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A Review On Naproxen, Methotrexate and Mannitol for the treatment of Rheumatoid Arthritis Disease

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Abstract: *Nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX), and mannitol are widely employed therapeutic agents in the management of pain, autoimmune diseases, and intracranial pressure, respectively. Naproxen, a traditional NSAID, remains a benchmark for analgesic and anti-inflammatory therapy owing to its efficacy in rheumatologic and musculoskeletal disorders, though it carries risks of gastrointestinal injury, renal impairment, and cardiovascular complications .In contrast, MTX is the anchor disease-modifying antirheumatic drug (DMARD) for rheumatoid arthritis (RA), exerting dual mechanisms of action: inhibition of dihydrofolate reductase at high doses (anticancer use) and enhancement of adenosine-mediated anti-inflammatory pathways at low doses . Despite its therapeutic utility, MTX toxicity, including hepatotoxicity, myelosuppression, and pulmonary injury, necessitates close monitoring and folate supplementation .*

Mannitol, a potent osmotic diuretic, is extensively used in neurocritical care to reduce intracranial and intraocular pressure. Its mechanism centre's on increasing tubular osmolarity to induce osmotic diuresis and create osmotic gradients across the blood–brain barrier. However, excessive or repeated dosing predisposes to osmotic nephrosis and acute kidney injury (AKI), particularly in vulnerable patients . Drug–drug interactions pose additional challenges: NSAIDs with anticoagulants or SSRIs heighten bleeding risks, while NSAIDs and PPIs can impair MTX clearance, amplifying toxicity .Similarly, co-administration of mannitol with other nephrotoxic drugs (e.g., aminoglycosides, cisplatin) aggravates renal injury .

Taken together, balancing efficacy with safety represents the central clinical challenge in the use of these agents. Naproxen remains effective with comparatively lower thrombotic risk than other NSAIDs, MTX provides durable remission in RA when optimally dosed and monitored, and mannitol continues as a mainstay for acute osmotherapy under strict biochemical surveillance. Future directions should emphasize safer regimens, early toxicity detection, and individualized therapeutic strategies integrating pharmacokinetics, pharmacodynamics, and patient comorbidities.

Keywords: Naproxen, Methotrexate, Mannitol, NSAIDs, Rheumatoid arthritis, Osmotic nephrosis, Adverse effects, Pharmacology

I. INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain central to the management of pain and inflammation and are among the most commonly prescribed drug classes worldwide (1). Despite their clinical effectiveness for rheumatologic, musculoskeletal, and febrile conditions, NSAIDs are a frequent cause of adverse drug reactions (ADRs) and contribute substantially to drug-related hospitalizations and morbidity (2). Among traditional NSAIDs, naproxen has frequently served as a standard comparator in randomized controlled trials, with decades of clinical evidence supporting its efficacy and an overall favourable benefit–risk profile (3).

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Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting approximately 0.5–1% of the population and is characterized by synovitis, progressive joint damage, and disability that markedly impair quality of life (4). Current treatment strategies emphasize remission or low disease activity, typically achieved with disease-modifying antirheumatic drugs (DMARDs). Among these, methotrexate (MTX) is considered the "anchor drug" due to its efficacy, cost-effectiveness, and relatively favourable safety profile (5). MTX exerts its effects through mechanisms such as folate-dependent enzyme inhibition and adenosine-mediated immunomodulation, while subcutaneous administration offers superior bioavailability compared with oral dosing at higher weekly doses (5).

Safety concerns, particularly nephrotoxicity, require careful clinical consideration. Osmotic nephrosis — a histopathological pattern marked by vacuolization of proximal tubular cells — has been linked to agents such as intravenous immunoglobulin, contrast media, and mannitol (6). Mannitol, though widely used as an osmotic diuretic to lower intracranial and intraocular pressure, has been associated with mannitol-induced acute renal failure (MI-ARF) and osmotic nephrosis when administered at high doses, especially in vulnerable patients (7).

Taken together, modern clinical practice must balance the therapeutic benefits of NSAIDs and MTX with their potential toxicities. This review therefore synthesizes current evidence on these agents in inflammatory diseases while highlighting the under-recognized risk of mannitol-associated renal injury.

