OTC Medication Abuse and the Community Pharmacist

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

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Objectives:
At the conclusion of this article, the participant should be able to:
1) Identify the two most commonly abused OTC medications.
2) Describe how these medications are abused.
3) Explain laws and regulations pertaining to these medications.
4) Identify prevention opportunities at the community level.

Background: Several over-the-counter-medications are commonly used for unintended recreational purposes or as ingredients for illicit drugs. Over the years, many restrictions have been placed on the purchase of these medications, but there are always those who seek to find a way around these regulations. As a pharmacist, you are the medication gatekeeper of the community and the responsibility falls on you to prevent the abuse of medication in order to protect your patients. This lesson will be broken down by individual medications in order to go into more depth.

Pseudoephedrine (PSE): Pseudoephedrine is commonly used for its decongestant properties and is found in many cold and allergy products such as Sudafed® and combination allergy products. It exerts its effect directly on alpha- and, to a lesser extent, beta-adrenergic receptors, while also indirectly releasing norepinephrine from its storage sites. This drug's
place in therapy is given primarily by its action at the alpha receptors. When these receptors are stimulated, it causes vasoconstriction in nasal mucous membranes; reducing tissue hyperemia, edema, and nasal congestion while also increasing airway patency. PSE may also relax bronchial smooth muscle contraction by acting on beta-2-adrenergic receptors\(^1\). This sympathomimetic activity is due to pseudoephedrine’s amphetamine structure and with a simple dehydroxylation reaction, it can be turned into the illicit drug methamphetamine\(^{2,3,4}\).

![Pseudoephedrine and Methamphetamine](image)

The conversion from one molecule to the other relies on the use of common products found in both hardware stores and pharmacies. For the purpose of this lesson, the focus will be on products which are easily acquired at the community pharmacy; these are shown in table 1. Most of these products are innocuous on their own, but when purchased in bulk or in combination with other products on this list should raise an alarm.

<table>
<thead>
<tr>
<th>Table 1: Common products used in the production of methamphetamine</th>
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<tbody>
<tr>
<td>Pseudoephedrine tablets</td>
</tr>
<tr>
<td>Iodine</td>
</tr>
<tr>
<td>Rubbing Alcohol</td>
</tr>
<tr>
<td>Coffee filters</td>
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</table>
Methamphetamine is produced illicitly primarily through three syntheses. The first two syntheses require extraction of pseudoephedrine from decongestant tablets before conversion into methamphetamine. These methods have fallen out of favor recently due to the rising popularity of the “one-pot” method. This “one-pot” method requires less work than the previous syntheses while producing acceptable amounts of methamphetamine for the user. This method allows for smaller amounts of PSE to be used which reduces the risk of being caught during purchase. Using a smaller amount also allows for easier concealment of paraphernalia used to produce methamphetamine. Following are descriptions of the three most popular syntheses of illicit methamphetamine production along with explanations of ingredients used and how they can be found in the community setting.

1) One of the earliest and most well-known methods is the Nagai method\(^{(2)}\), which uses hydrogen iodide and red phosphorous to reduce pseudoephedrine to methamphetamine. Due to its availability, iodine has been preferred as a key ingredient, this synthesis is referred to as the “Moscow route”\(^{(2)}\). In these routes, the pseudoephedrine is iodinated to form a leaving group. This leaving group is broken down by other reagents and returns to continue its reactions with pseudoephedrine. Hydrogen gas is produced as a byproduct which leaves the solution and allows the reduction reaction to continue. Many of the ingredients in this reaction can be found in the local department or hardware store which makes these reactions available to almost anyone. Iodine can be found in the first aid aisle of many pharmacies and some meth producers source their iodine from agricultural supply stores. Phosphorous can be
found on kitchen match boxes. Altogether, these materials are very easy to come by and may even be sold in your workplace.

2) Another popular synthesis is the Birch reduction\(^4\). In this reaction, pseudoephedrine is reduced using common ingredients like ammonia and lithium/sodium. The reagents involved in this reduction are extremely volatile and are the source of many methamphetamine laboratory explosion stories. Ammonia is kept under pressure and lithium reacts violently when exposed to water. This reaction has proven to be very popular in the Midwest where liquid anhydrous ammonia is sourced, albeit very dangerously, from pressurized rural fertilizer tanks\(^5\). Other reagents in this reaction are purchased from retail settings including rock salt and lithium batteries.

3) The last and most recently popular method is referred to as the one-pot or “shake-and-bake” method. In this synthesis, PSE tablets along with all the other reagents, are placed in the same container\(^6\). This synthesis gets its name from the fact that all the reactions are allowed to happen at once inside the same vessel. After these initial reactions are allowed to take place, a gas is created which is used to precipitate the methamphetamine crystals. The buildup of this gas requires the reaction vessel to be “burped” every so often to prevent explosion. This synthesis is by far the easiest one to accomplish for small-time methamphetamine producers because of its easily sourced reagents. Ammonium nitrate is a common fertilizer ingredient; lye can be ordered from many sites since it is used in many mundane processes such as soap production; finally, sulfuric acid can be sourced from drain cleaners. This reaction pops up time and time
again on the news when mobile methamphetamine laboratories are discussed because its small reaction vessel is very portable and very easy to hide.

Several laws have been enacted to regulate the sale of pseudoephedrine in an attempt to curb illicit production of methamphetamine. Most notably, the Combat Methamphetamine Epidemic Act of 2005 was signed into law under the USA Patriot Act, Title VII by President George W. Bush on March 9, 2006. Under this law, daily retail sales of PSE per individual were not to exceed 3.6 grams, monthly PSE per individual was not to exceed 9 grams, all non-liquid PSE products were to be sold in blister packs, and mail order fills of PSE were not to exceed 7.5 grams/patient per 30-day period. A logbook was required to be kept of all PSE purchases including such information as purchaser's name/address/signature, date and time of sale, as well as name and quantity of product sold. The purchaser’s information was required to be checked against their photo ID and records of the transaction were to be kept for 2 years. This legislation also required all PSE products to be kept behind the counter and all employees to be trained regarding purchase of PSE.

With these laws in place, those purchasing PSE for methamphetamine production were greatly limited in the quantities they could individually purchase. However, since not all records are electronic and are sometimes specific to stores, several purchases can be made from separate locations without being detected. This allows purchasers to visit multiple sites and bypass the daily and monthly restrictions on PSE purchases. These PSE purchasers trade the pseudoephedrine to methamphetamine producers for either cash or a share of the methamphetamine produced. This method of PSE purchase has continued to work despite the
restrictions imposed since 2006. The records of purchase are more useful in retrospective analysis of purchases than immediate cessation of sales over the limit. The pharmaceutical industry has reported recent annual sales of pseudoephedrine containing products at $600 million with only about half being attributed to legitimate purchases.

Since many procurers of pseudoephedrine for methamphetamine production may be users, it is useful to know common presentations of methamphetamine use. Long-term use of methamphetamine can lead to many negative side-effects including extreme weight-loss, severe dental problems (commonly referred to as "meth-mouth"), anxiety, confusion, violent behavior, insomnia, and mood disturbances. Other symptoms of chronic users may include various psychotic features such as paranoia, delusions, and hallucinations\(^7\). While many of these symptoms are extreme enough to prevent would be purchasers from even entering a pharmacy, several of these are easy ways to spot potential pseudoephedrine diverters.

The most notable sign of methamphetamine use is "meth mouth". Meth mouth occurs due to heavy use of methamphetamine during which a combination of psychological and physiological changes take place. These changes result in xerostomia (dry mouth), long periods of poor oral hygiene, increased consumption of high sugar soft drinks, and bruxism (teeth clenching and grinding)\(^8\). These factors leave the user with broken and blackish-brown teeth which is unmistakable.

To combat the actions of these pseudoephedrine purchases, many states have taken a tougher stance on the issue of sales. In recent years, states such as Oregon and Missouri have passed legislation requiring a prescription in order to purchase PSE. This has been reported to
dramatically decrease the amount of methamphetamine labs operating in these states by
drying up supply of raw materials. Federal legislation has been proposed by Senator Rob
Wyden of Oregon to make PSE available only by prescription. It is believed that this is the only
way to effectively combat illicit methamphetamine labs. Until then, community pharmacists
serve as the first and last line of defense in preventing non-therapeutic PSE sales.

Along with imposing restrictions on availability and access to reagents, novel
formulations of pseudoephedrine itself are being developed. Recently, two companies have
announced products that may dramatically decrease diversion of pseudoephedrine for
methamphetamine production without eliminating the access to products that many seek for
relief. These companies, Acura and Highland Pharmaceuticals, have created drug delivery
systems, named IMPEDE and Tarex, that turn to gel and bind up pseudoephedrine within their
matrices when extractions are attempted\(^9,10\). These devices do not affect absorption of the
drug by the body and thus will not impact those using these medications for their intended
purpose. The medications, named Nexafed (Acura) and Releva (Highland)\(^9\), are currently
undergoing testing to assess their efficacy against methamphetamine production. Trials done
on Nexafed were sponsored by Acura Pharmaceuticals and conducted by an independent
laboratory which then confirmed the results with a law enforcement agency. These trials found
Acura’s IMPEDE technology to stop extraction of pseudoephedrine from Nexafed tablets when
using the two most common pseudoephedrine extraction methods. The newest method of
producing methamphetamine, the one-pot method, does not require extraction before
producing methamphetamine. In one trial testing IMPEDE against the one-pot method, one
hundred tablets each of Nexafed and Sudafed containing 30 mg of pseudoephedrine were used.
After running multiple one-pot tests and using various solvents, an average only 38% of the maximum 2.7g of methamphetamine hydrochloride was able to be recovered from Nexafed. Comparatively, almost twice as much methamphetamine hydrochloride was able to be recovered from Sudafed tablets. Both of these products were found to produce end products averaging only 65% pure methamphetamine hydrochloride\(^{(10)}\). These drugs are expected to come out within the next few months and may prove to be valuable in decreasing pseudoephedrine diversion.

**Dextromethorphan (DXM):** Dextromethorphan is a cough suppressant that comes in several OTC cold remedies, the most popular brands being Robitussin-DM\(^*\) and Coricidin\(^*\). The abuse of this medication is largely done by youth ranging from 12-18 years old. DXM’s street names refer to the names and appearance of the products from which it is derived. Refer to table 2 for common street names of this medication when it is used illicitly\(^{(11)}\).

<table>
<thead>
<tr>
<th>Product</th>
<th>Street Vernacular</th>
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<tbody>
<tr>
<td>Robitussin-DM(^*)</td>
<td>“Robotrippin”</td>
</tr>
<tr>
<td>Coricidin(^*)</td>
<td>“skittling”</td>
</tr>
<tr>
<td>Liquid DXM preparations</td>
<td>“purple drank”</td>
</tr>
</tbody>
</table>

**Table 2**

Dextromethorphan exerts its cough suppressant effects through CNS stimulation, being a poor antagonist at NMDA receptors (a phencyclidine binding site). When taken in supratherapeutic doses, DXM becomes a dissociative hallucinogen.
In these high doses, DXM causes hallucinations, which are dramatic changes in a person’s perception of reality. Changes caused by hallucinogens include seeing images, hearing sounds, or feeling sensations which seem real but do not exist. These substances can also cause intense and rapid emotional swings. Hallucinogens affect the actions of the central nervous system by disrupting nerve interaction with serotonin. By acting as an antagonist at NMDA receptors, glutamate is stopped from being released which causes rapid release of serotonin \(^{(14)}\). Serotonin is a neurotransmitter whose receptors are found throughout the brain and spinal cord and exerts its effects in the control of behavioral, regulatory, and perceptual systems. These systems are in control of mood, hunger, thermoregulation, sexual behavior, muscle control, and sensory perception\(^{(12)}\).

A dissociative substance is one that distorts perception of sight and sound as well as producing feelings of detachment, otherwise known as dissociation, from the environment and self; while changing perception, these effects are not considered hallucinations. These dissociative effects are caused by blocking the neurotransmitter glutamate from binding to the NMDA receptor. Activation of this receptor is involved in nociception, memory, and response to environment. The most widely known dissociative drug is PCP (phencyclidine), which was developed as an anesthetic for use during surgery\(^{(12)}\). When taken in supratherapeutic doses, dextromethorphan can produce effects that are very similar to those of PCP, which is why dextromethorphan may be referred to as “poor man’s PCP”.
During metabolism of DXM, the liver produces an active metabolite called dextrorphan which is ten times more potent than its precursor molecule at activating these previously mentioned receptors.

When taken at various doses, DXM elicits different physiological responses referred to as plateaus (these are described in table 3) \(^{11}\).

<table>
<thead>
<tr>
<th>Plateau</th>
<th>Dose (in mg)</th>
<th>Behavioral Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{st})</td>
<td>100-200</td>
<td>Mild stimulation</td>
</tr>
<tr>
<td>2(^{nd})</td>
<td>200-400</td>
<td>Euphoria and hallucinations</td>
</tr>
<tr>
<td>3(^{rd})</td>
<td>300-600</td>
<td>Visual disturbances, loss of motor coordination</td>
</tr>
<tr>
<td>4(^{th})</td>
<td>500-1500</td>
<td>Dissociative hallucination</td>
</tr>
</tbody>
</table>

Table 3

The group most likely to abuse DXM is teenagers due to the medications easy accessibility. In the 2011 Monitoring the Future Study done by the National Institute on Drug Abuse; eight, tenth, and twelfth-graders were polled on commonly abused drugs. These groups
were estimated to intentionally abuse cough medication at the rates of 2.7%, 5.5%, and 5.3% respectively \(^{(13)}\).  

**Prevention:** By knowing the purchasing habits of OTC abusers, it is easier to prevent sales of these medications. Several steps can be taken to deter would-be-abusers such as:  

1) Educating staff regarding purchasing habits of OTC abusers: larger quantities, products bought in combination, reading body language of purchaser, knowing laws regarding purchase of PSE and abiding by them.  

2) Keeping commonly abused medications in plain sight of pharmacy to deter would be abusers from over-purchase and shoplifting.  

3) Having a close relationship with community law enforcement and reporting suspicious purchases.  

4) Pay attention to inventory of these medications and track large runs and times they occur at.  

**Conclusion:** There are many things that can be done to prevent over-the-counter medication abuse that are achievable at the community level. As a pharmacist, you can be involved with many decisions that affect the abuse potential of your OTC medications. Actions such as keeping commonly abused products in easy to watch spaces or becoming more proactive with customer service can easily deter both shoplifters and drug diverters. Having knowledge of the chemicals used in methamphetamine synthesis will allow you to be more observant during sales where store products are rung up with medications. By learning some common street vernacular and major side effects of drug abuse, you can more readily identify potential
diverters. On a more active level, medications can be stocked that offer less potential for abuse due to their drug delivery systems. If you are aware of a methamphetamine problem in your area, stocking these medications may aid in reducing the local supply. On the highest level, state legislature can be contacted about the selling of PSE products and discussion on prescription only access could be started. This is by far the most drastic action that can be taken, but patient benefit versus community risk should be considered before taking this route. With the purchase of these medications primarily taking place at the retail setting, it falls on the community pharmacist to police these sales. They are the first and last line of defense in the abuse of over-the-counter medications.

References: