys in China an increased prevalence of gout has been documented from 3.6/1,000 in 2002 to 5.3/1,000 in 2004 *(Roddy & Dohery 2010).* The John Hopkins Precursors Study documented an incidence of 1.73/1,000 patient-years studying over 1216 male patients. In the Framingham Heart Study, following 5,209 people of 28 median years, gout incidence recorded as 1.4 in women and 4.0 in men. In all epidemiology study, gout incidence was higher in men especially among elderly people *(Roddy & Doherty 2010).*

Hyperuricaemia either primary or secondary some other disorders is considered the most important risk factor for the development of gout. Among various secondary factors, impaired renal function is considered the most important risk factor for gout *(Tsai, Lin, Kuo & Huang 2017)*. And failure to recognize and manage HU when appropriate, renal and cardiovascular functions could be compromised *(Rincon-Choles et al., 2017; Mallat, Kattar, Tanios & Jurjus 2016).* Alongside, diet, alcohol consumption, metabolic syndrome, hypertension, obesity, diuretics and chronic renal disease and osteoarthritis (for local gout) also contribute in flaring up of gout. Increased gout prevalence could also be due to suboptimal management, especially at primary care facility *(Roddy & Doherty 2010).* In an interesting review work, Desphande (2014) mentioned debauchery, intemperance and hereditary as another three important etiological factors for gout causation.

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Familial clustering is evident in primary gout. The SLC22A12 and SLC2A9 genes code for human urate transporter 1 (URAT1), is important in controlling reabsorption of uric acid from the proximal renal tubules, though influenced by some drugs - Lactate, Nicotinate and Pyrazinoate cause an increased reabsorption of uric acid, whereas Benzbromarone, Probenecid and Losartan cause a reduction in uric acid reabsorption and polymorphism of these genes could cause under excretion of uric acid as observed as of SLC22A12 gene among German Caucasians. Polymorphisms of glucose and fructose transporter, ABCG2 (a urate efflux transporter in proximal collecting duct cells) and SLC17A3 (encoding NPT4 - a proximal tubule sodium/phosphate co-transporter), SLC17A1 gene, which codes for NPT1, a sodium-dependent phosphate co-transporter, have also been found to associate with gout. The 64Arg variant of the β_3-adrenergic receptor gene induces insulin resistance by reducing lipolysis and hence an increase in adipocytes – a possible explanation for metabolic syndrome. The 677T allele of the methylene tetrahydrofolate reductase (MTHFR) gene provides substrate for *de novo* purine synthesis. Mutation of aldolase B (ALDOB) and hypoxanthine guanine phosphorribosylpyrophosphate genes are responsible for juvenile gout, Lesch-Nyhan syndrome.

1.3. Effective screening where strong family history of gout is identified

Screening for uric acid among family members and relatives could be interesting as revealed in Hungarians in 1992 *(Mituszova et al., 1992)*. In the study including 105 1st degree relatives of 22 Hungarian male gout, hyperuricaemia and gout was found more prevalent than that of general population and it could be due to involvement of several genetic and environmental factors *(Mituszova et al., 1992)*. Before then, in 1970, uric acid

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clearance was studied in 96 1st degree relatives of 37 patients with primary gout and a graded correlation (closer in the case of male relatives than in female relatives) was found between clearance values for patients and mean values for their relatives. It was suggested that the concept of multifactorial influences regulating uric acid levels in the blood can be extended to the renal handling of uric acid *(Scott and Pollard 1970).*

1.4. Symptomatology and diagnosis of gout

Gout is a mono-articular arthritis and involvement of the first metatarsophalangeal joint is a norm at least in the first attack, however, many other peripheral joints, namely, ankle, mid-foot, knee, etc. also could be affected *(Khanna et al., 2012)*. Gout could also be poly-articular, especially in patients' with a history of previous multiple single attack involving small joints of hand and feet, mimicking inflammatory (rheumatoid arthritis, psoriatic arthritis) and degenerative arthritis (generalized nodal osteoarthritis) *(Khanna et al., 2012).* In a published case report deposition of chalky white materials in the lumbar spinal canal reportedly proliferated features alike lumbago sciatica unveiled under MRI of lumbar spine; and further examination of the aspirated materials from the lumbar spinal canal after surgical exploration revealed MSU crystal under polarized microscopy *(Jegapragasan, Calniquer, Hwang, Nguyen & Child 2014).* Furthermore, soft tissue inflammation from MSU deposition, for example olecranon bursitis, retro-calcaneal bursitis, pre-patellar bursitis could also be developed over the olecranon process (olecranon bursa), posterior heel (retrocalcaneal bursa), and patella (prepatellar bursa), respectively. Joint destruction with deformity could result from longstanding, treatment failure gout with or without tophi and X-ray foot could reveal punched out bony lesion with overhanging edge. Lesch-Nyhan syndrome, a rare example of gout among pediatric

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patients' due to deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase, due to mutations in the HPRT gene located on the X chromosome *(Torres & Puig 2007)*.

Besides unique clinical manifestations, musculoskeletal ultrasonogram (MSUS) may serve as a non-invasive bed side test while examining gout patients having high specificity, especially in patients' with gout with shorter disease duration and without tophi, however modest sensitivity in diagnosing the inflammatory arthritis *(Ogdie et al., 2017).* Notable ultrasonographic features of gout are - hyperechoic, irregular band over the articular hyaline cartilage, hypoechoic to hyperechoic, non-homogeneous material surrounded by a small anechoic rim (wet sugar clumps) signifying tophus, and bone erosion adjacent to tophus *(Thiele & Schlesinger 2007).* Even though identification of MSU in synovial fluid is confirmatory for acute gout and American College of Physicians suggests synovial fluid analysis in patients with features unique for acute gout, though based on low-quality evidence, however some healthcare facilities may not adopt this prudent approach for gout diagnosis *(Qaseem, McLean, Starkey & Forciea 2017).*

1.5. Pharmaceutical Management of Gout

1.5.1 ACR (American College of Rheumatology) and EULAR (European League Against Rheumatism) Generic Guidelines -

drugs that are used to treat gout (based on updated recommendations from ACR and EULAR) include anti-inflammatory agents (glucocorticoids; non-steroidal anti-inflammatory drugs, NSAIDs; Colchicine), anti-interleukine (anti-IL1) (Anakinra, Canakinumab), xanthine oxidase inhibitors (XOIs), uricosuric agents, intra-articular steroid, etc.

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Among NSAIDs, COX-1 inhibitors are widely prescribed, nevertheless, COX-2 inhibitors are also effective and require judicious selections of candidates based on their level of associated cardiac, renal, hepatic, pulmonary co-morbidities *(Khanna et al., 2012)*. Randomized-controlled trial (RCT) based findings revealed, single anti-inflammatory agent is effective in managing gout symptoms, however, based on expert opinion, ACR *(Khanna et al., 2012)* and EULAR gout managing guidelines *(Richette et al., 2017)* suggested that combined anti-inflammatory agents could also be used in case of failure of single drug in the group.

