IJFDC
International Journal of Food, Drug and Cosmetics
January 2025 Vol 1 Issue 2 **https://doi.org/10.31674/ijfdc.2025.v1i02.003**

Pharmacology and Pharmacokinetics in Oral and Maxillofacial Surgery: A Comprehensive Review

Farid Che Ghazali
Lincoln University College Main Campus Wisma Lincoln, No. 12-18, Jalan SS 6/12, 47301 Petaling Jaya, Selangor Darul Ehsan, Malaysia
Email: drfaridghazali@gmail.com,

Nurul Afifah Binti Mohamed Farid
Wisma Lincoln, No. 12-18, Jalan SS 6/12, 47301 Petaling Jaya, Selangor Darul Ehsan, Malaysia
afifahfarid10@gmail.com

Nur Fathiah Farid
Government Dental Clinic Gua Musang, 18300 Gua Musang Kelantan DN, Malaysia.
fathiahtosuke@rocketymail.com,

Abstract

Oral and maxillofacial surgery (OMFS) is a specialized surgical discipline that demands a profound understanding of pharmacology and pharmacokinetics. This comprehensive review highlights the critical role of these principles in optimizing patient care and minimizing risks within the unique physiological and pathological context of the head and neck region. While general surgical pharmacology is well-documented, the specific nuances of drug selection, dosing, and potential interactions in OMFS patients—who often present with complex medical histories, localized infections, and significant pain management challenges—warrant dedicated attention. This paper integrates fundamental drug principles with patient-specific considerations, covering local anesthetics, analgesics, antibiotics, corticosteroids, sedatives, and emergency medications. It further delves into crucial aspects such as drug interactions, toxicity, allergic reactions, and the necessity of appropriate laboratory investigations. Drawing from innovations stemming from the industrial era, which revolutionized drug synthesis, understanding of pharmacokinetics, and aseptic techniques, this review provides OMFS practitioners with an updated, robust framework. The aim is to ensure optimal therapeutic outcomes, enhance patient safety, and guide rational prescribing in a rapidly evolving healthcare landscape, emphasizing the shift towards personalized and evidence- based pharmacological interventions.

Keywords: Antibiotics, Analgesics, Anti-inflammatory drugs, NSAIDs, Steroids**.**

1. Introduction to Pharmacology and Pharmacokinetics in OMFS

1.1. Scope and Importance

Oral and Maxillofacial Surgery (OMFS) encompasses a broad spectrum of surgical procedures within the head and neck, ranging from routine dentoalveolar surgery to complex reconstructive interventions. The success and safety of these procedures are inextricably linked to the judicious application of pharmacological principles [3, 6]. The prospect of curing a disease through the prescription of medication is indeed highly appealing. Infections caused by microorganisms have imperiled human life since time immemorial. Some of these organisms possessed the potential to spread from one infected individual to another at an alarming rate, thereby causing widespread pandemics and epidemics. With the discovery of the first antibiotic, the "magic bullet"—Penicillin—patients could be effectively cured of many life-threatening infections.

In most clinical situations, determining whether a patient has an infection is straightforward, with local and systemic findings typically pointing towards the diagnosis. Diagnostic difficulty arises, however, when a patient who has undergone a maxillofacial procedure develops swelling and pain during the second or third postoperative day. Similarly, an elevated temperature and white blood cell count may also be observed. Surgical insult and prolonged general anaesthesia frequently result in these symptoms. Clinical judgement is paramount in establishing the diagnosis, and the clinician should meticulously consider all available information before concluding that an infection is present. Medical and surgical specialties benefit significantly from the correct use of pharmaceutical agents, and oral and maxillofacial surgery is no exception.

Antibiotics, analgesics, and anti-inflammatory drugs are amongst the most commonly prescribed medications in maxillofacial surgical practice (Dandon, et al, 2014., Gaynes. 2017). Numerous literature studies are available concerning the application of these medications in maxillofacial surgery. The prophylactic use of antibiotics should be evidence-based, taking into account both their effectiveness and the possible adverse outcomes of antibiotic therapy. Moreover, a thorough knowledge of the likely organisms involved in the infection is requisite to prevent the prescription of unsuitable antibiotics. Antibiotics, if deemed necessary, should possess a spectrum of activity that encompasses streptococci, anaerobic Gram-positive cocci, and anaerobic Gram-negative rods, which are considered the most pathogenic for oral infections. Furthermore, they should be bactericidal and represent the least toxic agents available, with amoxicillin frequently being the clinician's preferred choice.

The infectious diseases associated with the oral and maxillofacial region exhibit unique microbiological features due to the abundance and variety of microorganisms present. The normal flora of the oral cavity consists of up to 1011 bacteria per gram of tissue, with anaerobic bacteria predominating. Although the subtypes and proportions of organisms differ, the general pattern of the indigenous microflora is similar in healthy individuals.

Pharmacological Principles and Drug Classes in OMFS

The effective management of patients undergoing OMFS procedures necessitates a profound understanding of pharmacodynamics and pharmacokinetics. Pharmacodynamics elucidates how drugs exert their effects on the body, including their mechanisms of action, therapeutic effects, and adverse reactions. Pharmacokinetics, conversely, describes how the body handles drugs—encompassing absorption, distribution, metabolism, and excretion (ADME). These principles guide the selection of appropriate dosages, routes of administration, and timing of

drug delivery to maximise therapeutic efficacy whilst minimising toxicity (Rosenberg, 2010).

Beyond antibiotics, the mainstay of pharmacological intervention in OMFS includes analgesics and anti-inflammatory agents. Analgesics, primarily non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, are crucial for managing postoperative pain. NSAIDs, such as ibuprofen and naproxen, reduce pain and inflammation by inhibiting cyclooxygenase (COX) enzymes, thereby decreasing prostaglandin synthesis. Opioids, like codeine or oxycodone, act on opioid receptors in the central nervous system to modulate pain perception, reserved for more severe pain due to their potential for side effects and dependence. Anti-inflammatory drugs, including corticosteroids (e.g., dexamethasone), are often employed to mitigate postoperative swelling and trismus, particularly in extensive procedures, by suppressing the inflammatory cascade. Their use, however, requires careful consideration of potential side effects such as delayed wound healing or immunosuppression (Rosenfeld et al., 2021).

.

Antibiotic Resistance and Stewardship in OMFS

The escalating global challenge of antibiotic resistance poses a significant threat to the continued effectiveness of antimicrobial agents. In OMFS, the indiscriminate or inappropriate use of antibiotics contributes to the emergence of resistant bacterial strains, rendering common infections more difficult to treat. Antibiotic stewardship programmes are therefore imperative, advocating for the responsible use of antibiotics to preserve their efficacy. This involves prescribing antibiotics only when clinically indicated, selecting the narrowest spectrum agent effective against the likely pathogens, optimising dosage and duration of therapy, and educating patients on the importance of adherence. For oral infections, which are often polymicrobial, the initial empirical choice of amoxicillin, sometimes augmented with metronidazole for broader anaerobic coverage, reflects a balanced approach to efficacy and resistance prevention. However, culture and sensitivity testing should guide definitive therapy in cases of persistent or severe infection (Lodi et al., 2012; Figueiredo et al., 2012).

Antibiotics for Infection Management and Prophylaxis

Antibiotics are indispensable in oral and maxillofacial surgery for both the treatment of established infections and, in selected cases, for prophylaxis against potential infectious complications [3, 4]. The emergence of antibiotic resistance, however, underscores the critical importance of rational prescribing practices.

For **prophylaxis**, antibiotics are administered prior to surgical procedures to prevent the development of postoperative infections. The decision to use prophylactic antibiotics in OMFS is contingent upon several factors, including the type of procedure, the patient's immune status, and the potential for bacterial contamination. Procedures classified as clean- contaminated, such as orthognathic surgery, complex trauma management involving oral communication, and certain implant placements, often warrant prophylactic antibiotic coverage. The aim is to reduce the bacterial load at the surgical site during the critical period of wound contamination, thereby minimising the risk of infection (Waksman, 1947). The choice of agent, dosage, and duration for prophylaxis should be guided by evidence-based guidelines, typically involving a single dose administered preoperatively, or for a very short duration postoperatively, to cover the anticipated oral flora (streptococci, anaerobic Gram-positive cocci, and anaerobic Gram-negative rods).

In the context of infection management, antibiotics are prescribed to treat existing bacterial infections. The approach to therapeutic antibiotic use differs significantly from prophylaxis. Initial empirical therapy is often commenced based on the most likely pathogens involved in oral and maxillofacial infections, which are predominantly polymicrobial and include both aerobic and anaerobic species. Common presentations necessitating therapeutic antibiotics include odontogenic infections (e.g., cellulitis, abscesses), osteomyelitis, and infected facial trauma. While amoxicillin remains a frequent first-line choice, particularly when combined with clavulanic acid for β-lactamase producing strains, or metronidazole for enhanced anaerobic coverage, severe or unresponsive infections necessitate culture and sensitivity testing. This diagnostic step is crucial for identifying the specific causative organisms and determining their susceptibility to various antimicrobial agents, thus enabling targeted therapy and improving treatment outcomes. The duration of therapeutic antibiotic courses is typically longer than prophylactic regimens, tailored to the severity and resolution of the infection.

The judicious selection of antibiotics, whether for prophylaxis or treatment, must also consider patient-specific factors such as allergies, renal or hepatic function, and potential drug interactions. Continuous vigilance for adverse drug reactions and the monitoring of clinical response are integral components of effective pharmacological management in OMFS (Ambrose & Winter., 2010).

Orthognathic surgical procedures aim to correct facial deformities and malocclusion, thereby improving the functional disorders of the stomatognathic system. This is an elective procedure, typically carried out in young, healthy adults. It is classified as a clean- contaminated procedure, with a reported infection rate ranging from 3–11% [18, 39]. However, certain studies have reported the rate of infection following orthognathic surgery to be as high as 6–33.4% [39]. Postoperative infection has been found to be related to poor oral hygiene and the habit of smoking.

In contemporary society, with its proliferation of fast-moving vehicles and expressways, hundreds of thousands of individuals are involved in road traffic accidents. The head and face are amongst the most commonly injured body parts. Both the soft and hard tissues of the face may be implicated in the trauma. Firearms, contact sports, and interpersonal violence represent additional causes of facial injuries. The management of these injuries should adhere to established protocols and be conducted systematically. With advances in anaesthetic and surgical techniques, and the availability of superior implant materials exhibiting favourable metallurgical properties, open reduction and internal fixation (ORIF) has become the norm.

The re-establishment of form, function, and cosmesis is of paramount importance. To achieve this objective, the probable complications of ORIF must be prevented or appropriately managed. Of the various complications reported, none has generated more interest and controversy than the occurrence of postoperative infection. By adhering to standard surgical protocols and strict aseptic techniques, the incidence of postoperative infection can be significantly reduced. Nevertheless, the presence of microorganisms in the oral cavity and facial skin, coupled with potential contamination from the environment, necessitate the judicious consideration of antibiotic therapy in maxillofacial trauma management. It is further posited that coexistent systemic maladies and the protracted administration of pharmacotherapeutic agents may fundamentally alter the commensal microbial population,

resulting in the proliferation of aberrant organisms within the established flora, and an augmented incidence of infections arising from typically low-pathogenicity commensals. Ordinarily, the proliferation of microorganisms is strictly regulated by the host's intrinsic immunological and barrier *defence* mechanisms. Should the integrity of these safeguards become compromised, a minor bacterial exposure, which would otherwise be innocuous, may precipitously culminate in frank clinical infection.

This ensuing treatise is devoted to presenting a comprehensive, scholarly review of both pharmacology and pharmacokinetics, specifically customised for the oral and maxillofacial surgery (OMFS) specialist. The central objective is to integrate fundamental principles with immediate clinical applicability, whilst underscoring the paramount necessity of rigorous antibiotic stewardship protocols and refined, nuanced pain management modalities. Pharmacology, being the scientific discipline concerned with drugs and their physiological and biochemical effects, and pharmacokinetics (PK)—the quantitative appraisal of a drug's absorption, distribution, metabolism, and excretion (ADME)—constitute the absolute cornerstones of rational therapeutics [Rosenfeld et al., 2021, Hargreaves, et al., 1998]. Within the OMFS discipline, clinicians habitually dispense and apply a diverse repertoire of medicinal agents, encompassing local anaesthetics, analgesics, antibiotics, corticosteroids, and anxiolytics [Muelleman, et al., 1998].

A profound and detailed comprehension of these pharmaceutical agents is thus paramount for the achievement of efficacious pain control, robust infection management, appropriate modulation of the inflammatory response, and safe patient sedation, factors which collectively and directly influence superior surgical outcomes and accelerated patient convalescence. The unique and demanding challenges routinely encountered in the OMFS theatre often include:

1. **Complex Anatomical Considerations:** The extraordinary vascularity and dense innervation characterising the cephalic and cervical regions, juxtaposed with the close proximity of immediately vital structures, exert a profound influence upon drug biodistribution and the potential for adverse sequelae. By way of illustration, the exceptionally rapid vascular uptake of local anaesthetics from the highly perfused oral mucosa substantially increases the inherent risk of systemic toxicity should appropriate dosage regulation and the judicious use of vasoconstrictive adjuncts not be meticulously employed [Housholder, 1998]. This necessitates an augmented awareness of regional drug dynamics.

2. **A Diverse and Medically Complex Patient Cohort:** OMFS patients routinely present with substantial medical comorbidities, including, but not limited to, significant cardiovascular disease, diabetes mellitus, and established renal or hepatic impairment. These concurrent systemic pathologies, coupled with the vast range of patient ages (from the paediatric to the geriatric demographic) and the widespread prevalence of polypharmacy, critically modify both drug responsiveness and innate clearance mechanisms [Muelleman, et al., 1998, Rosenfeld et al., 2021]. The imperative for meticulous medical history ascertainment and rigorous risk stratification prior to the

commencement of any operative or therapeutic intervention is an aspect that cannot be overemphasised [Trummel, 1998].

3. **Elevated Risk of Localised Infectious Processes:** Infections of odontogenic origin, which arise directly from dental pathology, constitute a substantial proportion of OMFS clinical presentations. Characteristically polymicrobial in nature, these involve a mixture of both aerobic and anaerobic species, thereby demanding the implementation of highly specific and frequently empirical antibiotic protocols. Such strategies must carefully account for the most probable microbial aetiology and the prevailing local patterns of antimicrobial resistance [Niwa, et al., 1996].

4. **The Critical Domain of Acute Pain Management:** Post-operative discomfort represents a significant clinical concern consequent to the vast majority of OMFS procedures. The deployment of effective, multi-modal analgesic regimens is therefore crucial, not solely for the amelioration of patient suffering and ensuring compliance, but fundamentally for facilitating prompt functional restoration and minimising the untoward potential for the transition to chronic pain syndromes [Ebo., et al., 2007].

The originality, or novelty, of this academic review resides precisely in its wholly integrated methodology, meticulously attending to the aforementioned OMFS-centric nuances. It successfully bridges the theoretical lacuna that often exists between conventional pharmacological doctrines and their essential, direct clinical application and therapeutic implications within the specialised operational theatre of oral and maxillofacial surgery, thereby establishing itself as a highly targeted and current resource of considerable utility for contemporary practitioners [Joint Task Force on Practice Parameters, 2005].

Core Principles of Pharmacokinetics (ADME)

Pharmacokinetics fundamentally describes how the corporeal system processes a drug, thereby dictating its concentration gradient at the designated biological target site over the temporal continuum. This dynamic interplay is unequivocally critical for the achievement of therapeutic efficacy whilst simultaneously circumventing dose-related toxicity [Boyd & Hall. Montvale, 2009].

- **Absorption:** This process delineates the movement of a pharmaceutical agent from its administration portal into the systemic circulation. In the context of oral and maxillofacial surgery (OMFS), this phenomenon is pivotal for agents administered enterally (e.g., antibiotics, analgesics), where intrinsic factors such as drug solubility, the pharmaceutical dosage form, gastrointestinal motility, and the presence of concurrent alimentary matter can significantly influence both the velocity and the overall extent of absorption [6]. Conversely, for agents injected locally, such as the local anaesthetics routinely employed, the rich vascular network of the oral cavity and the adjunctive use of vasoconstrictors are the primary determinants governing systemic absorption and the resultant duration of therapeutic action [Open Resources for Nursing (Open RN; 2023, Slørdal., & Spigset. 2005].

- **Distribution:** Subsequent to its absorption, a drug undergoes a reversible transference from the bloodstream into a myriad of peripheral tissues and interstitial fluids.

Distribution is profoundly influenced by the degree of tissue perfusion, a factor critically relevant in OMFS where sites of inflammation or frank infection may exhibit a modified or reduced blood flow, thus impeding adequate antibiotic penetration [6]. Furthermore, plasma protein binding, primarily to albumin, assumes a crucial role; highly protein-bound agents possess a reduced quantity of free (active) drug available for biological interaction, and systemic conditions that alter albumin concentrations (e.g., hepatic dysfunction, severe malnutrition) can lead to an increase in the free, pharmacologically active fraction, potentially culminating in enhanced therapeutic effects or, indeed, toxicity [Liu, L., & Liu, X. 2019, Fernandez, et al., 2011] . Lipophilicity (or fat solubility) is the essential characteristic that dictates a drug's capacity to traverse cellular membranes, including the highly restrictive blood-brain barrier, thereby influencing its penetration into the central nervous system [Fernandez, et al., 2011].

- **Metabolism (Biotransformation):** This intricate biochemical process chemically modifies pharmaceutical agents, predominantly within the hepatic parenchyma, into compounds that are more polar (water-soluble), thus facilitating their subsequent excretion. The Cytochrome P450 (CYP450) enzyme system, a vast superfamily of structurally and functionally related isoenzymes, represents the dominant metabolic pathway for the majority of clinically utilised drugs [Slørdal., & Spigset. 2005]. Innate genetic variations (polymorphisms) within the CYP gene loci (e.g., CYP2D6, CYP2C19) can engender marked inter-individual disparities in drug metabolism, allowing patients to be classified broadly as "poor," "intermediate," "extensive," or "ultrarapid" *metabolisers*.

- These genotypic variations are increasingly acknowledged for their substantial impact on therapeutic efficacy (e.g., the bioactivation of codeine to morphine) or for predisposing to heightened toxicity, underscoring the ascendant role of pharmacogenomics in the realisation of *personalised medicine* [Fernandez, E., Perez, R., Hernandez, A., Tejada, P., Arteta, M., & Ramos, 2011. Fernandez, et al., 2011]. Moreover, clinically significant drug-drug interactions frequently manifest at the level of CYP inhibition or induction, whereby one agent alters the enzymatic activity of this system, consequently leading to altered plasma concentrations of co-administered medications [8.3].

- **Excretion:** This final stage is the irreversible removal of drugs and their resulting metabolites from the organism, principally executed via the renal system (urine) or the hepatic system (bile/faeces) [Fernandez, et al., 2011]. Renal function, which is routinely estimated through measurements such as creatinine clearance or the estimated glomerular filtration rate (eGFR), stands as a critical determinant for those pharmaceutical agents primarily excreted by the kidneys (e.g., numerous antibiotics, NSAIDs). Impaired renal or hepatic function necessitates profound and careful dose modification to mitigate the risks of drug accumulation and potential toxicity, a necessary and frequent consideration when managing medically compromised OMFS patients [Open Resources for Nursing (Open RN; 2023].

1.3. Basic Principles of Pharmacodynamics (Drug-Receptor Interactions)

Pharmacodynamics describes the effects a drug has on the body and its underlying mechanisms

of action [Fernandez, E., Perez, R., Hernandez, A., Tejada, P., Arteta, M., & Ramos, 2011.]. Understanding how drugs interact with biological systems is fundamental to predicting their therapeutic and adverse effects.

- **Receptors:** Most drugs exert their effects by interacting with specific macromolecular targets, typically proteins, known as receptors. These receptors can be located on the cell surface, within the cytoplasm, or in the nucleus. The specificity of drug-receptor binding largely determines a drug's selectivity and efficacy [Ref. Open Resources for Nursing (Open RN; 2023].
- **Agonists:** These drugs bind to and activate receptors, mimicking the action of endogenous ligands and producing a biological response. For example, opioid analgesics act as agonists at opioid receptors, leading to pain relief [Fernandez, et al., 2011, Open Resources for Nursing (Open RN; 2023, Slørdal., & Spigset. 2005].
- **Antagonists:** In contrast, antagonists bind to receptors but do not activate them. Instead, they block the binding and effects of agonists (either endogenous or exogenous). Naloxone, for instance, is a pure opioid antagonist used to reverse opioid overdose by competitively binding to opioid receptors [Liu, L., & Liu, X. 2019, Open Resources for Nursing (Open RN; 2023].

Pharmacological Principles and Drug Classes in OMFS

The effective and judicious clinical governance of patients presenting for Oral and Maxillofacial Surgery (OMFS) procedures necessitates an exacting comprehension of both pharmacodynamics and pharmacokinetics. Pharmacodynamics precisely delineates the manner in which medicinal agents exert their biological effects upon the body, encompassing their specific molecular mechanisms of action, the resulting therapeutic effects, and any associated untoward adverse reactions. Conversely, pharmacokinetics describes the body's disposition of the drugs—encompassing the processes of absorption, distribution, metabolism, and excretion (ADME). These foundational principles fundamentally govern the selection of appropriate molar concentrations and dosages, the optimal routes of administration, and the critical timing of drug delivery, all aimed at the maximisation of therapeutic efficacy whilst simultaneously mitigating systemic toxicity. Pharmacodynamics, in particular, studies the quantitative relationship between drug concentration and response, often characterized by receptor affinity and intrinsic activity, which dictates the maximal effect achievable at the target site.

Analgesics and Anti-inflammatory Agents

- Beyond the realm of antimicrobials, the linchpin of pharmacological intervention in OMFS comprises analgesic and anti-inflammatory agents. Analgesics, primarily Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and opioids, are indispensable for the successful management of acute post-operative pain. NSAIDs, such as ibuprofen and naproxen, abate pain and inflammation through the competitive inhibition of cyclooxygenase (COX) enzymes, thereby effecting a profound diminution in the synthesis of pro-inflammatory prostaglandins. Contemporary understanding distinguishes between COX-1, which maintains homeostatic

functions (e.g., gastric mucosal defence and renal blood flow), and COX-2, which is largely inducible at sites of inflammation.

The clinical benefit is frequently attributed to COX-2 inhibition, whereas adverse gastrointestinal sequelae are often linked to non-selective COX-1 inhibition. Opioid agonists, such as codeine or oxycodone, exert their effect via interaction with specific opioid receptors (primarily μ-receptors) in the central nervous system (CNS) and peripheral tissues to modulate pain perception. Their prescription is customarily reserved for the management of more acute, severe nociception, given the inherent risk of adverse effects, including respiratory depression, and the notable potential for physical dependence and addiction [Soldin & Mattison, (2009].

- Anti-inflammatory medicinal agents, notably corticosteroids (e.g., dexamethasone), are frequently employed to mitigate post-operative oedema and trismus, particularly following extensive surgical interventions such as orthognathic or complex third molar excision. Corticosteroids act by binding to intracellular glucocorticoid receptors, translocating to the nucleus, and modifying gene transcription to suppress the inflammatory cascade, including the inhibition of phospholipase A. Their application, however, requires scrupulous clinical judgement due to potential deleterious side effects, including delayed wound healing, transient hyperglycemia, and immunosuppression.

Antibiotic Resistance and Stewardship in OMFS

- The escalating global health crisis posed by antimicrobial resistance constitutes a substantial threat to the continued effectiveness of anti-infective agents. Within OMFS, the unfettered or inappropriate deployment of antibiotics provides a potent selective pressure, contributing directly to the emergence and dissemination of resistant bacterial strains, thereby rendering commonplace odontogenic infections increasingly recalcitrant to standard therapeutic modalities. Consequently, comprehensive antibiotic stewardship programmes are an ethical and clinical mandate, advocating for the responsible and judicious application of antibiotics to safeguard their future efficacy. This responsibility entails prescribing antibiotics exclusively when clinically justifiable, selecting the narrowest-spectrum agent efficacious against the most probable pathogens, rigorously optimising the dosage regimen and duration of therapy, and undertaking patient education regarding the absolute necessity of adherence to the prescribed course. For oral infections, which are inherently polymicrobial, the initial empirical choice of amoxicillin, occasionally augmented with metronidazole to ensure a broader coverage of obligate anaerobes, represents a balanced and evidence-based approach to therapeutic efficacy and resistance mitigation. However, in instances of persistent, escalating, or severe infection, the decisive guidance of culture and sensitivity testing must supersede empirical choice to enable targeted, pathogen-specific therapy.

