Training starts here...
You care for your patients with schizophrenia and want to offer treatment choices that are right for them.

So open up and have the important conversation about long-acting injections. You might be surprised by what comes of it.
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Making medicines that matter.

Everything we do at Genentech is driven by a desire to make a difference in the lives of patients. Their individual stories inspire our researchers to do groundbreaking science and motivate us all to continue developing new treatment options for people with serious or life-threatening diseases.

To learn more, please visit www.gene.com.
Greetings from the President

TRAINING, OUTCOMES AND ASSESSMENT

Training is an essential element of our industry. Correct Rx provides hundreds of educational sessions each year. The training modules may be part of a transition schedule or instructions on how to use a new technology or an in-service on the proper treatment of a particular disease state but the goal is always to provide necessary information to produce a successful outcome.

AUDIT ASSESSMENT AND TOOL

It all started with revamping our medication room audit tool. Correct Rx views the medication room audit as a valuable way to evaluate if the medication room is in compliance with the facility’s, accrediting bodies, State and Federal standards. As correctional standards have evolved over the years the tool utilized to monitor the compliance measures needs to be updated and expanded to reflect those changes. Almost six (6) months ago Correct Rx embraced this task and now we have a much better instrument. The audits now are more comprehensive and drill down to the necessary detail so that no shortcoming can be overlooked. When a deficiency is noted a corrective strategy is developed along with a follow up assessment plan that closes the loop.

EVALUATING THE EFFECTIVENESS

Evaluation of training can only be effective if the training itself is effective and appropriate. It sounds simple but for years Correct Rx has provided training on a myriad of subjects and although we have been very thorough and proud of the trainings we have provided it hasn’t been until now that our focus has changed to accurately assess the effectiveness of the training.

ONGOING, SUSTAINABLE, COMPREHENSIVE AND SYSTEMATIC

We needed an ongoing, sustainable, comprehensive and systematic approach to measure our learning goals for each training, validate our appraisal instruments, analyze the direct and indirect data and make the necessary adjustments when needed based on the results.

WHERE TO START

There have been entire books written on outcome measures for educational training but as an organization you have to start somewhere if you are going to begin measuring the effectiveness of your training. It was determined by Correct Rx that we would design and implement a more sophisticated formal training process for each of our education modules.

PRODUCTION BUSINESS: WE ARE IN THE MOVIES!

This process threw us literally into the video production business with actors, voice-overs and the development of an assessment tool with hands on case studies for each of the attendees. This major initiative took a significant investment in capital but also in written documentation. This provided the professional actors with a complete step by step script to use while producing the Correct Rx video training.

NOW COMES THE EDITING

Every detail is so important when producing a training video. If the content is not right then the desired outcome will be disappointing and the assessments will reflect the quality of the training. We had every department review each module and we provided our own subject matter experts to oversee the production of each training video while it was being filmed. This extra step was taken to ensure that all key points where included and nothing was overlooked. Finally, Correct Rx asked one of our client partners to review and grade the implementation training module. We were anxious to get feed-back on the content and assessment instruments. This independent critique was vital as we continue to refine and certify the benefits of our educational trainings.

ACCESS TO E-TRAINING PROGRAMS

Correct Rx will be distributing our training programs at each facility where we are the pharmacy vendor but our clients will have access to these training videos through our web site. Through the use of a password our e-training videos will be instantly available to each of our sites and clients for a quick training or refresher on a variety of subjects. With a simple click a Health Administrator can provide training for a newly hired nurse or medication technician on a variety of subjects e.g.: ordering, electronic check in process or proper MAR documentation.

RETURN ON INVESTMENT IS BETTER OUTCOMES FOR CLIENTS AND THEIR PATIENTS

As I wrote in one of my previous letters the purpose of “Innovation should always be to accelerate the success of your clients”. In our case success is defined as better patient care along with controlling unnecessary costs.

The outcome of a professionally produced educational program is medical staffs that have successfully completed the training module and are capable based on their evaluated skills to successfully perform their tasks.

This is Success in every sense of the word.

Best Wishes for an “Innovative” New Year filled with success.

Sincerely,

Ellen H. Yankellow, Pharm. D.
President and CEO
SEASONAL INFLUENZA VACCINE

Don Hamilton, RPh
Each year as the fall and winter season nears in the Northern Hemisphere, residents begin preparation for the anticipated influenza (flu) season. Influenza vaccination programs through local health departments, physician offices, and community pharmacies encourage all eligible patient populations to become vaccinated in an effort to decrease the numbers of individuals who may experience potentially life-threatening responses from the flu virus. Many people choose not to receive the flu vaccine citing various reasons including fears of “illness from the shot” however, the benefits of vaccination far outweigh the risks associated with lack of vaccine protection. The Centers for Disease Control and Prevention (CDC) reports a range of flu related death over the past 31 years between 3,300-49,000 deaths per year; additionally, seasonal influenza causes more than 200,000 hospitalizations in the United States annually resulting in economic costs estimated in the billions.

Flu-like illness was first mentioned in medical literature by Hippocrates some 2,400 years ago. The first influenza pandemic was recorded in 1580. Several major pandemics have been reported since that time including the Spanish Flu of 1918-1920 with more than 25 million deaths, the Asian flu of 1957-1958 with nearly 1.5 million deaths, and the Hong Kong Flu of 1968-1969 with nearly 1 million deaths. Most recently, the Swine Flu of 2009 caused more than 14,000 deaths.

Treatment modalities were limited during the early pandemics as physicians treated patients symptomatically and tried to find remedies that would slow down the spread of the illness. The flu virus was allowed to run its course as there was no pharmacological agent available to combat the disease. The first significant scientific advance towards vaccination occurred in 1931. Viral growth in embryonated hens' eggs was reported by researchers at Vanderbilt University. This work was extended by a small group of scientists leading to the first experimental influenza vaccines. By the Second World War, the U.S. military had developed the first inactivate vaccines. From that time until today, advances continue to be made in the influenza vaccine development.

Current influenza vaccine research includes work on molecular virology and evolution, host immune responses, genomics and epidemiology. From this work influenza countermeasure such as vaccines, therapies and diagnostic tools can be made. The goals of research are to determine how the virus enters human cells, replicates, mutates and evolves into new strains. Methods have evolved to streamline the development, production, and distribution of vaccines, enabling a quick response to new pandemic threats thereby potentially saving thousands of lives.

VACCINE STRAINS
The influenza viruses included in each year’s vaccine are chosen by the Food and Drug Administration (FDA) based on recommendations from the World Health Organization (WHO). Experts from the FDA, WHO, CDC and other institutions study viral samples collected from around the world to identify the viruses most likely to cause illness during the next season. The seasonal flu vaccine is a trivalent vaccine with each component selected to protect against one to the three main groups of flu viruses circulating in humans. Thus the chosen composition of the vaccine should maximize the chance that it will protect against the viruses most likely to spread and cause illness within the population.

The 2011-2012 U.S. seasonal influenza vaccine virus strains are identical to those contained in the 2010-2011 vaccine. The vaccine includes: A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The influenza A (H1N1) vaccine virus strain is derived from a 2009 pandemic influenza A (H1N1) virus.

<table>
<thead>
<tr>
<th>Table 1: Trivalent Inactivated Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>VACCINE PRODUCT</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Regular Dose Intramuscular (Fluzone ®)</td>
</tr>
<tr>
<td>High Dose Intramuscular (Fluzone-High Dose®)</td>
</tr>
<tr>
<td>Regular Dose Intradermal (Fluzone-Intradermal ®)</td>
</tr>
</tbody>
</table>

AVAILABLE VACCINE PRODUCTS
The flu vaccine currently comes in two forms: Live Attenuated Influenza Vaccine (LAIV) and Trivalent Inactivated Vaccine (TIV). The most commonly administered form of influenza vaccine is the Trivalent Inactivated Vaccine (TIV). The vaccine contains inactivated or killed virus. There are three types of TIV available on the market this year: Regular Dose Intramuscular (various manufacturers), High Dose
Intramuscular (Fluzone-High Dose®), and Regular Dose Intradermal Injection (Fluzone-Intradermal ®). (Table 1) The LAIV, also known as the nasal spray formulation contains weakened live virus. This product should only be used in healthy, non-pregnant patients. The nasal spray is an option for patients with a needle aversion who are between the ages of 2-49 years of age who meet the aforementioned criteria.

In May 2011, the intradermal formulation of the flu vaccine was approved by the FDA. This is a unique product which uses a novel microinjection delivery system which provides consistent depth of injection with no need to vary needle length or injection technique by patient age, sex, muscle mass or body mass index. The system also features needles that are approximately 90% shorter than those necessary for the intramuscular flu shot.

RECOMMENDATIONS FOR VACCINATIONS

The CDC recommends that everyone age six months or older receive an annual influenza immunization. For optimal production of protective antibody levels, immunization should occur prior to the onset of influenza activity in the community. Providers should offer the immunization as soon as the vaccine is available and vaccination should continue throughout the influenza season and be provided to patients for whom immunization was delayed. Vaccination is required yearly due to the decline of immunity over time and lack of reliable protection provided beyond one year.

The following groups have been designated as targeted populations to receive the vaccine:
- Pregnant Women
- Children < 5 years of age
- Adults ≥ 50 years of age
- Patients at an age with chronic medical conditions (i.e. Cardiovascular disease, Asthma, HIV/AIDS, COPD)
- Residents living in nursing homes or other long-term care facilities
- Those who live with or care for those at high risk of complication from flu (i.e. Healthcare workers)

PATIENTS WITH EGG ALLERGY

Special consideration must be given to patients who may have a hypersensitivity to eggs. The Advisory Committee of Immunization Practices (ACIP) recommendations depend on the severity of the patient’s allergy. For example, patients who experience hives after being exposed to egg can receive the vaccine. However, the patients should receive only the trivalent inactivated vaccine; it should be administered by a health care worker knowledgeable about the manifestations of egg allergy, and the patient should be observed for a minimum of 30 minutes post injection for signs of allergic reaction. For patients with a more severe allergic response to egg (i.e. anaphylaxis), administration of the vaccine should be referred to an expert in the management of allergic conditions for further assessment.

