WORKING THROUGH SHORTAGES OF PARENTERAL NUTRITION COMPONENTS

RENEE A. BELLANGER, PHARM.D., BCNSP
ASSOCIATE PROFESSOR,
PHARMACY PRACTICE
UNIVERSITY OF THE INCARNATE WORD

FEIK SCHOOL OF PHARMACY

OBJECTIVES

- Recognize and anticipate shortages of parenteral nutrition components (P,T)
- List three root causes of drug shortages (P,T)
- Identify and communicate a process by which product shortages should be handled by the involved parties (P,T)
- Outline the impact of product shortages on the quality and safety of parenteral nutrition therapy (P)

OUTLINE

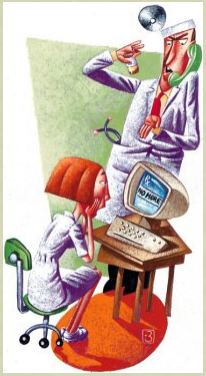
- Shortages of drug and PN components
- Reasons for drug shortages
- Impact of shortages on PN quality
- Impact of shortages on patient safety
- A.S.P.E.N. recommendations
- Legislative efforts

SHORTAGES OF PARENTERAL NUTRITION COMPONENTS

- Increasing trend
- Involves all drug classes
- All PN component products since 1988, except dextrose
  - Multivitamins 1988, then 1996-2007
  - IV Fat Emulsion 2010
  - Amino Acids 2010
  - Electrolytes, Trace Elements, Vitamins 2011

CAUSES OF SHORTAGES

- Manufacturing and regulatory issues
- Business
- Industry consolidation
- Raw material availability
- Supply chain issues
  - Depot
  - Hoarding

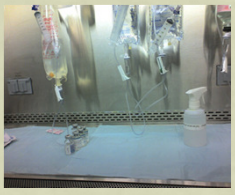


IMPACT ON QUALITY AND PATIENT SAFETY

- Changes in clinical practice
- Use of less desirable, unfamiliar alternatives
- Errors and poor patient outcomes due to absence or delay in treatment
- Preventable adverse events by poor use of alternatives
- Personnel time lost to time-consuming activities required to manage shortage

ERRORS DUE TO SHORTAGES

- Delayed or omitted treatment
- Dosing errors
- Suboptimal outcomes
- Contamination of PN
- Clinical deficiencies



ISMP SURVEY ON DRUG SHORTAGES SEPT 2010

- 35% respondents reported potentially harmful medication errors due to product shortages
- Due to drugs that became abruptly unavailable without adequate notice from manufacturers or wholesalers
- Mostly high alert medications (e.g., propofol, heparin, morphine, neuromuscular blockers, chemotherapy)

ISMP SURVEY RESULTS

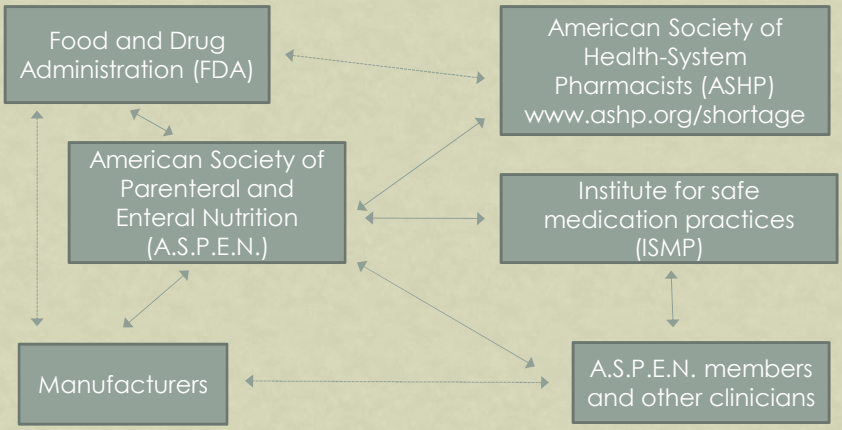
- Little or no information available about the duration of the drug shortage
- Lack of advanced warning from manufacturers
- No suggested alternatives
- Little or no information about the cause of the shortage

ISMP SURVEY RESULTS (CONT'D)

- Internal resources stretched to investigate and develop a plan of action
- Risk of adverse patient outcomes
- Financial impact
- Internal hoarding of medications associated with impending shortages
- Physician anger at staff

http://www.ismp.org/Newsletters/acutecare/articles/20100923.asp

IMPORTANT COLLABORATIONS



www.nutritioncare.org

A.S.P.E.N. GENERAL RECOMMENDATIONS FOR SHORTAGES

- Limit wastage
- Consider moving PN preparation to a central location to decrease waste
- Decrease the amount provided in PN
- Use oral formulation, if absorption possible
- Do not use IV product orally
- Do not stockpile

A.S.P.E.N. RECOMMENDATIONS FOR SHORTAGES

- Multivitamins
  - Adult
  - Pediatric
- Amino acids
- IV fat emulsions
- Electrolytes/minerals
- Trace elements

Professional resources> guidelines and standards> A.S.P.E.N. documents library
www.nutritioncare.org

MULTIVITAMINS - ADULT

- Reserve limited multivitamin products to those patients with most need
  - Long term malnutrition
  - On TPN > week
- Reduce multivitamin dose to 50% or MWF
- Give individual components as available
  - Daily:
    - Thiamine 6 mg
    - Ascorbic acid 200 mg
    - Pyridoxine 6 mg
    - Folic acid 0.6mg
  - Monthly:
    - Cyanocobalamin (vit. B_{12})
- Do not use pediatric products for this population

A.S.P.E.N. task force. Nutr Clin Pract 2005; 20:103-116

MULTIVITAMINS - PEDIATRIC

- Reserve limited multivitamin products to those patients with most need
  - Preterm Neonates
  - Older kids with long term malnutrition
- Reduce daily injectable multivitamin dose to 50%
- Use adult injectable formulation, if available
  - For infants < 2.5 kg (1 ml/kg – max 2.5 ml)
  - for infants > 2.5 kg to children 11 years (2 ml/kg – max. 5ml) supplement vitamin K (total 200 mcg / day)
  - Children > 11 years (dose = 10ml)

A.S.P.E.N. task force. J Parenter Enteral Nutr 2006. 30:177

AMINO ACIDS

- Use specialty products only for intended populations (Neonatal and Pediatric)
- Use creative purchasing and product decisions
  - "pre-mix" products for children over 11 and adult
- Be aware of product composition, pH and calcium/phosphate solubility differences
- Adjust TPN order sheets / computer profiles / labels
- Education of all involved parties – prescribers, nurses, dietitians, pharmacy personnel

A.S.P.E.N. task force. JPEN 2007; 31:441-8

L- CYSTEINE

- Restrict L-cysteine supplementation in PN to:
  - Neonates ≤1 kg
  - Neonates > 1 kg who are post-surgical or those with sepsis
- L-cysteine is provided as 20-40 mg/g of protein
- Re-evaluate the calcium-phosphorus solubility charts or software
  - Increased chance of precipitate due to the increase in the pH of the PN formulation when removed

http://www.nutritioncare.org/Professional_Resources/Guidelines_and_Standards/Guidelines/PN_Cysteine_Product_Shortage_Considerations/; accessed Sept 27, 2011

IV FAT EMULSIONS

- Prioritize neonatal patients and pediatric patients on long- term PN
- Adult patients on PN greater than 2 weeks
  - Provide essential fatty acids need with a total of 100 Gm weekly (250 ml 20% IVFE twice weekly)
  - PN dependent home health patients may need smaller daily infusions or to give calories
  - ICU patients on propofol infusion – no IVFE

A.S.P.E.N. task force. 2010.

ELECTROLYTES / MINERALS

- Prioritize patient – give only to vulnerable populations
  - Neonates
  - Pediatric patients
  - Short bowel or malabsorption syndrome patients
- Eliminate parenteral electrolyte/ mineral products in enteral formulas
- Minimize electrolyte/mineral additives to non-PN IV fluids
- Reconsider serum electrolyte algorithms or protocols, reserve for symptomatic patients
  - Use pre-mixed products for replacement

ELECTROLYTES / MINERALS –CONT'D

- Use standardized, commercial parenteral nutrition product with electrolytes for all appropriate patients
- Consider standardized, commercial multi-electrolyte products
- Consider decreasing or eliminating daily electrolytes
  - Monitor closely
  - Observe for clinically apparent electrolyte or mineral deficiencies

ELECTROLYTES / MINERALS –CONT'D-CALCIUM

- Monitor serum calcium, ionized calcium and albumin concentrations
- If calcium is needed, consider giving CaCl injection separately
  - Calcium chloride does not give the same solubility curve as Calcium gluconate
  - Do not use calcium chloride in 3-in 1 PN mixtures
- Signs and symptoms of calcium deficiency
  - Tetany
  - Other neuromuscular, CNS and CV symptoms

ELECTROLYTES / MINERALS –CONT'D- PHOSPHATE

- Reserve for neonatal and pediatric patients
- Consider provision of daily IV fat emulsion to provide 15 mmol / L of phosphate as egg phospholipids
- Monitor serum phosphate concentrations
- Signs and symptoms of phosphorus deficiency
  - Impaired diaphragmatic contractility
  - Paralysis
  - Weakness
  - Paresthesias
  - Neurologic dysfunction, seizures
  - Death