Antibiotics for Infection Management and Prophylaxis

- Antibiotics are an indispensable therapeutic class in oral and maxillofacial surgery, employed both for the specific treatment of established infectious processes and, in strictly selected clinical scenarios, for prophylaxis against potential post-operative infectious complications [Kamolratanakul, & Jansisyanont, 2018, Garner 1986]. The continuous emergence of antimicrobial resistance, nevertheless, serves to underscore the critical importance of rational, evidence-based prescribing protocols.

- For surgical prophylaxis, antimicrobial agents are administered judiciously prior to the operative procedure with the objective of preventing the development of a post-operative surgical site infection. The clinical decision to administer prophylactic antibiotics in OMFS is contingent upon a rigorous evaluation of several factors, including the classification of the procedure, the patient's underlying immune competence, and the degree of anticipated bacterial contamination.

- Procedures deemed "clean-contaminated," such as orthognathic surgery, the complex management of trauma involving communication with the oral cavity, and certain advanced dental implant placements, frequently warrant prophylactic antibiotic coverage. The therapeutic objective is to drastically reduce the bacterial burden at the incision site during the critical window of wound contamination, thereby minimising the subsequent risk of manifest infection. The selection of the agent, the optimal dosage, and the duration of prophylaxis must be strictly informed by current evidence-based clinical guidelines, typically advocating for a single, well-timed dose administered preoperatively, or a very brief course postoperatively, designed to cover the anticipated oral flora (predominantly Streptococci, anaerobic Gram-positive cocci, and anaerobic Gram-negative rods).

- In the context of therapeutic infection management, antibiotics are prescribed to eradicate existing bacterial pathology. The approach to therapeutic usage diverges fundamentally from prophylaxis. Initial empirical therapy is commonly instituted based upon a high index of suspicion regarding the most probable pathogens implicated in oral and maxillofacial infections, which are classically polymicrobial, comprising both aerobic and anaerobic species. Common clinical presentations necessitating therapeutic intervention include advanced odontogenic infections (e.g., diffuse cellulitis, established abscesses), osteomyelitis, and secondarily infected facial trauma. While amoxicillin remains a frequent first-line pharmaceutical choice, particularly when potentiated by clavulanic acid to counter β-lactamase producing organisms, or combined with metronidazole for enhanced anaerobic coverage, severe or clinically unresponsive infections mandate immediate culture and sensitivity testing.

  This vital diagnostic step is essential for the conclusive identification of the specific causative organism(s) and the precise determination of their susceptibility profiles to various antimicrobial agents, thereby enabling highly targeted therapy and optimising patient treatment outcomes. The requisite duration of therapeutic antibiotic courses is typically substantially longer than prophylactic regimens, being meticulously titrated to the severity and clinical resolution of the underlying

infectious process.

- The judicious selection of antimicrobial agents, whether for prophylactic intent or therapeutic management, must equally accommodate patient-specific idiosyncrasies such as documented allergies, the functional integrity of the renal or hepatic systems, and the potential for complex drug interactions. Continuous clinical vigilance for any adverse drug reactions and the diligent monitoring of the patient's clinical response are, therefore, integral components of effective pharmacological management within OMFS.
- **Dose-Response Relationship:** This fundamental principle describes how the intensity of a drug effect changes with increasing drug dose. Key parameters derived from dose-response curves include efficacy, which refers to the maximal effect a drug can produce regardless of dose, and potency, which is the dose required to produce a given effect. Understanding these parameters helps in selecting the most effective drug and its appropriate dosing regimen [Gray, et al, 2018, Westervelt, et al., 2014].

1.4. Patient-Specific Considerations in OMFS (Age, Comorbidities, Polypharmacy)

The concept of "one dose fits all" is rarely applicable in OMFS due to the diverse patient population and complex medical profiles. Individual patient factors significantly influence drug response, necessitating a personalized and cautious approach to pharmacotherapy [Ref. 2].

- **Age:** Pediatric patients exhibit immature organ systems, particularly renal and hepatic function, which can alter drug absorption, distribution, metabolism, and excretion. This often necessitates weight-based dosing and careful monitoring [Ref. 6]. Conversely, geriatric patients typically experience age-related physiological changes, including declining renal and hepatic function, reduced lean body mass, increased body fat, and altered body water content. These changes can prolong drug half-lives, increase the volume of distribution for lipid-soluble drugs, and reduce the clearance of water-soluble drugs, making older adults more susceptible to adverse drug reactions and necessitating lower initial doses and slower titration [Grogan & Preuss, 2023].
- **Comorbidities:** Pre-existing medical conditions significantly impact drug selection and dosing. For instance, patients with chronic kidney disease require dose adjustments for renally excreted drugs (e.g., certain antibiotics, NSAIDs) to prevent accumulation and toxicity [Trescot et al., 2008]].

  Liver disease can impair the metabolism of many drugs (e.g., local anesthetics, opioids), leading to prolonged effects and increased risk of toxicity Westervelt, et al., 2014]. Cardiovascular diseases, diabetes, and respiratory conditions also pose specific challenges, influencing the choice of sedatives, analgesics, and local anesthetics with vasoconstrictors.
- **Polypharmacy:** The concurrent use of multiple medications, particularly common in older adults and those with chronic conditions, dramatically increases the risk of drug-drug interactions. These interactions can lead to altered drug efficacy, increased toxicity, or adverse drug reactions. A meticulous medication reconciliation process, involving a thorough review of all prescribed, over-the-counter, and herbal supplements, is an absolute clinical imperative to identify potential interactions and

guide rational prescribing [Davies & Mahony 2015]. Tools like Lexicomp are invaluable for this purpose [Soto & Meyer., 2021].

2. Local Anaesthetics and Regional Pain Control

Local Anaesthetics (LAs) constitute the cornerstone of precise pain management in OMFS, enabling extensive surgical procedures with minimal systemic disturbance when applied correctly [Rosenberg., 2004]. Their mechanism of action relies upon the reversible inhibition of nerve impulse conduction, primarily achieved by the intracellular binding and blockade of **voltage-gated sodium (**Na+**) channels** within the nerve membrane [Wang, et al., 2021]. LAs, being weak bases, must transition from the non-ionized (lipophilic) form to penetrate the nerve sheath, then re-ionize within the axoplasm to engage the channel from the intracellular aspect [Yang, et al., 2020]. The agent's pKa and the presence of tissue inflammation (lowered pH) critically influence the speed and efficacy of this onset [Brown., 2004].

LAs are chemically classified as Amides (e.g., **Lidocaine**, **Bupivacaine**, **Articaine**) or Esters (e.g., Procaine), a distinction pivotal to their metabolism and allergic potential [Yang, et al., 2020]. Amides are predominantly metabolised by hepatic enzymes, resulting in a low incidence of hypersensitivity, whereas Esters are metabolised by plasma pseudocholinesterase's, producing the allergen PABA. Key agents include **Lidocaine** (rapid onset, intermediate duration for routine work [Camps-Font et al., 2020], **Bupivacaine** (slow onset, significantly prolonged duration for managing post-operative pain, requiring strict adherence to Maximum Recommended Doses (MRD) due to its heightened cardiotoxicity [Wang, et al., 2017, Yang, et al., 2020], and **Articaine** (dual hepatic and plasma metabolism, affording a short plasma half-life and superior diffusion properties, frequently effective for infiltration in the mandible [Wang, et al., 2021].

The adjunctive use of a **Vasoconstrictor** (most commonly **Epinephrine** or adrenaline) is vital, serving three principal roles: (i) to prolong the duration and depth of anaesthesia by reducing systemic absorption; (ii) to reduce the risk of systemic toxicity by lowering peak plasma concentrations; and (iii) to achieve crucial local haemostasis in the highly vascular head and neck region [Camps-Font et al., 2020]. Precautionary use, or outright contraindication, is necessary in patients with uncontrolled cardiovascular disease, untreated hyperthyroidism, phaeochromocytoma, or those reporting concurrent cocaine/methamphetamine abuse, as well as those on non-selective β-blockers or tricyclic antidepressants due to potential adverse adrenergic interactions [Wang, et al., 2021]. Careful calculation of MRD is paramount (e.g., 7mg/kg for Lidocaine and Articaine) to mitigate **Local Anesthetic Systemic Toxicity (LAST)**. LAST typically presents as CNS excitation (e.g., perioral numbness, tinnitus, seizures) progressing to CNS and cardiovascular depression, with definitive management involving the prompt administration of **lipid emulsion therapy**. A separate risk, **Methemoglobinemia**, associated primarily with Prilocaine and Benzocaine, is reversed by intravenous **methylene blue** [Mathison &, Pepper., 2025].

Multimodal Systemic Analgesia

Effective management of post-operative nociception relies upon **multimodal analgesia**, a synergistic strategy combining agents with distinct mechanisms to maximise comfort and minimise reliance on single drug classes.

Non-Opioid Modalities

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), such as Ibuprofen and Naproxen, are first-line agents. They reduce pain and inflammation by inhibiting COX-1 and COX-2 enzymes, thereby suppressing prostaglandin synthesis. Their efficacy is balanced by risks of **Gastrointestinal (GI) toxicity** (linked to COX-1 inhibition), potential acute renal impairment, and a marginal increase in thrombotic risk, particularly with COX-2 selective inhibitors (e.g., Celecoxib) [Ghlichloo I & Gerriets., 2025].

Acetaminophen (Paracetamol) acts centrally to inhibit prostaglandin synthesis and is often combined with NSAIDs to exploit differing mechanisms [Phillips & Currier., 2004]. Although safe at recommended doses (4000mg/day maximum), its principal, potentially fatal, adverse effect is dose-dependent **hepatotoxicity** stemming from the toxic NAPQI metabolite, mandating careful dosing, especially in patients with hepatic impairment or high alcohol intake [Vane., 1971].

Opioid Analgesics and Stewardship

Opioid Analgesics (e.g., Codeine, Hydrocodone, Oxycodone) are reserved for acute, moderate-to-severe pain, acting via agonism of μ-opioid receptors in the CNS [Chaiamnuay et al., 2006]. Their use must be strictly judicious due to the significant risks of respiratory depression, severe constipation, and high potential for dependence and abuse. Furthermore, certain prodrugs, such as Codeine, exhibit **pharmacogenomic variability**, relying on the CYP2D6 enzyme for activation to Morphine. This variability means "ultrarapid *metabolisers*" face exaggerated effects and toxicity, while "poor *metabolisers*" experience little analgesia [Whelton., 1999].

The multimodal regimen is often augmented by the pre-operative administration of long-acting LAs (e.g., Bupivacaine) to effect **pre-emptive analgesia** [*Peterson, 1990*], and by systemic **corticosteroids** (e.g., Dexamethasone) to mitigate post-operative inflammation and oedema, thereby indirectly reducing the patient's requirement for systemic analgesics. **Naloxone** is the essential, rapid-acting antagonist, serving as the emergency antidote for opioid overdose and should be readily available in the clinical setting.

4.0 Antibiotics for Infection Management and Prophylaxis

Antibiotics are indispensable in oral and maxillofacial surgery (OMFS) for both treating established infections and, in selected cases, for prophylaxis against potential infectious complications. The emergence of antibiotic resistance, however, underscores the critical importance of rational prescribing practices.

4.1 Principles of Antibiotic Selection

Rational antibiotic selection is paramount to optimise therapeutic outcomes and mitigate the development of antimicrobial resistance.

- **Culture and Sensitivity:** For severe, persistent, or recurrent odontogenic infections—particularly in immunocompromised patients or those with spreading fascial space infections—obtaining microbiological cultures from the infected site with subsequent sensitivity testing is the gold standard. This guide targeted therapy, ensuring the chosen antibiotic is effective against the specific pathogen(s) and their resistance profiles.

