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Review

Non-Dental Drugs A Dentist Should Know: A Review

Khadeeja Saleem[1†], Paras Ahmad[1†], Mohmed Isaqali Karobari[2], Mohammad Amjad Kamal[4,5,6], Jawaad Ahmed Asif[3*], Tahir Yusuf Noorani[2*]

[1] Oral Medicine Unit, [2] Conservative Dentistry Unit, [3] Oral and Maxillofacial Surgery Unit, School of Dental Sciences, Universiti Sains Malaysia, Health campus, 16150 Kubang Kerian, Kota bharu, Kelantan, Malaysia. [4]King Fahd Medical Research Center, King Abdulaziz University, Saudi Arabia; [5]Enzymoics, 7 Peterlee Place, Hebersham, NSW 2770; [6]Novel Global Community Educational Foundation, Australia.

† Both the authors contributed equally.

* Corresponding authors

Abstract: More than 15,000 prescriptions and over the counter drugs are available according to the US Food and Drug Administration website. Moreover, several herbal medicines and dietary supplements are readily available to add to the list of possible drugs, which can potentially cause adverse drug interactions. These are a pressing concern for all as they can interfere with many dental procedures. Additionally, the number of geriatric patients seen in routine dental practice has increased over time. This implies that there are more patients with multiple diseases and health conditions like hypertension, diabetes, problems associated with the cardiovascular, renal and gastrointestinal systems, arthritis, osteoporosis, etc. All these require patients to be on certain medications. Furthermore, advancement in the dental field has led to more complex dental procedures (implants, grafts) being carried out in a general dental practice. These advanced and slightly more invasive treatments require the use of certain drugs before, during and after the treatment like local anesthetics, vasoconstrictors, anxiolytics, analgesics and antibiotics. All of these can possibly interact with medications a patient is already taking and can also interfere with the current dental treatment and create complications. This article aims to provide necessary information about commonly encountered systemic diseases and associated treating medications, their mechanism of action, possible complications and their management. The classes of drugs discussed include anti-platelet agents, vitamin K antagonists, novel oral anticoagulants, bisphosphonates, disease-modifying anti-rheumatic drugs and oral contraceptives.

Clinical Relevance: Minor oral surgical procedures are performed daily by every practicing dentist around the globe. These procedures impose a substantial risk of bleeding, dry socket, infection and bone necrosis. Every patient is at risk of developing complications; however, it increases multitudinously in patients being treated for various systemic diseases. This article gathers and analyzes all those drugs which are used for treating various systemic conditions but can have a harmful effect over minor oral surgery procedures.

Keywords: Anti-platelets; Anti-rheumatic drugs; Bisphosphonates; Oral anticoagulants; Oral contraceptives; Vitamin K antagonist

Introduction

Minor oral surgical procedures are performed daily around the globe. These forms of minor oral surgery are not restricted to just removing impacted teeth or severely broken-down teeth; they also include apicectomy, biopsy, placement of dental implants, sinus lift and other procedures. These procedures impose a substantial risk of bleeding, dry socket, infection and bone necrosis. Every patient is at risk of developing a complication; however, the risk is increased in patients being treated

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for various systemic diseases. Table 1 describes the risk of common complications during or after dental procedures.

Table 1. Risk of common in-office dental procedures

	Very low-risk procedures	Low-risk procedures	Medium risk procedures	High-risk procedures
General procedures	• Examination • Radiography	• Low anesthetic infiltration	• Local anesthesia nerve block	-
Periodontics	• Periodontal probing	• Superficial prophylaxis	• Ultrasonic scaling • One to two quadrants deep cleaning • Localized gingival surgery	• Full mouth deep cleaning • Generalized gingival surgery
Oral and maxillofacial surgery	-	• Simple single dental extraction • Soft tissue biopsy less than 1cm in size	• Simple extractions ≤ 5 teeth • Soft tissue biopsy 1-2.5 cm in size • Placement of a single implant	• Multiple extractions of more than 5 teeth • Surgical extractions requiring raising of the periosteal flap and bone removal • Soft tissue biopsy ≥ 2.5 cm • Osseous biopsy • Torus removal • Placement of multiple implants
Restorative dentistry	• Certain orthodontic procedures such as wire adjustments • Denture fabrication and repair	• Rubber dam placement • Restorations (fillings) • Root canal treatment • Crown preparation • Prosthetic rehabilitation of implant • Certain orthodontic procedures, such as band and bracket removal.		• Endodontic surgery which involve osseous manipulation

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This article gathers and analyses those drugs which are used for treating various systemic conditions but can have a deleterious effect over minor oral surgery. These drugs can be termed as Non-Dental Drugs for Dentists (NDDD). Although, these drugs are not prescribed by a dentist, he/she will surely encounter patients using a spectrum of drugs, which are novel and post-dental treatment complications and management in such patients should be known to every dentist. Thus, these were termed as NDDD.

NDDDs include anti-platelet agents, novel oral anticoagulants (NOAs) (NOACs), bone modifying agents (BMAs), disease-modifying anti-rheumatic drugs (DMARD), chemotherapeutic and oral contraceptives (OCPs). Respective fields of medicine have advanced in research and developed novel drugs, which must be cautioned amongst the general dental practitioners and dental specialists.

