Most Commonly Prescribed Medications: Implications, Side Effects, Drug Interactions and Dental Implications

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Disclaimer
- I have no conflict of interest relating in the material covered today
- I do not serve on any speaker bureau
- I do not have any personal grants concerning the area of discussion today

All characters appearing in this work are fictitious. Any resemblance to real persons, living or dead, is purely coincidental.

Objectives
- 1) Identify new therapeutic agents recently introduced to the market and explain their appropriate uses that dentist should know.
- 2) Describe the indications and the most important adverse events and precautions of each new therapeutic agent.
- 3) Describe any important drug interactions and pharmacokinetic parameters that are clinically relevant for the dentist.
- 5) Discuss any evidence-based clinical trials that may be published about the medications to aid in therapeutic selection.
Objectives

6) Discuss the difference dosing antibiotic regimen duration for different dental infections.
7) Discuss MRSA and the current treatment for outpatient management.
8) Briefly describe the concepts of relative risk reduction, absolute risk reduction, number needed to treat (NNT) and number needed to harm (NNH), and how these statistical measures affect data interpretation.
9) Discuss POEMS from clinical research that should change your practice in dentistry.
10) Discuss low, medium and high risk surgeries and what needs to be done when a patient is on anticoagulation.

First thing we have to discuss!

- What is Evidence-Based Medicine (EBM)?
- What is Evidence-Based Dentistry (EBD)?
  - Your profession is embracing the concept of EBD!
  - See www.cebd.org
  - See www.ada.org/276.aspx

  “Evidence-based medicine is the conscientious, explicit, and judicious use of best evidence in making decisions about care of the individual patients.”
  - David Sackett

  “Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values.”

How do you know what you know?

- The area of study of this question is known as:
  
  Epistemology
Epistemology

- Should physician-assisted suicide be allowed in some situations?
- Should it be legal for people to buy organs for transplant, if they would not be able to receive an organ by waiting their turn through a national database?
- A woman has the right to choose an abortion.
- A woman does not have the right to choose an abortion.
- A woman has the right to choose an abortion in certain situations.

Knowing what we know!

- In medicine and dentistry, we utilize several things:
  - Experience
  - Opinion (although watch out for GOBSAT)
  - Empirical evidence
    - we should utilize evidence when we have it

You are responsible!

- Be like “Yoda”
- Your Own Data Analyzer

- The “Force” is not just knowing, it’s in the application
CAST Trial

- CAST evaluated the effect of antiarrhythmic therapy (encainide, flecainide, or moricizine) in patients with asymptomatic or mildly symptomatic ventricular arrhythmia (six or more PVCs per hour) after myocardial infarction.

- Results
  - 75% reduction in PVCs
  - Increase total mortality with encainide, flecainide
  - RRI = 60%
  - ARI = 4.7%

To read POEMS that change your practice!

- DOES:
  - Disease-oriented evidence
  - Pharmacology, pathophysiology, etiology
  - Surrogate markers for disease in medicine
    - Lowering cholesterol, lowering BP or blood glucose, increasing BMD, improved drug bioavailability, etc.
  - Surrogate markers for disease in dentistry
    - Reduction in plaques or bacterial counts (i.e., % Step mutans in plaques), alveolar bone loss, does your toothpaste have fluoride?, fluoride inhibits endolase, bacterial counts on toothbrushes, calcium levels

POEMs change our practice!

- POEMS:
  - Patient-oriented evidence that MATTERS
    - Morbidity, mortality and quality of life
    - Final outcomes of disease
      - Stroke, heart attack, hip fracture, admission to the hospital or SNF, performance of ADLs
      - Dentistry — lower gingivitis, reduce implant failure, fluoride and cavity development
  - POEMs should result in a change in your practice
Which of the following would you expect to be a POEM?

- The detection of arginine metabolism in dental plaques.
- Escitalopram (Lexapro) is 100X more potent in inhibiting serotonin reuptake than citalopram (Celexa).
- Efficacy of Pneumovax® in preventing pneumonia and improving survival in nursing home residents: double-blinded, randomised and placebo-controlled trial.
- Antibiotics prior to implant placement reduces dental implant failures.

DOEs and POEMs

- **POEM**
  - Often changes daily practice
- **DOE**
  - Does not always change daily practice
  - Ask questions that result in further study
  - A DOE often begets a POEM
  - Sometimes they are misused!
  - For example………..

There’s been a murder on Narcotic Row

- Propoxyphene killed by FDA
  - Murder weapon: QT elongation
- Death reports from propoxyphene are primarily due to overdose and suicides
  - Been on the market since 1957
  - 1969 to 2005
  - 473 domestic adverse event reports
  - 91 deaths, 74 linked to multi-drug overdoses (The MJ-PK Effect)
  - Propoxyphene ranks lower than hydrocodone and oxycodone for intentional exposures.

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Analyzing the POEM!