ELECTROLYTES / MINERALS –CONT'D- SODIUM

- Consider administering IV medications in 0.9% Sodium Chloride injection
- Consider administering 0.9% Sodium Chloride injection separately
- Signs and symptoms of sodium deficiency
  - Headache
  - Lethargy
  - Disorientation
  - Restlessness
  - Nausea, vomiting
  - Muscle cramps or weakness
  - Depressed reflexes
  - Seizures, coma, death

ELECTROLYTES / MINERALS –CONT'D- POTASSIUM

- Balance available potassium salt IV products – chloride, acetate, phosphate
- Use premixed, IV potassium products for maintenance or replacement therapy
- Signs and symptoms of potassium deficiency
  - Nausea, vomiting
  - Weakness
  - Constipation
  - EKG changes, cardiac arrhythmias
  - Sudden death
  - Paralysis, respiratory compromise
  - Rhabdomyolysis

ELECTROLYTES / MINERALS –CONT'D- MAGNESIUM

- Use premixed IV magnesium products as possible for IV maintenance or replacement therapy
- Signs an symptoms of magnesium deficiency
  - EKG changes
  - Arrythmias
  - Seizures
  - Coma
  - Death

TRACE ELEMENTS

- Use neonatal / pediatric products for that population only
- Multiple trace element product shortage
  - Ration available multi-trace products to 50% or three times a week in pediatric or adult patients
  - Withhold trace elements from patients receiving partial enteral/parenteral nutrition
  - Withhold trace element products for first month of therapy for newly-initiated PN adolescents or adults who do not have current deficiencies
  - When multiple trace element products are no longer available – administer individual trace elements

TRACE ELEMENTS – CONT'D

- IV Zinc shortage
  - Signs / symptoms of deficiency
    - Dermatitis, alopecia
    - Anorexia, Reduced taste sensitivity
    - Poor night vision
    - Growth failure, Delayed sexual maturity
    - Immune compromise, impaired wound healing
- IV Copper shortage
  - Signs / symptoms of deficiency
    - Hypochromic, microcytic anemia and neutropenia
    - Hypercholesterolemia
    - Pediatrics – skeletal demineralization
    - Premature neonates – depigmentation of hair and skin, aortic aneurysm, CNS dysfunction, hypotonia

TRACE ELEMENTS – CONT'D

- IV Selenium shortage- takes years to develop
  - Signs / symptoms of deficiency
    - Cardiomyopathy
- IV Manganese shortage (only supplement deficiency)
  - Signs / symptoms of deficiency
    - Weight loss
    - Transient dermatitis
    - Nausea/vomiting
- IV Chromium shortage (only supplement deficiency)
  - Signs / symptoms of deficiency
    - Glucose intolerance
    - Hyperlipemia
    - Peripheral neuropathy
    - encephalopathy

PRESERVING ACCESS TO LIFE-SAVING MEDICATIONS ACT - LEGISLATIVE SUMMARY

S.296 February 7, 2011
A Klobuchar (D-Minn) and R Casey (D-Pa)

H.R. 2245 June 21, 2011
DL DeGett (D-Colo) and TJ Rooney (R-Fla)

- Manufacturer reporting to FDA
- Public notification by FDA
- FDA required to develop criteria for drugs vulnerable to shortage
- FDA required to revise definition of medically necessary
- House bill adds penalties to manufacturers for non-compliance

ACTIVITY: SHORTAGES PROCESS

- What are your experiences with shortages?
- What happens at your institution when a shortage comes up?
- Have you seen errors due to shortages at your hospital or clinic?
- Discuss it with a few colleagues sitting around you for 5 minutes.
- Use your index card and write down a couple of ideas of how to handle a shortage when it comes up. – Pass them to the middle for sharing

INFORMATION RESOURCES

- American Society of Health-System Pharmacists (ASHP), Drug Shortages Resource Center: http://www.ashp.org/DrugShortages/Current/Bulletin.aspx?id=632
- A.S.P.E.N. News section (on homepage): http://www.nutritioncare.org/

CONCLUSIONS

- Shortages of medications and PN components are increasing
- Multiple causes
- Patient care is compromised
- Limited options when shortage arises
- Pharmacists often have the best information on shortages, we need to communicate to other health care providers to give the best patient care

QUESTIONS???

Update on Laws and Rules

Gay Dodson, R.Ph.
Executive Director/Secretary

Central Texas Society of Health-System Pharmacists' Fall Meeting
October 1, 2011

Goals

- Discuss some bills passed by the 2011 Legislative Session that affect the practice of pharmacy or the Board of Pharmacy.
- Review recent changes to pharmacy rules.
- Talk about some issues currently facing the Board.
- Answer your questions.

Board of Pharmacy Members

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Pharmacy Related Legislation

2011 Texas Legislative Session

Bills that Passed

HB 2069 by Naishtat /Lucio

- Effective Date: **9/1/2011.**
- This bill allows pharmacists to *"accelerate refills"* and dispense up to a 90-day supply of a dangerous drug if:
  - Total amount dispensed doesn't exceed the amount authorized on the Rx;
  - The patient consents to the change;
  - The physician is notified electronically or by phone; **AND**

HB 2069 by Naishtat /Lucio (cont.)

- If:
  - The physician does not specify it is medically necessary to dispense the initial quantity followed by the specified refills;
  - The dangerous drug is not a psychotropic; and
  - The patient is at least 18-years old.

SB 1438 by Van de Putte/Hopson

- Effective Date: **6/19/2011.**
- This bill amends the Pharmacy Act to clarify:
  - the records that are confidential in the impaired pharmacists program;
  - when the TSBP can release investigative files;
  - the temporary suspension provisions of the Act; and
  - the procedures for ordering a licensee to submit to a mental or physical examination.

HB 1137 by Darby/Ellis

- Effective Date: **9/1/2011.**
- This bill establishes a state real-time electronic system to track sales of pseudoephedrine (PSE).
- A business entity:
  - May not complete a sale if it results in the person obtaining more of the product than allowed by law.
  - Is not required to transmit information before **1/1/2012.**
- The system will be paid for by a non-profit organization established by the makers of PSE.

SB 594 by Van de Putte/Zerwas

- Effective Date: **9/1/2011.**
- This bill amends the Texas Controlled Substances Act to allow the electronic transfer of prescriptions for **Schedule II** controlled substances.
- **Note:** Written prescriptions for Schedule II Controlled Substances **must still be on the official prescription form.**

SB 158 by Williams/Fletcher

- Effective Date: **9/1/2011.**
- This bill makes it a felony:
  - To obtain a prescription for a controlled substance that is not medically necessary (Doctor Shopping).
  - For a person registered under the Controlled Substances Act or working for a registrant to knowingly take controlled substances:
    - For his/her own use; or
    - To divert for unlawful use by another person.

SB 1273 by Williams/Hamilton

- Effective Date: **9/1/2011.**
- This bill:
  - Deletes the requirement for the DPS number to be on a prescription but requires a registrant to notify DPS of their DEA number within 45-days after they get their DPS number.
  - Requires pharmacies to send CS Rx information to DPS every 7 days.
  - Gives Board of Nursing access to the DPS RX monitoring program information.

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Bills that DID NOT Pass

SB 1644 and SB 1756 by Uresti

- **DID NOT PASS.**
- These bills would have amended the Pharmacy Act to specify that a pharmacist may not substitute/interchange on a prescription for an *"tamper-resistant opioid analgesic drugs"* unless the drug is on a list developed by TSBP.

HB 2666/SB 1437 Truitt/Van de Putte

- **DID NOT PASS.**
- These bills would have amended the Pharmacy Act to allow pharmacists to administer vaccines *"that are required to attend junior high or middle school."*

HB 2092 by King

- **DID NOT PASS.**
- This bill would have established the Texas State Board of Pharmacy and the Texas Board of Nursing as Self-Directed and Semi-Independent agencies.

HB 3426/SB 1785 by Zedler/Patrick

- **DID NOT PASS.**
- These bills would have created a new agency, the Texas Department of Health Professions, to regulate the professions previously regulated by the following Boards of:
  - Pharmacy; Medical; Nursing; Dental Examiners; Optometry; Chiropractic Examiners; Podiatric Examiners; Examiners of Psychologists; Executive Council of Physical and Occupational Therapy Examiners; and Veterinary Medical Examiners.

HB 3414 by McClendon

- **DID NOT PASS.**
- This bill would have moved the controlled substance monitoring program and the issuance of a registration to dispense, prescribe, or distribute controlled substances from the Texas Department of Public Safety to the Texas State Board of Pharmacy.

SB 546 by Deuell

- **DID NOT PASS.**
- This bill would have allowed physicians to dispense Dangerous Drugs from their office and charge for those drugs.

Recent Changes to Rules

Controlled Substances

Federal Changes

DEA Rules for Electronic Prescriptions

- Effective Date: 6/1/10.
- Interim Final Rules.
- E-prescriptions are allowed for Schedule II – V controlled substance prescriptions.
- Because of the passage of **SB 594** prescriptions for Schedule II controlled substances **MAY be transmitted electronically beginning 9/1/2011.**

Pharmacy and Physician Requirements

- **Prior** to using a system to transmit or receive controlled substance prescriptions, the pharmacy's and the physician's software must comply with DEA rules.