General dentists and oral surgeons have been advised continuously about the importance of obtaining a thorough history from the patient about the past and common systemic diseases and their medicinal management to prevent any type of complications, mild or severe.

This article aims to provide necessary information about commonly encountered systemic diseases and associated treating medications, their mechanism of action, possible complications and their management. The classes of drugs discussed include anti-platelet agents, vitamin K antagonists, novel oral anticoagulants, bisphosphonates, disease-modifying anti-rheumatic drugs and oral contraceptives.

ANTI-PLATELET DRUGS

As the name suggests, these medications have been used to inhibit the platelet aggregation /agglutination to prevent clot formation, especially in individuals with compromised cardiovascular system, coronary artery thrombosis, stroke, deep vein thrombosis. Although aspirin has been used for inhibition of platelet aggregation for decades, new medications have flooded the current market with better efficacies. Currently, the anti-platelet medications being prescribed are acetylsalicylic acid (ASA) or aspirin (Aspirin®, Asaphen®, Entrophen®, Novasen®), Clopidogrel (Plavix®), Prasugrel (Effient®), Ticagrelor (Brilinta®), Cangrelor, eptifibatide, Tirofiban, Cilostazol (Pletal®), and dipyridamole (Persantine®). Table 2 describes the risk of procedures with regard to the type of anti-thrombotic agents.

Platelet aggregation is reversed and/or prevented by antiplatelet drugs in arterial thrombosis. This is most prominently seen in ischemic stroke and myocardial infarction. Hemostatic plugs form when platelets aggregate at the site of vascular injury.

Table 2. Risk of procedures with regard to type of anti-thrombotic agents

	Anti-platelets	**Vitamin K antagonist**	**Novel anticoagulant**
Low-risk procedures	• No change	• No change	• No change
Medium risk procedures	• No change • Local hemostatic measures	• For INR ≤ 4 no change • Local hemostatic measures	• No change • Local hemostatic measures
High-risk procedures	• No change • Local hemostatic measures	• For INR ≤ 3 no change • For INR greater than three consider: a) Low risk for thromboembolism:	• Withhold 24 hours prior to the procedure • Local hemostatic measures

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		• Withdrawal drug or reduce dose to allow INR to fall b) High risk for thromboembolism: • Withhold warfarin, convert to LMWH. Withhold LMWH on the morning of the procedure	• Restart after hemostasis is achieved

Aspirin

The name Aspirin for acetylsalicylic acid was coined by Bayer in 1899. Aspirin entered the Guinness World Records for being the most sold painkiller in 1950 [1]. It was one of the first drugs to come into common usage. Aspirin remains one of the most researched medicines in the world, with approximately 700 to 1,000 clinical trials conducted each year [2].

Mechanism of action

Aspirin (Aspirin®, Asaphen®, Entrophen®, Novasen®)

Acts on the arachidonic acid pathway where the acetyl groups of ASA bind with a serine residue of the cyclooxygenase-1 (COX-1) enzyme and inhibits the production of prostaglandins and thromboxane A2 (TXA2) which subsequently inhibits the platelet aggregation.

Platelet glycoprotein (GP) IIb/IIIa receptor inhibitors

Eptifibatide and Tirofiban act as an antagonist of fibrinogen binding to the GP IIb/IIIa receptor (surface receptor) and thus inhibits platelet aggregation.

Enzyme inhibitors

Cilostazol (Pletal®) and dipyridamole (Persantine®) inhibit both adenosine deaminase and phosphodiesterase in platelets and lead to elevation of intraplatelet cyclic AMP, which reduce thromboxane A2 activity leading to inhibition in platelet aggregation.

Dental considerations

The guidelines presented by the British Committee for Standards in Hematology [3] last updated in February 2019 states the following:

The risk of bleeding with a stable international normalized ratio (INR) that lies within the therapeutic range (less than 4) is minimal.

The risk of thrombosis may increase in patients if the oral anti-coagulants are temporarily stopped.

If INR in patients is unstable, the concerned physician should be consulted.

P2Y12 INHIBITORS

An interaction of ADP with the platelet P2Y12 receptor is a vital part of platelet aggregation. The P2Y12 receptor is the predominant receptor involved in the ADP-stimulated activation of the glycoprotein IIb/IIIa receptor [4,5].

A novel anti-aggregating agent, prasugrel, ticagrelor, and clopidogrel target the platelet adenosine diphosphate (ADP) 2 receptor. They induce irreversible platelet aggregation by binding to the ADP receptors present on the surface of platelets [6-8] ***Mechanism of action***

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Oral P2Y12 inhibitors like prasugrel, ticagrelor, and clopidogrel are the prodrugs that require an enzymatic transformation in the liver to their respective active metabolite. These medications inhibit platelet aggregation irreversibly.

Cangrelor (Kengreal®) is an intravenous, direct-acting, reversible P2Y12 inhibitor. It is an active drug not requiring metabolic conversion; it provides a rapid onset and offset of action. Cangrelor was approved by the FDA in June 2015 for intravenous application. They act as P2Y12 platelet receptor antagonists and inhibit ADP to be released from damaged blood vessels & RBCs, subsequently leading to inhibition in platelet aggregation.

