Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Hydroxychloroquine and the treatment of Sjogren syndrome, chronic ulcerative stomatitis, and oral lichen planus in the age of COVID-19

Heba Hussein, BDS, PhD,[a] and Ronald Brown, DDS, MS[b,c]

The Food and Drug Administration has recently approved the off-label use of hydroxychloroquine (HCQ) for the treatment of coronavirus disease 2019 (COVID-19) infections. However, a recent study not only failed to demonstrate HCQ efficacy but also documented a serious side effect of COVID-19 therapy with HCQ: QT prolongation and secondary arrhythmia. HCQ has been used as an off-label drug and deemed safe and effective for the treatment of oral lesions, such as Sjogren syndrome (SS), chronic ulcerative stomatitis (CUS), and oral lichen planus (OLP). Because HCQ may be appropriately used for the off-label treatment of SS, CUS, and OLP, relevant safety concerns regarding HCQ therapy with regard to dosage, drug-to-drug interactions, and QT prolongation and secondary arrhythmia are discussed here. Because of the possibility of decreased pharmacy supplies of HCQ, replacement drugs with respect to patients with SS, CUS, and OLP being successfully treated with HCQ are also discussed. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:e9–e13)

Hydroxychloroquine (HCQ) is a drug that has been approved by the U.S. Food and Drug Administration (FDA) for the prevention and treatment of malaria for many years.[1] HCQ has been used as an off-label drug and deemed safe and effective for oral conditions, such as Sjogren syndrome (SS), chronic ulcerative stomatitis (CUS), and oral lichen planus (OLP).[2-8] Because of the belief that HCQ could be a viable therapeutic agent to treat coronavirus disease 2019 (COVID-19) infection, the FDA recently granted approval of HCQ for the treatment of COVID-19 infection.[9] However, the very recent publication of a study by Mehra et al.[10] has changed our understanding of the efficacy and safety of HCQ therapy for COVID-19 infection, particularly with respect to increased mortality. Mehra et al.[10] reported the findings of a retrospective study of 96,032 hospitalized patients with COVID-19 infection (mean age 53.8 years; 46.3% women). Mehra et al. reported that they were not able to determine any benefit of HCQ or chloroquine therapy, either alone or combined with azithromycin. Furthermore, they noted that the drug protocols for COVID-19 treatment were associated with decreased survival and an increased frequency of ventricular arrhythmias. With the understanding that HCQ therapy has a dose-related risk of lethal arrhythmia related to QT prolongation, dentists, particularly oral medicine specialists, should be concerned about the potential interaction of HCQ with drugs that are known to increase QT prolongation.[2,11-13] Tisdale et al.[14] reported that in 2013, as many as 28% of patients admitted to hospital cardiac care units presented with QT cardiac (QTc) interval prolongation. However, despite the above-mentioned concerns, some countries continue to use HCQ therapy for COVID-19 infections.[15]

It has been noted that HCQ therapy is associated with sudden death as a rare complication resulting from a particular cardiac arrhythmia related to QT prolongation.[10-13] This side effect appears to be dose related. Because there are other drugs that are also known to cause QT prolongation, it is important for both dentists and physicians prescribing HCQ to be aware of potential additive drug-to-drug interactions.[2] Torsade de pointes (TdP) arrhythmia is associated with prolonged QT duration secondary to high-dose HCQ, and proarrhythmic toxicity appears to be dose related.[9-11] In 2006, Chen et al.[11] reported a case of a 67-year-old female patient with acquired prolonged QT duration and refractory arrhythmia. The patient was receiving HCQ for systemic lupus erythematosus and developed TdP arrhythmia. After discontinuing HCQ, the QT interval became shorter, and the patient recovered.

In 2016, O'Laughlin et al.[13] reported a case of HCQ-related QT interval prolongation and secondary TdP arrhythmia in a patient with renal failure. They concluded that HCQ-related TdP arrhythmia is relatively rare and may be related to higher HCQ dosage

Statement of Clinical Relevance

This review provides relevant information regarding replacement medications for hydroxychloroquine in the treatment of oral autoimmune conditions and the potential drug interactions in patients currently taking hydroxychloroquine.