Q & A from DEA Website

- **Q. How will a practitioner or pharmacy be able to determine that an application complies with DEA's rule?**

  A. The application provider **must either hire a qualified third party to audit the application or have the application reviewed and certified by an approved certification body.** The auditor or certification body will issue a report that states whether the application complies with DEA's requirements and whether there are any limitations on its use for controlled substance prescriptions.

Q & A from DEA Website (cont.)

A. The application provider **MUST** provide a copy of the report to practitioners or pharmacies to allow them to determine whether the application is compliant.

THEREFORE

Pharmacy and Physician Requirements (cont.)

- **Prior to accepting electronic prescriptions from a physician, a pharmacy must:**
  - Have a report from the pharmacy's software vendor showing the system is in compliance with DEA's regulations; **AND**
  - See a copy of the report showing the Dr.'s software is compliant with DEA regulations .

Electronic Prescriptions

- A Q&A on the e-prescription requirements for controlled substances is available on the DEA Website at:

http://www.deadiversion.usdoj.gov/ecomm/e_rx/index.html


U.S. Department of Justice Drug Enforcement Administration
Office of Diversion Control
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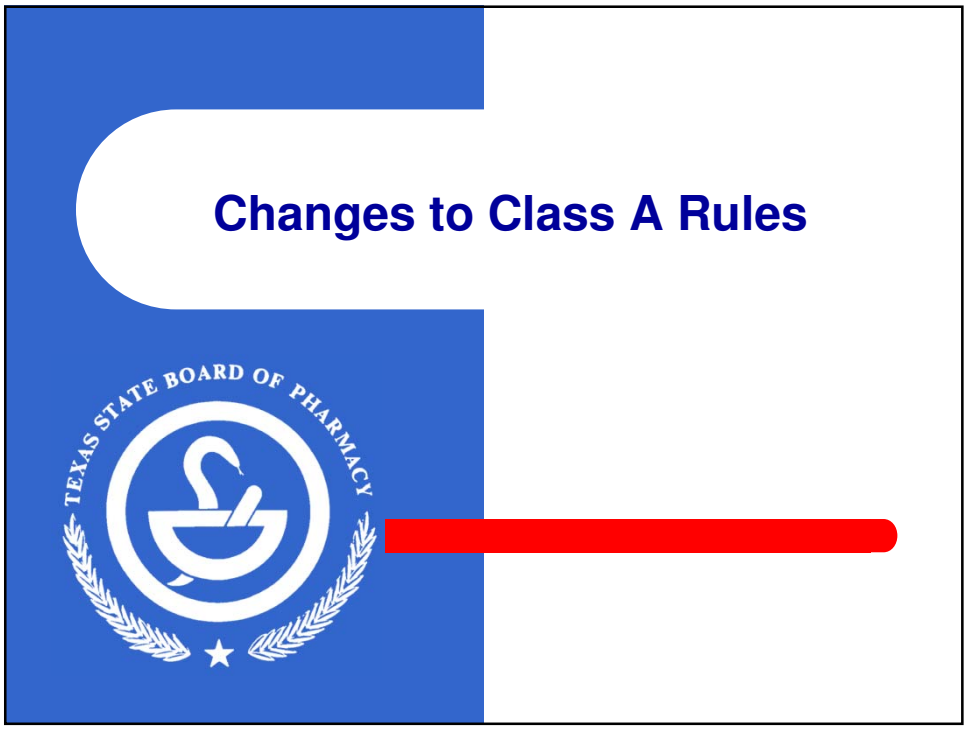
Registration
Reporting
Info & Legal Resources
Inside Diversion Control
Electronic Commerce Initiatives > Electronic Prescriptions for Controlled Substances
Information and Legal Resources at your fingertips
Got Drugs?
JAPAN Disaster Relief Efforts HAITI
ALERT Extortion SCAM
Regulations.gov
The voice in Federal decision-making
Good Medicine, Bad Behavior.
Electronic Prescriptions for Controlled Substances
On March 24, 2010, the Office of the Federal Register made available for public inspection an Interim Final Rule with Request for Comment from the Drug Enforcement Administration (DEA) entitled "Electronic Prescriptions for Controlled Substances" [Docket No. DEA-218, RIN 1117-AA61]. On March 31, 2010 the rule was published in the Federal Register. The official rule may be viewed at the Federal Register Web site. An unofficial copy of the rule is found below. The rule will become effective June 1, 2010.
The rule revises DEA regulations to provide practitioners with the option of writing prescriptions for controlled substances electronically. The regulations also permit pharmacies to receive, dispense, and archive these electronic prescriptions. These regulations are an addition to, not a replacement of, the existing rules. The regulations provide pharmacies, hospitals, and practitioners with the ability to use modern technology for controlled substance prescriptions while maintaining the closed system of controls on controlled substances.
Interim Final Rule with Request for Comment
Interim Final Rule with Request for Comment: Electronic Prescriptions for Controlled Substances (March 31, 2010)
PDF Version
Economic Impact Analysis of the Interim Final Rule (PDF)
Risk Assessment for the Interim Final Rule (PDF)
Outreach, Questions and Answers
Letter to Electronic Application Providers and Pharmacy Application Providers (April 2, 2010)
DEA letter to affected associations (March 26, 2010)
Questions and Answers
General Questions and Answers
For Prescribing Practitioners
For Pharmacies
For Providers of Electronic Prescription Applications, Pharmacy Applications, and Intermediaries
Historical documents
Electronic Prescriptions for Controlled Substances - Correction (July 14, 2008)
Electronic Prescriptions for Controlled Substances (June 27, 2008)
Initial Economic Impact Analysis of the Proposed Electronic Prescription Rule (PDF)
Texas State Board of Pharmacy
10/1/2011


Changes to Class A Rules
TEXAS STATE BOARD OF PHARMACY

Documentation of Patient Counseling

- Effective Date: **6/1/10.**
- The initials or identification code of the pharmacist providing the counseling must be documented either:
  - On the original hard-copy prescription;
  - In the pharmacy's data processing system;
  - In an electronic logbook; **OR**

Documentation of Patient Counseling (cont.)

- Effective Date: **9/12/11.**
- In a hard-copy log containing the:
  - Name of the patient;
  - Date of counseling;
  - Prescription number; and
  - Initials or identification code of the pharmacist providing the counseling.

Prescription Information

- Effective Date: **1/1/11.**
- Amendments to the Class A and Class E rules to implement the provisions of H.B. 19 (2009 Session) that require the written information accompanying the prescription **OR** the prescription label to contain the statement ***"Do not flush unused medications or pour down a sink or drain."***

Prescription Information (cont.)

- The rules also specify that a drug product on a **list developed by FDA** of medicines recommended for disposal by flushing is **NOT** required to bear this statement.

http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186187.htm#MEDICINES

MEDICINES RECOMMENDED FOR DISPOSAL BY FLUSHING

This list from FDA tells you what unused or expired medicines you should flush down the sink or toilet to help prevent danger to people and pets in the home. Flushing these medicines will get rid of them right away and help keep your family and pets safe.

FDA continually evaluates medicines for safety risks and will update the list as needed.

Medicine	*Active Ingredient*
Actiq, oral transmucosal lozenge *	Fentanyl Citrate
Avinza, capsules (extended release)	Morphine Sulfate
Daytrana, transdermal patch system	Methylphenidate
Demerol, tablets *	Meperidine Hydrochloride
Demerol, oral solution *	Meperidine Hydrochloride
Diastat/Diastat AcuDial, rectal gel	Diazepam
Dilaudid, tablets *	Hydromorphone Hydrochloride
Dilaudid, oral liquid *	Hydromorphone Hydrochloride
Dolophine Hydrochloride, tablets *	Methadone Hydrochloride
Duragesic, patch (extended release) *	Fentanyl
Embeda, capsules (extended release)	Morphine Sulfate; Naltrexone Hydrochloride
Exalgo, tablets (extended release)	Hydromorphone Hydrochloride
Fentora, tablets (buccal)	Fentanyl Citrate
Kadian, capsules (extended release)	Morphine Sulfate
Methadone Hydrochloride, oral solution *	Methadone Hydrochloride
Methadose, tablets *	Methadone Hydrochloride
Morphine Sulfate, tablets (immediate release) *	Morphine Sulfate
Morphine Sulfate, oral solution *	Morphine Sulfate
MS Contin, tablets (extended release) *	Morphine Sulfate
Onsolis, soluble film (buccal)	Fentanyl Citrate
Opana, tablets (immediate release)	Oxymorphone Hydrochloride
Opana ER, tablets (extended release)	Oxymorphone Hydrochloride
Oramorph SR, tablets (sustained release)	Morphine Sulfate
Oxycontin, tablets (extended release) **	Oxycodone Hydrochloride
Percocet, tablets *	Acetaminophen; Oxycodone Hydrochloride
Percodan, tablets *	Aspirin; Oxycodone Hydrochloride
Xyrem, oral solution	Sodium Oxybate

*These medicines have generic versions available or are only available in generic formulations.

List revised: March 2010

For specific drug product labeling information, go to DailyMed or Drugs@FDA.

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Partner Therapy

- Effective Date: **9/12/11.**
- A pharmacist may dispense a prescription when a physician has not established a professional relationship with a patient if the prescription is for:
  - Sexually transmitted diseases for partners of the physician's established patient; or
  - A patient's family members if the patient has an illness determined by the Centers for Disease Control and Prevention, the World Health Organization, or the Governor's office to be pandemic.