Dental considerations

The risks and protocol to follow for patient P2Y12 inhibitors are the same as a patient on Aspirin. A general agreement exists not to alter the treatment regimens in most cases. The risk of modifying the intake of anti-platelets outweighs the consequences of prolonged bleeding, which can be managed with local measures [9]. Dentists may encounter patients with P2Y12 inhibitors alone or in combination with aspirin. Various studies have been conducted demonstrating the safety of dental extraction in patients being treated with oral P2Y12 inhibitors where the dose was neither altered nor seized [10-12].

Protocol

According to the guidelines presented by Scully and Wolf [13] for oral surgery in patients on anticoagulant therapy, the following should be observed:

The procedure should be planned early in the day and week. A local anesthetic solution with a vasoconstrictor should be administered, preferably via infiltration or intra-ligament injection. The surgical procedure should be performed as less traumatic as possible, followed by local pressure, which can be adequately maintained employing a gauze. Packing hemostatic agents into the socket, along with suturing of the socket, is advocated. A 5% solution of tranexamic acid, used as a mouthwash in anti-coagulant-treated patients undergoing oral surgery, can be prescribed to be used four times a day for two days.

VITAMIN K ANTAGONISTS

Vitamin K antagonists are one of the most frequently used drugs globally. They inhibit the enzyme, vitamin K epoxide reductase, thereby exhibiting their anticoagulant effect. They are indicated in long-term anticoagulation therapy.

Warfarin

Warfarin is a pharmacologically potent compound derived from a plant. It is the most commonly used anticoagulant worldwide [14]. The name Warfarin is a derivative of WARF (Wisconsin Alumni Research Foundation) and –arin from coumarin [15]. It has been estimated that in the UK, at least 1% of the general population and 8% of the population above 80 years old take Warfarin regularly [16].

Mechanism of action

Warfarin interferes with the hepatic carboxylation of coagulation factors that are dependent on vitamin K. These include coagulation factors II, VII, IX and X and protein C and S. Warfarin consists of a racemic mixture of two active enantiomers. Both of these require necessary biotransformation by the liver. The CYP isoenzyme system has been recognized as an effective catalyst system responsible for that [17]. The antithrombotic effect is observed when there is sufficient depletion of prothrombin (half-life of 60-72 hours) [18].

Protocol

Warfarin has been the most debated drug in dental publications, especially concerning dental extractions and minor oral surgeries. The recommendations and protocols have been continuously

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modified. The protocols have ranged from hospitalization for withdrawal of Warfarin and, subsequently, heparinization to just monitoring the INR with or without local hemostatic measures post-dental extraction. Simple teeth extraction in patients on Warfarin treatment can be performed safely without a high risk of bleeding provided that INR is equal or less than 3.5 on the day of extraction [19].

Local hemostatic measures, which include antihemorrhagic agents, tissue adhesives and sutures, are recommended. If the INR is more than 3.5, then the treating physician should be informed about the condition and dental extractions should be avoided.

NOVEL ORAL ANTICOAGULANTS

Recently, in the USA and many European countries, including Italy, three kinds of NOACS have been approved. These include Apixaban and Rivaroxaban that act as factor Xa inhibitor (FXaI), Dabigatran, which functions as a direct thrombin inhibitor (DTI). Edoxaban, another FXaI, has been recently approved in Europe by the European Medicines Agency [20]. These drugs have a relatively fast onset and can reach their peak concentrations in just a few hours [21]. Besides, they also exhibit a wide therapeutic margin, fewer drug-to-drug interactions and no substantial food interactions [22].

The advanced diffusion of NOAs has a direct effect on various dental specialties, especially in a surgical context. The literature only contains studies of patients taking NOAs undergoing dental treatment from 2012 owing to their recent discovery. There is no data yet, concerning the dental management of patients, taking Edoxaban [20]. Figure 1 depicts the intrinsic, extrinsic and common coagulation pathways.