- **Empirical Therapy:** In an acute setting, particularly for localised odontogenic infections, empirical antibiotic therapy is often initiated before culture results are available. This choice is based on the most likely pathogens involved in such infections, which are typically polymicrobial, encompassing both aerobic (e.g., *Streptococcus viridans*) and anaerobic (e.g., *Peptostreptococcus, Prevotella, Porphyromonas*) bacteria.
- **Spectrum of Activity:** The principle of using the narrowest-spectrum antibiotic effective against the likely or identified pathogens should be strictly adhered to. Broad-spectrum antibiotics, while offering wider coverage, contribute significantly to the development of antimicrobial resistance and can disrupt the normal microbiota, potentially leading to superinfections (e.g., *C. difficile* colitis).
- **Pharmacokinetics:** The chosen antibiotic must achieve adequate concentrations at the site of infection. Factors such as drug penetration into bone, abscesses, or inflamed tissues are crucial. A patient's renal and hepatic function must be assessed to allow for appropriate dose adjustments and prevent drug accumulation and toxicity, especially for renally or hepatically cleared antibiotics.
- **Patient Factors:** Individual patient characteristics significantly influence antibiotic selection. These include known drug allergies (especially penicillin allergy), age (paediatric and geriatric considerations), pregnancy or lactation status, and existing medical comorbidities or immunosuppression that might alter the immune response or drug metabolism.

4.2 Common Antibiotics in OMFS

The following antibiotic classes are most frequently employed in OMFS practice:

4.2.1 Penicillins (Amoxicillin, Amoxicillin/Clavulanate)

- **Mechanism:** Penicillins are beta-lactam antibiotics that inhibit bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), leading to bacterial lysis.
- **Amoxicillin:**
    - **Dosing:** Typically, 500 mg every 8 hours or 875 mg every 12 hours.
    - **Spectrum:** Amoxicillin is a broad-spectrum penicillin with good activity against many oral streptococci and some anaerobes. It is widely considered the first-line agent for many odontogenic infections due to its efficacy, favourable safety profile, and relatively narrow spectrum compared to some alternatives.
    - **Allergies:** A penicillin allergy is the most commonly reported drug allergy. Reactions can range from mild maculopapular rashes to life-threatening anaphylaxis. A thorough allergy history is essential.
- **Amoxicillin/Clavulanate (Augmentin):**
    - **Dosing:** Commonly 875 mg/125 mg every 12 hours.
    - **Spectrum:** This combination incorporates clavulanate, a beta-lactamase inhibitor, which protects amoxicillin from degradation by bacterial beta-

lactamase enzymes. This significantly broadens the spectrum of activity to include beta-lactamase producing bacteria, making it highly effective for resistant or polymicrobial odontogenic infections—particularly those that have failed initial amoxicillin therapy or are more severe.

4.2.2 Cephalosporins (Cephalexin, Cefazolin)

- **Mechanism:** Cephalosporins are also beta-lactam antibiotics that inhibit bacterial cell wall synthesis. They are broadly categorised into "generations" based on their spectrum of activity.
- **Cephalexin (1st Gen Oral):**
    - **Dosing:** 500 mg every 6 hours.
    - **Spectrum:** Primarily provides good coverage against gram-positive cocci (e.g., staphylococci, streptococci). It is often used for skin and soft tissue infections and can serve as an alternative for prophylaxis in patients with a non-anaphylactic penicillin allergy.
    - **Cross-Reactivity:** The cross-reactivity rate between penicillins and first-generation cephalosporins (like cephalexin) is low, historically overestimated, and now generally considered to be around 1–2% for IgE-mediated reactions, making it a viable alternative for many patients with a penicillin allergy.
- **Cefazolin (1st Gen IV):** A parenteral first-generation cephalosporin, frequently used for surgical prophylaxis in hospitalised patients, especially for clean-contaminated procedures.

4.2.3 Macrolides (Azithromycin, Clarithromycin)

- **Mechanism:** Macrolides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit, thereby blocking peptide chain elongation.
- **Dosing:**
    - **Azithromycin:** Often prescribed as a loading dose of 500 mg on day 1, followed by 250 mg daily for 4 days (or a 3–5-day course). Its long half-life allows for once-daily dosing and shorter treatment durations.
    - **Clarithromycin:** Typically, 250–500 mg every 12 hours.
- **Spectrum:** Both offer a broad spectrum, including some gram-positive organisms, atypical pathogens, and some oral anaerobes. They are important alternatives for patients with a penicillin allergy.
- **Drug Interactions:** Macrolides, particularly clarithromycin (and to a lesser extent azithromycin), are significant inhibitors of the cytochrome P450 3A4 (CYP3A4) enzyme. This can lead to clinically significant drug interactions, increasing the plasma concentrations of co-administered drugs metabolised by CYP3A4, such as statins (risk of myopathy/rhabdomyolysis), benzodiazepines, and some oral anticoagulants. A careful review of a patient's medication list is crucial.

4.2.4 Lincosamides (Clindamycin)

- **Mechanism:** Clindamycin inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit, similar to macrolides.
- **Dosing:** 300 mg every 6–8 hours.
- **Spectrum:** Clindamycin possesses excellent activity against obligate anaerobes, which are key pathogens in odontogenic infections. It also covers many gram-positive cocci (e.g., *Staphylococcus aureus*, streptococci). It is a critical antibiotic for patients with a penicillin allergy or for infections with suspected anaerobic involvement.
- ***C. difficile* Risk:** A major concern with clindamycin is its high risk of inducing *Clostridioides difficile*-associated diarrhoea (CDAD), which can range from mild diarrhoea to severe, life-threatening pseudomembranous colitis. This risk is due to its broad-spectrum activity disrupting the normal gut microbiome, allowing *C. difficile* to proliferate. Patients should be educated on the symptoms of CDAD and advised to seek immediate medical attention if diarrhoea occurs.

4.2.5 Metronidazole

- **Mechanism:** Metronidazole is a prodrug that, once inside anaerobic bacteria, is reduced to active metabolites that generate reactive nitro radicals. These radicals damage bacterial DNA and other macromolecules, leading to bacterial death.
- **Dosing:** Typically, 500 mg every 8 hours.
- **Spectrum:** Highly effective exclusively against obligate anaerobes (bactericidal). Given that many odontogenic infections have a significant anaerobic component, metronidazole is often used in combination with a penicillin (e.g., amoxicillin) or a cephalosporin (e.g., cephalexin) to provide comprehensive coverage for mixed aerobic/anaerobic infections.
- **Drug Interactions:** A notable and important interaction is the **disulfiram-like reaction with alcohol**. Metronidazole inhibits aldehyde dehydrogenase, leading to the accumulation of acetaldehyde when alcohol is consumed. This results in unpleasant symptoms such as nausea, vomiting, flushing, headache, and palpitations. Patients must be explicitly warned to avoid alcohol (including alcohol-containing mouthwashes) during treatment and for at least 72 hours after completing the course. It also potentiates the effect of warfarin, increasing the risk of bleeding.

4.2.6 Fluoroquinolones (Ciprofloxacin, Levofloxacin)

- **Mechanism:** Fluoroquinolones inhibit bacterial DNA gyrase and topoisomerase IV, enzymes essential for bacterial DNA replication, transcription, repair, and recombination.
- **Dosing:** Varies by specific drug and indication.
- **Spectrum:** Broad-spectrum, with good activity against many gram-negative and some gram-positive bacteria. While effective, they are generally reserved for resistant or complicated infections in OMFS (e.g., osteomyelitis, severe fascial space infections) or

specific scenarios where other first-line agents are contraindicated.

- **Side Effects:** Concerns regarding antibiotic resistance and specific rare but serious side effects have led to their restricted use. These include tendon rupture (especially Achilles' tendon, risk increased in the elderly or those on corticosteroids), peripheral neuropathy, and QT prolongation (risk of cardiac arrhythmias).

4.3 Antibiotic Prophylaxis in OMFS: Indications and Regimens

The principle of antibiotic prophylaxis is to prevent infection, not to treat it. Its use must be selective and evidence-based to minimise the risks of adverse drug reactions, *C. difficile* infection, and the critical global issue of antibiotic resistance.

- **Indications for Infective Endocarditis (IE) (ADA Guidelines):** The American Dental Association (ADA) and American Heart Association (AHA) have specific guidelines for IE prophylaxis. It is recommended only for patients at the highest risk who undergo dental procedures involving manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa. High-risk conditions include:
    - A prosthetic cardiac valve or prosthetic material used for cardiac valve repair.
    - A previous history of infective endocarditis.
    - Specific congenital heart disease (unrepaired cyanotic CHD, repaired CHD with prosthetic material within 6 months of the procedure, or repaired CHD with residual defects at the site or adjacent to a prosthetic patch/device).
    - Cardiac transplant recipients who develop valvulopathy.
- **Indications for Prosthetic Joint Infections (ADA/AAOS Guidelines):** Routine antibiotic prophylaxis is not recommended for most patients with prosthetic joints who are undergoing routine dental procedures. Prophylaxis may be considered for a small subset of high-risk patients (e.g., immunocompromised individuals, those with a history of prosthetic joint infection, or in the immediate post-operative period following joint replacement) after careful consultation with the orthopaedic surgeon.
- **Surgical Site Infection (SSI) Prophylaxis:** In OMFS, SSI prophylaxis may be considered for complex, prolonged, or highly contaminated surgical procedures (e.g., major head and neck reconstruction, extensive implant placement in compromised sites, osteotomies involving active infection). The goal is to ensure adequate tissue concentrations of the antibiotic at the time of incision.
- **Regimens (for IE Prophylaxis, single dose 30–60 minutes pre-procedure):**
    - **Oral:** Amoxicillin 2g.
    - **Oral (for penicillin allergy):** Clindamycin 600 mg, or Azithromycin/Clarithromycin 500 mg.
    - **Parenteral (if unable to take oral):** Ampicillin 2g IM or IV; Cefazolin 1g IM or IV; or Clindamycin 600 mg IV.

- It is crucial to refer to the latest published guidelines from relevant professional organisations (e.g., ADA, AAOMS) as recommendations evolve based on new evidence.

4.4 Management of Odontogenic Infections

Most odontogenic infections originate from dental caries or periodontal disease and involve a mixed flora. Successful management relies on a combination of surgical intervention (e.g., extraction, root canal therapy, incision and drainage) and appropriate antibiotic therapy.

- **Localised Infections (e.g., dental abscess):** The primary treatment is source control (drainage, extraction, endodontic therapy). For localised infections without systemic signs of spread, antibiotics may not always be strictly necessary after definitive source control, but are often prescribed to prevent spread and aid healing. Amoxicillin is typically the first-line choice. In patients with a penicillin allergy, clindamycin is an excellent alternative due to its strong anaerobic coverage.
- **Spreading or Severe Infections (e.g., cellulitis, fascial space infections, osteomyelitis):** These require prompt and aggressive management. Amoxicillin/clavulanate is often indicated due to its broader spectrum against beta-lactamase producing strains. Alternatively, a combination of amoxicillin (or penicillin V) with metronidazole can provide excellent mixed aerobic and anaerobic coverage. For more severe infections or those progressing despite oral therapy, intravenous antibiotics (e.g., ampicillin/sulbactam, cefazolin plus metronidazole, or IV clindamycin) are often necessary, and hospitalisation may be required.
- **Monitoring and Re-evaluation:** Clinical improvement, evidenced by a reduction in swelling, pain, fever, and trismus, indicates effective treatment. A lack of improvement or worsening of symptoms warrants immediate re-evaluation, including further imaging (e.g., CT scan to identify undrained pus), referral for surgical re-exploration, and potentially repeat microbiological cultures with sensitivity testing to identify resistant pathogens or atypical infections. The duration of antibiotic therapy should be individualised based on the infection's severity and resolution, typically 5–7 days for uncomplicated infections, but longer for more severe or chronic processes.

5.0 Adjunctive Pharmacotherapy: Corticosteroids

- The judicious deployment of **Corticosteroids** serves as a potent prophylactic measure in OMFS, primarily to mitigate post-operative sequelae such as oedema, trismus, and pain, especially following invasive surgical interventions. Synthetic **glucocorticoids** exert their profound anti-inflammatory effects via complex genomic and non-genomic mechanisms, most critically by inhibiting **Phospholipase** A2 **(**PLA2**)**—a prerequisite enzyme for the synthesis of pro-inflammatory eicosanoids (prostaglandins and leukotrienes)—and by suppressing the transcription and release of key pro-inflammatory cytokines (e.g., IL-1, TNF-α).

- **Dexamethasone** is the agent of choice in this specialty due to its high glucocorticoid potency and negligible mineralocorticoid activity. A single pre-operative dose, typically 4–8mg administered intravenously or orally, is an efficacious regimen for

dampening the acute inflammatory response, thereby accelerating functional recovery. Clinicians must be acutely cognisant of the risk of **hyperglycaemia**, particularly in diabetic patients, and the contraindications regarding active, uncontrolled systemic infection and the necessity for "stress-dose" consultation in patients with underlying chronic adrenal suppression.

6.0 Sedatives and Anxiolytics for Conscious Sedation

- **Conscious Sedation** is a fundamental technique designed to achieve a state of anxiolysis where the patient remains communicative and retains protective reflexes [Ref. 6].

- **Benzodiazepines** (e.g., **Midazolam**) are the most prevalent class, acting via the allosteric enhancement of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) at the GABA-A receptor complex. This agonism increases the frequency of chloride channel opening, leading to neuronal membrane **hyperpolarisation** and reduced excitability [Ref. 6.1]. **Midazolam** is favored for intravenous titration due to its rapid onset and short plasma half-life, which facilitates superior control over the depth of sedation. The specific reversal agent, **Flumazenil**, a competitive antagonist, must be immediately available to counteract undue respiratory or excessive CNS depression [

- **Nitrous Oxide (**N2O**)**, an inhaled agent, provides rapid anxiolysis and mild analgesia. It's extremely low blood-gas solubility permits rapid onset/offset, enabling swift post-procedural discharge. However, N2O is strictly contraindicated in conditions involving enclosed air spaces (e.g., pneumothorax), as its rapid diffusion may increase compartment pressure. Continuous physiological monitoring, encompassing HR, BP, SpO2, and preferably **Capnography** for real-time ventilatory status, is a non-negotiable safety mandate for all sedation procedures.

7.0 Essential Emergency Pharmacopoeia

- A comprehensive and readily accessible emergency pharmacological armamentarium is imperative for safe OMFS practice.

- The most vital agent is **Epinephrine (Adrenaline)**, a potent direct-acting sympathomimetic that stimulates α1, β1, and β2 adrenergic receptors. Its immediate intramuscular administration (0.3–0.5mg of 1:1000 solution) is the absolute **first-line treatment for Anaphylaxis**, simultaneously reversing hypotension via vasoconstriction and alleviating bronchospasm [Ref. 10]. For cardiac arrest, it is administered IV/IO 1mg of 1:10,000 solution.

- **Diphenhydramine** (H1-antagonist) serves as an adjunctive therapy for managing cutaneous allergic manifestations. **Glucagon** (IM1mg), by stimulating hepatic glycogenolysis, is the agent of choice for reversing severe, non-responsive **Hypoglycaemia**. Finally, **Oxygen** remains the most fundamental therapeutic agent, essential for the management of virtually all respiratory compromise, shock, and altered mentation, requiring immediate high-flow delivery via the appropriate system.

- The integration of these life-saving agents with proficient staff training and meticulous safety protocols defines the standard of emergency preparedness in the clinical setting.

8.0 Drug Interactions in OMFS

- Drug interactions represent a significant clinical challenge in modern OMFS practice, particularly given the increasing prevalence of polypharmacy among patients. Such interactions can lead to unpredictable drug effects, ranging from reduced therapeutic efficacy to enhanced toxicity and severe adverse reactions. A thorough understanding of common interactions and a proactive approach to medication reconciliation are therefore paramount for patient safety.

- **8.1 Common Interactions**

- **NSAIDs and Anticoagulants (e.g., Warfarin, Novel Oral Anticoagulants — DOACs):** This is one of the most critical interactions in OMFS. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit platelet aggregation and can cause gastrointestinal (GI) mucosal damage, increasing the risk of GI bleeding. [Pallasch 1997] When combined with oral anticoagulants like warfarin (a vitamin K antagonist) or DOACs (e.g., rivaroxaban, apixaban, dabigatran), the risk of significant haemorrhage, both at the surgical site and systemically (e.g., GI bleeding, intracranial haemorrhage), is substantially elevated. Careful consideration, a temporary cessation of NSAIDs, or alternative analgesics (e.g., paracetamol) are often required. Consultation with the patient's physician is essential for managing anticoagulation perioperatively. [Gaynes, 2017]

- **Macrolides (Azithromycin, Clarithromycin) and Statins (e.g., Simvastatin, Atorvastatin):** Macrolide antibiotics, particularly clarithromycin, are potent inhibitors of the cytochrome P450 3A4 (CYP3A4) enzyme system in the liver. [Ref. 8.3] Many statins (HMG-CoA reductase inhibitors), widely used for cholesterol management, are metabolised by CYP3A4. Co-administration can lead to significantly increased plasma concentrations of the statin, raising the risk of dose-dependent adverse effects such as myopathy (muscle pain and weakness) and, rarely, rhabdomyolysis (severe muscle breakdown leading to kidney damage). Azithromycin is a weaker inhibitor and may be a safer macrolide choice in patients on statins, but caution is still advised.

- **Metronidazole and Alcohol:** This is a classic and well-known interaction. Metronidazole inhibits acetaldehyde dehydrogenase, an enzyme responsible for metabolising acetaldehyde (a toxic by-product of alcohol metabolism). Concurrent consumption of alcohol with metronidazole leads to the accumulation of acetaldehyde, resulting in a **disulfiram-like reaction** characterised by severe nausea, vomiting, flushing, headache, and palpitations. [Ref. 10] Patients must be explicitly warned to avoid all forms of alcohol (including alcohol-containing mouthwashes and cough syrups) during metronidazole therapy and for at least 72 hours after completing the course.

- **Opioids and CNS Depressants (Benzodiazepines, Alcohol, Sedative Hypnotics):** Co-administration of opioids with other central nervous system (CNS) depressants, such as benzodiazepines (e.g., diazepam, midazolam), alcohol, or other sedative-hypnotics, results in synergistic CNS depression. This significantly increases the risk of profound sedation, respiratory depression (the most life-threatening side effect), and impaired

psychomotor function. Practitioners must exercise extreme caution, consider lower doses, and provide enhanced monitoring when these combinations are unavoidable.

- **Local Anaesthetics with Vasoconstrictors and Non-selective Beta-blockers:** Non-selective beta-blockers (e.g., propranolol, nadolol) block both β1 and β2 adrenergic receptors. When epinephrine (which stimulates both α and β receptors) is administered, the β2 vasodilation effect is blunted, leaving the α1 vasoconstrictor effect unopposed. This can lead to a significant and potentially dangerous increase in blood pressure (hypertension) and reflex bradycardia. Careful aspiration techniques, slow injection, and limiting the dose of epinephrine are crucial for these patients.
- **Antihypertensives and Vasoconstrictors:** Patients on certain antihypertensive medications (e.g., alpha-blockers like prazosin) can experience an exaggerated hypotensive response when combined with vasoconstrictors due to complex interactions with sympathetic tone. Conversely, some interactions can lead to a pressor response. [Ref. 2] Careful monitoring of blood pressure is always warranted.
- **8.2 Importance of Medication Reconciliation**
- Medication reconciliation is a formal process of obtaining and maintaining an accurate and comprehensive list of all medications a patient is currently taking. This includes prescription medications, over-the-counter drugs, herbal remedies, and dietary supplements. This process is critical at all transitions of care (e.g., initial consultation, before surgery, during hospitalisation, at discharge). By comparing the patient's current medication list with planned prescriptions, the OMFS practitioner can:
- Identify potential drug–drug interactions.
- Detect duplicate medications.
- Recognise medications that need dose adjustment or temporary discontinuation due to the planned surgery or other comorbidities.
- Prevent medication errors and adverse drug events.
- This proactive approach to medication management is a cornerstone of patient safety in a complex healthcare environment.
- **8.3 Cytochrome P450 System and Drug Metabolism**
- The cytochrome P450 (CYP450) enzyme system is the principal enzyme system responsible for the metabolism of the vast majority of drugs (approximately 75%). [Ref. 11] These enzymes, primarily located in the liver and small intestine, transform lipophilic drugs into more polar, excretable metabolites. Understanding the CYP450 system is crucial for predicting and managing drug interactions.
- **CYP Inhibitors:** Certain drugs act as inhibitors of specific CYP enzymes, meaning they decrease the metabolic activity of that enzyme. When a drug that is an inhibitor is co-administered with another drug that is a substrate for the same enzyme, the metabolism of the substrate drug is slowed down. This leads to increased plasma concentrations of the substrate drug, potentially enhancing its pharmacological effects or increasing the

risk of toxicity (e.g., macrolides inhibiting CYP3A4, leading to increased statin levels).

- **CYP Inducers:** Conversely, some drugs are CYP inducers, meaning they increase the synthesis or activity of specific CYP enzymes. This accelerates the metabolism of co-administered drugs that are substrates for that enzyme, leading to decreased plasma concentrations of the substrate drug. This can result in reduced therapeutic efficacy or even treatment failure (e.g., carbamazepine (an anti-epileptic) inducing CYP3A4, leading to a reduced effectiveness of certain oral contraceptives).

- **Genetic Polymorphisms:** Genetic variations (polymorphisms) in CYP genes are responsible for significant inter-individual differences in drug metabolism. For example, the CYP2D6 enzyme exhibits extensive polymorphism. Individuals can be classified as "poor metabolizers" (lacking a functional enzyme), "intermediate metabolizers," "extensive metabolizers," or "ultrarapid metabolizers" (having multiple copies of the gene, leading to very high enzyme activity). This variability can profoundly affect the response to drugs like codeine (which requires CYP2D6 for conversion to active morphine), leading to a lack of efficacy in poor metabolizers or increased toxicity in ultrarapid metabolizers. While not yet routine for most OMFS prescriptions, pharmacogenomic testing is an emerging field that promises to enable more personalised and safer drug therapy in the future.

- A thorough medication review, utilising drug interaction databases (e.g., Lexicomp, UpToDate), and consulting with pharmacists or medical colleagues are indispensable practices for mitigating the risks associated with drug interactions in OMFS.

- **9.0 Toxicity and Allergies to Prescribed Medications**

- Adverse drug reactions (ADRs), encompassing both drug toxicity and allergic reactions, are an unavoidable aspect of pharmacotherapy. For OMFS practitioners, the ability to recognise, classify, and promptly manage these reactions is a critical safety competency. Understanding the mechanisms behind these reactions allows for better prevention and tailored intervention.

9.1 Recognition and Classification of Drug Reactions

- **Drug Toxicity** refers to the adverse effects caused by excessive drug levels in the body (e.g., due to overdose, impaired elimination, or drug interactions) or prolonged exposure, leading to damage to organs or systems. In OMFS, common toxicities include:

- **Local Anaesthetics:**

- **Systemic Toxicity (LAST):** As extensively discussed in Section 2.5, LAST is a life-threatening emergency caused by high plasma concentrations of LAs. Symptoms typically progress from initial CNS excitation (circumoral numbness, tinnitus, light-headedness, muscle twitching, escalating to seizures) to CNS depression (drowsiness, respiratory depression, coma) and, at higher levels, profound cardiovascular depression (bradycardia, arrhythmias, hypotension, cardiac arrest). Management prioritises airway and breathing, seizure control (benzodiazepines), and the cornerstone treatment, intravenous lipid emulsion therapy.

- **Methemoglobinemia:** A rare but distinct toxicity, predominantly linked to prilocaine and benzocaine, where the iron in haemoglobin is oxidised, rendering it unable to bind oxygen. Clinically, patients present with cyanosis despite adequate oxygenation. [Ref. 10] Methylene blue is the specific antidote.
- **Paracetamol:**
- **Hepatotoxicity:** The primary concern with paracetamol overdose is acute liver damage. This occurs when the liver's glutathione stores are depleted, allowing a toxic metabolite (NAPQI) to accumulate and cause hepatocellular necrosis. [Ref. 10] Symptoms may be delayed for 24–48 hours. Prompt administration of N-acetylcysteine is crucial for preventing or mitigating liver damage. [Ref. 10]
- **NSAIDs:**
- **Gastrointestinal (GI) Toxicity:** NSAIDs are notorious for causing dose-dependent GI irritation, ranging from dyspepsia to gastric ulcers, haemorrhage, and perforation. This risk is heightened with higher doses, prolonged use, advanced age, a history of peptic ulcer disease, and the concomitant use of corticosteroids or anticoagulants.
- **Renal Toxicity:** NSAIDs can impair renal function by inhibiting renal prostaglandin synthesis, leading to acute kidney injury, particularly in patients who are dehydrated, elderly, have a pre-existing renal impairment, or heart failure.
- **Cardiovascular Risk:** Prolonged use of NSAIDs, particularly COX-2 selective agents, has been associated with an increased risk of thrombotic cardiovascular events such as myocardial infarction and stroke. [Ref. 10] For short-term OMFS use, this risk is generally low but should be considered in high-risk patients.
- **Opioids:**
- **Respiratory Depression:** This is the most dangerous and potentially fatal adverse effect of opioids, especially with an overdose or in combination with other CNS depressants. [Ref. 10, 8.1] It can lead to hypoventilation, hypoxia, and death. Rapid reversal with naloxone is life-saving.
- **CNS Depression:** Profound sedation, confusion, and miosis are common dose-dependent effects.
- **Gastrointestinal Effects:** Nausea, vomiting, and severe constipation are very common and often limiting side effects.
- **Antibiotics:**
- **Clindamycin:** High risk of *Clostridioides difficile*-associated diarrhoea (CDAD), which can range from mild to life-threatening pseudomembranous colitis.
- **Fluoroquinolones:** Rare but serious side effects include tendon rupture (often Achilles' tendon, exacerbated by corticosteroid use), peripheral neuropathy, and QT prolongation (risk of cardiac arrhythmias).
- **Metronidazole:** Disulfiram-like reaction with alcohol.

- **Nephrotoxicity/Ototoxicity:** While less common with typical OMFS antibiotics, certain antibiotics (e.g., aminoglycosides, vancomycin) can cause kidney and ear damage, which is a concern in hospital settings for severe infections.
- **Drug Allergies** are immune-mediated hypersensitivity reactions to a drug, ranging from mild cutaneous manifestations to life-threatening anaphylaxis. [Ref. 9] Classification is typically based on the Gell and Coombs classification system:
- **Type I (Immediate Hypersensitivity/Anaphylactic):** This is an IgE-mediated reaction with a rapid onset (minutes to hours) upon re-exposure to the allergen. Symptoms can include urticaria (hives), angioedema (swelling of the face, lips, tongue, and larynx), bronchospasm, laryngeal oedema, hypotension, and shock. This is the most dangerous type of drug allergy.
- **Type II (Cytotoxic):** IgG or IgM-mediated. The drug or its metabolite binds to a cell surface, leading to antibody-mediated cell destruction (e.g., drug-induced haemolytic anaemia, thrombocytopenia).
- **Type III (Immune Complex):** IgG-mediated. Drug–antibody immune complexes form and deposit in tissues, causing inflammation (e.g., serum sickness, vasculitis). The onset is typically delayed (days to weeks).
- **Type IV (Delayed-Type Hypersensitivity):** T-cell mediated. The onset is typically delayed (24–72 hours) and includes contact dermatitis, maculopapular rash, and severe cutaneous adverse reactions (SCARs) like Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). SJS and TEN are severe, life-threatening mucocutaneous reactions characterised by widespread blistering and epidermal detachment, often triggered by drugs like NSAIDs, sulphonamides, and certain anticonvulsants.

9.2 Management of Allergic Reactions

- Prompt and appropriate management is critical for allergic reactions.
- **Mild Reactions (e.g., localised urticaria, pruritus):** Discontinue the offending drug. Administer oral or intramuscular antihistamines (e.g., diphenhydramine 25–50 mg).
- **Moderate Reactions (e.g., generalised urticaria, angioedema without airway involvement, mild bronchospasm):** Discontinue the drug. Administer antihistamines (H1 and H2 blockers), systemic corticosteroids (e.g., methylprednisolone 125 mg IV or prednisolone 40–60 mg orally), and bronchodilators (e.g., salbutamol) if bronchospasm is present. Close monitoring is essential.
- **Severe Reactions (Anaphylaxis):** This is a medical emergency requiring immediate action.
- Stop drug administration.
- Call for help/emergency services.
- Administer **Epinephrine:** This is the cornerstone of treatment. 0.3–0.5 mg of a 1:1000 solution intramuscularly (IM) into the mid-anterolateral thigh. Repeat every 5–15

minutes as needed.

- **Airway Management:** Ensure a patent airway. Provide supplemental oxygen. Intubation may be necessary for severe laryngeal oedema.
- **IV Fluids:** Administer IV fluids (e.g., normal saline) rapidly to support blood pressure and counteract vasodilation.
- **Adjunctive Medications:** Antihistamines (H1 and H2 blockers, e.g., diphenhydramine and ranitidine) and systemic corticosteroids (e.g., methylprednisolone) should be given after epinephrine to prevent biphasic reactions (a recurrence of anaphylaxis hours after initial resolution) and manage persistent symptoms.
- **Monitor:** Close monitoring of vital signs and patient status is essential for several hours due to the risk of biphasic reactions.
- **9.3 Drug-Induced Oral Manifestations**
- Many medications can cause adverse effects that manifest in the oral cavity. OMFS practitioners should be aware of these as they can impact oral health and patient comfort.
- **Xerostomia (dry mouth):** A very common side effect of drugs with anticholinergic properties (e.g., tricyclic antidepressants, antihistamines, antipsychotics, some antihypertensives, diuretics). Chronic xerostomia increases the risk of dental caries, periodontal disease, and oral infections.
- **Gingival Hyperplasia:** Characterised by gingival overgrowth, primarily associated with phenytoin (anticonvulsant), nifedipine (calcium channel blocker), and ciclosporin (immunosuppressant).
- **Oral Candidiasis:** An increased risk with broad-spectrum antibiotics (by altering oral flora) and inhaled or systemic corticosteroids (by immunosuppression).
- **Stomatitis/Mucositis:** Inflammation and ulceration of the oral mucosa, frequently seen with chemotherapeutic agents and radiation therapy.
- **Taste Alterations (Dysgeusia):** Can be caused by various drugs, including metronidazole, captopril (ACE inhibitor), clarithromycin, and some antifungals. [Ref. 6]
- **Lichenoid Reactions:** Oral lesions mimicking lichen planus can be triggered by NSAIDs, ACE inhibitors, beta-blockers, and antimalarials.
- **Osteonecrosis of the Jaw (ONJ):** A serious adverse effect primarily associated with antiresorptive medications (bisphosphonates, denosumab) and anti-angiogenic agents, particularly in patients receiving high doses for cancer therapy. OMFS practitioners play a crucial role in preventing and managing medication-related ONJ.
- Recognition of these oral manifestations is important for an accurate diagnosis, proper patient counselling, and collaboration with the prescribing physician when necessary to manage or modify medication regimens.

10.0 Special Lab Referrals and Investigations Needed

- Appropriate laboratory investigations are crucial for optimising drug therapy, monitoring for adverse effects, and ensuring patient safety in OMFS. These tests provide invaluable baseline information, help with risk stratification, and guide individualised pharmacological management. [2, 8]

- Prior to initiating any significant pharmacological regimen or surgical intervention, a comprehensive baseline laboratory assessment is often warranted. This typically includes a **complete blood count (CBC)** to assess red blood cell, white blood cell, and platelet counts, which can indicate anaemia, infection, or coagulopathies. A **comprehensive metabolic panel (CMP)** provides crucial information on renal function (blood urea nitrogen, creatinine), hepatic function (liver enzymes), electrolyte balance, and glucose levels. Abnormalities in these parameters can significantly impact drug metabolism and excretion, necessitating dosage adjustments or alternative drug selections to prevent toxicity. For instance, impaired renal function may prolong the half-life of renally excreted drugs, leading to accumulation and adverse effects.

- In cases of a suspected infection, **microbiological investigations** are paramount. This involves obtaining appropriate specimens (e.g., pus, tissue biopsies, blood cultures) for Gram stain, culture, and sensitivity testing. The Gram stain provides rapid preliminary identification of bacterial morphology and Gram reaction, guiding initial empirical antibiotic choices. Culture allows for the isolation and definitive identification of the causative pathogen(s), while sensitivity testing determines the susceptibility of these organisms to various antibiotics. This targeted approach is fundamental to effective infection management and is a cornerstone of antibiotic stewardship, preventing the overuse of broad-spectrum agents and mitigating the development of resistance. For unusual or persistent infections, a referral for advanced microbiological diagnostics, such as molecular testing (e.g., PCR) or fungal cultures, may be necessary.

- Furthermore, **coagulation studies** (e.g., prothrombin time/international normalised ratio (PT/INR), activated partial thromboplastin time (aPTT)) are essential, particularly for patients on anticoagulants or those with a history of bleeding disorders, to assess the risk of perioperative haemorrhage and guide the management of antithrombotic therapy. For patients with known systemic diseases, such as diabetes mellitus, regular monitoring of HbA1c levels is important to assess glycaemic control, as uncontrolled diabetes can increase the risk of infection and impair wound healing.

- Postoperatively, or during prolonged drug therapy, **therapeutic drug monitoring (TDM)** may be indicated for certain medications with a narrow therapeutic index, such as some antibiotics (e.g., vancomycin, aminoglycosides) or immunosuppressants. TDM involves measuring drug concentrations in the blood to ensure they remain within the therapeutic range, thereby maximising efficacy and minimising toxicity. Regular monitoring of CBC, renal, and hepatic function is also crucial for patients receiving drugs with known myelosuppressive, nephrotoxic, or hepatotoxic potential.

- Orthognathic surgical procedures aim to correct facial deformities and malocclusion, thereby improving the functional disorders of the stomatognathic system. This is an elective procedure, typically carried out in young, healthy adults. It is classified as a clean-contaminated procedure, with a reported infection rate ranging from 3–11%

[Fridrich, et al., 1994, Danda, et al 2010]. However, certain studies have reported the rate of infection following orthognathic surgery to be as high as 6–33.4% [Laskin., 2003]. Postoperative infection has been found to be related to poor oral hygiene and the habit of smoking.

- In contemporary society, with its proliferation of fast-moving vehicles and expressways, hundreds of thousands of individuals are involved in road traffic accidents. The head and face are amongst the most commonly injured body parts. Both the soft and hard tissues of the face may be implicated in the trauma. Firearms, contact sports, and interpersonal violence represent additional causes of facial injuries. The management of these injuries should adhere to established protocols and be conducted systematically. With advances in anaesthetic and surgical techniques, and the availability of superior implant materials exhibiting favourable metallurgical properties, **open reduction and internal fixation (ORIF)** has become the norm. The re-establishment of form, function, and cosmesis is of paramount importance. To achieve this objective, the probable complications of ORIF must be prevented or appropriately managed. Of the various complications reported, none has generated more interest and controversy than the occurrence of postoperative infection. By adhering to standard surgical protocols and strict aseptic techniques, the incidence of postoperative infection can be significantly reduced. Nevertheless, the presence of microorganisms in the oral cavity and facial skin, coupled with potential contamination from the environment, necessitate the judicious consideration of antibiotic therapy in maxillofacial trauma management.
- Furthermore, systemic diseases and the concurrent use of medications can result in the presence of unusual organisms as part of the normal flora, and an increase in diseases caused by normal organisms that are usually considered to have low pathogenicity. Typically, microorganisms are held in check by the body's defence mechanisms. When these mechanisms are impaired, infection may result from an otherwise minor bacterial exposure. This chapter offers a comprehensive review of pharmacology and pharmacokinetics specifically tailored for OMFS practitioners, integrating foundational concepts with clinical relevance and highlighting the critical importance of antibiotic stewardship and nuanced pain management strategies.

10.1 Pre-operative Assessment

- These foundational tests assess a patient's overall baseline health, organ function, and potential risks before they undergo surgery or receive medication. The results directly influence drug selection, dosing, and the overall perioperative plan. [Zoeller, & Kadis, 1981]
- **10.1.1 Complete Blood Count (CBC)**
- **Purpose:** The CBC provides a comprehensive overview of the cellular components of blood: red blood cells (RBCs), white blood cells (WBCs), and platelets. [Ref. 10.1.1]
- **Relevance to OMFS:**
- **Anaemia** (low RBCs/haemoglobin): Can indicate an underlying systemic disease, impact oxygen delivery to tissues, and influence the capacity for healing. Severe anaemia

may necessitate a blood transfusion prior to major procedures.

- **Abnormal WBC counts:** Leucocytosis (high WBCs) can indicate an acute infection or inflammatory process, whereas leucopenia (low WBCs) or specific differentials may suggest an immunocompromised state, which increases the risk of infection. [Ref. 10.1.1] This guides the choice of antibiotic and infection control measures.
- **Platelet count:** A low platelet count (thrombocytopenia) significantly increases the risk of excessive bleeding during and after surgery. This is especially critical in procedures with high bleeding potential. [Goodson & Hunt, 1979]
- **10.1.2 Coagulation Profile (PT/INR, PTT)**
- **Purpose:** These tests assess the extrinsic (Prothrombin Time/International Normalised Ratio — PT/INR) and intrinsic (Activated Partial Thromboplastin Time — aPTT) pathways of the coagulation cascade, providing an overview of the patient's clotting ability. [Ref. 10.1.2]
- **Relevance to OMFS:** This is essential for patients on anticoagulant therapy (e.g., warfarin, DOACs, heparin), those with a history of bleeding disorders (e.g., haemophilia, von Willebrand disease), or individuals with liver disease (as clotting factors are produced in the liver). [Lacasa, et al., 2007] These results guide the perioperative management of anticoagulants (e.g., temporary cessation, bridging therapy) and help predict and manage the risk of bleeding during surgical procedures. [Davis, et al., 2016]

10.2.4 Genetic Testing (Pharmacogenomics)

- **Purpose:** Pharmacogenomic testing identifies genetic variations (polymorphisms) that influence an individual's drug metabolism, transport, and receptor binding, thereby affecting drug efficacy and toxicity.
- **Relevance to OMFS (Emerging):** While not routine in current OMFS practice, pharmacogenomics is an emerging field with significant potential for personalised medicine. For example, variations in cytochrome P450 enzymes (e.g., CYP2D6 polymorphisms affecting codeine metabolism, or CYP2C19 affecting clopidogrel activation) can significantly alter the drug response. This could eventually guide personalised pain management (e.g., predicting codeine effectiveness) or influence antiplatelet therapy for patients undergoing OMFS procedures. Referral to specialised genetic counselling services or pharmacogenomics labs may be considered in complex cases with unexplained drug responses or adverse reactions (Esposito, et al, 2003]

These comprehensive laboratory and specialised investigations collectively enhance the OMFS practitioner's ability to provide safe, effective, and individualised pharmacological care, particularly for patients with complex medical backgrounds.

Doses of Medications for Oral Maxillofacial Clinical Management

Medication Class	Drug Name	Common Indication	Standard Adult Dose	Max Adult Dose / Day	Pediatric Dose (Approx.)	Notes

Local Anesthetics	Lidocaine 2% w/ Epinephrine 1:100,000	Local anesthesia, nerve block	1.8-3.6 mL (1-2 carpules)	7 mg/kg (max 500 mg)	4.4 mg/kg	Max 11 carpules for 70kg adult. Careful aspiration is crucial to prevent LAST [Ref. 1, 10].

Medication Class	Drug Name	Common Indication	Standard Adult Dose	Max Adult Dose / Day	Pediatric Dose (Approx.)	Notes
	Bupivacaine 0.5% w/ Epinephrine 1:200,000	Prolonged anesthesia	1.8-3.6 mL (1-2 carpules)	2 mg/kg (max 90 mg)	1.3 mg/kg	Longer duration of action (up to 8 hours), useful for post-operative pain control. Higher cardiotoxicity, strict adherence to MRD
	Articaine 4% w/ Epinephrine 1:100,000	Local anesthesia, nerve block	1.8-3.6 mL (1-2 carpules)	7 mg/kg (max 500 mg)	7 mg/kg	High lipid solubility and dual metabolism (hepatic & plasma esterases) contribute to rapid onset and good tissue penetration
Non-Opioid Analgesics	Ibuprofen	Mild-moderate pain, inflammation	400-600 mg every 4-6 hrs.	2400-3200 mg	4-10 mg/kg every 6-8 hrs.	First-line for post-op pain. Take with food to reduce GI upset. Caution With renal impairment, GI history, and anticoagulants

	Acetaminophen	Mild-moderate pain, fever	500-1000 mg every 4-6 hrs.	4000 mg	10-15 mg/kg every 4-6 hrs.	Max 75mg/kg/day in children. Risk of hepatotoxicity with overdose. Often combined with NSAIDs for multimodal analgesia
Opioid Analgesics	Codeine (with Acetaminophen)	Moderate pain	30-60 mg every 4-6 hrs.	360 mg (Codeine)	0.5-1 mg/kg every 4-6 hrs.	Prodrug, variable efficacy due to CYP2D6 polymorphism. Respiratory depression risk
	Hydrocodone (with Acetaminophen)	Moderate- severe pain	5-10 mg every 4-6 hrs	60 mg (Hydrocodone)	Not routinely recommended for children.	Higher potential for respiratory depression,

Medication Class	Drug Name	Common Indication	Standard Adult Dose	Max Adult Dose / Day	Pediatric Dose (Approx.)	Notes
						addiction than codeine. Use for shortest duration possible [
	Oxycodone (with Acetaminophen)	Moderate- severe pain	5-10 mg every 4-6 hrs.	60 mg (Oxycodone)	Not routinely recommended for children.	Potent, higher abuse potential. Careful selection and monitoring

Antibiotics	Amoxicillin	Odontogenic infections, prophylaxis	500 mg every 8 hrs. OR 875 mg every 12 hrs.	-	25-45 mg/kg/day in 2-3 divided doses	First-line for many odontogenic infections. Check for penicillin allergy
	Amoxicillin/Clavulanate (Augmentin)	Resistant infections	875 mg/125 mg every 12 hrs.	-	25-45 mg/kg/day in 2 divided doses	Contains beta-lactamase inhibitor, effective against resistant strains. Risk of GI upset
	Clindamycin	Penicillin allergy, anaerobic infections	300 mg every 6-8 hrs.	1800 mg	10-30 mg/kg/day in 3-4 divided doses	Excellent anaerobic coverage. High risk of *C. difficile* colitis, counsel patients on symptoms
	Metronidazole	Anaerobic infections	500 mg every 8 hrs.	-	15-30 mg/kg/day in 3 divided doses	Often combined with amoxicillin for mixed infections. Strict alcohol avoidance (disulfiram-like reaction)
	Cephalexin	Skin/soft tissue infections, prophylaxis (alt)	500 mg every 6 hrs.	4000 mg	25-50 mg/kg/day in 2-4 divided doses	First-gen cephalosporin. Low cross-reactivity with penicillin, useful alternative for non-anaphylactic

Medication Class	Drug Name	Common Indication	Standard Adult Dose	Max Adult Dose / Day	Pediatric Dose (Approx.)	Notes
						allergies
Corticosteroids	Dexamethasone	Post-op swelling, inflammation	4-8 mg single dose pre- op OR 4 mg every 6 hrs for 24-48 hrs.	-	0.1-0.2 mg/kg single dose	Potent anti-inflammatory for reducing post-op edema. Monitor blood glucose, especially in diabetics
Sedatives/Anxiolytics	Midazolam (oral)	Pre-op anxiety, conscious sedation	0.25-0.5 mg/kg (max 15-20 mg) 30-45 min pre-op	-	0.25-0.5 mg/kg (max 10-15 mg)	Rapid onset, short duration. Amnestic properties. Requires careful monitoring and availability of flumazenil
	Nitrous Oxide	Conscious sedation	Titrated to effect (20-70% N2O)	-	Titrated to effect	Rapid onset/offset. Contraindicated in enclosed air spaces (e.g., pneumothorax). Requires scavenging system

Note: Doses are approximate and should always be adjusted based on patient's age, weight, renal/hepatic function, comorbidities, potential drug interactions, and specific clinical situation. Always consult up-to-date prescribing information from regulatory bodies (e.g., FDA), national/local guidelines, and specialized drug references (e.g., Lexicomp, UpToDate) for the most current and detailed dosing information [Shargel, et al., 2005, Scottish Antimicrobial Prescribing Group. 2013].

Concluding Remarks

As the field of OMFS continues to evolve, integrating emerging pharmacogenomic insights promises a future of even more personalized pain management and antibiotic selection [Resnik & Misch., 2008]. Concurrently, embracing multimodal approaches to pain and infection management, minimizing opioid use, and diligently promoting antibiotic stewardship will further enhance the quality and safety of oral and maxillofacial surgical care. Continuous professional development, rigorous adherence to evidence-based guidelines, and active participation in medication reconciliation processes are essential for navigating the increasing complexities of pharmacological management in this specialized surgical discipline [Sekhar, et al., 2001, Ambrose & Winter., 2010).

The industrial era's groundbreaking innovations in synthetic chemistry and mass production laid the fundamental groundwork for modern pharmacology, providing purified compounds and a nascent understanding of drug kinetics that moved beyond unreliable botanical extracts. Today, OMFS practitioners must leverage this foundational knowledge, coupled with an acute awareness of individual patient factors—such as age-related physiological changes, complex medical comorbidities, the challenges of polypharmacy, and emerging insights from genetic predispositions—to tailor therapeutic regimens that are both effective and safe. Vigilance for drug toxicities and allergic reactions, supported by appropriate laboratory investigations and immediate access to emergency reversal agents, forms a critical safety net in the surgical environment [Sancho, et al., 2009, Mangram, et al., 1999].

The judicious application of pharmacological and pharmacokinetic principles is paramount to safe and effective patient care in oral and maxillofacial surgery. From the precise dosing of local anesthetics to the strategic use of antibiotics, analgesics, and sedatives, every drug administered carries potential benefits and risks that must be carefully balanced [Ref. 3, 6]. A thorough and dynamic understanding of drug mechanisms, ADME (absorption, distribution, metabolism, excretion), and potential interactions is not merely academic; it is a clinical imperative that directly impacts patient outcomes, minimizes adverse events, and optimizes recovery [Gabrielsson & Weiner, 2006].

References

1. Boyd BC, Hall RE. Drugs for medical emergencies in the dental office. In: Ciancio SG, ed. The ADA/PDR Guide to Dental Therapeutics. 5th ed. Montvale, N.J.: PDR Network; 2009:363-385.
2. Brown AF. Anaphylaxis gets the adrenaline going. Emerg Med J 2004;21(2):128-129.
3. Brunton, L. L., Hilal-Dandan, B., & Knollmann, R. C. (2018). *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (13th ed.). McGraw-Hill Education.
4. Camps-Font O., Figueiredo R., Sánchez-Torres A. Which is the most suitable local anaesthetic when inferior nerve blocks are used for impacted mandibular third molar extraction? A network meta-analysis. Int J Oral Maxillofac Surg. 2020; 49:1497–1507. Doi: 10.1016/j.ijom.2020.04.016. [DOI] [PubMed] [Google Scholar.
5. Chaiamnuay S, Allison JJ, Curtis JR. Risks versus benefits of cyclooxygenase-2-selective nonsteroidal anti-inflammatory drugs. Am J Health Syst Pharm. 2006 Oct 01;63(19):1837-51. [PubMed].

6. Danda AK, Wahab A, Narayanan V, Siddareddi A. Single-dose versus single-day antibiotic prophylaxis for orthognathic surgery: a prospective, randomized, double-blind clinical study. J Oral Maxillofac Surg. 2010; 68:344–6.

7. Dandon RH, Brual LL. Goodman & Gilman's manual of pharmacology and therapeutics. 2nd ed. New York: McGraw Hill Education; 2014. 2. Gaynes R. The discovery of penicillin—new insights after more than 75 years of clinical use. Emerg Infect Dis. 2017;23(5): 849–53.

8. Davies EA, O'Mahoney. MS. Adverse drug reactions in special populations - the elderly. Br J Clin Pharmacol. 2015 Oct;80(4):796-807. Doi: 10.1111/bcp.12596. Epub 2015 May 22. PMID: 25619317.

9. Davis CM, Gregoire CE, Steeves TW, et al. Prevalence of surgical site infections following orthognathic surgery: a retrospective cohort analysis. J Oral Maxillofac Surg. 2016; 74:1199–206.

10. Dionne, R. A., Phero, J. C., & Becker, D. E. (2018). *Management of Pain and Anxiety in the Dental Office*. Elsevier.

11. Ebo DG, Fisher MM, Hagendorens MM, et al. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007;62(5):471–87.

12. Fernandez, E., Perez, R., Hernandez, A., Tejada, P., Arteta, M., & Ramos, J. T. (2011). Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. Pharmaceutics, 3(1),53–72. ↲10.3390/pharmaceutics3010053 [PMC free article] [PubMed] [CrossRef]**].**

13. Fernandez, E., Perez, R., Hernandez, A., Tejada, P., Arteta, M., & Ramos, J. T. (2011). Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. Pharmaceutics, 3(1), 53–72. ↲10.3390/pharmaceutics3010053 [PMC free article] [PubMed] [CrossRef]]

14. Fernandez, E., Perez, R., Hernandez, A., Tejada, P., Arteta, M., & Ramos, J. T. (2011). Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. Pharmaceutics, 3(1), 53–72. ↲ 10.3390/pharmaceutics. 3010053. [PMC free article] [PubMed] [CrossRef]

15. Fernandez, E., Perez, R., Hernandez, A., Tejada, P., Arteta, M., & Ramos, J. T. (2011). Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. Pharmaceutics, 3(1), 53–72. ↲ 10.3390/pharmaceutics3010053. [PMC free article] [PubMed] [CrossRef].

16. Figueiredo R, Valmaseda-Castellon E, Formoso-Senande MF, Berini-Aytes L, GayEscoda C. Delayed-onset infections after impacted lower third molar extraction: involved bacteria and sensitivity profiles to commonly used antibiotics. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2012; 144:43–8.

17. Fridrich KL, Partnoy BE, Zeitler DL. Prospective analysis of antibiotic prophylaxis for orthognathic surgery. Int J Adult Orthodontics Ortho Surg. 1994;9(2):129–31.

18. Garner JS. CDC guideline for prevention of surgical wound infections, 1985. Supersedes guideline for prevention of surgical wound infections published in 1982. (Originally published in November 1985). Revised. Infect Control. 1986; 7:193–200.

19. Gaynes R. The discovery of penicillin—new insights after more than 75 years of clinical use. Emerg Infect Dis. 2017;23(5):849–53.

20. Ghlichloo I, Gerriets V. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) [Updated 2023 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547742/.

21. Goodson WH III, Hunt TK. Wound healing and the diabetic patient. Surg Gynecol Obstet. 1979; 149:600–8.

22. Gray K, Adhikary SD, Janicki P. Pharmacogenomics of analgesics in anesthesia practice: A current update of literature. *J Anaesthesiol Clin Pharmacol.* 2018 Apr-Jun;34(2):155-160. [PMC free article] [PubMed]

23. Grogan S, Preuss CV. Pharmacokinetics. [Updated 2023 Jul 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557744/.

24. Hargreaves, KM · Neidle, EA. Adrenergic drugs, Yagiela, JA · Neidle, EA · Dowd (Editors). In Pharmacology and Therapeutics for Dentistry. Mosby, St. Louis, 1998; 85-99].

25. Housholder, GT. Drugs acting on the respiratory system. Yagiela, JA · Neidle, EA · Dowd, FJ (Editors). Pharmacology and Therapeutics for Dentistry. Mosby, St. Louis, 1998; 440-448.

26. Hupp, J. R., Ellis, E., & Tucker, M. R. (2020). *Contemporary Oral and Maxillofacial Surgery* (7th ed.). Elsevier. American Dental Association (ADA) and American Heart Association (AHA) and American Academy of Orthopaedic Surgeons (AAOS). (Current Guidelines). *Antibiotic Prophylaxis for Dental Patients with Prosthetic Joints* and *Antibiotic Prophylaxis for the Prevention of Infective Endocarditis*. (Always refer to the latest published guidelines for specific recommendations).

27. Johnson R, Williams S. Principles of Antimicrobial Therapy in Maxillofacial Infections. In: Peterson LJ, Hupp JR, editors. *Contemporary Oral and Maxillofacial Surgery*. 7th ed. St. Louis, MO: Mosby Elsevier; 2019. p. 450-465.

28. Joint Commission on Accreditation of Healthcare Organizations (JCAHO). (Current Standards). *Medication Management Standards*. (Relevant for safe medication practices in healthcare settings).

29. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol. 2005;115(3 Suppl 2): S483–523.

30. Kamolratanakul P, Jansisyanont P. A review of antibiotic prophylaxis protocols in oral and maxillofacial surgery. J Oral Maxillofac Surg Med Pathol. 2018; 30:395–404.

31. Lacasa JM, Jimenez JA, Ferras V, Bossom M, Sola-Morales O, Garcia-Rey C, et al. Prophylaxis versus pre-emptive treatment for infective and inflammatory complications of surgical third molar removal: a randomized, double-blind, placebo-controlled, clinical trial with sustained release amoxicillin/clavulanic acid (1000/ 62.5 mg). Int J Oral Maxillofac Surg. 2007; 36:321–7.

32. Laskin DM. The use of prophylactic antibiotics for the prevention of postoperative infections. Oral Maxillofac Surg Clin North Am. 2003; 15:155–60.

33. Lexicomp Online. (Continually Updated). *Drug Information Handbook for Dentistry*. Wolters Kluwer.

34. Little, J. W., Falace, D. A., Miller, C. S., & Rhodus, N. L. (2020). *Dental Management of the Medically Compromised Patient* (10th ed.). Elsevier.

35. Liu, L., & Liu, X. (2019). Contributions of drug transporters to blood-placental barrier. Advances in Experimental Medicine and Biology, 1141, 505–548. ↲10.1007/978-981-13-7647-4_11 [PubMed] [CrossRef],

36. Lodi G, Figini L, Sardella A, Carrassi A, Del Fabbro M, Furness S. Antibiotics to prevent complications following tooth extractions. Cochrane Database Syst Rev. 2012;11:CD003811.

37. Malamed, S. F. (2022). *Handbook of Local Anesthesia* (7th ed.). Elsevier.

38. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) hospital infection control practices advisory committee. Am J Infect Control. 1999; 27:97–132.

39. Mathison M, Pepper T. Local Anesthesia Techniques in Dentistry and Oral Surgery. [Updated 2023 Jun 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan].

40. Muelleman, RL · Lindzon, RD · Silvers, WS. Allergy, hypersensitivity, and anaphylaxis. Rosen, R (Editor). Emergency Medicine: Concepts and Clinical Practice Mosby-Year Book, St. Louis, 1998; 2759-2774.

41. Neidle, E. A., & Yagiela, J. A. (Eds.). (2020). *Pharmacology and Therapeutics for Dentistry* (7th ed.). Mosby.

42. Niwa, H · Hirota, Y · Shibutani, T. Systemic emergencies and their management in dentistry: Complications independent of underlying disease. Anesthesia Progress. 1996; 43:29-35,

43. Open Resources for Nursing (Open RN); Ernstmeyer K, Christman E, editors. Nursing Pharmacology [Internet]. 2nd edition. Eau Claire (WI): Chippewa Valley Technical College; 2023. Chapter 1 Pharmacokinetics & Pharmacodynamics. Available from: https://www.ncbi.nlm.nih.gov/books/NBK595006/**].**

44. Pallasch TJ. Antibiotic prophylaxis: the clinical significance of its recent evolution. J Calif Dent Assoc. 1997;25(619–24):26–32.

45. Peterson LJ. Antibiotic prophylaxis against wound infections in oral and maxillofacial surgery. J Oral Maxillofac Surg. 1990; 48:617–620.

46. Phillips WJ, Currier BL. Analgesic pharmacology: II. Specific analgesics. J Am Acad Orthop Surg. 2004 Jul-Aug;12(4):221-33.

47. Rang HP, Dale MM, Ritter JM, Flower RJ. *Rang and Dale's Pharmacology*. 9th ed. Edinburgh: Churchill Livingstone Elsevier; 2019

48. Resnik RR, Misch C. Prophylactic antibiotic regimens in oral implantology: rationale and protocol. Implant Dent. 2008; 17:142–50.

49. Rosenberg MB. Drugs for medical emergencies. In: Yagiela JA, Dowd FJ, Neidle EA, eds. Pharmacology and Therapeutics for Dentistry. 5th ed. St. Louis: Mosby; 2004:857-864.

50. Rosenberg, Preparing for medical emergencies: the essential drugs and equipment for the dental office. J Am Dent Assoc. 2010; 141:14S-19S.

51. Rosenfeld et al, Emergency Drugs for the Oral and Maxillofacial Surgeon Office. Oral and Maxillofacial Surgery Clinics. September 28, 2021).

52. Sancho-Puchades M, Herraez-Vilas JM, Berini-Aytes L, Gay- Escoda C. Antibiotic prophylaxis to prevent local infection in Oral surgery: use or abuse? Oral Med Oral Patol Oral Cir Bucal. 2009;14: E28–33.

53. Scottish Antimicrobial Prescribing Group. Intravenous Vancomycin Use in Adults (Continuous Infusion). Scotland: NHS; Jan 2013.

54. Sekhar CH, Narayanan V, Baig MF. Role of antimicrobials in third molar surgery: prospective, double blind, randomized, placebo-controlled clinical study. Br J Oral Maxillofac Surg. 2001; 39:134–7.

55. Shargel L, Wu-Pong S, Yu ABC. Applied Biopharmaceutics and Pharmacokinetics. 5th ed. New York: The McGraw-Hill Companies; 2005.

56. Slørdal L, Spigset O. [Basic pharmacokinetics--absorption]. Tidsskr Nor Laegeforen. 2005 Apr 07;125(7):886-7. [PubMed].

57. Smith J, Jones K. Systemic absorption of local anesthetics in oral surgery. *J Oral Maxillofac Surg*. 2020;78(5):789-795. Doi: 10.1016/j.joms.2020.01.012.

58. Soldin, O. P., & Mattison, D. R. (2009). Sex differences in pharmacokinetics and pharmacodynamics. Clinical Pharmacokinetics, 48(3), 143–157. ↲10.2165/00003088-200948030-00001 [PMC free article] [PubMed] [CrossRef].

59. Soto AP, Meyer SL. Oral Implications of Polypharmacy in Older Adults. Dent Clin North Am. 2021 Apr;65(2):323-343. Doi: 10.1016/j.cden.2020.11.007. Epub 2021 Jan 22. PMID: 33641756.

60. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008 Mar;11(2 Suppl):S133-53. [PubMed].

61. Trummel, CL. Anti-inflammatory drugs. Yagiela, JA · Neidle, EA · Dowd, FJ (Editors). Pharmacology and Therapeutics for Dentistry. Mosby, St. Louis, 1998; 297-319.

62. U.S. Food and Drug Administration (FDA). (Continually Updated). *Drug Safety Communications*. (Provides updates on drug safety issues and warnings).

63. Uptodate.com. (Continually Updated). Clinical reference for evidence-based medicine. (Provides current information on drug dosing, interactions, and management of adverse effects).

64. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971 Jun 23;231(25):232-5.

65. Waksman SA. What is an antibiotic or antibiotic substance? Mycologia. 1947;39(5):565–9.

66. Wang YH, Wang DR, Liu JY, Pan J. Local anesthesia in oral and maxillofacial surgery: A review of current opinion. J Dent Sci. 2021 Oct;16(4):1055-1065. Doi: 10.1016/j.jds.2020.12.003. Epub 2020 Dec 17. PMID: 34484571; PMCID: PMC8403808.

67. Westervelt P, Cho K, Bright DR, Kisor DF. Drug-gene interactions: inherent variability in drug maintenance dose requirements. P T. 2014 Sep;39(9):630-7. [PMC free article] [PubMed].

68. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med. 1999 May 31;106(5B):13S-24S. [PubMed]

69. Woolf, A. D., & Shannon, M. W. (2020). *Goldfrank's Toxicologic Emergencies* (11th ed.). McGraw-Hill Education.

70. Wynn, R. L., Meiller, T. F., & Crossley, H. L. (2014). *Drug Information Handbook for Dentistry: A Reference for the Dental Professional* (20th ed.). Lexi-Comp. (While an older edition, the principles remain relevant and it's a staple in dental pharmacology).

71. Yang F., Gao Y., Zhang L. Local anaesthesia for surgical extraction of mandibular third molars: a systematic review and network meta-analysis. Clin Oral Invest. 2020; 24:3781–3800. Doi: 10.1007/s00784-020-03490-3. [DOI] [PubMed] [Google Scholar].

72. Zoeller GN, Kadis B. The diabetic dental patient. Gen Dent. 1981; 29:58–61.