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Partner Therapy – Prescription Label

- The name of the patient's partner or family member **is not required to be on the label** of a drug prescribed for a partner for a:
  - Sexually transmitted disease; or
  - Patient's family members if the patient has an illness determined by the Centers for Disease Control and Prevention, the World Health Organization, or the Governor's office to be pandemic

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PIC Requirements

- Effective Date: **9/12/11.**
- Each Class A pharmacy shall have one full-time PIC who may be the PIC for only one pharmacy; provided, however, a pharmacist may be the PIC of:
  - more than one Class A pharmacy, if the additional Class A pharmacies are not open to provide pharmacy services simultaneously; **OR**

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PIC Requirements (cont.)

- A pharmacist may be the PIC of:
  - **During an emergency**, up to two Class A pharmacies open simultaneously, if the PIC works at least 10 hours per week in each pharmacy **for no more than 30 consecutive days.**

Returning Undelivered Rxs to Stock

- Effective Date: **9/12/11.**
- When returning undelivered Rxs to stock:
  - The returned product:
    - may not be mixed within the manufacturer's container.
    - should be used as soon as possible and stored in the dispensing container.
  - The expiration date of the medication is the lesser of one year from the dispensing date on the prescription label or the manufacturer's expiration date if dispensed in the manufacturer's original container.

Returning Undelivered Rxs to Stock (cont.)

- At the time of dispensing, the medication must be placed in a new container and **NOT** dispensed in the previously labeled container **UNLESS** the label can be completely removed.
- If the medication is in the manufacturer's original container, **the pharmacy label must be removed** so that no confidential patient information is released.

Pharmacists

§291.29 Professional Responsibility of Pharmacists

- Effective Date: **9/12/11**

  (**Note:** new language is **underlined**).
- A prescription drug order may not be dispensed or delivered if the pharmacist has reason to suspect that the prescription drug order may have been authorized in the absence of a valid patient-practitioner relationship, or otherwise in violation of the practitioner's standard of practice to include that the practitioner:

§291.29 Professional Responsibility of Pharmacists (cont.)

- The practitioner:
  - Did not establish a diagnosis through the use of acceptable medical practices for the treatment of patient's condition;
  - Prescribed prescription drugs that were not necessary for the patient due to a lack of a valid medical need or the lack of a therapeutic purpose for the prescription drugs; or
  - Issued the prescriptions outside the usual course of medical practice.

§291.29 Professional Responsibility of Pharmacists (cont.)

- If a pharmacist has reasons to suspect that a prescription was authorized solely based on the results of a questionnaire and/or in the absence of a documented patient evaluation including a physical examination, the pharmacist shall ascertain if that practitioners standard of practice allows that practitioner to authorize a prescription under such circumstances.

§291.29 Professional Responsibility of Pharmacists (cont.)

- Reasons to suspect that a prescription may have been authorized without a valid patient-practitioner relationship, or in violation of the practitioners standard of practice, **include:**
  - The number of prescriptions authorized on a daily basis by the practitioner;
  - **A disproportionate number of patients of the practitioner receive controlled substances**;

§291.29 Professional Responsibility of Pharmacists (cont.)

- Reasons to suspect:
  - the manner in which the prescriptions are authorized by the practitioner or received by the pharmacy;
  - the geographical distance between the practitioner and the patient or **between the pharmacy and the patient**;
  - knowledge by the pharmacist that the prescription was issued solely based on answers to a questionnaire;

§291.29 Professional Responsibility of Pharmacists (cont.)

- Reasons to suspect:
  - Knowledge the pharmacy he/she works for directly or indirectly participates with an Internet site that markets prescription drugs to the public without requiring the patient to provide a valid prescription order from the patients practitioner; or
  - **Knowledge that the patient has exhibited doctor-shopping or pharmacy-shopping tendencies**.

§291.29 Professional Responsibility of Pharmacists (cont.)

- A prescription drug order may not be dispensed or delivered if issued by a practitioner practicing at a pain management clinic that is not in compliance with the rules of the Texas Medical Board in 22 TAC §§195.1 -195.4 (relating to Pain Management Clinics).

§291.29 Professional Responsibility of Pharmacists (cont.)

- A pharmacist shall ensure that prescription drug orders for the treatment of chronic pain have been issued in accordance with the **guidelines set forth by the Texas Medical Board in 22 TAC §170.3 (relating to Guidelines)**, prior to dispensing or delivering such prescriptions.


