



Review article

What the dental practitioner needs to know about pharmaco-therapeutic modalities of COVID-19 treatment: A review



Najla Dar-Odeh ^{a,b}, Shadia Elsayed ^{a,c*}, Hamzah Babkair ^a,
Shaden Abu-Hammad ^d, Nebras Althagafi ^a, Rayan Bahabri ^a,
Yasmin Salah Eldeen ^e, Wejdan Aljohani ^a,
Osama Abu-Hammad ^{a,b}

^a College of Dentistry, Taibah University, Al Madinah, Al Munawara, Saudi Arabia

^b School of Dentistry, University of Jordan, Amman, Jordan

^c Faculty of Dental Medicine for Girls, Al-Azhar, University, Cairo, Egypt

^d Dental Department, Queen Alia Military Hospital, Amman, Jordan

^e Faculty of Pharmacy, Nahda University, Bani Sweif, Egypt

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Ibuprofen;
Paracetamol

Abstract *Background/purpose:* Several pharmacotherapeutic methods have been used for the treatment of COVID-19 with varying degrees of success. No definitive treatment or vaccine has been officially approved to-date. This review aimed to highlight COVID-19 pharmacotherapeutic agents that are relevant to dental practice in terms of their clinical indications in COVID-19 and dental practice, as well as their adverse effects as they impact the dental patient.

Material and methods: Systematic search was performed using the following keywords combinations: Pharmacotherapy AND COVID-19 OR Pharmacotherapy AND SARS-CoV-2 OR Treatment AND COVID-19. Studies were categorized according to the type of pharmacotherapy used. Pharmacotherapeutic agents were extracted and only those relevant to dental practice were included for review.

Results: For analysis, a total of 79 clinical trials research articles were included that included COVID-19 pharmacotherapeutic agents relevant to dental practice. Those were analgesics (paracetamol; non-steroidal anti-inflammatory agents); antibiotics (azithromycin, doxycycline, metronidazole); antivirals (penciclovir); and immunomodulatory agents (hydroxychloroquine, corticosteroids). While some COVID-19 drugs are less relevant to dental practice, as antivirals and hydroxychloroquine, their association with long-term adverse effects requires adequate knowledge among dental practitioners.

* Corresponding author. Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine for Girls, Al Azhar University, Cairo, Egypt.

E-mail addresses: shadiaelsayed@azhar.edu.eg, ssayed@taibahu.edu.sa (S. Elsayed).

Conclusion: Many of COVID-19 pharmacotherapeutic agents are used to treat oral diseases particularly orofacial pain and inflammatory conditions. Furthermore, some of these drugs may induce adverse effects that complicate dental treatment. Thorough knowledge of COVID-19 therapy and its dental implications is essential for dental practitioners, and is expected to contribute to a better understanding and effective utilization of these therapeutic agents.

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Introduction

The year 2019 was about to end when a disease outbreak was declared in Wuhan province of China. The disease was identified as coronavirus disease 2019 (COVID-19) that was caused by a novel coronavirus, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It was clear that severe disease outcomes and rapid global spread were two main characteristics of the disease; both indicating serious public health threat posed by the virus.¹ The disease is also characterized by symptoms influencing multiple systems in addition to primarily affecting the respiratory system, with approximately 20% of patients worldwide having an increased risk of severe COVID-19 disease, due to underlying comorbidities.²

It was also evident that SARS-CoV-2 differs from other coronaviruses that emerged in the past two decades and that have been linked to other significant, albeit less brutal, disease outbreaks with cases mainly detected in East Asia and the Middle East.³

Soon thereafter, clinicians, researchers and scientists intensified their efforts to design appropriate treatment plans for the COVID-19 patients to improve treatment outcomes and reduce mortality rate. Their target was two-fold: to identify appropriate treatment that could eliminate the virus efficiently, and to produce a successful and safe vaccine to prevent the infection. However, all treatments suggested so far were palliative in nature, and were not capable of eliminating the virus.⁴ Further, none of the clinical trials conducted so far have produced the eagerly anticipated vaccine.

Therefore, a number of treatment regimens have been employed in various countries until a suitable vaccine is produced. The treatment is symptomatic, and oxygen therapy represents the first step for management of respiratory impairment. In cases of respiratory failure refractory to oxygen therapy mechanical ventilation may be necessary, and intensive care is further needed to address complicated forms of the disease.^{5,6} Several pharmacotherapeutic agents are indicated for various symptoms of the disease. Corticosteroids, antiviral agents, immunomodulatory drugs, anticoagulants, and other agents are being used with varying degrees of success.