1.5.2 Implications for use of other drugs

In cases of renal impairment, conventional NSAIDs should be avoided and situation like this, oral or intra-articular steroid are recommended *(Khanna et al., 2012).* Similarly, evidence suggests that anti-IL1, such as, Anakinra, Canakinumab, etc. could also be effective in preventing flaring of gout symptoms, and they could be a suitable alternative approach where other conventional anti-inflammatory agents are failed or found inappropriate. However, more study including its indications and overall safety concern in gout patients is required *(Khanna et al., 2012, Alexandre & Alexander 2015; Thueringer, Doll & Gertner, 2015).* Critically ill hospitalized patients with contraindications to conventional anti-inflammatory drugs, intra-muscular injection of ACTH could also be of great value *(Daoussis, Antonopoulos & Andonopoulos 2014).*

1.5.3 Urate Lowering Therapy

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Urate lowering therapy (ULT) is indicated to normalize increased sUA level and for this purpose xanthine oxidase inhibitors (XOIs) and uricosuric agents are the two mostly prescribed drug classes. Among XOI, Allopurinol and Febuxostat (non-purine XOI) are being used widely and Benzbromarone and Probenecid are the two commonly used uricosuric agents and recommended by EULAR and ACR to use in combination with XOI where appropriate *(Khanna et al., 2012)*. More recently study result suggest, Lesinurad is a promising serum urate lowering option and appears effective when used in combination with XOI *(Singh 2017)*. However, little is known about the safety profile of it and we are yet to have any RCT assessing superiority of one uricosuric over another, warranting further research addressing the fact. Lesinurad is not cost effective either. Effect of Lesinurad in minimizing tophus size is also not promising *(Richette et al., 2017)*.

1.5.4 Uric acid Conversion

Refractory gout, meaning that both symptoms amelioration and sUA level control are not achieved using above conventional (NSAIDs, Allopurinol) drugs and situation like this, ACR and EULAR recommends the use of pegloticase in their updated guidelines *(Richette et al., 2017)*. Pegloticase, a recombinant pegylated (PEG) uricase, it converts uric acid into more water soluble allantoin for easy excretion through kidney - first approved to use in the United States in chronic tophaceous gout, however later has got approval to be used in several European countries. Pegloticase failure could be the result of developing anti-pegloticase antibodies and infusion related adverse events. The drug is not cost effective either

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and could restrict physicians from prescribing this promising gout drug even when indicated *(Khanna et al., 2012)*.

1.6. Non-pharmaceutical options for management of gout

Alongside medicinal agents, patients' education regarding gout pathophysiology, clinical manifestation, diseases and drugs triggering gout (metabolic syndrome, diet, drugs), available treatment options and life-style modifications could contribute in effective control of sUA level and thereby could impede appearing painful gout manifestations and because of this ACR *(Khanna et al., 2012)* and EULAR *(Richette et al., 2017)* adopted them as recommendations to follow while managing gout in day to day clinical practice. Moreover, limited air-flow could contribute in developing HU and gout and it is important to address this issue while managing gout as well *(Fukuhara et al., 2017).*

1.6.1. Dietary factors - consumption of caffeinated coffee (≥ 4 cups/day), low-fat dairy products (skim milk, yogurt) and vitamin C supplementation have uricosuric effects *(Towiwat & Li 2015)*, however, impact of tea on serum uric acid level is inconclusive, rather depends on different tea varieties *(Towiwat & Li 2015)*. Based on a meta-analysis of 13 RCT, it was revealed that Vitamin C has the potential of reducing sUA while used in different clinical conditions *(Juraschek, Miller & Gelber 2011)*. In a Cochrane based review involving two RCT it was revealed that vitamin C has less potential than that of allopurinol in terms of reducing sUA level in gout patients *(Stamp, O'Donnell, Frampton, Drake, Zhang & Chapman 2013)*. Moreover, alcohol (beer, spirit, wine) *(Towiwat & Li 2015)*, vitamin D insufficiency *(Peng, Li, Li, Chao, Zhang & Zhang 2013)*, Western diet *(Rai, Fung, Lu, Keller, Curhan & Choi 2017)*, and purine containing diets of animal

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sources *(Zhang et al., 2012)*, sugar-sweetened drinks *(Roddy & Doherty 2010)* cause increased gout risk.

1.6.2. Drugs triggering and preventing gout manifestations - anti-hypertensive agents including angiotensin converting enzyme (ACE) inhibitors, diuretics, beta-blockers, non-Losartan angiotensin receptor blocker (ARB), etc. reportedly could induce gout flare up, in contrast, losartan, calcium channel blockers (CCB), statin, and fenofibrate cause a reduction in serum uric acid level and hence impede gouty flare up *(Choi, Soriano, Zhang & Rodriguez 2012*). In an original work with Korean gout patients' receiving ULT, fenofibrate was found effective in reducing sUA level further (Lee, Lee & Lee 2006). Low-dose aspirin also caused approximately twofold increased in recurrent gout attacks *(Zhang, Neogi, Chen, Chaisson, Hunter, & Choi 2013).*

Diuretics increase the net reabsorption of uric acid in the proximal tubule of the nephron with resultant HU and increase gout risk; and patients' could experience this hyperuricaemic effect within few days of starting treatment. Beta-blockers, including propranolol, atenolol, metoprolol, timolol, and alprenolol, also have been shown to increase sUA level, though the exact mechanism is yet to explore. Similarly, ACE inhibitors have also been associated with sUA levels *(Choi, Soriano, Zhang & Rodriguez 2012)*.

In contrast, CCB, namely nifedipine, amlodipine and diltiazem could cause an increase in glomerular filtration rate and thereby decrease reabsorption of uriac acid at proximal renal tubules causing increased clearance of uric acid and its metabolites. It has been reported that, Amlodipine and Nifedipine, respectively caused a 21% and 13% reduction of gout risks. Among various ARB, only Losartan reduces sUA level by about 20 to 25% because

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of its URAT1 inhibiting potential similar to other uricosuric agents as revealed among healthy volunteers, hypertensive individuals, and transplant recipients *(Choi, Soriano, Zhang & Rodriguez 2012).*

1.6.3. Airflow obstruction and gout - in a general population based study among 9865 sleep apnea subjects, 270 incident cases of gout was documented at 1-year follow-up with crude and multivariable rate ratios of incident gout 1.7 and 1.5, respectively. However, Zhang and colleagues (2015) recommended further study to test whether any benefit could register in terms of reducing gout risk, if appropriate measures are taken to correct sleep apnea-induced hypoxia *(Zhang, Peloquin, Dubreuil, Roddy, Lu, Neogi & Choi 2015).* Moreover, Fukuhara et at., reported a link between hyperuricaemia and airflow limiting disorders (AL) with respiratory symptoms among smokers in 156 patients aged over 40 *(Fukuhara et al., 2017).* So, elevated sUA in association with respiratory symptoms, high smoking index, and low BMI could predict the risk of developing of AL risk.

1.6.4. Metabolic syndrome - when evaluating and planning to manage gout, searching whether other components of metabolic syndrome, for example, obesity, insulin resistance, hypertension, dyslipidemia, and or cardiac failure could be of great value for effective management of gout *(Doherty et al., 2016).*

If we don't address all these factors while managing gout, treatment outcomes could be disappointing even following the most prudent gout managing guidelines, as described in a recent audit in a UK primary care practice *(Cottrell, Crabtree, Edwards & Roddy 2013).*

1.7. The challenge with managing gout

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Gout is a challenging condition to treat effectively due to the varying nature of disease severity and progression, as well as the other secondary and associated conditions/symptoms which may occur. It is this author's view that few (if any) single and objective works exist for the agreed management of gout on an international scale, other than the guidelines by ACR and EULAR. Research quality and consistency is varied and may differ between clinics and on a wider healthcare front, between countries. Though, ACR *(Khanna et al., 2012)* and recent EULAR *(Richette et al., 2017)* recommendations for gout management could help physicians regarding the issue, some of their recommendations were not based on RCT, rather adapted in line with expert opinion.

2.0. Methodology

2.1. Study aims and objectives: The research question asked by the author 'what evidence is available for 'pharmacological' and 'non-pharmacological' treatment options for gout?' Through critical synthesis of current and widely acknowledge treatment strategies for managing gout, this author aims to create an up-to-date evidence-based gout management review. It is plausible that making available updated information about gout treatment could assist practicing physicians' efficiency in treating gout. Here in this new synthesis, the author will present both pharmacological and non-pharmacological approaches for managing gout based on past ten years published works.

Peer-reviewed literature were searched and screened systematically. Preferred Reporting Items for Systematic Meta-Analysis (PRISMA) *(Larissa et al., 2015)* guidelines were consulted for this study. Using the PubMed database, keywords: 'clinical trials in gout

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management' were used during the period of 1st September 2018 to 30th October 2018. A total of 173 articles were found for further analysis.

2.2. Inclusion and Exclusion criteria

To ensure recent and relevant research was the primary focus, the author aimed to include articles published within past ten years and for this purpose articles published before January, 2008 were not considered in this new synthesis (50 out of total 173). As this was a systematic search and review work, there were no strict excluding and including criteria while screening published works. However, articles meeting any of the following criteria were also excluded in this new draft (Figure-1) – (a) articles published other than English language (2, one published in Chinese & one in Serbian), (b) duplication of publication in the used database (1), (c) articles not relevant to any aspect of gout management (20), (d) research protocols for future works (5), and (e) expert opinion, perspective and editorial (4). Irrelevant article means, articles don't have any information about gout management, rather describe disease other than research interest, for example – 'Treat to Target in Axial Spondyloarthritis: What Are the Issues?'; 'Colchicine in recurrent pericarditis', 'Rilonacept in the management of cryopyrin-associated periodic syndromes (CAPS)'; 'Efficacy and safety of colchicine for pericarditis prevention - systematic review and meta-analysis'; 'Efficacy and safety of colchicine in preventing pericarditis', etc. As expert opinion, perspective and editorial are neither main research work nor main stream review work, the author also excluded them while synthesis this new draft.

3.0. Results:

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Out of 173, finally 91 articles were considered eligible for further consideration. EULAR and ACR are two premier authorities recommending guidelines for diagnosing and managing rheumatic disorders, however, being unfortunate, the author's search result didn't find articles as of EULAR and ACR based recommendations for the treatment of HU and gout, so, in addition to this 91 PubMed database retrieved articles, the author further included ACR and EULAR updated gout managing guidelines, leaving a total of 93 articles for final analysis (Figure -1). Among them, narrative review, RCT, systematic review and meta-analysis, Cochrane review were 38, 17, 9, and 6, respectively (Table - 1). Other types of articles were - non-RCT (5, 4-phase I, 1-phase III), cohort study (5), time-event series (3), clinical guidelines (3), cross-sectional study (2), exploratory study (1), case-control study (1), Quasi-experimental study (1), post-hoc analysis (1), and practical therapy (1). In the discussion section (4.0), all the retrieved information from the published work has been displayed into two broad sub-headings - non-pharmacological (4.1) and pharmacological (4.2) approaches for gout management. The University of South Wales, UK ethical committee approved the work.

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Table-1. Article types involved in this draft (based on Oxford Centre for Evidence-based Medicine, 2009).

Types of article	Number of article	Level of evidence
Randomized-controlled trial (RCT)	**17**	**IB**
Systematic review and meta-analysis	**09**	**IA**
Narrative review	**38**	**IV?**
Cochrane review	**06**	**?IA**
Non-RCT	**05**	
Cohort study	**05**	**II**
Cross-sectional study	**02**	**III**
Quasi-experimental study	**01**	
Case series / case report	**00**	**1V / IIIB**
Time-event series	**03**	
Clinical guidelines	**03**	
Post-hoc analysis	**01**	
Practical therapy	**01**	**IV**

CEBM (2009) Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). Available at: https://www.cebm.net/2009/06/oxford-centre-evidence-based medicine-levels-evidence-march-2009/. Accessed on (April 01, 2018).

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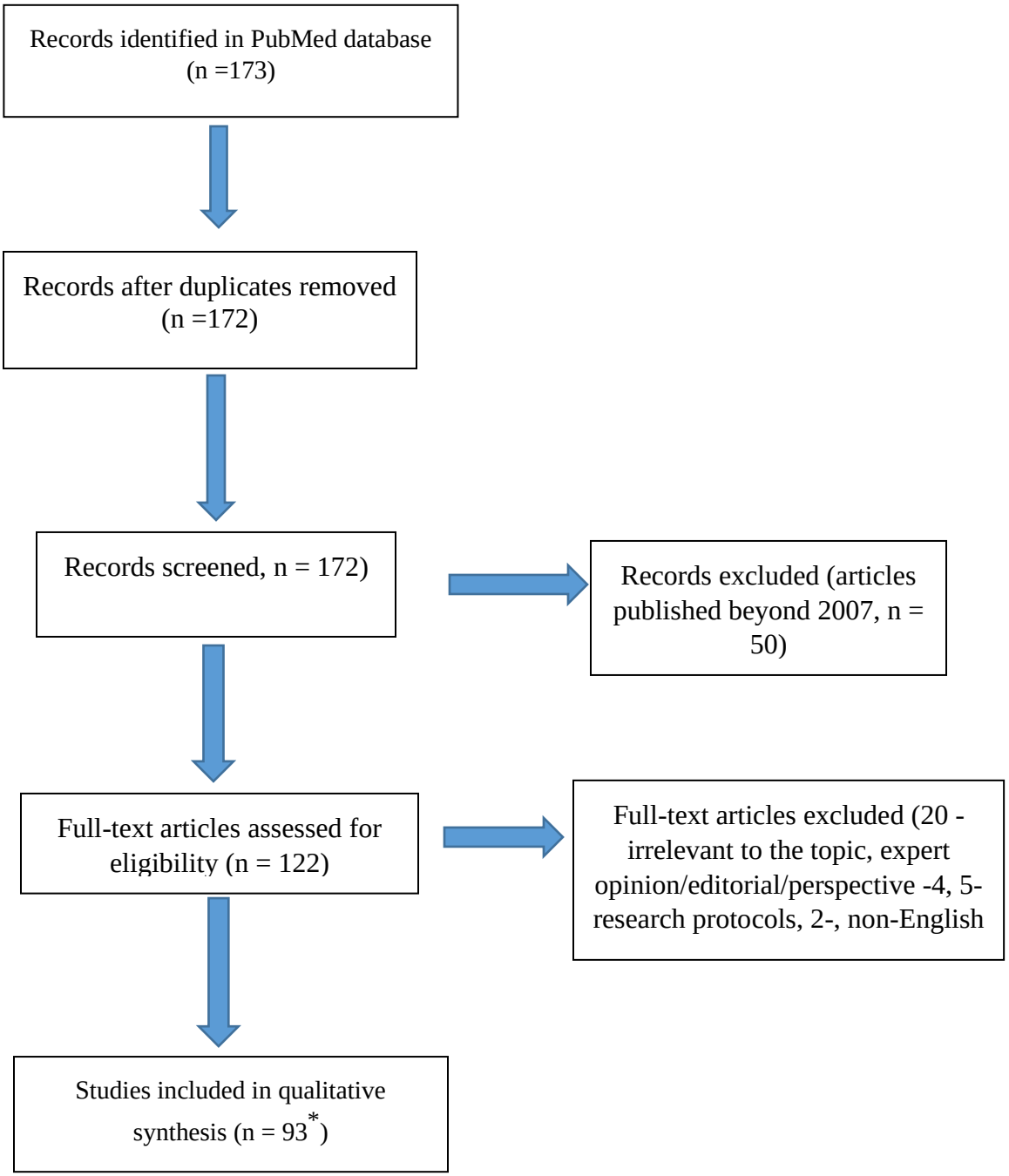
Figure -1: Flow chart of screening and selecting articles for review.