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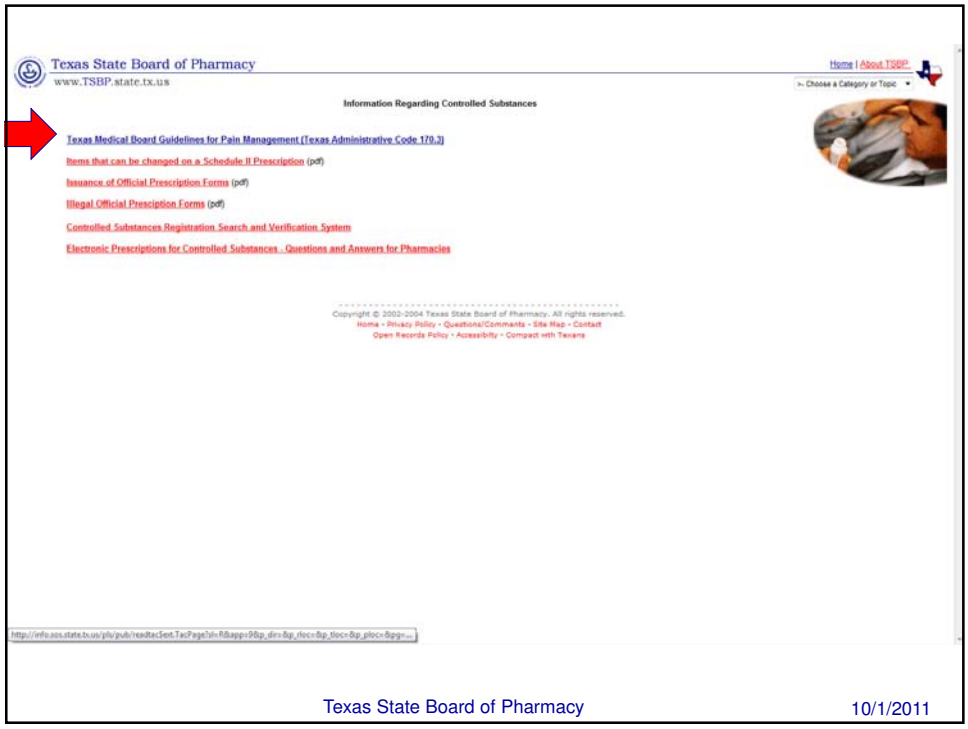
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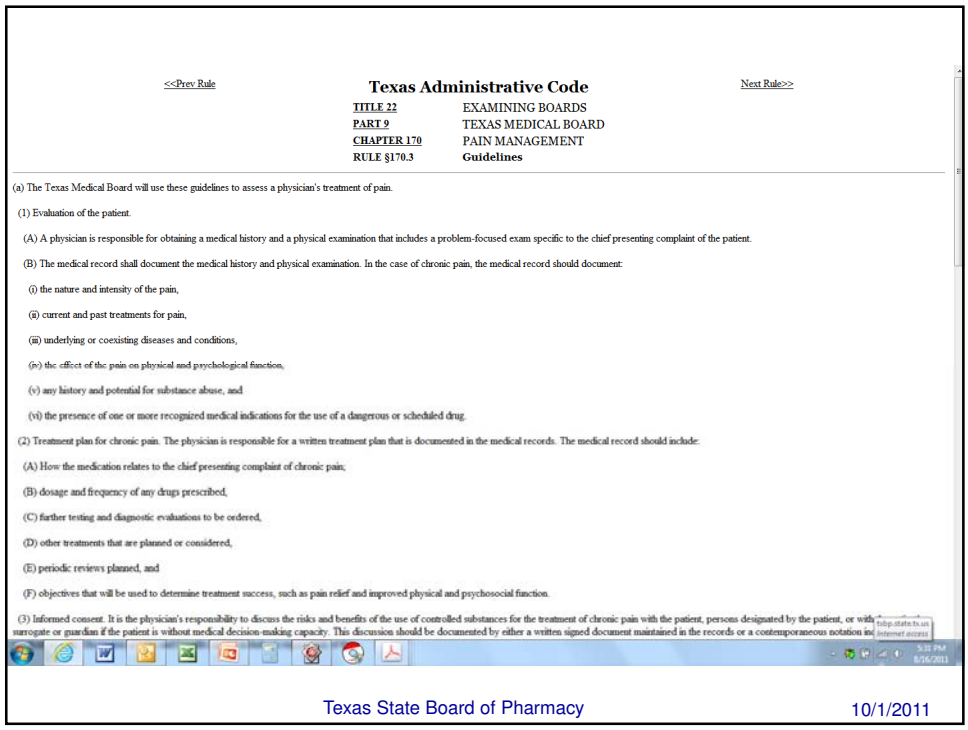
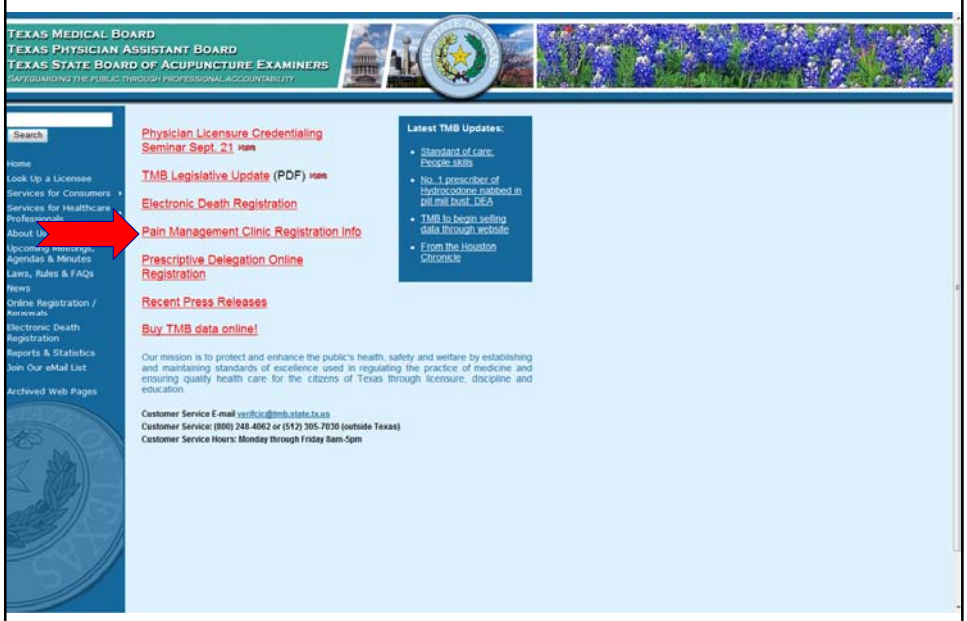
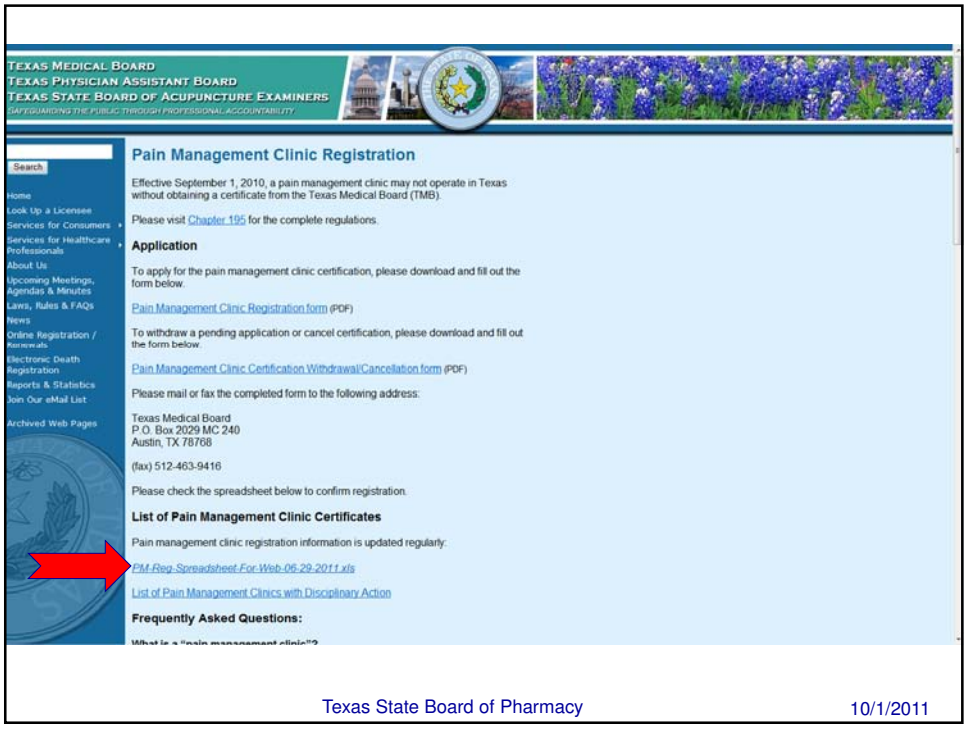
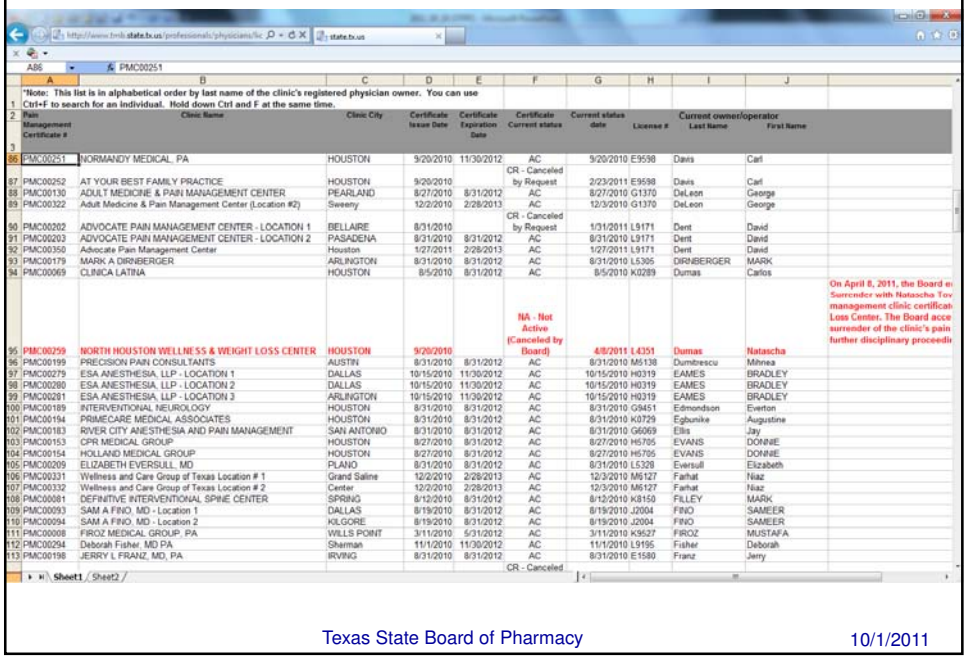

<<Prev Rule
Next Rule>>
Texas Administrative Code
TITLE 22 EXAMINING BOARDS
PART 9 TEXAS MEDICAL BOARD
CHAPTER 170 PAIN MANAGEMENT
RULE §170.3 Guidelines
(a) The Texas Medical Board will use these guidelines to assess a physician's treatment of pain.
(1) Evaluation of the patient.
(A) A physician is responsible for obtaining a medical history and a physical examination that includes a problem-focused exam specific to the chief presenting complaint of the patient.
(B) The medical record shall document the medical history and physical examination. In the case of chronic pain, the medical record should document:
(i) the nature and intensity of the pain,
(ii) current and past treatments for pain,
(iii) underlying or coexisting diseases and conditions,
(iv) the effect of the pain on physical and psychological function,
(v) any history and potential for substance abuse, and
(vi) the presence of one or more recognized medical indications for the use of a dangerous or scheduled drug.
(2) Treatment plan for chronic pain. The physician is responsible for a written treatment plan that is documented in the medical records. The medical record should include:
(A) How the medication relates to the chief presenting complaint of chronic pain;
(B) dosage and frequency of any drugs prescribed,
(C) further testing and diagnostic evaluations to be ordered,
(D) other treatments that are planned or considered,
(E) periodic reviews planned, and
(F) objectives that will be used to determine treatment success, such as pain relief and improved physical and psychosocial function.
(3) Informed consent. It is the physician's responsibility to discuss the risks and benefits of the use of controlled substances for the treatment of chronic pain with the patient, persons designated by the patient, or with
surrogate or guardian if the patient is without medical decision-making capacity. This discussion should be documented by either a written signed document maintained in the records or a contemporaneous notation in

Pain Management Clinics

- Medical Board is posting the names of registered Pain Management Clinics on their Web-Site.
- Go to **www.tmb.state.tx.us**
  - Select “Pain Management Registration Info.”

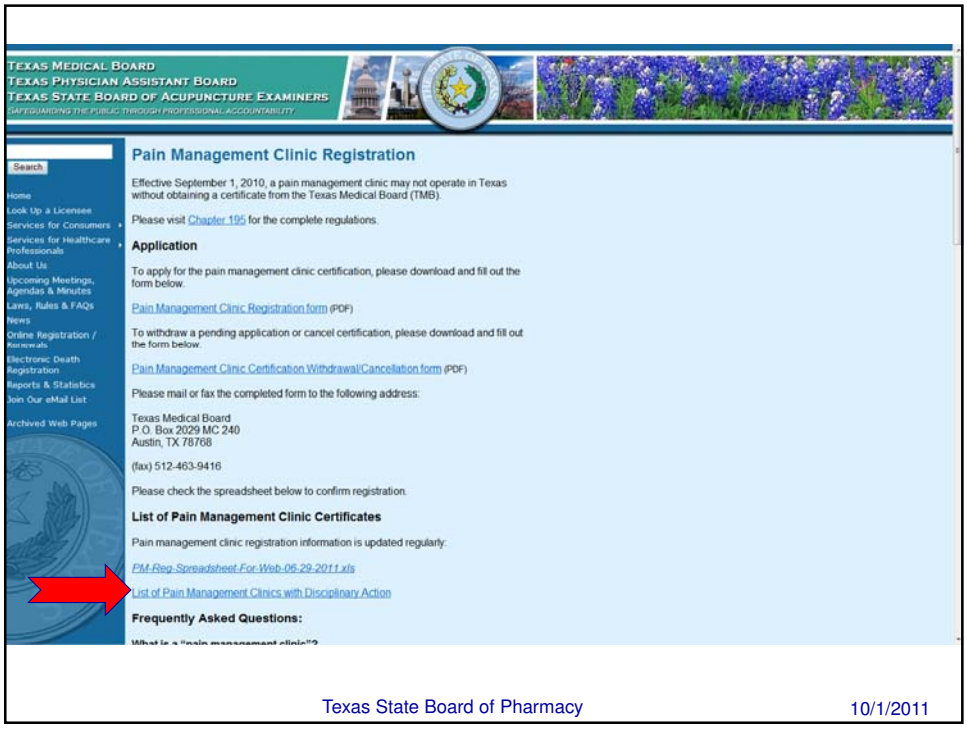






*Note: This list is in alphabetical order by last name of the clinic's registered physician owner. You can use Ctrl+F to search for an individual. Hold down Ctrl and F at the same time.