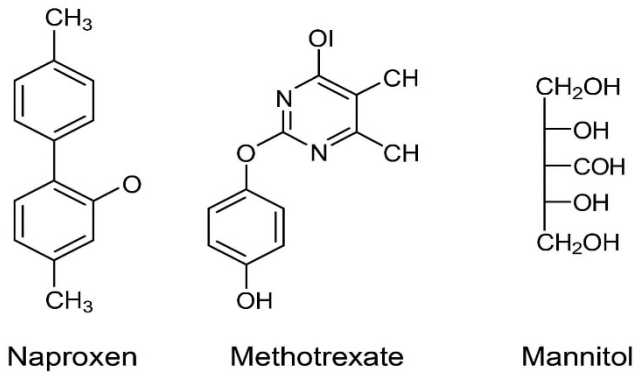

Figure no. 1(Structural formula of Naproxen, Methotrexate, Mannitol)

Mechanism of Action:

1. **Naproxen — Mechanism of Action**

Naproxen is a reversible, non-selective inhibitor of cyclooxygenase enzymes (COX-1 and COX-2). By blocking COX-mediated conversion of arachidonic acid to prostaglandins (e.g., PGE_2, PGI_2, TXA_2), naproxen reduces pain, inflammation, and fever. Inhibition of prostanoid formation decreases nociceptor sensitization, dampens inflammatory cell recruitment, and lowers the hypothalamic set-point for fever. Its COX inhibition explains efficacy in musculoskeletal and rheumatologic conditions, dysmenorrhea, and migraine, while also accounting for typical NSAID adverse effects such as gastrointestinal mucosal injury, platelet dysfunction, and renal hemodynamic changes [8,9].

Terse statement: Naproxen acts by COX-1/COX-2 inhibition, suppressing prostanoid biosynthesis and thereby reducing pain, inflammation, and fever, while adverse effects reflect prostaglandin depletion [8].

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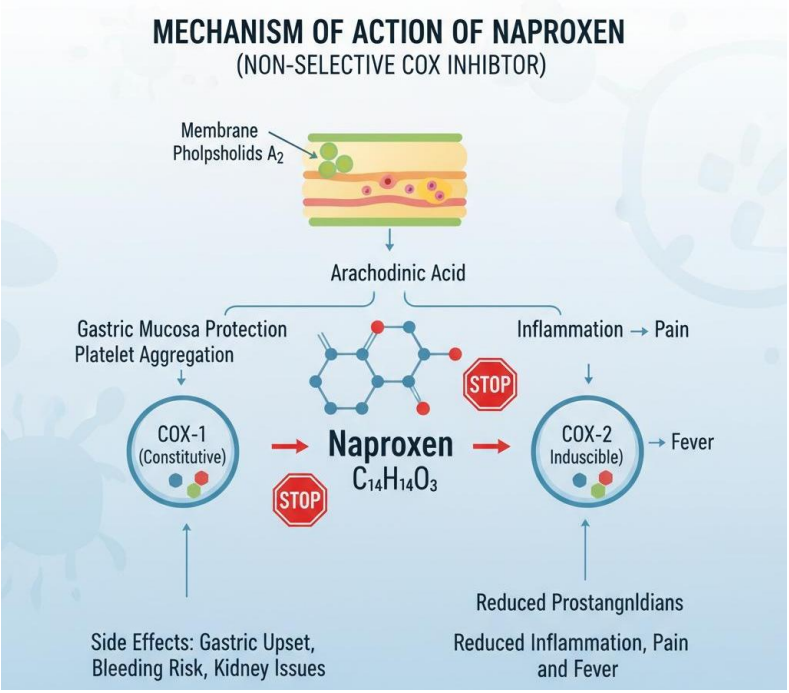

Figure no. 2 (Mechanism of action of Naproxen)

2. Mannitol — Mechanism of Action:

Mannitol is an osmotic diuretic, freely filtered at the glomerulus and poorly reabsorbed. It increases tubular fluid osmolality, which retains water in the lumen, reduces passive water reabsorption, decreases sodium uptake, and increases distal tubular flow. Mannitol also reduces intracranial and intraocular pressure by creating an osmotic gradient across the blood–brain barrier. At high or repeated doses, osmotic nephrosis, tubular stress, and hemodynamic changes may cause acute kidney injury [10,11].

Terse statement: Mannitol induces osmotic diuresis and ICP reduction via tubular osmolality effects; excessive doses may provoke nephrotoxicity [10].

