Montgomery Bucks
DENTAL SOCIETY

The Art of Dental Therapeutics

Better Medicine, Better Dentistry

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Our Clinician:

Dr. Mark Donaldson BSP, RPH, PHARMD, FASHP, FACHE received his baccalaureate degree from the University of British Columbia and his Doctorate in Clinical Pharmacy from the University of Washington. He completed a residency at Vancouver General Hospital, and has practiced as a clinical pharmacy specialist, clinical coordinator and director of pharmacy services at many healthcare organizations in both Canada and the United States. He is currently the Associate Principal of Clinical Pharmacy Performance Services for Vizient, in Whitefish, Montana.

Dr. Donaldson is a Clinical Professor in the Department of Pharmacy at the University of Montana in Missoula, and Clinical Associate Professor in the School of Dentistry at the Oregon Health & Sciences University in Portland, Oregon. He has a special interest in dental pharmacology and has lectured internationally to both dental and medical practitioners. He has spent the last 22 years focusing on dental pharmacology and dental therapeutics, and is a leader in the field.

Dr. Donaldson has published numerous peer-reviewed works and textbook chapters. He currently serves on the Editorial Board for the Journal Healthcare Executive and the Journal of the American Dental Association, and is a reviewer for over ten other different journals. He is board certified in healthcare management and is the Past-President and current Regent of the American College of Healthcare Executives' Montana Chapter. Dr. Donaldson was named as the 2014 recipient of the Bowl of Hygeia for the state of Montana and is the 2016 recipient of the Dr. Thaddeus V. Weclew Award. This award is conferred by the Academy of General Dentistry upon an individual who has made outstanding contributions to the medical, dental and pharmacy literature. In 2019, Dr. Donaldson was conferred by the Canadian Dental Association (CDA) in Ottawa with the, "Special Friend of Canadian Dentistry Award." This award is given to an individual outside of the dental profession in appreciation for exemplary support or service to Canadian dentistry and/or to the profession as a whole.

Dr. Mark Donaldson

The Art of Dental Therapeutics: Better Medicine, Better Dentistry

Our Program

If the term "relevant and useful pharmacology" sounds like a program you would like to avoid – think again! Providing dental care to anxious, fearful and medically-complex patients continues to be a major challenge facing oral healthcare providers. Now more than ever, dental professionals are faced with the additional challenges of treating these patients' oral health needs in the face of polypharmacology, drug interactions, potential illicit drug use and multiple chronic conditions. The simple approach to, "drilling and filling" continues to get cranked up a few more notches. Imagine if all of this could be made much easier by just going back to the basics.

Have you ever had to face the prospect of treating a medically-complex patient? Have you ever had a patient needing treatment for a dental emergency who has more than one underlying chronic disease? What about your patients of record who are on more than five medications? Now what if these same patients are also experimenting with cannabinoids or illicit drugs? How does the use of marijuana, cocaine, methamphetamine, crack, *Salvia divinorum*, khat bush, or designer drugs such as MDPV change your treatment plan?

Designed for dentists, dental hygienists, and dental assistants, this course will review the pharmacology and current state of medicinal marijuana as it relates to oral health care. The information presented in this course should be considered essential knowledge for all oral healthcare professionals (OHCPs), both seasoned and newly credentialed.

Finally, with the increasing popularity of CAMs, a new issue has arisen: herbal-drug interactions, of which OHCPs must be aware. A survey of patients with heart disease, diabetes, psychiatric disorders, and/or hypertension found that 79% were taking supplements concurrently with prescription medications. Among those with cardiac disease, 20% reported regular use of herbals. If this raises your blood pressure, then you need to take this course.

Again, this interactive program is designed for dentists, hygienists and dental assistants, case studies will augment the delivery of key points and a problem-based learning approach is encouraged so that each participant's questions are addressed.

08:30 a.m.	Cannabinoids and the Dental Patient
10:00 a.m.	**Break**
10:15 a.m.	Illicit Drugs and the Dental Patient
12:00 p.m.	**Lunch**
1:00 p.m.	Money Makes the World Go Round, But Drugs Can Make it Spin!
2:30 p.m.	Pharmaceuticals and Nutraceuticals – What do I Really Have to Know??
3:30 p.m.	**Wrap Up**

Medical Cannabinoids

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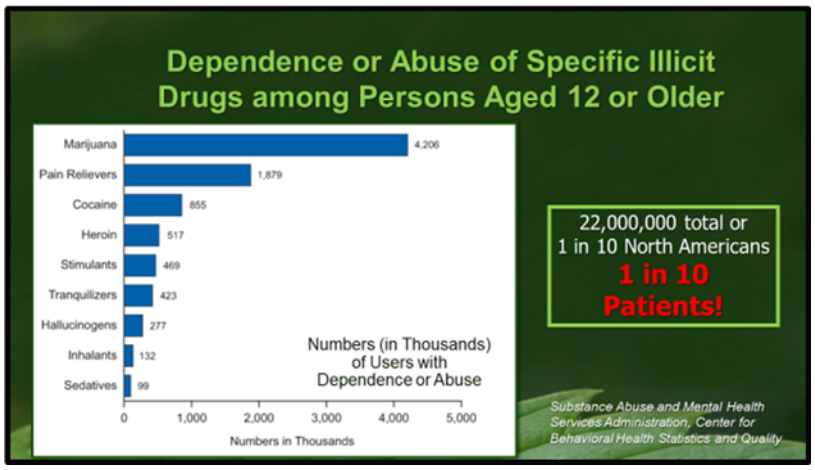
What is the scope of the "problem"?



Reasons noted for refusing to reveal information on a health history form	
Unimportant information	17%
Privacy	62%
Afraid of refusal of treatment	7%
Other	14%

McDaniel TF, Miller D, Jones R, Davis M. Assessing patient willingness to reveal health history information. J Am Dent Assoc. 1995;126(3):375-9.

- 23% of respondents would be reluctant to note current drug abuse on a medical history questionnaire!

As of October 17th, 2018, the Cannabis Act is in force (Bill C-45). In Canada, provides legal access to cannabis and to control and regulate its production, distribution and sale. In the United States, thirty-eight states and the District of Columbia currently have passed laws broadly legalizing marijuana in some form. The District of Columbia and 11 states -- Alaska, California, Colorado, Illinois, Maine, Massachusetts, Michigan, Nevada, Oregon, Vermont and Washington -- have adopted the most expansive laws legalizing marijuana for recreational use. Most other states allow for limited use of medical marijuana under certain circumstances. Some medical marijuana laws are broader than others, with types of medical conditions that allow for treatment varying from state to state. Louisiana, West Virginia and a few other states allow only for cannabis-infused products, such as oils or pills. The Cannabis Patient Protection Act went into effect July 1, 2016 (RCW 69.51A). Neither dentists nor chiropractors are allowed to authorize the use of medical marijuana.

What are Cannabinoids?

- Species: Pure or hybrid varieties of Cannabis.
- C. Indica and C. Sativa, C. Ruderalis (Ruderalis is not used for medical or recreational purposes)
- Approximately 24 plant strain varieties, hybrids are very common
- All have varying THC:CBD ratios and varying concentration of other cannabinoids and other bioactive molecules depending on:
    - Genetics
    - Potency
    - Benefits
    - Skill Level
    - Flower Time

Other Notes or Questions to Ask:

- Cannabis plants contain up to 500 distinct chemical compounds, including over 100 "cannabinoids." The term "phytocannabinoid" distinguishes natural cannabis-derived cannabinoids from synthetic cannabinoids (*Hanus, et al. Nat Prod Rep. 2016;33:1357-1392*).

- The two major cannabinoids are:
  - **Δ9-Tetrahydrocannabinol (Δ9-THC, often simplified to "THC")**
  - **Cannabidiol (CBD)**

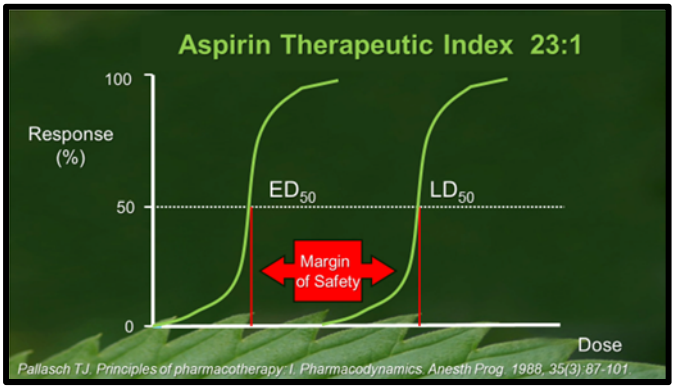
- Recreational cannabis typically has a greater THC:CBD ratio while medical cannabis can vary from high THC:CBD to high CBD:THC ratios.
- *Cannabis sativa* with little THC (< 0.3%) is cultivated as "hemp", for use in food, textiles, etc.

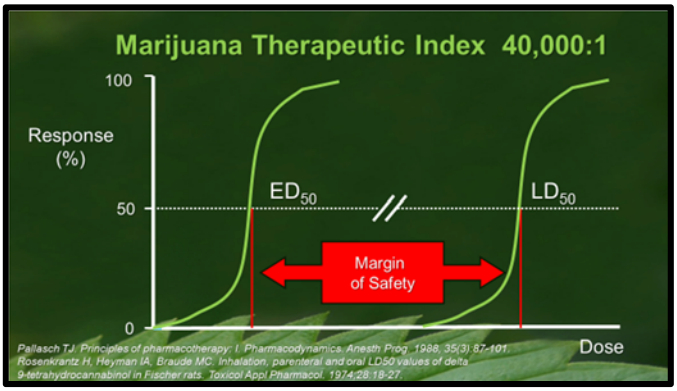
- Other active cannabinoids and metabolites may contribute to biological activity, including:
  - Δ8-Tetrahydrocannabinol (Δ8-THC)
  - Cannabinol (CBN)
  - Cannabidivarin (CBDV)
  - 11-hydroxy-Δ9-Tetrahydrocannabinol (11-OH-THC)
  - many others
- There are also hundreds of potentially bioactive flavonoids and terpenes that have the potential to cause or modulate the pleasurable, medicinal, or adverse effects of cannabis (*Hanus, et al. Nat Prod Rep. 2016;33:1357-1392*).

- Cannabis plants have 2 genders:
  - "Males" grow fast and tall and have little THC
  - "Females" produce flowers rich in cannabinoids
- THC concentrations peak when female plant flowers. At the floral stage, oils high in phytocannabinoids are secreted and concentrated on trichomes (small "hairs" rich in resin). This is when cannabis plants are harvested and non-flowering portions of the plant are removed.

- Most cannabinoids in the cannabis plant are in a carboxylated (i.e., acidic) form such as THCA not THC, and CBDA not CBD. THCA breaks down (e.g., decarboxylates) into THC very slowly over time as cannabis product dries (slow) or very quickly as the plant material is heated. There is very little evidence that carboxylated cannabinoids have any biological activity (i.e., eating the plant does not get you high).
  (Wang M, et al. Cannabis Cannabinoid Res. 2016;1:262-71.)

<u>Are Cannabinoids Safe?</u>





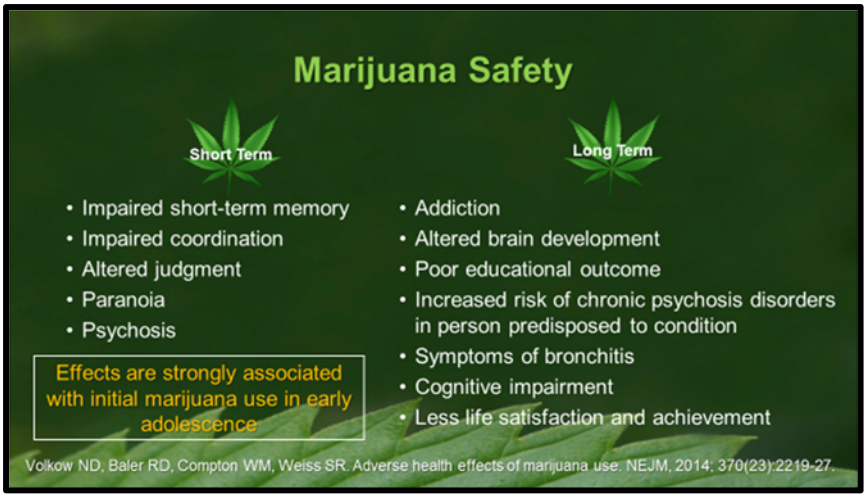
Lethal Smoked Dose: "1500 pounds smoked within 15 minutes" (*Annas. N Engl J Med. 1997 Aug 7;337(6):435-9).*

Other Notes or Questions to Ask:

"Federal authorities should rescind their prohibition of the medical use of marijuana for seriously ill patients and allow physicians to decide which patients to treat. The government should change marijuana's status from that of a Schedule I drug … to that of a Schedule II drug … and regulate it accordingly."

AMA Editorial: The New England Journal of Medicine, January 30, 1997.

Marijuana Safety



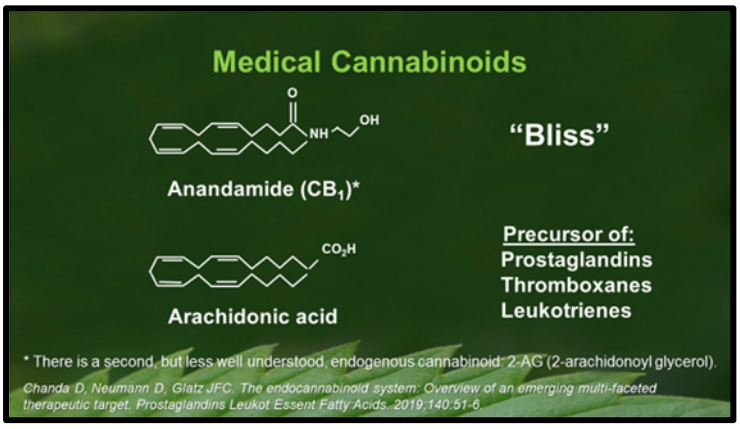
Unfortunately with the rise in THC content (3% in the 1980s and 15%+ in 2018), there are some dire consequences to include:
- Increase in percentage of fatal motor-vehicle accidents
- Increase in driving while under the influence of drug

Consider the most recent published evidence from Colorado:
Roberts BA.Legalized Cannabis in Colorado Emergency Departments: A Cautionary Review of Negative Health and Safety Effects. West J Emerg Med. 2019 Jul;20(4):557-572.

Are Cannabinoids Effective (and how do they work)?

- Marijuana contains over 400 chemicals and hundreds more are produced when smoked. Over 100 are cannabinoids with Delta-9-tetrahydrocannabinol (THC) being the most psychoactive, and is most often used as a marker to gauge potency.
- These phytocannabinoids interacts with a cannabinoid system of receptors in humans to produce different effect. The discovery of the endocannabinoid system was the result of, "reverse engineering." First, we radiolabeled THC molecules to see where they would naturally concentrate in the body: in areas of the limbic system also known as the "reward center" (nucleus accumbens, caudate nucleus, prefrontal cortex and the cerebellum). From this information we were able to locate and eventually clone CB1 receptors in 1990. These receptors are concentrated in areas within the "reward system" of the human brain and help explain cannabinoid actions in the hippocampus such as memory interference and action in the cerebellum which may be responsible for the cannabinoids ability to cause incoordination and loss of balance. CB1 also seems to be important in mediating pain relief, body temperature and gut activity (*Zou, et al. Int J Mol Sci 2018;19:833*).
- At these very specific receptors, cannabinoids inhibit adenylate cyclase via both brain and peripheral G-protein-coupled cannabinoid receptors which leads to increased levels of dopamine in the nucleus accumbens. Opioids and cannabinoids share common signaling pathways in the brain and can interact to promote each other's reinforcing properties.

Other Notes or Questions to Ask:



The CB2 receptor was first cloned in 1993 and shares only 44% identity with CB1. It is present in lymphocytes and the monocyte/macrophage population of the spleen but not the brain. CB2 appears to be confined to the immune system and may mediate the chemical communications between different types of immune cells or between sensory fibers and blood cells

Zou S and Kumar U. Cannabinoid receptors and the endocannabinoid system: Signaling and function in the central nervous system. Int J Mol Sci 2018;19:833

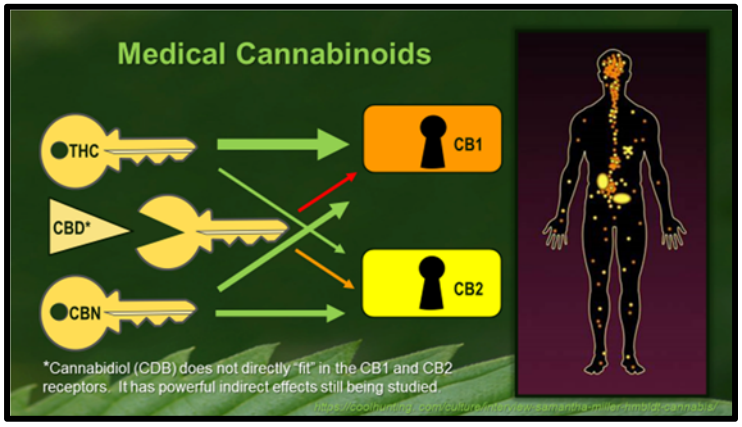
- THC exerts the most psychoactive effects of cannabis and some peripheral/physical effects, including effects on pain, appetite, emotions, thought processes and others. It is a "partial agonist" at both CB1 and CB2 receptors.
- CBD antagonizes or modulates CB receptors which explains why it is a "non-psychoactive" or "non-euphoric" cannabinoid. It has analgesic, anti-inflammatory, anxiolytic, and other effects on the body. CBD may activate serotonin and adrenergic receptors, ion channels, transcription factors, and blocks other types of receptors.
- Δ8-Tetrahydrocannabinol (Δ8-THC) less well characterized compared to THC. It may contribute to the psychoactive and adverse effects and therapeutic effects (and possibly anti-emetic effects).
- Cannabinol, also not well-characterized and is estimated to have ~10% of the activity of THC.
- 11-hydroxy-Δ9-Tetrahydrocannabinol is one of the major psychoactive metabolites of Δ9-THC and is produced by the first-pass effect in the liver when THC is consumed orally. This hydroxyl radical is three times more psychoactive than THC and may explain many of the paranoid and anxiety-type reactions displayed in people who consume edibles versus those individuals who inhale cannabinoids.

Lucas CJ, et al. Br J Clin Pharmacol. 2018;84:2477-82

Other potentially important cannabinoids:

- CBG (cannabigerol)
- CBC (cannabichromene)
- THCV (tetrahydrocannabivarin)
- CBDV (cannabidivarin)
- CBGV (cannabigerivarin)
- CBCV (cannabichromevarin)
- Many others. . .

Hanus, et al. Nat Prod Rep. 2016;33:1357-1392.



Looking through history and folklore, marijuana has been considered important in treating a variety of ailments including:
Poor appetite, pain, seizures, insomnia, spasticity, depression, rheumatism, migraines, menstrual cramps, PMS symptoms, constipation, and others.

In the modern era, many guidelines have approved marijuana for the following indications even though the medical evidence of benefit may still be unclear: cancer, cachexia (appetite stimulation), HIV/AIDS, chronic pain, spasticity / MS, glaucoma, peripheral neuropathy, epilepsy, Crohn's disease, Hospice admit (comfort care).

Other Notes or Questions to Ask:

Medical Cannabinoid Products

Dronabinol (Marinol®) - 1992 - Purified THC indicated for the treatment of refractory CINV and as an appetite stimulant in patients with anorexia due to AIDS or cancer.

- It is only approved in adults and elderly and has not been studied in adolescents and children.
- It is available as 2.5, 5, 10 mg oral capsules and the average wholesale price (AWP) is about $2.36/mg.

Nabilone (Cesamet®) - 1985 - Synthetic THC – two methyl groups are added to the methyl chain and one methyl group on the ring system is replaced with an oxygen molecule). It is indicated for prophylaxis and treatment of CINV.

- It is only approved in adults and elderly although it has an off-label indication in adolescents and children.
- It is available as 1 mg oral capsules and the average wholesale price (AWP) is about $21.00/mg.

Sativex® (Nabiximols) by Bayer (GW Pharmaceuticals) - 2005 – is a 50:50 mixture of tetrahydrocannabinol (THC and cannabidiol (CBD). Each buccal spray contains 2.7mg THC and 2.5mg CBD.

- It is an oromucosal Spray, indicated in adult patients with moderate to severe spasticity due to multiple sclerosis who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.
- The dose is titrated for efficacy and side effects. It is available in Canada and 18 other countries, but not yet available in the US (although clinical trials are ongoing in the US for cancer pain).
- Peppermint-flavored, extracted from cannabis plants and costs around $282 CAD per bottle

Epidiolex® (Cannabidiol) by GW Pharmaceuticals - 2018 – is an oral, strawberry-flavored solution of Cannabidiol 100mg/1mL without THC.

- Studies in children with epilepsy (age range 1 month to 18 years) have proved effective in Dravet Syndrome and Lennox-Gastaut Syndrome.
- Typical doses are 2.5-20mg/kg/day as bid.
- This is the first FDA-approved prescription CBD Drug (C-V) and is only available in the USA at this time and the average wholesale price (AWP) is about $14.82/mL ($1482/bottle) – USD$ (10 doses for a 50kg patient getting 20mg/kg/day)

THC:CBD ratios

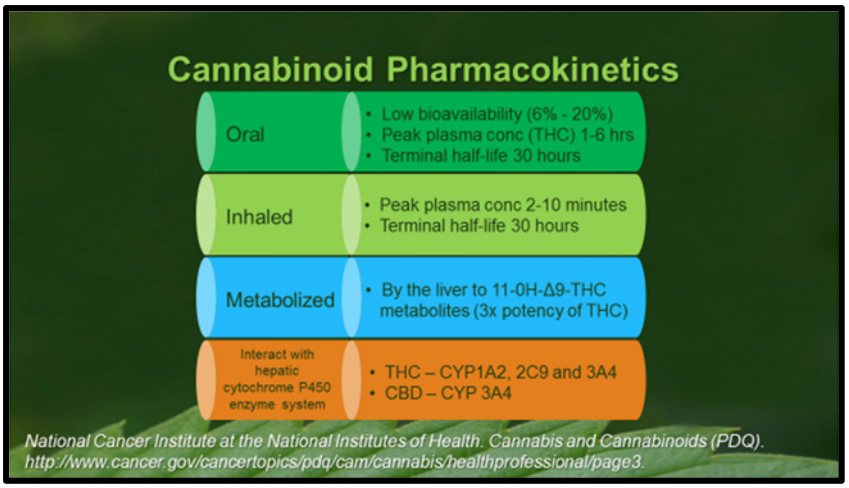
- The unregulated market is driven to produce/sell cannabis with high THC and low CBD. This has led to an increase in THC in cannabis (3% to 15%+).
- The regulated system typically labels products with %THC and %CBD, all products contain some amount of THC.
- Medical strains are selected to provide a range of ratios, from low to high THC:CBD ratios and these must be listed on the labeling of products.
- There are a number of unregulated Cannabidiol (CBD) Oil products which are a form of concentrated cannabis extract, usually sticky and viscous in appearance and administered orally. They are typically prepared with whole cannabis plant, the addition of a solvent, then heat is applied, followed by filtering and cooling. They can also contain 20 to 80% THC depending on strain. The typical solvents used are: petroleum ether, ethanol, naphtha (butane/hexene), and olive Oil (Organic). Naptha can be hazardous and some, such as hexane and benzene, may be neurotoxic. Both naphtha and petroleum-ether are considered potential cancer hazards according to their manufacturers. While the most prominent delivery method of marijuana is inhalation, the second most popular formulation is the cannabidiol oil, and it is quickly gaining popularity – especially in the pediatric space.

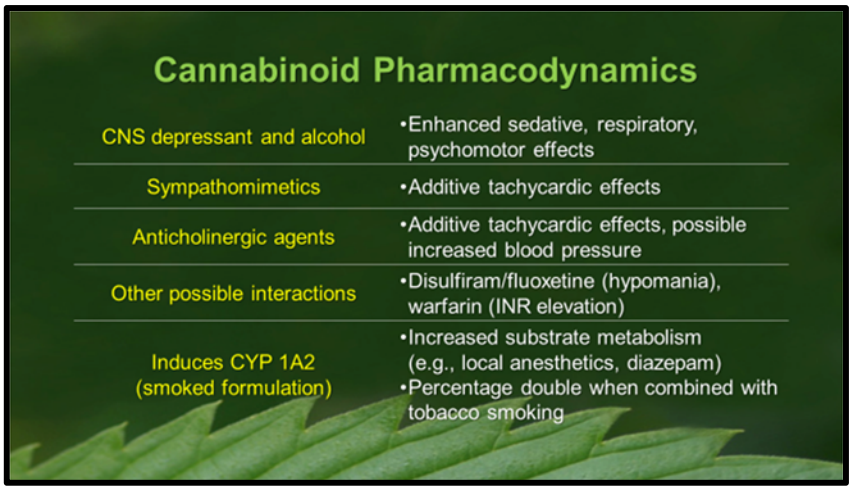
Other Notes or Questions to Ask:

Cannabis Precautions
Avoid driving for at least:

- Inhalation: 4 hours
- Ingestion: 6 hours
- If euphoria: 8 hours
- Impairment may last 24 hours

Cannabis for Medical Purposes Evidence Guide, Information for Pharmacists and Other Health Professionals. CPhA, Jan 25, 2018.





Cannabinoid Side Effects
In general cannabinoids can cause the following effects, both desirable and undesirable:

- Dizziness
- Drowsiness
- Short-term memory loss
- Euphoria
- Dry mouth
- Blurred Vision, Dry eyes
- Reddening of the conjunctiva
- Mydriasis, Photophobia
- Weight Gain
- Vomiting

There are some more serious side effects to include: severe anxiety, psychosis, respiratory depression, altered central nervous system responsiveness, increased heart rate and vasodilation. These cannabis risks are higher in people aged <25 and can further lead to long-term impairment of cognition, suicidal ideation, cannabis use disorder, and certainly an earlier onset of psychosis when used before age 25.

Fischer, et al. Am J Public Health. 2017;107:e1-12.

Cannabis Respiratory Effects
While respiratory issues are generally considered long-term risks, smoke has the same contents as tobacco smoke (i.e., carbon monoxide, bronchial irritants, ↑ tar, ↑ carcinogens). In fact, 3-4 marijuana cigarettes is equivalent to 20 tobacco cigarettes given the fact that they have no filter and the user usually has a deeper inhalation. It has been suggested that water pipes and vaporizers may increase safety but recent data has shown that this may not necessarily be the case. There are increasing reports on the negative effects of e-cigarette ingredients and their notable deterioration on oral health, as well as explosions while vaping and burn injuries from e-cigarettes leading to disfigurement of oral soft tissues.

Versteeg, et al. Int J Dent Hyg. 2008 Nov;6(4):315-20.

Other Notes or Questions to Ask:

A vaporizer heats cannabis product (dried, flowering portion of the plant) to above the volatilization point of cannabinoids, but below the combustion point. Cannabinoids start to vaporize around 160°C through to 230°C (THC first, then CBD, and others). The assumption then is that this is a "healthier" alternative to smoking, since vaporizers heat the material at a much lower temperature (when compared to smoking) and that the active compounds contained in the plant material produce an aromatic vapor (instead of smoke): volatilization versus combustion.

Pomahacova, et al. Inhale Toxicol. 2009;21:1108-12.

Emerging dosage forms, including the cannabinoid-containing e-cigarette liquids, are now available for purchase online but are not regulated, lack quality control, expiry date, and conditions of preservation and there is essentially no toxicological or clinical data. E-cigarettes are battery-powered devices that work by heating a liquid to generate an aerosol that the user inhales. The liquid in the e-cigarette, called e-liquid, is usually made up of propylene glycol, glycerin, flavorings, water, and THC +/- nicotine.

The temperature control of E-cigarettes may be less controlled and hotter than traditional vaporizers. Propylene glycol (PG) acts as a carrier for the e-liquid and when used orally, the breakdown products include acetic acid, lactic acid, and propionaldehyde, which are all toxic to enamel and soft tissues. In addition, PG is a hygroscopic product, which means water molecules in saliva and oral tissue will bond to the PG molecules, leading to tissue desiccation. The result of this is xerostomia leads to an increase in cavities, gum disease, and other oral health issues.

The other major component of e-liquids are glycerin and flavorings. Vegetable glycerin (VG) is a colorless, odorless, viscous, and sweet-tasting liquid. It serves as a humectant, solvent, and sweetener. VG is 60% as sweet as sucrose and is not metabolized by cariogenic bacteria, and is therefore thought not to cause cavities. However, studies have shown that the combination of VG with flavorings produces a four-fold increase in microbial adhesion to enamel and a two-fold increase in biofilm formation. In addition, a 27% decrease in enamel hardness was demonstrated when flavorings were added to e-liquid as compared to unflavored controls.

Kim, et al. PLoS One. 2018;13(9):e0203717.

Although the percentage of nicotine is much lower (0.3%–1.8%) than traditional tobacco products, one electronic cartridge (200–400 puffs) can equal the smoking of two to three packs of regular cigarettes. The dangerous effects of nicotine on gum tissue are well known as nicotine affects gingival blood flow as it is a vasoconstrictor. It also affects cytokine production, neutrophil function, and other immune cell function as well as decreasing connective tissue turnover. All of this results a much higher chance of developing gum disease and tooth loss.

The first known case of a fatal e-cigarette explosion occurred in May 2018 when an e-cigarette exploded in a St. Petersburg, Florida man's face. More recently, a 24-year-old man from Texas was killed when his vape pen exploded, and part of the device wound up severing his jugular vein (January 29, 2019). Although these types of sensationalized deaths are rare with e-cigarettes and vaping pens the explosions of these pens are not. The problem lies within the vape pen and the lithium batteries overheating and exploding. A recent report shows that there were 2,035 e-cigarette explosions and burn injuries in the United States between 2015 and 2017—more than 40 times the initial estimate by the US government. These injuries are serious and often lead to disfigurement of oral soft tissue.

Electronic cigarette fires and explosions in the United States 2009–2016. Lawrence A. McKenna Jr. Research Group. National Data Fire Center. United States Fire Administration. U.S. Department of Homeland Security.

The health risks associated with smoking are many. Each year, 430,000 North Americans die of smoking-related illnesses, more than all American deaths in wars in the 20th century combined; around the world, 5 million people die each year.

Other Notes or Questions to Ask:

Smoking both tobacco and marijuana synergistically increases the risk of respiratory symptoms (2.5x) and COPD (3x).

Tan WC, Lo C, Jong A, Xing L, Fitzgerald MJ, Vollmer WM, Buist SA, Sin DD; Vancouver Burden of Obstructive Lung Disease (BOLD) Research Group. Marijuana and chronic obstructive lung disease: a population-based study. CMAJ. 2009 Apr 14;180(8):814-20. iCapture Centre for Cardiovascular and Pulmonary Research, St. Paul's Hospital and the University of British Columbia, Vancouver, Canada.

- The incidence of tobacco smoking in Canada is 20%
- The incidence of marijuana smoking in Canada is 16% (27% in those people younger than 34)
- Prior to the legalization of marijuana the incidence of COPD in Canada was 4%
- COPD is on the rise and it is a true contraindication to the use of nitrous oxide
- Cannabis also ↑ carboxyhemoglobin concentrations

Other Oral Effects of Cannabis

- Xerostomia
- Periodontal disease – possibly b/c of immunosuppresion, heavy smokers have a 3x increased risk of periodontal disease
- "Cannabis stomatitis" – chronic use may cause inflammation of the oral epithelium (similar to nicotine stomatitis).
- Leukoedema – may progress to leukoplakia
- Increased risk of mouth and neck cancers
- Synergistic risk when combined with tobacco smoking
- Increased prevalence and density of Candida albicans.

Cannabis Cardiovascular Effects

- Dose-related tachycardia of up to 50% increase in heart rate and myocardial oxygen demand
- THC increases catecholamine release which leads to increased demand on the heart (careful with epinephrine)
- Tolerance may develop within 1 week
- Generalized vasodilation (hypotension after 1 week)
- ↑ carboxyhemoglobin concentrations

Cannabis Other Effects

- Cannabis used to treat nausea/vomiting in chemotherapy
- Can also cause chronic vomiting (hyperemesis)
- Related to chronic use in recreational users
- Repeated episodes of nausea and vomiting
- Abdominal pain that requires emergency management
- Nausea relieved by a hot shower
- Stops with cessation of cannabis, recurs if cannabis use restarted
- Case reports of death from cannabis hyperemesis

Richards JR. J Emerg Med. 2018 Mar;54(3):354-363.

What do Oral Healthcare Providers really need to know?
Dentists may prescribe medications and controlled substances ONLY FOR DENTAL-RELATED conditions. Under no circumstances may a dentist prescribe anything whatsoever outside the course of his/her practice of dentistry.

Other Notes or Questions to Ask:

The Cannabis for Medical Purposes Evidence Guide, Information for Pharmacists and Other Health Professionals (CPhA, Jan 25, 2018. Available at: https://www.cfpc.ca/Release_Dried_Cannabis_Prelim_Guidance/) begins with three general principles:

> **Recommendation 1**
> There is no research evidence to support the authorization of dried cannabis as a treatment for pain conditions commonly seen in primary care, such as fibromyalgia or low back pain (Level III). Authorizations for dried cannabis should only be considered for patients with neuropathic pain that has failed to respond to standard treatments (Level I).
>
> **Recommendation 2**
> If considering authorizing dried cannabis for treatment of neuropathic pain, the physician should first consider a) adequate trials of other pharmacologic and non-pharmacologic therapies and b) an adequate trial of pharmaceutical cannabinoids (Level I).
>
> **Recommendation 3**
> Dried cannabis is not an appropriate therapy for anxiety or insomnia (Level II).

One recent report has suggested a role for cannabidiol for oral mucositis since the control of oxidative stress may prevent and alleviate oral mucositis. Studies have demonstrated that cannabidiol is safe to use and possesses antioxidant, anti-inflammatory and analgesic properties, however, more studies are needed before this can be considered an evidence-based recommendation (and oral cannabinoids have not yet been approved for prescribing).

Cuba, et al. J Clin Pharm Ther. 2017 Jun;42(3):245-250.

Cannabis and Dentistry Conclusions

- The use of cannabis, particularly marijuana smoking, has been associated with poor quality of oral health.
- The etiology has been complicated by the number of associated factors with frequent users, including high tobacco, alcohol, and other drug use; poor oral hygiene practices; and infrequent visits to dentists.
- Cannabis use also leads to xerostomia which can contribute to a number of oral health conditions.
- Further, the main psychotropic agent, THC, is an appetite stimulant, which often leads users to consume cariogenic snack foods.
- Regular cannabis users are known to have significantly higher numbers of caries than nonusers, particularly on normally easy-to-reach smooth surfaces.

- Leukoedema is more common among cannabis users than non-users but it is unclear whether associated irritants, such as orally inhaled smoke, rather than cannabis itself, may be contributing causes.
- Smoking marijuana is associated with gingival enlargement, erythroplakia and chronic inflammation of the oral mucosa with hyperkeratosis and leukoplakia, sometimes referred to as “cannabis stomatitis” that can develop into malignant neoplasias.
- It has been reported that a synergistic effect between tobacco and cannabis smoke may increase oral and neck cancer risk for people who smoke both.

- The risk and aggressiveness of cancers associated with cannabis appear to be higher in younger (i.e., <50 years old) users.
- Immunosuppressive effects of cannabis, especially in association with oral papillomavirus in smokers, may contribute to these increased risks of cancer.

Other Notes or Questions to Ask:

- The immunosuppressive effects of cannabis may contribute as well to a higher prevalence of oral candidiasis compared to non-users (hydrocarbons in cannabis provide an energy source for *Candida).*
- The generally poor oral hygiene among many cannabis smokers may promote candidiasis colonization.
- Viable microbiota may be transmitted from contaminated marijuana, which could further exacerbate a pathogenic oral environment.

- A number of studies have suggested a direct relationship between cannabis use and periodontal disease, including a 2019 systematic review (*J Periodontal Res. 2019 Aug;54(4):311-317*).
- Significantly higher rates of periodontitis are observed among frequent users compared to non-users, with significantly higher numbers of sites with high pocket depths (≥4mm) and attachment loss.
- Periodontitis may occur at an earlier age in marijuana users than the general population with chronic periodontitis.

- In a histometric experiment, laboratory rats exposed to marijuana smoke had a significant increase in alveolar bone loss due to periodontitis, despite research that has indicated that specific cannabinoids, such as the non-psychotropic cannabidiol (CBD), may prevent bone loss.
- Avoid treating active (currently intoxicated) users: euphoria, hyper-activity, tachycardia, paranoia, delusions and hallucinations.
- Increased anxiety, paranoia and hyperactivity may heighten the stress experience of a dental visit – caution if sedatives are to be considered given their synergistic effects.

- Increased heart rate and other cardiorespiratory effects of cannabis make the use of epinephrine potentially life-threatening.

Cannabis and Screening Tools

- CUDIT-R
- ASSIST
- Severity of Dependence Scale
- E-TOKE
- Additional screening tools include: CAGE-AID and the Modified ORT
- https://www.cpha.ca/cannabis-screening-tools

Dental Considerations with Illicit Drug Users

	Cardiovascular Effects	Respiratory Effects	Xerostomia	Interaction with local anesthesia	Interaction with vasoconstrictors	Interaction with narcotic analgesics
Cannabis	+	++	++	-	+	-
Cocaine	++	+	++	+++	+++	+++
Narcotics	++	++	++	-	-	+++
METH	+++	+	+++	-	+++	+++

Other Notes or Questions to Ask:

Dental Considerations with Illicit Drug Users

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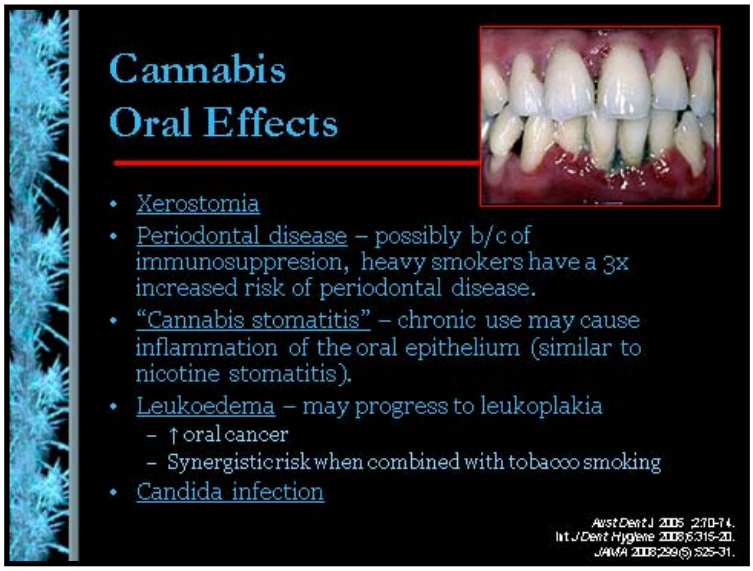
Narcotics	++	++	++	-	-	+++
METH	+++	+	+++	-	+++	+++

- In 2012, there were 2.4 million persons aged 12 or older who had used marijuana for the first time within the past 12 months; this averages to about 6,600 new users each day.
- From the plant Cannabis Sativa main psychoactive constituent: Delta-9-tetrahydrocannabinol (THC)
- There are three main forms:
  - Marijuana (0.5-5% THC)
  - Hashish (2-20% THC)
  - Hash oil (15-50+% THC)



Marijuana is the most common and least potent form, made up of dried leaves and flowers while Hashish is a sticky, thick, dark-colored resin (like sap) which is made from the cannabis plant flower heads compressed to form small light brown or black blocks. Hash Oil is a thick, oily liquid extracted from hashish, and is the most potent form.

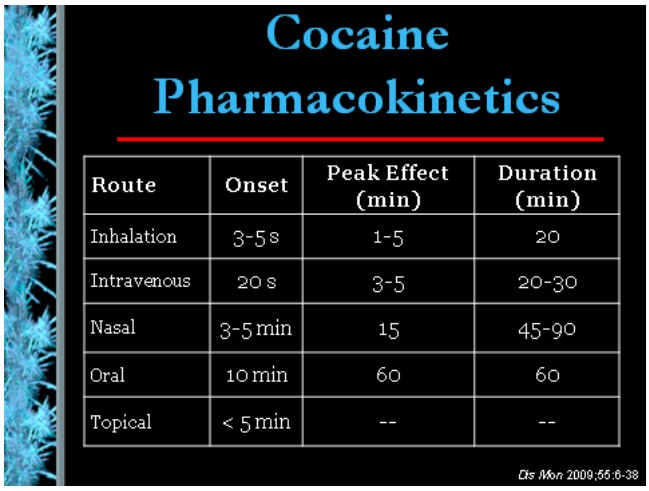
Cannabis Effects

- Immediate effects: creation of a pleasant, dreamy state with impairment of attention, cognitive and psychomotor impairment with no acute life-threatening effects; sometimes called a "soft drug."
- Negative effects: dose-related tachycardia of up to 50%, increased heart rate and myocardial oxygen demand, generalized vasodilatation, ↑ carboxyhemoglobin concentrations.
- Generally considered long-term risks, smoke has same contents as tobacco smoke (i.e., carbon monoxide, bronchial irritants, ↑ tar, ↑ carcinogens). 3-4 marijuana cigarettes = 20 tobacco cigarettes
- "Smoking both tobacco and marijuana synergistically increased the risk of respiratory symptoms (2.5x) and COPD (3x). Smoking only marijuana was not associated with an increased risk of respiratory symptoms or COPD." *CMAJ 2009;180(8):814-20*

Other Notes or Questions to Ask:

Cocaine

- Cocaine is one of the alkaloids present in the leaves of *Erythroxylon coca*.
- Main psychoactive constituent is benzoylmethylecgonine.
- The principal method of administration is snorting.
- Interferes with reabsorption of Dopamine and stimulates pleasure centers of brain.



- Cocaine powder (cocaine hydrochloride) is made from the leaves of the coca plant, it is separated with alcohol, gasoline, or kersosene.
- Freebase - a method using ammonia and ether that separates the free-base molecule of cocaine, can be smoked, high potency, ↑ toxicity.
- Crack - a method that converts cocaine hydrochloride into a smokable form using bicarbonate. Results in lower potency than freebase, ↑ impurities.

- Half-life: 0.7-1.5 hrs
- Detectable in the body for up to 10 days after use. Cocaine can be found on the street using an infinite number of street names and slang. It can be snorted, injected, smoked, or eaten. The level and length of the effects depend on how the drug was induced.

Cocaine Effects
Immediate effects: Within a few minutes a euphoric 'high' feeling occurs which can last for up to 90 minutes.

"There's no happy ending to cocaine. You either die, you go to jail, or else you run out."
- Sam Kinison

- Anesthetic effect.
- CNS excitation → CNS/Respiratory depression.
- ↑ Heart rate, ↑ oxygen demand.
- Vasoconstriction of coronary arteries causing ↓ oxygen supply.
- Peripheral vasoconstriction increases BP 15-20%.

Lethal Snorted Dose: "1.4 grams for a 70kg male." One 'line' of cocaine ~ 50-100mg.

Cocaine Oral Effects
- Nasal Septum perforation & palatal perforation (vasoconstriction → local ischemia).
- "Saddle-nose" deformity
- Increased BP
- Local anesthetic toxicity
- Vasoconstrictor toxicity – potentially fatal
- Xerostomia
- Bruxism

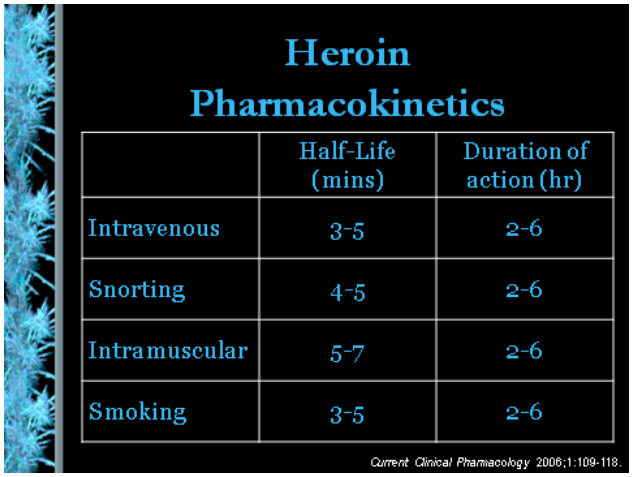
Other Notes or Questions to Ask:

Narcotic: A drug derived from opium or opium like compounds, with potent analgesic effects associated with significant alteration of mood and behavior, and with the potential for dependence and tolerance following repeated administration.

Opiate: A medication or illegal drug that is either derived from the opium poppy, or that mimics the effect of an opiate (a synthetic opiate).

Heroin

- The most powerful known non-synthetic painkiller (medical name: diacetylmorphine).
- Heroin is not a naturally occurring drug, it is refined from morphine.
- Can be snorted or injected: "Chasing the dragon."
- In its purest form, Heroin is a white powder but it is most commonly seen is brown due to impurities.
- Black tar heroin is not really heroin, but an unrefined mixture of lesser acetylated morphine derivatives.



Heroin Effects

- The immediate effect of intravenous heroin is often described by heroin dependents as a "flash", a warm and intensively pleasant sensation.It is felt with IV , IN, and smoking. No flash with oral or rectal.
- The "flash" is followed by an euphoric, benumbed state, which may be more related to morphine.
- Slows down circulation and heart rate. Heroin also causes generalized vasodilation (users feel warm).
- Depresses bowel activity, which can result in constipation. First-time users often vomit.
- Respiratory Depression.
- At high doses users become drowsy. An excessive dose can produce stupor and coma, and possible death.

Lethal Injected Dose is "22 mg/kg for a 70kg male." One "stamp bag" is 100 mg Heroin and costs $10-$15.

Heroin Dental Considerations

- Xerostomia.
- Drug Interactions (synergistic with any other narcotic).
- Allergic thrombocytopenia (Quinine).
- ↑ risk of endocarditis.
- ↑ risk of HIV and Hepatitis.
- 40% of IV users exposed to some form of Hepatitis.

Methadone

- Synthetic opiate in use since the 1960's as a narcotic pain reliever and an adjunct to addiction detoxification (1mg/mL concentration).
- Methadone Pharmacokinetics.
- Syrup (Sugar-free? - Sugar-based has a high sugar content [0.9g/5mL]).
- Onset ~ 30 mins; Duration of action 24-36 hrs ; $T_{½}$ = 15-25 hrs.

Methadone Dental Considerations

- Xerostomia
- Increased caries rate with sugar-based formulations
- Consider fluoride supplementation
- Possibly contributes to erosion (↓ pH)
- Same systemic effects as the other opioids

Other Notes or Questions to Ask:

Consider that people who are opioid-dependent are likely to require greater analgesia post-operatively; will require a pain management plan to manage existing tolerance and to ensure provision of adequate analgesia; may have best outcomes if commenced or stabilized on maintenance pharmacotherapies pre-operatively; and May require careful management not to reinstate opioid dependence if abstinence was achieved pre-operatively (caution in recovering addicts!)

Why is Meth so popular?

In contrast to Cocaine…

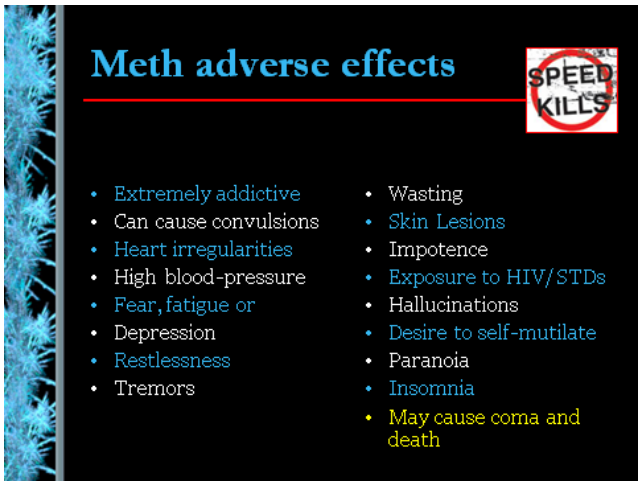
- Meth is easily manufactured – precursors can be bought over-the-counter (OTC).
- The high can last up to 8 hours.
- How used: snorted, injected, smoked, swallowed

Methamphetamine can be easily produced with toxic precursors:

- Pseudoephedrine or Ephedrin
- Acetone
- Red Phosphorus
- Denatured alcohol
- Battery acid
- Iodine
- Muriatic Acid
- Freon
- Annhydrous ammonia
- Drain cleaner
- Paint thinner
- Sulfuric Acid

Methamphetamine is the more powerful and more addictive cousin of amphetamine:

- Positive outcomes: rush, flash, enhances mood, energy, alertness.
- Duration: minutes (rush) up to 12 hours.
- Physical effects: increased heart rate, blood pressure, respiration, flush, sweating.
- Lethal Dose: "70-120mg/kg" or 4-8 grams
- Addicts may use up to 8 grams per day, fatalities reported with as little as 3 grams.



Causes massive release of neurotransmitters dopamine and norepinehrine, also blocking reuptake:

- Results in neurotransmitter depletion.
- Rapid tolerance, withdrawal symptoms.
- Psychosis, violent behavior.

Methamphetamine – "Crank Bugs"

All Meth users suffer from what they call "Crank Bugs." Meth is manufactured with chemicals that are toxic to the human body, and once the drug is taken the chemicals remain. The body's natural reaction is to try and eliminate the toxins (usually slowly leech out through the skin). Users itch and scratch which causes the open sores

"Meth Mouth"

The phenomenon is thought to be the result of the ingredients used to make Meth, however, Studies have shown that the ingredients are most likely NOT responsible for the rapid destruction to dentition.

- *Navarro et al. 2001. pH decline from 7.4 to 6.9*
- *Critical pH for demineralization of enamel is 5.5*

Current literature suggests that "Meth Mouth" is the result of: Hyposalivation, High sugar intake, Bruxism, and Poor oral hygiene.

Other Notes or Questions to Ask:

Dental Management of the Meth patient:

- Postpone all dentistry if history of recent use.
- For Emergency Procedures:
  - No vasoconstrictor in local anesthetic preparations
  - No Narcotic-containing analgesics
- IV users have increased risk of endocarditis.
- ↑ risk of HIV and Hepatitis.

Dental Modifications for Meth Patients:

- Postpone elective care.
- No vasoconstrictor (for 24 hours after most recent use).
- Recommend avoidance of carbohydrate-rich soft drinks (e.g., water).
- Increased preventive measures.

Strategies to promote saliva flow:

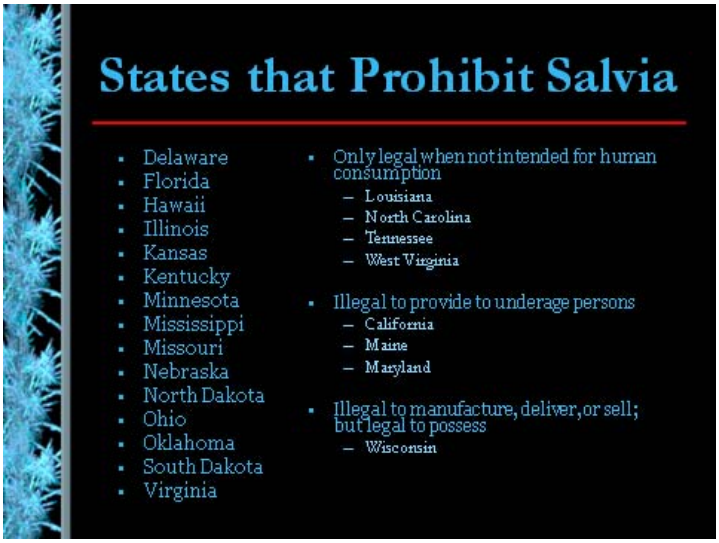
- Sugarless gum
- Saliva replacement (Moi-Stir®)
- Oral moisturizers (Optimoist®)
- Pilocarpine (Salagen®)
- Cevimeline (Evoxac®)
- Biotene® Products

The state of Oregon ranks among the top ten states nationally in per capita treatment admissions for methamphetamine. The social costs are staggering. The human costs are incalculable.

- 52% of children in foster care are there due to Meth. Cost to the State: $12 million a year.
- 50% of adults in prison are there due to Meth-related crime. Cost to the State: $43 million a year.
- 20% of adults in treatment are there for Meth addiction. Cost to the State: $10 million a year.

Dental Management of the Recovering Meth patient:

- For the recovering Meth user, who is now clean, there are no contraindications to dentistry!



Salvia Divinorum

- Hallucinogenic Plant in the mint family.
- Used by the Mazatecs in Mexico for its psychoactive properties during traditional spiritual practices.
- Salvinorin A is the active agent.
- K – opioid receptor agonist.
- Hallucinations, dysphoria, delirium, dissociation.
- Can be smoked or swallowed.
- Leaves must be held in the mouth for absorption, stomach acids deactivate the drug.
- Lethal Dose: Unknown.

Khat Bush . . . Bath Salts

- Active ingredient in the leaves is cathinone.

Plant is found in East Africa and Southern Arabia and pharmacologic profile closely resembles that of amphetamine. Cause dopamine and norephineprhine release in the brain and has led to the development of cathinone-based "Designer Drugs" such as MDPV (Methylenedioxypyrovalerone).

Other Notes or Questions to Ask:

Effects very similar to amphetamine, methamphetamine, and MDMA (ecstasy). Intense cravings and as little as 5mg dose can be effective. Can be swallowed, snorted, smoked, or IV. 5-20mg is the usual dose and a 500mg packet can be purchased for as little as $20.

Duration of action is usually 3-4 hours and side effects may last a total of 6-8 hours. While the lethal dose is unknown, typical effects consist of:

- Hallucinations
- Fever / increased body temperature
- Paranoia
- Tachycardia followed by bradycardia and hypotension
- Vasoconstriction
- Suicidal thoughts

"The LD50 of MDPV is not known, although it is suggested that non-fatal overdose would be possible at relatively low doses compared to mephedrone."

Psychonaut WebMapping Research Group (2009). MDPV Report. Institute of Psychiatry. Kings College: London, UK

State and local law enforcement officials encountered MDPV in 2009 and 2010 in Iowa, Kentucky, North Dakota, Oklahoma, Texas, and Wisconsin. Currently, MDPV is not a scheduled drug under the Controlled Substances Act (CSA). However, if intended for human consumption, MDPV can be considered an analogue of a schedule I drug under the CSA. Therefore, law enforcement cases involving MDPV can be prosecuted under the Federal Analogue Act of the CSA.

Is anyone here afraid of crocodiles? How about krokodil (Russian: "Крокодил")

Russian junkies created krokodil which they made by mixing codeine with chemicals such as gasoline, red phosphorus, and hydrochloric acid, because heroin was scarce and codeine was available over the counter. Codeine is converted by the liver to desomorphine which is the most active drug in this toxic mixture. It is around 8-10 times more potent than morphine and is described as having a fast onset and a short duration of action, with relatively little nausea or respiratory depression compared to equivalent doses of morphine.

The high associated with krokodil is akin to that of heroin, but lasts for a much shorter period. While the effects of heroin use can last four to eight hours, the effects of krokodil do not usually extend past one and a half hours, with the symptoms of withdrawal setting in soon after.

"Krokodil" (Flesh-eating "zombie drug") gets its name from the fact that similar to crank bugs and methamphetamine, Krokodil is notorious for producing severe tissue damage, phlebitis and gangrene (making the users skin similar to that of a crocodile); sometimes requiring limb amputation in long-term users.

The Take-Home Message

An estimated 22 million Americans-almost 10 percent of the population-suffer from chemical dependence or abuse drugs, alcohol or both, according to the latest statistics from the Substance Abuse and Mental Health Services Administration of the Department of Health and Human Services. That means 10% of YOUR patients!

Medical histories should include complete pharmacological histories with an emphasis on what constitutes a "drug" and why your patients need to tell you the truth. In this world of polypharmacology and illicit drug use, the interplay of drug interactions with traditional medical therapy is becoming more difficult every day!

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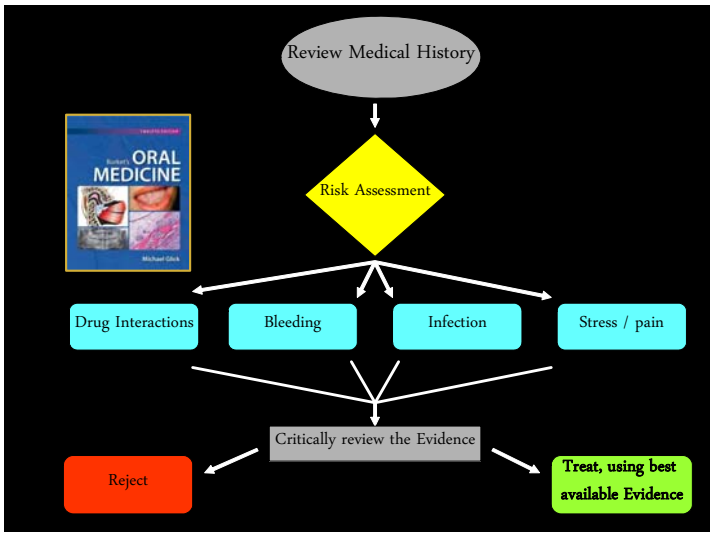
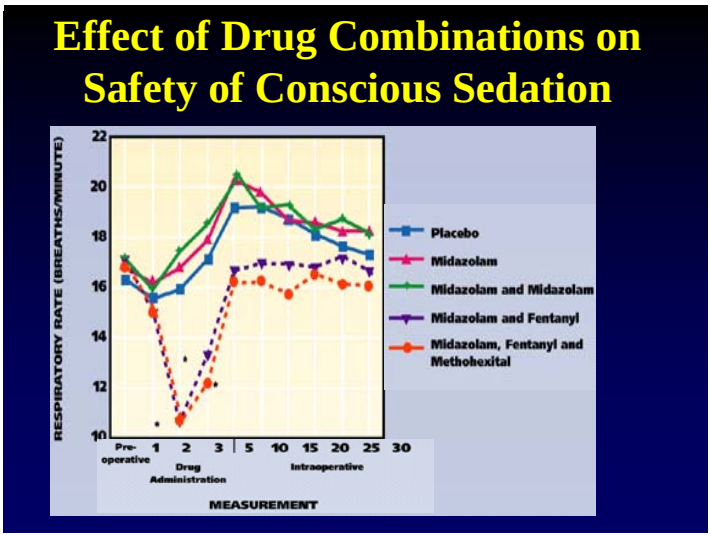
Other Notes or Questions to Ask:

Money Makes the World Go Around, But Drugs Can Make it Spin!

The goal of oral conscious sedation is to create, by pharmacologic or other means, a comfortable environment such that the patient can safely and effectively receive dental care.

There is an inverse relationship between the depth of sedation and the degree of safety associated with it. Clearly, general anesthesia and deep sedation hold the greatest risk of serious morbidity and mortality as well as the highest efficacy. On the other hand, nitrous oxide and oral conscious sedation have the lowest risk and a lower clinical efficacy.





Multiple Agent Protocols

When benzodiazepines are administered alone, only mild changes occur in respiratory rate and oxygen saturation levels. However, adding a barbiturate or a narcotic in a multiple drug regimen with a benzodiazepine creates a statistically significant decrease in both respiratory parameters.

Why should drug interactions concern me? - because polypharmacy is the norm especially in those patients over 65 years old. A Canadian Medical Association policy survey showed that more than 20% of acute care hospital admissions for seniors may result directly from adverse drug reactions. Polypharmacy is used as: complementary therapy; co-morbid conditions and; non-comorbid conditions.

Many of our patients are on multiple drug regimens. **The potential for drug interactions increases dramatically with the number of medications prescribed.**

Chronic illness leads to polypharmacy so that there is a high probability of a drug interaction. But how is this related to dentistry? Almost all of your patients will be on some kind of medication (prescription, OTC, herbals, supplements, recreational). And just because dentists prescribe less than 10% of all available drugs, your patients may be taking others from the 90% you're not familiar with, and not all of your patients will tell you what they are taking. So who is more "at risk" - you or your patient?

"67% of patients do not discuss complementary and alternative medicine (CAM) with their health care providers because the clinicians did not ask."

http://nccam.nih.gov/news/camstats/2010/introduction.htm. (Accessed Sept 7, 2015)

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Donaldson M. The Spiderman Principle. J Am Dent Assoc 2011;142(11):1-4.

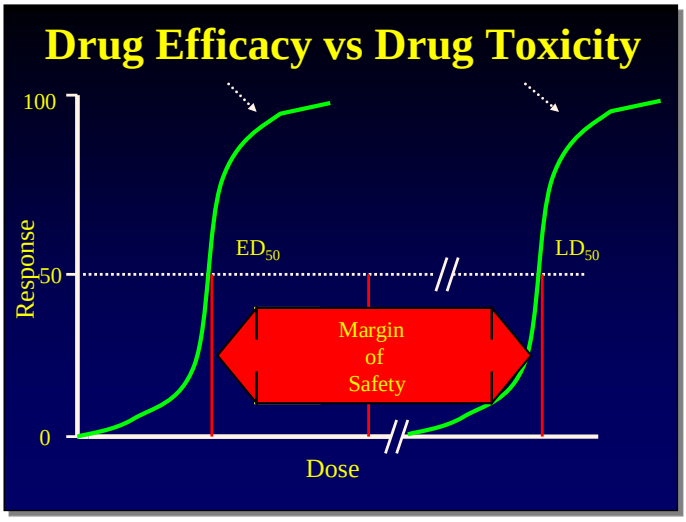
Start with Intrinsically SAFE Drugs (e.g., for sedation)

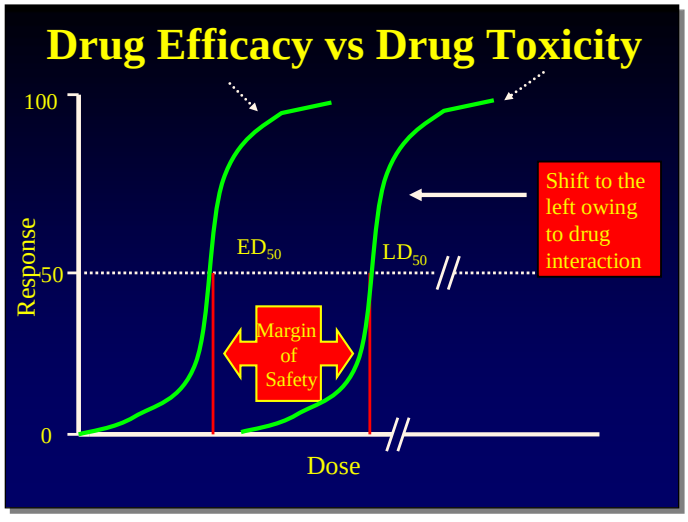
Most Common	Less Common	Least Common
Nitrous Oxide	Opioids	Barbiturates
Benzodiazepines	Alcohols	Antidepressants
Antihistamines	Phenothiazines	Anticholinergics

To first understand drug interactions it is important to revisit metabolism. The primary organ of ***metabolism*** is the liver (although some similar enzymes exist in the cells of the gastrointestinal mucosa). The enzyme complexes in the liver chemically transform the medication molecules into either active or inactive metabolites. These enzymes are known as the **Cytochrome P_{450} (CYP450)** Family of enzymes, and can be further stratified into the individual isoenzymes, which comprise this family. In terms of dental pharmacology, the most prominent isoenzymes to consider are: **CYP3A4, CYP2D6, CYP2C9, CYP1A2 and CYP2C19.**

Metabolism is also known as biotransformation as some drugs are "pro-drugs". Drug metabolites are usually more polar and less lipid soluble than the parent molecules (this enhances their excretion and distribution half –life). Hepatic oxidation is the major drug metabolizing process. This process, or what the patient does to the drug (pharmacokinetics), and its balance with what the drug does to the body (pharmacodynamics), determines the effectiveness of the medication.

Drug interactions are common causes of treatment failure and adverse reactions. Most drug interactions remain unrecognized because of a wide margin of safety (therapeutic index) compared to inter- and intra-patient variability seen in practice. The effect of inappropriate drug combinations may lead to drug interactions or inaccurate assessment of the clinical effect.





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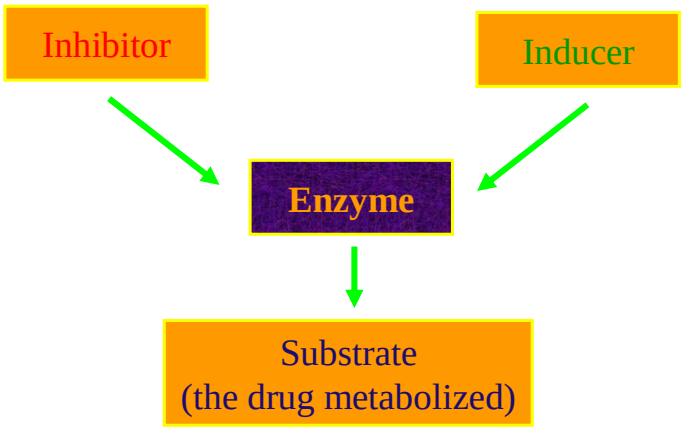
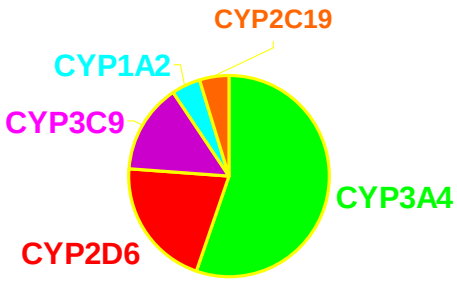


It is possible for a drug to be both a substrate and an inhibitor of an enzyme

Relative Proportions of Enzymes



The therapeutic index of a drug relate its effective dose fifty (ED50) to its lethal dose fifty (LD50) and is a measurement of drug safety. The greater the therapeutic index, the greater the difference between the ED50 and the LD50, the greater the margin of safety. Chloral Hydrate, an alcohol, has a much lower therapeutic index than the benzodiazepine, diazepam. If, however, the two drugs were to be administered together, the LD50 representing the combination would shift significantly to the left, resulting in a much lower degree of safety.

Some points are important to keep in mind:

- ✓ The management of a condition with a drug depends on the predicted effect of that drug
- ✓ The predicted effect depends on the drug being present:
  - in the clinically active dose
  - for the appropriate duration
- ✓ Anything that changes the dose or duration of effect makes drug management unpredictable

Drug interactions give rise to a modified response from the expected or normal response; can cause increased drug levels leading to an enhanced response or increased side effects (clinical relevance depends on the therapeutic indication) or; can cause decreased drug levels leading to sub-clinical or lack of response. Finally, drug interactions can be permanent because of polymorphism (i.e. patient does not have enzyme). **The bottom line is that variability in patient response may be the result of changed metabolism which can be caused by drug interactions.**

Classifying the enzymes responsible for drug metabolism

- Drugs are usually metabolized to inactive metabolites for excretion
- The main route of metabolism for exogenous substances is the liver by the cytochrome P450 mono-oxygenase system
- The P450 system is made up of many enzymes. However, the majority of drug metabolism is by five enzymes: 1A2, 2C9, 2C19, 2D6, and 3A4

There are significant interpatient and intrapatient variability with respect to effects of medications and current research indicates that the genetic expression of these liver enzymes may play a prominent role in determining who and why different patients react differently. In the case of isoenzyme CYP2D6, for example, this ***genetic polymorphism*** in metabolism is common, and can lead to 10 times the difference in drug clearance, leading to either therapeutic failures or increased adverse events and toxicities.

Other Notes or Questions to Ask:

CYP 1A2

Substrate	Inducer	Inhibitor
Caffeine	Carbamazepine	BCPs
Chlordiazepoxide	Clarithromycin	Cimetidine
Diazepam	Cigarette Smoke	Ciprofloxacin
Estrogens	Erythromycin	Fluvoxamine
Haloperidol	Insulin	Isoniazid
LAs	Lansoprazole	Ticlopidine
Olanzapine	Omeprazole	
Propranolol	Phenobarbital	
Tamoxifen	Phenytoin	
TCAs	Rifampin	
Theophylline	Ritonavir	

CYP 2C9

Substrate	Inducer	Inhibitor
ASA	Carbamazepine	Amiodarone
Dapsone	Phenobarbital	Azole Antifungals
Diazepam	Phenytoin	Cimetidine (weak)
Dicoumarol	Rifampin	Fluvoxamine
Fluoxetine		Omeprazole
Losartan		Ritonavir
Most NSAIDs		"Statins"
Phenobarbital		Tolbutamide
Phenytoin		
Sulfonamides		
Temazepam		
Tolbutamide		
Zidovudine		

The ultrarapid metabolizer phenotype (where CYP2D6 activity is overactive) leads to a reduced effectiveness of drug at standard doses. The prevalence of this polymorphism among different patient populations is Northern European countries (2%-4%); Mediterranean area (7%–12%); Ethiopians, (29%) and; Saudi Arabian (21%). Conversely, 5%–10% of the Caucasian population have a CYP2D6 deficiency which often leads to an increased potential for drug interactions and side effects due to an accumulation of CYP2D6 metabolized drugs and higher serum drug concentrations, despite administration of "standard doses".

CYP 2C19

Substrate	Inducer	Inhibitor
Barbiturates	Carbamazepine	Azole Antifungals
Diazepam	Norethindrone	Cimetidine (weak)
Lansoprazole	Phenobarbital	Fluoxetine
Omeprazole	Phenytoin	Fluvoxamine
Phenytoin	Prednisone	Lansoprazole
Propranolol	Rifampin	Omeprazole
TCAs		Paroxetine
Temazepam		Ritonavir
Valproic Acid		Ticlopidine
Zidovudine		

CYP 2D6

Substrate	Inducer	Inhibitor
Several β-Blockers	None Known	Amiodarone
Codeine		Cimetidine
Dextromethorphan		Chlorpheniramine
Encainide, Flecainide		Encainide
Haloperidol		Fluoxetine
Halothane		Haloperidol
Hydrocodone		Ketoconazole
MDMA (Ecstasy)		Nefazodone
Omeprazole		Paroxetine
Phenothiazines		Phenothiazines
Propafenone		Quinidine
Selegeline		Ritonavir
SSRIs, TCAs		Sertraline
Venlafaxine		"Statins"
		TCAs
		Venlafaxine

<u>Clinical Relevance of Drug Interactions</u>

- Drug interactions can be caused by enzyme induction, inhibition, or competition
- If an enzyme is induced by a drug, metabolism occurs faster (e.g. Phenobarbital)
- If inhibition occurs the drug is not metabolized as fast (increased blood levels)
  - Two or more drugs (competing for) the same enzyme will lead to variations in blood levels

Other Notes or Questions to Ask:

Case Study #1
A 45 year old woman has been using diazepam intermittingly. She has suffered from GERD for 5 years. Her reflux symptoms are controlled by omeprazole but she has recently begun to feel drowsy. She asks if this can be caused by the drugs that she is taking.

Omeprazole is metabolized by CYP 3A4 and by CYP 2C19 and has many interactions with the P450 enzyme system. Omeprazole inhibits the metabolism of drugs (such as diazepam) which are metabolized by CYP 2C19, which can result in increased plasma concentrations.

Not all drugs in the same class are metabolized by the same pathway. Thus when prescribing a second or subsequent drug, potential drug interactions should be considered and drug choice made accordingly. Where a drug interaction occurs, it is often possible to select another drug in the same drug class with a different metabolic pathway. Note that there is also polymorphism with CYP 2C19. 2-6% of Asians do not have the enzyme and are therefore poor metabolizers.

Case Study #2

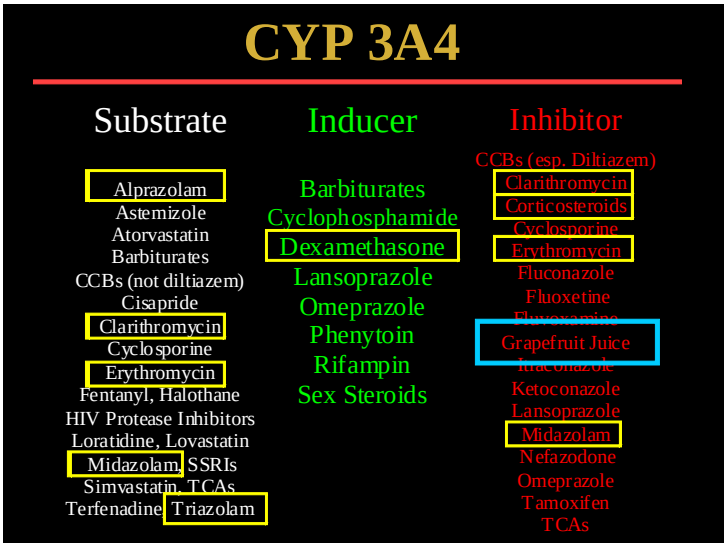
28 year old female who presents for hygiene, operative, and extraction of her wisdom teeth. Past medical history includes: Depression, Social anxiety disorder and Asthma. She takes Prozac, and albuterol prn. She has NKDA. Surgery went well and she is given codeine syrup postoperatively because, "tablets make me gag."

That night there is a frantic phone call to the after-hour service from mother, "my daughter is in excruciating pain!" Recommendation given to double codeine dose to 60mg every six hours and if there is still no relief to come back to the office the following day. Patient presents to the office the next morning in tears and obvious pain. No noticeable abscess or swelling . . . What could be going on?? Codeine is a "prodrug" that requires "activation" by the liver. The CYP 2D6 isoenzyme is responsible for converting codeine to its active form, morphine (***Br J Anaesth 2002; 89: 839–45***).

Up to 10% of the Caucasian population have a deficiency in this isoenzymes so they cannot activate codeine. Since pain of dental origin is primarily related to inflammation and narcotics like codeine are not antiinflammatory agents, ibuprofen and acetaminophen should be the combination of choice (helps avoid "codeine failures" also).
Donaldson M and Goodchild JH. Appropriate analgesic prescribing for the general dentist. Gen Dent 2010; 58(4):291-7.

Case Study #3
A 73-year old man who has been on lovastatin (Mevacor®) 20mg daily for the past seven years is given six courses of erythromycin (9 grams over 2 weeks) for subacute bacterial endocarditis (SBE) prophylaxis. Most of the procedures involved simple crowns and fillings. Doses were all appropriate as per the old American Heart Association guidelines (***J Am Dent Assoc. 1997 Aug;128(8):1142-51***).

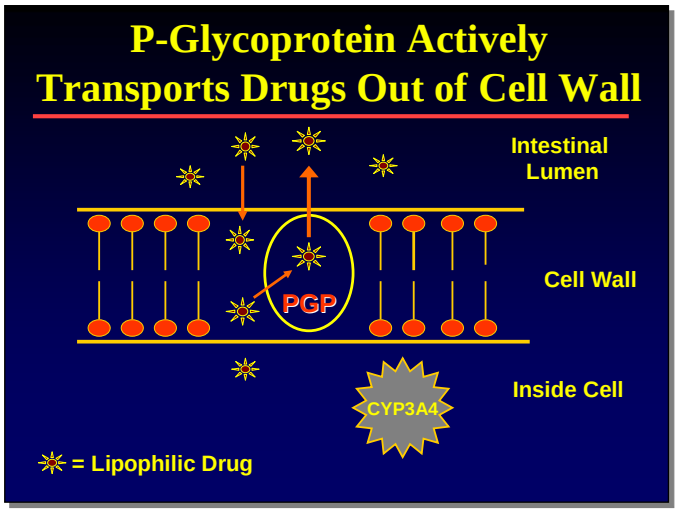
One day after his last erythromycin dose he experiences generalized muscular weakness, anorexia, nausea and vomiting. Four days after his last erythromycin dose he presents to the Emergency Room at his local hospital complaining of muscle weakness with noticeable abdominal distension. He was admitted to hospital and rapidly deteriorated, developing rhabdomyolysis, acute renal failure, pancreatitis, ileus, and elevated liver function tests.

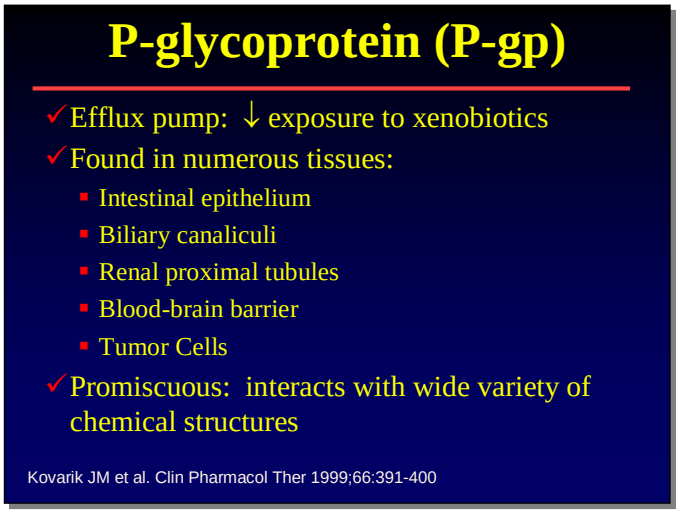


Other Notes or Questions to Ask:

He spent the next ten days in the intensive care unit, where his condition ultimately stabilized and the severity of his condition was down-graded as slow improvements were noted. It took a further seven days as hospital inpatient before he had recovered enough to be appropriately discharged. Happily he survived the ordeal.

Oral Erythromycin and the Risk of Sudden Cardiac Death (*NEJM 2004;351:1089-96*): "The adjusted rate of sudden death from cardiac causes was twice as high as placebo and amoxicillin . . . The adjusted rate of sudden death from cardiac causes was 5 times as high among those who concurrently used CYP3A4 inhibitors." "During 5 days of azithromycin therapy, there was a small absolute increase in cardiovascular deaths, which was most pronounced among patients with a high baseline risk of cardiovascular disease (*NEJM 2012; 366:1881-1890*).





Grapefruit Juice is considered a **Suicide Inhibitor** because it completely destroys some of the CYP3A4 in the small intestine. Normal enzyme levels of this isoenzyme are reestablished after body makes more, usually in 2 to 3 days after the juice leaves body. Juice from the frozen concentrate is a more potent inhibitor than fresh juice or ½ grapefruit.

Besides the liver, metabolism also occurs in other parts of the body such as: the intestinal epithelium, biliary canaliculi, renal proximal tubules, blood-brain barrier, and some tumor cells. The mechanism responsible for this is the **P-Glycoprotein** efflux pump, which has gained particular notoriety in explaining the interaction between grapefruit juice and some medications.

There are, of course, risk factors for drug interactions. The high risk situations are: administration to the very young and elderly; administration to medically compromised patients; the use of chronic drug therapies involving drugs that are excreted slowly and; the use of drugs with small margins of safety:

digoxin, warfarin, opioids, lithium, theophylline, thyroid medications

Other points to note: The majority of drug interactions occur with chronic therapy (antibiotics are the exception) and; most drug interactions occur with cardiovascular, NSAIDs and CNS drugs.

Summary

- Be careful: titrate to minimize the possibility of severe reaction occurring (go low, go slow)
- Be aware: If patients come back and say, "I don't feel well on this medication", drug interactions should be one of your considerations
- The less that a drug is metabolized, the lower the chance of a drug interaction
- If the drug is not producing the anticipated results, altered metabolism is a possibility (whether inhibition, or induction of the substrate or absence of the enzyme)

Other Notes or Questions to Ask:

- In polypharmacology, drugs with fewer potential drug interactions should always be considered (e.g., Escitalopram, pantoprazole, other…)

Unique Characteristics of Dental Therapeutics

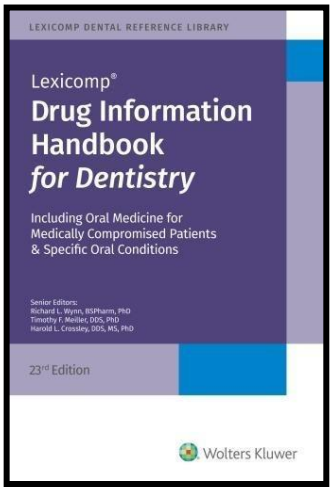
- Usually single dose or short-term therapy (5-10 days)
- Most dental drugs have large margin of safety
- Use of IV drugs is limited
- Procedures are usually elective
- Drug armamentarium is limited

There are numerous potentially dangerous medication interactions and clinically significant factors to consider:

- Metronidazole and Alcohol
- Watch for duplications
- Tetracycline and certain cations
- Ask about ALL the drugs your patient takes
- Antibiotics and Birth Control Pills
- Consider theoretical vs. clinical significance
- NSAIDS & ASA and Warfarin
- Consider age, weight, renal and liver function
- Always consider a drug's therapeutic index

Consider Your Resources

- Texts (Lexicomp's Drug Information Handbook for Dentists)
- Lexicomp Dental Drug Database
- Web-based Services (Drug Reax by Micromedex)
- www.naturaldatabase.com
- Clinical Pharmacology by Gold Standard Multimedia
- order1@adecllc.info by Dr. Michael Glick
- PDAs (Epocrates, Tarascon and others)



Lexi-Comp's Drug Information Handbook for Dentistry: Oral Medicine for Medically-Compromised Patients and Specific Oral Conditions is one of the most compact text references available. This resource contains abbreviated monographs on prescription medications and is well known for its useful charts and comparison tables. It is easy to use and is organized in alphabetical order according to a drug's generic name. The handbook provides useful information when looking for a quick response to a simple drug information request, such as indications, dosages, general adverse effects, and drug interactions. The *Drug Information Handbook* provides an updated edition annually to include new drugs and updates to current medications.

Physicians' Desk Reference (PDR): The *PDR* is a compilation of drug package inserts. It does not include all prescription medications because of space limitations. A new *PDR* is published every year; however, it is important to note that the information may not be updated with each annual publication. It is also important to note that only FDA-approved indications and dosages can be found within the *PDR*.

Lexi-Comp Online: In addition to the compact handbook, Lexi-Comp also provides Web-based and PDA resources with annual subscriptions. Lexi-Comp Online offers a convenient way to search medications quickly and easily. Once a medication is searched, the user can scroll through various parts of the drug monograph using the simple drop-down menu. This allows the user to move from section to section with ease and speed. Other features included are a drug-interaction reviewing tool, patient education leaflets, a drug-identification database, lists of drug recalls and shortages, and recent drug news.

Micromedex: Micromedex is a popular Web-based resource. Using one search box, a clinician is able to search many different databases that include detailed and summarized drug information, toxicology, alternative medicine, and reproductive risk evaluation. Micromedex's detailed information highlights Drugdex, *PDR*, and

Other Notes or Questions to Ask:

Martindale's (for use in searching foreign medications). The toxicology information that is included with these resources is trademarked as *Poisindex* and *Identidex*. Poisindex identifies ingredients for commercial, biological, and pharmaceutical products and delivers summarized toxicology data. Identidex allows the clinician to identify a medication using its embossed lettering or numbering and other descriptive characteristics, such as color and shape. Other useful tools in this resource include a drug interaction reviewing tool, patient education leaflets for both prescription drugs and dietary supplements, and clinical calculators to help determine body mass index, ideal body weight, metric conversions, and others.

Clinical Pharmacology: Clinical Pharmacology is a Web-based application providing a vast array of information that is both thorough and practical. It has multiple functions, allowing users to obtain product information, view monographs, identify medications, and print patient education materials. The site also contains drug class overviews, various interactions (including drug–drug, drug–herbal, drug–nutritional, and drug–food interactions), and full-color product images.

ICE's Medical Support System, a website providing resources on medical conditions as they relate to oral health care. "This unique software will enhance oral health care professionals' ability to help a patient population that presents with medical conditions that impact the provision of dental care," said Dr. Michael Glick, author of the content on the site. Dr. Glick is professor of oral medicine and dean, School of Dental Medicine, University at Buffalo, N.Y., and editor of The Journal of the American Dental Association. The site is located at "www.icemedicalsupport.com".

The Medical Support System provides up-to-date, point-of-care oral care information that is continually updated in more than 50 languages. Using the information available on the site, dentists and other dental team members can assess a patient's potential for medical complications and the need for dental modifications. Additionally, subscribers can amass up to three hours of continuing education credits through use of the site. A demo of the site is available at www.icemedicalsupport.com/demo. For more information about the Medical Support System, visit http://icemedicalsupport.com/ada or you can call 1-866-292-9725 or email info@icehealthsystems.com.

Other Notes or Questions to Ask:

Herbal Interactions

All cultures on all continents have herbal healing traditions. Until the 20th century, most people everywhere had close contact with foods and herbs where they were grown. Through the 1930s, MDs in US studied and relied on plant drugs as primary medicines. Medical schools taught plant taxonomy and medicinal plant therapeutics (pharmacognosy). In 1870, the US Pharmacopeia listed 636 herbal entries. The 1990 edition listed 58. Some were found unsafe, most were replaced by pharmaceuticals.

Dietary Supplement Health and Education Act of 1994 (DSHEA) allows 4 types of statements:

1. Role of nutrient in affecting "structure and function" in humans.
2. Documented mechanism that supplement acts on to affect "structure and function".
3. Benefits due to dietary deficiency-must report the prevalence of disease in USA.
4. Statements of general well-being from consumption of the supplement.

Depression Example:	Treat depression	No
	Elevate mood	Yes
Vitamin A is essential to proper eye function		Yes
Calcium is essential for bone health		Yes
Saw palmetto promotes prostate health		Yes

But "disease" claims not permitted:

Saw palmetto cures or relieves BPH: Not OK
CardioHealth: OK, Hepaticure: Not OK
"Reduces the stiffness of arthritis" not permitted
"Promotes joint health" is permitted

Depending on state law, these kinds of distinctions may also apply to health care practitioners such as chiropractors. Any structure/function claims must also include:

> *"This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease"*

Under the US Dietary Supplement Health and Education Act of 1994, the FDA can:

- Promulgate good manufacturing practices.
- Refer for criminal action the sale of toxic products.
- Obtain injunction against false claims.
- Seize products that pose unreasonable risk
- Sue company making claims of cure or treating disease.

The FDA cannot regulate supplements as drugs, requiring the same level of proof of efficacy in order for the supplements to be marketed (this applies to vitamins, minerals, herbs, nutriceuticals etc.). The FDA is therefore developing the National Center for Complementary and Alternative Medicine (NCCAM) which can deal with issues of safety, labeling, enforcement, science based research so that some self-regulation/standards exist.

NCCAM
NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Other Notes or Questions to Ask:

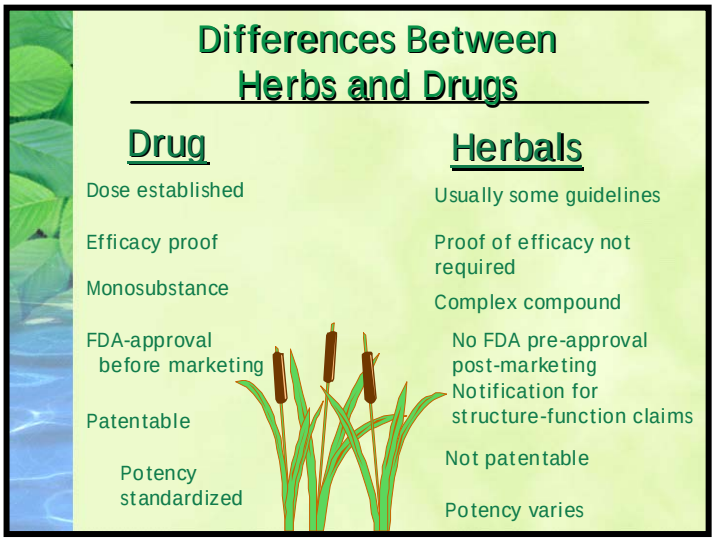
Up to 42% of Americans are using some sort of dietary supplement for both prevention and therapeutic purposes, 26.8 billion dollar industry in 2018.

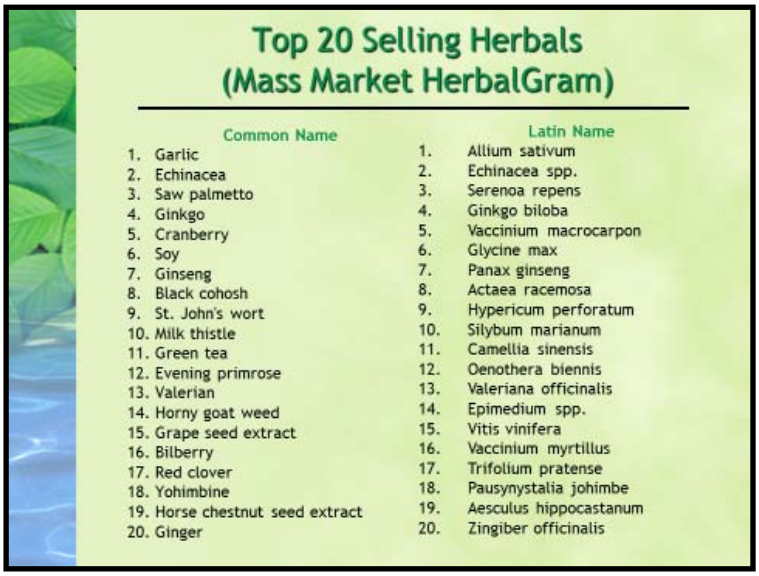
1. General Health
2. Colds
3. Arthritis
4. Energy Enhancement
5. Cholesterol Lowering
6. Cancer Prevention
7. Allergies
8. Weight Management

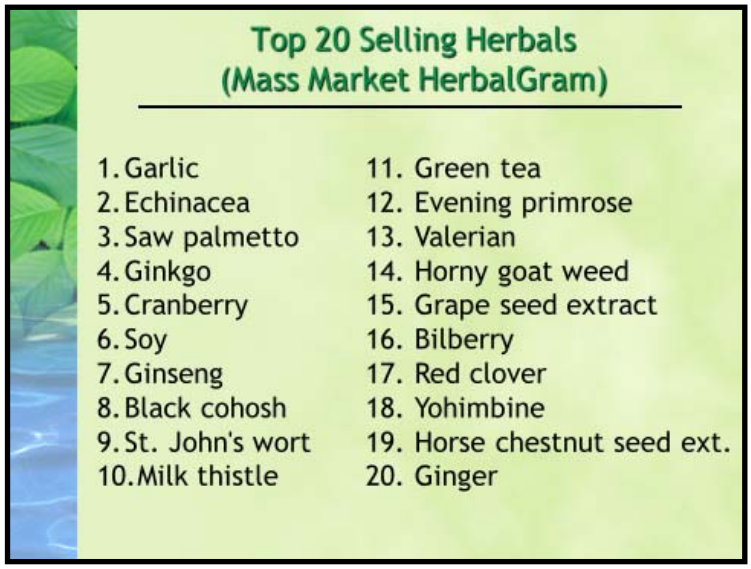
Many conventional medications are derived from herbs:

- 35% prescription drugs
- 60% OTC drugs

Over 50 population: average of 7 or more supplements. Someone turns 50 every 10 seconds in the US.







Herbals and Dentistry: What are we really worried about?

1. Bleeding / Hemostasis (Patients on Anticoagulants)
2. Thromboembolism (Patients on Blood Thinners)
3. CNS Interactions (Patients who may receive Sedatives)
4. Blood Pressure Issues (Patients who may be receiving Antihypertensives)

Other Notes or Questions to Ask:

Top 20 Selling Herbals that may affect Bleeding / Hemostasis (Patients on Anticoagulants)

1. Garlic
2. Echinacea
3. Saw palmetto
4. Ginkgo
5. Cranberry
6. Soy
7. Ginseng
8. Black cohosh
9. St. John's wort
10. Milk thistle
11. Green tea
12. Evening primrose
13. Valerian
14. Horny goat weed
15. Grape seed extract
16. Bilberry
17. Red clover
18. Yohimbine
19. Horse chestnut seed ext.
20. Ginger

Honorable mentions: Alfalfa, Beer, Danshen, Dong Quai, EDTA, Glucosamine, Licorice, Policansol, Vitamin K, Willow Bark, Wintergreen.

Top 20 Selling Herbals that may affect Thromboembolism (Patients on Blood Thinners)

1. Garlic
2. Echinacea
3. Saw palmetto
4. Ginkgo
5. Cranberry
6. Soy
7. Ginseng
8. Black cohosh
9. St. John's wort
10. Milk thistle
11. Green tea
12. Evening primrose
13. Valerian
14. Horny goat weed
15. Grape seed extract
16. Bilberry
17. Red clover
18. Yohimbine
19. Horse chestnut seed ext.
20. Ginger

Honorable mentions: Danshen, Dong Quai, Policansol, Willow Bark

Top 20 Selling Herbals that may affect Blood Pressure (Patients on Antihypertensives)

1. Garlic
2. Echinacea
3. Saw palmetto
4. Ginkgo
5. Cranberry
6. Soy
7. Ginseng
8. Black cohosh
9. St. John's wort
10. Milk thistle
11. Green tea
12. Evening primrose
13. Valerian
14. Horny goat weed
15. Grape seed extract
16. Bilberry
17. Red clover
18. Yohimbine
19. Horse chestnut seed ext.
20. Ginger

Honorable mentions: Dolomite, Hawthorn, Indian Snakeroot, Oleander, Thuja, Yellow Dock

Top 20 Selling Herbals that may affect Cognition (Patients on Sedatives)

1. Garlic
2. Echinacea
3. Saw palmetto
4. Ginkgo
5. Cranberry
6. Soy
7. Ginseng
8. Black cohosh
9. St. John's wort
10. Milk thistle
11. Green tea
12. Evening primrose
13. Valerian
14. Horny goat weed
15. Grape seed extract
16. Bilberry
17. Red clover
18. Yohimbine
19. Horse chestnut seed ext.
20. Ginger

Honorable mentions: 5-HTP, Ergot, Hawaiian baby woodrose, Kava Kava, L-tryptophan, Lithium, SAMe, Thuja

Top Selling Herbals that are Most Prone to Drug Interactions - Indications

Garlic – Atherosclerosis; Colorectal & Gastric Cancer; HT
Echinacea – Common Cold; Vaginal Candidiasis
Ginkgo – Memory; Dementia; Retinopathy; Glaucoma; PMS
Soy – Breast CA; Diabetes; Hyperlipidemia; Menopausal symptoms; Osteoporosis
Ginseng – Diabetes; Respiratory tract infections
St. John's wort - Depression
Evening primrose – Mastaglia; Osteoporosis
Horny goat weed - Osteoporosis
Yohimbine – Erectile Dysfunction (ED); sexual dysfunction

Other Notes or Questions to Ask:

Top Selling Herbals that are Most Prone to Drug Interactions - EBM

Garlic – Atherosclerosis; HT
Echinacea – No Evidence
Ginkgo – No Evidence
Soy – Possibly Effective
Ginseng – No Evidence
St. John's wort - Depression
Evening primrose – Possible Effective
Horny goat weed – No Evidence
Yohimbine – Possibly Effective

The H.E.R.B.A.L. Mnemonic

- H ear the Patient out with respect
- E ducate the patient
- R ecord and document
- B eware
- A gree to discuss
- L earn about new & popular supplements

Web Resources on Herbs

- American Herbalists Guild: www.americanherbalistsguild.com
- Herb Research Foundation www.herbs.org
- Natural Medicines Comprehensive Database www.naturaldatabase.com
- National Center for Complementary and Alternative Medicine www.nccam.nih.gov
- Office of Dietary Supplements www.ods.od.nih.gov

Which Drugs Do You REALLY Have to Worry About?

Warfarin, Cyclosporine, Digoxin, HIV protease inhibitors, Theophylline, Carbamazepine, Lithium, Thyroid medications, Opioids

Steps for Detecting and Advising on Herbal/Drug Interactions

- Is the patient taking any herbal supplements?
- Does the herbal have efficacy for the intended use?
- Is the product reliable? (i.e., what are they REALLY taking?)
- Is the Rx drug one with a narrow therapeutic margin (warfarin, cyclosporine, digoxin, HIV protease inhibitors, theophylline, carbamazepine, lithium, thyroid medications, opioids)?

General Guidelines on Use of Herbal Medicines

- Take a good history of patient use of herbs and supplements.
- Diagnosis needed before using herbs for symptomatic treatment.
- Natural does not equal safe.
- Generally avoid herbs during pregnancy and lactation.
- In children, pay close attention to dosage according to weight.

Other Notes or Questions to Ask: