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Drug Interactions With Oral Inhaled Medications

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Abstract

Objective: To evaluate the potential for drug interactions with oral inhaled medications (OIMs). OIMs include bronchodilators (β-agonists and antimuscarinics), corticosteroids, combination products (2 or more agents combined within a single inhalation device), antibiotics, prostacyclins, anesthetics, acetylcysteine, mucolytics, insulin, antivirals, nitric oxide, and nicotine replacement. **Data Sources:** A systemic literature search (1980 to May 2018) was performed using PubMed and EBSCO to locate relevant articles. The MESH terms used included each specific medication available as an OIM as well as "drug interactions." DAILYMED was used for product-specific drug interactions. **Study Selection and Data Extraction:** The search was conducted to identify drug interactions with OIMs. The search was limited to those articles studying human applications with OIMs and publications using the English language. Case reports, clinical trials, review articles, treatment guidelines, and package labeling were selected for inclusion. **Data Synthesis:** Primary literature and package labeling indicate that OIMs are subject to pharmacokinetic and pharmacodynamics interactions. The most frequently identified clinically significant drug interaction is an inhaled corticosteroid when combined with a potent CYP 450 inhibitor such as a protease inhibitor or antifungal. **Conclusions:** The available literature indicates that OIMs are associated with clinically significant drug interactions and subsequent adverse reactions. Clinicians in all practice settings should be mindful of this potential to minimize adverse effects and optimize therapy.

Keywords

drug interactions, oral inhaled medication, β-agonist, antimuscarinic, corticosteroid, antibiotics, prostacyclins, antivirals, mucolytics, nicotine

Introduction

Oral inhaled medications (OIMs) are widely used for acute and chronic treatments of various respiratory diseases including asthma, chronic obstructive pulmonary disease, pulmonary arterial hypertension, cystic fibrosis, pulmonary infections, and nicotine use disorder. OIMs include bronchodilators (β-agonists and antimuscarinics), corticosteroids, combination products (2 or more agents combined within a single inhalation device), antibiotics, prostacyclins, anesthetics, acetylcysteine, mucolytics, insulin, antivirals, nitric oxide, and nicotine replacement.

Most clinicians believe the main advantage of OIMs is significant drug deposition to the site of action (the lungs) with minimal systemic effects. In reality, OIM products can have tracheobronchial absorption, can undergo metabolism, and can subsequently lead to drug interactions with oral or injectable medications.[1] Commonly used classes of OIMs with the greatest potential for systemic drug interactions include bronchodilators, corticosteroids, antibiotics, prostacyclins, anesthetics, acetylcysteine, mucolytics, insulin, antivirals, nitric oxide, and nicotine. The underappreciation of potential systemic effects of OIMs stems from the relatively limited clinical data regarding the systemic absorption of OIMs.

Medication metabolism can occur within the liver, kidney, intestines, and to a lesser extent within the blood. Many medications are metabolized by the liver. Phase I metabolism involves liver metabolic reactions of oxidation, reduction, and hydrolysis. The cytochrome (CYP) 450 isoenzymes are largely involved with phase I metabolism. The CYP 450

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isoenzymes are a group of heme-containing enzymes embedded primarily in the lipid bilayer of the endoplasmic reticulum of hepatocytes. While there are more than 30 CYP 450 isoenzymes identified to date, CYP 3A4, CYP 2D6, CYP 1A2, and the CYP 2C subfamilies are responsible for the vast majority of drug metabolism in the liver. Phase II hepatic metabolism involves the metabolic process of conjugation.[2]

Drug interactions can occur with food (eg, blocking drug absorption), with disease (eg, producing worsened of symptoms), or with other drugs (eg, resulting in exacerbated or antagonistic effects). Drug-drug interactions can further be classified as pharmacodynamic or pharmacokinetic interactions. A pharmacodynamic interaction is where 2 or more medications act at the same receptor or interrelated receptors producing additive, synergistic, potentiated, or antagonistic effects. An example with OIM would be an inhaled β-agonist (eg, albuterol) potentiating the risk of hypokalemia when given concurrently with a loop (eg, furosemide) or thiazide diuretic (eg, hydrochlorothiazide). A pharmacokinetic drug interaction involves changes in the absorption, distribution, metabolism, and excretion of a drug and/or its metabolite(s). Pharmacokinetic drug interactions commonly occur when the administration of one drug results in the inhibition or induction of hepatic metabolism of another drug. An example of a pharmacokinetic interaction involving an OIM would be when the inhaled corticosteroids (ICS) budesonide (metabolized by the liver isoenzyme CYP P450 3A4) is given concurrently with a known inhibitor of CYP 3A4 such as the antifungal ketoconazole. The resultant effect in this instance is increased corticosteroid exposure, which may manifest as adrenal suppression and/or weight gain.