During the early days of the pandemic dental practitioners were requested to deal with only emergency dental cases so as to prevent transmission of infection, and to preserve the much needed personal protective equipment.⁷

Later, several studies emerged to report on the potential oral and cutaneous manifestations of the disease.^{8,9} Other reports highlighted the various drug regimens that are used for treatment of COVID-19, and that have implications in dental practice either by producing oral adverse effects, or by complicating the dental treatment with subsequent need for modification of the treatment plan.⁷ Dental practitioners are required as a part of the healthcare team to increase their awareness, and continuously update their knowledge of the different aspects of COVID-19 pandemic with particular focus on transmission, and treatment. Although dental practitioners are not involved directly in the primary healthcare of COVID-19 patients, they may encounter dental patients who are asymptomatic carriers of the disease. Nevertheless, dental practitioners are generally considered experts in cross-infection control, and their awareness of the cross-infection control practices including the use of PPE is undoubtedly high which helped in minimizing the infection rate among this particular category of healthcare professionals. On the other hand, there needs to be more focus on understanding COVID-19 therapy as it impacts dental practice especially the patient related factors. This would contribute to better appreciation and effective utilization of these therapeutic agents with an important aim to prevent various complications and adverse outcomes of treatment.

This review aimed to highlight COVID-19 pharmacotherapeutic agents that were also used in dental practice, to compare their uses in COVID-19 and oral diseases, and to describe their adverse effects as they impacted the dental patients.

Material and methods

This review was conducted in two steps. The first step was conducted to answer the following focused question: What are the pharmacotherapeutic agents that are used for the treatment of COVID-19 infection? This step was done following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for transparent reporting of systematic reviews and meta-analyses.¹⁰

Eligibility criteria

We used the following inclusion criteria for this review:

1. Papers published in English; 2. Papers published in the 2020/2021 volumes or the time frame (December 2019 to August 2020); 3. Studies performed on humans; 4. Clinical trials; 5. Case reports and series; 6. Clinical guidelines;
2. Patients: Adult patients infected with SARS-CoV-2
3. Intervention: Pharmacotherapy in COVID-19.

We used the following exclusion criteria:

1. Commentaries or correspondence letters,
2. Discussions

Search strategy

A thorough systematic search was performed in the following online databases: Science Direct, PubMed, Wiley, Springer and Trial Registries, using the following combinations of keywords: Pharmacotherapy AND COVID 19 OR Pharmacotherapy AND SARS-CoV-2 OR Treatment AND COVID-19.

Screening strategy and data extraction

Titles and abstracts of papers were independently screened by two reviewers (N. D-O. and S. E.). If keywords and other eligibility criteria were in titles and/or abstracts, the papers were selected for full text review. All articles were freely available in full text format. We finished gathering optimal searches by August 24, 2020. Full text was critically reviewed by the same authors and papers that fulfilled all of the selection criteria were processed for data extraction. The reference lists of all selected studies were hand searched for additional relevant articles. Any discrepancies

in the selection of articles were systematically addressed and discussed in a group before agreement was reached. This process is summarized in Fig. 1.

The second step was performed to answer the question: Which of the resulting list of drugs is used in dental practice as well? This step was performed by authors (S. A-H.) and (Y. S-E.). The two authors referred independently to Scottish Dental Clinical Effectiveness Programme, Drug Prescribing for Dentistry, Dental Clinical Guidance, third Edition, to retrieve the names of drugs common with the list prepared in the first step.

A narrative (descriptive) synthesis of data was employed in this review, due to heterogeneity of studies. Studies were categorized according to the type of pharmacotherapy used in these studies.

Results

The final selected compatible studies were 79 clinical trials and research articles.

Medications used for treatment of COVID included: Antiviral drugs, interferon, corticosteroids, immunoglobulin, herbal medicines, immunomodulators, interleukin-6 (IL-6) inhibitors convalescent plasma therapy, and adjunctive use of some antibiotics as azithromycin and tetracycline. The pharmacotherapeutic agents that were identified to have an impact in dental practice are described.