Note: A total *93 including ACR and EULAR-based recommendations for treating hyperuricaem

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4.0. Discussion

4.1. Non-pharmacological options:

4.1.1. Education – Education regarding various aspects of gout management should include gout sufferers, general practitioners, nurses and treating physicians (rheumatologist) in order to register maximum success in gout management. As rheumatologist' is the premier person in managing rheumatic disorders including gout, they need to have updated information about the recommendations to be useful in serving patients better. However, sometimes there could be lack of updated knowledge as of gout management even among rheumatologists as unveiled in an online based cross-sectional survey including 309 randomly selected, Brazilian rheumatologist *(Vargas-Santos, Gda, Coutinho, Schumacher, Singh & Schlesinger 2015)* and to improve the situation, staff involving with gout management regular arrangement of CME / CPD could be useful. In a recent UK based study with 517 gout patients - nurse-led approach was found superior over general practitioners-led approach in achieving target sUA concentration (less than 6 mg/dL), reducing gout attack and tophi size, hence improve quality of life and quality-adjusted life-year (QALY) gain at 2-year follow-up as well *(Doherty et al., 2018).* Same results were echoed in a pharmacist-staffed gout management program performed over a 26-week period with 105 gout patients and found helpful in achieving target sUA among patients *(Goldfien, Pressman, Jacobson, Ng and Avins 2016).*

According to ACR 2012 guideline, effective gout management should include educating patients' about contribution of diet, drugs, and physical activity in regulating sUA level and managing gout *(Khanna et al., 2012)*. However, based on a RCT outcomes, dietary

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education according to British Society of Rheumatology guidelines in patients' under ULT coverage didn't differ significantly in terms of achieving target sUA, and it could be due to the poor sample size (less than 30 patients) used in the study, so, further study with large sample size could draw a different conclusion *(Holland & McGill 2015).* Sometimes too much information about drug safety could influence gout management negatively as seen in a time-event study with Taiwanese gout patients under sUA lowering agents - there was a profound reduction in allopurinol and benzbromarone users though probenecid and sulfinpyrazone users were remained unaffected significantly *(Cheng, Chao, Hsu, Weng, On & Yang 2014).*

Education could also include importance of family member screening, where appropriate. In a prospective study among British people with primary gout, graded correlation between male gout patients and incident gout in 1st-degree was revealed *(Scott & Pollard, 1970).* Thereafter, in another study among 1st degree relatives of Hungarian male gout patients, gout was found more prevalent than that of general population *(Mituszova et al., 1992).* However, using the PubMed search engine within the given tenure, the author didn't find any published work addressing the issue and it is being hoped that further study could draw a conclusive remark.

4.1.2. Discipline and life-style modifications –

In a RCT with crossover, Dalbeth and colleagues (2010) documented uricosuric effect of milk, whereas ingestion of soy control caused an increase in sUA concentrations by about 10% ($p<0.0001$) in 16 healthy male volunteers. However, this result could be challenged in large number of study sample *(Dalbeth et al., 2010).* This study result provide rationale for long-term intervention with such dietary interventions in the management of individuals

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with HU and gout. Nguyen and colleagues (2017) demonstrated that BMI is directly related to gout risk - the more the BMI, the more the gout risk and vice versa *(Nguyen et al., 2017)*. Weight loss either by dietary intervention or bariatric surgery is also found effective in reducing serum uric acid concentration. In their study among obese Swedish, Maglio et al., (2017) demonstrated reduced gout incidence following bariatric surgery and it was statistically significant (95% CI, $p<0.001$); and the number needed to be treated by bariatric surgery to prevent one incident gout and hyperuricaemic event was 32 (95% CI 22 to 59) and was 8 (95% CI 6 to 13), respectively.

Moreover, excessive consumption of meat (beef, pork, lamb) *(Khanna et al., 2012)*, sea-fish *(Khanna et al., 2012)*, sugar-sweetened drinks, fructose rich food, and orange or apple juice, and alcohol (especially beer) *(Khanna et al., 2012)* could cause an increase in gout incidence and flares up as well. However, relation between gout incidence and consumption of caffeinated coffee, cherries, skimmed milk, low-calorie yoghurt is inverse - EULAR evidence-based recommendation mentioned skimmed milk powder derivatives has anti-inflammatory effects in acute gout. ACR encourages low-fat or non-fat dairy products and vegetables *(Khanna et al., 2012)*. So for effective management of gout should include intervention with lifestyle modifications, physical fitness steps, limit use of table salt, smoking cessation, plenty of vegetables, water, and vitamin C could be of great importance *(Bove, Cicero, Veronesi & Borghi 2017)*. However, more research are warranted with large number of patients in multiple centers to give power that these life style modifications to recommend in daily practice *(Richette et al., 2017)*. Cardiovascular comorbidity could be a consequence of uncontrolled HU, so, these lifestyle modifications could also be beneficial in terms of positive cardiovascular outcomes *(Richette et al.,*

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2017). Alongside newer recommendations from ACR and EULAR, research work regarding influence of life-style modifications are with lower LoE and inconclusive, warranting further research.

4.1.3. Drugs need to be monitored –

According to African American Study of Kidney Disease and Hypertension (AASK) trial, African Americans with CKD were randomly assigned to metoprolol (a beta-blocker), ramipril (an angiotensin-converting enzyme inhibitors, or amlodipine (a dihydropyridine calcium-channel blocker) and comparison between baseline and 12-month sUA was done. And study result revealed that, metoprolol increased sUA by 0.3 mg/dl, whereas ramipril or amlodipine had no effect on it; and gout-related hospitalizations rate was not significantly differ between anti-hypertensive users *(Juraschek, Appel & Miller 2017).* When considering management of hypertension in patients with gout, EULAR evidence-based recommendation suggest use of losartan and calcium channel blockers and advised to discontinue with loop or thiazide diuretics. This EULAR-recommendation is partially contrast to AASK trial outcome and increased sUA level was not seen in patients receiving ramopril *(Juraschek, Appel & Miller 2017).* Moreover, uricosuric property of lipid lowering agents, for example, statin and fenofibrate appear effective in managing hyperuricaemia *(Richette et al., 2017).*

In an open-label pilot study involving 14 male Korean patients with chronic tophaceous or recurrent acute attacks of gout, though stable on XOI or uricsuric agents for more than three months and without any gout attack within last one month received fenofibrate (160 mg per day) and registered a further 23% decrease in sUA and triglyceride levels at follow up. Alongside, there was an increase in serum creatinine and high-density lipoprotein as

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well after the treatment. However, all these result reversed to baseline levels after withdrawal of fenofibrate treatment *(Lee YH, Lee CH & Lee J 2006).* However, uricosuric effect of statin has not been mentioned in any recent published works reviewed here including both ACR and EULAR evidence based gout managing guidelines, rather later one recommended cautious use of it, especially with concomitant use of prophylaxis colchicine in order to prevent developing neurotoxicity and or muscular toxicity (Richette et al., 2017). So, further exploration regarding effect of lipid lowering agents in gout management is required.

4.1.4. Diseases to consider –

4.1.4.1.Comorbidity - in a longitudinal cohort study (retrospective) including 35,118 (Germany), 24,607 (UK), 121,591 (US), and 17,338 (France) gout patients, following co-morbidities were found common – CKD, renal failure, hypertension, ischemic heart disease (IHD), myocardial infarction *(Nyberg et al., 2016).* Stroke, obesity, peripheral arterial disease and diabetes mellitus (DM) has also been considered as independent risk factor for hyperuricaemia and gout *(Richette et al., 2017; Khanna et al., 2012).* In another review work, Mortada et al (2017) reported hyperuricaemia as an emerging independent risk factor for developing type 2 diabetes mellitus (DM) and HTN and effective control of sUA could reduce HTN and DM risk among them, though further study with large sample was suggested *(Feig 2014; Mortada 2017).* Based on pre-clinical study result, uric acid could cause vasoconstriction and a progressive ateriolopathy. In a US population-based study, the prevalence of CKD (stage ≥2) in patients with hyperuricaemia (sUA ≥10 mg/dl) and gout was documented as 86% and 53%, respectively. In the study, CKD appeared to be a major risk factor for gout, however gout might cause renal impairment in the course of the

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disease, require more research. So at the time of gout diagnosis, staging of CKD based on estimated glomerular filtration rate (eGFR) should be done and then could be done at regular interval to see whether further deterioration of renal function has occurred. Sleep apnea *(Zhang, Peloquin, Dubreuil, Roddy, Lu, Neogi & Choi 2015)* and air-flow limiting disorders (COPD, bronchial asthma) especially among smokers *(Fukuhara et at., 2017)* are also found has association with increased sUA level, though further multicenter longitudinal study could provide details whether there is a causal link between them.

4.1.4.2. Conditions cause increased uric production and reduced excretion of uric acid – genetic and acquired causes of uric acid overproduction, for example, inborn error of purine metabolism, psoriasis, myeloproliferative, or lymphoproliferative disease, etc. and conditions causing reduced uric acid excretion, such as CKD, glomerular, or interstitial renal disease (e.g., analgesic nephropathy, polycystic kidney disease), concomitant use of drugs for other comorbidities should consider when evaluating hyperuricaemia and gout *(Khanna et al., 2012).* So when evaluating and treating gout, all these conditions should keep in mind.

4.1.4.3. Asymptomatic hyperuricaemia (HU) and its consequences if left untreated – The definition of asymptomatic HU remains unclear, as no consensus exists about the serum urate cut-off or the relevance of ultrasound findings. Comorbidities associated with HU have increased in frequency over the past two decades. HU and or gout may be a cause or a consequence of a comorbidity. Epidemiological studies suggest that HU may be associated with cardiovascular, metabolic, and renal comorbidities, though there causal link are yet to prove. The risk/benefit ratio of ULT in mere asymptomatic HU is unclear, however, medications that are used to treat associated comorbidities could cause a rise in

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sUA and should be discontinued and replaced with appropriate alternatives. Therapeutic lifestyle changes, weight reduction, and adequate physical activity could improve health in general and asymptomatic HU as well *(Chales 2018).*

A systematic review as of treatment of HU based on Cochrane Library, Medline, Embase, clinical trials registries of the World Health Organization and the US National Institutes of Health, and abstracts from American College of Rheumatology/European League Against Rheumatism meetings results revealed that HU without renal disease and HU with preexisting renal disease treatment resulted in increased eGFR and no significant elevation of serum creatinine, respectively at 1-year follow-up. However, differences in renal function between the treatment and no-treatment groups were not statistically significant in any of the identified studies and data were scarce to draw a conclusion. HU should be treated to halt gout flaring, developing renal impairment and cardiovascular events *(Vinik et al., 2014).* However, calculated Framingham 5-year CVD risk was high in patients with hyperuricaemia and gout (with or without tophus) and therefore, implementing CVD screening for these patients could provide better patients' management *(Colvine et al., 2008).* Based on current evidence, uric acid is considered as a marker of both HTN and CKD and XOIs or uricosuric agents could be effective in these conditions, however, study with large sample could draw a conclusion whether other than gout and tumor lysis syndrome, ULT has any potential in treating HTN halting progression to CKD and CVD *(Feig 2014; Mallat et al., 2016).*

So after reviewing papers on non-pharmacological management of gout it can be summarized – patients understanding of gout pathophysiology, causation, risk factors,

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treatment, treatment side effects is important while managing gout. Purine rich diet, alcohol, certain drugs could aggravate gout features, hence restricting and avoiding there use could prevent gout flare up. Low BMI and weight loss also affect gout outcome positively. However, all these outcome are not based on higher LoE and further exploration with large sample size could be of great importance.

4.2. Pharmacological options: Based on ACR recommendations, anti-inflammatory agents for managing acute gout should start within 24 hours of gout symptoms *(Khanna et al., 2012)*. In case of treating acute gout, ULT should be continued if patients are on ULT already, however, ULT in new patients usually is recommended after settling acute features, but ACR suggests launching of ULT could be appropriate even in acute attack *(Khanna et al., 2012, 2147-61).*

4.2.1. Anti-inflammatory drugs (NSAIDs, steroids) – NSAIDs most commonly prescribed medication in acute gout. COX-1 inhibitors, for example, naproxen, indomethacin, and sulindac are the drug of choice, however, COX-2 inhibitors found effective as well and have better gastrointestinal tolerability than that of COX-1 inhibitors. However, risk/benefit ratio of celecoxib regimen in terms of gout management is yet to clear *(Khanna et al., 2012).*

In a meta-analysis of three RCT, oral prednisolone was compared with NSAID in 584 gout patients and results were as follow – in terms of effective pain control, during first 6 hours, oral prednisolone (30–35 mg/day) was comparable with naproxen (500 mg/day) and indomethacin (50–100 mg/day) and during the subsequent 4 to 6 days, prednisolone was also found as effective as NSAID both in activity and rest. Prednisolone had less adverse events (AEs) over NSAID, though

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authors recommended further study *(Yu, Lu & Zhou et al., 2018)*. Before this meta-analysis, Rainer and colleagues (2016) conducted a multicenter, double-blind, randomized trial among 416 gouty arthritis patients, aged over 18 years compared the efficacy and safety profile of prednisolone with that of indomethacine and study result didn't reveal any superiority of one drug over another while managing acute gout symptoms, However, further study including meta-analysis as of usefulness of different anti-inflammatory agents in gout, could draw a conclusive remark. Moreover, data based on emergency department and in medical admission per patient treated in Hong Kong, prednisolone appeared cost effective than indomethacine *(Cattermole, Man, Cheng, Graham & Rainer 2009).*

4.2.2. Neutrophil stabilizers (for example, colchicine) –

ACR adopts task forceps recommendations regarding use of colchicine no later than 36 hours of gout symptoms. And, in acute attack, a loading dose of 1.2 mg, could be followed by 0.6 mg 1 hour later and this regimen can be followed by gout attack prophylaxis dosing 0.6 mg once or twice daily (unless dose adjustment is required) 12 hours later, until the gout attack resolves. In countries where 1.0 mg or 0.5 mg are not available could be replaced with 1.2 mg and 0.6 mg, respectively. ACR say no for parenteral colchicine as this formulation is not availability, could be misused, and with more lethal effects. Prophylactic use of colchicine in patients under ULT therapy, especially during earlier period is indicated. Alongside NSAID, ACR recommends low dose oral colchicine (0.5 or 0.6 mg, once or twice a day, which one is available) as the first-line anti-inflammatory gout prophylactic option. Colchicine dose should be adjusted according to renal function level and potential drug-drug

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interactions, however, adjusted colchicine dose could be based on the decision of the treating clinician *(Khanna et al., 2012).*

Both high and low-dose of colchicine improve gout pain and they are equally effective in relieving pain at 36 hours, though AEs were more with high dose. As of today, trails documenting withdrawal of colchocine because of AEs from either dose of colchicine are lacking *(van Echteld et al., 2014).* And we are yet to have trials comparing conventional NSAIDs, steroids and colchicine in gout patients *(van Echteld et al., 2014).* The usual adult dose for acute and prophylactic gout is 1.2 mg/day and 0.5-0.6 mg/day three to four times / week, respectively. In usual dose, colchicine poisoning is rare, but not impossible and failure to recognize such event death could be inevitable. Besides history of colchicine ingestion, gastroenteritis, hypotension, lactic acidosis, and pre-renal azotemia are the signature of colchicine poisoning. Furthermore, co-administration of macrolids (clarithromycin, erythromycin), antifungals (ketoconazole), ciclosporin and grape juice could further increase serum colchicine concentration and thereby makes colchicine poisoning features even prominent. However, gastrointestinal decontamination of colchicine could be done with activated charcoal, but large, recent (<60 min) ingestions warrants gastric lavage. Administration of granulocyte colony-stimulating factor could also be useful *(Finkelstein et al., 2010).*

4.2.3. Xanthine oxidase inhibitors (XOIs) (selective / non-selective) –

Allopurinol is the most commonly used ULT in gout management. We are yet to have its optimal dose with or without impaired renal function; its consideration in patients under dialysis is less explored and warrant further research. Recent time, scope of

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allopurinol use is being suggested in CKD patients without gout. Based on outcomes of observational studies an association between increased serum urate level and CKD - end stage renal failure has been documented. The effect of allopurinol on progression of kidney disease has been examined in small studies with varying results *(Stamp, Chapman & Palmer 2016).*

Allopurinol is not recommended within first 10-14 days of acute gout attack. However, in a recent RCT, difference was not statistically significant between early- and late allopurinol receivers, in terms of daily pain, recurrent flares and inflammatory markers *(Taylor, Mecchella, Larson, Kerin & Mankenzie 2012).* 2012 ACR 2012 guidelines recommend use of ULT even during acute attack. In a RCT over 28-day period, Hill and colleagues evaluated whether commencing allopurinol during acute attack had prolonged duration of acute gout attack and study result revealed that initiation of allopurinol during acute attack did not prolong acute gout symptom duration *(Hill, Sky, Sit, Collamer & Higgs 2015).* Long-standing use of allopurinol caused effective control in sUA levels (< 0.36 mmol/L) as revealed in Auckland practice *(Arroll, Bennett, Dalbeth, Hettiarachhi, Ben, & Shelling 2009).* However, Management of gout in elderly (≥65 years) patients could be challenging due to high rates of comorbidities for example, renal impairment, cardiovascular disease, and concomitant use of other medications. However, research addressing the efficacy and safety of available ULT in the elderly is scarce. In a RCT, Jackson and colleagues examined the efficacy and safety of febuxostat / allopurinol in a subset of elderly subjects in CONFIRMS trial with 374 elderly people with gout; and in the trial, febuxostat was found more efficacious than allopurinol in terms of achieving

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efficacy. In cases of mild-to-moderate renal impairment febuxoxstat was more effective and with lower AEs compared with foxed dose allopurinol (200-300 mg). Both XOIs are well tolerated. *(Jackson, Hunt, & MacDonald 2012).*

Febuxostat is a non-purine, selective XOI, a suitable alternative to allopurinol in order to manage gout in cases of allopurinol hypersensitivity, intolerance and allopurinol inefficacy *(Hair, McCormack & Keating 2008) (Hu and Tomlinson 2008; Ernst & Fravel 2009; Stevenson & Pandor 2009; Gary & Walters-Smith 2011; Schlesinger 2010).* Febuxostat's potential in controlling target sUA has been established in short-term Phase II and III clinical trials, and long-term open-label studies (Schlesinger 2010). Febuxostat is available as 40- and 80-mg tablets and recommended starting dosage is 40 mg orally once daily; and if serum uric acid concentration does not go below 6 mg/dl even after 40 mg dose for two weeks, the dosage can be increased to 80 mg orally once daily. In a RCT among Chinese healthy volunteer, febuxoxstat dose ranged between 40 and 120 mg was found well tolerated *(Zhou et al., 2016).* Dosage adjustments are not needed in elderly patients or patients with mild or moderate renal or hepatic impairment. In a meta-analysis of RCT, febuxostat had the best efficacy and safety profile. Febuxostat 120 mg was reported to be more effective and safer than allopurinol *(Li et al., 2016).* Compared with allopurinol, febuxostat was found cost-effective in US and Spanish gout patients' *(Gandhi, Gentry, Ma & Bottorff 2015); (Perez-Ruiz, Diaz-Torne & Carcedo2016); (Ernst & Fravel 2009).*

Frequent AEs reported in clinical trials with febuxostat are - impaired liver function, nausea, arthralgias, and rash. Based on RCT outcome, cardiovascular thromboembolic events could have been occurred in patients receiving febuxoxstat

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and patients should be carefully monitored for clinical features of myocardial infarction and stroke. Febuxostat is well tolerated in gout patients irrespective of age groups and both male and female have no clinically significant effect on its pharmacokinetics, pharmacodynamics, or safety and it doesn't require any dose adjustments based on age and sex *(Khosravan, Kukulka, Wu, Joseph-Ridge, Vernillet 2008).* However, Febuxostat does not suit in critically compromised cardiac function (*Bardin, Schiavon & Punzi 2015)* and caution should be taken. Like allopurinol, its pharmacokinetics is not greatly dependent on renal clearance and could be useful for CKD patients. Based on a general practice cohort in Japan, febuxostat may provide an easier option than allopurinol for clinicians specializing in CVDs (Hiramitsu et al 2014). However, trials are ongoing on to see the impact of febuxostat on cardiovascular and renal systems *(Chinchilla, Urionaguena & Perez-Ruiz 2016).*

Several studies suggest that chronic hyperuricaemia could cause developing hypertension, obesity, hypercholesterolemia, atherosclerosis, metabolic syndrome, chronic heart failure, and chronic kidney disease. So, early detection and careful management of hyperuricaemia is required. In particular, the effect of lowering sUA levels via XO inhibition includes an attenuation of oxidative stress and related endothelial dysfunction that largely contribute to the pathophysiology of metabolic syndrome and cardiovascular diseases. However, more studies are required to confirm antioxidant role of XO inhibitors that contribute in preventing cardiovascular and chronic kidney disease *(Bove, Cicero, Veronesi & Borghi 2017).*

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Hyperuricaemia causes renal impairment, which is a risk factor for gout and hence, a barrier to standard gout management. In a multicenter RCT, ninety-six gout patients with moderate-to-severe renal impairment were followed for 12-months to see whether febuxoxstat is safe or it further deteriorates eGFR. At the end of the study, findings favors use of febuxostat in hyperuricaemia and it appeared that febuxoxstat didn't deteriorate renal function *(Saag, Whelton, Becker, MacDonald, Hunt & Gunawardhana 2016).*

LC350189 is a novel selective XOI, under clinical development for the management of hyperuricaemia in gout patients. A dose-block randomized, double-blind, active and placebo-controlled study revealed, single- and multiple-dosing of LC350189 was well tolerated in the dose ranged between 10 to 800 mg had the potential of lowering serum and urine uric acid levels. The extent of the decrease in the sUA level in the 200 mg dose group was similar or higher compared to that of febuxostat 80 mg group in multiple ascending dosing study. So it is being hoped that LC350189 could be safely administered once daily to patients with hyperuricaemia or gout, to reduce sUA where appropriate *(Yoon, Shin, Lee, Jang & Yu 2015).*

4.2.4. Uricosuric agents -

Among various uricosuric agents, probenecid, benzbromarone are recommended as add-on therapy when XOI alone is not effective in gout management *(Khanna et al., 2012).* Recent time, Lesinurad has shown promise promise in clinical trials, especially in combination with XOIs. Lesinurad is a selective uric acid transporter 1 (URAT1) inhibitor inhibiting reabsorption of uric acid from proximal renal tubules *(Gupta, Sharma, Misra & Singh 2016).* Based on RCT (CLEAR1, CLEAR2,

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CRYSTAL) outcomes, Lesinurad achieves marketing authorization in both European union and US to use for the treatment gout and found most effective in terms of reducing sUS and safety perspective, especially when combines with XOI at 200mg daily *(Robinson & Dalbeth 2017).* In a review work based on phase II and III trials outcomes, Haber et al (2018) described that with increased Lesinurad dose, better efficacy (reducing sUA <6 mg/dl) could be achieved with acceptable safety profile *(Huneycutt, Board & Clements 2017).* Only authorized daily dose is 200 mg and beyond this dose the patients may have more renal toxicity and the drug is not recommended for asymptomatic hyperuricaemia with estimated creatinine clearance (eGFR) <45 mL/min. Sometimes at the 200 mg/day dose, 11% patients could experience irreversible raised serum creatinine level *(Sanchez-Niño et al., 2017).* Moreover, its significance in reducing gout flares or tophi size is yet to register. Comparative uricosuric safety profile is yet to have and more research are required *(Gupta, Sharma, Misra & Singh 2016).*

4.2.5. Synthetic uricase (for example, pegloticase) –

Some patients are intolerant or unresponsive to conventional ULT (XOIs and or uricosuric categories) and are referred as refractory gout. Treatment-failure gout refers to a group of patients who neither able to tolerate allopurinol nor experience normalization of sUA when on it and it is being estimated that about 1-1.5% of the total (3-8 million) gout people in US could have fallen in this group. And situation like this, pegloticase, a polyethylene glycol (PEG) conjugated mammalian recombinant uricase could be the answer in reducing sUA, tophi size, hence

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improving functional status and quality of life among gout sufferers based on phase III trial outcomes *(Sherman, Saifer & Perez-Ruiz 2008; Dave, Kelly & Krishnan 2012).* Loss of urate-lowering response and the risk of infusion reactions is associated with pegloticase immunogenicity *(George Jr. & Sundy 2012) (Sherman, Saifer & Perez-Ruiz 2008).* Based on a review work involving 6-month RCTs and an open-label extension study, infusions related (IR) - adverse events (biweekly or monthly) as of pegloticase registered in 94/208 (45%) patients: in 10 patients at first infusion and 84 experience during subsequent infusions and among them following were most common - chest discomfort (15%), flushing (12%), and dyspnea (11%). Infusion-related reactions were associated with pre-infusion sUA concentration greater than 6 mg/dL (45%) than that of less than 6 mg/dl (1%). And slowing or stopping the infusion caused a resolution of the IR-adverse events *(Baraf, Yood, Ottery, Sundy & Becker 2014).* In a phase-III trial, patients with chronic tophaceous gout with CKD (stage 1 to 4) treating with PEG, didn't cause a reduction of eGFR. In an open-label phase-I study also revealed that administration of IV PEG in chronic tophaceous gout requiring hemodialysis for end-stage renal disease (ESRG) appeared to be feasible *(Bleyer, Wright & Alcorn 2015).*

In an open-label, multicenter, phase-III study, Digumarti and colleagues documented rasburicase, another uricase analogue safe and effective in preventing and treating malignancy-associated hyperuricaemia *(Digumarti, Sinha, Nirni, Patil & Pedapenki 2014). Furthermore,* a retrospective medical record review, over a total of 373 patients with a diagnosis of a hematologic malignancy or solid tumor, dose dependent reduction of sUA was documented within 24 hours after receiving rasburicase.

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However, statistical difference in terms of treatment response at 24 hours after rasburicase administration was not revealed among treatment groups (3-mg, 6-mg, 7.5-mg, and weight-based dosing groups). Among various rasburicase treatment groups, 3-mg is the most cost-effective hyperuricaemia reducing agent in tumor lysis syndrome. Further prospective multicenter study with large sample size could reveals factors that contribute repetition of rasburicase administration *(McBride, Lathon, Boehmer, Augustin, Butler & Westervelt 2013).*

4.2.6. Miscellaneous options –

4.2.6.1. When gout patients fail to sustain improvement with NSAIDs, colchicine, and steroid, anti-interleukin-1 (IL-1) could play a pivotal role in resolution of gout manifestations and could be used successfully as a 4th-line anti-inflammatory agent in treating this common metabolic arthritis based on outcomes of clinical trials. Anti-IL is not cost effective and further trials with large patients' size are warranted to see its clinical efficacy and safety concern as well *(Schlesinger 2011)*. Other than anakinra, rilonacept, and canakinumab are also found effective- anakinra is an IL-1 receptor antagonist that inhibits the activity of both IL-1α and IL-1β, rilonacept is a soluble decoy receptor and canakinumab is an anti-IL-1β monoclonal antibody. Anakinra was found effective in reducing acute gout pain, whereas, rilonacept caused a decrease in gout attacks. But, canakinumab has caused both a reduction in gout inflammation and gout attack. All three IL-1 inhibitors are reportedly well tolerated *(Schlesinger 2014).* IL-1 inhibitors may also be helpful in polyarticular and tophaceous gout as they when patients are on uric acid

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lowering-lowering therapy. *(Tran, Pham, Shafeeq, Manigault & Arya 2013; Schlesinger 2011).* ACR and US-FDA don't recommend use of anti-IL-1 inhibition in critically ill patients *(Khanna et al., 2012).*

4.2.6.2. Moderate LoE documented that, a single 40-mg dose of intramuscular injection of triamcinolone acetonide was better than subcutaneous dose of 150 mg of canakinumab in terms of pain relief, joint swelling and patient-reported global assessment of treatment response in an acute gout attack. AEs were more with 1st approach, whereas latter option is not cost-effective. Studies comparing the anti-IL over the conventional first-line anti-inflammatory agents while treating are rare. Based on lower LoE outcome, 150 mg of indomethacine was found more effective in gout pain relieving over maximum dose of rilonacept 320 mg/day), though AEs profile were almost equal in both groups *(Sivera, Wechalekar, Andres, Buchbinder & Carmona 2014).*

4.2.6.3. In a prospective RCT among Swedish Obese Subjects (SOS) it was revealed that bariatric surgery was associated with a reduced incidence of hyperuricaemia (adjusted HR 0.47, 95% CI, $p<0.001$) and gout (adjusted HR 0.60, 95% CI, $p<0.001$) as per national registers and questionnaires. And the effect of bariatric surgery on gout incidence was not influenced by baseline risk factors, for example, body mass index and the number of participants needed to be treated (NNT) by bariatric surgery to prevent hyperuricaemia was 8 (95% CI 6 to 13) *(Maglio et al., 2017).*

4.2.6.4. Complementary medicines and others - In a systematic review Li and colleagues evaluated the effectiveness and safety of Chinese herbal medicine

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for gout including 57 trials with a total of 4,527 gout patients. Herbal medicine was found superior over conventional medications in terms of improving functional limitation. However, evidence whether herbal medicine caused a reduction in gout attack were scarce. Among 57 trials, 25 (involving 23 different herbal prescriptions) documented a statistical significant reduction in sUA, and the overall inflammation relieving effect from Chinese herbal medicine was better over conventional therapies as depicted in 19 trials (with 17 different prescriptions). Herbal medicine had fewer AEs compared to conventional drugs. However, trials with higher LoE are required in future *(Li, Han, Wang & Liu 2013).* Based on non-randomized trials, topical ice application was found useful in relieving pain and swelling in acute gouty arthritis when applied in association with NSAIDs. However, efficacy of oral complementary agents, such as, cherry juice or extract, salicylate-rich willow bark extract, ginger, flaxseed, charcoal, strawberries, black currant, burdock, sour cream, olive oil, horsetail, pears, or celery root, etc. appear unsatisfactory in acute gout *(Khanna et al., 2012).*

4.2.7. Management of gout in critically ill patients:

4.2.7.1. To treat gout in hospitalized patients' under nothing per mouth (NPO), ACR 2012 recommends use of intra-articular (IA) injection of corticosteroids for involvement of 1 or 2 joints adjust dose based on joint size. However, intravenous or intramuscular methylprednisolone at an initial dose of 0.5–2.0 mg/kg could also be applied where appropriate. Patients' in NPO, subcutaneous synthetic ACTH at 25–40 IU dose could be used. ACR 2012 also

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recommends repetition of ACTH or intravenous steroid regimens when required. However, critically ill patients' experiencing acute gout features, no consensus has not been reached regarding use of intramuscular ketorolac or intramuscular triamcinolone acetonide monotherapy *(Khanna et al., 2012)*.

4.2.7.2. Chronic kidney disease - Observational studies have shown that asymptomatic hyperuricaemia could increase the risk of hypertension, CKD, end-stage renal disease, cardiovascular events, etc. Whether these factors represent gout cause, consequence or incidental associations are yet to explore. Hyperuricaemia could be a consequence of impaired kidney function, diuretic therapy or oxidative stress, such that elevated sUA represents a marker, rather than a cause of CKD. On the other hand, small, short-term, single-center studies have shown improvements in blood-pressure control and slowing of CKD progression following allopurinol, however, RCT is required to determine whether ULT slows the progression of CKD *(Badve et al., 2011).*

4.2.7.3. Compromised cardiac functions – *(Pillinger, Banglore, Klein, Baumgartner & Morlock 2017).* Based on survey of US physicians audit with gout who performed in-depth patient chart audits over 1,159 patients, 738 patients had CVD and gout and 421 had mere gout. In case of gout with comorbidity, the disease duration was longer with delayed launching of ULT and was more likely to develop tophi, organ damage, joint damage, and gout flares in the past 12 months. In this group, patients' also had other comorbidities, like obesity, diabetes, osteoarthritis, CKD, and prostate disease *(Pillinger, Bangalore, Klein, Baumgartner & Morlock 2017).* Clinical trials outcomes appeared that

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ULT could lower blood pressure, appears to be a growing evidence linking hyperuricaemia, HTN and cardiovascular disease, though with some controversies. In the future, in an effort to halt progressing cardiovascular events, ULT could be a great value *(Hsu et al., 2013).*

4.2.8. Interventions -

4.2.8.1. Injectable steroids – 2012 ACR guidelines recommend use of both IA and oral corticosteroids for acute gout of 1 or 2 large joints where dosing should be based on joint size; and this approach could be practiced in association with NSAIDs or colchicine *(Khanna et al., 2012).* Intramuscular (IM) single dose triamcinolone acetonide (60 mg), followed by oral prednisone or prednisolone could also be useful, though consensus for the use of IM triamcinolone acetonide as monotherapy has not been reached *(Khanna et al., 2012).* In NPO patients with acute gout, there was no consensus on the use of IM- ketorolac or IM - triamcinolone acetonide monotherapy *(Khanna et al., 2012).*

4.2.8.2. Intra-muscular ACTH injection - the presence of comorbid conditions, for example, bronchial asthma, ischaemic heart disease, renal impairment, etc. advancing age, could impede use of commonly used drugs for gout management; and situation like these, ACTH injection could be a solution and clinical experiment revealed that a fast-acting and relieves pain within 24 hours of introduction and the duration of pin relief with IM-ACTH is almost similar to that of triamcinolone injection *(Nisar 2018)*. Patients usually respond after 1-3 doses of IM-ACTH and is found to be well-tolerated with transient AEs. ACTH has no clinically significant effect on serum glucose and potassium

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levels or blood pressure, however more studies are required *(Nisar 2018).* There is no consensus whether ACTH should be used for acute gout in patients who are able to take oral NSAIDs medications *(Khanna et al., 2012).* ACR recommends use of subcutaneous synthetic ACTH at an initial dose of 25–40 IU, with repetition of doses as clinically indicated *(Khanna et al., 2012).*

5.0. Conclusion

Effective management of gout includes both medicinal and non-medicinal approaches. However, accurate diagnosis should consider as the most important step of treatment and failure to do so, even applying most prudent updated gout managing guideline would not be useful for the patients and in order to precise diagnosis, besides clinical features, ultrasonographic exploration of the joint for characteristic 'double contour sign' favoring gout diagnosis and or identification of monosodium urate crystal under polarized microscopy analyzing synovial fluid appear appropriate. Most of the pharmacological approaches for managing this inflammatory arthritis are based on clinical trials outcomes, though still there are some areas where further research are required, such as head-to-head comparison between different NSAIDs, NSAID and prednisolone, NSAID and colchicine, appropriate urate lowering combination, long-standing effect of urate lowering drugs on internal organs or effective maximum does of urate lowering agents. Non-pharmacological approaches are also reportedly useful while managing gout in day-day clinical practice. Among the various approaches, avoidance of purine-rich diets (animal and vegetable sources),

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fructose containing drinks, avoid excessive amount of alcohol, concomitant use of some drugs, weight loss, intake of sufficient vitamin C, etc., are important; though most of them are based on outcomes of lower level of evidence and are inconclusive as well, warrant further study.

6.0. Recommendations

6.1. For improving gout management –

6.1.1. Following most updated gout managing guidelines, respective physicians including internist, rheumatologist could serve gout sufferers even better,

6.1.2. Coordinated multidisciplinary approaches from different healthcare facilities could be useful in managing gout,

6.1.3. Educating patients and care giver based on recent information as of gout management could increase patients' adherence to the treating guideline and thereby could improve gout management,

6.1.4. Clinical audit could be of great value in order to find out flaws regarding gout management. CPD (continued professional development) / CME (continued medical education) are the two most important components of audit cycle and both could play significant role in improving treating physicians' level of knowledge to handle patients' with gout with more ease and confidence.

6.2. For further research -

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6.2.1. Comparison between treat-to-target approach and treat-to-avoid-symptoms while treating gout warrant further research.

6.2.2. Impact of ULT in different diseases other than gout requires further attention.

6.2.3. Maximum treatment duration and long-term effects of ULT requires further evaluation.

6.2.4. Whether gout treatment outcome varied depending on demography, associated comorbid conditions, gout severity, gout types, clinical manifestations, or laboratory findings, etc., require further exploration.

6.2.5. Effective family screening among gout sufferers could be useful.

6.2.6. Role of diet and dietary restriction in flaring gout manifestations and treating gout, respectively is inconclusive and based on lower LoE, hence require more research.

6.2.7. Long - term treatment outcomes with febuxoxstat warrant further analysis.

6.2.8. Head-head comparison between different uricosuric agents is required in order to find the most suitable one would be appropriate.

6.2.9. Further study to find the effective maximum dose of allopurinol in achieving target sUA is required. Association between allopurinol dose and progressive renal impairment should be tested.

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6.2.10. Combined use of ant-inflammatory agents for management of acute gout is sometimes required and is found more effective over monotherapy, though not based on clinical trial outcome rather expert opinion, hence, further experimental study is warranted.

6.2.11. In achieving target serum urate level, sometimes combined ULT (both XOI and uricosuric agent) is required, however, we are yet to find the most effective combination of its kind; so further study is required.

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