Over-the-Counter Sinonasal Medicines and Potential for Misuse

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Contents

Abstract

Over-the-counter (OTC) medications are widely available to the general public and, as such, carry potential for misuse and abuse. Sinonasal medications can be

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divided into broad categories: mucoactive agents, oral antihistamines, topical intranasal corticosteroids, oral decongestants, and topical decongestants. Healthcare providers should be well-versed in the potential adverse effects of these easily obtained medications and be capable of identifying patients who are at a high risk for misuse or abuse.

Keywords

Sinonasal medications · Rhinitis medicamentosa · Over-the-counter medicines · Diversion · Mucoactive agents · Methamphetamine production · Topical decongestant · Antihistamines · Corticosteroids · Oral decongestant · Expectorant · Combined formulation · Dextromethorphan · Fluticasone · Pseudoephedrine

Introduction

Medications that are available without a prescription are known as over-the-counter (OTC). Consumers have the ability to choose from a wide array of different medications that are purported to treat many different symptoms. Medicines that treat sinus, cold, or allergy symptoms can be broadly categorized as sinonasal medications. The variety of brands, strengths, and formulations available can be confusing even to many well-informed consumers. Sinonasal medications are also widely consumed. Currently, sinonasal medications make up the largest segment of the OTC drug market in the United States, comprising of approximately 20% of annual sales (Johnsen 2017). A combination of broad availability, wide consumption, and array of brands make sinonasal medications a potential target for misuse and even abuse. While any individual can be at risk for abuse of OTC sinonasal medications, adolescents are particularly high risk because these medications are easily obtained without much cost or effort (Tables 1, 2, 3, and 4). In fact, in a 2005 survey of individuals in grades 7–12, 10% admitted to abusing over-the-counter cough syrup (Partnership for a Drug-Free America 2005).

Currently, the main types of OTC sinonasal medications can be categorized as mucoactive agents, oral antihistamines, topical intranasal corticosteroids, and oral or topical decongestants. Combined formulations are also commonly available over-the-counter.

Common Over-the-Counter Medications

Expectorants

Expectorants are mucoactive agents that loosen secretions in order to allow patients to more easily expectorate them. The most commonly available OTC expectorant is guaifenesin (marketed as Mucinex and Robitussin), which was approved by the

Table 1 Overview of sinonasal medications

Drug class	Examples	Mechanism of action	Sequelae of misuse
Expectorants	Guaifenesin	Unknown – may thin and loosen mucous to allow expectoration	Overuse has been shown to cause kidney stones in animal models
Antihistamines			
First generation	Diphenhydramine	Nonselective blockade of histamine-1 receptors	Drowsiness, "brain fog," withdrawal symptoms of delirium or seizure-like events
Second generation	Fexofenadine, loratadine, cetirizine	Selective blockade of histamine-1 receptors	Generally safe, some reports of withdrawal symptoms of nasal congestion, throat irritation
Intranasal corticosteroids	Fluticasone, triamcinolone, beclomethasone, budesonide	Glucocorticoid receptor agonists, downregulate inflammation	Epistaxis, nasal irritation, more rarely mucosal atrophy and nasal septal perforation
Decongestants			
Topical	Oxymetazoline, neosynephrine	Causes vasoconstriction, decreasing nasal mucosal edema	Long-term use may cause rhinitis medicamentosa, or rebound nasal congestion
Oral	Pseudoephedrine, phenylephrine	Causes vasoconstriction, decreasing nasal mucosal edema	Acutely may elevate blood pressure. Common target for diversion for methamphetamine production
Combined formulations	Many, containing the above categories and other drugs as well	Numerous, depends on active ingredients	Potential for confusion in patient populations due to over-marketing and use of many brand names

FDA for use in 1952. Despite its marketing, it has not been shown to be effective at thinning secretions at the currently approved dosage (Hendeles 1993).