VACCINE SAFETY REPORTING

Some side effects from the injectable vaccine that may be experienced by a patient include soreness or redness at the injection site, low-grade fever, body aches, and nausea. These effects, should they occur begin soon after the

Table 2: Egg Assessment Flow Chart

<table>
<thead>
<tr>
<th>Can the person eat lightly cooked egg (e.g., scrambled egg) without reaction?*</th>
<th>Yes</th>
<th>Administer vaccine per usual protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>After eating eggs or egg-containing foods, does the person experience ONLY hives?</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Does the person experience other symptoms such as:</td>
<td>Yes</td>
</tr>
<tr>
<td>- Cardiovascular changes (e.g., hypotension)</td>
<td>- Respiratory distress (e.g., wheezing)</td>
<td>- Gastrointestinal (e.g., nausea/vomiting)</td>
</tr>
<tr>
<td>- Reaction requiring epinephrine</td>
<td>- Reaction requiring emergency medical attention</td>
<td></td>
</tr>
</tbody>
</table>
injection and last for 1-2 days. Adverse effects following administration of LIAV include runny nose, headache, sore throat and cough.

Should a patient experience uncommon adverse reactions, there are two reporting agencies in place to receive data. The Vaccine Adverse Event Report System (VAERS-http://vaers.hhs.gov) is a national program conducted jointly by the FDA and the CDC to monitor the safety of all vaccines licensed in the U.S. VAERS relies on information included in these reports to monitor for clinically serious adverse events or health problems that follow vaccination. Healthcare providers are encouraged to voluntarily report possible adverse events after vaccination even if they are not certain that the vaccination was a causative factor. The Vaccine Safety Datalink (VSD) project is a vaccine safety system used to both identify and confirm adverse outcomes after immunization. This project is a joint venture between the CDC and eight large managed care organizations. This database contains nearly 9 million patients. The VSD project monitors health data weekly for certain adverse events that could be associated with newly licensed vaccines.

Providing the Influenza vaccine to the target population in a timely manner ensures a safer environment for patients, family and caregivers alike. Utilization of the VAERS or VSD systems to report adverse reactions, should they occur provides vital outcome data necessary to provide higher quality vaccine products for the following years. Following the administration guidelines as given by the CDC related to administration of the influenza vaccination and target population is vital to supporting your community successfully through this seasonal flu season.

REFERENCES:
I have decided after many years of dealing with patients both in the ER and in correctional facilities whose chief complaint is constipation that bowel health may be the last taboo subject. No one seems to talk about how to have a proper bowel movement. It is a subject that inevitably causes uncomfortable laughter and too often, is simply not spoken of in society. As a result many people do not understand how their bowels work. I have found this to be a big problem in the jails I work in. Inmates complain of constipation and are bowel-fixated when they are not really constipated nor justified to worry. Often, they need education more than they need laxatives. To this end, I want to discuss several essential factors relating to understanding and treating constipation that may help make your correctional medicine practice a little easier.

1. **THE MOST COMMON CAUSE OF CONSTIPATION IS TOO LITTLE STOOL, NOT TOO MUCH STOOL.**

This is a little counterintuitive, but very true and important to understand. The small intestine absorbs the nutrients from the food we eat and deposits the indigestible bits (mixed with a lot of water) into the colon. The job of the colon is to reabsorb most of the water and thus create feces. The indigestible bits are better known as fiber. The colon moves the mass of fiber and water along by means of peristalsis—the systematic contraction and relaxation of the wall of the colon. If the mass of stool is small, peristalsis has a much harder time moving things along.

For peristalsis to work efficiently there has to be enough stool. If there is too little, the colon has to generate high pressures to move it along and it moves inefficiently. This leads to constipation. The essential teaching point here is that in order to relieve constipation, the absolute most important thing we need is more fiber. Other remedies are not even close to as important. Just about everyone with complaints of constipation should receive more fiber. While it may be difficult to get sufficient fiber from correctional diets alone, you can supplement dietary fiber with fiber tablets or soluble fiber. These should be available on the commissary so inmates can obtain them without requiring a sick call visit.

Similarly, another solution to constipation is to drink more water. Remember that the colon reabsorbs water from the stool given it by the small intestine. If you are dehydrated, the colon will absorb a lot of water, leaving the stool small and hard to pass. So, like a reflex, if you are my patient and you say “constipation,” I am going to say “fiber and water.” These are the single most important parts of constipation therapy.

Incidentally, the “stool softener” laxatives like mineral oil and colace work by making the surface of the stool more permeable to water thereby attracting water back into the stool. This, of course, makes the final product moister and bigger. However, you can achieve the exact same effect by drinking more water. If you are not dehydrated, the colon will leave more water in the stool to begin with.

2. **BOWEL MOVEMENTS OCCUR ON A CIRCADIAN RHYTHM.**

By this I mean that we naturally tend to have bowel movements at approximately the same time every day, usually in the morning. You can’t just have a bowel movement any time you wish. If you try to have a bowel movement at the wrong time of the day, your body may not cooperate.

This is very similar to another natural event that occurs in a circadian fashion—sleep. We tend to go to sleep at approximately the same time every day. If you try to go to sleep at the wrong time of day when your body is wide awake, you may not be very successful.
This fact—the circadian nature of bowel movements—becomes important when prescribing osmotic or stimulant laxatives including dulcolax, milk of magnesia, magnesium citrate, senna and others. These laxatives work by stimulating the colon to contract. They are properly used to try to re-establish a natural rhythm.

Also, just like sleeping aids, if you take laxatives every day, you can become habituated to them so that it becomes hard to have a bowel movement without them. Laxatives are properly used intermittently to re-establish the body’s natural circadian rhythm of bowel movements.

4. YOU NEED TO BE ABLE TO IDENTIFY THOSE “RED FLAG” PATIENTS WHO ARE AT HIGH RISK TO HAVE TRUE CONSTIPATION PROBLEMS.

In most patients, constipation is a nuisance rather than a bad medical problem. I mean by this that even if you don’t treat these patients with anything, they will eventually work things out themselves. I have not seen any patients in my jails explode from constipation. However, there are certain patients who can develop constipation so severe that it becomes a true and urgent medical problem. The most common way for this to happen is to develop a fecal obstruction so large, that the patient literally cannot pass it. Think basketball sized.

It is important to identify who these high-risk patients are.

a. The elderly.
b. Debilitated patients, such as those with cancer or AIDS.
c. Chronic narcotic users (narcotics decrease peristalsis).

If you identify a high risk patient, how can you tell if they have a fecal obstruction? Simple—you do a rectal exam. You will not miss the huge stool mass.

5. THERE ARE TWO OBJECTIVE TESTS TO DETERMINE IF A PATIENT IS TRULY CONSTIPATED.

One of the problems with diagnosing constipation is that we have to take the patient’s word that they are not having normal bowel movements. Often, especially in corrections, the patients may not tell us the truth. When you run into a patient with repeated and incessant complaints of not having bowel movements or in whom nothing works, you can check the validity of the history in two ways.

The first is the rectal exam. Remember that the rectum is the repository for stool preparatory to evacuating it in a bowel movement. The rectum is analogous to the dumpster in my office complex. During the day, all the medical offices take their garbage out to the dumpster. Then once a day, the city garbage truck comes around and empties it. This is very much like our large intestine—during the day, the colon adds finished stool to the rectum and once a day or so, the rectum is emptied.

But what happens if nobody put any garbage into the dumpster? Let’s say that you generally have a bowel movement every day but recently, well, you just have not been eating very much fiber. It may be that your body has not created enough stool for a bowel movement this day. Or maybe, peristalsis slowed down somewhat for whatever reason and your rectum is empty. On that day, you will not feel the urge to have your normal daily bowel movement. That
NOW FDA APPROVED

COMPLERA™
emtricitabine 200mg/rilpivirine 25mg/
tenofovir disoproxil fumarate 300mg tablets

For more information, please speak to your Gilead representative or visit www.complera.com

Please see following pages for brief summary of the COMPLERA Full Prescribing Information, including Boxed WARNINGS about lactic acidosis, severe hepatomegaly with steatosis, and exacerbations of hepatitis B upon discontinuation of therapy.
Adverse Reactions from Clinical Trials Experience: Because serious drug reactions are rare, the incidence of serious drug reactions was determined in clinical trials with 15 mg tablets of "Correct Rx" 200 mg tablets of 80 mg. Inhalation of the drug should not be discontinued until the inhaler. A summary of adverse drug reactions is presented in the following table.

### Table 1: Selected Adverse Reactions by Grade (G1–G4) Reported in ≥2% of Subjects Receiving Correct Rx

<table>
<thead>
<tr>
<th>Grade</th>
<th>Reaction</th>
<th>NCTD</th>
<th>NCTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Headache</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>G2</td>
<td>Nausea</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>G3</td>
<td>Vomiting</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>G4</td>
<td>Anaphylaxis</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Table 2: Selected Laboratory Abnormalities by Grade (G1–G4) Reported in ≥2% of Subjects Receiving Correct Rx

<table>
<thead>
<tr>
<th>Grade</th>
<th>Reaction</th>
<th>NCTD</th>
<th>NCTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Elevated AST</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>G2</td>
<td>Elevated ALT</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>G3</td>
<td>Elevated ALP</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>G4</td>
<td>Elevated BUN</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Table 3: Summary of Other Adverse Events by Grade and System Organ Class

<table>
<thead>
<tr>
<th>Grade</th>
<th>System Organ Class</th>
<th>Event</th>
<th>NCTD</th>
<th>NCTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Cardiac</td>
<td>Palpitations</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>G2</td>
<td>Skin</td>
<td>Rash</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>G3</td>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>G4</td>
<td>Respiratory</td>
<td>Dyspnea</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Table 4: Table of Other Adverse Events by Grade and System Organ Class

<table>
<thead>
<tr>
<th>Grade</th>
<th>System Organ Class</th>
<th>Event</th>
<th>NCTD</th>
<th>NCTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Cardiovascular</td>
<td>Angina</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>G2</td>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>G3</td>
<td>Respiratory</td>
<td>Wheezing</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>G4</td>
<td>Dermatologic</td>
<td>Pruritus</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Table 5: Table of Other Adverse Events by Grade and System Organ Class

<table>
<thead>
<tr>
<th>Grade</th>
<th>System Organ Class</th>
<th>Event</th>
<th>NCTD</th>
<th>NCTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Nervous System</td>
<td>Dizziness</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>G2</td>
<td>Gastrointestinal</td>
<td>Vomiting</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>G3</td>
<td>Respiratory</td>
<td>Breathlessness</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>G4</td>
<td>Dermatologic</td>
<td>Pruritus</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Table 6: Table of Other Adverse Events by Grade and System Organ Class

<table>
<thead>
<tr>
<th>Grade</th>
<th>System Organ Class</th>
<th>Event</th>
<th>NCTD</th>
<th>NCTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Cardiovascular</td>
<td>Angina</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>G2</td>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>G3</td>
<td>Respiratory</td>
<td>Wheezing</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>G4</td>
<td>Dermatologic</td>
<td>Pruritus</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Table 7: Table of Other Adverse Events by Grade and System Organ Class

<table>
<thead>
<tr>
<th>Grade</th>
<th>System Organ Class</th>
<th>Event</th>
<th>NCTD</th>
<th>NCTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Cardiovascular</td>
<td>Angina</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>G2</td>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>G3</td>
<td>Respiratory</td>
<td>Wheezing</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>G4</td>
<td>Dermatologic</td>
<td>Pruritus</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Drugs with No Observed or Predicted Interactions with COMPLERA

No clinically significant drug interactions have been observed between entecavir and tenofovir or tenofovir disoproxil fumarate. Similarly, no clinically significant drug interactions have been observed between tenofovir disoproxil fumarate and food, methadone, nefazodone, nimodipine, ritonavir, or tizanidine.

USE IN SPECIFIC POPULATIONS

Pregnancy

Category B

Teratogenic effects: no significant teratogenic effects were observed in animal reproduction studies. However, no adequate and well-controlled studies in pregnant women have been conducted. Hence, COMPLERA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Lactation

The excretion of tenofovir disoproxil fumarate into human milk has not been studied. However, for other nucleoside reverse transcriptase inhibitors, it is known that these drugs can be excreted in human milk. Though no adequate and well-controlled studies in pregnant women have been conducted, it is not known whether tenofovir or entecavir can be excreted in human milk.

Children

Drug interactions with COMPLERA are not expected to be clinically significant, since tenofovir disoproxil fumarate and entecavir are not metabolised to any clinically significant extent.

Pediatric Use

COMPLERA is not recommended for patients less than 18 years of age because there are no adequate and well-controlled studies of the use of COMPLERA in children less than 18 years of age. However, in view of the potential benefits of tenofovir disoproxil fumarate and entecavir in patients who are not taking any antiretroviral drug, it is appropriate to conduct studies in children on the safety and efficacy of COMPLERA.

Geriatric Use

Drug Interactions: Tenofovir disoproxil fumarate can displace other cationic drugs from plasma albumin-binding sites, resulting in increased plasma concentrations of such drugs.

Drug-Laboratory Test Interactions: Tenofovir disoproxil fumarate may alter the results of certain laboratory tests. Tenofovir disoproxil fumarate may increase the levels of serum ALT, AST, and γ-glutamyltransferase. Tenofovir disoproxil fumarate may decrease the levels of serum calcium, and increase the levels of serum phosphorus.

Tenofovir disoproxil fumarate may also decrease the levels of serum bilirubin, alkaline phosphatase, and alanine transaminase.

Drug-Allergy: A whooping cough vaccination has not been studied in patients who are taking COMPLERA and therefore, it is not known whether the incidence of whooping cough is increased in patients taking COMPLERA.

Drug-Drug: No clinically significant drug interactions have been observed between entecavir and tenofovir disoproxil fumarate. Similarly, no clinically significant drug interactions have been observed between entecavir and tenofovir disoproxil fumarate and food, methadone, nefazodone, nimodipine, ritonavir, or tizanidine. However, no adequate and well-controlled studies in pregnant women have been conducted. Hence, COMPLERA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

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Although the causes and the treatment goals of glaucoma are not completely understood, the ocular disorder is the second leading cause of blindness affecting 60 million people worldwide. Glaucoma is a progressive optic neuropathy characterized by irreversible vision field loss with or without increased intraocular pressure. Increased intraocular pressure (IOP) was once a diagnostic criterion, yet reduction of IOP (<21mm Hg) is still the current goal of therapy for all types of glaucoma to prevent loss of functional vision. Unfortunately, glaucoma can be asymptomatic until it progresses to late stages. The risk factors are elevated IOP, age over 50 years old, family history of glaucoma, African or Latino ancestry, type 2 diabetes mellitus, low ocular perfusion pressures, and thinner central cornea. Once glaucoma is identified, the therapeutic approach includes multiple ophthalmic medications and/or surgery to either decrease aqueous humor production or to increase the excretion of the aqueous humor. This article will compare the currently available medication treatment options by their proven clinical efficacy, dosing, and place in therapy.

GLAUCOMA CLASSIFICATION
There are two types of primary glaucoma, open-angle (POAG) and closed-angle (CAG) as shown in figure 1. POAG is a slow, progressive form of glaucoma primarily in adults over 50 years old. Although the causes of POAG are not completely understood, microvascular changes, increased susceptibility of optic nerve ischemia, dysregulated blood flow, autoimmune reactions, as well as a genetic predisposition are thought to contribute to the ineffective flow of aqueous humor through trabecular meshwork. On the other hand, CAG accounts for less than 5% of all glaucoma cases. It is associated with symptomatic episodes of extreme fluctuations of IOP (40-90mm Hg), blurred vision, and headaches. Although CAG is rare, acute episodes are medical emergencies where vision can be completely lost in a few hours. An excess of aqueous humor and a narrowed angle between the cornea and iris are not the only causes of glaucoma. Drug-induced glaucoma can be caused from side effects of some medications such as glucocorticoids, topical anticholinergics, and vasodilators.

TREATMENT
Currently there are five classes of topical medications used to lower IOP: prostaglandin analogs, beta-adrenergics antagonists, cholinergic agonists, alpha2-adrenergic agonist, and topical and oral carbonic anhydrase inhibitors. The goal of therapy is to preserve visual function by achieving a target IOP, which typically constitutes an initial 25-30% reduction in IOP. The target IOP is under clinical debate because IOP is highly variable between patients and the necessary degree of IOP reduction to prevent...
blindness is unclear. Although the IOP goal could be considered arbitrary, the results of the Early Manifest Glaucoma Trial support immediate treatment of early POAG stages to slow the disease progression and the current American Academy of Ophthalmology’s Preferred Practice Patterns even recommend treating high-risk individuals to prevent development of glaucoma. Choos-
ing the appropriate therapy requires balancing cost-effectiveness, side effects, and adherence issues. Based on cost-
effectiveness studies, only patients with increased intraocular pressure (ocular hypertension) lacking optic nerve dam-
age can forgo medical treatment with close monitoring. Current first-line medications are prostaglandin analogs and beta-blockers, but prostaglandin analogs have surpassed timolol as the gold standard of therapy.

PROSTAGLANDIN ANALOGS

The prostaglandin analogs, including bimatoprost, latanoprost, and travoprost increase the trabecular and uveo-
scleral outflow of aqueous humor thus reducing IOP in POAG. As shown in Table 1, the prostaglandin analogs, which are dosed once a day in the evening, have been proven most efficacious at reducing IOP compared to topical beta-blockers, which are dosed twice-
a-day. In some studies, travoprost has shown increased efficacy in African Americans compared to the other pros-
taglandin analogs and beta blockers, yet has been associated with the most ad-
verse drug effects such as eye redness, eye lash growth, and permanent iris color change. More research needs to be done to validate the increased efficacy in the African American population. The advantages of the prostaglandin analogs are proven clinical superiority (IOP reduction of 25-35%), lack of sys-
temic side effects, and once a day dos-
Topical beta-blockers produce local hypotensive effects by decreasing the aqueous humor production. The beta-blockers include timolol, betaxolol, carteolol, levobunolol, and metipranolol, which vary by potency and selectivity. Overall, their effects on IOP are comparable (20-30% reduction), but the differences in adverse effect potential and cost can be considered when choosing therapies.\(^4\) Levobunolol and timolol gel (Timoptic XE) are the only beta-blockers that are dosed once a day. Betaxolol is selective for beta 1; therefore, it would be likely to

