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ORIGINAL-RESEARCH-ARTICLE

Routine Medications in Otolaryngology with Not So Routine Consequences

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Abstract

Objective(s): We aimed to provide a directed summary of lesser-known side effects and pharmaceutical interactions of common medications used in otolaryngology practice.

Study Design: Evidence-based literature review.

Methods: We reviewed the current evidence-based literature concerning adverse effects and interactions that are of high consequence for well-known medications.

Results: This report provides a current synopsis of under-acknowledged adverse effects and interactions of intranasal corticosteroid sprays, anti-reflux medications, and antibiotics.

Conclusions: Although rare, the interactions and adverse effects presented in this article represent severe sequelae with which practicing otolaryngologists should be familiar. The information discussed in this report will aid in the identification of at-risk patients and provide otolaryngologists with proper prescribing practices in aim to promote patient safety.

Key words: Otolaryngology Medications, Drug-Drug Interactions, Medication Interactions, Adverse Effects, Side Effects.

1 | INTRODUCTION

In the modern era of healthcare, multiple medications exist for the treatment of a particular aliment, giving otolaryngologists options and flexibility in their prescribing patterns. Accordingly, the knowledge required to avoid potential drug-drug interactions and counsel patients on possible side effects has increased, making pharmaceutical surveillance a complex task. Although electronic prescribing (e-prescribing) may reduce the incidence of error, limited evidence suggests that e-prescribing significantly improves patient safety.[(1),(2),(3)] Instead, quality improvement is heavily dependent on physician utilization rather than the automated process itself.[(4)]

This holds particular relevance amongst individuals with multiple comorbidities and medication regimens. Population-based studies demonstrate that 40 to 50 percent of adults ages 65 years and older are

taking five or more medications chronically.[5],[6],[7] By 2050, the elderly population is projected to reach 84 million nationwide.[8] The National Ambulatory Medical Care Survey estimates that over 50 percent of all Otolaryngology office visits comprise of patients ages 45 and older, and that medications are prescribed or provided at 55 percent of visits.[9]

In the setting of such high prescribing patterns and a growing population of patients taking multiple medications, the complexity of medication management in Otolaryngology increases. Therefore, reviewing serious and unfamiliar interactions with contemporary ENT medications is imperative. In an effort to promote physician awareness and improve patient safety, this report assesses common medications used in the practice of Otolaryngology and summarizes lesser-known interactions and side effects.

2 | METHODS

We reviewed the clinical pharmacology and pharmacokinetic data provided in the Lexicomp, Micromedex, and Medscape databases for select classes of medications common to Otolaryngology practice. The categories of medications for review were designated based upon the experience of the Department of Otolaryngology – Head & Neck Surgery at our academic, tertiary-care institution. Identified interactions and adverse effects were secondarily cross-referenced using The Oxford Handbook of Clinical Pharmacology and the UpToDate database. For each selected assertion, the authors appraised the Lexi-Interact Risk Rating (summarized in **Table 1**) based on the accompanying evidence, and performed supplemental literature review using the PubMed database. Upon completion of final data collection, the authors retrospectively assigned management recommendations using the Grading of Recommendations Assessment, Development and Evaluation system for rating clinical guidelines, wherein high indicates that further research is very unlikely to change the confidence of the recommendation, moderate designates that further research is likely to impact these estimates and may change the confidence of the recommendation, low indicates that additional research will likely change the recommendation, and very low indicates extreme uncertainty in the recommendation. In an effort to promote the application of these findings, we identified at-risk patient populations based upon the diagnosis of a disease and the current standard of care used in its treatment. When applicable, we included a brief discussion regarding safe alternative treatment options available for use in these populations. All finalized summaries were subsequent to individual review by a Clinical Pharmacist and Infectious Disease specialist to ensure their accuracy and relevance.

Table 1: *The Lexi-Interact Risk Rating designated for concurrent use of two pharmaceutical agents. Progression from A to X indicates escalating clinical urgency based upon the pharmacokinetic and pharmacodynamic data present in clinical trial and medical literature.*

Risk Rating	Description	Action
X	The specified agents interact in a clinically significant manner. Concurrent use is generally contraindicated, as the risks usually outweigh the benefits.	Avoid Combination
D	The specified agents may interact in a clinically significant manner. A patient-specific benefit-to-risk assessment must be conducted. Risk should be minimized via empiric dosage adjustments and aggressive monitoring. Strongly consider alternative agents.	Modify Regimen
C	The specified agents may interact in a clinically significant manner. If the benefits of concurrent use outweigh the risks, appropriate monitoring should be implemented and dosage adjustments may be required.	Closely Monitor Therapy
B	The specified agents may interact. There is little to no evidence that warrants a clinical concern.	No Action Required
A	No evidence of pharmacodynamics and pharmacokinetic interactions exists.	No Interaction

3 | RESULTS

Intranasal Steroid Sprays

The three most commonly prescribed medications in Otolaryngology are intranasal fluticasone, intranasal mometasone, and oral omeprazole.[9] As endorsed by the AAO-HNS [10] and IDSA,[11] topical intranasal corticosteroids are used as empiric and adjunct treatment for a variety of ailments, including allergic rhinitis, nasal polyps, and

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rhinosinusitis. Herein, we describe clinically significant drug-drug interactions for the two most commonly used intranasal corticosteroids (Table 2).

Table 2: *Select interaction profile of the intranasal corticosteroids, fluticasone and mometasone. Note, the table is not all-inclusive for the potential interactions of this medication class.*
†Stribild® = Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
††Genvoya® = Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
†††Kaletra® = Lopinavir/ritonavir

		Adverse Effect (ADE)	Category	Recommendation
Intranasal Corticosteroids	**Antiretroviral Regimens Containing Pharmacologic Boosters** i.e. †Stribild®, ††Genvoya®, †††Kaletra®	Adrenal suppression; Cushing Syndrome	X	High
	Desmopressin (Noctiva®)	Hyponatremia	X	Low

Fluticasone and Mometasone

Patients Populations at Risk: **HIV, Diabetes Insipidus**

Aqueous fluticasone (Flonase®) and mometasone (Nasonex®) typically exhibit low systemic absorption, making them an attractive first line treatment option with a low side effect profile.[12] Their metabolism occurs via the hepatic enzyme cytochrome P450 3A4 (CYP3A4). Concurrent use of medications known to strongly inhibit this enzyme poses the risk of increased systemic steroids concentrations.

Select antiretroviral medications including protease inhibitors (i.e ritonavir) and cobicistat are known to inhibit CYP3A4. Many combination antiretroviral therapies (cART) take advantage of this inhibition to reduce the metabolism of the other agents in the regimen, known as a "pharmacologic boost". Consequently, HIV therapies that contain pharmacokinetic boosters or protease inhibitors may interfere with the metabolism of corticosteroids, including steroids administered via intranasal route. This interaction may be easily overlooked in patients taking cART formulated as single pill medications such as Stribild®, Genvoya®, and Kaletra®. Several reports have attributed adrenal suppression and iatrogenic Cushing Syndrome to concurrent intranasal fluticasone and cobicistat or ritonavir, with up to 100-fold increases in systemic fluticasone exposure noted and 86 percent decreases in plasma cortisol concentrations.[13],[14],[15],[16],[17] The University of Liverpool HIV Interactions database similarly advises against the co- administration of these medications.[18] Comparable pharmacokinetic effects have been noted with the concurrent use of systemic ketoconazole, a known CYP3A4 inhibitor, and intranasal fluticasone.[13]

The use of intranasal corticosteroids should be avoided in patients taking desmospressin (Noctiva®), as this may enhance the hyponatremic effects of desmopressin. Such scenarios may be encountered in patients who undergo transsphenoid hypophysectomy, as diabetes insipidus is a linked complication to pituitary surgery. It should be noted that the supporting evidence is limited to a single clinical trial and rare case reports.[19],[20] Although the risk likely exists with all desmopressin products, the risk has been specifically reported with the Noctiva® brand. Further, this association may be more prevalent with systemic corticosteroids rather than in those administered intranasally.[20] Nonetheless, the consequences of this potential interaction pose severe health risks to patients and should be avoided.

As an alternative to intranasal corticosteroids, saline irrigation should be considered in the aforementioned patient populations. In a recent Cochrane Review, the difference in patient-reported disease severity was uncertain between the use of saline irrigations or intranasal corticosteroids, displaying no superiority to steroid sprays.[21] In patients on cART regimens or those actively receiving desmopressin, the potential risks of intranasal corticosteroid sprays strongly outweigh the benefits.

Recommendations

• Utilize alternate intranasal therapies such as saline irrigations in patients taking select HIV regimens or desmopressin (High).

3.1 | Anti-Reflux Medications

Between 1990 and 2001, there has been a 500% increase in Otolaryngology visits due to laryngopharyngeal reflux (LPR).22 With the rapid expansion in diagnosis and treatment of LPR, antireflux medications have become a mainstay in the medication arsenal of otolaryngologists. To summarize potential interactions for this family of medications,

we examined two model drugs in the Proton Pump Inhibitors (PPIs) and Anti-Histamine Receptors Antagonists (H2RAs) classes, omeprazole and ranitidine, respectively (Table 3).

Table 3: *Select interaction profile of the anti-reflux medications, proton pump inhibitors and H2 receptor antagonists. Note, the table is not all-inclusive for the potential interactions of these medication classes. † This interaction applies to oral cefuroxime only. A similar decrease in antibiotic efficacy is also seen with concurrent H2 Receptor Antagonist use and therefore should be avoided (Category X; Recommendation High). †† Interaction is specific to Omeprazole.*
††† Special considerations in patients with renal impairment.

		Adverse Effect (ADE)	Category	Recommendation
Proton Pump Inhibitors	**Cefuroxime**† (Ceftin®)	Decreased antibiotic efficacy	X	High
	Citalopram (Celexa®), Escitalopram (Lexapro®)	Increased toxicity risk (Serotonin Syndrome, QT prolongation)	D	Moderate
	Clopidogrel†† (Plavix®)	Decreased antithrombotic efficacy	D	High
	Mesalamine	Diminished therapeutic effect	D	Moderate
H2 Receptor Antagonists	**Glipizide, Glyburide**	Hypoglycemia	C	Low
	Varenicline††† (Chantix®)	Headache, nausea, and abnormal dreams	C	Low

PPIs: Omeprazole

Patient Populations at Risk: **Depression, Vasculopathic Disease Requiring Anti-Platelet Therapy, Ulcerative Colitis**

As previously mentioned, oral omeprazole is one of the three most common drugs prescribed in outpatient otolaryngology clinics. A British survey showed that up to 86% of otolaryngologists will prescribe PPIs empirically for symptoms of globus sensation, episodic choking, or chronic cough in the setting of arytenoid or vocal cord erythema.[23] The long-term side effects of this class of medications has been the focus of contemporary research, evident by the FDA warnings regarding the increased risk of fractures, hypomagnesemia, and Clostridium difficile associated diarrhea.[24],[25],[26] Further, these medications are known to be potent CYP2C19 inhibitors and alter the gastric acid content, affecting the metabolism and absorption of many medications.

Both citalopram (Celexa®) and escitalopram (Lexapro®) belong to the Selective Serotonin Reuptake Inhibitor class of anti-depressants and are metabolized via hepatic CYP2C19 enzyme pathways. Thus, co-administration of these medications with omeprazole may increase their concentration and toxicity risks. Minor side effects known to SSRIs include xerostomia, nausea, restlessness, and reduced sexual libido. More serious effects include QT prolongation and serotonin syndrome. Two studies in healthy volunteers demonstrated that citalopram levels were approximately 1.5-2.2 fold higher in patients with concurrent use of omeprazole.[27],[28] Similarly, geriatric patients treated with 10 mg escitalopram and 20 mg omeprazole daily had an average 30msec increase in QTc interval.29 Since their co-administration may necessitate SSRI dose reduction, we recommend otolaryngologists avoid the use of PPIs in patients taking thesemedications.[30] Alternative acid reducing therapies such as H2RAs may be more appropriate in this population.

Clopidogrel (Plavix®) is used in a variety of vasculopathic disease processes including the prevention of thrombosis after placement of a coronary stent and recurrent stroke prophylaxis. It is metabolized into its active form via the CYP2C19 enzyme. Simultaneous omeprazole usage may decrease serum concentrations of its active metabolite and diminish its antiplatelet effects. In support of these claims, multiple meta-analyses have reported significant increases in the odds of major adverse cardiovascular effects when both medications are co-administered.[31],[32],[33],[34],[35],[36] Despite the presence of such evidence, this interaction is still frequently overlooked prompting the FDA to release a reminder Safety Communication.[37]

Mesalamine is an oral 5-aminosalicylic acid derivative used to treat ulcerative colitis. It relies on local differences in gastrointestinal tract pH for its time controlled release to promote delivery to the colon and distal GI tract. PPIs mediate an increase in gastric pH which may cause the premature release of mesalamine, as its coating is designed to dissolve at pH of 6-7 and above.[38],[39],[40] Consequently, PPIs may diminish the therapeutic effect of mesalamine, as reflected in prescribing information for this product which recommends avoiding their co-administration.

Recommendations

- Avoid the use of PPIs in patients taking oral cefuroxime (High), clopidogrel (High), select SSRIs (Moderate), and mesalamine (Moderate).
- Consider alternate anti-reflux treatment using H2RAs

in those taking clopidogrel or SSRIs (Moderate).
• Avoid the use of any gastric acid-reducing treatments in patient taking oral cefuroxime (High) or mesalamine (Moderate).

H2RAs: Ranitidine

Patient Populations at Risk: **Tobacco Smoking, Diabetes, Chronic Kidney Disease**

Unlike cimetidine and traditional H2RAs, ranitidine structurally lacks the imidazole ring responsible for the inhibition of cytochrome P450 enzymes. However, inhibitory effects on particular cellular transports proteins including renal organic cation transport (OCT) and protein P-glycoprotein (Pgp) have been demonstrated.[41],[42] As a result, the distribution of medications which use these transporters is enhanced, generally leading to increased absorption and decreased elimination.

Varenicline (Chantix®), a partial nicotinic receptor agonist used to aid with smoking cessation, is known to be partially secreted via renal OCT. Concurrent use with ranitidine may decrease varenicline elimination, resulting in higher incidence of side effects and toxicity.[42] Chantix® prescribing informationsuggests close monitoring for the development of side effects including headache, nausea, agitation, and abnormal dreams when used with a H2 receptor antagonist.[43]

The monograph for the Canadian product,Champix®, warns against the concurrent use of ranitidine in patients with severe renal impairment (estimated creatinine clearance <30 mL/min).[44] More serious side effects such as suicidal ideation and depression have been associated with varenicline use, although a recent meta-analysis found no evidence of increased suicide ideation, attempt, or death in patients taking the medication.[45]

The sulfonylureas, glipizide and glyburide, are used as adjunct therapy in diabetes mellitus management. Hypoglycemia is the most common and serious side effect of this medication class. Two studies have suggested that the blood sugar-lowering effects of these medications may be augmented by ranitidine use.[46],[47] However, additional studies have demonstrated conflicting results specific to ranitidine.[48],[49]

Recommendations

• Avoid the concurrent administration of H2RAs in patients with severe renal dysfunction taking varenicline (Moderate).
• Despite the conflicting evidence to support the interaction, we suggest avoiding the use of H2RAs in patients with diabetes who are receiving sulfonylureas agents, as hypoglycemia is a potentially serious adverse effect. Consider the use of PPIs as an alternate anti-reflux treatment in these patients (Low).

3.2 | Antibiotics

With a myriad of antibiotics available, the task of creating an all-encompassing summary is out of the scope of this report. Rather, this discussion focuses on the commonly used antibiotics in the outpatient setting, per the Pocket Guide to Antimicrobial Therapy in Otolaryngology – Head and Neck Surgery.[50] These include respiratory fluoroquinolones such as levofloxacin, aminopenicillins such as amoxicillin/clavulanate (Augmentin®), azithromycin, and clindamycin (Table 4).

Table 4: *Select interaction profile of commonly used antibiotics. Note, the table is not all-inclusive for the potential interactions of these medication classes.*
† This interaction only applies to oral luoroquinolfones and oral calcium salts.

		Adverse Effect (ADE)	Category	Recommendation
Respiratory Fluoroquinolones	**QTc Prolonging Agents:** i.e. Amiodarone, Procainamide, Sotolol	QT prolongation, ventricular tachyarrhythmias	X	High
	Calcium Salts†	Decreased antibiotic efficacy	D	High
Aminopenicillins	**Probenecid**	Increase antibiotic half-life	D	High
	Allopurinol	Hypersensitivity rash	C	Moderate
Macrolides	**QTc Prolonging Agents:** i.e. Haloperidol (Haldol®), Quetiapine (Seroquel®)	QT prolongation, ventricular tachyarrhythmias	X	High

Respiratory Fluoroquinolones: Levofloxacin

Patient Populations at Risk: **Adolescents, Elderly, Myasthenia Gravis, Underlying Cardiac Disease, Diabetes**

The most notorious adverse effects of respiratory fluoroquinolones include tendon rupture and QTc prolongation, which may be more prevalent in the elderly population. Fluoroquinolones may also exacerbate muscle weakness in patients with myasthenia gravis and should be avoided completely in this population.[51] Recently, the FDA released a Drug Safety Communication stating that

fluoroquinolones may cause significant decreases in blood sugar and certain psychiatric side effects.[52] Thus, otolaryngologists should be aware of the potential risk of glucose homeostasis abnormalities, including the risk of hypoglycemic coma, when prescribing to patients, especially those taking oral hypoglycemic medicines or insulin. Product labeling, case reports, and large scale studies have all described such outcomes associated with fluoroquinolone use.[53],[54],[55],[56],[57]

Fluoroquinolones are among the numerous non-cardiac medications associated with QTc prolongation and their usage should be avoided in patients taking other QTc-prolonging agents. The breadth of medications associated with QTc changes is too vast for this discussion. In an effort to illustrate this potential interaction, we highlight patients taking Class III anti-arrhythmics-amiodarone, procainamide, or sotolol-as an example. Concomitant fluoroquinolone use with these medications has been associated with significantly increased risk of ventricular tachyarrhythmias and torsades de pointes.[58],[59],[60],[61] Patients with underlying risk factors such as older age, metabolic arrangements, and underlying heart disease are at an elevated risk for these potential fatal toxicities.

Finally, fluoroquinolones should not be taken simultaneously with oral calcium or magnesium products, including calcium carbonate antacids.[62],[63],[64] These divalent cations chelate the antibiotics, decreasing their absorption and reducing their antimicrobial efficacy. Such, the intake of fluoroquinolones and calcium supplements should be spaced in time. For example, levofloxacin should be administered at least 2 hours before or 2 hours after antacid administration.

Recommendations

• As a result of their serious adverse reactions and associations, we suggest that fluoroquinolone use be reserved, such as for treatment-resistant acute sinusitis (Low).

• Fluoroquinolones administration should be strictly avoided in patients concurrently taking cardiac or non-cardiac agents known to cause QTc prolongation (High).

• Otolaryngologists should counsel patients on the early symptoms of glucose hemostasis derangements when prescribing fluoroquinolones (High).

Aminopenicillins: Amoxicillin/Clavulanate (Augmentin®)

Patient Populations at Risk: **Gout**

Perhaps the most widely used antibiotic for infectious diseases of the head and neck, the adverse effects of aminopenicillins are well established. Life-threatening anaphylaxis or hypersensitivity reactions may occur in patients on penicillin therapy, and amoxicillin should be avoided in patients with a history of a beta-lactam allergy. The pediatric incidence of antibiotic associated diarrhea is estimated to be 8% for amoxicillin use and 20% for amoxicillin/clavulanate use.[65]

Allopurinol, a medication used to treat gout, may increase the serum concentrations of aminopenicillins and potentiate the risk of developing an allergic cutaneous reaction. Two epidemiological studies demonstrated an increase in the incidence of skin rashes in those taking both medications compared to those taking aminopenicillins alone.[66],[67] Another medication used in the treatment of gout, probenecid, may increase the serum concentration of amoxicillin when co-administered. Several studies have shown that probenecid competes for renal tubular excretion of aminopenicillins and may double its circulating half-life.[68],[69],[70]

Recommendations

• Avoid the use of aminopenicillins in patients actively receiving probenecid or allopurinol therapy for gout (High).

Macrolides: Azithromycin

Patient Populations at Risk: **Neonates, Hepatic Impairment, Stem-Cell Transplants, Mental Health Disease Requiring Antipsychotics**

Belonging to the macrolide class of antibiotics, azithromycin is frequently prescribed in high doses for a short interval. Their usage should be used with caution in patients with preexisting liver disease, as macrolides have been linked to drug-induced liver injury and hepatoxicity.[71] The use of macrolide antibiotics in newborn infants is strongly associated with the development of hypertrophic pyloric stenosis. Also, maternal use of macrolides during the first two postpartum weeks is associated with an increased risk of infantile hypertrophic pyloric stenosis.[72] Therefore, otolaryngologists should avoid the use of these antibiotics in neonates and new mothers.

The FDA issued a warning against chronic azithromycin use in patients with a history of hematopoietic or lymphatic cancers who have received a stem cell transplant. A large clinical trial found that chronic azithromycin use in such patients was associated with an increased rate of neoplastic relapse and subsequent death.[73]
Similar to fluoroquinolones, azithromycin is considered a QTc-prolonging agent of moderate risk. Therefore, the aforementioned conclusions concerning fluoroquinolone use are applicable to azithromycin. In another example to further demonstrate the extent of the medications known to prolong QTc interval, azithromycin use should be avoided in patients taking anti-psychotics such as haloperidol (Haldol®) or quetiapine (Seroquel®).

Recommendations

• Avoid the use of macrolide antibiotics in neonates or mothers within two weeks postpartum (High).
• Avoid the concurrent use of macrolides in patients taking agents known to cause QTc-prolongation such as antipsychotics (High).
• Avoid the long-term use of azithromycin in patients with a history of allogenic stem cell transplant for hematological malignancies (Moderate)

Clindamycin
Patient Populations at Risk: **None identified**
Commonly linked with clindamycin, the development of Clostridium difficile associated diarrhea is a severe adverse effect that is potentially fatal if left untreated. C. difficile colitis should be considered in all patients who develop diarrhea up to two months following its use.[74] A recent population based study demonstrated that patients receiving clindamycin were 3 times more likely to develop a MRSA infection and 2.76 times more likely to develop C. difficile infection compared to matched controls.[75]

Recommendations

• We recommend prompt escalation of care for patients whom develop intractable diarrhea following a course clindamycin (High).

4 | CONCLUSION

Various adverse effects and drug interactions of common medications used in the practice of Otolaryngology are of severe consequence to patient safety. Although health technology and multidisciplinary care aim to reduce their incidence, the majority of adverse sequelae remain physician-dependent. The summaries presented in this report serve to promote otolaryngologists' awareness of potential implications in the prescription of commonly utilized intranasal corticosteroid sprays, anti-reflux medications, and antibiotics. Further, this data will aid in the identification of at-risk patient populations. By providing a consolidated collection of this data and evidence-based recommendations, we believe this report is significant in both tooling otolaryngologists for proper prescribing practices and improving the health outcomes of our patients.

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