Pain Management Certificate #	Clinic Name	Clinic City	Certificate Issue Date	Certificate Expiration Date	Certificate Current status	Current status date	License #	Current owner/operator Last Name	First Name	
PMC00251	NORMANDY MEDICAL, PA	HOUSTON	9/20/2010	11/30/2012	AC	9/20/2010	E9598	Davis	Carl	
					CR - Canceled by Request	2/23/2011	E9598	Davis	Carl	
PMC00252	AT YOUR BEST FAMILY PRACTICE	HOUSTON	9/20/2010		CR - Canceled by Request	12/3/2010	G1370	DeLeon	George	
PMC00130	ADULT MEDICINE & PAIN MANAGEMENT CENTER	PEARLAND	8/27/2010	8/31/2012	AC	8/27/2010	G1370	DeLeon	George	
PMC00322	Adult Medicine & Pain Management Center (Location #2)	Sweeny	12/2/2010	2/28/2013	AC	12/3/2010	G1370	DeLeon	George	
PMC00202	ADVOCATE PAIN MANAGEMENT CENTER - LOCATION 1	BELLAIRE	8/31/2010		CR - Canceled by Request	1/31/2011	L9171	Dent	David	
PMC00203	ADVOCATE PAIN MANAGEMENT CENTER - LOCATION 2	PASADENA	8/31/2010	8/31/2012	AC	8/31/2010	L9171	Dent	David	
PMC00350	Advocate Pain Management Center	Houston	1/27/2011	2/28/2013	AC	1/27/2011	L9171	Dent	David	
PMC00179	MARK A DIRNBERGER	ARLINGTON	8/31/2010	8/31/2012	AC	8/31/2010	L5305	DIRNBERGER	MARK	
PMC00069	CLINICA LATINA	HOUSTON	8/5/2010	8/31/2012	AC	8/5/2010	K0289	Dumas	Carlos	
PMC00259	NORTH HOUSTON WELLNESS & WEIGHT LOSS CENTER	HOUSTON	9/20/2010		NA - Not Active (Canceled by Board)	4/8/2011	L4351	Dumas	Natascha	On April 8, 2011, the Board e... Surrender with Natascha Tov... management clinic certificat... Loss Center. The Board acce... surrender of the clinic's pain... further disciplinary proceedi...
PMC00199	PRECISION PAIN CONSULTANTS	AUSTIN	8/31/2010	8/31/2012	AC	8/31/2010	M5138	Dumbrescu	Mihnea	
PMC00279	ESA ANESTHESIA, LLP - LOCATION 1	DALLAS	10/15/2010	11/30/2012	AC	10/15/2010	H0319	EAMES	BRADLEY	
PMC00280	ESA ANESTHESIA, LLP - LOCATION 2	DALLAS	10/15/2010	11/30/2012	AC	10/15/2010	H0319	EAMES	BRADLEY	
PMC00281	ESA ANESTHESIA, LLP - LOCATION 3	ARLINGTON	10/15/2010	11/30/2012	AC	10/15/2010	H0319	EAMES	BRADLEY	
PMC00189	INTERVENTIONAL NEUROLOGY	HOUSTON	8/31/2010	8/31/2012	AC	8/31/2010	G9451	Edmondson	Everton	
PMC00194	PRIMECARE MEDICAL ASSOCIATES	HOUSTON	8/31/2010	8/31/2012	AC	8/31/2010	K0729	Egbunike	Augustine	
PMC00183	RIVER CITY ANESTHESIA AND PAIN MANAGEMENT	SAN ANTONIO	8/31/2010	8/31/2012	AC	8/31/2010	G6069	Ellis	Jay	
PMC00153	CPR MEDICAL GROUP	HOUSTON	8/27/2010	8/31/2012	AC	8/27/2010	H5705	EVANS	DONNIE	
PMC00154	HOLLAND MEDICAL GROUP	HOUSTON	8/27/2010	8/31/2012	AC	8/27/2010	H5705	EVANS	DONNIE	
PMC00209	ELIZABETH EVERSULL, MD	PLANO	8/31/2010	8/31/2012	AC	8/31/2010	L5328	Eversull	Elizabeth	
PMC00331	Wellness and Care Group of Texas Location # 1	Grand Saline	12/2/2010	2/28/2013	AC	12/3/2010	M6127	Farhat	Niaz	
PMC00332	Wellness and Care Group of Texas Location # 2	Center	12/2/2010	2/28/2013	AC	12/3/2010	M6127	Farhat	Niaz	
PMC00081	DEFINITIVE INTERVENTIONAL SPINE CENTER	SPRING	8/12/2010	8/31/2012	AC	8/12/2010	K8150	FILLEY	MARK	
PMC00093	SAM A FINO, MD - Location 1	DALLAS	8/19/2010	8/31/2012	AC	8/19/2010	J2004	FINO	SAMEER	
PMC00094	SAM A FINO, MD - Location 2	KILGORE	8/19/2010	8/31/2012	AC	8/19/2010	J2004	FINO	SAMEER	
PMC00008	FIROZ MEDICAL GROUP, PA	WILLS POINT	3/11/2010	5/31/2012	AC	3/11/2010	K9527	FIROZ	MUSTAFA	
PMC00294	Deborah Fisher, MD PA	Sherman	11/1/2010	11/30/2012	AC	11/1/2010	L9195	Fisher	Deborah	
PMC00198	JERRY L FRANZ, MD, PA	IRVING	8/31/2010	8/31/2012	AC	8/31/2010	E1580	Franz	Jerry	
					CR - Canceled					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Pain Management Clinic Registration
Effective September 1, 2010, a pain management clinic may not operate in Texas without obtaining a certificate from the Texas Medical Board (TMB).
Please visit Chapter 195 for the complete regulations.
Application
To apply for the pain management clinic certification, please download and fill out the form below.
Pain Management Clinic Registration form (PDF)
To withdraw a pending application or cancel certification, please download and fill out the form below.
Pain Management Clinic Certification Withdrawal/Cancellation form (PDF)
Please mail or fax the completed form to the following address:
Texas Medical Board
P.O. Box 2029 MC 240
Austin, TX 78768
(fax) 512-463-9416
Please check the spreadsheet below to confirm registration.
List of Pain Management Clinic Certificates
Pain management clinic registration information is updated regularly.
PM-Reg-Spreadsheet-For-Web-06-29-2011.xls
List of Pain Management Clinics with Disciplinary Action
Frequently Asked Questions:


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Pain Management Clinics with Disciplinary Action
Click on PDFs below to read Board Orders regarding the certificates of registered pain clinics.
Houston Pain & Rehab Clinic – PMC00140 - 4/25/2011
Winrock Medical Clinic – PMC00118 - 4/25/2011
South Houston Treatment Center, LLC – PMC00298 - 4/15/2011
Alliance Medical – aka Alliance Treatment Center, LLC – PMC00297 - 4/15/2011
North Houston Wellness and Weight Loss Center – PMC00259 - 4/8/2011
UMAT Clinic – PMC00105 - 2/22/2011
IMED Clinic – PMC00104 - 2/22/2011
Oaks Medical – PMC00103 - 2/22/2011
Preferred Medical– PMC00102 - 2/22/2011
Spring Wellness Center – PMC00146 - 2/4/2011
Spring Wellness Center – PMC00146 - 1/11/2011
Better Life Pain Clinic – PMC00046

TSBP Emergency Suspension Action

- TSBP is now posting the results of Emergency Suspension Actions on the Website.
- Go to www.tsbp.state.tx.us
- Click on – Recent Disciplinary Notifications.


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August 3, 2011
Board temporarily suspends pharmacist license of Bright Omemgboji Wokocha, R.Ph.
Board temporarily suspends pharmacy license of Adbright Pharmacy, Incorporated
Board temporarily suspends pharmacy license of Richmond Professional Pharmacy
July 13, 2011
Board temporarily suspends pharmacist license of Shantae Shepard, R.Ph.
Board temporarily suspends pharmacy license for River's Edge Pharmacy
May 9, 2011
Board Temporarily Suspends pharmacist license of Hetty Osaro Umeh, R.Ph.
Board Temporarily suspends pharmacy license for Medsure RX
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10/1/2011


All Licensees/Registrants
TEXAS STATE BOARD OF PHARMACY

Fee Reductions (Effective 12/1/2011)

Licensee/ Registrant	Current Fee	Fee on 12/1/2011	Difference
Pharmacists	$306	$223	- $83
Pharmacies	$479	$396	- $83
Pharmacy Technicians	$80	$62	- $18
Technician Trainees	$53	$42	- $11

Current Issues

New TSBP Regulatory Database System

- The system is **ACTIVE** as of May 31, 2011.