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>IOP Reduction</th>
<th>Dosing</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latanoprost (Xalatan(^\circ))</td>
<td>Increases uveoscleral and/or trabecular outflow</td>
<td>23-35%</td>
<td>1 gtt HS</td>
<td>Redness, foreign body sensation, iris color change, burning, blurred vision, increase eyelash growth</td>
</tr>
<tr>
<td>Bimatoprost (Lumigan(^\circ))</td>
<td></td>
<td>27-31%</td>
<td>1 gtt HS</td>
<td></td>
</tr>
<tr>
<td>Travaprost (Travatan-Z)</td>
<td></td>
<td>25-30% (more efficacy in African Americans)</td>
<td>1 gtt QD to BID</td>
<td></td>
</tr>
<tr>
<td>Betaxolol (Betoptic S)</td>
<td>Decrease aqueous production</td>
<td>25%</td>
<td>1-2 gtt BID</td>
<td>Local: ocular stinging, blurred vision, edema, hyperemia</td>
</tr>
<tr>
<td>Timolol (Timoptic)</td>
<td></td>
<td>30-33%</td>
<td>1 gtt BID</td>
<td>Systemic: hypotension, bradycardia, headache, rash, bronchospasm, arrhythmias</td>
</tr>
<tr>
<td>Carteolol</td>
<td></td>
<td>22-25%</td>
<td>1 gtt BID</td>
<td></td>
</tr>
<tr>
<td>Levobunolol (Betagan)</td>
<td></td>
<td>20-30%</td>
<td>1 gtt QD to BID</td>
<td></td>
</tr>
<tr>
<td>Metipranolol (Optipranol)</td>
<td></td>
<td>20-26%</td>
<td>1 gtt BID</td>
<td></td>
</tr>
<tr>
<td>Dorzolamide (Trusopt)</td>
<td>Decrease aqueous production</td>
<td>15-26%</td>
<td>1 gtt TID</td>
<td>Metallic taste, corneal edema, allergic conjunctivitis</td>
</tr>
<tr>
<td>Brinzolamide (Azopt)</td>
<td></td>
<td>15-26%</td>
<td>1 gtt TID</td>
<td></td>
</tr>
<tr>
<td>Acetazolamide (Diamox)</td>
<td></td>
<td>25-40%</td>
<td>250mg-1000mg by PO QD in divided doses</td>
<td>Renal stones, Stevens-Johnson syndrome, electrolyte imbalance, aplastic anemia, thrombocytopenia, metallic taste, fatigue</td>
</tr>
<tr>
<td>Bromonidine (Alphagan)</td>
<td>Selective - decrease aqueous production and increase uveoscleral outflow</td>
<td>20-25%</td>
<td>1 gtt TID</td>
<td>Allergic conjunctivitis, hyperemia, itching, burning, syncope, edema, ocular discomfort, reduced vision</td>
</tr>
<tr>
<td>Apraclonidine (Iopidine)</td>
<td></td>
<td>20-25%</td>
<td>1-2 gtt TID</td>
<td></td>
</tr>
<tr>
<td>Dipivefrin (Propine)</td>
<td>Non-selective – Improves aqueous outflow through vasoconstriction</td>
<td>15-25%</td>
<td>1 gtt BID</td>
<td>Ocular burning</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td>15-25%</td>
<td>1 gtt QD – BID</td>
<td>Cardiac palpitations, dizziness, shortness of breath, headache, anxiety, tremor</td>
</tr>
<tr>
<td>Pilocarpine (Isopto Carpine)</td>
<td>Increases trabecular outflow (miosis)</td>
<td>20-25%</td>
<td>2 gtt TID-QID</td>
<td>Blurred vision, stinging, headache, night blindness, shortness of breath, tremors, sweating, eye brow pain, cataracts, clouding of cornea and retina</td>
</tr>
<tr>
<td>Carbachol (Isopto Carbachol)</td>
<td></td>
<td>20-25%</td>
<td>2 gtt TID</td>
<td></td>
</tr>
<tr>
<td>Echothiophate (Phospholine Iodide)</td>
<td>Acts directly to block cholinesterase</td>
<td>20-25%</td>
<td>1 gtt BID</td>
<td>Blurred vision, burning, night blindness, headache</td>
</tr>
</tbody>
</table>

Table 1

Adapted from reference: 2,4,7, and 10 with modifications
produce the least bronchoconstriction. Local effects of beta-blockers are tolerable, although stinging is most common, which metipranolol is the biggest culprit of ocular stinging (56%). As far as generics are concerned, betaxolol is the most expensive and timolol is the least expensive. The topical beta-blockers are contraindicated in patients with respiratory and cardiovascular conditions due to their systemic absorption. Therefore, the disadvantages are twice a day therapy, side effects, and contraindications in certain patient populations.

**CARBONIC ANHYDRASE INHIBITORS (CAI)**

An adjunctive therapy for both POAG and CAG, carbonic anhydrase inhibitors decrease IOP by up to 40% in some patients. Their mechanism of action is unique because they directly target the enzymatic production of aqueous humor by disrupting carbonic anhydrase. Although a significant reduction of IOP is seen with systemic CAI, such as acetazolamide, they are used most often as third line therapies due to the intolerable side effects such as renal stones and blood dyscrasias. Topical CAIs, such as dorzolamide and brinzolamide, can be considered second line therapies due to moderate reduction in IOP (15-26%) and synergy with adrenergics, prostaglandin analogs, and cholinergics. The disadvantages include four times a day dosing, side effects such as metallic taste, corneal edema, and allergic conjunctivitis, and contraindications in patients with sulfonamide allergies. Oral CAIs’ place in therapy is only after maximal topical therapy has failed.

**ALPHA2-AGONISTS**

Adrenergics such as brimonidine and apraclonidine, work selectively to decrease IOP by 20-25%. They primarily reduce aqueous humor production and to some extent increase uveoscleral outflow. Brimonidine has been shown to be superior to apraclonidine and associated with significantly less allergic like reactions (8% compared to 30%). Brimonidine is used clinically as second line due to the three times a day dosing, limited benefit as monotherapy, and systemic side effects (decreased heart rate and blood pressure). Apraclonidine is not recommended for chronic use due to the allergic reactions and tachyphylaxis. Brimonidine has been shown to be inferior to timolol (beta blocker) and brinzolamide (CAI).

**CHOLINERGICS/MIOTICS**

Cholinergics, also known as parasympathomimetics, decrease IOP by constricting the pupil, which physically opens the canal of Schlemm to increase outflow of aqueous humor. Thus pilocarpine and carbacbol can be used for POAG and acute CAG. Cholinergics can act directly such as pilocarpine and carbacbol or indirectly such as echothiophate. Although echothiophate is more potent, the two subtypes can reduce IOP by at least 20-25%. The indirectly acting long-acting inhibitors of cholinesterase to potentiate the activity of acetylcholine. This class of medication is used clinically as last line due to local adverse effects and required dosing of up to four times a day. The adverse effects extend from local irritation, decreased vision (miosis), twitching, cataracts, and headache to systemic effects such as nausea, vomiting, diarrhea, bronchospasms, and heart block with high concentrations of pilocarpine. Pilocarpine or carbacbol can be used in combination with adrenergics or carboxonic anhydrase inhibitors. But like oral CAIs, parasympathomimetics are reserved for failed therapies.

**COMBINATION THERAPY**

Combination therapy has become an essential treatment plan to achieve an adequate IOP reduction. Two drug combinations for glaucoma currently being marketed are brimonidine/timolol (Combigan) and dorzolamide/timolol (Cosopt), both of which are twice a day therapies. Combigan only provided an additional 1-3mm Hg IOP decrease compared to the brimonidine and/or timolol twice a day, but the IOP lowering effect was actually 1 mm Hg less than concomitant therapy of brimonidine 2% three times daily and timolol 0.5% twice a day (as FDA approved). Dorzolamide has been shown to be equally efficacious as brimonidine, but was associated with twice the frequency of ocular stinging. The advantage of these fixed combination products are not the increased efficacy over adjunctive therapy but to enhance patient satisfaction and adherence to therapy.

Although studies have shown timolol to be effective especially when in combination with alpha agonists or CAIs, the current studies strongly favor prostaglandin analogs in combination with CAIs and alpha-agonistor even beta-blockers. In multiple head-to-head studies, travoprost with CAIs (brinzolamide) were superior to travoprost with alpha agonists (brimonidine). Bimatoprost monotherapy resulted in a clinically more effective reduction of IOP (6.8-7.6 compared to 4.4-5mm Hg) than Cosopt dosed twice a day. Another promising combination is prostaglandin analogs and beta-blockers. In one double-blind study, the combination of latanoprost and timolol produced a statistically significant IOP reduction than latanoprost or timolol as monotherapy. Another study compared a beta-blocker/prostaglandin combination versus a current marketed combination product. The fixed combination of latanoprost/timolol once daily treatment resulted in more patients reaching the target IOP (<16mm Hg) than Cosopt twice a day, although the average reduction in IOP between the two groups was not statistically significant (-9.7 and -9.5mm Hg). Travoprost and timolol have been formulated together under the trade name DuoTrav in Europe, but it is not available yet in the United States.

The future of anti-glaucoma medicines will include novel mechanisms and new drug delivery modes to increase patient compliance and disease management. Possible new medications involve chelating agents, serotoninergics,
melatonins, nucleotide agents, and expansion of cannabinoids.\(^\text{17}\)

**PHARMACIST’S ROLE**

Adherence to glaucoma treatment is a significant barrier to therapeutic outcomes. As for other similar chronic conditions, pharmacy-refill data has shown that glaucoma patients only take around 60-70% of their prescribed doses of eye drops.\(^1,2\) In order to significantly reduce the risk of optic nerve damage, IOP must be consistently reduced; therefore, a high level of adherence is required to adequately prevent blindness.\(^9\) Pharmacists and ophthalmologists can work together to ensure patients receive the most out of their pharmacotherapy regimens by clearly written regimens, proper technique counseling, and repetition of the instructions with each refill.\(^4\)

Not only is proper compliance important for cost-effectiveness and disease management, but also the proper technique can reduce the systemic side effects of these medications. The technique of nasolacrimal occlusion (NLO) is accomplished by patients closing their eyes and placing their index finger over the nasolacrimal drainage system (inner corner of the eye) for 1-3 minutes.\(^1,7\) This technique improves the ocular bioavailability of the medicine and reduces the systemic absorption. Also the separation of doses is crucial to maximize drug efficacy. When more than one medication is to be administered, installations should be separated by 5-10 minutes to prevent flushing of the previous medicine. Lastly, the pharmacist should counsel on the correct administration technique to prevent contamination of multi-dose bottles, which can result in bacterial keratitis.\(^7\)

**Figure 1. Depiction of the two forms of primary glaucoma.**  
B) Open Angle Glaucoma. C) Closed angle glaucoma.

**REFERENCES:**

10. ePocrates (ePocrates Rx) [computer program]. ePocrates, Inc; Ver 3.19/Aug 14, 2011.
Onychomycosis (OM) is a fungal infection that affects any portion of the structure of the nail of the toes or fingers. Although this disease state is non-life threatening it is responsible for physical disfigurement, pain or nail loss if not treated properly. OM accounts for 50% of all of nail disease seen in adults and is the most common infection type.

ANATOMY

In order to understand how onychomycosis (OM) affects the nail, reviewing the general anatomy of the nail is necessary.

The nail consists of seven main parts. Of these, four are affected by OM: (1) The nail matrix (where the nail begins—this portion is mostly invisible), (2) the cuticle (folded skin where the skin of the toe meets the nail), (3) the nail plate (actual nail body made up of translucent keratin proteins, layers of dead cells and amino acids) and (4) the nail bed (dermal and epidermal soft tissue located underneath the nail on which it rests).

Janene L. Cornish, Pharm.D.
CAUSES
Onychomycoses are caused by dermatophytes (Trichophyton sp., Epidermophyton sp., Microsporon sp.), yeast (Candida sp.), and nondermatophytic molds. The dermatophytes, which commonly infect hair, skin and nails feed on the keratinous structure of body tissue (i.e. nail). This results in early cosmetic changes due to fungal invasion and later clinical symptomology such as parasthesias or loss of nail. Trichophyton rubrum and T. mentagrophytes cause most cases of the two most common sub-types of OM worldwide DLSO and PSO. While Candida albicans most commonly causes the sub-type of OM known as chronic mucocutaneous candidias.

Table 1

<table>
<thead>
<tr>
<th>RISK FACTORS FOR DEVELOPMENT OF ONYCHOMYCOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing Age (&gt; 65 years report up to 90 % OM rates)</td>
</tr>
<tr>
<td>Communal Bathing Showers</td>
</tr>
<tr>
<td>Covered Shoes w/ Restrictive Airflow</td>
</tr>
<tr>
<td>Family History</td>
</tr>
<tr>
<td>Fitness Activity</td>
</tr>
<tr>
<td>Foot Trauma</td>
</tr>
<tr>
<td>Immunosuppression (HIV, Medication Induced)</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (any blood flow issues)</td>
</tr>
<tr>
<td>Poor Health</td>
</tr>
</tbody>
</table>

RISK FACTORS OM SUB-TYPES
There are five sub-types of onychomycosis: Distal Lateral Subungual Onychomycosis (DLSO), White Superficial Onychomycosis (WSO), Proximal Subungual Onychomycosis (PSO), Eponychy Onychomycosis (EO) and Candidal Onychomycosis. Each subtype causes a different disruption of the cuticle, nail bed, matrix and or nail plate. Of the five subtypes the most commonly treated are DLSO and WSO.

Figure 1

PSO although not commonly seen in the average patient population should be noted as patients with compromised immune function (i.e. HIV/AIDS) have a higher frequency of this subtype. These three frequently encountered OM subtypes are detailed in Table 2.

SYMPTOMS
Typically people seek medical attention for OM due to the cosmetic changes that they experience: thickening, clouding, yellowing, speckling, and streaking of the toenail. Physical pain is not the primary complaint; however as the disease process progresses parasthesias, pain, and discomfort can occur should the toe(s) be left untreated.

DIAGNOSIS
OM can be identified by appearance although caution must be exercised as there are other conditions that look similar to this disease state (i.e. psoriasis, yellow nail syndrome). In outpatient settings OM is confirmed by removal of nail samples from the patient which are subjected to laboratory testing, histological staining with PAS (periodic acid Schiff stain) and fungal culturing to determine the genus and species of the infecting organism. Prior to beginning more expensive treatments physicians may await lab results due to the extended length of treatment, potential risks of treatment and expense to the average outpatient. While awaiting confirmation, topical treatment modalities are often started empirically based on visual diagnosis.

TREATMENT
Generally speaking, treatment includes sharing common sense basics of skin care with each patient. Keeping the infected area dry, clean and eliminating exposure to the source of infection is the best way to prevent infection and/or reinfection.

Treatment of OM is difficult due to several factors: (1) the similarity of the fungal cell to the human cell structure, (2) slow nail growth, and (3) poor blood supply to the feet and toes. Failure rates in treatment of OM are often as high
TREATMENT: ORAL AGENTS

Terbinafine (Lamisil ®) is an allyamine that has its greatest activity against dermatophytes. It also has good activity against non-dermatophyte molds and marginal activity against Candida species. Terbinafine is keratino- and lipophilic which allows it to penetrate quickly into all portions of the nail and slowly release from it. Uptake occurs within one week, while traces of the drug can be found up to 36 weeks following the final dose.

The dose of Terbinafine that should be administered for OM is one tablet (250 mg) by mouth every day for 12 weeks. Patients should be tested prior to first dose for abnormal liver function test (LFTs). If LFTs are abnormal (>5 times normal), this medication should be avoided. Terbinafine is not recommended in patients with CrCl < 50ml/min or any form of hepatic insufficiency. Retest of the LFTs should re-occur at week six for transient rises in values. Adverse effects that are commonly experienced are gastrointestinal (GI) complaints (diarrhea, nausea and vomiting), headache and rash. Caution should be exercised with medications that utilize CYP2D6 as Terbinafine is a strong inhibitor. Patients typically experience an up to 76% cure rate when therapy is completed. This medication is a first line choice for those facilities that have it on the formulary and it can be combined with a topical agent for increased efficacy. Itraconazole (Sporanox®) is an azole antifungal that has broad spectrum activity against dermatophytes, non-dermatophyte molds, and Candida species. Like terbinafine it is keratino- and lipophilic and has excellent penetration into all parts of the nail resulting in quick absorption (present within one week) and slow excretion (drug present twenty-seven weeks following last dose). LFT's must be evaluated at baseline and then at six weeks for patients on this medication as well. Any patient with chronic or acute liver dysfunction or congestive heart failure (negative ionotropic effects) should not be on Itraconazole. Renally

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>DLSO</th>
<th>PSO</th>
<th>WSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Most common</td>
<td>Generally uncommon but frequent in AIDS patients</td>
<td>Makes up 10% of cases of OM</td>
</tr>
<tr>
<td>Progress of infection</td>
<td>Infection begins with invasion of the space under the nail edge where the nail separates from the nail bed</td>
<td>Infection begins at the nail fold (where the nail meets the finger or toe) and affects newly forming nail</td>
<td>Infection begins at the surface of the nail (nail plate) and progresses to deeper layers</td>
</tr>
<tr>
<td>Clinical appearance</td>
<td>Separation of the nail from the nail bed (onycholysis), thickening of the area under the nail</td>
<td>Subungual hyperkeratosis, white discoloration (leukonychia), separation of the nail from the nail bed (onycholysis), and destruction of the nail unit</td>
<td>White areas on the nail surface, eventually involving the entire nail surface</td>
</tr>
<tr>
<td>Most common causative organism</td>
<td>Trichophyton rubrum</td>
<td>Trichophyton rubrum</td>
<td>Trichophyton mentagrophytes, Aspergillus terreus, Acremonium roseogriseum, Fusarium oxysporum</td>
</tr>
<tr>
<td>Affected nails</td>
<td>Toenails most commonly affected but may affect fingernails as well</td>
<td>Much more common on the toenails, rarely affects fingernails</td>
<td>Mainly affect toenails The term total dystrophic onychomycosis is not a subtype, but is, instead, the final stage of any of the previously described forms of onychomycosis, candidal onychomycosis, or both</td>
</tr>
</tbody>
</table>
impaired patients should follow dose adjustments of 50% of the dose once renal function reaches CrCl <10ml/min.

Itraconazole can be dosed by pulse dosing or continuous. The pulse dose is: 200 mg by mouth twice daily for one week, then three weeks off, then repeat week one's course directions for week four; or dose continuously at 200 mg by mouth daily for 12 weeks. Adverse reactions include nausea, diarrhea, headache, itching, rash, hypertension and chest pain. Caution should be exercised regarding drug-drug interactions as itraconazole is a strong CYP3A4 inhibitor and will cause interactions when given concomitantly with other medications that utilize CYP3A4. As a second line medication choice, due to its drug-drug interaction profile, it has a relatively high eradication rate when therapy is completed of up to 63%.

Fluconazole (Diflucan®) although not FDA approved for treatment of OM has some activity against dermatophytes, non-dermatophytic molds as well as its proven treatment ability of Candida species. Cure rate for OM with Fluconazole is about 48%. Compared to both Itraconazole and Terbinafine it is cheaper and has a lower cost of distribution as well as the saddened rate of only 28% of patients had clinical and mycological cure as proven by culture. (Appendix one) The dose of Vicks® for this pilot study was application of a small amount to the affected toe(s) with a clean

TREATMENT: TOPICAL AGENTS

For most cases, topical therapy alone is not adequate for clearing nail infections, likely due to inadequate penetration of the medication into the affected tissues and nail bed. This requires the utilization of topical agents for longer time frames. An exception to the topical therapy rule are patients with superficial white onychomycosis (WSO), which is easily treated with a topical agent alone because the organism grows on the upper nail plate rather than in the nail bed. Selection of an appropriate topical agent, patient compliance and completion of the regimen will typically eradicate this superficial onychomycosis. There are numerous topical agents on the market; a sampling of which are listed in Table 3. For the purposes of this article, we will discuss agents commonly prescribed in the correctional setting for the topical treatment of OM.

Clotrimazole (Lotrimin®) is an imidazoles topical agent with broad spectrum fungistatic and antifungal activity against all three causative agents of OM. Dosing is application to the affected area twice daily for four weeks, then re-evaluation for improvement. It may be necessary to change to an alternative topical therapy if no improvement in symptomology is noted in four weeks. (Table 3)

Terbinafine (Lamisil®) is an allylamines-benzylamines that has both fungistatic and fungicidal effects against Candida sp., dermatophytes, and non-dermatophytic molds. Dosage is application to affected are once daily for four weeks then re-assessment for improvement.

Vicks Vapo-Rub® is an ointment containing thymol, camphor, menthol/ oil of eucalyptus. It is a non-FDA approved folk remedy that is commonly used in Correctional medicine with some success for treatment of OM. A recent (2010) small study performed by the U.S. Air Force 375th Medical group showed that after 48 weeks 28% of patients had clinical and mycological cure as proven by culture. (Appendix one)
fingertip or Q-tip at least once per day. Although this was a small case series study, it does shed light on the question of the efficacy of this medication as treatment. Vicks® is cost effective and has no drug interactions. Of concern is the possibility of contamination of the ointment from constant dipping for application onto the infected toe(s). Hygiene counseling is best to prevent this concern.

**FINAL THOUGHT:**

While optimally oral plus topical therapy provides the best rates for eradication of OM and decreased chances for recurrence, judicious use of the medication(s) on the formulary can provide a patient with treatment success with regular counseling on adherence to the medication regimen and hygiene.

**REFERENCES:**


**Table 3: Common Antifungal Medications and Their Forms**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Rx or OTC</th>
<th>Solution or spray</th>
<th>Lotion</th>
<th>Cream</th>
<th>Gel or ointment</th>
<th>Powder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolnaftate (Tinactin)</td>
<td>OTC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ciclopirox (Loprox; Penlac)</td>
<td>Rx</td>
<td>Lacquer</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Clotrimazole (Lotrimin)</td>
<td>OTC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Miconazole (Micatin)</td>
<td>OTC</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Terbinafine (Lamasil AT)</td>
<td>OTC</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ketoconazole (Nizoral)</td>
<td>Rx</td>
<td>Shampoo</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

**Appendix One: Vapo Rub® Study Toe Results.**

Participant 2 - initial 24 weeks 48 weeks - no mycological cure partial clinical cure, "very satisfied"

Participant 17 - initial 24 weeks 48 weeks - mycological and clinical cure, "very satisfied"

Participant 9 - initial 24 weeks 48 weeks - mycological and clinical cure, "very satisfied"
The first once-daily Single Tablet Regimen
One tablet, once daily, alone or in combination, on an empty stomach, preferably at bedtime.

3 MEDICATIONS IN 1 ADDS UP TO A COMPLETE HIV REGIMEN

ATRIPLA can be used alone or in combination with other antiretroviral agents.

ATRIPLA is the only DHHS-preferred HIV regimen available as 1 pill daily for antiretroviral-naïve patients.

INDICATION

• ATRIPLA is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

IMPORTANT SAFETY INFORMATION

WARNINGS: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST-TREATMENT EXACERBATION OF HEPATITIS B

• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including tenofovir disoproxil fumarate (DF), a component of ATRIPLA, in combination with other antiretrovirals.

• ATRIPLA is not approved for the treatment of chronic hepatitis B virus (HBV) infection, and the safety and efficacy of ATRIPLA have not been established in patients coinfected with HBV and HIV-1. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued EMTRIVA® (emtricitabine) or VIREAD® (tenofovir DF), which are components of ATRIPLA. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue ATRIPLA. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

*Pill not shown at actual size.

Important Safety Information About ATRIPLA

Contraindications
• ATRIPLA is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz, a component of ATRIPLA
• Coadministration of ATRIPLA with bepridil, cisapride, midazolam, pimozide, triazolam, or ergot derivatives is contraindicated, since competition for CYP3A by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse reactions
• Concomitant use of ATRIPLA with voriconazole, atazanavir (with or without ritonavir), St. John’s wort (Hypericum perforatum) or St. John’s wort-containing products is not recommended

Warnings and Precautions
Coadministration with Related Products
• Since ATRIPLA contains efavirenz, emtricitabine, and tenofovir DF, ATRIPLA should not be coadministered with SUSTIVA® (efavirenz), EMTRIVA, VIREAD, or TRUVADA® (emtricitabine/tenofovir DF). Due to similarities between emtricitabine and lamivudine, ATRIPLA should not be coadministered with drugs containing lamivudine including Combivir® (lamivudine/zidovudine), Epivir® or Epivir-HBV® (lamivudine), Epzicom® (abacavir sulfate/lamivudine), or Trizivir® (abacavir sulfate/lamivudine/zidovudine)
• ATRIPLA should not be administered with HEPERSA® (adefovir dipivoxil)

Psychiatric Symptoms
• Serious psychiatric adverse experiences, including severe depression (2.4%), suicidal ideation (0.7%), nonfatal suicide attempts (0.5%), aggressive behavior (0.4%), paranoid reactions (0.4%), and manic reactions (0.2%), have been reported in patients receiving efavirenz. In addition to efavirenz, factors identified in a clinical study that were associated with an increase in psychiatric symptoms included a history of injection drug use, psychiatric history, and use of psychiatric medication. There have been occasional reports of suicide, delusions, and psychosis-like behavior, but it could not be determined if efavirenz was the cause. Patients with serious psychiatric adverse experiences should be evaluated immediately to determine whether the risks of continued therapy outweigh the benefits

Nervous System Symptoms
• Fifty-three percent of subjects reported central nervous system symptoms (including dizziness [28.1%], insomnia [16.3%], impaired concentration [8.3%], somnolence [7.6%], abnormal dreams [6.2%], and hallucinations [1.2%]) when taking efavirenz compared to 25% of subjects receiving control regimens. These symptoms usually begin during Days 1-2 of therapy and generally resolve after the first 2-4 weeks of therapy; they were severe in 2.0% of subjects, and 2.1% of subjects discontinued therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in subjects treated with regimens containing efavirenz. Nervous system symptoms are not predictive of the less frequent psychiatric symptoms

New Onset or Worsening Renal Impairment
• It is recommended that creatinine clearance (CrCl) be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with ATRIPLA, and routine monitoring of CrCl and serum phosphorus be performed for patients at risk of renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil. ATRIPLA should not be given to patients with CrCl <50 mL/min. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir DF. ATRIPLA should be avoided with concurrent or recent use of a nephrotoxic agent

Reproductive Risk Potential
• ATRIPLA may cause fetal harm when administered during the first trimester to a pregnant woman. Women should not become pregnant or breastfeed while taking ATRIPLA. Barrier contraception must always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives). Because of the long half-life of efavirenz, adequate contraceptive measures are recommended for 12 weeks after discontinuation of ATRIPLA. If the patient becomes pregnant while taking ATRIPLA, she should be apprised of the potential harm to the fetus

Please see Important Safety Information, including Boxed WARNINGS, for ATRIPLA and brief summary of Full Prescribing Information on adjacent pages.

Rash
• Mild-to-moderate rash is a common side effect of efavirenz. In controlled clinical trials, 26% of subjects treated with efavirenz experienced new-onset skin rash compared with 17% of subjects treated in control groups. ATRIPLA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever

Hepatotoxicity
• Liver enzymes should be monitored before and during treatment in patients with underlying hepatic disease, including hepatitis B or C infection; in patients with marked transaminase elevations; and when ATRIPLA is administered with tenofovir or other medications associated with liver toxicity. A few of the postmarketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterized by a fulminant course, progressing in some cases to transplantation or death. Liver enzyme monitoring should be considered for patients without pre-existing hepatic dysfunction or other risk factors

Decreases in Bone Mineral Density
• Bone mineral density (BMD) monitoring should be considered for patients who have a history of pathologic bone fracture or are at risk for osteopenia. Decreases in BMD have been seen with tenofovir DF. Cases of osteomalacia (associated with proximal renal tubulopathy and which may contribute to fractures) have been reported in association with the use of tenofovir DF

Seizure
• Use ATRIPLA with caution in patients with a history of seizures. Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures

Immune Reconstitution Syndrome
• Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of ATRIPLA

Fat Redistribution
• Redistribution/accumulation of body fat has been observed in patients receiving antiretroviral therapy

Adverse Reactions
• In Study 934, through 144 weeks, the most frequently reported Grades 2-4 adverse reactions reported in ≥5% of subjects receiving efavirenz + emtricitabine + tenofovir DF were diarrhea (9%), nausea (9%), fatigue (9%), depression (9%), dizziness (8%), sinusitis (8%), upper respiratory tract infection (8%), rash (7%), headache (6%), insomnia (5%), anxiety (5%), and nasopharyngitis (5%)
• The most common adverse reactions (incidence ≥10%, any severity) occurring in Study 934 include diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash

Drug Interactions
• Coadministration of ATRIPLA with didanosine should be undertaken with caution. Patients receiving this combination should be monitored closely for didanosine-associated adverse reactions
• Lopinavir/ritonavir has been shown to increase tenofovir concentrations. Patients on lopinavir/ritonavir plus ATRIPLA should be monitored for tenofovir-associated adverse reactions. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse reactions
• Coadministration of ATRIPLA and atazanavir is not recommended. Efavirenz and tenofovir DF have been shown to decrease concentrations of atazanavir. Atazanavir has also been shown to increase tenofovir concentrations
• Saquinavir should not be used as the only protease inhibitor in combination with ATRIPLA

See Full Prescribing Information for complete list of drug-drug interactions.

Hepatic Impairment
• ATRIPLA is not recommended for patients with moderate or severe hepatic impairment because of insufficient data; use caution in patients with mild hepatic impairment

Dosage and Administration
• The dose of ATRIPLA is 1 tablet (containing 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir DF) once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms. ATRIPLA is not recommended for use in patients <18 years of age or in patients with CrCl <50 mL/min
ATRIPLEX [ stavudine 400 mg/emtricitabine 200 mg/tenofovir 120 mg]

discrograd fumarate 300 mg tablets

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

Correct Rx
Emtricitabine - No postmarketing adverse reactions have been identified for this medication in this section.

Narcotic analgesics — Methadone, methadone-conversion. Co-administration of efavirenz in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Efavirenz is not recommended when administered with methadone.

Emtricitabine and tenofovir DF — Since emtricitabine and tenofovir are primarily cleared by the kidneys, co-administration of these agents with efavirenz should be avoided. Monitoring of renal function is recommended. Co-administration of efavirenz with tenofovir and emtricitabine should be avoided.

Emtricitabine and Tenofovir DF — Tenofovir DF is not recommended for patients with moderate or severe renal impairment because there may be a risk of toxic kidney effects.

Emtricitabine and Tenofovir DF — In patients with renal impairment, treatment with tenofovir DF should be avoided.
BACKGROUND
The parathyroid glands functions to regulate serum calcium and phosphorus levels through the secretion of parathyroid hormone (PTH). This hormone acts on two organs, the bone and the kidney, to maintain the correct balance of calcium and phosphorus in the body. PTH increases plasma calcium and phosphorus concentration by stimulating osteoclast activity and the release of calcium from bone to prevent hypocalcaemia. It also acts on the kidney to stimulate production of 1, 25 dihydroxyvitamin D which in turn, increases calcium reabsorption in the distal renal tubule. In addition to the above functions, the parathyroid hormone can also decrease the reabsorption of phosphorus in the proximal renal tubules. PTH has no direct activity on the intestine; however, it indirectly increases intestinal calcium and phosphorus absorption by stimulating Vitamin D production. In brief, PTH production and secretion may be stimulated by hypocalcaemia, hyperphosphatemia, and vitamin D deficiency. The consequences of hyperparathyroidism however, are hypercalcemia, hypophosphatemia, and altered urinary excretion of calcium and phosphorus.
The incidence of hyperparathyroidism increases with age. Hyperparathyroidism occurs in one out of every thousand men between the ages of 52 and 56 years. The incidence of hyperparathyroidism in women is two to three times that of men. Very rarely is hyperparathyroidism caused by parathyroid cancer. The two main types of hyperparathyroidism are primary hyperparathyroidism and secondary hyperparathyroidism (SHPT).

Primary hyperparathyroidism accounts for most hyperparathyroidism cases. This condition results from excessive release of PTH and manifests as hypercalcemia due to enlargement of one or more of the four parathyroid glands. Most persons with this condition are asymptomatic and routine laboratory tests have not been shown to assist in predicting development of overt manifestations of the disease.

Secondary hyperparathyroidism on the other hand, occurs when the parathyroid glands are chronically stimulated to release PTH in response to low serum calcium levels in an attempt to maintain calcium homeostasis. Hypocalcemia can occur due to either vitamin D deficiency or low calcium intake. In secondary hyperparathyroidism, serum PTH level is elevated but calcium level may be normal or low. This may be due to insufficient dietary intake of vitamin D or calcium or caused by malabsorption. Chronic renal failure, rickets, and malabsorption syndrome are the conditions that most frequently lead to secondary hyperparathyroidism. Among these, chronic renal failure is the most prevalent cause. The focus of this article is the management of SHPT, a complex and challenging condition in patients with chronic kidney disease.

The prevalence of chronic renal disease is a significant health issue in the United States and most often is the consequence of chronic diseases such as uncontrolled diabetes and hypertension. Secondary hyperparathyroidism resulting from chronic kidney disease occurs due to the overproduction of PTH. When renal function is compromised, GFR of <60ml/min, excretion of phosphorus decreases tremendously, resulting in phosphorus retention leading to hyperphosphatemia. Excess calcium and phosphorus may form an insoluble calcium-phosphorus complex formation which with time can precipitate and lead to extra skeletal calcification and calciphylaxis to cause cardiac complications.

In general, associated symptoms of SHPT may include: bone pain, multiple fractures, muscle weakness, myopathy, skeletal deformities, and tetany with changes in serum pH. The most common laboratory abnormalities are: high alkaline phosphatase, increased PTH, low calcium and high phosphorus concentrations.

**COMPLICATIONS OF SECONDARY HYPERPARATHYROIDISM (SHPT)**

**Bone Mineral Defects and Disease**

Several bone disorders; collectively known as renal osteodystrophy, occur during functional changes of bone and mineral metabolism in chronic renal disease. Osteitis fibrosa cystica is characterized by high-turnover bone disease secondary to increased serum PTH.

---

### Table 1: Classification of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>SCr (mg/dl)</th>
<th>Description</th>
<th>GFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.8-1.2</td>
<td>Normal GFR</td>
<td>120-125</td>
</tr>
<tr>
<td>I</td>
<td>&gt;1.2</td>
<td>Normal-mild kidney damage, normal/increased GFR</td>
<td>≈ 90</td>
</tr>
<tr>
<td>II</td>
<td>&lt;2.5</td>
<td>Mild kidney damage with mild decrease in GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>III</td>
<td>2.6-6.0</td>
<td>Moderate decrease in GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>IV</td>
<td>6.2-10</td>
<td>Severe decrease in GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>V</td>
<td>&gt;10</td>
<td>Uremia-kidney failure</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>

*Adapted from 8, 9 with modifications*

### Table 2: Target Ranges and Monitoring Frequency of Biochemical Parameters Based on Stage of Chronic Kidney Disease (CKD)

<table>
<thead>
<tr>
<th>GFR ml/min/1.73 m²</th>
<th>CKD stage</th>
<th>Phosphorus level (mg/dl)</th>
<th>Corrected Ca level (mg/dl)</th>
<th>Ca x P mg²/dl²</th>
<th>Monitoring Freq. of Ca, P, &amp; Ca x P</th>
<th>iPTH level (pg/ml)</th>
<th>Monitoring Freq. of iPTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-59</td>
<td>3</td>
<td>2.7-4.6</td>
<td>Within nl. limits</td>
<td>&lt;55</td>
<td>Every year</td>
<td>35-70</td>
<td>Every year</td>
</tr>
<tr>
<td>15-29</td>
<td>4</td>
<td>2.7-4.6</td>
<td>Within nl. limits</td>
<td>&lt;55</td>
<td>Every 3 months</td>
<td>70-110</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>&lt;15</td>
<td>5</td>
<td>3.5-5.5</td>
<td>8.4-9.5</td>
<td>&lt;55</td>
<td>Every month</td>
<td>150-300</td>
<td>Every 3 months</td>
</tr>
</tbody>
</table>

*Adapted from: Diabetes Spectrum Vol. 21, Number 1 2008*
concentrations that stimulate osteoclast activity, bone breakdown, and resorption. Osteomalacia (soft bone), another type of osteodystrophy is characterized by low bone turnover and abnormal mineralization. This is usually associated with aluminum toxicity from aluminum containing phosphate binders. The third type of osteodystrophy is Adynamic bone diseases which results from low bone turnover usually arising from excessive suppression of PTH from use of mono or combination use of Vitamin D agents, calcimimetics, and phosphate binders.8, 9

Cardiovascular Calcification
There is a correlation between complications due to cardiovascular calcification with morbidity and mortality in individuals with chronic kidney disease. Cardiovascular calcification occurs as a result of altered serum levels of calcium, phosphorus, vitamin D, and PTH in patients with end stage renal disease. Hyperphosphatemia, increased calcium-phosphate insoluble complex formation, hypercalcemia, vitamin D supplementation, increased doses of calcium-containing phosphate binders and calcium supplements have also been implicated to exacerbate cardiovascular complications in patients with CKD.8, 9

TREATMENT STRATEGIES
The management of SHPT is recommended to be started at the beginning of stage III CKD. The goals of treatment of SHPT are to maintain the correct balance of calcium and phosphorus to prevent progressive bone disease and systemic consequences of disordered mineral metabolism. Stage III CKD usually will not show biochemical abnormalities on routine assessment; however, intact parathyroid hormone (iPTH) level is often increased before clinical hyperphosphatemia occurs. Based on this rationale, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommends that individuals with GFR <60 ml/min be evaluated for serum levels of calcium, phosphorus, and iPTH.8 Se rum levels of 25(OH) D, the precursor of activated vitamin D2 and Vitamin D3 must be assessed and treated following iPTH concentrations that exceeds the CKD stage specific target. This precautionary measure will help improve bone and mineral metabolism and prevent associated complications of fracture, pain, and cardiovascular calcification.8, 9 (Table 2). Treatment of SHPT basically consists of dietary restriction of phosphorus, phosphate binders, Vitamin D derivatives, calcimimetics, and parathyroidectomy as the last resort (Table 3).

Dietary Phosphate Restriction
Dietary phosphorus restriction is an important part of the nonpharmacological treatment of hyperphosphatemia. A low phosphorus diet should be initiated when serum phosphorous is above 5.5 mg/dL in patients with stage V CKD or when iPTH serum level is above the target range of the CKD stages III and IV with normal levels of phosphorus and calcium. Food sources high in phosphate include: dairy products, and processed foods such as meats, cheeses, salad dressings, bakery products, nuts and beverages such as: dark sodas and beer.8, 9 Many foods that are phosphate rich are also primary sources of protein, particularly meat. In general, a high-protein/low-phosphorus diet is recommended to prevent malnutrition due to hypoalbuminemia, which has been associated with increased morbidity and mortality in CKD patients.8, 9
PHOSPHATE BINDING AGENTS

These agents bind to dietary phosphate in the gastrointestinal tract to form insoluble complexes which are excreted in the stool. Thus, these agents are generally recommended to be administered three times daily with food for optimal effects. Different phosphate binders from different classes may be combined to achieve target concentrations of phosphorus and calcium. Combination use of Calcium-containing phosphate binder and a non-calcium containing phosphate binder may be used to reduce serum phosphorus level while maintaining calcium concentration. The same goes for use of one or more non-calcium containing phosphate binders in patients with hyperphosphatemia with concurrent hypercalcemia. Typically in CKD patients with high serum levels of iPTH and phosphorus, phosphate binders plus a vitamin D analog or calcimimetic agent are used to control all the biochemical parameters: calcium, phosphorus, calcium-phosphorus complexes, and iPTH.\(^7,8\) Available phosphate binders include calcium acetate (Phoslo®), alternagel, sevelamer (Renagel®, Renvela®) and lanthanum (Fosrenal®).

VITAMIN D THERAPY
(based on KDOQI guidelines)
The first abnormality seen in stages III-V CKD is increased iPTH. For iPTH concentrations exceeding the target range, serum 25 (OH) D levels must be checked. For serum level of 25 (OH) D less than 30 ng/ml in Vitamin D deficiency or Vitamin D insufficiency in patients with CKD stages III and IV, oral ergocalciferol (Vitamin D2) therapy must be started and serum 25 (OH) D level must be checked after 6 months of therapy.\(^5,9\) For Serum 25 (OH) D level greater than 30 ng/ml with iPTH concentration exceeding the target range (> 70 ng/ml), activated Vitamin D should be started to treat secondary hyperpara-

---

**Table 5: Vitamin D Sterol Therapy to Treat Elevated iPTH in Patients with CKD**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Dose</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol (Rocaltrol®)</td>
<td>0.25 mcg daily or every other day</td>
<td>by 0.25 mcg at 4 to 8 weeks</td>
</tr>
<tr>
<td>Doxercalciferol (Hectrol®)</td>
<td>1 mcg daily or every other day</td>
<td>by 0.5-1 mcg every 2 weeks</td>
</tr>
<tr>
<td>Paricalcitol (Zemplter®)</td>
<td>1-2 mcg daily or every other day</td>
<td>by 1-2 mcg every 2-4 weeks</td>
</tr>
</tbody>
</table>

**CKD Stage V-Hemodialysis Patients**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage is based on iPTH level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol (Rocaltrol®)</td>
<td>Administer oral or IV with each dialysis session 3 times/week</td>
</tr>
<tr>
<td>0.25-1 mcg po qd or qod</td>
<td>Increase po dose at 2-4 week intervals</td>
</tr>
<tr>
<td>1-2 mcg IV 3 times/week</td>
<td>Adjust IV dose 2-4 week intervals</td>
</tr>
</tbody>
</table>

| Doxercalciferol (Hectrol®)   | Dosage is based on the most recent serum iPTH level. Hold dose for 1 week and resume at a reduced dose if iPTH is < 100 pg/ml |
| 10-20 mcg/day x3/wk po       | Administer IV 3 times/week after dialysis as a bolus dose |
|                             | Adjust dosages at 8 weeks interval    |

| Paricalcitol (Zemplter®)     | Dosage is based on the most recent serum iPTH level. Indicated when serum Ca is <9.5 g/dl and Ca x P is < 55 |
| po:1 mcg qd or 2 mcg 3 times/week | Administer IV as a bolus every other day at any given time during dialysis. |
| IV: 0.04 - 0.24 mck/kg 3 times/week | Adjust dose based on iPTH levels, every 2 to 4 weeks |