Pharmacotherapeutic agents in COVID-19 with implications in dental practice

The following drugs are common between COVID-19 and dentistry and could be identified as analgesics,

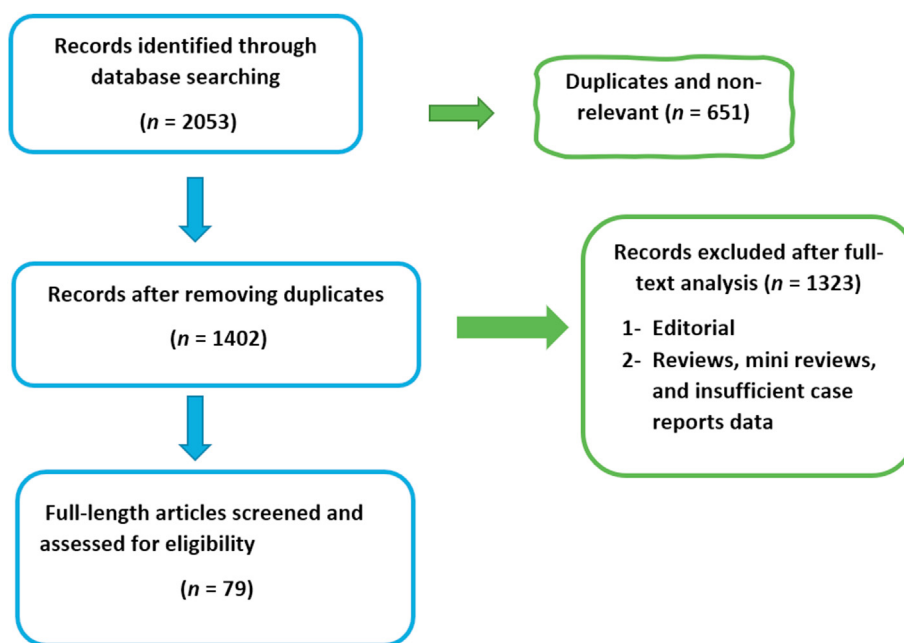


Figure 1 Study flowchart adopted and modified from the original PRISMA statement to identify eligible studies for pharmacotherapeutic agents for COVID-19.

| Analgesics | Immunomodulators/ Immunosuppressives | Antibiotics | Antivirals |
|--|---|--|---|
| <ul style="list-style-type: none"> • Paracetamol • Ibuprofen • Indomethacin • Naproxen | <ul style="list-style-type: none"> • Hydroxychloroquine • Dexamethasone | <ul style="list-style-type: none"> • Azithromycin • Doxycycline • Metronidazole | <ul style="list-style-type: none"> • Penciclovir |

Figure 2 List of drugs used in the treatment of COVID-19 that are relevant to dental practice.

immunomodulators/immunosuppressives, antibiotics, and antivirals. Detailed lists of these agents are presented in Fig. 2.

Discussion

Analgesics

Since the recognition of COVID-19 pandemic, provision of dental treatment in many countries was halted except for emergency cases. This measure was mainly followed to prevent transmission of the highly contagious virus particularly that some dental patients may be asymptomatic carriers of COVID-19. Supportive therapy consisting of pain relief and control of orofacial infections was the predominant form for dental management.

Non-opioid analgesics in the form of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are often considered the first-line analgesics for relief of acute dental pain, having an analgesic efficiency that should not be underestimated.¹¹ On the other hand, supportive analgesic/antipyretic therapy has been recommended for the treatment of mild to moderate cases of COVID-19 to control fever and pain with paracetamol being the first-line analgesic recommended in feverish COVID-19 patients.¹²

Paracetamol is particularly appreciated in dentistry being the most frequently prescribed analgesic in dental settings.^{13,14} Scientific discoveries leading to paracetamol have started in 1886, however, it was not until 1955 when it was officially introduced into the pharmacological market initially as a prescribed, and a year later as over-the-counter analgesic and antipyretic.¹⁵ Compared to NSAIDs, the mechanism of action of paracetamol is less clear, but is believed to involve a central analgesic effect that is mediated through activation of descending serotonergic pathways.¹⁶ Paracetamol is the analgesic drug of choice for mild dental pain, or when NSAIDs are contraindicated in patients with allergy or peptic ulcer. Due to its weak efficacy for moderate to severe dental pain, and its lack of anti-inflammatory properties, it is replaced by NSAIDs. However, NSAIDs as a group should not be considered equally potent in their analgesic and antipyretic properties. Whereas paracetamol is equally potent to aspirin,¹⁷ it is potentially inferior to ibuprofen. Some researchers believe that among NSAIDs there is no particular drug shown to be more effective or safer than the others,¹¹ however, it was demonstrated that the analgesic effect of ibuprofen is superior to aspirin in terms of potency and duration.¹⁸

