INTRODUCTION

1.1 Gout

Gout is a health condition usually characterized by intermittent attacks of acute inflammatory arthritis—a hot, tender, red, swollen joint [1]. Gout has become more common in recent decades, impacting about 1–2% of the population at some point in their lives. The increment is believed due to increasing uncertainty factors in the population, such as metabolic syndrome, longer life expectancy and changes in diet. Gout was historically known as "the disease of kings" or "rich man's disease"[1, 2]. Gouty arthritis is an inflammatory arthritis characterized by the presence of monosodium urate crystal deposition which can occur both within a joint or the surrounding tissue [3-5]. Dating as far back as ancient Egypt references and physical findings of gout has been documented throughout history [6]. Gouty arthritis has been referred to as the “unwalkable disease” and later coined the “disease of the wealthy” and “disease of the kings” due to its occurrence in affluent populations[7]. It was not until 1859 that the relationship between gouty arthritis and monosodium urate crystals was recommended by Garrod and then established in 1961 with the use of polarizing microscopy to identify the crystals. This critical advancement in science approved for the accurate diagnosis of gouty arthritis differentiating it from diseases with a similar arrangement and setting the stage for research and development of therapeutic modalities [8-10]. The fine balance of serum urate (sUA) acquaint in the body is determined by the combination of de novo production, dietary intake and excretion [6, 7]. It is well known that monosodium urate deposition for prolonged periods leads to destructive arthropathy. Damage from deposition of these crystals is not limited to the
joints but also the surrounding tissues; crystals can deposit in the kidneys extending to nephrolithiasis[11, 12]. Hyperuricemia is also often associated with cardiovascular disease, chronic kidney disease, metabolic syndrome and insulin resistance. In addition, monosodium urate crystals have been shown to act as “danger signals” that trigger the inflammasome, leading to the release of potent inflammatory cytokines, IL1β and IL18, throughout the body [13, 14]. Progression of gout includes the asymptomatic stage of hyperuricemia, symptomatic hyperuricemia and chronic gouty arthritis – a transition period that can span years. Gouty arthritis appears to be a steadily rising clinical entity [15, 16]. According to the national health interview survey (NHIS), the prevalence of gouty arthritis in a one year period was 940 per 100,000 adults age≥18 years old, with prevalence rising with age. The peak age affected is from 70-79 years old, with an estimated occurrence of 8,000 per 100,000. In total, it is figured that 6.1 million adults ≥ 20 years old have been told they have gout [15-17]. Looking back we have come a long way in our knowledge of the pathogenesis and management of gouty arthritis; we have learned that there are potential genetic predispositions to expand gout in addition to the role of NALP3 inflammasome. Despite this awareness, the advancement in treatment has not been as robust. There are still many obstacles in treatment of gout, particularly in those patients with abnormal renal and hepatic function [18, 19].

Progression of gout includes the asymptomatic stage of hyperuricemia, symptomatic hyperuricemia and chronic gouty arthritis – a transition period that can span years. Gouty arthritis typically affects middle aged to elderly adults especially men; there is an increase in prevalence among postmenopausal women secondary to decreased circulating estrogen which behaves as a uricosuric agent. The most commonly employed agent to accomplish a target sUA (≤6 mg/dl) is allopurinol. Allopurinol, first approved for use in 1964, is clinically effective in lowering sUA and reducing number of gout flares, and it is the mainstay of urate lowering therapy. Allopurinol is approved for primary and secondary hyperuricemia at dosages up to 800mg daily requiring adjustment in dosage with renal insufficiency. Its mechanism of action involves disruption of purine biosynthesis via competitive inhibition of activity of the oxidized form of xanthine oxidase, an enzyme needed to oxidize both hypoxanthine and xanthine to uric acid [20-22].
Few options are available for those patients that have been unsuccessful to attain target sUA levels or are intolerant of allopurinol. Alternative uricosuric pharmacologic therapies that do not involve xanthine oxidase inhibition include benzbromarone (withdrawn from US market), probenecid, sulfinpyrazone and pegloticase. These agents, aside from pegloticase, increase renal elimination of uric acid. Pegloticase, a pegylated uric acid specific enzyme, reduces uric acid by increasing its conversion to allantoin which is readily cleared by renal excretion. While under excretion is the predominant issue in most patients with gout, xanthine oxidase inhibitors remain the most frequently used agents [23-26]. Finally, the novel medication febuxostat has proven to be a valid treatment modality for these patients.

1.1.1 Febuxostat

Febuxostat (INN; trade names: Adenuric in Europe and New Zealand, Febutaz in India and Takeda's Uloric in the US) is a urate lowering drug, an inhibitor of xanthine oxidase that is pointed for use in the treatment of hyperuricemia and chronic gout. Febuxostat functions as a urate lowering drug approved for use in Europe on April 21, 2008 for gouty arthritis shortly adopted by US FDA approval on February 13, 2009 [1, 2]. US FDA sanctioned doses include 40 mg or 80 mg daily dosing (clinical trials have shown safety with doses up to 240 mg) [27, 28]. Dosing recommendations are to start with 40mg daily and check sUA at two weeks, if sUA remains >6 mg/dL increasing dose to 80mg daily is recommended. Although in Europe higher doses of febuxostat are approved for clinical use, USFDA elected not to approve 120 mg or 240 mg due to pertain of side effects and trial data representing efficacy of febuxostat at lower prescribing doses of 40mg and 80mg daily [29-40].

1.1.1.1 Mechanism of action

Febuxostat is a non-purine selective inhibitor of xanthine oxidase. It works by non-competitively obstructing the molybdenum pterin center which is the active site on xanthine oxidase. Xanthine oxidase is needed to successively oxidize both hypoxanthine and xanthine to uric acid. Hence, febuxostat inhibits xanthine oxidase, therefore diluting production of uric acid. Febuxostat inhibits both oxidized as well as reduced form of xanthine oxidase, because of which febuxostat cannot be easily displaced from the molybdenum pterin site [1, 3, 29, 41].
Febuxostat (TEI-6720, TMX-67), 2-(3-cyano-4-[2-methylpropoxy]phenyl)-4-methylthiazole-5-carboxylic acid (Figure 1.1), is a thiazolecarboxylic acid derivative with the empirical formula $C_{16}H_{16}N_{2}O_{3}S$ [42-47]. This compound has a molecular mass of 316.38 g/mol and is highly bound to albumin with a volume of distribution at steady state of 0.7 mg/kg. It is a non-purine selective inhibitor of xanthine oxidase that non-competitively blocks molybdenum pterin (active site on xanthine oxidase)[48, 49]. As febuxostat inhibits both the oxidized and reduced form of xanthine oxidase, it is not easily displaced from the molybdenum pterin site [42-47, 50-52]. In addition, febuxostat does not have noteworthy effect on other enzymes involved in purine and pyrimidine metabolism. Structurally, febuxostat differs from allopurinol due to its lack of purine ring [1, 2, 29, 41, 48, 49].

![Chemical structure of febuxostat](image)

**Figure 1.1 Chemical structure of febuxostat**

1.1.1.3 Pharmacokinetics/Metabolism

In healthy human subjects febuxostat is absorbed at a rate of 49%, of which 99.2% of the compound is bound to albumin. It is excreted both renally and in the feces - in the urine 49% is excreted as metabolite and 3% as unchanged compound whereas in the feces 45% is excreted as metabolite and 12% excreted as unchanged compound. The half-life of febuxostat is 5-8 h [1, 2, 29, 41]. Febuxostat is metabolized via both conjugation by uridine diphasphate glucuronosyltransferase (UGT) enzymes (UGT1A1, UGT1A3, UGT1A9 and UGT2B7) and oxidation by cytochrome P450 enzymes (CYP1A2, CYP2C8 and CYP2C9); oxidation of the isobutyl side chain leads to the formation of active metabolites. The metabolites comprise both acyl glucuronide metabolites and oxidative metabolites (67M-1, 67M-2, 67M-4, and a secondary metabolite from 67M-1). The metabolite 67M-3 is also formed via CYP 1A1 but in low amounts. Mukoyoshi et al., also found that although oxidation via CYP 3A4 forms the
metabolite 67M-2, 67M-3 its role is limited; this is a key finding since CYP 3A4 is a predominate enzyme in the liver involved with the metabolism of many medications[8, 48, 49, 53].

The necessity for safe and effective therapy for hyperuricemia with gout has been a long term issue. Febuxostat has been found to be effective in the treatment of chronic hyperuricemia in patients with gout [54]. Several examines throughout the studies, have revealed the efficacy of febuxostat in reaching target sUA levels compared with allopurinol. Febuxostat has constantly proven efficient in lowering sUA in up to five years of follow up, while considerably reducing the rate of flares [53, 55-57].

1.2 Alzheimer's and senile dementia

Alzheimer's disease (AD), also known in the medical literature as Alzheimer disease, is the most common form of dementia [58]. It is an incurable disease, which worsens as it progresses, and eventually, leads to life threatening. It was first described by German psychiatrist and neuropathologist Alois Alzheimer in 1906 and was named after him [58, 59]. Most often, AD is diagnosed in people over 65 years of age, though the less-prevalent early-onset Alzheimer's can suffer much earlier. In 2006, there were 26.6 million people worldwide with AD. Alzheimer's is predicted to affect 1 out of 85 people globally by 2050 [58-63].

Although Alzheimer's disease develops differently for every individual, there are many common indications [33, 64]. Prior symptoms are often mistakenly thought to be ‘age-related factors, or manifestations of stress. In the early phases, the most common indication is difficulty in memorizing recent events, called as short term memory loss. When AD is suspected, the diagnosis is usually confirmed with tests that evaluate behaviour and thinking powers, often accompanied by a brain scan if available [64-66], however, examination of brain tissue is required for a definitive diagnosis. As the disease advances, indications can include confusion, irritability, aggression, mood swings, trouble with language, and long-term memory loss. As the person declines they often withdraw from family and society. Consequently, bodily functions are lost, ultimately leading to death. Since the disease is different for each individual, predicting how it will affect the person is difficult. AD arises for an unknown and variable amount
of time before becoming fully manifest, and it can progress undiagnosed for years. On average, the life expectancy following diagnosis is roughly seven years. Around three percent of individuals live more than fourteen years after diagnosis [67-69].

Once intended to be successful for improving cognition in Alzheimer's disease and senile dementia patients, the evidence is now appeared as too inconsistent to facilitate the use of piracetam for these conditions [59, 66, 69].

1.2.1  Piracetam

Piracetam has been studied in an extensive number of clinical experiments, and has shown positive results in the treatment of post-stroke aphasia, epilepsy, cognitive decline following brain and heart surgery, dementia, and myoclonus. Piracetam is a nootropic drug. It is one of the groups of racetams. Piracetam is prescribed by doctors for some terms, mainly myoclonus, however is used off-label for a much wider range of applications [58, 59].

1.2.1.1  Mechanism of action

Piracetam's mechanism of action, as with racetams in general, is not completely inferred. The drug regulates neuronal and vascular functions and influences cognitive function without working as a sedative or stimulant [58, 59, 70]. Piracetam is a positive allosteric modulator of the AMPA receptor. It is hypothesized to pretend on ion channels or ion carriers; thus leading to increased neuron excitability. GABA brain metabolism and GABA receptors are not impacted by piracetam. Piracetam has ascertained to increase blood flow and oxygen consumption in parts of the brain but this may be a side effect of increased brain process rather than a primary effect or mechanism of action for the drug. Piracetam ameliorates the function of the neurotransmitter acetylcholine via muscarinic cholinergic (ACh) receptors, which are implicated in memory processes. In addition, piracetam may have an effect on NMDA glutamate receptors, which are affected with learning and memory processes. Piracetam is thought to increase cell membrane permeability. Piracetam could exert its global effect on brain neurotransmission via modulation of ion channels (i.e., Na+, K+). It has been found to increase oxygen consumption in the brain, apparently in association with ATP metabolism, and raises the activity of adenylate kinase in rat brains. Piracetam, although in the brain, appears to increase the synthesis of cytochrome, which is a part
of the electron transport mechanism in mitochondria. But in the brain, it also improves the permeability of the mitochondria of some intermediaries of the Kreb’s cycle [71, 72].

1.2.1.2 Chemistry

Piracetam is chemically known as 2-oxo-1-pyrrolidine acetamide (Figure 1.2); it shares the same 2-oxopyrrolidone base structure with 2-oxo-pyrrolidine carboxylic acid (pyroglutamate). Piracetam is a cyclic derivative of GABA. Piracetam is prescribed by doctors for some conditions, mainly myoclonus, however is employed off-label for a much broader range of applications[58, 59]. The structure containing pyrrolidone ring in common which also seems to be important for their activity. This is interesting, since 2-pyrrolidone has been found to occur naturally in man. In the series of analogues of piracetam, oxiracetam, pramiracetam and etiracetam it seems that the acetamide moiety is important for activity [71, 73].

![Chemical structure of piracetam](image)

**Figure 1.2 Chemical structure of piracetam**

1.2.1.2 Pharmacokinetics/Metabolism

The bioavailability of oral formulations of piracetam is near to 100%. Piracetam is quickly absorbed and it gets about 30 minutes to reach peak plasma concentrations. Meals does not impact the extent of absorption of piracetam, however it does decrease the maximal plasma concentration of it about 17% and prolongs peak plasma by one and half hours. The piracetam is easily excreted in the urine. Piracetam crosses blood–brain and placental barriers and is found in all tissues, except adipose tissue. The uptake into the brain is less rapid than into the circulation, and, at nearly 8 h, half-life in cerebrospinal fluid is longer than in plasma (about 5 h) [73].
Despite the many reported benefits of piracetam and its many applications of treatment, research is inadequate; many trials are inconclusive, their mechanisms of action are largely baffling, and potential biases in the design and interpretation of trials are hard to depart. Piracetam and its compounds exhibit promising grades for many indications, most notably for cognitive and memory functions. A large segment of the aging population, the present trend will be to acquire research that will provide a better clinical understanding of these drugs, and to be able to test them for new indications, particularly CNS disorders. Their potential neuroprotective and neuroregenerative effects are the least explored, so with well controlled studies and more modern techniques, the potential efficacy of piracetam and piracetam-like compounds is even additional accomplishment [59, 70-73].

1.3 References


