



Top 5 drugs prescribed: Adverse Drug Reactions, Drug Interactions and Dental Treatment.

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Outline of this lecture:

- Intro to pharmacotherapy
- Intro to ADR and DI
- Top 5 prescribed drugs (pharmacology, ADR, DI and dental treatment)

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COI

I do not have any conflict of interest

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Pharmacology (from pharmakon, the Greek word for drug) is the study of drugs (substances that produce changes in the body).

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Pharmacokinetics

What the body does to the drugs
 Absorption, distribution, metabolism, excretion

Pharmacodynamics

What drugs do to the body.

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- Medications are designed to have an effect on the body.
- The desired effects – the effects we hope they will have - are the reasons why we take them.
- However, introducing any medication into the body also raises the possibility that the drug will have other effects beyond what we expect.

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What is an ADR?

Any noxious, unintended and undesired effect of a drug, that is observed at doses usually administered therapeutically in humans

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ASA has an antiprostaglandin effect which leads to the dentally useful effect of decreasing inflammation and pain.

At the same time, a drug may have effects on other physiological systems and, thus, may not be useful to the dentist. For example, ASA and its antiprostaglandin effects also prevents platelets from adhering. Therefore, a side effect can be excessive bleeding.

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What is the difference between side effects and ADRs?

- Side effects are expected, well-known effects of a drug that is not the intended therapeutic outcome, resulting in little or no change in patient management.
- When an actual injury is involved, it becomes an ADR.
- The term "side effect" tends to normalize the concept of injury from drugs. It has been recommended that this term should generally be avoided in favor of ADR.

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Risk Factors

- Age (children and elderly)
- Polypharmacology
- Multiple co-morbid conditions
- Altered physiology
- Prior Hx of ADRs
- dose and duration of exposure

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INTRO to DRUG INTERACTIONS

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"A measurable modification (in magnitude or duration) of the action of one drug by prior or concomitant administration of another substance"

Wright 1993. Drug Interactions. In: Melmon and Morrell. Clinical Pharmacology

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Drug interactions can occur through pharmacokinetic, pharmacodynamics, physical or chemical mechanisms and may result in enhanced action, reduced drug efficacy, increased incidence of adverse effects or misinterpretation of laboratory tests. In some clinical situations the use of interacting drugs may be deliberate.

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- ❑ Drug interactions represent 3-5 % of preventable in-hospital ADRs
- ❑ Drug interactions are an important contributor to the number of ER visits and hospital admissions.

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NSAIDs Interactions:

1. CVS meds: ACE inhibitors, diuretics, beta blockers, digoxin
2. CNS meds: e.g. Lithium, SSRI
3. Anti-coagulants
4. Methotrexate
5. Acetaminophen
6. Other NSAIDs
7. More...

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Misoprostol

- Beneficial Drug interaction with NSAIDs
- Cytotec
- PG analog
- To prevent gastric bleeding
- Absolute contraindication during pregnancy

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- ❑ A drug interaction occurs when a drug interferes in a negative (or positive) way with another drug
- ❑ Can increase or lower drug levels
- ❑ Can occur between: Two drugs (prescription, over the counter, vitamins, supplements and illegal drugs)
- ❑ Drugs and foods/drinks

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METABOLISM

Interactions that happen through CYP enzymes are either based on enzyme **induction** or **inhibition**.

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METABOLISM

INDUCTION

- Drug A induces the body to produce more of an enzyme which metabolized Drug B
- This reduces the amount of drug B, which may lead to loss of drug B's effectiveness

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METABOLISM


INHIBITION

- Drug A inhibits the production of enzymes to metabolize Drug B
- This increases the amount of Drug B in the body and could lead to an overdose or toxic effects

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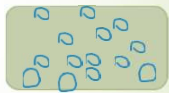
Inducers

Warfarin



60% --- INR: 2.5

Warfarin + Inducer (Rifampin)




10% --- INR : 1.2
This pt is not anticoagulant

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Inhibitors

Warfarin



60% --- INR: 2.5

Warfarin + Inhibitor Ketoconazole



90% --- INR : 5.2
Increased Bleeding

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TOP 5 Prescribed Drugs

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Top 5 Rx Drugs

1. Levothyroxine
2. Lisinopril
3. Metoprolol
4. Metformin
5. Phenytoin

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Levothyroxine



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Hypothyroidism

- "syndrome resulting from deficiency of thyroid hormones."
- Prevalence: 5% general population.
- Mean age of Dx: 5th decade of life
- Female to male ratio: 10:1

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Risk Factors

- Age (older than 50)
- Female gender
- Obesity
- Thyroid surgery
- X-ray or radiation treatments to the neck

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Classical presentation:

Fatigue ("no energy"), cold intolerance, constipation, weight gain, problems with concentration ("mental clouding"), dry skin.

Laboratory

- High levels of thyroid stimulating hormone (TSH) indicate that the thyroid is not producing sufficient levels of thyroid hormone.
- Low free T3 and T4



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Signs and Symptoms:

- ❑ cool, pale, dry skin and brittle hair
- ❑ Periorbital edema, drooping eyelids
- ❑ Decreased... HR, SV, CO
- ❑ Hypoventilation, CO2 retention
- ❑ Decreased appetite, constipation
- ❑ Muscle fatigue/stiffness, loss of deep tendon reflexes
- ❑ Renal impairment
- ❑ General decreased metabolic rate

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Tx of Hypothyroidism

Administration of pharmacological preparations of thyroid hormone



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synthetic levothyroxine (synthetic T4)

- Brand names: Eltroxin, Euthyrox, Levoxyl, Levothroid, Synthroid
- for hormone replacement therapy in hypothyroidism

DOSE

- Average dose for an adult – 1.7micrograms/kg/d
- Once daily

Pharmacokinetics

- should be taken 30min before or 1 hour after meals (delayed absorption for soy, other foods and drugs)
- takes 6-8 weeks to reach steady state levels

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Facts:

- Choice of Drug is T4 (over T3)
- T4 has a long $\frac{1}{2}$ -life (7 days) = can be taken o.d.
- (T3 $\frac{1}{2}$ -life = 1-2 days)
- Recall...giving T4 provided pro-hormone...allows for peripheral tissue conversion to T3 as needed
- Giving T3 is not recommended because of its shorter $\frac{1}{2}$ -life ...requiring multiple daily doses...harder to monitor (blood tests) and has greater cardiotoxicity

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- For the well-controlled hypothyroid patient taking a longstanding stable dose of levothyroxine, there are no specific interactions between levothyroxine and dental treatment.
- For patients who are recently diagnosed with hypothyroidism and are not yet euthyroid, elective treatment is best deferred and emergent treatment carried out with caution.
- The concern in the uncontrolled patient is that if the thyroid levels are too high then thyrotoxicosis can ensue.

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Hypothyroidism rarely results in an emergent situation; however, these patients are at risk for arrhythmias, heart failure, and myxedema coma if severely deficient

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MYXEDEMA COMA

- Severe weakness
- Untreated hypothyroidism (also not taking meds)
- Hypoventilation
- Hypoglycemia
- Hypothermia
- Shock and coma
- death

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Tx of MYXEDEMA COMA:

- State of emergency
- Requires prompt treatment. Mortality of 50%.
- IV T3
- Glucose to correct hypoglycaemia
- Rewarming

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Adverse effects of hypothyroidism /Dental manifestations

- Salivary gland enlargement
- Macroglossia
- Glossitis
- Delayed dental eruption
- Compromised periodontal health—delayed bone resorption
- Dysgeusia (alteration in taste)

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Lisinopril



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Treatment of:

1. HBP
2. CHF

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- Its an ACE inhibitor
- Mechanism of action: Dilate arteries and veins by blocking formation of angiotensin II (AII, a vasoconstrictor) vasodilatation, thus reduces arterial pressure, preload and afterload on the heart
- Promote renal excretion of sodium and water. This reduces blood volume, venous pressure and arterial pressure.

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Adverse effects

- The specific side effects include **postural hypotension, coughing, and angioedema**, with angioedema potentially being life threatening.
- Postural hypotension is a decrease in blood pressure that occurs when one rises from a supine position to an upright position; this can potentially lead to dizziness and syncope. To prevent issues related to postural hypotension, the patient should be uprighted from the supine position slowly.
- Dry cough

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- ❑ This cough may impact the delivery of dental care. The cough is believed to arise from increase in bradykinin production that stimulates the release of prostaglandins.
- ❑ The cough usually develops within the first month and disappears within 1 week of cessation of the drug.

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- ❑ A rare and potentially life-threatening condition linked to ACEi is the development of angioedema.
- ❑ Oral or perioral angioedema describes a process of rapid swelling of the lips, tongue, mucosal, and submucosal surfaces.
- ❑ The incidence of ACEi induced angioedema is 0.1% to 0.2%.
- ❑ Angioedema can occur in any organ system and at anytime, but more commonly the head and neck are affected typically occurs within the first month of treatment. Patients of African descent are 3 times more likely to be affected.
- ❑ Patients with perioral swelling may present to their dentist thinking they have a tooth infection; therefore, the dentist should recognize the link between ACEi and angioedema, and refer the patient to emergency department for definitive management.

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Ouanounou, A. 2016. Xerostomia in the Geriatric Patient: Causes, Oral Manifestations, and Treatment. *Comp Con. Den. Ed.* 37 (5): 316-322.

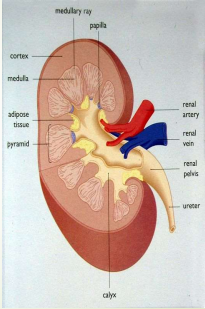
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DRUG INTERACTIONS

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NSAIDS + Lisinopril

- ❑ Diminished effect with:
 - ❑ angiotensin converting enzyme inhibitors (ACE inhibitors)
- ❑ Rx NSAID if need for < 5-6 days
- ❑ Avoid NSAID in severe congestive heart disease
- ❑ Monitor BP if concern



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Metoprolol



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- It's a B- blocker.
- Used as antihypertensive and antiarrhythmic drug.
- 83.3 million prescription dispensed in the United States in 2014.

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The indications for metoprolol:

- hypertension, angina pectoris, and to reduce mortality from myocardial infarction.

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- Metoprolol is a beta-1 selective (cardio selective) beta-blocker. The beta-1 adrenergic receptor modulates heart rate; the beta-2 adrenergic receptor modulates smooth muscle relaxation.
- Beta-blockers are used to treat tachycardia and hypertension by blocking the activity of endogenous catecholamines at the cardiac beta-1 receptors and by inhibiting renin secretion by the kidneys.

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- Beta-blockers are also used to treat angina pectoris. The mechanism of action is likely related to reductions in heart rate, myocardial contractility, and cardiac oxygen demand.
- Beta-blockers have also been shown to improve survival after myocardial infarction.

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Adverse effects

Xerostomia
orthostatic hypotension
Dysgeusia
oral lichenoid reactions.

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Drug Interactions

1. Local anaesthesia

- If a pt taking a beta blocker receive a systemic dose of epi, the beta blocker prevents the vasodilation, leaving unopposed alpha constriction
- Hypertensive reaction-- Increase in BP

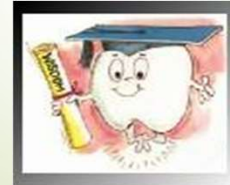
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2. NSAIDs

(same as with the ACE inhibitors)

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Dental Management



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A thorough medical history is necessary for all prospective patients.

■ It should include:

1. A current and previous history of medication use (including self-medication)
2. Medical conditions, as well as any symptoms the patient is experiencing (including shortness of breath and chest pain)

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3. A family history for medical conditions, including cardiovascular disease
4. Regular medical record revisions every time the patient is recalled

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BP and HR to be measured at every appointment

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Minimizing stress — achieved through patient management, pain-free dentistry techniques, and, where appropriate, the use of sedatives and analgesics (taking into consideration potential drug interactions) is important.

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Drug Interactions

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Statins

- Statins with Erythromycin, clarithromycin (renal failure and pancreatitis).
- Azole antifungals

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Epinephrine

- Epinephrine stimulates both alpha and beta adrenergic receptors.
- Beta receptors increase the heart rate, conduction velocity, and contractile force of the cardiovascular system.

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- Vasoconstrictors interact with several classes of drugs used to treat CVD, including beta blockers.
- Where local anesthetics containing vasoconstrictors are used in patients with CVD, there are guidelines limiting the amount of Vasoconstrictor to 0.04 mg OR to the equivalent of two carpules of lidocaine (1:100,000 epinephrine).

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- **Retraction cord** impregnated with epinephrine exposes patients to uptake of potentially large amounts of the vasoconstrictor systemically. Its use is controversial, and it has been recommended that dental professionals **do not use** epinephrine-impregnated retraction cord in patients with cardiovascular disease.

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NSAIDs

ACE inhibitors, Beta blockers and diuretics.

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Adverse Drug Reactions

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Xerostomia

Lisinopril
Calcium channel blockers
Anti-cholesterol drugs



Ouanounou, A. 2016. Xerostomia in the Geriatric Patient: Causes, Oral Manifestations, and Treatment. *Comp Con. Den. Ed.* 37 (5): 316-322.

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Taste Disturbances

Calcium channel blockers
Captopril, Enalapril
(ACE inhibitors)

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- Dental treatment in CVS patients necessitates special attention.
- Control of pain and anxiety is very important in patients with high medical risk.
- Local anesthetics with epinephrine produce a longer and more effective anesthesia than simple LA, thus avoiding an exaggerated response to stress

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- The maximum recommended dose of epinephrine in a patient with cardiac risk is 0.04 mg, which is equal to that containing about two cartridges of LA with 1 : 100000 epinephrine or 4 cartridges with 1 : 200000 epinephrine.
- In patients with severe disease it may be useful to measure BP and heart rate after anesthetic injection. Slow administration and aspiration can prevent undesirable reactions.

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- Initial evaluation of each patient with CVS Disease should include detailed family history of cardiovascular disease and other related diseases, medications and dosages and duration.

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Metformin



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- Metformin is an oral hypoglycemic drug
- 76.9 million prescriptions dispensed in 2014.
- Metformin is a first-line drug of choice for the treatment of type 2 diabetes mellitus.

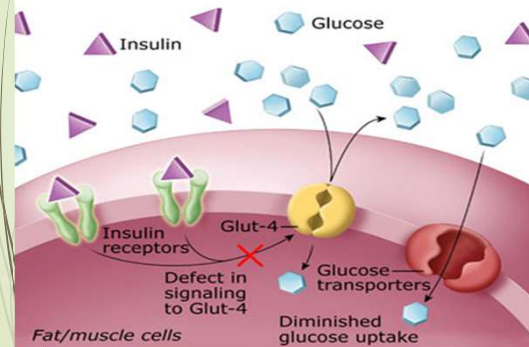
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Type 2 Diabetes

- Non-autoimmune (Unknown specific cause)
 - Treated with Hypoglycaemic agents ± Insulin
- Two metabolic defects:
- Decreased insulin secretion
 - Inability of tissues to respond to insulin due to a receptor defect

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Type 2 Diabetes: Insulin Resistance



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Clinical manifestations of Type 2 DM

- Non-specific symptoms
- Fatigue
- Recurrent infections
- Prolonged wound healing
- Visual changes

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MOA:

- Direct effect on muscle to increase glucose uptake and utilization.
- Reduced hepatic gluconeogenesis
- Reduce glucose absorption from the GI
- Increased insulin binding to insulin receptors

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ADR:

- **Metallic taste** is associated with the use of metformin.
- Long-term use of metformin may result in **vitamin B12 deficiency** (burning, enlarged or sore tongue).

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Angioedema:

- Facial or tongue swelling.
- The skin of the face, particularly the perioral region, the oral and pharyngeal mucosa, and the tongue, may swell over the period of minutes to hours.
- This is an Emergency !

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Tx of angioedema

1. **Ref to hospital emerg**
2. **Antihistamines**
3. **Oral Corticosteroids**
4. **Supportive Tx**

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Type II Diabetes and the oral cavity

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Periodontal disease

- DM when poorly controlled, increased the risk of periodontitis.
- Altered cell-mediated immune response and impaired of neutrophil chemotaxis.
- Increased Ca⁺ and glucose lead to plaque formation.
- Increased collagen breakdown

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Salivary Gland Dysfunction

- Xerostomia in 40-80 % of DM pts (Sreebny et al., 1992; Quirino et al., 1995).
- Poorly controlled DM pts have lower stimulated parotid flow rates than well-controlled and non-diabetic control subjects (Chavez et al., 2000).

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Dental caries

- Increase caries prevalence in adult with diabetes. (xerostomia, increase saliva glucose)
- Hyperglycemia state shown a positive association with dental caries.

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Fungal Infections

- Increased oral candidiasis
- Denture stomatitis
- Angular Chelitis

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Angular Chelitis

Denture stomatitis

Epstein et al., 2001

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Increased risk of infection

- Reasons unknown, but macrophage metabolism altered with inhibition of phagocytosis.
- Peripheral neuropathy and poor peripheral circulation
- Immunological deficiency

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Delayed healing of wounds

- Due to microangiopathy and utilisation of protein for energy, may retard the repair of tissues.
- Increase prevalence of dry socket.

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Dental Management

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Medical history : take hx and assess glycemic control at initial appt.

- Glucose levels and HBA1C
- Frequency of hypoglycemic episodes
- Medication, dosage and times.

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Scheduling of visits

- Morning appt.
- Do not coincide with peak activity.
- Diet (Ensure that the patient has eaten normally and taken medications as usual).
- Blood glucose monitoring.
- Measured before beginning. (<70 mg/dL)
- Prophylactic antibiotics (??)

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During treatment

- The most complication of DM occur is hypoglycemia episode.
- Hyperglycemia

After treatment

- Infection control
- Dietary intake

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Diabetes Emergencies

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Hypoglycemia
 ■ **Very serious emergency**

Signs and symptoms:


- Warm sweaty skin
- Rapid bounding pulse
- Dilated (reacting) pupils
- Anxiety, tremor, aggression
- Confusion
- Tingling sensation around the mouth
- Loss of consciousness

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Tx of Hypo

If pt is conscious oral carbohydrate



If pt is NOT conscious

Activate your emerg protocol (911 etc.)
 50 % dextrose IV
 1 mg glucagon IM



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Hyperglycemia
 Less serious than hypoglycemia

Signs and symptoms:

1. Vomiting
2. Hyperventilation
3. Acetone breath
4. Dehydration
5. Hypotension
6. Tachycardia
7. Dry mouth and skin

Tx---- Hospitalization--- Insulin

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Phenytoin



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- Dilantin
- Anticonvulsant
- Chronic pain

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Anti-Epileptic Drugs

Phenytoin

- Can be given IV or PO
- Still one of the most effective against Tonic-Clonic and Partial Seizures
- MOA: Alter multiple channels (Na Channels)

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EPILEPSY

GENERAL CONCEPTS:

1. **One of the first diseases noted in history**
2. **Approx. 1 % of the population has epilepsy**
3. **Primarily because of drug therapy, 80% of epileptics in US are fairly well controlled. However, there are still 500,000 people in US with uncontrolled seizures.**

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EPILEPSY

Etiology:

1. **Neurological diseases**
2. **Infections**
3. **Cancer**
4. **Head injury**
5. **Drugs**
6. **Hereditary**

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Epilepsy

- Epileptiform events are characterized by a sudden & excessive neuronal depolarization that may remain localized (focal epilepsy) or become widespread (generalized epilepsy)

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EPILEPSY

Three Types of Seizures:

- Partial
- Generalized
- Status Epilepticus

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EPILEPSY

PARTIAL SEIZURES

- Simple Partial Seizures
- Complex Partial Seizures

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EPILEPSY

Generalized Seizures

Generalized Tonic-Clonic (Grand Mal)

- Tonic Phase: lack of consciousness, muscle rigidity, respiratory arrest
- Clonic Phase: jerking of body, lip or tongue biting.

Absence (Petit Mal)

- Impaired consciousness sometimes with loss of postural tone

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Anti-Epileptic Drugs

Mechanism of Action

- Reduce voltage regulated Calcium channels
- Enhance GABA neurotransmission
- Interact with Glutamate Neurotransmission

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■ Partial seizures

■ Tonic clonic

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ADRs:

Drowsiness, gingival hyperplasia, nystagmus (changes in eye muscle movements), hair growth, Hepatic dysfunction (rare)

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■ Drug-induced Gingival Hyperplasia



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DIs

- Phenytoin is a **potent inducer** of hepatic metabolizing enzymes affecting itself and other drugs (carbamazepine, warfarin, adrenal and gonadal steroids, thyroxine, tricyclic antidepressant, doxycycline, vitamin D, folate).
- Drugs that **inhibit** phenytoin metabolism include: valproic acid, cimetidine, co-trimoxazole, isoniazid, chlorphenicol, NSAIDs, disulfiram

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- When treating epileptic patients, the major difficulty a dentist faces is the high risk of seizures occurring.
- In order to prevent such seizures, three fundamental principles should guide the dentist:
 - 1) **Knowledge of the patient's previous seizure episodes and medication,**
 - 2) **Knowledge of the conditions that provoke epileptic seizures, in order to avoid such conditions, and**
 - 3) **The dentist should be able to recognize the early signs of a seizure, take precautions before it occurs, and provide the patient with supportive care if it does occur.**

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Before starting treatment, a detailed Med Hx:

- The frequency of seizures;
- The date of the patient's last seizure;
- The consciousness and respiratory state of the patient during seizures;
- The physical condition of the patient after a seizure;
- The factors provoking seizures.

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- Trauma
- Dentofacial trauma
- Generalized tonic-clonic seizures often cause minor oral injuries, such as tongue biting, also frequently lead to tooth injuries and in some cases to maxillofacial trauma.

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Periodontal Problems:

- Drug-induced Gingival Hyperplasia
- Valproic acid can cause bone marrow suppression--- impaired healing and increase post op bleeding and infections.

Prosthodontics:

- Epilepsy pts have a tendency to become edentulous earlier.
- Replacement of missing teeth is important to prevent the tongue from being caught in the edentulous spaces during seizures.
- Fixed vs removable prosthesis.


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- Phenytoin--gingival hyperplasia.
- It has been reported that this side effect is observed in 50% of patients taking this medicine for three months
- Carbamazepine causes xerostomia, ulcer, glossitis

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Actions to Be Taken If a Patient Has an Epileptic Seizure during Dental Treatment

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- As always ABCs
- Call 911
- Treatment should be stopped and dental instruments should be removed.
- The patient should be helped into the supine position.
- It is not necessary to restrain the patient.
- Any tight clothing the patient is wearing should be loosened.


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Status Epilepticus

- Exists when seizures recur within a short period of time
- Last at least 30 minutes
- Can occur with any type of Epilepsy
- Can lead to systemic hypoxia, cerebral damage, metabolic complications, cardiovascular collapse, renal shutdown and death

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Tx of Status Epilepticus

- Benzodiazepine: Diazepam IV 5-10 mg (1-2 mg/min) Lorazepam IV 2-6 mg (1 mg/min)

Or

- Lorazepam 4 mg IM.
- or
- Midazolam 5 mg IM.

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Thank You!!!

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