The therapeutic and most of the side effects of NSAIDs are attributed to their ability to inhibit the cyclooxygenase

enzyme required for synthesis of prostaglandins implicated in pain, fever and inflammation.¹⁹ Ibuprofen, in particular, has elicited some controversy during early days of COVID-19 pandemic, mainly due to initial observations and doubts regarding its role in aggravating the clinical manifestations of the disease due to increasing the expression of angiotensin-converting enzyme-2 which is the binding receptor of the virus to the cells. It was also stated that use of an NSAID for sustained fever suppression may decrease the immune response and prolong viral shedding.²⁰ Consequently, a warning was issued against the use of ibuprofen in the treatment of COVID-19.²¹ Other researchers questioned this conception, since it is based on theoretical pharmacology rather than evidence-based clinical trials, and that deterioration of the clinical picture could be attributed to the severity of infection itself rather than the theoretical potentiating action of the drug.²² A recent systematic review confirmed the scarcity of clinical trials that investigated ibuprofen in treatment regimens of COVID-19, which has eventually contributed to the scarcity of conclusive data on its involvement in adverse outcomes of the disease.²³ Currently, the WHO recommends paracetamol as first-line treatment, while ibuprofen comes as second-line treatment.²⁴ Further, the National Institute for Health and Care Excellence (NICE) confirm that there is no evidence from published scientific studies to determine whether acute use of NSAIDs is related to increased risk of developing COVID-19 or increased risk of a more severe illness.²⁵

In dentistry, paracetamol can be used as a first-line analgesic, however, if it is not effective, ibuprofen or other NSAIDs are used unless there is a contraindication. Selecting an analgesic for dental patients should address the fact that most cases of postoperative dental pain have an inflammatory component for which NSAIDs are considered the most appropriate first-line agents. Should a patient present a contraindication to NSAIDs, paracetamol is a suitable alternative. Generally, non-opioid analgesics exhibit a ceiling to their analgesic response, and optimal doses should be established before it is assumed that the drug has failed, wherein optimal doses are in the range of 400–800 mg for ibuprofen, and 1000 mg for paracetamol.²⁶ The combination of an NSAID with paracetamol is characteristically notable in providing greater analgesic efficacy than does either agent alone, because they have different sites for their analgesic action.²⁷

Within the context of NSAIDs, the potential role of naproxen and indomethacin as proper substitutes for ibuprofen to reduce fever in viral infections was also highlighted based on their antiviral properties as inhibitors of viral replication.²⁸ The antiviral properties of

indomethacin is significantly being reported in relation to SARS coronavirus infection.²⁹ In dental patients, indomethacin is characterized by substantive anti-inflammatory effect which makes it suitable for muscle and joint pain,³⁰ for example in patients with temporomandibular joint disorders. On the other hand, naproxen is effective for moderate to severe acute postoperative dental pain.³¹

Implications for dentists regarding the above mentioned analgesics necessitates a continuous update as more information emerges on the topic, and entails weighing benefits against harm when prescribing analgesics for patients with dental pain. Dentists should also be aware of the potential side effects of these drugs whenever operative dental treatment had to be postponed and these drugs had to be used to control dental symptoms. The safety profile for paracetamol particularly for liver and kidney patients adds to its favorable properties, however, its potential to produce hepatotoxicity should not be overlooked.

Several side effects may be associated with NSAIDs due to their ability to inhibit the production of prostaglandins, which perform useful physiological functions, such as stimulating the production of a mucous lining that protects the stomach and small intestine. Hence, a very common side effect of NSAIDs is gastrointestinal erosions and ulcers.¹¹ Another side effect is the antiplatelet action since inhibition of cyclooxygenases in platelets reduces the synthesis of thromboxane A₂, which is important for platelet aggregation. This effect is most obvious in aspirin which is the only NSAID that has shown effectiveness in preventing thrombotic events due to the irreversible antiplatelet action, lasting the life span of the platelet (10–14 days). On the contrary, other NSAIDs bind weakly and reversibly to platelet cyclooxygenases, which results in loss of their mild antiplatelet influence after drug elimination, and hence platelet function returns to normal within 24 h after terminating regular ibuprofen use in healthy individuals.³² In the clinical setting NSAIDs other than aspirin do not produce significant bleeding following minor surgical procedures, however, they should be avoided, and replaced by other analgesic alternatives in patients who suffer bleeding disorders including anticoagulant use such as warfarin and powerful antiplatelet drugs.³²