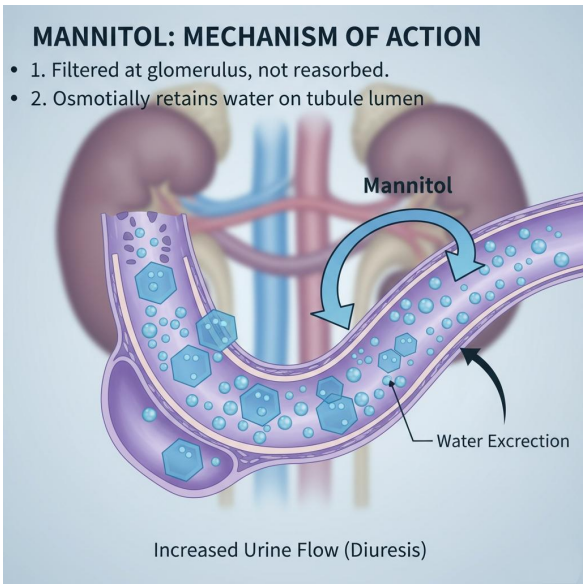

Figure no. 3(Mechanism of action of Mannitol)

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3.Methotrexate — Mechanism of Action:

Methotrexate (MTX) is a folate analogue that inhibits dihydrofolate reductase (DHFR), blocking tetrahydrofolate formation required for purine and thymidylate synthesis. This leads to impaired DNA synthesis and cell proliferation, forming the basis of its antineoplastic use. At low doses, MTX exerts immunomodulatory effects through accumulation of adenosine, which suppresses inflammatory cytokines (e.g., TNF-α, IL-6) and modulates immune cell activity. This dual mechanism explains its role as both an anticancer agent and a cornerstone in autoimmune diseases like rheumatoid arthritis [12].

Terse statement: Methotrexate blocks folate metabolism (anticancer action) and enhances adenosine-mediated cytokine suppression (anti-inflammatory action) [12].

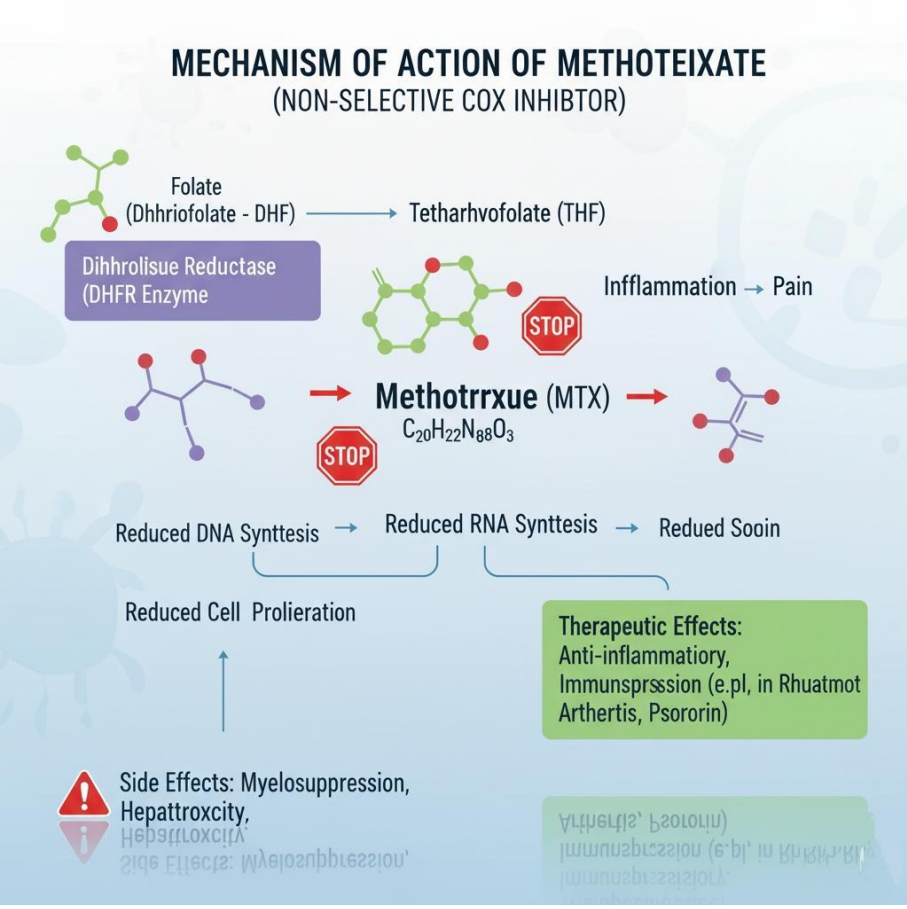

Figure no. 4(mechanism of action of methotrexate)

Safety and Tolerability of Naproxen, Methotrexate, and Mannitol

1. Naproxen:

Naproxen is a generally used NSAID with an established efficacy and safety profile. Its tolerability is generally good, particularly at usual doses and short-term use. Common adverse effects include dyspepsia, nausea, abdominal pain, constipation, or diarrhoea. Serious risks include gastrointestinal (GI) ulceration and bleeding, renal impairment, fluid retention, and hypertension. Regarding cardiovascular profile, compared with other NSAIDs, naproxen appears to have a relatively lower risk of thrombotic cardiovascular events, though caution is advised in patients with existing cardiovascular disease [13,14]. Preventive considerations: risk increases with age, history of ulcer, or concomitant use of anticoagulants, corticosteroids, or SSRIs; gastroprotective strategies should be used in high-risk patients.