Antihistamines

Antihistamines can be categorized into first- and second-generation antihistamines. First-generation antihistamines, such as diphenhydramine, were introduced in the 1940s, prior to the existence of regulatory oversight (Simons and Simons 2011). First-generation antihistamines are nonselective in blockade of H_1 receptors, but also commonly have anticholinergic properties as well. They readily cross the blood-brain barrier which can lead to side effects of sedation and memory impairment. Additionally, these medications may not cause users to be sedated, but the other side effects of slowed cognition and impaired psychomotor performance may still be present (Finkle et al. 2002). Thus, users of first-generation antihistamines need to be

Table 2 Common conditions treated by OTC sinonasal medications

Medication	Symptom treated	Common conditions
Expectorants	Thick nasal mucous	Seasonal allergy/hay fever, upper respiratory infections (including viral and bacterial), chronic rhinosinusitis
Antihistamines	Itchy, watery eyes, runny nose, sneezing	Seasonal allergy/hay fever, less likely upper respiratory infections
Intranasal corticosteroids	Runny nose, sneezing, nasal congestion	Seasonal allergy/hay fever, chronic rhinosinusitis, some evidence for treatment of acute bacterial sinusitis, rhinitis medicamentosa
Decongestants (oral and topical)	Runny nose, nasal congestion	Upper respiratory infections, seasonal allergy/hay fever
Dextromethorphan	Cough	Upper respiratory infections
Combined formulations	Thick nasal mucous, pain, fever, cough, runny nose, congestion	Upper respiratory infections, seasonal allergy/hay fever, chronic rhinosinusitis

Table 3 US regulatory legislation pertaining to OTC medications

Act	Year	Effect
Federal Food, Drug, and Cosmetic Act	1938	Set requirements for safety, but not efficacy of drugs
Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act	1951	Prescriptions required for drugs that are habit-forming, require physician supervision for use or drugs originally approved to be prescription only
Kefauver-Harris Amendment to the Federal Food, Drug, and Cosmetic Act	1962	Required pharmaceutical companies to assess efficacy of new drugs
Combat Methamphetamine Act	2005	Limited amount of pseudoephedrine available for purchase by customers, required pharmacies to log pseudoephedrine purchases, required ID for purchase of pseudoephedrine

aware that they may be at risk of injury or harm if using these drugs in certain circumstances.

Second-generation antihistamines, such as fexofenadine, loratadine, and cetirizine, were developed for medical use in the 1990s. Originally prescription only, these medications were approved by the FDA for OTC use in 2001 (Spencer 2002). The primary difference between the first- and second-generation antihistamines is their profile of adverse effects. Second-generation antihistamines are more selective for H_1 receptor blockers than their first-generation counterparts. As such, they avoid the anticholinergic and sedating properties of their predecessors.

Table 4 Common over-the-counter medicines with multiple brand names

Medication	Number of different brand-name formulations	Selected common combination brand names
Phenylephrine hydrochloride	261	Sudafed PE, Advil Congestion Relief, Alka-Seltzer Plus Cold and Sinus Relief, Benadryl-D Allergy Plus Sinus, Robitussin Cough and Cold, Theraflu Cough and Cold, Tylenol Allergy Multi-Symptom
Dextromethorphan hydrobromide	218	Mucinex DM, Robitussin, Vicks DayQuil Cough and Congestion, Zicam Cough MAX, Tylenol Cold and Cough Daytime, Sudafed PE Cold and Cough
Pseudoephedrine hydrochloride	130	Sudafed, Advil Allergy Sinus, Aleve-D Sinus and Cold, Clarinex-D, Claritin-D, Mucinex-D, Sudafed 12 h
Guaifenesin	127	Mucinex, Cheratussin AC, Robafen DM Max, Guaiatussin AC, Mucinex Fast-Max
Diphenhydramine hydrochloride	34	Benadryl, Unisom, Advil PM, Aleve PM, Bayer PM, Excedrin PM, Tylenol Severe Allergy

Adapted from McCoul (2020a), Assessment of Pharmacologic Ingredients in Common Over-the-Counter Sinonasal Medications

Intranasal Corticosteroids

Corticosteroids act as agonists of the glucocorticoid receptor which is expressed in many cells in the human body. Clinically, the intended action is to downregulate inflammatory cellular reactions. While corticosteroids are associated with many side effects, such as weight gain and hair loss, intranasal corticosteroids are topical and thus do not exhibit the same drastic side effect profile as oral or parenteral corticosteroids.

Intranasal corticosteroids are commonly used to treat symptoms of allergic rhinitis or chronic rhinosinusitis. First developed in the 1950s, they were available by prescription only for several decades until 2014, when Nasacort Allergy 24HR (triamcinolone acetate, marketed by Sanofi) was approved for OTC use (McCoul 2020b).