Inhibition of cyclooxygenase by NSAIDs results in another side effect due to shifting of the arachidonic pathway towards leukotriene synthesis which mediates bronchospasm and anaphylaxis.³³ Based on the above mentioned side effects, NSAIDs are contraindicated in patients who have a kidney disease, gastrointestinal ulcers, bleeding susceptibility, or allergy to NSAIDs. NSAIDs should also be avoided throughout pregnancy, particularly during the third trimester, because of the role of prostaglandins in maintaining ductus arteriosus during fetal development.¹¹ Further, ibuprofen has been found to be the only NSAID that interacts with aspirin by competitively inhibiting its antiplatelet action,³⁴ however, the clinical implications seem to be negligible.³⁵

Antivirals

Currently a number of antivirals are being investigated for COVID-19 treatment including those inhibiting viral RNA polymerase/RNA synthesis (remdesivir, favipiravir), and

those inhibiting viral protein synthesis (lopinavir, ritonavir).³⁶ These antivirals are generally not used in dental practice. Oral viral infections are primarily treated by acyclovir, famciclovir, valaciclovir, and penciclovir.³⁷ Among these only penciclovir was mentioned as a potential antiviral agent in COVID-19 treatment.³⁸ Penciclovir is used for various herpes virus infections and it acts by inhibiting the RNA-dependent-RNA-polymerase.³⁹ The use of penciclovir in treatment of COVID-19 may carry a potential implication because this drug was shown to have the ability to bind to SARS-CoV-2 and establish various interactions.^{39,40}

In the dental field it is used to treat recurrent episodes of herpes labialis (HSL) caused by herpes simplex virus (HSV).⁴¹ It was approved for topical application for prevention or suppression of recurrent HSL in patients with normal immune system,⁴² and its half-life in cells infected with HSV is reportedly 10 to 20 times longer than that of acyclovir.⁴³ It is associated with low cytotoxicity and better viral DNA selectivity than host DNA, displaying more favorable results than acyclovir due to the longer intracellular half-life in HSV-infected cells.⁴³ It is especially recommended for topical application in children and adolescents, due to its safety.⁴²

Antibiotics

Azithromycin had been used in combination with hydroxychloroquine in the treatment of COVID-19, however, recent systematic reviews have shown that this combination is significantly associated with increased mortality.⁴⁴

Azithromycin is a macrolide broad spectrum antibiotic that has anti-inflammatory effects. It is commonly used for bacterial respiratory infections, and it could have antiviral activity against some RNA viruses.⁴⁵ Although its efficacy against SARS-CoV-2 is not yet fully established, it is currently a heavily prescribed outpatient therapy for COVID-19 patients, mainly due to its ability to combat any superimposed bacterial infections in infected patients who are medically compromised. The drug is described as potentially effective in combating SARS-CoV-2 due to its antiviral and immunomodulatory effects.⁴⁶

It is particularly important in dental practice. It is a recommended antibiotic in the empiric treatment of odontogenic infections mainly in penicillin-allergic patients.⁴⁷ It is one of the top five most frequently prescribed antibiotics by dentists in the USA, Brazil, and Belgium.^{48–50} The pharmacokinetic profile of azithromycin is characterized by good oral bioavailability, excellent tissue penetration and persistence, and long elimination half-lives, which allow for once-daily or twice-daily dosing especially in children and patients who lack compliance and for whom a once daily oral dosage is recommended.⁵¹ It is effective in the management of respiratory infections in young children, and in community-acquired pneumonia in hospitalized patients.⁵² The antiviral activity of azithromycin against Zika and Ebola viruses has been reported by *in vitro* studies.^{53–55} This is supplemented by its ability to prevent severe respiratory tract infections when administered to patients suffering viral infection.⁵² However, the efficacy of azithromycin in combination with hydroxychloroquine in

the treatment of COVID-19 patients has not been confirmed yet,^{56,57} and more studies are needed to further investigate its clinical effects.

As dental treatment relies more on the provision of emergency treatment, there could be an increase in antibiotic prescriptions for severe orofacial infections. Although amoxicillin and amoxicillin/clavulanic acid combination are the most commonly used antibiotics in dental settings,⁵⁸ many cases may require replacement with another equally effective antibiotic. Some patients are allergic to penicillins, and some cannot tolerate amoxicillin, or more frequently amoxicillin/clavulanic acid due to their potential in eliciting gastrointestinal disturbances of nausea, vomiting and diarrhea. In such cases, azithromycin may seem to be the ideal alternative. Although this antibiotic is considered relatively safe in adults, children, and pregnant women,⁵⁹ a number of side effects have been identified especially with intravenous administration, including gastrointestinal disturbances, ototoxicity, pain and inflammation of the injection site.⁶⁰ Its use may also be associated with development of bacterial resistance,⁶¹ and proarrhythmic events⁶² attributed to QT prolongation (summation of action potential of ventricular myocytes), which could lead to a life-threatening arrhythmia. It should be noted, though, that the latter side effect is usually encountered in patients with other confounders such as old age, heart disease, and concomitant use of other QT prolonging drugs.⁶³

The use of azithromycin in dentistry should be monitored, especially that its use in dental practice as a favorable antibiotic is reported in countries with a high toll of COVID 19 infections. Alternative antibiotics such as amoxicillin or clindamycin (in penicillin-allergic patients) should be considered for indicated cases, provided that no contraindications are present.

An important example is patients who has a history of pseudomembranous colitis or ulcerative colitis, and hence cannot use clindamycin.⁶⁴ Dentists and physicians working in the treatment of emergency dental cases should be prudent in prescribing antibiotics only for indicated cases and should consider the use of analgesics as the appropriate modality in controlling dental pain. Avoiding the development of side effects and antibiotic resistance should be considered among the goals of treatment.

Doxycycline is a tetracycline antibiotic that is used to treat several types of bacterial infections, such as respiratory infections.⁴¹ Some formulations of doxycycline are used for the prevention of malaria, the treatment of anthrax, and viral infections caused by Ebola, Zika, and HIV.^{65,66} Due to risks arising from combination of Azithromycin and Hydroxychloroquine,^{67,68} some suggest the use of doxycycline in combination with Hydroxychloroquine or alone because of its known antiviral activity against some RNA viruses and also because of its anti-inflammatory activity which reduces lung damage.^{69,70} Its main indication in dentistry is for the management of periodontal diseases.^{71,72} Doxycycline can only be used in situations of serious or life-threatening conditions for children younger than 8 years and only when necessary during pregnancy, because it can cause permanent yellowish or gray discoloration of the teeth in children.⁷³

Metronidazole is another antibiotic mentioned for its potential in therapy of COVID-19.⁷⁴ Few case reports showed that its use as part of treatment regimens in COVID-19 patients with gastrointestinal symptoms has been associated with a successful outcome.^{75,76} It was originally developed as an anti-parasitic drug, which has gained popularity later on as an antibiotic.⁷⁷ In the dental settings it is mainly used for its activity against anaerobic bacteria, which makes it the drug of choice for certain oral infections such as pericoronitis and necrotizing ulcerative gingivitis.⁷⁸ Necrotizing ulcerative gingivitis is not a common type of infection; however, pericoronitis is common and it is more prevalent in young patients due to its association with partially erupted permanent teeth particularly second and third molars.⁷⁹ Metronidazole was cited among the most popular antibiotics prescribed by dentists in several countries.⁸⁰ It is safe, and tolerable with only few side effects reported such as headache and bitter or metallic taste.⁸¹ However, it is considered a high risk antibiotic for patients on warfarin due to the increased susceptibility to bleeding. Recently, a group of researchers highlighted the potential use of this drug in the treatment of COVID-19, due to its characteristic immune-pharmacological behavior that influences several essential biological processes.⁷⁴ Based on the reported immunological manifestations of COVID-19 infection, its use can be considered as a potential candidate to counteract majority of the immune-pathological features of the disease. Metronidazole was shown to induce immunosuppression by down-regulating cytokines, reducing the number of neutrophils and macrophages, reducing antibodies and influencing lymphocyte proliferation.⁸²

Immunomodulators and immunosuppressants

Chloroquine is an antiparasitic drug that is primarily used as antimalarial drug since the 1930s.

It has recently attracted a lot of attention due to its incorporation in the treatment regimens of COVID-19. The drug shows antiviral activity in vitro against coronaviruses, and specifically, SARS-CoV-2.⁸³ On the other hand, its use in the treatment of some oral diseases has been recognized for a long time. It notably possess efficacy towards autoimmune diseases and has been implemented since the 1980s in the treatment of systemic lupus erythematosus (SLE), a connective tissue disease which could be manifested intraorally as ulcerative lesions. It was suggested for the treatment of primary Sjögren's syndrome,⁸⁴ and was recommended for the treatment of chronic ulcerative stomatitis.⁸⁵ Interestingly, it was also suggested in the treatment of oral squamous cell carcinoma due to its role in cell protection by eliminating excessive proteins and injured/aged organelles in the microenvironment of tumors with subsequent acceleration of tumor cell death.⁸⁶

The antiviral activity of the drug has long been recognized. In the current epidemic of COVID-19 many countries announced its use in their trials to eradicate this disease. Scientists stated that the drug, which has established antiviral activity over the past 40 years, inhibited SARS-CoV-2 viral replication in vitro and human clinical application indicated apparent efficacy.⁸³

Table 1 Drugs common between COVID-19 and dental practice, and their relevant applications.

| Drug | Applications in COVID-19 Therapy | Applications in Dental Practice |
|--------------------|--|--|
| Paracetamol | First-line analgesic and antipyretic in feverish COVID-19 patients | First-line analgesic and antipyretic for mild to moderate dental pain |
| Ibuprofen | Second-line analgesic and antipyretic in feverish COVID-19 patients | Preferred analgesic in dental pain/postoperative dental pain with inflammatory component |
| Indomethacin | A potential analgesic substitute to ibuprofen | Suitable for muscle and joint pain |
| Naproxen | A potential analgesic substitute to ibuprofen | Effective in moderate to severe acute postoperative dental pain |
| Penciclovir | Antiviral, currently under investigation for treatment of COVID-19 | Recurrent episodes of herpes labialis |
| Azithromycin | Antibiotic, used alone or in combination with HCQ for treatment of COVID-19 | Empiric treatment of odontogenic infections mainly in penicillin-allergic patients |
| Doxycycline | Antibiotic, currently under investigation Suggested for use alone or in combination with HCQ | Management of periodontal diseases |
| Metronidazole | Antibiotic, used as part of treatment regimens in COVID-19 patients with gastrointestinal symptoms | Oral infections caused by anaerobic bacteria namely pericoronitis and acute ulcerative gingivitis/periodontitis |
| Dexamethasone | Corticosteroid, short-term treatment course | Prophylactic uses in oral surgery Topical and systemic application in patients with autoimmune diseases with oral manifestations |
| Hydroxychloroquine | Immunomodulator, prophylaxis to | Systemic diseases with oral |

Table 1 (continued)

| Drug | Applications in COVID-19 Therapy | Applications in Dental Practice |
|------|--|---|
| | prevent SARS-CoV-2 infection Used in combination with some antibiotics/antivirals as treatment | manifestations like: Sjogren's syndrome, SLE, chronic ulcerative stomatitis May have potential in treatment of OSCC |

COVID-19: coronavirus disease 2019; HCQ: Hydroxychloroquine; SLE: Systemic lupus erythematosus; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; OSCC: Oral squamous cell carcinoma.

Hydroxychloroquine is a derivative of chloroquine with significantly higher solubility, and lower toxicity, therefore fewer side effects are anticipated.⁸⁷ Pharmacological modelling based on observed drug concentrations and in vitro drug testing suggest that prophylaxis with hydroxychloroquine at approved doses could prevent SARS-CoV-2 infection and ameliorate viral shedding.⁸⁸ The combination of antiviral drugs, such as remdesivir and chloroquine, has been considered highly effective in the control of infection in vitro especially that it has a high safety profile.⁸⁹ However, clinical trials conducted so far are limited in sample size and their lack of randomization cast doubt on reported outcomes.

It is still unknown how this drug exerts its anti-viral activity, but some researchers believe that it can maintain the alkaline media in endosomes and hence prevent viral transfer from cell membrane to cytoplasm thus limiting viral replication.⁹⁰ The drug activity against autoimmune diseases, is probably due to its action in preventing production or release of IL-6 and TNF- α , and its inhibitory action on autophagy.⁹¹ This activity of hydroxychloroquine has been demonstrated in vitro against influenza and coronaviruses, however, clinically in humans and on animals the therapeutic activity was less successful. The drug is generally safe, with poisoning being associated with the dangerous side-effects of retinopathy and immunosuppression.⁹² During the current pandemic of COVID-19, and due to increased demand, severe shortages of the drug were reported and adversely affecting the regular autoimmune disease patients with countries banning its export. Dentists have to be aware that shortages of chloroquine may influence their patients who are dependent on this drug especially SLE and Sjogren's syndrome patients who have oral manifestations. They also should be aware of the possible oral complications caused by the drug, namely melanotic pigmentation of the oral mucosa and lichenoid reactions.^{93,94}

Corticosteroids are steroid hormones that are produced in the adrenal cortex. Their synthetic analogues are used in dentistry in a wide range of prophylactic and therapeutic applications. In the field of oral surgery they are the preferred pharmaceutical agents for decreasing the

severity of the natural inflammatory response after surgical extractions of wisdom teeth to reduce postoperative edema and swelling.⁹⁵ Several oral diseases that affect the oral mucosa, and that have an immune-based etiology are managed by corticosteroids. On the other hand, many dental patients are on corticosteroids either as a replacement therapy or as treatment for autoimmune diseases. Glucocorticoids are actually the first line therapy for autoimmune diseases⁹⁶ among which are oral vesiculobullous diseases such as pemphigus vulgaris and mucous membrane pemphigoid.

There is a conflicting evidence for the beneficial effects of corticosteroids in the treatment of COVID-19 patients.⁹⁷ The rationale behind using corticosteroids here is the reduction of inflammation and damage associated with the immune reaction to viral infection,⁹⁷ however, their use is associated with numerous complications that may cause deterioration of patients' health condition.

One particular corticosteroid that was used in the treatment of COVID-19 is dexamethasone. Dexamethasone is one of the top three administered types of corticosteroids after surgical removal of impacted wisdom teeth.⁹⁵ It has negligible mineralocorticoid effects and it suppresses endogenous cortisone. It has been used in dental patients in various topical and systemic preparations to control oral manifestations of ulcerative and vesiculobullous diseases, many of which are autoimmune in etiology. Many of these diseases are chronic in nature which necessitates the chronic use of corticosteroids with the potential for developing complications. Within the context of COVID-19 therapy a clinical trial among COVID-19 patients used 6 mg dexamethasone daily for up to 10 days with encouraging results as the group of patients who received dexamethasone had a lower death rate.⁹⁸ However, this dose is equivalent to 40 mg prednisolone which is considered a high dose.⁹⁶ Although the duration of dexamethasone use in COVID-19 patients is considered short, it should be emphasized that short term use of corticosteroids could be associated with complications. As low as 10 mg prednisolone was noticeably associated with effects on peripheral white blood cell lines within the first day of drug intake.⁹⁹ Other adverse events that have been associated with short term use of corticosteroids include fracture, sepsis and thromboembolism.⁹⁹ A study that investigated short term use of dexamethasone (6 mg daily for 5 days), found that it acutely decreased resting heart rate, and increased HDL-cholesterol.¹⁰⁰ Furthermore, dexamethasone in particular, has a long half-life which means that complications can start after discontinuation of therapy.⁹⁶

Therefore, dentists are required to have a reasonable knowledge on corticosteroids therapeutic indications and potential complications. They should be vigilant regarding complications caused by corticosteroids like dexamethasone, based on their applications in the treatment of COVID-19 patients. [Table 1](#), summarizes drugs common between COVID-19 and dental practice, and their relevant applications.

Conclusions

Pharmacotherapy of COVID-19 is likely to impact dental practice because many of these pharmacotherapeutic

agents are widely used for the dental patient particularly analgesics and antibiotics. Non-opioid analgesics namely paracetamol and NSAIDs are recommended in both COVID-19 and dental diseases for their antipyretic and analgesic effects. Azithromycin is also a preferred antibiotic in the dental setting for certain patient categories. Dental practitioners should bear in mind that corticosteroids may be considered in some treatment protocols in COVID-19 patients who could subsequently develop side effects. Although some COVID-19 drugs such as antivirals and hydroxychloroquine are less relevant to dental practice, their association with long term adverse effects necessitates sufficient awareness about them among dental practitioners. Finally, selecting the appropriate drug therapy for the dental patient involves not only the therapeutic indications, but also the potential adverse effects and the individual systemic condition of the patient.

Declaration of Competing Interest

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