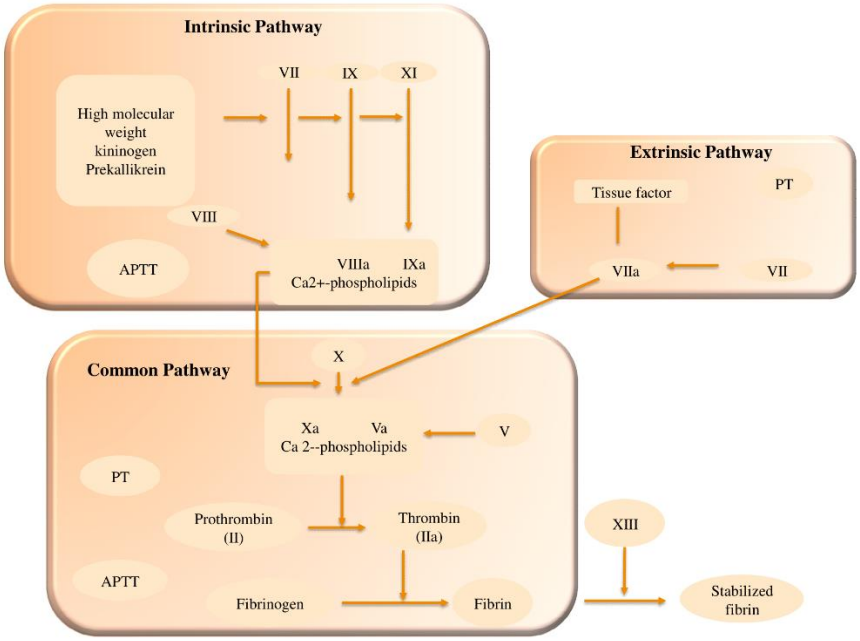

Figure 1. The classical coagulation pathway model. Two pathways, extrinsic and intrinsic, merge in the common pathway at factor X (FX) level. Core coagulation tests activated partial thromboplastin time (APTT) and prothrombin time (PT) results are interpreted using this model.

Dabigatran

Dabigatran belongs to a class of drugs that directly bind to thrombin and block its effect. They are called direct thrombin inhibitors (DTIs). Dabigatran etexilate is the first approved orally administered DTI in the USA [23]. A reduction in the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation was the first FDA approved indication for Dabigatran.

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Dabigatran had no specific antidote until 2011 [24]. But, recently, Idarucizumab, has been approved as an antidote to Dabigatran [25].

Mechanism of action

It binds with the thrombin molecule (IIa) on its active site, thus inhibiting the catalysis of fibrin from fibrinogen. Dabigatran inhibits clot bound and free thrombin, both, unlike warfarin [26].

Dental considerations/risks

Many studies demonstrate the risk of hemorrhage to be similar to that of warfarin amongst patients taking DTIs. This is so when the INR value ranges between 2 and 3, excluding gastrointestinal bleeding [27,28].

For the patients needing minor oral surgical procedures such as simple extraction, apicectomy, incisional or excisional biopsies of localized mucosal abnormalities, localized periodontal surgery, the risk of bleeding is presumed to be comparable to one consuming vitamin K antagonists with an INR of less than 3 [29].

Protocol

The onset of action of dabigatran is rapid (approximately 2 hours) and it has a short half-life (11.5 hours). It is recommended that all dental procedures be scheduled as late as possible after the most recent dose, ideally more than 12 hours.

For single uncomplicated tooth extractions, local hemostatic measures such as mechanical pressure, suturing and topical hemostatic agents (such as Gelfoam™ or Surgicel™) should be adequate to control the bleeding.

Once the surgery is completed, local hemostatic measures, for example, suturing, cellulose mesh, gelatin sponge, and tranexamic acid mouth wash (twice daily for 3-5 days) may aid in regulating postoperative bleeding [28]. Even though there is no direct interaction with NSAIDs, prescription of NSAIDs should be avoided as they cause an increase in the risk of bleeding [29]. Alternate analgesics such as paracetamol may be prescribed. The antidote for dabigatran is Idarucizumab, which rapidly reverses the effects of dabigatran in bleeding patients and in those undergoing urgent procedures. It is a monoclonal antibody fragment that specifically binds to dabigatran and reverses its anticoagulant activity [25].

Apixaban

Apixaban was approved in 2012 by The European Medicines Agency (EMA) to be used for the prevention of ictus and systemic clots in adult patients with non-valvular atrial fibrillation. It is a reversible and potent factor Xa inhibitor, which is consumed orally. Apixaban has similar therapeutical indications as Dabigatran and Rivaroxaban [31].

Mechanism of action

Apixaban is a strong, effective and reversible factor Xa inhibitor indirectly inhibiting the platelet aggregation induced by thrombin. It prevents the formation of thrombin and, hence, clot formation. Whether in its soluble form or bound to the prothrombinase complex, it attaches itself to the active site of factor Xa, consequently, interfering with its interaction with thrombin [32]. The drug is absorbed rapidly, and its maximum concentrations are reached at 3-4 hours after administration. It's binding to human plasma proteins is approximately 8% and it has a half-life of 8-15 hours [33].

Protocol

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Low-risk procedures such as simple extractions, mucogingival surgical procedures (if the hemorrhage is not very extensive) and surgical procedures lasting less than 45 minutes can be carried out 12 hours after the last administration of apixaban or at 24 hours if a dose is missed [34].

In case of invasive procedures, apixaban must be suspended for at least 24 hours prior to a procedure of medium risk and at least 48 hours in cases of high risk. Owing to the short withdrawal time, no replacement therapy with low molecular weight heparin is necessary. If the period of drug suspension is prolonged, the administration of low-molecular-weight heparin is recommended.

Heparin, an indirect coagulant, shows its anticoagulant property by activating antithrombin. In the unfractionated heparin (UFH) form, it has a molecular weight of 5,000 to 30,000 Da and is a highly sulfated mucopolysaccharide. Enzymatic or chemical depolymerization is used to derive low-molecular-weight heparin (LMWH) from UFH. LMWH's mechanism of anticoagulant action is like UFH's, with a longer half-life, more predictable pharmacodynamic and pharmacokinetic properties, and an alleviated risk of non-hemorrhagic adverse effects [35]. Figure 2 depicts the management strategy for the patient with anticoagulation therapy scheduled for invasive dental treatment.