Decongestants

Decongestants are available in both oral and topical formulations. Common oral formulations include phenylephrine and pseudoephedrine, both of which are sympathomimetic drugs that bind to alpha-1 receptors to cause vasoconstriction. The most commonly reported side effects of oral decongestants are difficulty sleeping and headaches (Deckx et al. 2016).

Pseudoephedrine is of particular interest, because it can be used in the production of methamphetamine, a highly addictive stimulant (FDA 2017).

Topical decongestant formulations are also widely available. Oxymetazoline and phenylephrine are common OTC remedies that are also sympathomimetics similar to the oral formulations. Adverse effects of headache and difficulty sleeping are less commonly reported (Deckx et al. 2016).

Combined Formulations

Many of the above medications are available in combined formulations with each other and with other drugs, such as guaifenesin, acetaminophen, ibuprofen, and dextromethorphan hydrobromide. In fact, three quarters of all OTC sinus and allergy medications have more than one active ingredient (Agrawal 1999). While these additives may be safe at dosages available in common formulations, medications such as dextromethorphan can cause dissociative experiences and hallucinations (NSDUH 2008).

Regulation of OTC Medications

Before 1951, there were no criteria to establish the difference between OTC drugs and prescription drugs. That year, the Durham-Humphrey Amendment stated that drugs that are habit-forming require supervision by a health professional to be used safely, and drugs that are originally approved as prescription-only require a prescription for use. Prior to this, the Federal Food, Drug, and Cosmetic Act of 1938 set requirements for establishing the safety, but not efficacy of newly developed drugs. It was not until 1962 with the Kefauver-Harris Amendments that pharmaceutical manufacturers were required to assess the efficacy of newly developed drugs (Ventola 2011). These regulations are largely in place today, with some exceptions for certain medications, such as pseudoephedrine.

Regulation of Pseudoephedrine

Pseudoephedrine, available as an oral and topical decongestant, is of particular interest, because it is widely used in many formulations of sinonasal medications. It is also commonly diverted for use in the production of methamphetamine, a potent and highly addictive stimulant. In an effort to combat illicit manufacture of methamphetamine with pseudoephedrine, the Combat Methamphetamine Epidemic Act of 2005 was enacted. This Act required individuals to present photo identification to purchase products containing pseudoephedrine. It also required stores to limit the amount of pseudoephedrine that an individual could purchase to no greater than 3.6 g/day/purchaser and no greater than 9 g/month/purchaser. Stores are also

required to keep personal information about consumers for at least 2 years in a logbook (FDA 2017).

The Combat Methamphetamine Act has caused pseudoephedrine to occupy a middle ground in terms of regulation between over-the-counter and prescription only, as it is required to be stored in a locked cabinet behind the pharmacy counter. This "behind-the-counter" status still does not require a doctor's supervision, however, creates an additional regulatory barrier in an effort to decrease illicit use of pseudoephedrine. Other common "behind-the-counter" items include supplies such as needles for patients to inject insulin and occasionally formulations containing dextromethorphan (Achey n.d.).

Prevalence of OTC Medicine Use and Misuse

Over-the-counter medications are widely available without a prescription to the general public. While rates of use are difficult to study in the general public, sales of OTC sinonasal medications in 2016 topped all other OTC drug sales with 19.9% of the market, a total of $9.1 billion US dollars (Johnsen 2017). Currently, the leading brand of nasal spray is Flonase (fluticasone propionate, marketed by GlaxoSmithKline), which brought in USD $345 million in sales in 2016 (Johnsen 2016). It is difficult to ascertain total sales of all OTC medications because of their wide variety in brand names and formulations. For instance, according to one study, 47 separate products had the brand name Mucinex, and there were 261 different brand-name formulations of products containing the oral decongestant phenylephrine hydrochloride (McCoul 2020a).

According to the National Survey on Drug Use and Health (NSDUH) in 2006, greater than 3 million people between the ages 12 and 25 report a misuse of OTC medications (NSDUH 2008). Most recent literature explores the use and misuse of dextromethorphan, also known as DXM, in younger populations, which is typically marketed as a cough suppressant rather than a sinonasal medication. More than 140 OTC medications contain dextromethorphan and abuse rates are rising (Ford 2009).

Marketing of OTC Sinonasal Medications

Pharmaceutical marketing can generally be divided into two methods: direct-to-provider and direct-to-consumer advertising. For decades, physicians have been the target of paper, telephone, and door-to-door advertising of new pharmaceutical drugs with the intended effect of increasing prescriptions of those drugs. Physician's offices were provided with branded material including posters, pamphlets, displays, and samples (McCoul 2019). In 2010, the Physician Payments Sunshine Act was enacted and required drug manufacturers and medical supply and device companies to track all financial relationships between healthcare providers and pharmaceutical companies with the intention of decreasing conflicts of interest in the healthcare

industry (Donohue 2006). After the Sunshine Act of 2012, direct-to-provider advertising became much more infrequent (McCoul 2019).

While direct-to-provider advertising has subsided, direct-to-consumer advertising (DTCA) has become much more common. In fact, pharmaceutical company expenditures on DTCA ballooned from $166 million in 1993 to $4.2 billion in 2005 (Donohue 2006). Even in the span of 4 years, between 2012 and 2016, the number of television commercials for drugs doubled (Kaufman 2017). DTCA began in the 1980s in conjunction with increased visibility of patient and consumer rights movements. DTCA opponents say that this increased advertising may mislead patients (Donohue 2006). Indeed, DTCA is far from the norm throughout the world. The United States and New Zealand are the only two countries that allow DTCA with product claims (Blenkinsopp 1996).

DTCA encourages patients to seek out their own treatments without the aid of a prescribing physician. It allows patients to quickly and easily forgo the time and cost of seeing a physician and saves the cost associated with that clinical encounter. This behavior also has drawbacks – patients are more likely to self-diagnose, even if they are poorly informed about health and physiology. Additionally, patients may not be aware of the risks of drug interactions with other medications they may be taking (McCoul 2019).

Financial Cost of OTC Sinonasal Medication Use

Common sinonasal conditions such as chronic rhinosinusitis and allergic rhinitis are a significant cost burden to the healthcare system. Medications to treat upper respiratory ailments accounted for the best-selling segment of the OTC drug market at 1.15 billion units sold in 2017 (Consumer Healthcare Products Association 2017). In 2016, these medications represented the largest share of any over-the-counter medicine at 19.9% of the market, which accounted for $9.1 billion in sales (Johnsen 2017). Chronic rhinosinusitis saw an increased healthcare expenditure in the United States from $5.8 billion in 1996 to $8.6 billion in 2007 (Smith et al. 2015). Patients with allergic rhinitis attend an office visit 3.3 times per year on average and fill 9 prescriptions per year with an associated cost of $1400 per patient per year (Bhattacharyya 2011).

Despite the wide availability and marketing of OTC sinonasal medications, these remedies are associated with a large amount of healthcare expenditure (Fig. 1). This increasing expenditure illustrates that even with increased availability of OTC drugs, healthcare costs still increased over time. Thus, it is difficult to say whether DTCA and the increased awareness of the availability of OTC remedies truly does decrease the cost burden.

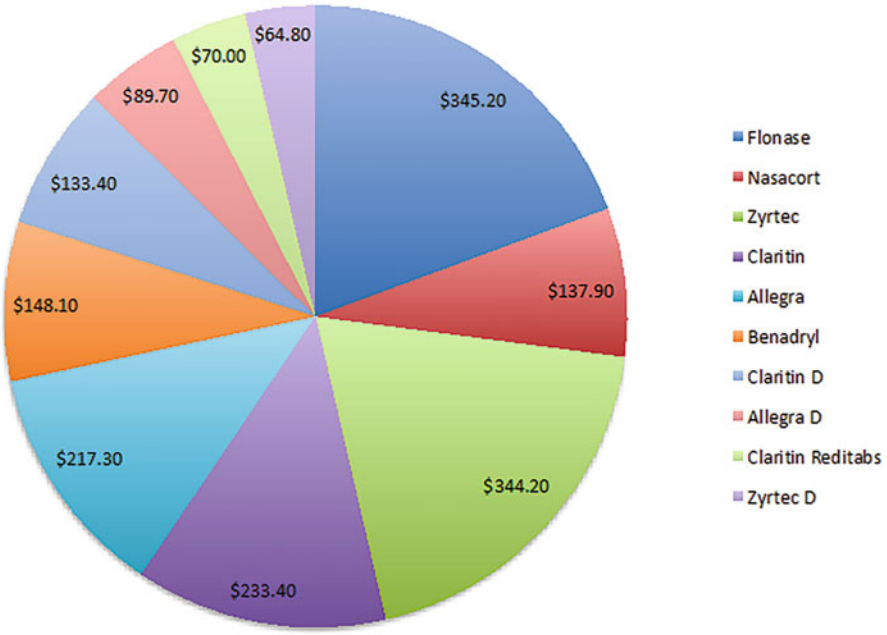

Fig. 1 2016 market share of various brand name over-the-counter medications (in millions of US dollars). (Adapted from Johnsen (2016) – "Flonase continues market strength")

Effects of Misuse of Sinonasal Medications

The misuse of sinonasal medications can be categorized as either divergence or dependence. The wide array of mechanisms of the above medications can lead to sequelae ranging from refractory nasal congestion to death. As such, it is important for the clinician to understand the effects that each of the above groups can have on physical health.

Expectorants

Reports of overdose and abuse of expectorants such as guaifenesin for psychotropic purposes are not currently found in the literature. However, expectorants are commonly found in combined formulations with drugs that are targets for misuse such as dextromethorphan. Guaifenesin may be associated with increased formation of urinary calculi, with one study showing that some uroliths were composed of a common metabolite of guaifenesin, a calcium salt of beta-(2-methoxyphenoxy)-lactic acid (Pickens et al. 1999).

Antihistamines

As mentioned previously, the principal side effects of antihistamines are drowsiness and slowed cognition. Although generally considered safe, the sedating effects are widely known and may be the basis for widespread off-label use. First-generation antihistamines are reported to be the most widely used medication to treat insomnia worldwide (Simons and Simons 2011). If taken in large quantities, antihistamines can produce psychosis, tremors, and seizure-like events (Saran 2017). For diphenhydramine, the typical dose required to produce such effects is thought to be from 300 to 700 mg, while a typical therapeutic daily dose is anywhere from 12.5 to 25 mg (Radovanovic et al. 2000).

Chronic antihistamine abuse has also reportedly caused withdrawal symptoms when the medication is withheld. While not widely reported in the literature, antihistamine withdrawal has been described as causing nausea, nasal congestion, throat discomfort, and irritability. This period lasted approximately 2 weeks, and an oral naltrexone trial was initiated with great improvement of the patient's symptoms (Gracious et al. 2010).

Intranasal Corticosteroids

Abuse of intranasal corticosteroids is not reported in the literature. In fact, intranasal corticosteroids are often used as a treatment for intranasal decongestant dependence, known as rhinitis medicamentosa (RM). Despite the relatively low potential for abuse, it behooves the clinician to be aware of possible adverse effects of intranasal corticosteroids.

Adverse effects of intranasal corticosteroids are more frequently local than systemic. The most frequently cited side effects are epistaxis, throat irritation, nasal dryness, burning, and discomfort with use of the medication. Rarely, more serious side effects such as mucosal atrophy, ulceration, and septal perforation have been reported as well (Sastre and Mosges 2012).

Due to their topical nature, systemic side effects of intranasal corticosteroids are rare. Typical effects of systemic steroids such as suppression of the hypothalamic-pituitary-adrenal axis and stunted growth are rarely reported with intranasal use (Donaldson et al. 2020). Randomized controlled trials have proven the safety of intranasal corticosteroids regarding systemic adverse effects (Allen et al. 2002).

Decongestants

As previously mentioned, decongestants come in two varieties – topical and systemic. Both modalities of treatment have the potential for misuse with untoward consequences. Older decongestants such as dimethylamylamine (DMAA), originally marketed in the 1950s, have the potential to be potent stimulants and have

been found in weight loss supplements. There have been adverse events as severe as cerebral hemorrhage associated with DMAA toxicity (Gee et al. 2010).

Pseudoephedrine is a particular target for misuse in the form of diversion into methamphetamine production, which is discussed below.

Topical decongestant misuse, while not a target for diversion to illicit drug manufacturing, also has potentially harmful effects on patients. Rhinitis medicamentosa is the phenomenon of rebound nasal congestion associated with long-term topical nasal decongestant use. Symptoms are typically nasal mucosal swelling and tolerance induced by topical decongestants. This condition may be precipitated by exposure ranging from 3 days to 6 weeks of chronic decongestant use may predispose patients to rhinitis medicamentosa (Wallace et al. 2008). While the prevalence of RM is difficult to assess due to the ease-of-access of OTC nasal decongestants, the incidence of RM has been estimated to be anywhere from 1% to 9% in otolaryngology offices (Lockey 2006).

The cause of rhinitis medicamentosa has not been firmly established. A leading theory is that nasal decongestants induce tachyphylaxis, a phenomenon wherein higher and higher doses of medications are necessary to achieve the desired effect. Other theories include changes in vasomotor tone or an imbalance of beta-adrenergic activity of decongestants over alpha-adrenergic effects, leading to rebound congestion (Wahidah and Shermetaro 2021).

First-line therapy for RM is typically monotherapy or combination therapy with oral and topical corticosteroids to attempt to wean patients from the nasal decongestant (Black and Remsen 1980). While various corticosteroid regimens are reported, currently there is insufficient data to support a standardized treatment plan for RM (Zucker et al. 2018).

Applications to Other Areas of Addiction

As discussed previously, the most widely known sinonasal medication with ties to other areas of addiction is pseudoephedrine diversion to methamphetamine production. In the United States, it is estimated that approximately 350,000 people abuse methamphetamine yearly (U.S. Department of Health and Human Services 2011). The production of methamphetamine also creates hazardous wastes that require expensive cleanup operations (Missouri Department of Natural Resources n.d.). Additionally, methamphetamine is relatively easy to produce, with many "cooks" or producers being successful on their first attempt. Production of methamphetamine from pseudoephedrine involves a Birch reduction reaction on crushed tablets (Brzeczko et al. 2014).

There have been pharmacologic efforts to attempt to combat the production of methamphetamine. Nexafed is a formulation of pseudoephedrine marketed by Acura Pharmaceuticals, reportedly contains technology that limits the production of methamphetamine while being bioequivalent to other formulations of pseudoephedrine (Brzeczko et al. 2014). The specific production of methamphetamine production is beyond the scope of this chapter.

Other medications discussed in this chapter are not as broadly applied to other areas of addiction, but some may be considered in clinical settings for treatment of sequelae of addiction. For example, mucolytics or nasal corticosteroids may be considered for use in patients who become immunocompromised as a result of intravenous drug use.

Conclusions

Due to the vast market of OTC sinonasal medications and their near-ubiquitous use, it is difficult to truly define the extent of the misuse. These medications are at a high risk for misuse because they are heavily marketed to patients without physician supervision. Additionally, they may have adverse clinical effects that are not immediately recognizable to non-healthcare providers. Oral and topical decongestants and older antihistamines are particularly notable in their potential for misuse. Clinicians should be knowledgeable about the effects of OTC medication misuse to educate patients on their proper use.

Summary Points

- Over-the-counter sinonasal medications account for a large portion of the pharmaceutical market, making them a ripe target for misuse.
- Due to the large number of individuals using these medications, pharmacists and clinicians should be aware of their potential for abuse and misuse.
- While these medications are generally considered "benign," some may have harmful sequelae if used without physician supervision.
- Some sinonasal medications may be used to treat the sequelae of abuse of other sinonasal medications.
- Diversion of over-the-counter medications remains a challenge for prevention of illicit drug production.

Key Facts of Over-the-Counter Sinonasal Medications and the Potential for Misuse

- Greater than three million people ages 12–25 in 2016 reported misuse of over-the-counter medications.
- Combination formulations may contain any number of the mentioned medications, which may cause patient confusion and lead to inadvertent overuse.
- Oral decongestants such as pseudoephedrine are frequent targets for diversion for production of methamphetamine.

- Topical decongestant misuse can lead to a condition known as *rhinitis medicamentosa,* or rebound nasal congestion due to frequent decongestant use.
- Rhinitis medicamentosa can manifest as soon as 3 days of nasal decongestant use.

Mini-Dictionary

- Antihistamine – a type of drug that acts against receptors for histamine, which is commonly released in allergic responses. Thus, antihistamines can be broadly classified as drugs that treat seasonal allergies or hay fever.
- Corticosteroid – a hormone produced by the body that is involved in a variety of responses, but also a type of anti-inflammatory drug for the purposes of this chapter.
- Decongestant – a type of drug that may allow patients to relieve nasal congestion during acute or chronic rhinitis, or inflammation of the nasal passages. Typically they decrease the caliber of blood vessels in the area to create space.
- Epistaxis – clinical term for nosebleed.
- Expectorant – a drug that purports to loosen mucous to allow an individual to more easily expel it from the body (i.e., expectorate).
- Over-the-Counter (OTC) – refers to a drug available for purchase without a prescription.
- Tachyphylaxis – diminishing response to similar doses of a drug causing it to be less effective.

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