[a]Department of Oral Medicine, Diagnosis, and Periodontology, Faculty of Dentistry, Cairo University, Cairo.
[b]Department of Oral Diagnosis & Radiology, Howard University College of Dentistry, Washington, DC.
[c]Department of Otolaryngology, Georgetown University Medical Center, Washington, DC.
Received for publication Apr 30, 2020; returned for revision Jun 1, 2020; accepted for publication Jun 10, 2020.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2020.06.011

regimens. In 2018, McGhie et al.[16] reported potential conduction abnormalities on electrocardiography secondary to antimalarial drug therapy. With respect to the treatment of 453 patients, they reported approximately 16% with conduction disorders and concluded that an association existed between cumulative antimalarial dose above a particular median dose and structural electrocardiography abnormalities. In contrast, Sharma et al.[17] evaluated 1266 patients with rheumatoid arthritis and reported that of the 547 patients treated with HCQ and 719 patients treated without HCQ, HCQ therapy in patients with rheumatoid arthritis resulted in a 72% decrease in the risk of cardiovascular disease incidents.

Long QT syndrome (LQTS) is a unique cardiovascular condition that results in dysfunctional cardiac ion channels. Because of a long repolarization phase of the ventricle, the QT interval increases. Increased QT duration leads to progression to TdP, ventricular fibrillation, and sudden death. Precipitating factors with respect to LQTS include emotional stress, load noise, physical activity, and certain medications that influence QT duration.[18]

There are several questions related to HCQ and oral medicine: (1) What are the secondary drugs to consider as replacement drugs when patients with SS, CUS, or OLP who are successfully managed with HCQ are unable to fill their HCQ prescriptions because of low pharmacy supplies? (2) What are the potential drug interactions between HCQ and dentist- and physician-prescribed systemic drugs?

REPLACEMENT DRUGS

Replacement therapeutic strategies include immunosuppressant and steroid-sparing drug therapies. With respect to drug therapy for SS, replacement drugs for HCQ would be limited to systemic drugs. Systemic steroid therapeutic drugs include prednisone, prednisolone, mycophenolate mofetil, and dexamethasone. Azathioprine can be used as an immuno suppressant steroid-sparing therapeutic. Topical steroid therapeutic drugs include fluocinonide, triamcinolone, clobetasol, betamethasone, and rinses, such as dexamethasone and cyclosporine rinses. Topical immunosuppressant therapeutic drugs include tacrolimus and pimecrolimus. Injectable steroid therapeutic drugs include triamcinolone and betamethasone. Other alternative therapeutics include topical retinoid therapy and low-level laser therapy.[19-27]

FACTORS ASSOCIATED WITH INCREASED RISK OF DRUG-INDUCED EXCESSIVE QT PROLONGATION AND/OR TDP

The major issue with respect to dental patients taking HCQ is drug-to-drug interactions with concerns regarding arrhythmogenic potential, specifically the TdP arrhythmia, which is potentially lethal. In 1997, the drug terfenadine (a histamine 1−blocking nonsedating antihistamine) was taken off the market because of fatal arrhythmias caused when used in combination with other drugs and specifically with some drugs, such as ketoconazole and erythromycin, used in dental therapy. These dental drugs were thought to mainly cause competitive inhibition drug-to-drug interaction to slow down the 3 A4 cytochrome P450 elimination pathway, resulting in increased serum values of the problematic drug terfenadine.[28-30]

In 2009 and 2016, Cubeddu[31,32] reviewed the mechanisms and clinical significance of drug-induced QT abnormalities with lethal arrhythmias. His report included certain drug categories, such as antibiotics, antiprotozoals, antifungals, antineoplastics, prokinetics, 5 HT3-receptor antagonists, antihistamines, 5-HT1 D agonists, antipsychotics, antidepressants, opioids, and drugs with cardiac and vascular effects. Of these categories, antibiotics, antifungals, antidepressants, and opioids are used in dentistry. Specific drugs prescribed by dentists that have documented drug-induced QT prolongation potential include erythromycin, clarithromycin, azithromycin,[33-35] ketoconazole, itraconazole, fluconazole, miconazole, posaconazole, voriconazole, desipramine, imipramine, doxepin, and methadone.[34]

Azithromycin is a unique macrolide antibiotic in that it does not have the problematic elimination pathway used by other macrolides, resulting in its improved safety.[36] However, azithromycin has been demonstrated to be proarrhythmic similar to other macrolides.[33-35] In a retrospective study, Choi et al.[34] reported that azithromycin use increased the risk of QT prolongation, particularly in older adults.

Fiets et al.[37] evaluated QT prolongation with erythromycin use and determined that erythromycin at a dose of 200 mg twice daily significantly prolonged QT duration. Ebert et al.[38] Drici et al.,[39] and Arya[40] reported that erythromycin and clarithromycin created a greater risk with respect to LQTS in women.

Erythromycin, clarithromycin, ketoconazole, miconazole, and itraconazole are all known to interfere by competitive inhibition of the cytochrome P450−3 A4 elimination pathway. These drugs when prescribed concomitantly with drugs that prolong the QT duration and share the same elimination pathway would tend to increase serum values of other drugs that prolong QT duration and, thus, increase the likelihood of TdP arrhythmia and death.[37-40]

Tett et al.[41] reported that the elimination half-life of HCQ was approximately 44 days after intravenous administration. McChesney et al.[42] reported that the elimination/detoxification pathway for HCQ occurred after degradation of HCQ into a secondary amine—either desethyl chloroquine or desethyl hydroxychloroquine—or into a primary amine (4'-aldehyde), and, last, the

4'-carboxy derivative. It is noted HCQ is not eliminated through the cytochrome P450−3 A4 elimination pathway.[41,42]

The report by Karp and Moss[43] regarding dental treatment of patients with long QT syndrome did not mention HCQ. Furthermore, HCQ would not be recommended for patients with an existing diagnosis of prolonged QT duration, those with a history of syncope and/or seizures, or those with a family history of long QT syndrome, syncope, seizures, or sudden cardiac death. Also, Karp and Moss[43] listed a number of other drugs, which they noted are drugs used in dentistry and which are associated with inducing QT prolongation; these drugs included several not noted by Cubeddu, such as dolasetron, droperidol, chloral hydrate, haloperidol, albuterol, amiodarone, epinephrine, ephedrine, metaproterenol, and cocaine. Chloral hydrate is not currently used, and use of epinephrine in local anesthesia in patients with prolonged QT duration certainly is a matter of debate. The other drugs are not currently used in dentistry. Karp and Moss[43] referenced Ackerman et al.,[44] who evaluated patients who received epinephrine infusions, rather than intramuscular injections, which have considerably different kinetics. Furthermore, using 2 to 3 cartridges of epinephrine local anesthetic formulations appears to be safe and effective for patients with medically complex conditions, including cardiac disease. Physicians use an epinephrine concentration of 1:1000 and are unfamiliar with the 1:100,000 concentration typically used in dentistry. Epinephrine definitely has β_1 effects that result in increased heart rate; however, it also is important with respect to pain control, and lack of pain control tends to result in increased endogenous production of norepinephrine, which is more problematic with respect to both heart rate and blood pressure.[28,45-48] In 2006, Karp and Moss[43] defended their recommendations regarding epinephrine risks with respect to LQTS by stating, "Epinephrine-containing local anesthetics have never been shown to be safe and effective for patients with LQTS." However, in 2007, Wynn[49] reported that articaine 4% with 1:200,000 epinephrine was deemed safe and effective in dental patients with LQTS.

In 2009, Rochford and Seldin[18] reviewed the management of a dental patient with LQTS. They recommended consulting with the patient's physician and making every effort to reduce stress and anxiety. Those authors suggested that atropine should be avoided in dental patients with LQTS. They also discouraged the use of epinephrine within local anesthetic formulations for patients with LQTS (although there is disagreement on this issue).[45-49] With respect to the treatment for TdP arrhythmia, Rochford and Seldin[18] advocated immediate intravenous bolus of magnesium sulfate at 30 mg/kg over a 2- to 3-minute period, followed by an infusion of 2 to 4 mg of magnesium sulfate per minute. They concluded that treating dental patients with LQTS requires understanding of the seriousness of LQTS and the elimination of precipitating factors that could elicit TdP arrhythmia. They suggested that dental treatment for these patients should be provided in a hospital setting.

Snitker et al.[50] defined QTc (QT interval corrected for heart rate) as prolonged when it is 450 ms or greater. They evaluated a cohort of 3252 patients with chronic renal insufficiency with at least 1 assessment with electrocardiography. They evaluated QT-prolonging medications used in 100 or greater visits (n = 16,451 visits) along with diuretics and proton pump inhibitors for QT interval prolongation. Six drugs—fluoxetine, citalopram, escitalopram, venlafaxine, hydroxyzine, and amiodarone—were shown to be associated with QTc prolongation as a continuous variable. The same 6 drugs were associated with an increased odds ratio (QTc $\geq$ 450 ms) except venlafaxine. Nortriptyline was associated with QTc shortening rather than prolongation but was not associated with a lower odds ratio of QTc greater or equal to 450 milliseconds. They evaluated selective serotonin reuptake inhibitors, such as sertraline, fluoxetine, citalopram, paroxetine, and escitalopram; other antidepressants, such as amitriptyline, trazodone, venlafaxine, nortriptyline, and mirtazapine; and central nervous system drugs, such as hydroxyzine and quetiapine. None of the proton pump inhibitors demonstrated QT prolongation, and other drugs, such as diphenhydramine, famotidine, metoclopramide, quinine, cilostazol, and tolterodine, also were evaluated as negative for QT prolongation.

Table I illustrates potential drug-to-drug interactions between HCQ and drugs used by oral medicine specialists in the treatment of oral conditions. Table II provides a list of physician-prescribed drugs that are noted to increase the risk of TdP arrhythmia. To our knowledge, there are no known incidences of HCQ-induced arrhythmias with respect to treatments for oral autoimmune conditions. With respect to low-dose HCQ prophylactic

Table I. Drug classes used in dentistry with torsade de pointes (TdP) potential

Drug class	*Drugs names*
Antibiotics (macrolides)	Erythromycin, clarithromycin, azithromycin
Antifungals	Ketoconazole, itraconazole, fluconazole, miconazole, posaconazole, voriconazole
Antidepressants (tricyclic antidepressants)	Desipramine, imipramine, doxepin
Opioids	Methadone

Adapted from Cubeddu.[31,32]

Table II. QT prolongation drugs most used by physicians

Drug	*Drug class*
Albuterol	Inhaled β_2 agonist
Amiodarone	Antiarrhythmic
Azithromycin	Antibiotic
Citalopram	SSRI
Clarithromycin	Antibiotic
Cocaine	CNS stimulant; local anesthetic
Desipramine	TCA
Dolasetron	Antiemetic
Doxepin	Antidepressant
Droperidol	Antiemetic/Tranquilizer
Ephedrine	Nonselective adrenergic agonist
Erythromycin	Antibiotic
Escitalopram	SSRI
Fluconazole	Antifungal
Fluoxetine	SSRI
Haloperidol	Antipsychotic
Hydroxyzine	Histamine-1 (H_1) antagonist
Imipramine	TCA
Itraconazole	Antifungal
Ketoconazole	Antifungal
Metaproterenol	Bronchodilator
Methadone	Opioid
Miconazole	Antifungal
Posaconazole	Antifungal
Venlafaxine	SSNRI
Voriconazole	Antifungal

CNS, central nervous system; *SSNRI,* selective serotonin and norepinephrine reuptake inhibitor; *SSRI,* selective serotonin reuptake inhibitor; *TCA,* tricyclic antidepressant.

therapy for malaria and HCQ therapy for rheumatoid conditions, HCQ-induced arrhythmia as a side effect is a rare event.[51] We understand that as a result of the use of relatively low-dosage regimens in the treatment of oral autoimmune conditions, secondary HCQ-related arrhythmia is avoided. However, clinicians need to perform a risk assessment regarding such potential QT prolongation with respect to HCQ administration and additive drug-to-drug interactions. Also, it is necessary for clinicians employing HCQ therapy to alert patients regarding conjunctivitis as a potential side effect.[52,53] Communication with patients' physicians is particularly helpful with regard to changes in prescription medications and ocular concerns.[54]

CONCLUSIONS

We noted that with the present decrease in the availability of HCQ, it may be necessary for treating dentists to consider alternative medications to replace this agent. HCQ is a relatively safe drug when used at appropriate therapeutic dosage levels for malaria prophylaxis and in the treatment rheumatologic conditions. However, at increased dosage levels and with drug-to-drug interactions with other drugs known to cause increased QT prolongation, its proarrhythmic toxicity may be enhanced. Thus, it is important for dentists to understand the toxicity of HCQ used in the treatment of dental diseases.

REFERENCES

1. Plantone D, Koudriaviseya T. Current and future use of chloroquine and hydroxychloroquine in infectious, immune, neoplastic, and neurological diseases: a mini-review. *Clin Drug Investig*. 2018;38:653-671.
2. Brown R. Hydroxychloroquine and "off-label" utilization in the treatment of oral conditions. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020;129(6):643-644.
3. Islam MN, Cohen DM, Ojha J, Stewart CM, Katz J, Bhattacharyya I. Chronic ulcerative stomatitis: diagnostic and management challenges—four new cases and review literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007;104:194-203.
4. Fourie J, van Heerden WF, McEachen SC, van Zyl A. Chronic ulcerative stomatitis: a distinct clinical entity. *SADJ*. 2011;66:119-121.
5. Yeshurun A, Bergman R, Bathish N, Khamaysi Z. Hydroxychloroquine sulphate therapy of erosive oral lichen planus. *Australas J Dermatol*. 2019;60:e109.
6. Cankaya H, Alpöz E, Karabulut G, Güneri P, Boyacioglu H, Kabasakal Y. Effects of hydroxychloroquine on salivary flow rates and oral complaints of Sjogren patients: a prospective sample study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2010;110:62-67.
7. Vivino FB, Carsons SE, Foulka G, et al. New Treatment guidelines for Sjogren's disease. *Rheum Dis Clin North Am*. 2016;42:531-551.
8. Manzo C, Pollio N, Natale M. Sweet's syndrome following therapy with hydroxychloroquine in a patient with primary Sjogren's syndrome. *Medicines (Basel)*. 2019;6:111.
9. Kim AHJ. FDA approves hydroxychloroquine new drug application to address COVID-19 related shortage. *FDA News*. April 7, 2020. Available at: https://www.healio.com/rheumatology/lupus/news/online/%7Ba34fd607-0241-49d2-b57f-885d79ab94ca%7D/fda-approves-hydroxychloroquine-new-drug-application-to-address-covid-19-related-shortage. Accessed April 13, 2020.
10. Mehra MR, Desai SS, Fuschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. doi:10.1016/S0140-6736(20)31180-6, accessed June 25, 2020. (retracteded on June 25, 2020).
11. Chen CY, Wang FL, Lin CC. Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. *Clin Toxicol (Phila)*. 2006;44:173-175.
12. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers YM. Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. *Drug Saf*. 2018;41:919-931.
13. O'Laughlin JP, Mehta PH, Wong BC. Life threatening severe QTc prolongation in patient with systemic lupus erythematosus due to hydroxychloroquine. *Case Rep Cardiol*. 2016;2016:4626279.
14. Tisdale JE, Jaynes HA, Kingery JR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes*. 2013;6:479-487.
15. Soylu R. Hydroxychloroquine: Turkey insists on using drug despite WHO concerns. *Middle East Eye*. 2020. 5-36-Available at: https://www.middleeasteye.net/news/hydroxychloroquine-coronavirus-turkey-lancet-study-who-trial (Accessed 5-30-2020).
16. McGhie TK, Harvey P, Su J, Anderson N, Tomilson G, Touma Z. Electrocardiograph abnormalities related to anti-malarials in systemic lupus erythematosus. *Clin Exp Rheumatol*. 2018;36:545-551.
17. Sharma TS, Wasko MCM, Tang X, et al. Hydroxychloroquine use is associated with decreased incident cardiovascular events in rheumatoid arthritis patients. *J Am Heart Assoc*. 2016;5:e002867.

18. Rochford C, Seldin RD. Review and management of dental patient with long QT syndrome (LQTS). *Anes Prog*. 2009;56:42-48.
19. Siegel MA, Silverman S, Sollecito TP, eds. *Clinician's Guide to Treatment of Common Oral Conditions*, 8th ed., Seattle, WA: American Academy of Oral Medicine; 2017.
20. Dalmau J, Puig L, Roé E, Peramiquel L, Campos M, Alomar A. Successful treatment of oral erosive lichen planus with mycophenolate mofetil. *J Eur Acad Dermatol Venereol*. 2007;21:259-260.
21. Hargitai IA. Painful oral lesions. *Dent Clin North Am*. 2018;62:597-609.
22. Sun SL, Liu JJ, Zhong B, et al. Topical calcineurin inhibitors in the treatment of oral lichen planus: a systematic review and meta-analysis. *Br J Dermatol*. 2019;181:1166-1176.
23. García-Pola MJ, González-Álvarez L, Garcia-Martin JM. Treatment of oral lichen planus. Systematic review and therapeutic guide. *Med Clin (Barc)*. 2017;149:351-362.
24. Elad S, Epstein JB, von Bültzingslöwen I, Drucker S, Tzach R, Yarom N. Topical immunomodulators for management of oral mucosal conditions, a systematic review. Part II: Miscellaneous agents. *Expert Opin Emerg Drugs*. 2011;16:183-202.
25. Gupta S, Ghosh S, Gupta S. Interventions for the management of oral lichen planus: a review of the conventional and novel therapies. *Oral Dis*. 2017;23:1029-1042.
26. Fantozzi PJ, Treister N, Shekar R, Woo SB, Villa A. Intralesional triamcinolone acetonide therapy for inflammatory oral ulcers. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2019;128:485-490.
27. Liu C, Xie B, Yang Y, et al. Efficacy of intralesional betamethasone for erosive oral lichen planus and evaluation of recurrence: a randomized, controlled trial. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;116:584-590.
28. Wynn RL. Dental drug interactions with the greatest potential for serious adverse effects. *Gen Dent*. 1994;42:116-117.
29. Woosley RL. Cardiac actions of antihistamines. *Annu Rev Pharacol Toxicol*. 1996;36:233-253.
30. Gottlieb S. Antihistamine drug withdrawn by manufacturer. *BMJ*. 1999;319:7.
31. Cubeddu LX. Iatrogenic QT abnormalities and fatal arrhythmias: mechanisms and clinical significance. *Curr Cardiol Rev*. 2009;5:166-176.
32. Cubeddu LX. Drug-induced inhibition and trafficking disruption of ion channels: pathogenesis of QT abnormalities and drug-induced fatal arrhythmias. *Curr Cardiol Rev*. 2016;12:141-154.
33. Yan Z, Prinsen JK, Bersell KR, et al. Azithromycin causes a novel proarrhythmic syndrome. *Circ Arrhythm Electrophysiol*. 2017;10:e003560.
34. Choi Y, Lim H-S, Chung D, et al. Risk evaluation of azithromycin-induced QT prolongation in real-world practice. *Biomed Res Int*. 2018;2018:1574806.
35. Howard A. Azithromycin-induced proarrhythmia and cardiovascular death. *Ann Pharmacother*. 2013;47. 1547-1541.
36. Rapp RP. Pharmacokinetics and pharmacodynamics of intravenous and oral azithromycin: enhanced tissue activity and minimal drug interactions. *Ann Pharmacother*. 1998;32:785-793.
37. Fiets RB, Bos JM, Donders ART, et al. QTc prolongation during erythromycin used as prokinetic agent in ICU patients. *Eur J Hosp Pharm*. 2018;25:118-122.
38. Ebert SN, Liu XK, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. *J Womens Health*. 1998;5:547-557.
39. Drici MD, Clement N. Is gender a risk factor for adverse drug reactions? The example of drug-induced long QT syndrome. *Drug Saf*. 2001;24:575-585.
40. Arya A. Gender-related differences in ventricular repolarization: beyond gonadal steroids. *J Cardiovasc Electrophysiol*. 2005;16:5257.
41. Tett SE, Cutler DJ, Day RO, Brown KF. A dose-ranging study of the pharmacokinetics of hydroxychloroquine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol*. 1988;26:303-313.
42. McChesney EW, Conway WD, Banks WF, Rogers J.E. Jr., Shekosky JM. Studies of the metabolism of some compounds of the 4-amino-7-chloroquinoline series. *J Pharmacol Exp Ther*. 1966;151:482-493.
43. Karp JM, Moss AJ. Dental treatment of patients with long QT syndrome. *J Am Dent Assoc*. 2006;137:630-637.
44. Ackerman MJ, Khositseth A, Tester DJ, Hejlik JB, Shen WK, Porter CB. Epinephrine-induced QT interval prolongation: a gene specific paradoxical response in congenital long QT syndrome. *Mayo Clin Proc*. 2002;77:413-421.
45. Brown RS. Long QT syndrome. *J Am Dent Assoc*. 2006;137:1068-1069.
46. Rhodus NL, Little JW. Dental management of the patients with cardiac arrhythmias: an update. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003;96. 659-658.
47. Brown RS, Rhodus NL. Epinephrine and local anesthesia revisited. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2005;100:401-408.
48. Brown RS. The chicken little syndrome. *J Am Coll Dent*. 2006;73:25-29.
49. Wynn RL. Articaine 4% with 1:200,000 epinephrine: an acceptable option for patients with long QT syndrome. *Gen Dent*. 2007;55:176-178.
50. Snitker S, Doerfler RM, Soliman EZ, et al. Association of QT prolonging medication use in CKD with electrocardiographic manifestations. *Clin J Am Soc Nephrol*. 2017;12:1409-1417.
51. Ben-Zvi Kvity S, Langevitz Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. *Clin Rev Allerg Immunol*. 2012;42:145-153.
52. Peponis V, Kyttaris VC, Chalkiadakis SE, Bonovas S, Sitaras NM. Ocular side effects of anti-rheumatic medications: what a rheumatologist should know. *Lupus*. 2010;19:675-682.
53. Wiacek MP, Bobrowska-Snarska D, Lubinski W, Brzosko M, Modrzejewska M. What is new in recommendations on ophthalmological screening in patients treated with chloroquine and hydroxychloroquine? Update and literature review. *Niger J Clin Pract*. 2017;20:919-923.
54. Brown RS, Farquharson AA, Pallasch T. Medical consultations for medically complex dental patients. *J Calif Dent Assoc*. 2007;35:343-349.

Reprint requests:

Ronald S. Brown
Howard University College of Dentistry
600 W Street
NW
Washington DC 20059
NW
rbrown@howard.edu