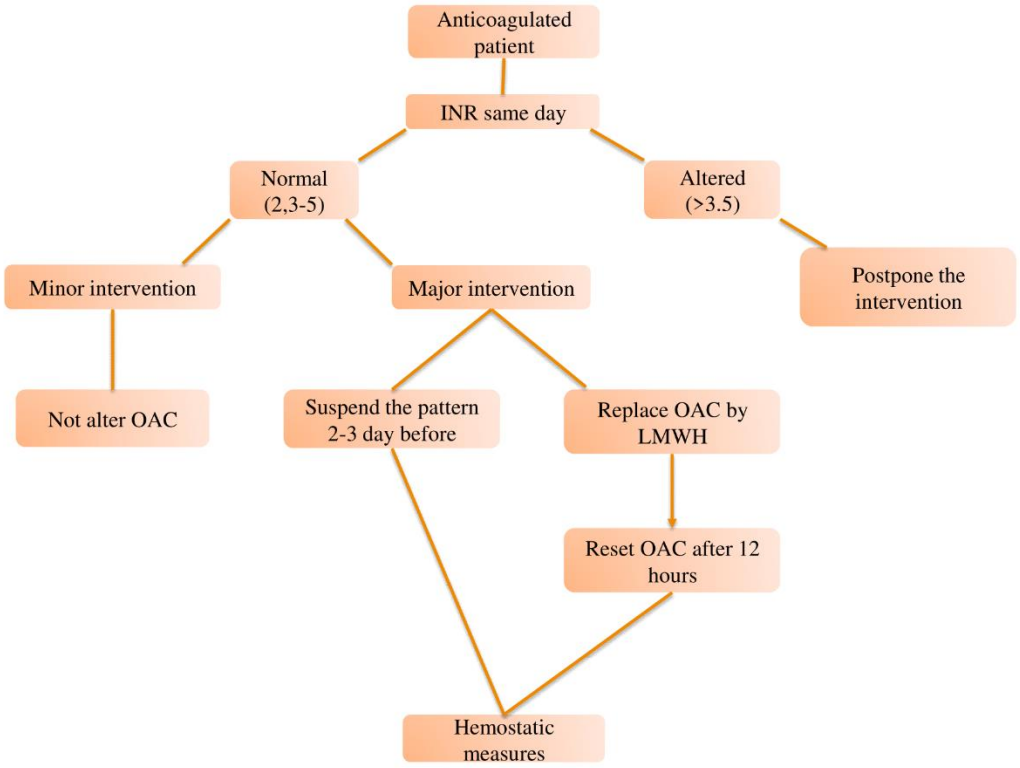

Figure 2. Management strategy for the patient with anticoagulation therapy scheduled for invasive dental treatment. INR: international normalized ratio; OAC: oral anticoagulant; LMWH: low-molecular-weight heparin.

However, local hemostatic measures should be carried out after completion of surgical procedure irrespective of the risk levels.

For major oral surgery, or in patients with bleeding comorbidities, the drug should be suspended 24 hours prior to surgery and then, restarted once hemostasis is achieved. This requires around 24 hours [36].

BISPHOSPHONATES (BPs) AND DENOSUMAB

Bisphosphonates (BPs) are bone modifying agents (BMAs) that interfere with bone turnover, mainly through their influence on osteoclasts [37]. In the contemporary pharmacological arsenal, they

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are the primary drugs used against osteoporosis, malignancies metastatic to bone, Paget's disease, multiple myeloma [38] and associated skeletal conditions such as osteogenesis imperfecta and low bone density [39]. However, the association of bisphosphonates with osteonecrosis of the jaw, low bone turnover conditions resulting in pathological fracture, and a heightened incidence of atrial fibrillation have increased the scrutiny on their widespread use [40].

Recently, denosumab was added to the list of BMAs. They have similar clinical applications as the BPs [41,42], but denosumab is not prescribed for treating multiple myeloma [43].

Mechanism of action

Bisphosphonates are either nitrogen-containing (NBPs) or non-nitrogen containing (non-NBPs). Both types indirectly act as anti-resorptive medications. NBPs bind to the calcium in bone. The calcium is ingested by the osteoclast, which is impregnated with NBPs. NBPs impair the mevalonic acid pathway and thus interferes with the bone resorption process. They impair the ability of the osteoclasts to form the ruffled border, to adhere to the bony surface, and to produce the protons necessary for continued bone resorption. Non-NBPs replace the terminal pyrophosphate of osteoclasts' ATP and destabilizes the energy production of the cell. Thus, cells (osteoclasts) initiate apoptosis.

On the other hand, denosumab acts as a receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitor, which occurs as a fully humanized antibody against RANK-L. It acts by inhibiting osteoclast activity and related bone resorption [43].

