

The Role of Macrolides and Doxycycline in Chronic Rhinosinusitis



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KEYWORDS

- Macrolides • Doxycycline • Chronic • Sinusitis • Rhinosinusitis • Polyps
- Immunomodulation

KEY POINTS

- The role of macrolides in the management of chronic rhinosinusitis relates more to their immunomodulatory properties than their antibacterial properties. Macrolides can reduce proinflammatory cytokines, neutrophil infiltration, and oxidative damage to mucosal tissue.
- Macrolide antibiotics may be useful in the management of recalcitrant chronic rhinosinusitis without nasal polyposis, particularly in patients with low immunoglobulin E and eosinophil levels.
- Doxycycline has been effective in chronic rhinosinusitis with nasal polyposis because of its ability to inhibit matrix metalloproteinase activity.
- Macrolides have an increased risk of cardiac side effects. A review of the patient's medications and cardiac risk factors is advised before initiating therapy.

INTRODUCTION

Although antibiotics are commonly used for the treatment of acute rhinosinusitis, there is growing interest in their role for controlling upper-airway inflammation in conditions such as chronic rhinosinusitis (CRS).¹ In 1987, Kudoh and colleagues² reported on the use of erythromycin, a macrolide antibiotic, in patients with diffuse panbronchiolitis, resulting in improved 5-year survival from 25% to greater than 90%. This discovery led to further widespread adoption of macrolides in the management of other airway

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diseases, such as cystic fibrosis, bronchiectasis, and CRS. In addition to the well-known antimicrobial properties, macrolides exhibit anti-inflammatory and immunomodulatory effects on airway tissues, even at subtherapeutic doses. More recently, doxycycline, a tetracycline antibiotic, has been found to have similar immunomodulatory properties in CRS.

CLINICAL APPLICATIONS
Macrolides

Macrolides, which include erythromycin, clarithromycin, azithromycin, and roxithromycin, exert their antimicrobial effect by reversibly binding to the 50S ribosomal subunit, preventing bacterial protein synthesis. These antibiotics have a propensity to accumulate in high concentrations within leukocytes and subsequently at sites of active infection or inflammation. They provide good coverage of gram-positive cocci (excluding *Enterococcus* species) as well as intracellular and atypical pathogens; however, gram-negative coverage is limited (Table 1). Macrolides are often used as the first-line treatment of upper-respiratory tract infections in penicillin-allergic patients.

Macrolides also affect the virulence of some bacteria without having direct antimicrobial effects through the 50S subunit. Macrolides inhibit the production of alginate, an important component in biofilm formation, at levels below the minimal inhibitory concentration for *Pseudomonas aeruginosa* and other bacteria.³ They also impair the motility of *Pseudomonas* by inhibiting flagellin expression, thereby preventing a mechanism of adherence to respiratory mucosa.^{4,5} Finally, macrolides impair the quorum-sensing system by blocking expression of signals known as “autoinducers.”⁶

Macrolides’ role as immunomodulators has been used in the management of CRS, because they have been shown to have multiple anti-inflammatory properties.

Table 1 Spectrum of antimicrobial coverage of macrolides and doxycycline		
Gram positive	<i>S aureus</i> ^a	
	Methicillin-resistant <i>S aureus</i> ^c	
	<i>Streptococcus pyogenes</i> ^a	
	<i>Streptococcus pneumoniae</i> ^a	
	<i>Streptococcus viridens</i> ^c	
	<i>Enterococcus</i> ^c	
	<i>Corynebacterium diphtheria</i> ^b	
	<i>Propionibacterium acnes</i>	
	<i>Listeria monocytogenes</i>	
Gram negative	<i>H influenzae</i> ^a	<i>Campylobacter jejuni</i>
	<i>Moraxella catarrhalis</i> ^a	<i>Escherichia coli</i> ^c
	<i>Bordetella pertussis</i> ^b	<i>Enterobacter</i> ^c
	<i>Bacillus anthracis</i> ^c	<i>Serratia</i> ^c
	<i>Neisseria gonorrhea</i>	<i>Shigella</i> ^c
	<i>Helicobacter pylori</i>	<i>Vibrio</i> ^c
Atypical	<i>Chlamydia</i>	<i>Treponema pallidum</i>
	<i>Legionella</i>	<i>Borrelia burgdorferi</i>
	<i>Mycoplasma</i>	<i>Rickettsia</i> ^c
	<i>Ureaplasma</i>	<i>Actinomyces</i> ^c
	<i>Mycobacterium</i>	

^a Common pathogens in sinusitis.
^b Susceptible only to macrolides.
^c Susceptible only to doxycycline.

Macrolides promote decreased production of proinflammatory cytokines, such as interleukin-1 β (IL-1 β), IL-6, tumor necrosis factor- α (TNF- α), and IL-8.^{7,8} IL-8 is a potent neutrophil chemoattractant but is also released by neutrophils, and in vivo studies have shown macrolide administration to reduce both IL-8 and neutrophil infiltration in nasal epithelium.⁹ Macrolides have also been found to decrease the production of reactive oxygen species (ROS), thereby reducing epithelial cell damage.

The beneficial effects of macrolides on mucus production and clearance have also been described. In lower-airway diseases, such as chronic bronchitis and bronchiectasis, clarithromycin has been found to decrease sputum production by 50%.¹⁰ Similarly, early studies of nasal secretions in CRS patients showed improved viscosity, decreased quantity,¹¹ and improved clearance.¹² Later studies found that mucociliary clearance, as measured objectively by saccharin transit time (STT), improved following macrolide administration.^{8,13,14}

Following the encouraging results of macrolide use in the management of lower-airway diseases, several cohort studies of macrolides in CRS emerged. Moriyama and colleagues¹⁵ retrospectively reviewed outcomes of 149 patients with CRS with nasal polyposis (CRSwNP) treated with endoscopic sinus surgery (ESS), 57 of whom received long-term low-dose erythromycin postoperatively. The erythromycin group, despite having worse disease preoperatively, had improved rhinorrhea and postnasal drainage as well as improved edema and polyps on endoscopic examination compared with the ESS-only patients. Other studies have found the symptoms most likely to respond to macrolide therapy are rhinorrhea and postnasal drainage.^{11,13,16}

Several studies have investigated the role of macrolides in different CRS phenotypes. Ichimura and colleagues¹⁷ noted that roxithromycin decreased nasal polyp size in about 50% of CRSwNP patients, but also that patients with smaller polyps were more likely to respond to macrolide therapy than those with large polyps. Patients with higher levels of IL-8 in nasal secretions have a greater response to macrolides both for CRSwNP¹⁸ and without nasal polyposis (CRSsNP).¹⁹ In a study of CRS patients treated with macrolides, Haruna and colleagues²⁰ determined the efficacy was lower in CRSwNP than CRSsNP, but increased following polypectomy, suggesting polyp burden may predict macrolide response. Patients with higher polyp eosinophil levels were more likely to be poor responders to macrolide therapy, a finding corroborated by a recent retrospective review of macrolide responders and nonresponders.²¹ Finally, patients with high serum immunoglobulin E (IgE) had less symptom improvement than those with normal IgE, and both serum and nasal eosinophil counts inversely correlated with symptom improvement.²² These studies suggest that patients with eosinophilic or Th2-dominant disease are less likely to respond to macrolide therapy.

In 2006, Wallwork and colleagues⁸ published results of a randomized controlled trial (RCT) demonstrating the benefit of roxithromycin over placebo, providing the first level I evidence in support of macrolide therapy for CRSsNP. Patients reported significant symptom improvement as well as SNOT-20 scores in the roxithromycin-treated group and had improved mucociliary clearance (as measured by STT) and nasal endoscopy scores at the end of the 3-month treatment period. Furthermore, patients with low IgE levels had greater improvement in SNOT-20, nasal endoscopy scores, and STT compared with patients with high IgE. Since then, 3 RCTs have failed to convincingly demonstrate the benefit of macrolides over placebo in CRS.^{23–25} However, these trials included patients both with and without nasal polyposis, and two of the studies^{24,25} evaluated macrolide use specifically in the postoperative period.

Multiple RCTs in recent years have compared macrolide therapy to intranasal corticosteroid spray (INCS) for CRS.^{26–31} Overall, these studies failed to demonstrate a clear benefit of macrolides over INCS for symptoms, nasal endoscopy, or computed tomographic (CT) scores. Two studies examined clarithromycin in the perioperative period for patients with CRSwNP: one administered clarithromycin for 8 weeks before ESS,³² whereas the second randomized patients to receive clarithromycin after ESS for either 12 or 24 weeks.²⁸ Both studies showed improved nasal endoscopic scores in the clarithromycin-treated patients (although without significant symptomatic improvement), suggesting macrolides may prevent or postpone nasal polyp regrowth after surgery.

Because of the contradictory results from these studies, systematic reviews and metaanalyses have been performed in an attempt to draw broader conclusions from the existing literature. Shen and colleagues³³ included 7 RCTs and 4 cohort trials in their recent metaanalysis. Interestingly, when comparing Asian and non-Asian subgroups, they found that the Asian subgroup had significant improvement in SNOT scores in the macrolide-treated group compared with the control group; however, no significant difference was found for the non-Asian subgroup. This finding may be explained by findings from previous studies that Asian patients with CRS have a neutrophil predominance in nasal polyps and cytokine profiles suggestive of Th1-dominance.^{34,35} Huang and Zhou³⁶ performed a systematic review and metaanalysis specifically of clarithromycin in CRS, which included 17 RCTs with 1738 patients. They found the addition of clarithromycin to INCS showed improvement in symptoms and endoscopic scores in the medium term (1–3 months) and long term (>3 months), but insufficient evidence to support the use of clarithromycin monotherapy when compared with INCS.

Macrolide antibiotics can be a useful adjunct in the treatment of recalcitrant CRS that has failed previous medical and surgical therapies because of its anti-inflammatory and immunomodulatory effects. It may be more effective in patients with rhinorrhea and postnasal drainage, with noneosinophilic CRS subtypes, such as CRSsNP, normal serum IgE, and low serum and nasal eosinophil levels.

Doxycycline

Doxycycline is a synthetic derivative of the tetracycline class of antibiotics, which also includes demeclocycline, minocycline, and tigecycline. Similar to macrolides' antimicrobial activity, tetracyclines inhibit protein synthesis by reversibly binding to the 30S ribosomal subunit. Doxycycline broadly covers gram-positive species, including methicillin-resistant *Staphylococcus aureus*, as well as some gram-negative bacteria (see [Table 1](#)).

Doxycycline has been found to have immunomodulatory effects in addition to antimicrobial properties, which has gained attention for its potential use in CRSwNP. In CRSwNP, increased levels of matrix metalloproteinase-9 (MMP-9) have been found in nasal polyps and are thought to contribute to the process of matrix remodeling, edema, and chronic inflammation.^{37–39} Doxycycline exerts its anti-inflammatory effect by inhibiting MMP activity, including decreasing MMP-9 in CRSwNP.^{39,40} Doxycycline administration has also been found to decrease eosinophilic cationic protein (ECP) and myeloperoxidase levels in nasal secretions, suggesting decreased activity of eosinophils and neutrophils, respectively.^{39,40} Doxycycline reduces the damaging effects of ROS, decreases levels of nitric oxide synthase, and suppresses proinflammatory cytokines, including TNF- α , IL-1 β , and IL-6.

To date, there have been 2 clinical trials investigating the utility of doxycycline in CRSwNP. The first RCT had 3 treatment arms: methylprednisolone taper, doxycycline, and placebo, taken for 20 days.³⁹ The effect on symptoms, polyp size, and

inflammatory markers in nasal secretions and blood was evaluated up to 12 weeks after initiation of treatment. They found that with methylprednisolone, polyp size quickly and dramatically decreased while taking the medication, but by the end of the study period, had returned to their baseline size. In the doxycycline group, however, the decrease in polyp size was moderate by the end of the 20-day treatment period, but was maintained until the end of the trial period. When evaluating inflammatory markers, the doxycycline group had significantly decreased MMP-9, myeloperoxidase, and ECP levels in the nasal secretions, the latter two suggesting decreased neutrophil and eosinophil activity, respectively.

A second RCT evaluated the efficacy of long-term doxycycline in CRSwNP patients with persistent symptoms despite appropriate medical and surgical treatment.⁴¹ Patients were randomized to receive a 12-week course of doxycycline plus INCS and nasal irrigations, or INCS and nasal irrigations alone. After 12 weeks, patients in the doxycycline group had significantly improved symptoms and nasal endoscopy compared with the control group. They also found that patients with aspirin-exacerbated respiratory disease, asthma, and elevated serum IgE levels were less likely to demonstrate clinically significant improvement in SNOT-20 scores, suggesting that CRSwNP with allergy or eosinophilia may be less responsive to doxycycline therapy, similar to what has been found for macrolides.

Doxycycline has been found to improve symptoms and decrease polyps specifically in the subset of patients with CRSwNP. However, this is based on a limited number of studies in small cohorts, and further research is needed in larger numbers of patients to strengthen these conclusions and determine optimal length of treatment.

DOSING AND ADMINISTRATION

For low-dose maintenance therapy for CRS with antibiotics, the general recommendation for both macrolides and doxycycline has been half the dose used to treat acute infection (Table 2).

Macrolides

Macrolide antibiotics demonstrate excellent penetration of sinus mucosa, partly because of their uptake by leukocytes, leading to their transportation to sites of infection and inflammation. Erythromycin was initially the most commonly used macrolide because it was the first to be discovered. However, it required 4-times-a-day dosing and was associated with high rates of gastrointestinal (GI) side effects and has now been replaced by second-generation macrolides. Clarithromycin and roxithromycin have similar half-lives and distribution, with once-daily dosing providing appropriate concentrations in nasal and sinus mucosa for CRS therapy. However, during acute CRS exacerbations, increasing to twice daily dosing is recommended for 5 to 10 days. Azithromycin is unique from the other macrolides in that it has a much longer half-life and can be detected in sinus mucosa up to 6 days following oral administration.⁴² As such, it can be dosed less frequently, such as every other day, 3 days a week, or even weekly.²³

The dose of macrolides for CRS is likely of less significance than duration of treatment. Several studies have shown increasing efficacy with prolonged use, and that clinical benefit may not become apparent until 4 to 8 weeks after initiation of treatment.^{11,16,43} A trial of at least 12 weeks is recommended to determine whether a patient demonstrates responsiveness to macrolide therapy; if there is no clinical improvement after 3 months, discontinuation of macrolides and investigation into alternative treatments is appropriate. However, if the patient demonstrates improvement in symptoms and/or endoscopic examination on

Table 2 Recommended dosing and side effects of macrolides and doxycycline for use in acute exacerbation and maintenance therapy for chronic rhinosinusitis			
	Dosing: Maintenance Therapy for CRS	Dosing: Acute Exacerbation CRS	Side Effects
Azithromycin	250 mg every other day	500 mg loading dose Then 250 mg daily × 4 d	GI: Nausea, vomiting, abdominal pain, diarrhea
Clarithromycin	250 mg daily Pediatric: 5 mg/kg daily	250 mg bid × 5–10 d Pediatric: 5 mg/kg bid × 5–10 d	Cardiac arrhythmias ^a Hearing loss ^a
Roxithromycin	150 mg daily Pediatric: 2.5–5 mg/kg daily	150 mg bid Pediatric: 2.5–5 mg/kg bid	Drug interactions: Warfarin, benzodiazepines, cyclosporine, statins (all CYP3A4 pathway)
Doxycycline	200 mg loading dose, then 100 mg daily	200 mg daily × 5–7 d OR 100 mg bid × 5–7 d	GI: Nausea, vomiting, abdominal pain, diarrhea Skin reactions: Rash, pruritus, photosensitivity Tooth discoloration, enamel hypoplasia (children <8 y) ^a Esophageal ulceration ^a Drug interactions: Calcium supplements, antacids, iron; anticonvulsants (barbiturates, carbamazepine, phenytoin); warfarin

^a Rare side effects.

macrolide therapy, an additional 3 to 9 months of treatment may result in further improvement.^{11,13,43}

For patients with creatinine clearance less than 30 mL/min, clarithromycin dosing should be reduced by half, or the dosing interval doubled; however, no adjustments are required for azithromycin.

Doxycycline

The studies on doxycycline for CRS have been remarkably consistent on the dosing, with a loading dose of 200 mg on the first day followed by 100 mg once a day thereafter (see [Table 2](#)). Doxycycline has rapid and very high absorption (>90%) in the duodenum, making oral dosing preferred to other methods of administration.⁴⁴ It is able to penetrate sinus mucosa and maintain therapeutic concentrations until 24 hours after administration, supporting the once-daily dosing scheduling.⁴⁵ No dosing adjustments are needed in patients with renal failure, but should be considered in patients with severe hepatic dysfunction. There is currently limited evidence as to the optimal duration therapy in CRS given the limited number of studies to date. However, patients benefited from both short-term (<3 week) and long-term (12 week) courses of doxycycline in terms of

symptoms and endoscopic examinations,^{39–41} suggesting there may be utility to different treatment durations in certain clinical scenarios.

SIDE EFFECTS

Macrolides and doxycycline most commonly cause adverse GI symptoms, including nausea, vomiting, diarrhea, and abdominal pain. The incidence is highest with erythromycin (15%–20%) but is reported as 5% to 10% for clarithromycin, azithromycin, and doxycycline.⁴⁶

Development of resistance to antibiotics has been a concern for decades as multidrug-resistant bacteria have become increasingly prevalent. Bacteria have adopted 2 main strategies of resistance against macrolides and doxycycline: efflux of antibiotic out of the cell and modification of the antibiotic-binding site via ribosomal methylation.⁴⁷ Although growing rates of antibiotic resistance remain a global concern, particularly for macrolides, there has not been convincing evidence of increase in resistant strains following long-term, low-dose macrolide treatment in CRS.^{8,13,23,28,31}

Both macrolides and doxycycline have unique side-effect profiles as well that deserve mention.

Macrolides

Macrolides cause prolonged QT interval, which can subsequently lead to the fatal cardiac arrhythmia, torsades de pointes. Several large observational studies have identified an increased risk of cardiovascular death in patients taking macrolides, citing 37 to 47 additional deaths per 1 million antibiotic courses.^{48,49} This risk is higher in patients with an increased baseline risk of cardiovascular disease⁴⁹ and women⁴⁸; however, 1 study found no increased risk between azithromycin and penicillin in a young and middle-aged, healthy cohort.⁵⁰ This increased cardiac risk seems limited to the period of macrolide use, with no evidence of long-term toxicity after administration.^{51,52} These studies do not specify medication dose, and there are no similarly large studies on cardiac risk specifically in low-dose macrolide therapy. However, Azuma and Kudoh⁵³ commented on the incidence of torsades de pointes in the Japanese population taking erythromycin, in which 60% of the prescriptions are long-term, low-dose treatment. They found only 4 cases out of approximately 34,000 patients treated annually for more than 10 years, which they attributed to the subtherapeutic doses compared with other studies. Before initiation of macrolides, it is recommended to take a thorough cardiac history on patients (including family history), check for cardiac medication use, and consider a baseline electrocardiogram to evaluate for QT prolongation in high-risk patients. Macrolide use is advised against in patients with QT prolongation, ventricular arrhythmias, bradycardia, electrolyte abnormalities (eg, hypomagnesemia, hypokalemia), or other significant risk factors for cardiac events.

Hearing loss has also been reported with macrolide use, which is usually transient and more likely to occur with higher doses of medication. In a large study of 1577 patients with chronic obstructive pulmonary disease (COPD), the rate of hearing loss was significantly higher in the azithromycin group at 25% compared with the placebo group at 20%.⁵⁴

Doxycycline

The second most common side effect of doxycycline is skin reactions, such as rash, pruritus, and photosensitivity.⁵⁵ Patients should be cautioned on the increased susceptibility to sunburn, particularly during summer months.

A side effect unique to the tetracyclines is enamel hypoplasia, causing teeth discoloration in young children.⁴⁴ Historically, the use of doxycycline has been contraindicated in children less than 8 years of age and pregnant women based on reports of yellow or brown staining of teeth following use of tetracycline specifically. However, doxycycline binds calcium significantly less than tetracycline, making this risk with doxycycline extremely low. As such, the American Academy of Pediatrics recently changed its recommendation that now children of any age can take up to a 21-day course of doxycycline.⁵⁶

Although rare, doxycycline use has been linked to the development of esophageal ulceration, which occurs more commonly with the capsule than the tablet form of medication.⁵⁵ Patients may experience substernal burning pain and odynophagia shortly after administration, which can be avoided by taking pills with plenty of fluids while in the upright position.

DRUG INTERACTIONS

Macrolides

Erythromycin, clarithromycin, and roxithromycin are all metabolized via the cytochrome p450 pathway, specifically, through enzyme CYP3A4. Many macrolide drug interactions arise from interactions with other medications using the same CYP3A4 pathway. Of note, azithromycin is unique among the macrolides in that it is not metabolized via this pathway, so it has fewer drug interactions by comparison.

Coadministration of macrolides with warfarin can lead to slower metabolism and clearance of the warfarin, leading to potentially supratherapeutic anticoagulation. Close monitoring of international normalized ratio (INR), with warfarin dosing adjustments as needed, is recommended.

Concomitant use of benzodiazepines with macrolides can lead to increased bioavailability of the benzodiazepines; their use should be avoided or the dose decreased to avoid the potentially fatal consequences such as respiratory depression.

Cyclosporine is another drug metabolized through the CYP3A4 pathway, and taking it with macrolides can lead to elevated cyclosporine levels that can subsequently cause renal toxicity. It is important to monitor renal function (eg, serum creatinine) closely if these medications are taken together.

Finally, some studies have shown that patients taking statin medications with macrolides can develop acute renal failure, rhabdomyolysis, and increased all-cause mortality, particularly for clarithromycin and erythromycin.^{57,58}

Doxycycline

Doxycycline is not metabolized by any p450 system, which decreases the potential drug interactions that it has. However, it can become bound to divalent and trivalent cations, which becomes particularly important when taking this medication orally. Doxycycline should not be taken within 1 to 2 hours of having milk, antacids, iron supplements, or other substances containing calcium, magnesium, aluminum, or iron, because these substances can bind the doxycycline and prevent its absorption from the GI tract.

Anticonvulsants, specifically barbiturates, carbamazepine, and phenytoin, can influence the metabolism of doxycycline and lead to decreased half-life. Coadministration with these medications may require alteration in the dose or frequency of doxycycline. Doxycycline can also potentiate the effects of warfarin, and close monitoring of INR is required if these medications are taken together.

FUTURE CONSIDERATIONS

The conflicting evidence on long-term, low-dose macrolide treatment in CRS derives from several RCTs with small study populations and variability in their inclusion criteria and treatment protocols. Because of this, it is difficult to draw strong conclusions as to the specific clinical scenarios in which macrolide therapy will provide the greatest benefit. A large RCT currently underway is the MACRO trial, which seeks to compare symptomatic improvement between clarithromycin and placebo in patients with CRS, with a goal recruitment of 600 patients.⁵⁹

Use of macrolide antibiotics has been a primary focus of the past several decades, and only in recent years has doxycycline gained attention for use in CRS. There are very few studies by comparison investigating the use of doxycycline, all of which have been specifically in CRSwNP. However, these studies have shown encouraging results, and in combination with its favorable side-effect profile and antimicrobial coverage, further research into its role in CRS will likely continue to emerge.

Finally, there have been several in vitro studies on several macrolide derivatives that maintain the immunomodulatory effects of macrolides but without the antimicrobial properties. For instance, EM900 is an erythromycin derivative that has been shown to suppress IL-1 β , TNF- α , and IL-8 production in human airway epithelial cells.^{60,61} Another example is CSY0073, an azithromycin derivative. In a murine model, CSY0073 did not affect growth of *S aureus*, *Haemophilus influenzae*, or *P aeruginosa*, but did lead to decreased levels of proinflammatory cytokines and neutrophils in lung tissue and secretions similar to azithromycin.⁶² These medications have great potential in long-term management of diseases such as CRS while mitigating concerns about antibiotic resistance. However, their use not yet been evaluated in human subjects and thus will not become available for several years.

SUMMARY

Macrolides and doxycycline can be useful adjuncts in the management of CRS. When administered as long-term, low-dose therapy, they exert an immunomodulatory effect on the sinuses by decreasing neutrophil infiltration, production of proinflammatory cytokines, and secretion of mucus. Macrolides, such as clarithromycin and azithromycin, are particularly effective in patients with CRSsNP with normal serum IgE and low serum and nasal eosinophil levels. Doxycycline can improve symptoms and decrease polyps in patients with CRSwNP. The most common side effect for both macrolides and doxycycline is GI symptoms, including abdominal pain, nausea, or diarrhea. Macrolides can cause prolonged QT interval, which may lead to torsades de pointes or other cardiac arrhythmias. As such, they should be used with caution in patients with increased cardiac risk.

DISCLOSURE STATEMENT

J.A. Alt is a consultant for Medtronic, Optinose, Intersect ENT, and GlycoMira Therapeutics. R.R. Orlandi is a consultant for Medtronic, Lyra Therapeutics, and BioInspire. K.A. Lees and G. Oakley have nothing to disclose.

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