Adapted from: 8 & 9 with modifications

**Table 6: Calcimimetic Treatment of SHPT in Patients on Dialysis**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinacalcet (Sensipar®)</td>
<td>Obtain serum Ca and phosphorus within 1 week of start of dose or dosage change</td>
</tr>
<tr>
<td>30 mg po qd</td>
<td>Obtain serum iPTH within 1 to 4 weeks of initiation of dose or dosage change</td>
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<tr>
<td></td>
<td>Increase dose every 2 to 4 weeks incrementally at 60 mg, 90 mg, 120 mg, 180</td>
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<td></td>
<td>mg once daily as necessary to maintain iPTH level between 150-399 pg/ml.</td>
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<td></td>
<td>If serum calcium levels decrease below normal, any of the following can be done:</td>
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<tr>
<td></td>
<td>i. Provide supplemental calcium</td>
</tr>
<tr>
<td></td>
<td>ii. Initiate or increase the dose calcium-based phosphate binder</td>
</tr>
<tr>
<td></td>
<td>iii. Initiate or increase the dose of vitamin D</td>
</tr>
<tr>
<td></td>
<td>iv. Withhold treatment of Sensipar</td>
</tr>
</tbody>
</table>

Adapted from: 9
thyroidism. Vitamin D should be used only when serum calcium level is less than 9.5 mg/dl and serum phosphorus is less than 4.6 mg/dl (Tables 5 and 6).

CALCIMIMETIC THERAPY
This agent acts by binding to calcium-sensing receptors in the parathyroid glands thereby mimicking the effects of extracellular calcium. This increases the sensitivity of the receptors to serum calcium and suppresses PTH secretion. Cinacalcet is effective in decreasing serum levels of iPTH and maintain calcium and phosphate serum concentrations. This medication is very useful in patients with high serum calcium levels because of its ability to decrease serum calcium levels. Cinacalcet is contraindicated in patients with calcium levels less than 8.4 mg/dl. Cinacalcet may be used alone, with phosphate binders, or in combination with phosphate binders and Vitamin D therapy. The most important side effect of Cinacalcet is hypocalcaemia. Nausea and vomiting are transient. Dosing and recommendation to manage Sensipar toxicity is shown in Table 6.

REFERENCES:
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The Therapeutic Risks of Benzodiazepine Use in Jails

Stephen B. Goldberg, M.D. and Johannes Dalmasy, M.D.

The use of Benzodiazepines in the correctional setting has historically been a point of discussion as well as a source of disagreement among various medical providers and security staff working in this setting. The topic has become increasingly relevant as the use and abuse of this class of medications in the general population has continued to increase and as the negative effects of their use, abuse and abrupt discontinuation in jails has been demonstrated time and time again.

Of all the drugs marketed in the United States that affect central nervous system function, benzodiazepines are now among the most widely prescribed medications. Fifteen benzodiazepines are presently marketed in the United States, and about 20 additional benzodiazepines are marketed in other countries. Benzodiazepines are “controlled substances” and are found within Schedule IV of the Controlled Substances Act (CSA). While benzodiazepines are quite effective for a range of medical and psychiatric conditions, caution must be exercised with their use. This is true in any setting, but particularly in a correctional setting where misuse, diversion of medications and safety must also be a primary consideration. When considered in the context of active Substance Abuse or during the early stages of recovery, these agents can be even more troublesome for patients with both addictive and drug seeking behaviors.

The rise in prescription drug abuse is one of the major causes of a growing death toll across the United States with the number of deaths caused by prescription drugs now higher than those caused by heroin and cocaine combined.

According to the Substance Abuse and Mental Health Administration (SAMHSA), alprazolam (Xanax) is the most commonly misused benzodiazepine, followed by clonazepam (Klonopin), lorazepam (Ativan) and diazepam (Valium), with an equal distribution of abuse between men and women. Benzodiazepines are more commonly misused than prescribed opiates and benzodiazepines were the most frequently misused pharmaceutical agent accounting for 35% of drug related visits to the Emergency Department (ED). Furthermore, between 1995 to 2002, drug abuse related ED visits involving benzodiazepines increased 41%, and 26% of attempted suicides involved benzodiazepines.

The benzodiazepines as a class are used therapeutically for many valid reasons, but are most commonly used to relieve anxiety, reduce muscle spasms, induce sleep, treat seizures and to manage withdrawal from alcohol or another benzodiazepine. Desirable effects in the correctional setting include sedation, their hypnotic effect and their benefits as a sleep aid. In general, benzodiazepine act as hypnotics in high doses, anxiolytics in moderate doses, and sedatives in low doses.

Although a detailed pharmacological review is outside the scope of this article, a basic overview will help put the concerns over their discontinuation into context. Benzodiazepines have a high affinity for g amino butyric acid (GABA) receptors which are rather abundant throughout the central nervous system (CNS). The neurotransmitter GABA is the most prominent inhibitory neurotransmitter in the CNS and, through a complex
activation process that is induced by the benzodiazepines (as well as barbiturates and alcohol), it is responsible for producing the therapeutic anxiolytic effects of those drugs. It also mediates many of the side effects and, possibly, dependence and withdrawal from them.

The fact that benzodiazepines, barbiturates and ethanol all have related actions on a common GABA receptor type explains their pharmacologic synergy and cross tolerance. Combining alcohol with benzodiazepine can result in deeper intoxication and more complicated withdrawal syndromes resulting in higher morbidity and mortality for such events. When high-dose benzodiazepines or ethanol are abruptly discontinued, the state of strong inhibitory transmission ceases as well, thus inducing characteristic withdrawal symptoms such as anxiety, insomnia, autonomic hyperactivity and, possibly, seizures. This is also why benzodiazepines are useful for alcohol and benzodiazepine detoxification. By gradually, rather than abruptly, reducing the occupancy of the GABA receptors you can modulate the rapid disruption in the CNS that occurs with abrupt discontinuation, thus avoiding the dangerous withdrawal symptoms described above. Higher doses, high frequency, long duration and combinations of use/abuse (particularly daily alcohol and one or more benzodiazepines) are associated with a higher risk of complicated and more severe withdrawal syndromes.

Given the high prevalence of benzodiazepines as therapeutic agents as well as drugs of abuse in the community, it is strongly recommended that all inmates be assessed at intake for the potentially serious medical complications associated with their use/stoppage. We have initiated and recommend that others institute strong protocols that can identify those at risk individuals and ensure the safe and therapeutic management of benzodiazepine use, and, more importantly, the management of withdrawal.

Our clinical experience in correctional settings is that the risks associated with the use of benzodiazepines, including misuse, overdose and/or withdrawal, are considerably increased in jails, and thus outweigh the potential benefits that their use may otherwise offer to the same individual in the community. Since a substantial percentage of jail inmates use or abuse tranquilizers and/or other psychotropic drugs (e.g. quetiapine, amitriptyline, trazodone, etc.) as a primary and unsuccessful strategy for coping with stress, our recommendation is that these agents not be used as a matter of course, but
rather be reserved for the treatment of withdrawal and, in rare instances, when their continued use outweighs these concerns. Prescribing benzodiazepines and some other sedating medications as the primary treatment modality in a jail does little more than perpetuate maladaptive lifestyles for the individual, increase risk of medical complications while in detention, and potentially cause larger inmate population conflicts.

In practice, avoiding their use in the correctional setting is not so cut and dry. Demands for very specific drugs and dosages occur regularly and the typical assertion is that such regimens are the only viable, proven one to acquiesce the person’s idiosyncratic symptoms. Like many decisions in medicine, the risk/benefit analysis is essential. In this analysis, the setting in which these particular decisions are made must be a part of the consideration. Medication diversion, strong-arming for someone else’s medications, black market sale and a wish to “sleep away” time are some of the motivations for seeking such medications. Also included in the risk/benefit analysis is the unfavorable risk imbalance inherent to the jail related to suicidal behaviors, which are more common in correctional settings. Careful consideration must be given to any decision to provide medications that can culminate in suicide when taken in overdose, purposefully or even accidentally, by a population that statistically already carries higher than average risk for suicidal behaviors.

Furthermore, differentiating those who are truly in need versus those who are primarily seeking medications for secondary gain, is nearly impossible. Therefore, using other, non-controlled, anxiety-relieving agents as the treatment of choice allows compassionate care for those in need of treatment, but also helps to sort out those who were trying to “game” the system. Compared with benzodiazepines, medications like the SSRI’s may have a longer onset of action, but are the better agents for long-term treatment of anxiety disorders. Depending on the symptoms being targeted, anticonvulsants, antipsychotics, antihypertensives and buspirone are among the armamentarium of effective, safer drug choices with an intermediate onset of action. In fact, benzodiazepines are classified as CNS depressants and can therefore act as the primary cause for someone’s depressive illness or even as a reason for ineffective response to concomitant antidepressant treatments that might otherwise be effective.

Even when clinically justifiable and ethically preferable, by restricting the use of benzodiazepines the correctional prescriber must be prepared to deal with inmate complaints and pressure from the inmate’s families, their community-based providers and their attorney. Jail administrators or even members of the judiciary may push for their continued use in jail. Professional reassurance to the patient and proper documentation of the therapeutic decisions in the healthcare record should adequately protect the practitioner from any formal complaints based on the perceptions that the jail’s bias against prolonged use of benzodiazepines might be based on nonmedical reasons.

Despite these potential challenges, we recommend benzodiazepine detoxification and therapeutic substitutions for incarcerated individuals. Our experience repeatedly reinforces that maintenance of strict control and regulation of the benzodiazepines allows for better care and safer environments. It is not only safer in the correctional setting; it is consistent with sound medical and psychiatric care and responsive to the unique realities of care within detention facilities.

REFERENCES:
and continues with you.

“If it’s the right way, it’s the correct way.”