Medication-related osteonecrosis of the jaw (MRONJ)

Bisphosphonates and Denosumab, in addition to anti-angiogenic drugs such as monoclonal antibodies and tyrosine kinase inhibitors, have been identified as drugs that are responsible for medication-related osteonecrosis of the jaw (MRONJ) [44].*Dental considerations*

A comprehensive oral evaluation and comprehensive dental treatment are suggested before commencing BMA therapy to reduce the risk of developing MRONJ [45]. Although the incidence of MRONJ in the osteoporosis patient population is very low and is estimated at 1–90 per 100,000 patient-years of exposure. However, in the oncology patient population, MRONJ prevalence has been estimated to be as high as 18.6 % [46]. , The majority of the patients encounter this bone pathology after dental treatment [47]. Therefore, if the systemic circumstances allow, a crucial decision involving the treating physician, dentist and other specialists must be taken to defer the commencement of anti-resorptive therapy until dental health is either improved or treated [48,49].

Patients should be educated about the risk of developing MRONJ and the significance of maintaining proper dental health [43].

Dental procedures that involve direct osseous trauma such as dental extraction or dental implants must be avoided in asymptomatic patients during active BMA therapy. Removal of the crown and endodontic therapy of the remaining roots may be opted as the most suitable treatment for any non-restorable teeth [50].

If the systemic conditions allow, discontinuation of oral bisphosphonates for at least two months before dental surgery should be considered in those patients who have received an oral bisphosphonate. BMA therapy should be resumed after the osseous healing has taken place [43]. Treatment goals for patients having established MRONJ include pain elimination, controlling the hard and soft tissue infection, curtailing the advancement and development of bone necrosis [51]. Figure 3 depicts the algorithm for dental management in patients treated with oral bisphosphonates.

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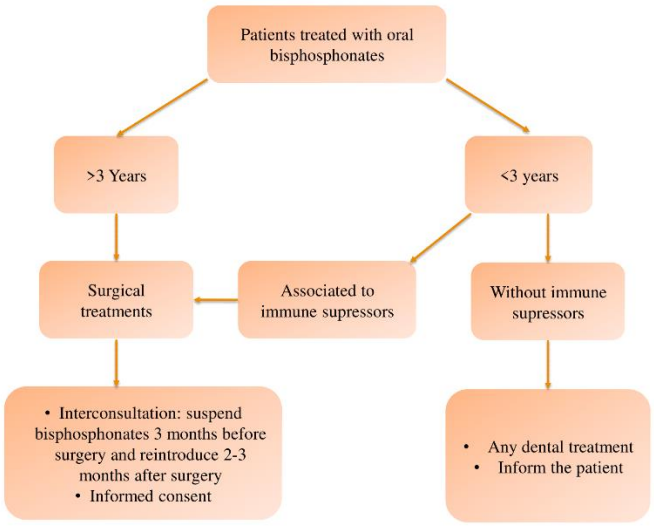

Figure 3. Algorithm for dental management in patients treated with oral bisphosphonates.

DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

DMARDs belong to a class of drugs used in various arthritic conditions for arresting the advancement of disease along with eliminating the associated pain. They have an important role in the treatment of rheumatoid arthritis (RA), psoriatic arthritis, Crohn's disease, myasthenia gravis, and juvenile idiopathic arthritis. Cardiovascular side effects associated with COX-2 inhibitors and short-term action associated with glucocorticoids resulted in the development of newer DMARDs. Presently, non-biological DMARDs such as sulfasalazine, azathioprine, methotrexate, and hydroxychloroquine reduce pain and prevent the progression of the disease. Biological DMARDs, including infliximab, abatacept, adalimumab, golimumab, and tocilizumab, have proved to be more efficient. They exhibit fewer side effects than non-biological DMARDs, but they are expensive [52].

Mechanism of action

They act by different mechanisms against inflammation, including inhibition of tumor necrosis factor (TNF), suppression of TNF-α and interleukin-1, induction of inflammatory cells apoptosis, by increasing chemotactic factors, inhibition of purine synthesis, purine or pyrimidine metabolism [52]. Figure 4 shows the mechanism of action of DMARDs.

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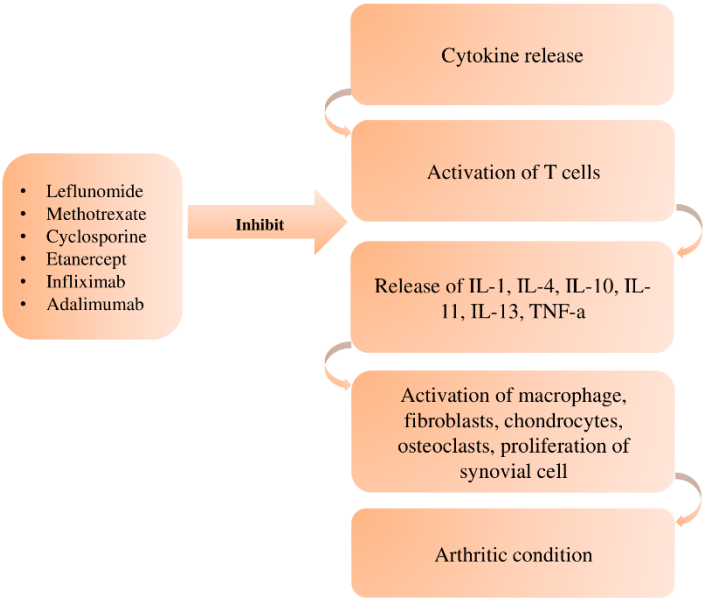

Figure 4. Mechanism of action of disease-modifying anti-rheumatic drugs (DMARDs).

Methotrexate

Methotrexate has emerged as a popular treatment of choice in rheumatoid arthritis due to its anti-inflammatory and immunosuppressive effects [53]. Some promising results have been shown by combining methotrexate with other biologic agents [54,55].

Dental considerations

It is imperative that the dentist has up to date knowledge regarding the medications a patient with RA is currently taking, their interaction with other medications, and possible adverse effects. The most common side effects DMARDs include gastrointestinal disturbances, alopecia, hepatotoxicity, stomatitis, infrequent myelosuppression, rash and life-threatening pulmonary toxicity. The dentist must evaluate the patient's current medication schedule in order to avoid any complications prior to prescribing DMARDs, especially in patients with a history of peptic ulcers or renal impairment [56]. Although stomatitis is a relatively less severe side effect of methotrexate, its severity may be reduced by folic acid [57]*Dental management of the patient receiving disease-modifying anti-rheumatic drugs (DMARDs): Before dental treatment*****:**

- When indicated, administer antibiotic prophylaxis due to immunosuppression.
- When indicated, administer glucocorticoid replacement therapy.
- Evaluate the potential risk of hemostasis impairment.

During dental treatment:

- Identify and treat medication-related gingival overgrowth and ulceration.
- Identify and treat xerostomia-related complications.
- Identify and treat disease-associated periodontitis.

After dental treatment:

- Assessment of the patient's current medication schedule to avoid any drug interactions and complications.
- Instruct the patient to improve oral hygiene.

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According to the American Dental Association and the American Association of Orthopedic Surgeons [58], patients who are currently receiving DMARDs and have had surgically replaced joints with prosthetic joints may mandate prophylactic therapy before invasive dental surgery. Following are the dental procedures for which antibiotic prophylaxis is mandatory:

- Implant placement.
- Dental extraction.
- Re-implantation of avulsed tooth.
- Endodontic therapy only beyond the apex.
- Initial placement of orthodontic bands (not for brackets).
- Intra-ligament local anesthetics.
- Teeth scaling when bleeding is anticipated

ORAL CONTRACEPTIVES PILLS (OCPs)

Oral contraceptives are the drugs that are used to prevent an unwanted pregnancy after unprotected sexual intercourse [59]. These OCPs are of two types, either progesterone-only or progesterone combined with estrogen. Depending on their concentrations, they are termed as either monophasic when equal or phasic when there is a variation in concentrations.

Mechanism of action

The progesterone functions by thickening the cervical mucus, which hampers the passage of spermatozoa and thinning the lining of endometrium, which ultimately inhibits the implantation of an embryo. The estrogen functions by cessation of ovulation. The combination of these mechanisms prevents pregnancy. Figure 5 depicts the metabolism of oral contraceptives.

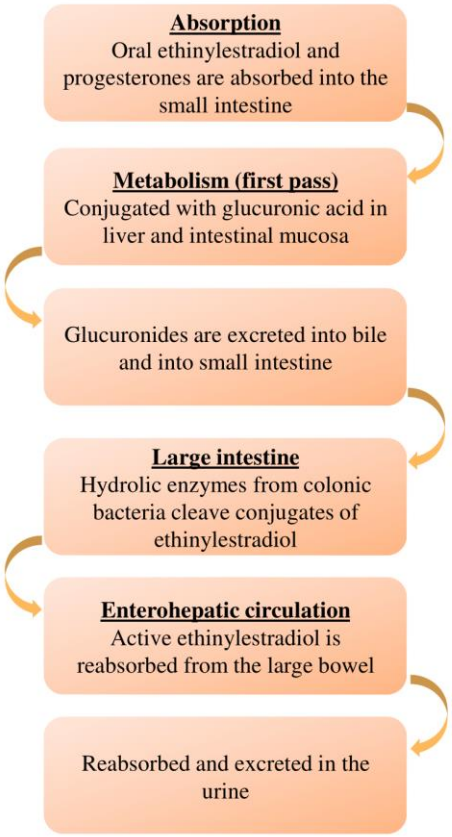

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Figure 5. Metabolism of oral contraceptives

Effects on the oral cavity

According to a clinical study conducted in 2016, the results showed that the rate of developing dry socket following by surgical removal of impacted mandibular third molar increased in females who were using oral contraceptives [60]. Another study demonstrated that oral contraceptives containing estradiol are involved in the colonization of Candida albicans in the oral cavity [61]. The use of combined oral contraceptives can influence the periodontal condition of patients, resulting in increased gingival disease and hyperplastic edematous gingivitis [62]. This adverse effect can be enhanced by the use of newer generations of OCPs, especially in high-risk populations [63].

Dental considerations and protocol

Things to consider in females using OCPs are the development of alveolar osteitis and drug interaction with antibiotics. In 1994, an article was published in the British Dental Journal regarding the possible interactions between oral contraceptives and antibiotics that emphasized the obligation of dentists to stick to the current national guidelines as a part of fair dental practice [64].

Recently, there has been an alteration in the advice the dentist should be giving patients regarding this scenario [65]. This new advice is evidence-based and is formulated following a review of relevant reports focusing on the association of non-enzyme-inducing antibiotics. Numerous studies and clinical trials have evaluated the levels of ethinylestradiol in patients taking antibiotics and the combined oral contraceptive pills (COCP) and have not observed alleviated levels of ethinylestradiol or any alteration to the pharmacokinetics of ethinylestradiol [66-69].

In 2010, the *Medical eligibility criteria for contraceptive use* was updated by the World Health Organization (WHO) to encompass evidence-based guidance on contraceptive use and drug interactions [70]. On this basis, in January 2011, the Clinical Effectiveness Unit of the Faculty of Sexual and Reproductive Healthcare (Royal College of Obstetricians and Gynecologists) formulated new clinical guidance which proposes that 'additional contraceptive precautions are not required even for short courses of antibiotics that are not enzyme inducers when taken with combined oral contraception' [71]. This new suggestion has been included in the clinical guidance given in the British National Formulary [65].

The association of vitamin D and endothelin-1 with periodontitis and coronary heart disease

Vitamin D, a fat-soluble vitamin, is obtained from an endogenous formation by the skin after being exposed to the sunlight or from food intake [72]. The protective effect of vitamin D has been reported as an inflammatory response modulator in several systemic diseases, including diabetes, CHD, cancer and endothelial dysfunction [73]. Mounting evidence advocates the hypothesis that high vitamin D levels are beneficial for good oral hygiene. Recent reports have concluded that both lower and higher serum vitamin D levels may lead to an increased risk of developing caries [74], gingivitis [75], periodontitis and, eventually, tooth loss [76]. According to a recently conducted cross-sectional study, including 179 patients [77], low serum vitamin D levels were presented in the patients suffering from periodontitis and periodontitis plus CHD when compared with CHD and healthy individuals. Additionally, vitamin D was significantly associated with periodontitis and was negatively affected by periodontitis.

In the human body, during the progression of inflammation, endothelin (ET)-1 is one of the most common findings expressed within the tissues [78]. ET-1 is released by endothelial cells following exposure to pathogenic bacteria. It serves as a potent vasoconstrictor and a mediator of vascular inflammation [79]. According to a recently performed case-control study, including 136 patients [80], the patients with CHD and periodontitis plus CHD had raised levels of salivary and serum ET-1 than individuals with periodontitis and healthy controls.

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Hence, this warrants an evaluation of vitamin D levels, especially in patients having periodontitis, which should be recommended at the start of periodontal therapy as it could lead to prediction and reduction of the possible advancement and risk of developing periodontitis.

Authors have tried to compile the list of all the drugs in a tabular form to ease their understanding, oral risks, dental considerations and management of such patients in a dental setup. (Figure 6). We recommend the table to be a handy tool for quick references, but further specialist consultation/reference must be considered in all cases.

CATEGORY	DRUG	COMMERCIAL NAMES	MECHANISM OF ACTION	DENTAL CONSIDERATIONS	MANAGEMENT
Anti-platelet drugs	Aspirin	Cardiprin, ecosprin	Anti-platelet	Excessive bleeding, delayed healing	INR test No alteration in dose is required. Perform the procedure as minimally invasive as possible, use of local hemostatic measures
	Clopidogrel	Plavix			
vitamin K antagonist	Warfarin	Aldocumar, Anasmol, Anticoag, Befarin, Cavamed, Cicoxil, Circuvit, Coumadin		Uncontrolled bleeding	Close monitoring of INR Use of local hemostatic agents Discuss with patient's physician before any alteration in dose
Novel Oral Anticoagulants (NOACs)	Dabigatran	Pradaxa	Thrombin inhibitor	Haemorrhage	TT, PTT test are advised Use of local hemostatic agents For extensive procedures; Discuss with patient's physician before any alteration in dose
	Rivaroxaban	Xarelto			
	Apixaban	Eliquis	factor Xa inhibitors		
	Edoxaban	Savaysa			
Anti-resorptive drugs	Bisphosphonates	alendronate (Fosamax ®), etidronate (Didrocal ®), risedronate (Actonel ®) and zoledronic acid (Aclasta®)		Risk of MRONJ	Pain and infection control Good oral hygiene maintenance Avoid, elective and invasive dental procedures
	Denosumab	Prolia and Xgeva			
DMARDs	Methotrexate	Rheumatrex, Trexall, Otrexup, Rasuvo	Disease-modifying drugs act on the immune system to slow the progression of rheumatoid arthritis	Xerostomia, Gingival enlargement, Ulcers, Stomatitis,	Consider prophylactic antibiotics
	Leflunomide	Arava			
	Cyclosporine	Neoral			
	Etanercept	Enbrel			
	infliximab	Remicade			
	adalimumab	Humira			
Oral contraceptive drugs	Progesterone	Cerazette		Dry socket, Possible candidal infection	Maintenance of good oral hygiene and follow-up
	oestrogen and progesterone	Microgynon, Rigevidon, Cilest, Yasmin			

Figure 6. A summary of non-dental drugs, oral risks, dental considerations and management of such patients in a dental setup (DMARDs = Disease-Modifying Anti-Rheumatic Drugs).

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