First we need perspective

RRR vs ARR
Risk vs Benefit

Do you understand risk?

- What is the risk of stroke in an elderly patient with atrial fibrillation?
- Warfarin reduces strokes by ~50% in patients with atrial fibrillation
- What's the risk of a stroke in AF?
  - 5% per year
  - Risk of stroke with warfarin is ~2.5%
  - A 50% reduction is really a 2.5% absolute reduction
  - Risk of stroke with aspirin is 4%

Do you understand risk?

- What's this patient's risk of a stroke?
- A female age 70 yrs, BP ~174/86
- 44% reduction of stroke when treated
- In the Syst-Eur trial, the risk of having a stroke in this type patient over 4 years was 2.5%
- A 44% reduction is 1.4%
What’s the risk of a nonfatal MI in this patient?

- male, 60 years of age, white, nonsmoker, BP = 165/95, BMI = 29, glucose = 112, SCr = 1.3, baseline TC = 212, baseline LDL = 130, HDL = 50, diabetes in family
- Lipitor® 10 mg reduces nonfatal MI by 37%
- Risk is ~ 3% over 5 years
- 37% reduction = 3% to 1.9%

ASCOT Trial Lancet 2003;361:1149-58 (April 5)

The Numbers of EBM

- Incidence of hip fracture (Lancet 1996;348:1535)
- Placebo 2.2%
  - Must always use event rate which is the number of events divided by the total in group ("n")
- Alendronate 1.1%
- RRR 50%
  - RRR = control - treatment / control (2.2%-1.1%/2.2% = 50%)
- ARR 1.1%
  - ARR = control - treatment (2.2% - 1.1% = 1.1%)
- NNT 91
  - NNT = 1/ARR (100/1.1% = 91)

What about harm?

- The number-needed-to-harm (NNH) is the term for assessing side effects/harm of treatments
  - Same type of calculation as NNT
Women Health Initiative

- The Women’s Health Initiative
  - Stopped early because of a 26% increase in risk of breast cancer in women using HT
  - What you saw on the “Today Show”… 26%!!!
- Incidence of the Outcome
  - Placebo Group 0.30%
  - Hormone Therapy Group 0.38%
- RRI = 0.38% - 0.30% / 0.30% = 26%
- ARI = 0.38% - 0.30% = 0.08%
- NNH = 100 / 0.08% = 1250
  - Assume 10,000 women - 10,000 / 1250 = 8

JAMA 2002;288(3):321-33 (July 17)

Risk/Benefit

- Weigh the risk/benefit of a treatment.
- We must look at medications based on harm and not just efficacy.
- We weigh risk/benefit every day.

Our values will dictate our presupposition!

- If we like the medication, we stand on efficacy.
- If we don’t like the medication, we stand on side effects.
- We need balance!
- We need to understand our values.
  - Also our patient values.
- Are you an optimist?
- Are you a pessimist?
Today it is Risk/Fear

Medication risk must be balanced with benefit not FEAR!

Medications are NOT perfect!

- Why does FEAR creep in to motivate people for change instead of good thinking and analysis?
- Just check your email! Check out the daily FDA alerts.
- The latest is that ceftaroline (Teflaro®) increases the risk of death.
- Tylenol® kills livers!
- Testosterone causes heart attacks!
- Caffeine is bad one day, good one day.
- Salt is good one day, bad one day!
- Fear definitely motivates people to get the flu shot.

Do we live in a no risk world?

2002 data
- Odds of dying from any injury - 1 in 1,755
- Odds of dying from an auto injury - 1 in 17,625
- Odds of dying from a firearm - 1 in 377,876
- Odds of being struck by lightning - 1 in 250,000
- Odds of dying - 1 in 750,000
- Odds of dying from fireworks - 1 in 57,588,244
- Odds of dying from complications from medical and surgical care - 1 in 101,281
The meaning of risk medicine

- “Risk is basic to medical progress.”
- “Where risk medicine is abolished, medical advance is also abolished.”
- “A society which wants good innovations and no risks is asking for the impossible. It is denying the freedom to progress.”
- “To deny the possibility of failure is to deny the reality of success.”

RJ Rushdoony, Roots of Reconstruction

Becoming a Jedi

- Putting it all together
- Evidence-based dentistry thinking allows the practitioner to begin making better “dental decision making”
- Secrets of the Jedi
  1. Patient-focused
  2. Efficacy-Safety-Cost
  3. NNT-NNH-Cost

Darth Vader: NO!

Data rules, right?

They are just NUMBERS!
Green Bay is not just known for the Packers!

Karl Paul Link was the first to link cattle demise from hay mixed with sweet clover. He worked under the Wisconsin Alumni Research Fund.

Bleeding

- Frequency of bleeding is related to the intensity of warfarin therapy
- Other risk factors:
  - Increasing age (>65)
  - Hypertension
  - History of strokes
  - Atrial fibrillation
  - Renal insufficiency
  - Anemia

Warfarin Bleeding Update

- Retrospective analysis of pharmacy and hospital data, 2007-2008, patients > 65 years with AF and taking warfarin
- Risk of hemorrhage
  - Overall 4% per year
  - 3% per year 66 – 75 years
  - 5% per year > 75 years
  - Higher CHADS2 score the greater risk
  - Risk is highest in first month
  - Admitted to hospital due to a bleed, NNH = 5 to die

CMAJ 2013;(2):E121-7
Warfarin Reversal

<table>
<thead>
<tr>
<th>INR range</th>
<th>Vitamin K dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.5, no bleeding</td>
<td>no vitamin K</td>
</tr>
<tr>
<td>4.5 to 10, no bleeding</td>
<td>no vitamin K</td>
</tr>
<tr>
<td>&gt; 10 and no bleeding</td>
<td>hold dose, 3 to 5 mg oral, should see effect in 24-48 hrs</td>
</tr>
</tbody>
</table>

Bleeding or > 10
10 mg slow I.V. infusion + FFP, check INR in 6 hours, may repeat every 12 hours

Life-threatening bleed
replace with 4 factor prothrombin complex + 10 mg vitamin K I.V.

Adapted from: Chest 2012,141:7S-47S
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOA</strong></td>
<td>Direct thrombin inhibitor</td>
<td>Factor 10a inhibitor</td>
<td>Factor 10a inhibitor</td>
<td>+</td>
</tr>
<tr>
<td><strong>Reduce the risk of stroke and embolism with atrial fibrillation.</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>DVT/PE Treatment</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>DVT/PE Prevention</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Embolism prevention for orthopedic surgery</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Bleeding issues</strong></td>
<td>Higher risk of GI bleeds vs warfarin (ARI 0.49%; NNH 204)</td>
<td>Bleeding similar to warfarin</td>
<td>Bleeding similar to warfarin</td>
<td>+</td>
</tr>
</tbody>
</table>

> More intracranial bleeding with warfarin (ARI 0.44%; NNH 227)

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Box warning</strong></td>
<td>Do not stop</td>
<td>Do not stop</td>
<td>Do not stop</td>
<td>Do not stop</td>
</tr>
<tr>
<td><strong>Unique side effect</strong></td>
<td>MI - NNH 470</td>
<td>Symipto NNH 200</td>
<td>Do not use CrCl&gt; 93</td>
<td>+</td>
</tr>
<tr>
<td><strong>Doses</strong></td>
<td>75, 150 mg caps</td>
<td>10, 15, 20 mg tabs</td>
<td>2.5, 5 mg tabs</td>
<td>15,30,60 mg</td>
</tr>
<tr>
<td><strong>Dose adjustment</strong></td>
<td>Dose 15-30, 75 mg + 15, dialysis – do not use</td>
<td>See table</td>
<td>Can dose to 2.5 mg for any 2 of the three - age &gt; 80; weight &lt; 60 kg; SCr&gt; 1.5</td>
<td>Reduce dose from 60 mg to 30 mg for CrCl 15 to 50</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Must use within 6 hrs after opening</td>
<td>Can be given via NG tube</td>
<td>Can be given via NG tube</td>
<td>?</td>
</tr>
<tr>
<td><strong>No INR measures</strong></td>
<td>No INR measures</td>
<td>No INR measures</td>
<td>No INR measures</td>
<td>No INR measures</td>
</tr>
</tbody>
</table>

**Transitioning from other anticoagulants**

**Converting from warfarin**
D/C warfarin and start dabigatran once INR < 2.0

**Converting to warfarin**
CrCl >50 mL/min: start warfarin 3 days before stopping dabigatran
CrCl 31–50 mL/min: start warfarin 2 days before stopping dabigatran
CrCl 15–30 mL/min: start warfarin 1 day before stopping dabigatran
CrCl <15 mL/min: no recommendations can be made

**Converting to parenteral anticoagulation**
Wait 12 hours if CrCl ≥ 50 mL/min or 24 hours if CrCl < 30 mL/min after the last dose of dabigatran before starting parenteral anticoagulation

**Converting from parenteral anticoagulation**
Start dabigatran 0 to 2 hours before the time that the next dose of parenteral drug was to be given or at the time of D/C of a continuously administered parenteral drug (e.g. UFH)

**Surgical/invasive interventions**
Start dabigatran 0 to 2 hours before the time that the next dose of parenteral drug was to be given or at the time of D/C of a continuously administered parenteral drug (e.g. UFH)

Dabigatran

Price
- Capsules
  - 75 mg, 150 mg
  - $250 for #60, 150 mg

Simplicity
- not that simple, but simple
- Assess renal function yearly in those with
  - CrCl<50 and > 75 years of age
  - 150 mg twice a day
  - t/2 = 12 to 17 hrs
- Can be given with or without food
- Do not break, chew, open capsule
- Do not double dose if missed
- more than 6 hours should exist between doses
- 80% clearance in urine
  - Change dose based on kidney function
    - CrCl 15 – 30 – 75 mg twice daily
    - CrCl < 30 or dialysis - not recommended

Idarucizumab (Praxbind®)

Mab fragment (FAB)
- Reversal of the anticoagulant effect of dabigatran
  - Binds free drug and drug that is bound to thrombin
- For emergency surgeries
- Uncontrolled or life-threatening bleeding
- Injection 2.5 g/50 ml
- Dose 5 g – give 2.5 g and repeat in 15 min

Concerns
- thromboembolic risk
- Main side effect – headache, hypokalemia, delirium, constipation, pyrexia, pneumonia

Research
- Reverses clotting times, but death rate was 18 patients out of 90 total – 10 deaths were from bleeding
- 5 patients had thrombotic events

Rivaroxaban

Price
- Tablets, 10 mg (light red), 15mg (red) and 20mg (dark red)
  - ~$245 / #30

Simplicity
- Take with or without food (orthopedic thromboprophylaxis)
- Take WITH food (evening meal) for A. fib indication and DVT/PE treatment indications
- No need for INR monitoring
- Do not use with other anticoagulants at this time
- Avoid in patients with renal dysfunction (specific dosing)
- Can be given via feeding tube
Apixaban (Eliquis®)

- **Price and Simplicity**
  - 2.5 mg, 5 mg tablets
  - Price - $4.00/tab, so ~$250/mth
  - Recommended dose is 5 mg twice daily
  - Lower dose to 2.5 mg in patients with at least 2 of following:
    - Age > 80; weight < 60 kg; SCr > 1.5
- **Conversions**
  - Discontinue 48 hrs before high risk bleeding surgery
  - Discontinue 24 hrs before low risk bleeding surgery
  - Switching from warfarin: let INR get below 2
  - Switching to warfarin: DC apixaban, give LMWH + warfarin at the next dose due of apixaban

Edoxaban (Savaysa®)

- **Indication**
  - Prevention of stroke and systemic embolism in nonvalvular a. fib. It should NOT be used in patients with CrCl > 95 because of an increase risk of ischemic stroke compared to warfarin
  - Treatment of acute DVT and PE following 5 to 10 days of initial therapy with parenteral anticoagulant
- **Price**
  - ~$325/mth for either dose
- **Simplicity**
  - 15 mg, 30 mg, 60 mg tablets
  - 60 mg for those with CrCl > 50 to < 95
  - 30 mg for those with CrCl 15 to 30
  - Once daily therapy

A Conundrum

- What happens to YOU when you need to extract a tooth and the patient is on an anticoagulant or antiplatelet or both?
Dental surgery and anticoagulants!

- Professional cleanings, fillings and crowns have not shown to cause a bleeding risk
- Dental surgery in anticoagulant patients:
  - 30 studies
  - Based on 2014 surgical procedures in 774 patients on continuous warfarin therapy
  - Mouth extractions, alveoectomies, surgical extractions
  - INR levels were therapeutic

Recommendations

- 3 control trials found no difference in postoperative bleeding
- More than 98% of patients had no serious bleeding other than minor ooze controlled with local measures
- Local measures: gelfoam, tranexamic acid, biologic adhesive, Surgicel, fibrin sealant, biting on tea bag
- Only 12 of 2014 patients had postoperative bleeding not controlled by local measures, but:
  - 5 of 12 had PT above therapeutic levels

Is it OK to withdraw warfarin before dental procedures?

- There have been several documented cases of serious embolic complications, including death
  - 16 papers, 493 patients
  - 5 serious events including 4 deaths
  - 3 occurred within 5 days of the interruption
Therapeutic Conundrum

› Balance the risk of postprocedural bleeding with continued therapy to prevent thrombotic events.

› "In general a patient undergoing a procedure associated with a low risk of bleeding (low-risk procedure) can safely continue antithrombotic therapy and should do so, particularly if the patient is at risk for a thrombotic event (high-risk patient)."

› Therefore, a low-risk patient undergoing a high-risk procedure can temporarily discontinue antithrombotic agent.

› The challenge is the high-risk patient undergoing a high-risk procedure!

NEJM 2013;368(22):2113-24

Procedure Risk

Table 1. Common Performed Procedures and Risk Stratifications for Bleeding in the Status of Frequency and/or Clinical Importance

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Low Risk Bleeding (≤5%)</th>
<th>High Risk Bleeding (≥5%, or in vulnerable areas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraction</td>
<td>Extracted extraction</td>
<td>Spontaneous hemorrhage</td>
</tr>
<tr>
<td>Fracture</td>
<td>Nonothopedic fracture</td>
<td>Traumatic or elective fracture</td>
</tr>
<tr>
<td>Congenital</td>
<td>Dental complex congenital (congenital)</td>
<td>Traumatic or elective fracture</td>
</tr>
<tr>
<td>Dental</td>
<td>Tooth extraction</td>
<td>Reconstructive procedures</td>
</tr>
<tr>
<td></td>
<td>Endodontic procedure</td>
<td></td>
</tr>
</tbody>
</table>

NEJM 2013;368(22):2113-24, supplementary material

Oral Surgery Document

› Minor Dental Surgical Procedures

› No need for anticoagulation or antiplatelet changes

› Extraction up to 3 teeth (bring patient back)

› Gingival surgery

› Crown and bridge procedures

› Supragingival scaling

› Surgical removal of teeth

### Last dose to procedure

- **Warfarin**
  - Stop 1-8 days before procedure depending on INR, goal INR to <1.5 (93% of patients can get to 1.5 in 5 days)

- **Dabigatran, Rivaroxaban, Apixaban**
  - Stop 1-2 days before procedure if patient has good renal function. Stop 3-5 days for patients with CrCl < 50 ml/min.

- **Aspirin or Aspirin/dipyridomole**
  - Stop 7-10 days before procedure

- **Clopidogrel, prasugrel, ticagrelor**
  - Stop 7 days for prasugrel
  - Stop 5 days for the others

#### NEJM 2013;368(22):2113-24

### Statements from ADA

- **From the American Dental Association**
  - "...it is generally agreed that anticoagulant drug regimens should not be altered prior to dental treatment. A systematic review and meta-analysis found no increased risk of bleeding associated with continuing regular doses of anticoagulant ……for patients undergoing single or multiple tooth extraction."

- The American Academy of Neurology recommend patients undergoing dental procedures continue taking aspirin or warfarin for stroke procedures.
  - 2013 statement Neurology 2013;80:2065-9

- For stents – ADA recommends contacting the patients cardiologist

#### www.ada.org/2526.aspx

### Ticagrelor (Brilinta®)

- **New antiplatelet – becoming more popular**
- **First reversible oral direct P2Y<sub>12</sub> receptor antagonist**

#### Indications

- Reduce CV events (stent thrombosis, CV death and MI) in patients with acute coronary syndrome (unstable angina, non-STEMI or STEMI) or with a history of MI
  - Reduces composite of CV death, MI or Stroke
Ticagrelor (Brilinta®)

- **Safety**
  - Only use with aspirin 81 mg; more aspirin is associated with less efficacy (>100 mg)
  - Bleeding - same as clopidogrel

- **Tolerability**
  - More patients discontinued ticagrelor due to side effects than clopidogrel, p=0.001, NND 71
  - Main side effect: Dyspnea (14%)
    - watch in COPD
  - Bleeding: 12% (similar to clopidogrel in PLATO)
  - PI cautions bradycardia
    - watch in patients with syncope

- **Price:** $325/#60

- **Simplicity**
  - 90 mg tablets
  - Initiate a loading dose of 180 mg (two tabs)
  - Then 90 mg twice a day
  - Aspirin dose < 100 mg
  - Stop 5 days before surgery (could get away with 3 days)

- **Advantages**
  - All-cause mortality reduction vs clopidogrel, 1.4%, NNT 77
  - Not a prodrug as clopidogrel needing no conversion
  - Faster onset
  - The bleed risk is similar to clopidogrel
  - Reversible binding
  - But watch drug interactions

*NEJM 2009;361:1108-11*
Two types of antibiotics

- **Time-dependent killers**
  - Penicillin, cephalosporin, imipenem
  - clindamycin, macrolides, TMP/SMX, tetracyclines
    - Accumulation at the site of infection is important at inhibiting bacterial growth

- **Concentration-dependent killers**
  - Quinolones (really fluorquinolones), Aminoglycosides, Metronidazole
  - “qAm”

**Time-dependant Killers**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
</tr>
</tbody>
</table>
Concentration-dependant Killers

- Quinolones
- Aminoglycosides
- Metronidazole
- MIC

Dosing Issues

- Three times a day and four times a day dosing is a set up for adherence problems.
- Use total daily dose twice a day.
- This can be done with:
  - Cephalexin
  - Penicillin
  - Amoxicillin

The industry understands!

- The concept has made it to market.
- Amoxicillin (Moxatag®)
  - Once-daily form, for Strep pharyngitis and tonsillitis
  - Pulsys delivers staccato pulses (3) over 6 hrs
  - 775 mg tablet
    - 1 immediate release, 2 delay-release
    - 10 day course is $160
Dosing Issues: Concentration Killers

- “qAm”
- More is better!
  - Examples: Fluoroquinolone
    - Levofloxacin
    - 250 mg (#10 cost $10)
    - 500 mg (#10 cost $10)
    - 750 mg (#10 cost $15)
      - 5 day therapy for CAP
  - Metronidazole for trichomonas infection
    - 2 gram single dose is better than 500 mg bid for 7 days

New Formulation - Patent Extender

- Doxycycline hyclate (Acticlate®)
  - A new age Vibramycin®
  - Can take once or twice daily
  - Use as you would other doxycyclines
  - 75 mg and 150 mg ($660 for #30), oblong shaped with 2 score marks
  - Can cut in thirds
  - Calculate days supply using mg/dose – if patient takes 100 mg – take 2/3 tablet – therefore a 30 day supply = 20 tabs

For dosing – get Epocrates or Lexicomp
Know how to price meds!
Get the App!!

New Dosage Forms for Pain

- Xartemis XR®
  - extended release oxycodone/acetaminophen
  - 7.5 mg/325 mg – 2 tabs every 12 h
- Oxycodone (Oxecta®)
  - Immediate release that deter abuse
  - Hard to crush or dissolve
- Oxycodone + naloxone (Targiniq ER®)
  - 10/20/40 mg with naloxone
  - Dose q 12h
- Oxycodone (Oxaydo)
  - Immediate release form with deterrent properties
  - 5 mg, 7.5 mg – can’t crush, etc
  - Accura pharmaceuticals - uses AVERSION® technologies

Deterring Abuse

Novel Approaches to Deterring Drug Abuse

<table>
<thead>
<tr>
<th>Coating</th>
<th>Unlikely to dissolve</th>
<th>Antagonist</th>
<th>Punishment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard coating</td>
<td>Gummy pills become gummy</td>
<td>Inactive drug</td>
<td>Take too much or longer with it and you will feel sick instead of high.</td>
</tr>
</tbody>
</table>

Oxycodone: Purdue Pharma
Remoxy: Pain Therapeutics, King Pharmaceuticals
Embrada: King Pharmaceuticals
Acurex: King Pharmaceuticals
Accura Pharmaceuticals
Aversion Technology

Drug Delivery Systems

- Drug delivery systems are advancing
  - Film technology
  - Nanotechnology to target delivery
  - Microneedle technology in transdermal systems for insulin delivery
  - Microchip control of implantable pumps
    - There will be an App for that one day
  - Self-injection devices
  - Check out West Pharmaceuticals
    - They are studying hydrophobic matrix coating to delay hydration, mask unpleasant taste, pH, temperature, etc
    - Allows for drug to be put in chewing gum preps, nougat, syrup
  - Abuse deterrent technology

Abuse Deterrent Technologies

- Hot topic, especially if more people died of prescription drug overdose that car accidents per day in most states.
- Nexafed (IMPEDE technology)
  - Polymer matrix technology that disrupts pseudoephedrine extraction – it forms a thick gel
NSAID Technology

- Diclofenac (Zorvox®) – 18 mg, 35 mg caps
- Solumetrix fine particle technology
  - A dry milling technology that makes particles 50 to 200 times smaller and prevents agglomeration.
  - Iroko Pharmaceuticals
- Indicated for mild to moderate acute pain
- Makes the diclofenac function as a diclofenac potassium – comparable time to peak plasma concentrations, therefore more power with a lower dose
- Given three times a day
- $85 for either dose for #30 (10 days)

Solumetrix Technology

- Tivorbex® (indomethacin) – new product!
  - low dose, 20 mg ($320/#90), 40 mg ($320/#90) capsules
  - Dose tid for mild to moderate pain
  - Can use higher dose bid
- Vivlodex (meloxicam)
  - Low dose 5 mg, 10 mg
  - New low dose naproxen in the works and 2 other preps

More to consider!

- Presupposition
  - Drugs in solution get faster peaks in the serum and therefore faster analgesic activity.
- Gelcap products might have more efficacy in patients
- OTC ibuprofen all come in liquid gelcap formulations
- New Advil® Film-coated (ibuprofen sodium, 256 mg)
  - Uses an ion core technology that increase the speed of dissolution
  - Marketed in a white box (others are blue and red)
Unique NSAID Formulation

- **Ketorolac (Sprix®)**
  - Nasal spray NSAID for moderate pain
  - 15.75 mg per nostril
  - Dose is 1 spray per nostril every 6 to 8 hours prn, max 63 mg
  - Only last 24 hours after open bottle
  - NO indication in pediatrics
  - Box of 5 bottles, $180

- **Diclofenac Potassium for Oral Solution (Cambia®)**
  - Oral solution for acute migraines, get level within 5 min max in 15 min
  - 50 mg dose, mix powder in 1-2 oz of water
  - Buy in a co-joined dose pack of three or a box of nine ($300)
  - **Diclofenac (Zipsor®)**
  - Liquid-filled capsule formulation for mild to moderate pain
  - 25 mg, $260/#60

Very Unique Medication

- **Evzio® - naloxone auto-injector for opioid overdose**
  - Comes with electronic voice instructions and a trainer kit
  - Device is used even when you are not sure of the exact problem
  - Use device
  - Call 911

Pathophysiology Changes

- **Let's use peptic ulcer disease as a case study**
  - **Gastric model**
    - Gastric hypersecretion due to an increase in parietal-cell mass or imbalance in gastrin levels
    - These levels increase HCl acid and this causes irritation to gastric mucosa
    - Take an antacid
  - **Stress model**
    - Stress leads to smoking and alcohol consumption and these things lead to gastric irritation.
Pathophysiology is changing

- **Medication model**
  - Medications lead to irritation and ulcers
    - Aspirin, BC powders, NSAIDs, KCl, bisphosphonates

- **Elderly model – 1980's**
  - Loss of prostaglandins due to age

- **Inflammation model - 1990's**
  - H. pylori was identified as an important cause of peptic ulcer disease through inflammation caused by a cytokine cascade

Inflammation model

- Eradication of H. pylori infection has resulted in high ulcer healing rates and lower recurrence rates.
- Lower gastric cancer rates

The new pathology:

**Inflammology**

Types of mAb’s

- There are different ways the mAb bind to the target.
  - Binding mAb
  - Blocking mAb’s
  - Signaling mAb’s

Neurology 2010;74:S
Mab nomenclature

- **Certolizumab**
  - Mab suffix - monoclonal antibody
  - Antibody source
    - $u$ = human
    - $o$ = mouse
    - $a$ = rat
    - $i$ = human/hybrid
    - $r$ = primate
  - $x$ = chimeric (made from recombinant DNA from murine source)
  - Disease target
    - **viral** = **vir**
    - **bacterial** = **bac**
    - **immune** = **lim**
    - **bone** = **os**
    - **tumors** = **col** (colon), **mel** (melanoma), **mar** (mammary), **pro** (prostate), **got** (testis), **gov** (ovary), **tum** (Misc.), **cir** (cardiovascular), **mulu** (musculoskeletal)

mAb’s are plentiful

- 62 mAb’s on the market with many in study
- Many reasons for use
  - Platelet aggregation inhibition
  - RA
  - Cancer
    - Lymphoma, colorectal cancer, GI cancer diagnosis, non-Hodgkin lymphoma, ovarian, leukemia, breast cancer, melanoma
  - Organ rejection prevention
  - Psoriasis
  - Crohn’s disease
  - Osteoporosis
  - Macular degeneration
  - Asthma
  - RSV Prevention

Famous mAb’s

- Abciximab (ReoPro®)
  - antiplatelet
- Adalimumab (Humira®)
  - RA, psoriasis, etc
- Bevacizumab (Avastin®)
  - Metastatic colon cancer, Mac degeneration (anti-VEGF)
- Certolizumab (Cimzia®)
  - Crohn’s disease
- Denosumab (Prolia®, Xgeva®)
  - Osteoporosis, Prevention of skeletal-related events in patients with bone metastases from solid tumors
- Efalizumab (Raptiva®)
  - Psoriasis – now off market
Famous mAb’s

- Golimumab (Simponi®)
  - RA, psoriasis, ankylosing spondylitis
- Infliximab (Remicade®)
  - RA, psoriasis, ankylosing spondylitis, UC, Crohn’s
- Omalizumab (Xolair®)
  - Asthma
- Palivizumab (Synagis®)
  - RSV prevention
- Ranibizumab (Lucentis®)
  - Mac degeneration
- Trastuzumab (Herceptin®)
  - Breast cancer

Many mAb’s in research

- Dental caries
  - Glucosyltransferase-B (GTFB) of Streptococcus mutans produces an insoluble glucan, a key to the bacterial attachment onto dental surfaces, leading to the formation of dental caries. 2012 article
- Neuroblastoma
- Sepsis
- Lung cancer and many others cancers including pancreatic
- Severely injured patients
- Alzheimer’s disease (bapineuzumab)
- Influenza A (CR6261)
- Gram negative sepsis
- Invasive candidiasis

Many Indications

- MI, Stroke, traumatic shock
- Hepatitis B
- Rabies prophylaxis (foravirumab)
- Pulmonary fibrosis (fresolimumab)
- Reduction of scarring after glaucoma surgery
- Scleroderma
- Type 1 diabetes (Otelixizumab)
- Pseudomonas infections (Panobacumab)
- HIV
Many Indications

- Anthrax
- Hemorrhagic shock
- Cytomegalovirus
- Lupus
- Polymyositis
- Muscular dystrophy
- PCI (cath lab)
- Diarrhea caused by e.coli.
- MS

PCSK9 Inhibitors

- **Proprotein convertase subtilisin/kexin type 9**
- LDL-C is removed from the blood when it binds to an LDLR on the surface of liver cells
- When PCSK9 binds to an LDLR, the receptor is destroyed along with the LDL particle.
- If PCSK9 does not bind, the receptor can return to the surface of the cell and remove more cholesterol

_Curr Opin Lipidol 2013;24:30_
Alirocumab (Praluent®)  
Evolocumab (Repatha®)  

- **Indication**  
  - Adjunct to diet and maximum tolerated statin for adults with heterozygous familial hypercholesterolemia or clinical CV disease who need additional LDL lowering  
  - The package insert says that CV morbidity and mortality has NOT been determined.  
- **LDL cholesterol level was reduced an average of 62% in trials**  
- **Adverse Effects – well tolerated**  
  - Injection-site reactions (5.9% vs. 4.2%)  
  - Myalgia (5.4% vs. 2.9%)  
  - Neurocognitive events (1.2% vs. 0.5%, NNH 143)  

Alirocumab-Praluent®  

- **Price** - ~$14,000/yr  
- Injection 75 mg/ml  
- Injection 150 mg/ml  
  - Both dose come in a single-dose, pre-filled syringe or pen  
- **Simplicity**  
  - Dose is 75 mg every 2 weeks  
  - Assess LDL 4-8 weeks  
  - Increase to 150 mg every 2 weeks if needed  
- **Self-injection pen**  
  - Take out of refrigerator and let it warm up for 30-45 min  
  - Do not use if solution is yellow or cloudy, air bubbles are OK  
  - Inject thighs, stomach, upper arms – alternate site  
  - Release injector from skin when window has turned yellow, ~20 sec
Evolocumab (Repatha®)

- 140 mg/ml prefilled syringe
- 140 mg/ml, single-dose SureClick autoinjector

Dose
- 140 mg every 2 weeks
- 420 mg monthly
  - Given as 3 injections consecutively within 30 min

Just Approved for 2016!

- Buymeumab®
  - After 2 doses, 63% of men suddenly have the urge to buy their wives expensive jewelry
- Negasporzumab®
  - This drug causes men to turn off televised sports and actually converse with family members.
- Direczumab®
  - A dose of this drug given to men before leaving on car trips causes 72% of them to stop and ask directions.
- Projectuzumab®
  - Men were far more likely to actually finish a household repair project before starting a new one.

Medications that are considered safe in pregnancy that can be used by Dentist

- Antibiotics
  - Penicillin, cephalosporin, clindamycin
  - Metronidazole in first trimester?
  - Do not use doxycycline
  - Novacaine, et al are safe
  - Use with epinephrine is controversial
  - Avoid inhaled anesthesia

- Pain medications
  - Acetaminophen
  - Ibuprofen up to 32 weeks
  - Short term narcotics (< 7 days)
    - Lorcet®
    - Percocet®

- Anti-emetics
  - Benadryl, Phenergan, Zofran
OTC Meds in Pregnancy!

- Headache and Fever
  - Tylenol®
- Backaches
  - Heating Pad, Tylenol®
- Nausea
  - Vitamin B6 50 mg twice a day
  - Emetrol
  - Meclizine 1-2 tab sat bedtime as needed
- Indigestion
  - Mylanta or Maalox
- Constipation
  - Colace®, Metamucil
- Cough and Cold
  - Benadryl®, pseudoephedrine
  - Afrin Nasal spray

Insulin has gone crazy!

Novo Nordisk
- Novolin
  - Novolin N (NPH)
  - Novolin R (regular)
  - Novolin 70/30
  - Novolog (lispro)
  - Novolog mix 70/30

Wal-Mart
- ReliOn N (NPH)
- ReliOn R (regular)
- ReliOn 70/30

Lilly
- Humulin
  - Humulin N (NPH)
  - Humulin R (regular)
  - Humulin 70/30, 50/50
  - Humalog (lispro)
  - Humalog mix 75/25

Aventis
- Lantus (glargine)
  - Toujeo (glargine, 300 units/ml)
  - Apidra (glulisine)

Yikes---------Basaglar® (glargine)---------
(LillyBi) 5-3 ml KwikPen
**Insulin Glargine (Toujeo®)**

- Basically Lantus in a 300 unit/ml formulation
- 1:1 conversion from other basal insulin
- Twice daily NPH – use 80% of total daily NPH dose
- Insulin naïve – 0.2 units/kg
- Titrate every 3-4 days
- SoloStar® - 1.5 ml pen (3 for $336) – 450 units

![Insulin Glargine Diagram](image)

**Degludec (Tresiba®)**

- Degludec
  - Addition of hexadecanedioic acid to lysine at the B29 position allows for the formation of multi-hexamers in subcutaneous tissues and long activity
  - Ultra long-acting
    - Last 40 hours while Lantus last up to 24 hours
    - May need less dose – can use once daily
    - Can mix with short-acting insulins
      - Ryzodeg® 70/30
      - Not approved by FDA in 2013 – awaiting additional cardiovascular data

![Degludec Diagram](image)
Degludec (Tresiba®)
- Any time of day dosing
- Can last 8 weeks out of frig
- Flextouch, each 3 ml pen
- U-100 (5 pens, $460)
  - 1500 units total
- U-200 (3 pens, $550)
  - 1800 units total
- U-200 can deliver up to 160 units at a dose
- There is also a new Humalog 200 units/ml pen

The End
E-mail questions:
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Or
PharmReach.org

Master Yoda