It is important for clinicians to identify and understand the clinical relevance of drug interactions with OIMs to better assist patients and improve therapeutic outcomes. Accordingly, this review was undertaken to provide health care providers with a clinically applicable review regarding the potential drug interactions attributable to common OIMs. Currently available OIMs are summarized in Table 1. Case reports/series from the primary literature and product-specific recommendations from the manufacturer are summarized herein by therapeutic class. Much of data available for drug interactions with OIMs were found in package labeling and not from the primary literature. In clinical trials, drug interaction evaluation was limited to other inhaled medications. Drug interaction screening programs may not include package labeling as these data do not lend to the same quality of clinical evaluation as a published study or case report.

Data Sources

A systemic literature search (1980 to May 2018) was performed using PubMed and EBSCO to locate relevant articles. The MESH terms used included each specific medication available as an OIM as well as "drug interactions." DAILYMED was used for product-specific drug interactions. The search was limited to those articles studying human applications with OIMs and publications using the English language. Case reports, clinical trials, review articles, treatment guidelines, and package labeling were selected for inclusion.

Drug Interactions With β-Agonists

Short-acting β-agonists (SABAs) include albuterol (nebulizer solution, inhalers) and levalbuterol (nebulizer solution and inhaler). SABAs have potential interactions with β-blockers, diuretics, digitalis, and monoamine oxidase inhibitors (MAOIs).[3-9] Beta-blockers can decrease the effectiveness of SABAs and produce severe bronchospasm in asthmatic patients. If a β-blocker is required in an asthmatic or chronic obstructive pulmonary disease patient (eg, prophylaxis after myocardial infarction), a cardioselective agent such as metoprolol should be chosen, and its use should be carefully monitored. When given concurrently with non-potassium-sparing diuretics (loop or thiazide), SABAs can potentiate hypokalemia or electrocardiography (ECG) changes—especially if the SABA use exceeds the recommended dose. Careful monitoring of serum potassium is mandatory in this situation. MAOIs (phenelzine, isocarboxazid, tranylcypromine) and tricyclic antidepressants (TCAs; amitriptyline, doxepin) may potentiate the effect of albuterol on the cardiovascular system by prolonging the QTc interval. Coadministration of these agents with albuterol results in an increased risk of ventricular arrhythmias. Increased incidence of cardiac events can be seen with the concurrent use or when albuterol is used within 2 weeks of stopping MAOI or tricyclic therapy. In addition, other sympathomimetic bronchodilators such as epinephrine should not be routinely used concomitantly with SABAs.

Long-acting β-agonists (LABAs) include salmeterol, formoterol, arformoterol, indacaterol, and olodaterol. LABAs have a similar drug interaction profile as SABAs with regard to other adrenergic medications, β-blockers, diuretics, MAOIs, and TCAs.[10-14] Salmeterol is a substrate of CYP 3A4. The use of strong CYP P450 3A4 inhibitors (ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, ketoconazole, telithromycin) is not recommended with salmeterol as concurrent administration can lead to increased risk of cardiovascular adverse effects.[10] Concomitant use of a LABA with xanthine derivatives (aminophylline, theophylline) or steroids (prednisone, methylprednisolone) may potentiate any hypokalemic effect of adrenergic agonists.[11,12,14] Drug interaction studies indicate that CYP 450 3A4 and P-gp inhibitors (ketoconazole, erythromycin, verapamil, ritonavir) may decrease the systemic clearance of indacaterol; however, no dose adjustment is required for the 75 μg dose.[13] Ketoconazole can also

Table 1. Oral Inhalation Therapies.

Agent	Formulation
SABA	
Albuterol (generic)	Neb
Albuterol HFA MDI (ProAir, Proventil, Ventolin)	MDI
Albuterol (ProAir RespiClick)	DPI
Levalbuterol (generic)	Neb
Levalbuterol (Xopenex HFA)	MDI
LABA	
Salmeterol (Serevent Diskus)	DPI
Formoterol (Perforomist)	Neb
Arformoterol (Brovana)	Neb
Indacaterol (Arcapta)	DPI
Olodaterol (Striverdi Respimat)	ISI
SAMA	
Ipratropium (generic)	Neb
Iptratropium (Atrovent HFA)	MDI
LAMA	
Tiotropium (Spiriva HandiHaler)	DPI
Tiotropium (Spiriva Respimat)	ISI
Aclidinium (Tudorza Pressair)	DPI
Umeclidinium (Incruse Ellipta)	DPI
Glycopyrrolate (Seebri Neohaler)	DPI
Glycopyrrolate (Lonhala Magnair)	Neb
SABA/SAMA combination	
Albuterol/ipratropium (Combivent Respimat)	ISI
Albuterol/ipratropium (DuoNeb)	Neb
LAMA/LABA combination	
Umeclidinium/vilanterol (Anoro Ellipta)	DPI
Tiotropium/olodaterol (Stiolto Respimat)	ISI
Glycopyrrolate/indacaterol (Utibron Neohaler)	DPI
Glycopyrrolate/formoterol (Bevespi Aerosphere)	MDI
ICS	
Becomethasone (QVAR HFA)	MDI
Budesonide (Pulmicort Respules)	Neb
Budesonide (Pulmicort Flexhaler)	DPI
Ciclesonide (Alvesco)	MDI
Flunisolide (Aerospan HFA)	MDI
Fluticasone propionate (Flovent Diskus)	DPI
Fluticasone propionate (Flovent HFA)	MDI
Fluticasone propionate (ArmonAir RespiClick)	DPI
Fluticasone furoate (Arnuity Ellipta)	DPI
Mometasone (Asmanex Twisthaler)	DPI
Mometasone (Asmanex HFA)	MDI
ICS/LABA combination	
Fluticasone propionate/salmeterol (Advair Diskus)	DPI
Fluticasone propionate/salmeterol (Advair HFA)	MDI
Fluticasone propionate/salmeterol (AirDuo RespiClick)	DPI
Fluticasone furoate/vilanterol (Breo Ellipta)	DPI
Budesonide/formoterol (Symbicort)	MDI
Mometasone/formoterol (Dulera)	MDI
ICS/LAMA/LABA	
Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta)	DPI
Antibiotics	
Azteronam (Cayston)	Neb
Tobramycin (TOBI, Bethikis, Kitabis PAK)	Neb
Tobramycin (TOBI Podhaler)	DPI
Protacyclins	
Iloprost (Ventavis)	Neb
Trepostinil (Tyvaso)	Neb
Anesthetic agents	
Desflurane (Suprane)	Solution
Isoflurane (Forane)	Solution
Sevoflurane (Ultane)	Solution
Miscellaneous agents	
Acetylcysteine	Neb
Dornase alfa (Pulmozyme)	Neb
Human insulin (Afrezza)	Cartridge
Pentamidine (NebuPent)	Neb
Ribavirin (Virazole)	Neb
Nitric oxide (INOmax)	Gas
Nicotine (Nicotrol)	Cartridge

Abbreviations: DPI, dry powder inhaler; ICS, inhaled corticosteroids; ISI, inhalation spray inhaler; LABA, long-acting β-beta agonist; LAMA, long-acting anticholinergic agent; MDI, metered dose inhaler; Neb, nebulizer; SABA, short-acting β-agonist; SAMA, short-acting anticholinergic agent.

increase the plasma concentration of olodaterol via dual CYP P450 3A4 and Pg inhibition, but clinical studies indicate no dosage adjustment is necessary.[14,15]

Drug Interactions With Anticholinergics

Ipratropium is the sole short-acting antimucarinic agent (SAMA). This product is available as inhalation solution (generic) and HFA inhaler (Atrovent HFA). No drug interactions are included in the ipratropium inhalation solution package label.[16] The HFA product label indicates that ipratropium may have additive anticholinergic effects with concurrently used anticholinergic-containing medications.[17] Examples of medications with anticholinergic activity include antidepressants (amitriptyline, paroxetine), antihistamines (diphenhydramine, hydroxyzine, chlorpheniramine), agents for overactive bladder (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium), anti-Parkinson agents (benztropine, trihexyphenidyl), antipsychotics (olanzapine, quetiapine, haloperidol), cardiovascular agents (disopyramide), atropine, hyoscyamine, and cyclobenzaprine.[18]

This potential interaction is better described with the long-acting antimuscarinic agents (LAMAs), as they were marketed much later than ipratropium.

LAMAs include tiotropium, aclidinium, umeclidinium, and glycopyrrolate. While these agents have minimal systemic absorption, they do have the potential to cause dry mouth, increased intraocular pressure, and urinary retention. As mentioned above, there is also a potential for an additive interaction with concomitantly used anticholinergic medications.[19-24] Such additive anticholinergic effects could be a concern for patients with narrow angle glaucoma, prostatic hyperplasia, or bladder neck obstruction. It is generally recommended to avoid the use of LAMAs in combination with systemic medications that may lead to an increased anticholinergic adverse effect.

Drug Interactions With β-Agonist and Anticholinergic Combination Products

SAMA/SABA combination products include ipratropium/albuterol soft mist inhaler (Combivent Respimat) and nebulizer solution (DuoNeb). Drug interactions include the additive effect of ipratropium with anticholinergic agents, and the concerns for β-agonist (albuterol) use with other adrenergic agents, β-blockers, diuretics (loop or thiazide), and MAOIs and/or TCAs as described in the β-agonists section.[25,26]

LAMA/LABA combination products include umeclidinium/vilanterol (Anoro Ellipta), tiotropium/olodaterol (Stiolto Respimat), glycopyrrolate/indacaterol (Utribron Neohaler), and glycopyrrolate/formoterol (Bevespi Aerosphere). In general, many of the same potential drug interactions with each monotherapy product are a concern for the combination products. The use of concurrent β-blockers should be done with caution in patients receiving LABAs, as the bronchodilatory effects may be blocked and subsequent bronchospasm may occur. Diuretics (loop or thiazide) can produce additive hypokalemia or produce electrocardiographic changes. MAOIs and TCAs can potentiate LABA cardiovascular effects (QTc prolongation and risk of ventricular arrhythmias). LAMAs can have an additive effect on concurrently administered anticholinergic medications. This combination should be avoided.[27-30] The use of strong CYP 3A4 inhibitors (ketoconazole, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) with vilanterol may produce cardiovascular effects. Caution should be exercised with this combination as vilanterol is a substrate for CYP 3A4.[27] Other adrenergic medications should be used with caution with olodaterol, indacaterol, or formoterol as the β-agonist effect may be potentiated. Concurrent xanthine derivatives (theophylline, aminophylline) or corticosteroids may potentiate the hypokalemic effect of olodaterol, indacaterol, or formoterol.[28-30] No formal drug-drug interaction studies were conducted with indacaterol/glycopyrrolate or glycopyrrolate/formoterol.[29,30]

Drug Interactions With Inhaled Corticosteroids

ICS monotherapy represents the largest category of inhaled medications as over 10 different products are commercially available. Among all classes of OIMs, the ICS agents are most frequently cited in the literature as a contributor to drug interactions. Most ICS products are substrates of CYP 450 3A4. Significant drug interactions have been reported with budesonide, fluticasone, and mometasone.[31-38] In general, caution should be exercised when these ICS agents are used concurrently with long-term known CYP3A4 inhibitors. Concurrent administration of known inhibitors of 3A4 (ketoconazole, itraconazole, clarithromycin, erythromycin, ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, telithromycin) may inhibit the metabolism and increase the systemic exposure to budesonide, fluticasone, and mometasone.

Potential risks of CYP 3A4 inhibition during therapy with ICS include hyperglycemia, Cushing's syndrome, adrenal suppression, weight gain, osteoporosis, and steroid accumulation. No specific drug interactions are identified with beclomethasone dipropionate HFA, ciclesonide, and flunisolide; these agents may be considered in patients taking concurrent CYP 3A4 inhibitors if clinically appropriate.[39-41]

Not surprisingly, certain patient populations may be at more risk for this interaction when given an ICS. HIV-infected patients may be receiving concurrent protease inhibitors (ritonavir, atazanavir, darunavir, fosamprenavir, saquinavir, indinavir, nelfinavir, tipranavir), which are potent inhibitors of 3A4.[42] Another population with increased risk for toxicity is patients taking prolonged, concurrent azole antifungal therapy.[43] The most common azole-implicated antifungals (fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole) all demonstrate an ability to inhibit CYP 3A4. To date, there are over 60 case reports of drug interactions with ICS both as monotherapy products and as an ingredient in a combination product describing adverse reactions (in both children and adults) as a consequence of combining an ICS with a CYP 450 inhibitor such as a protease inhibitor or antifungal agent.[44-54]

Drug Interactions With ICS and LABA Combinations

There are currently 6 marketed ICS/LABA inhalers. Four of the products contain fluticasone combinations, 1 contains budesonide, and 1 contains mometasone. As expected, the drug interaction potential for this category consists of the additive effects of each individual component. Given the inclusion of fluticasone—a substrate for CYP 3A4—in fluticasone propionate/salmeterol (Adviar Diskus, Advair HFA, AirDuo RespiClick), the concurrent use of strong CYP 3A4 inhibitors is not recommended with these products. As mentioned above, MAOIs and TCAs can potentiate the cardiac effects of salmeterol, β-blockers can antagonize

the effect of salmeterol, and diuretics can potentiate ECG changes and/or associated hypokalemia.[55-57]

Fluticasone furoate and vilanterol (Breo Ellipta) has the same drug interaction profile as products containing fluticasone propionate.[58] Budesonide/formoterol (Symbicort) has the potential for interaction with strong CYP 450 3A4 inhibitors, as these agents can increase the systemic corticosteroid effect of budesonide. MAOIs and TCAs can also potentiate the effect of formoterol on the vascular system when given with budesonide/formoterol. Beta-blockers can antagonize the effect of formoterol and cause bronchospasm while diuretics can produce additive ECG changes or hypokalemia with formoterol.[59]

Mometasone/formoterol (Dulera) is also subject to multiple potential drug interactions. Strong CYP 3A4 inhibitors can increase the systemic corticosteroid effects. Concurrent adrenergic agents can potentiate sympathetic effects. Coadministration of theophylline and/or diuretics can potentiate ECG changes and/or hypokalemia with formoterol. MAOIs, TCAs, and macrolides have additive effect on QTc interval prolongation. Formoterol should be used with caution with β-blockers. Finally, halogenated hydrocarbons have an additive elevated risk of arrhythmias with this combination.[60]

Drug Interactions With ICS, LAMA, and LABA Combinations

The recently approved triple drug combination inhaler containing fluticasone furoate, umeclidinum, and vilanterol (Trelegy Ellipta) has drug interaction potential with each of the individual ingredients as described above.[61]

Drug Interactions With Antibiotics

Tobramycin is available as nebulizer solution and capsule for inhalation.[62-65] No formal drug interaction studies have been performed with TOBI Podhaler.[65] The concurrent and/or sequential use of tobramycin with other medications with neurotoxic, nephrotoxic, or ototoxic potential should be avoided.[62-65] Certain diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Tobramycin should not be administered concurrently with ethacrynic acid, furosemide, or intravenous mannitol.[62-65] Recent clinical studies suggest that oral azithromycin may antagonize the effect of inhaled tobramycin in cystic fibrosis patients with *Pseudomonas aeruginosa* infection.[66] No formal clinical studies of drug interactions with inhaled aztreonam (Cayston) have been conducted.[67] Colistimethate sodium is the prodrug of colistin. This agent is administered off-label via nebulizer for treatment of gram-negative infections. Cephalothin, aminoglycosides, amphotericin B, and nonsteroidal anti-inflammatory drugs may enhance the nephrotoxicity of colistimethate. Colistimethate may potentiate the effect of neuromuscular blocking agents.[68,69] Colistimethate should be compounded immediately before use to reduce possibility of lung toxicity.[70] The aminoglycoside amikacin can also be used off-label via nebulizer for treatment of gram-negative infections. Amikacin has the same drug interaction concern as the aminoglycoside gentamicin.[71]

Drug Interactions With Prostacyclins

Available inhalation-delivered prostacyclins include iloprost (Ventavis) and treprostinil (Tyvaso). Iloprost has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents. There is a potential increased risk of bleeding when iloprost is given to patients maintained on anticoagulants given that iloprost inhibits platelet function. Based on available data, iloprost does not inhibit CYP 450 drug metabolism.[72] The concurrent use of treprostinil with diuretics, antihypertensive agents, or other vasodilators may increase the risk of symptomatic hypotension. No pharmacokinetic or pharmacodynamics studies have been conducted with inhaled treprostinil; however, some studies have been done with oral or subcutaneously administered treprostinil. Treprostinil inhibits platelet aggregation, and as such, may increase the risk of bleeding in patients receiving anticoagulants. In vitro studies indicate treprostinil does not appear to be an inhibitor or inducer of CYP 450 isoenzymes.[73] Epoprostenol (Flolan)[74] is labeled for intravenous use but may be used off-label as inhalation therapy in institution-specific protocols. Epoprostenol is a strong vasodilator and potent inhibitor of platelets, and subsequently has the potential to increase the therapeutic effects of other antiplatelet agents, anticoagulants, and antihypertensive agents.[74]

Drug Interactions With Anesthetics

Inhaled general anesthetics include desflurane (Suprane), isoflurane (Forane), and sevoflurane (Ultane). The agents are halogenated volatile anesthetics and are known to cause QT prolongation and subsequently should be used with caution with other QT-prolonging medications.[75] Midazolam and fentanyl decrease the amount of desflurane needed for anesthesia. Concurrent use of nitric oxide reduced the minimum alveolar concentration of desflurane. Desflurane decreases the dose requirement of neuromuscular blockers utilized in induction of anesthesia.[76] Isoflurane potentiates the muscle relaxant effects of nondepolarizing muscle relaxants, and minimum alveolar concentration is reduced with concomitant nitric oxide.[77] Benzodiazepines, opioids, and nitric oxide would be expected to decrease the minimum alveolar concentration of sevoflurane. Sevoflurane may potentiate the neuromuscular blockade of vecuronium, pancuronium, and atracurium.[78]

Drug Interactions With Miscellaneous Agents

Miscellaneous agents include acetylcysteine, dornase alfa (Pulmozyme), pentamidine (NebuPent), ribavirin (Virazole), nitric oxide gas, and nicotine inhaler (Nicotrol). The available data indicate there are no clinically significant drug interactions involving acetylcysteine or dornase alfa.[79,80] Oral inhaled human insulin has a boxed warning for risk of acute bronchospasm in patients with chronic lung disease. This product may have additive effects when administered concurrently with other medications that can produce hypoglycemia. The glucose-lowering effect of oral inhaled human insulin may be decreased when coadministered with antipsychotics, corticosteroids, estrogens, oral contraceptives, sympathomimetic agents, and thyroid hormones. Dosage adjustment and frequency of glucose monitoring may be required in this situation.[81] No formal drug interaction studies have been conducted with pentamidine. Because of potential additive nephrotoxic effects, the concomitant or sequential use of pentamidine with aminoglycosides, amphotericin B, cisplatin, foscarnet, or vancomycin should be closely monitored and avoided if possible.[82] No formal drug interaction studies with ribavirin have been conducted.[83]

Nitric oxide gas may increase the risk of developing methemoglobinemia with prilocaine, sodium nitroprusside, and nitroglycerin.[84] Inhaled nicotine is a viable option for smoking cessation. Concurrent cimetidine may inhibit the hepatic metabolism of nicotine, thereby increasing the serum concentration. Oral varenicline may enhance the adverse effects of the nicotine inhaler. Inhaled nicotine may induce the hepatic metabolism of theophylline, thereby reducing serum theophylline concentrations. Medication dose adjustment may be required for TCAs or theophylline once patients quit smoking and inhaled nicotine therapy is discontinued.[85]

Conclusion

OIMs may be subject to multiple pharmacokinetic and pharmacodynamic interactions. These interactions are specific to the individual OIM and have various effects including altered drug levels, potentiation of hypokalemia or QTc prolongation, enhanced risk of arrhythmia, additive anticholinergic effects, corticosteroid accumulation with resultant Cushing's syndrome, enhanced risk of toxicity (neurologic, renal, or aural), altered hemodynamics, and increased risk of bleeding. Because some OIMs are less well studied (inhaled antibiotics, dornase alfa, pentamidine, ribavirin), the true potential for drug interactions is not clearly defined with these agents. The OIMs with the most documented potential for drug interactions in the literature outside of the package label are ICS. Adverse effects or potential toxicity may occur when ICS products are combined with a protease inhibitor or an antifungal.

To optimize clinical outcomes, clinicians should have adequate knowledge of all the medications their patients may be taking. Drug interactions with inhaled medications—while commonly not appreciated—are simultaneously important and manageable. As with any other product, the identification, prevention, and resolution of drug interactions with OIMs is a multidisciplinary team responsibility.[86] All prescribers should review and justify each patient's medication regimen regularly with particular attention to screening for drug interactions. Pharmacists are an important resource for interpretation and management of suspected drug interactions. This is a multifaceted effort that includes assisting in medication selection, reviewing every medication order for potential interactions, communicating potential drug interactions to other members of the multidisciplinary team, and assisting in monitoring for adverse reactions. As highlighted in the current review, this endeavor includes attention to recognizing potential drug interactions with OIMs.

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