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2. Methotrexate (MTX):

Methotrexate is a first-line DMARD extensively used for rheumatoid arthritis and other autoimmune conditions. It is effective and generally well tolerated at low weekly doses when appropriate monitoring and folic acid supplementation are implemented. Common adverse effects include nausea, stomatitis, fatigue, and mild cytopenias. Serious risks include hepatotoxicity, myelosuppression, pulmonary toxicity, nephrotoxicity, and increased infection risk [15,16]. Monitoring of CBC, liver function, and renal function is recommended regularly—initially every 2–4 weeks, then every 1–3 months once stable [15]. Preventive measures: avoid alcohol, use folic acid supplementation to reduce mucositis and cytopenia, and note that interactions with NSAIDs and certain antibiotics may increase toxicity.

3. Mannitol:

Mannitol is an osmotic diuretic primarily used to lower intracranial and intraocular pressure. Its efficacy is well established, but tolerability depends on careful monitoring of fluid balance and renal function. Common effects include diuresis, electrolyte disturbances (hypo-/hypernatremia), and hypotension. Serious risks include acute kidney injury (AKI), pulmonary edema, and rebound intracranial pressure if misused or in renal impairment [16,17]. Preventive measures: monitor serum osmolality, electrolytes, and renal function; avoid use in severe renal or heart failure; and discontinue if serum osmolality exceeds 320 mOsm/kg [16].

Pharmacokinetics of Naproxen, Methotrexate, and Mannitol:

Naproxen

Absorption: Rapid and almost complete after oral administration, with peak plasma levels in 2–4 h; oral bioavailability >95%. Distribution: Highly protein-bound (~99%), with a small volume of distribution (~0.16 L/kg). Metabolism: Extensively metabolized in the liver to inactive conjugates, mainly glucuronides. Elimination: Excreted largely in urine as conjugates, with a half-life of 12–17 h, supporting twice-daily dosing [19].

Methotrexate (MTX):

Absorption: Oral absorption is dose-dependent; bioavailability ranges 60–70% at ≤30 mg/m², but decreases at higher doses. Distribution: ~50% plasma protein bound; distributes widely, accumulating in tissues such as liver and kidney; volume of distribution ~0.4–0.8 L/kg. Metabolism: Undergoes hepatic metabolism to active polyglutamated forms that prolong intracellular action; minor conversion to 7-hydroxymethotrexate. Elimination: Primarily renal (glomerular filtration and active tubular secretion); 80–90% excreted unchanged. Half-life is biphasic—~3–10 h at low doses, longer at high doses or with renal impairment [20].

Mannitol:

Absorption: Not absorbed orally; administered intravenously for therapeutic effects. Distribution: Confined to extracellular fluid with a volume of distribution ~0.2 L/kg. Metabolism: Not metabolized in humans. Elimination: Excreted unchanged by glomerular filtration without tubular reabsorption; clearance approximates GFR. Half-life is 0.5–2 h in normal renal function, prolonged in renal impairment [21].

Pharmacodynamics of Naproxen, Methotrexate, and Mannitol

Naproxen:

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) that exerts its effects through non-selective inhibition of cyclooxygenase (COX-1 and COX-2) enzymes, thereby reducing prostaglandin synthesis. Its therapeutic effects include analgesic, antipyretic, and anti-inflammatory actions, making it effective in conditions such as pain, dysmenorrhea, and arthritis. Inhibition of COX-2 reduces inflammation and pain, while COX-1 inhibition explains gastrointestinal and platelet effects. Naproxen also provides reversible antiplatelet activity through suppression of thromboxane A_2 synthesis [22].

Methotrexate (MTX):

Methotrexate is a folate antagonist with dose-dependent pharmacodynamic actions. At high doses (oncology), MTX competitively inhibits dihydrofolate reductase (DHFR), impairing tetrahydrofolate formation and blocking purine/thymidylate synthesis, thereby suppressing rapidly dividing cells. At low doses (rheumatology), MTX increases extracellular adenosine, leading to anti-inflammatory and immunomodulatory effects through reduced cytokine

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production and immune cell activation. Thus, MTX acts as anti proliferative at high doses and anti-inflammatory/immunosuppressive at low doses [23].

Mannitol:

Mannitol is an osmotic diuretic that raises plasma osmolality, shifting water from intracellular and interstitial compartments into the vascular space. In the CNS, it lowers intracranial pressure (ICP) and reduces cerebral edema by creating an osmotic gradient across the blood–brain barrier. In the kidneys, mannitol is freely filtered at the glomerulus but not reabsorbed, increasing tubular osmolarity, reducing water and sodium reabsorption, and promoting diuresis. It transiently expands intravascular volume, which can improve preload but may precipitate pulmonary edema in susceptible patients [24,25].

Drug–Drug Interactions

Naproxen (NSAID):

1. Anticoagulants / Antiplatelet agents (warfarin, DOACs, aspirin, clopidogrel) — co-administration increases gastrointestinal (GI) bleeding risk and clinically important hemorrhage due to additive platelet inhibition and mucosal injury. Monitoring of INR and clinical signs of bleeding is essential, and gastroprotection with PPIs should be considered (26).
2. SSRIs / SNRIs — combined use raises GI bleeding risk through impaired platelet function and mucosal injury; patients should be counseled and monitored (27).
3. Renin–angiotensin system inhibitors (ACE inhibitors/ARBs), diuretics — NSAIDs reduce prostaglandin-mediated renal perfusion, attenuating antihypertensive effect and increasing risk of renal dysfunction. Monitor BP and renal function when used together (26,28).
4. Lithium — NSAIDs reduce renal clearance of lithium, increasing serum concentrations and risk of toxicity; lithium monitoring is required (26).
5. Methotrexate — NSAIDs reduce renal clearance of MTX, increasing exposure and toxicity risk; especially important with high-dose MTX. Caution is advised even in low-dose therapy with additional risk factors (29,30).

Methotrexate (MTX):

1. NSAIDs (including naproxen) — can reduce renal clearance of MTX, increasing risk of myelosuppression, hepatotoxicity, and mucositis; risk is highest with high-dose MTX (29,30).
2. Penicillins (e.g., high-dose amoxicillin/ampicillin) — may impair renal tubular secretion of MTX, raising toxicity risk (29).
3. Trimethoprim / Sulphonamides — potentiate marrow suppression and impair MTX clearance; blood counts must be monitored (29).
4. Proton pump inhibitors (PPIs) — case reports indicate delayed MTX elimination and toxicity, particularly with high-dose MTX (29,30).
5. Other nephrotoxic drugs (aminoglycosides, cisplatin, high-dose NSAIDs) — any drug impairing renal function can increase MTX exposure and toxicity (30).

Mannitol:

1. Nephrotoxic drugs (aminoglycosides, amphotericin B, cisplatin, NSAIDs) — co-administration increases renal injury risk due to osmotic diuresis; renal function monitoring required (31).
2. Other diuretics — additive effects may lead to dehydration, electrolyte imbalance, and hemodynamic instability; fluid/electrolyte monitoring recommended (31).
3. Neurotoxic drugs — co-use in ICP management may enhance neurologic toxicity (31).
4. Blood products — mixing mannitol with whole blood may cause haemolysis or infusion incompatibility; avoid per labeling guidance (31).

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Effect of Regimens

Naproxen:

Typical adult OTC dosing (naproxen sodium/Aleve) is 220 mg every 8–12 hours as needed, with an optional initial dose of 440 mg; maximum OTC dose should not exceed 660 mg/day unless directed by a prescriber. Prescription use for inflammatory conditions often involves 250–500 mg twice daily, with some regimens reaching 500–1,000 mg/day in divided doses. Initial loading doses of 550 mg followed by 275–550 mg every 6–12 hours are also employed depending on indication and formulation. Due to its long elimination half-life (12–17 h), naproxen is well suited to twice-daily dosing. Dose adjustments are recommended in elderly patients and those with renal or hepatic impairment. Clinicians should monitor for gastrointestinal (GI) and cardiovascular risks with chronic use (32).

Methotrexate (MTX):

In non-oncologic indications such as rheumatology and dermatology, typical starting doses are 7.5–15 mg once weekly (oral or subcutaneous), titrated every 2–4 weeks as needed. The effective range is generally ≤25 mg/week (up to 30 mg/week with parenteral dosing when indicated). In cases of oral intolerance or absorption issues, parenteral routes are preferred. Oncology regimens use much higher gram-scale doses with leucovorin rescue and are managed distinctly. Importantly, once-weekly administration must be emphasized to prevent dangerous daily-dosing errors. Folic acid supplementation (e.g., 1 mg daily or 5–10 mg except on MTX day) reduces mucosal and hematologic toxicity. Routine monitoring of CBC, liver, and renal function is essential. The clinical effect often appears after 4–12 weeks, explained by the persistence of methotrexate polyglutamates in tissues (33,34).

Mannitol:

For osmotherapy in intracranial pressure (ICP) or cerebral edema, typical bolus dosing in adults is 0.5–1.5 g/kg IV (most protocols use 0.5–1 g/kg) administered over 15–60 minutes depending on urgency. For refractory ICP crises, higher boluses (≥1.5 g/kg) have been reported, though with greater risk of adverse effects. Repeat dosing every 4–6 hours is common, guided by ICP monitoring, serum osmolarity, and renal function. Many institutions recommend avoiding dosing more frequently than every 6–8 hours. Monitoring includes serum osmolarity (avoid >320 mOsm/kg), electrolytes, renal function, and fluid balance. Because mannitol is renally excreted, impaired renal function increases risk of accumulation and toxicity (35).

Contraindications and Clinical Considerations

Naproxen

Class, Mechanism & Uses: Naproxen is a non-steroidal anti-inflammatory drug (NSAID) that inhibits both COX-1 and COX-2, thereby reducing prostaglandin synthesis and leading to analgesic, antipyretic, and anti-inflammatory effects. It is widely used in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gout, tendonitis, dysmenorrhea, and other painful inflammatory conditions (36).

Dosage & Administration: In adults with arthritis, typical dosing is 500–1000 mg/day divided (e.g., 250–500 mg twice daily), or as extended-release formulations once daily. For acute pain, an initial 250–500 mg every 6–8 hours or 375–500 mg twice daily is used. Pediatric

dosing (≥5 years, e.g., in juvenile rheumatoid arthritis) is usually 10 mg/kg/day, divided into two doses (36).

Contraindications & Warnings: Contraindicated in moderate/severe renal impairment (creatinine clearance <30 mL/min). Caution in patients with GI bleeding risk, peptic ulcer disease, cardiovascular disease, or concomitant anticoagulants/NSAIDs. During late pregnancy, risk of premature closure of the ductus arteriosus exists. Monitoring includes renal and hepatic function, blood pressure, and GI toxicity (36).

Methotrexate (MTX):

Class, Mechanism & Uses: Methotrexate is an antimetabolite and disease-modifying antirheumatic drug (DMARD). At low doses, it is standard therapy for rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and psoriasis (37).

Dosage Guidelines: Initial dose in RA is typically 10 mg/week orally, increased every 4–6 weeks if inadequate response, up to 20 mg/week depending on tolerance. In JIA, MTX is a first-line DMARD after failure or in combination with NSAIDs or corticosteroids. Oral is preferred, though SC/IM routes are used if GI intolerance or poor response (37).

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Monitoring & Safety: Baseline labs include CBC, liver enzymes, renal function, hepatitis B/C serology, chest radiograph, and pulmonary evaluation if needed. Follow-up includes labs every 2–4 weeks initially, then every 4–12 weeks. Folic acid supplementation (5 mg weekly, separate from MTX) reduces mucosal and hematologic toxicity. Adverse effects include hepatic toxicity, bone marrow suppression, and pulmonary toxicity. Concomitant NSAIDs (e.g., naproxen) may reduce renal clearance of MTX, increasing toxicity risk (37).

Mannitol:

Class & Indications: Mannitol is an osmotic diuretic used to reduce intracranial pressure (ICP) in traumatic brain injury, intracerebral hemorrhage, and cerebral edema. It is also used in acute glaucoma and occasionally for renal protection (38).

Dosage & Pharmacodynamics: A typical bolus is 0.5–1.0 g/kg IV of 20% mannitol over 5–15 minutes, repeatable every 4–6 hours if needed. In ICH, 20% mannitol 125 mL every 4–8 hours/day may be administered, titrated to ICP response. Onset occurs in 15–20 minutes, with effects lasting 1–5 hours. Higher doses provide more sustained ICP reduction.

Monitoring & Safety: Monitor renal function, serum osmolality, electrolytes, and fluid balance. Risks include hypovolemia, hypotension, and electrolyte disturbances. Overuse can cause rebound ICP increase, requiring careful monitoring (38).

Adverse Effects

Naproxen

1.Gastrointestinal (most common): Gastritis, nausea, vomiting, indigestion, heartburn, abdominal pain, diarrhoea or constipation. Severe events include peptic ulcer disease, gastrointestinal bleeding, or perforation, which are dose- and duration-related [39].

2.Cardiovascular: Increased risk of hypertension, fluid retention, edema, and higher incidence of myocardial infarction, stroke, and thromboembolic events, particularly in long-term use or in patients with pre-existing cardiovascular disease [39].

3.Renal: Reduced renal blood flow leading to acute kidney injury; sodium and water retention causing edema and worsening heart failure; hyperkalemia (rare); interstitial nephritis (rare) [40].

4.Hepatic: Elevated liver enzymes (AST, ALT); rarely hepatitis, jaundice, or severe hepatic injury [40].

5.Hematologic: Prolonged bleeding time due to platelet inhibition (less than aspirin); rare cases of anaemia, thrombocytopenia, or agranulocytosis [39].

6.CNS: Headache, dizziness, drowsiness, fatigue; rarely aseptic meningitis, especially in autoimmune disorders [40].

7.Hypersensitivity / Skin: Rash, pruritus, urticaria, photosensitivity [39].

Methotrexate

1. Common Adverse Effects: Gastrointestinal—nausea, vomiting, diarrhoea, stomatitis, loss of appetite. Hematologic—bone marrow suppression (anaemia, leukopenia, thrombocytopenia). Hepatic—elevated liver enzymes, hepatotoxicity, fatty changes, fibrosis with chronic therapy. Pulmonary—interstitial pneumonitis and pulmonary fibrosis. Dermatologic—rash, alopecia, photosensitivity. Neurologic—headache, dizziness, fatigue [41].

2. Serious/Long-Term: Liver damage (fibrosis/cirrhosis, especially with alcohol), bone marrow aplasia leading to infection and bleeding risk, pulmonary toxicity (life-threatening pneumonitis), and rare malignancies (lymphoma, skin cancers). Renal toxicity may occur at high oncologic doses [41].

3. Teratogenicity: Contraindicated in pregnancy (fetal death, malformations). Excretion in breast milk—avoid during lactation [41].

Mannitol

1. Fluid and Electrolyte Imbalance: Dehydration; hyponatremia (early, due to dilution), hypernatremia (late, due to greater water loss), and variable potassium imbalance [42].

2. Cardiovascular: Pulmonary edema from fluid shifts, exacerbation of congestive heart failure, hypo- or hypertension [42].

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3. Renal: Acute kidney injury in predisposed patients; osmotic nephrosis with prolonged therapy [42].
4. Neurological: Headache, dizziness, seizures secondary to electrolyte imbalance or rebound intracranial pressure [42].
5. Other: Nausea, vomiting, and thrombophlebitis at infusion site [42].

II. CONCLUSION

Naproxen, methotrexate, and mannitol exemplify the therapeutic benefits and toxicological challenges of modern pharmacology. Naproxen remains a reliable NSAID for inflammatory conditions but demands vigilance for GI, renal, and cardiovascular risks. Methotrexate is indispensable in RA management due to its dual mechanisms, yet requires stringent laboratory monitoring and folate rescue to mitigate toxicity. Mannitol plays a pivotal role in acute care by lowering intracranial pressure, though its nephrotoxic potential underscores the importance of serum osmolarity and renal function monitoring. Collectively, these drugs highlight the delicate balance between efficacy and adverse effects, necessitating personalized therapy and careful drug–drug interaction management. Optimizing their use will rely on integrating mechanistic insights, vigilant safety monitoring, and patient-specific risk stratification.

REFERENCES

[1]. Weisman SM, Graham DY. Evaluation of the benefits and risks of nonsteroidal anti-inflammatory drugs. Pharmacology Thera. 2002;95(2):95–138.
[2]. Giardina C, Cutroneo PM, Mocciaro E, et al. Adverse drug reactions in hospitalized patients: results of the FORWARD (Facilitating the Reporting of Adverse Drug Reactions) study. Front Pharmacol. 2018;9:350.
[3]. Derry CJ, Derry S, Moore RA. Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. Cochrane Database Syst Rev. 2009;(4):CD004234.
[4]. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388(10055):2023–2038.
[5]. Hoekstra M, Haagsma CJ, Neef C, et al. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol. 2004;31(4):645–648.
[6]. Dickenmann M, Oettl T, Mihatsch MJ. Osmotic nephrosis: acute kidney injury with accumulation of substances in proximal tubular cells. Am J Kidney Dis. 2008;51(3):491–503.
[7]. Visweswaran P, Massin EK, Dubose TD Jr. Mannitol-induced acute renal failure. J Am Soc Nephrol. 1997;8(6):1028–1033.
[8]. Vane JR. Inhibition of Prostaglandin Synthesis as a Mechanism of Action for Aspirin-like Drugs. Nature New Biol. 1971;231:232–235.
[9]. StatPearls. Naproxen. NCBI Bookshelf. 2023.
[10]. StatPearls. Mannitol. NCBI Bookshelf. 2024.
[11]. Shawkat H, Westwood MM, Mortimer A. Mannitol: a review of its clinical uses. Continuing Education in Anaesthesia Critical Care & Pain. 2012;12(2):82–85.
[12]. Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. Nat Rev Rheumatol. 2020;16(3) :145-154
[13]. Angiolillo DJ, et al. Clinical pharmacology and cardiovascular safety of NSAIDs. Curr Cardiol Rep. 2016.
[14]. Bello AE, et al. Cardiovascular effects of NSAIDs: review and perspective. Curr Rheumatol Rep. 2014.
[15]. Onel KB, et al. 2021 American College of Rheumatology guideline for treatment and monitoring of juvenile idiopathic arthritis (includes methotrexate monitoring). Arthritis Rheumatol. 2021.
[16]. Hanoodi M, et al. Methotrexate. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
[17]. Kim JH, et al. Optimizing mannitol use in managing increased intracranial pressure. Neurocrit Care. 2023.
[18]. Tenny S, et al. Mannitol. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024
[19]. Runkel R, Chaplin M, Boost G, Segre E, Forchielli E, Hill R. Absorption, distribution, metabolism, and excretion of naproxen in various laboratory animals and man. J Pharm Sci. 1972;61(5):703-708. Doi:10.1002/jps.2600610505
[20]. Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. Cancer. 1978;41(1):36-51. Doi:10.1002/1097-0142(197801)41:1<36::AID-CNCR2820410107>3.0.CO;2-G

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[21]. Elisaf M, Merkouropoulos M, Tsianos EV, Siamopoulos KC. Pathophysiologic and therapeutic aspects of the renal handling of mannitol. Kidney Int. 1997;52(5):1188-1198. Doi:10.1038/ki.1997.453
[22]. Brutzkus JC. Naproxen. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
[23]. Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. Nat Rev Rheumatol. 2020;16(3):145-154. doi:10.1038/s41584-019-0363-1
[24]. Kim JH, Park JH. Optimizing Mannitol Use in Managing Increased Intracranial Pressure. Neurocrit Care. 2023;38(1):121-132. doi:10.1007/s12028-022-01568-0
[25]. Tenny S, Thorell W. Mannitol. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
[26]. Patrono C, Morais J, Baigent C, Collet J-P, Fitzgerald D, Halvorsen S, Rocca B. Antiplatelet drugs: The role of aspirin in primary prevention. European Heart Journal. 2022;43(34): 3414–3426. doi:10.1093/eurheartj/ehac261
[27]. de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: Mechanisms, clinical outcomes and implications for use in elderly patients. Drugs & Aging. 2011;28(5):345–367. doi:10.2165/11589340-000000000-00000
[28]. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: Physiologic foundations and clinical implications. American Journal of Medicine. 1999;106(5B):13S–24S. doi:10.1016/S0002-9343(99)00160-7
[29]. May KP, West SG, McDermott MT, Huffer WE. Methotrexate and penicillin: Clinical and pharmacokinetic interaction. Annals of Pharmacotherapy. 1996;30(7–8): 780–785. doi:10.1177/106002809603000711
[30]. Jafari A, Mohammadpour AH, Rezaee H, et al. A critical review of methotrexate clinical interactions: Role of transporters. European Journal of Drug Metabolism and Pharmacokinetics. 2023;48(3): 349–361. doi:10.1007/s13318-023-00868-8
[31]. Srivastava T, Alon US. Osmotic diuretics: Mannitol. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. [Available at: https://www.ncbi.nlm.nih.gov/books/NBK470392/]
[32]. Rostom A, Dube C, Wells GA, Tugwell P, Welch V, Jolicoeur E, McGowan J. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database Syst Rev. 2002;(4):CD002296.
[33]. Visser K, van der Heijde DM. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis. 2009;68(7):1094–1099.
[34]. Chan ES, Cronstein BN. Methotrexate—how does it really work? Nat Rev Rheumatol. 2010;6(3):175–178.
[35]. Wakai A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev. 2013;(8):CD001049.
[36]. Rostom A, Muir K, Dubé C, et al. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. Clin Gastroenterol Hepatol. 2007;5(7):818-828.
[37]. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological DMARDs: 2019 update. Ann Rheum Dis. 2020;79(6):685-699.
[38]. Wakai A, McCabe A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev. 2013;2013(8):CD00
[39]. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. Gastroenterology. 2001;120(3):594–606.
[40]. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: Physiologic foundations and clinical implications. Am J Med. 1999;106(5B):13S–24S.
[41]. Visser K, van der Heijde DM. Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: A systematic review of the literature. Clin Exp Rheumatol. 2009;27(6):1017–1025.
[42]. Palmer BF, Clegg DJ. Fluid, electrolyte, and acid-base disorders associated with mannitol therapy. N Engl J Med. 2015;373:2547–2556