Pharmacy Technician/Trainee Registration

- Must be registered **BEFORE** they begin work.
- Must POST their registration certificate in the pharmacy.
- Pharmacy Technicians must renew that registration every 2-years and they **CANNOT WORK** with a delinquent registration. (Note: Tech Trainee registration expires after 2-years and cannot be renewed.)

TSBP Website
www.tsbp.state.tx.us

Questions?


Thank You!
TEXAS STATE BOARD OF PHARMACY

Procedural Pain Management in Children

CTSHP Fall Seminar 2011

Objectives

- List the options for procedural pain management in children
- Describe methods to access pain in children
- Give indications for medications used for procedural pain management
- Recognize developmentally appropriate non-pharmacological comfort measures.

Pediatric Update?

- TJC new and revised standards for pediatric population:
  - MM.02.01.01 – the addition of "population(s) served" as a criteria for selecting and procuring medications
  - PC.01.02.08 – pediatric population added to fall's risk assessment

PC.01.02.07

- The hospital assesses and manages the patient's pain.
  - EP 2 (revised) – the hospital uses methods to assess pain that are consistent with the patient's age, condition, and ability to understand.
  - EP 6 (new) – for hospitals that provide care treatment, and services to the pediatric population: in order to reduce stress and pain related to procedures, the hospital intervenes before the procedure using pharmacologic and non-pharmacologic (comfort) measures.

Procedural Pain

- Blood draws
  - Including heel sticks
- IV starts
- Access IV ports
- Vaccinations
- Laceration repairs
- Abscess I&D
- Dressing changes
- Skin testing

Pain related to age and development

- Myth – Infants do not feel pain
- Children < 2 years: highly reactive to environment and strangers, respond to immediate stressor or stimuli
- Children > 2 and < 5 years: may misinterpret pain as punishment
- School age: can express pain, fear and anxiety
- Adolescents: are body conscious, sensitive to praise, criticism and humor in relation to painful stimuli

Non-pharmacological interventions

- Children < 2 years
  - Cuddling, swaddling, voice and distraction
- Children > 2 and < 5 years
  - Play, bubbles, distraction, family support, kissing an injury and praise
- School age
  - Procedural preparation, play, questions and being oriented to equipment and environment
- Adolescents
  - Require further exploration by staff to determine open up to discuss fear, anxiety and pain

Pain Assessment in Children

- Wong-Baker FACES

Pain Assessment

- Numeric scale 1- 10
- Physical exam:
  - Appearance
    - Are they alert? Crying? Easily distracted?
  - Work of breathing
    - Spontaneous or rapid regular rate
    - Splinting
  - Circulation
    - Pale skin color

Pharmacologic Interventions

Sucrose solution

- 24% solution
- Works best for neonates, but may be tried in infants up to 3 months old
- 0.2 – 2 ml swapped in mouth or pacifier dipped in
- Wait 2 minutes before starting procedure; should last up to 8 minutes

Sucrose solution

- Indications:
  - Circumcision
  - Chest tube placement
  - Heel sticks / Injections / IV line placements
  - Lumbar punctures
- Contraindications:
  - High risk for NEC
  - At risk for aspiration or sedated
  - Esophageal or tracheal abnormalities

Lidocaine 4% topical cream

- L.M.X.4™ (ELA-Max)
- Cream is applied in a thick layer and covered by an occlusive dressing
- Maximum application time
  - < 1 year – 1 hour
  - > 1 year – 2 hours
- Can be used on all ages, including newborns
  - Use in preterm infants has not been established
- Onset of anesthesia: 30-45 minutes

Lidocaine topical cream

- EMLA™ (Eutectic mixture of local anesthetics)
  - Lidocaine 2.5% and prilocaine 2.5%
- Cream is applied in a thick layer and covered by an occlusive dressing
- Maximum application time
  - < 1 year – 1 hour
  - > 1 year – 4 hours
- Can be used on all ages, including newborns
- Onset of anesthesia: 45-60 minutes

Lidocaine topical creams

- Indications:
  - IV placements
  - Blood / lab draws
  - Port access
  - Lumbar punctures
- Contraindications:
  - Not on an open wound or mucous membranes
  - Receiving nitric oxide or nitroprusside
  - Children receiving class I or class III antiarrhythmic medications
  - Known congenital or idiopathic methemoglobinemia (EMLA)

Vapocoolant Spray

- Causes a transient freezing of the skin surface
- Onset is immediate but lasts less than 1 minute
- Only applied to intact skin
- Will cause hypopigmentation of the skin
- May be applied directly or with a saturated cotton ball

Vapocoolant spray

- Indications
  - Injections
  - IV placements
  - Abscess I&D
  - Chest tube placement
  - Lumbar puncture
- Contraindications
  - Patients with peripheral vascular conditions
  - Avoid getting spray into face, eyes or inhaling

J-tip syringe

- A needle free device for injections
  - Lidocaine

Buffered lidocaine

- Alkalinizing lidocaine with sodium bicarbonate
- 1 part sodium bicarbonate with 9 parts lidocaine 2% (1:10 ratio)
- May be better tolerated in combination with LMX4 or vapocoolant spray
- Indications:
  - Lumbar punctures
  - Bone marrow biopsies
  - Arterial punctures
  - PICC line placements

LET solution or gel

- Topical mixture of Lidocaine 4%, epinephrine 0.1% and tetracaine 0.5%
- Onset of action 15-30 minutes
- Duration 45-60 minutes
- Applied to simple lacerations in children > 6 months of age
- Contraindicated:
  - Fingers, toes, nostrils, earlobes due to the vasoconstriction action of epinephrine

QUESTIONS

What's New with Bugs & Drugs in 2011

Jim Lewis, Pharm.D., FIDSA
ID Pharmacy Programs Mgr
University Health System &
Clinical Associate Professor
UTHSCSA Division of Infectious Diseases

What We'll Cover

- Gram negatives: Gloom and doom
- MRSA: The king vs new and old drugs
- A few tidbits
  - Antibiotic stewardship
  - Procalcitonin
  - Raging diarrhea

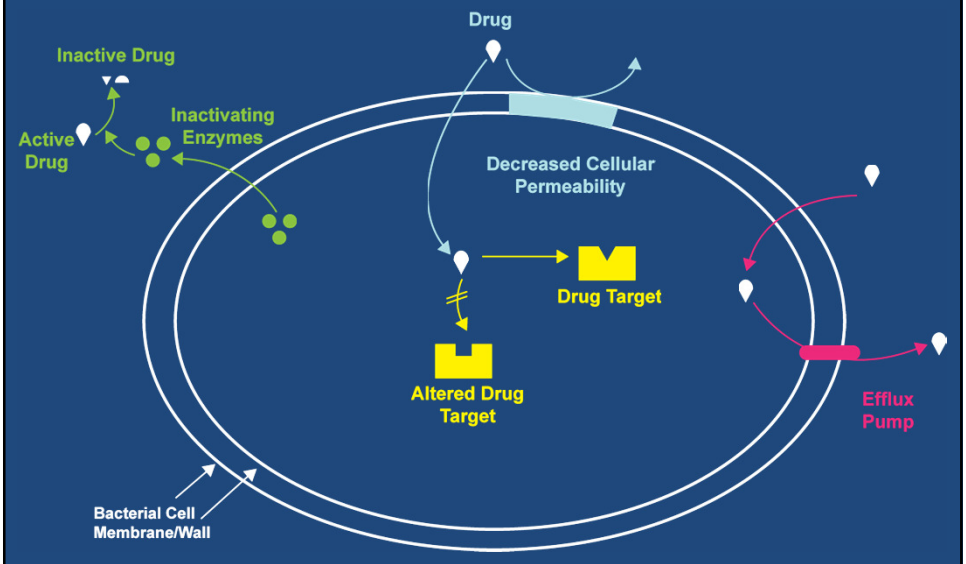
Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis B. Rice,[9,10] Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]

- E = *Enterococcus faecium*
- S = *Staphylococcus aureus*
- K = *Klebsiella pneumoniae*
- A = *Acinetobacter baumanii*
- P = *Pseudomonas aeruginosa*
- E = *Enterobacter species*

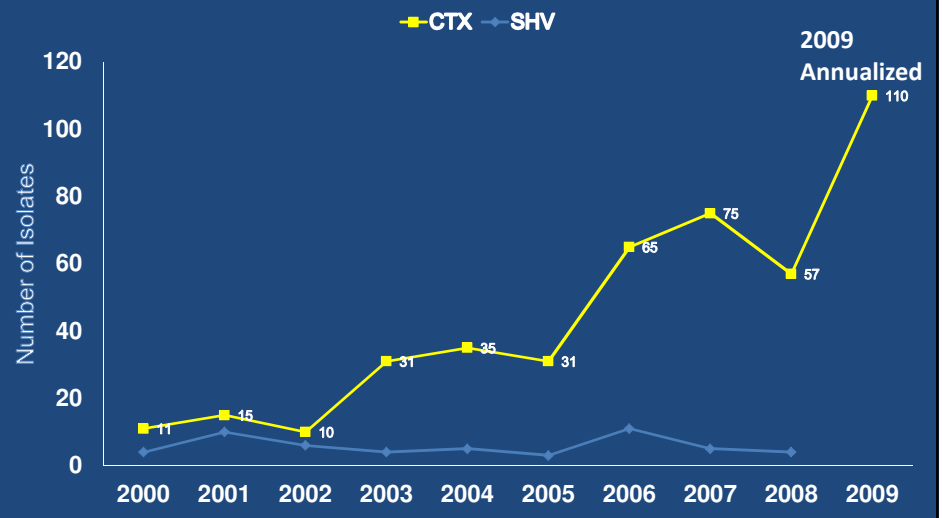
Boucher HW, et al. *Clin Infect Dis* 2009;48:1-12.
Peterson LR. *Clin Infect Dis* 2009;49:992-3.

Mechanisms of Resistance



Nicasio AM, et al. *Pharmacotherapy*. 2008;28:235-249.

Increasing Numbers of CTX-M ESBLs



Lewis JS, et al. *Antimicrob Agents Chemother* 2007;51:4015-21.

All Good Things Happen While Getting your Christmas Tree

- *K. pneumoniae*
  - Meropenem R
  - Cefotaxime R
  - Cefepime R
  - Aztreonam R
  - Pip/Tazo R
  - Cipro R
  - Gent S (2)
  - TMP/SMX R
  - Tigecycline S (1)
  - Amikacin I (32)

AND…

COLISTIN > 16mcg/ml

Did I mention his Scr was 2.8 on admit?

KPC: This is NOT what We're Talking About!

http://www.kfc.com

Carbageddon

- *K. pneumoniae* carbapenemase (KPC) - #1 mechanism of carbapenem (CBP) R among *Enterobacteriaceae (EB)* in the US
- NDM-1 (New Delhi Metallo-β-lactamase): new enzyme →R to CBP and other β-lactam antibiotics among *EB*.
- NDM producing *EB* linked to medical care in India & Pakistan.

Limbago B, et al. ICAAC 2010 Abstract LB C1-675d

New Delhi Metallo - Susceptibility

	UK (n=37)	
	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*
Imipenem	32; 128	0%
Meropenem	32; 32	3%
Piperacillin-tazobactam	>64; >64	0%
Cefotaxime	>256; >256	0%
Ceftazidime	>256; >256	0%
Cefpirome	>64; >64	0%
Aztreonam	>64; >64	11%
Ciprofloxacin	>8; >8	8%
Gentamicin	>32; >32	3%
Tobramycin	>32; >32	0%
Amikacin	>64; >64	0%
Minocycline	16; >32	0%
Tigecycline	1; 4	64%
Colistin	0·5; 8	89%†

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Karthikeyan KK, et al. *Lancet Infect Dis* 2010;10:597-602

Carbageddon 2

- 3 urine isolates from different states, including *K. pneumoniae*, *E.coli* and *Enterobacter cloacae*, were + for bla_{NDM}.
- Pan R: β-lactams including CBPs, FQs, and aminoglycosides.
- 1 isolate was S to tigecycline; MICs for all 3 ≤0.5 ug/ml for colistin.
- All patients had recently traveled to India, 2/3 had inpatient healthcare.
- 3 distinct plasmids in each isolate.
- Isolates are resistant to nearly all available therapeutic agents.

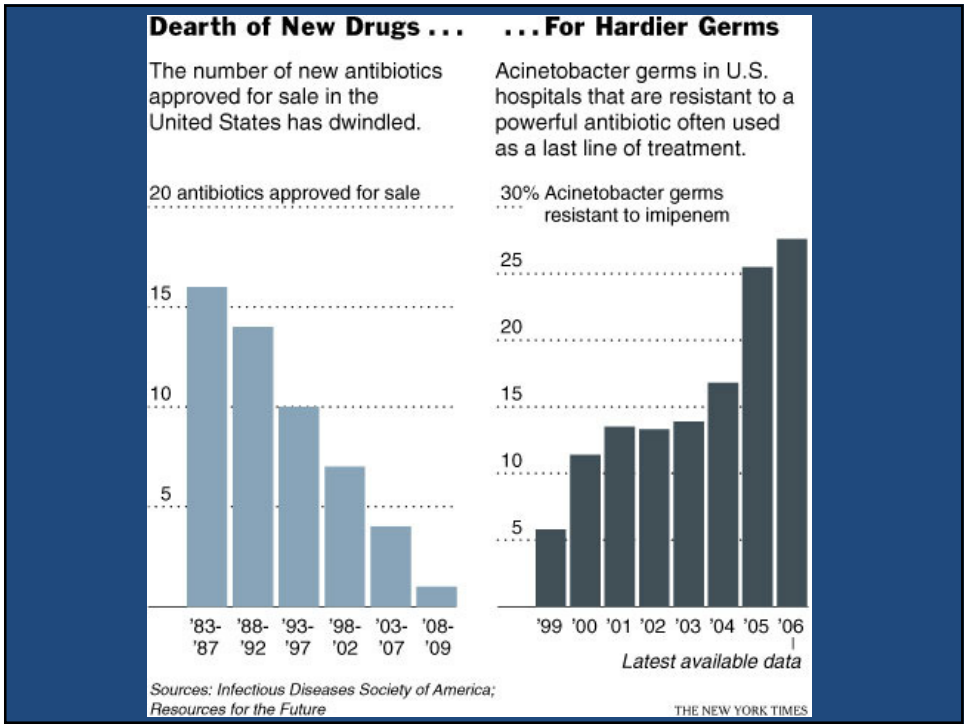
Limbago B, et al. ICAAC 2010 Abstract LB C1-675d

Detection of *Enterobacteriaceae* Isolates Carrying Metallo-Beta-Lactamase --- United States, 2010

MMWR: June 25, 2010 / 59(24);750

Detection of Verona Integron-Encoded Metallo-Beta-Lactamase in *Klebsiella pneumoniae* --- United States, 2010

***MMWR:* Sept 24, 2010 / 59(37);1212**



New Drugs for MDR Gram Negatives

- NXL-104
  - Beta-lactamase inhibitor
  - Inhibits class A and C enzymes
  - Currently in development with ceftaroline & others
- CXA-101
  - Vs carbapenem R *P. aeruginosa* MIC50/90=1/4mcg/ml
  - Primary challenge remained MBLs or unusual ESBLs
  - Currently being developed by Cubist

Juan C, et al. *Antimicrob Agents Chemother* 2010;54:846-51
Moya B, et al. *Antimicrob Agents Chemother* 2010;54:1213-7

Colistin: We Don't Know What We're Doing

- Increasing use due to increasing resistance
- Colistimethate in the pharmacy (aka poly E)
- CMS = Prodrug converted to colistin
- Developed 50 years ago – different standard
- To quote Dr. Graybill…

Garonzik SM, et al. *Antimicrob Agents Chemother* 2011;55:3284-94

The Problem is…

- Equations for CrCl <70ml/min
- Equations for different dialysis modalities
- Good renal function = bad colistin levels
- "not… expected to be reliably efficacious"
- MIC >0.5? Can we get there from here?

Garonzik SM, et al. *Antimicrob Agents Chemother* 2011;55:3284-94

MRSA

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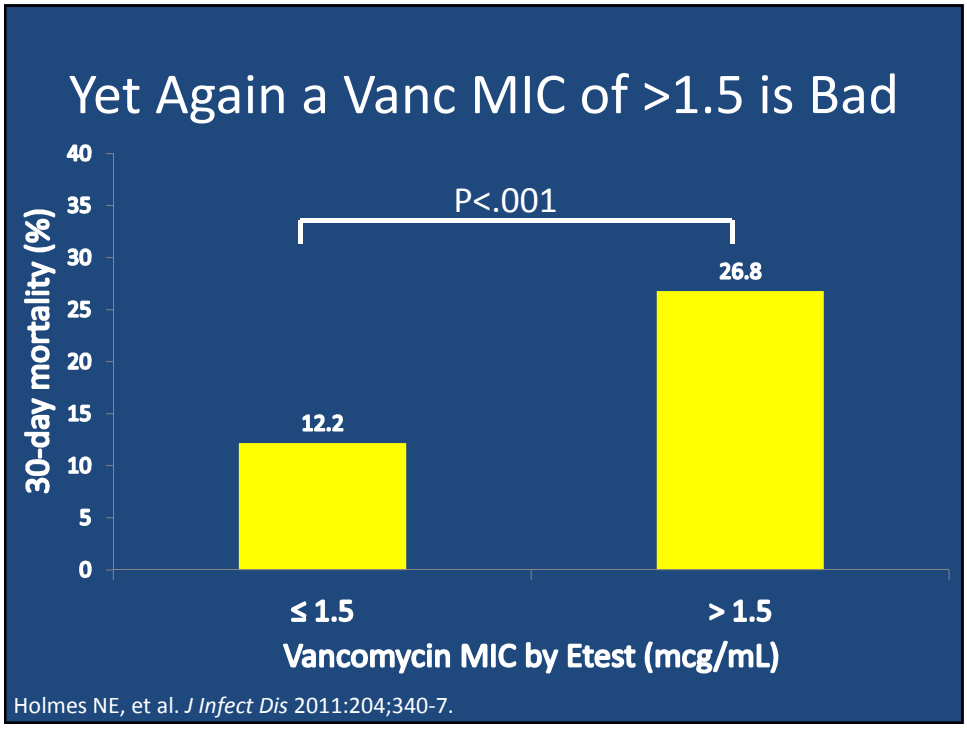
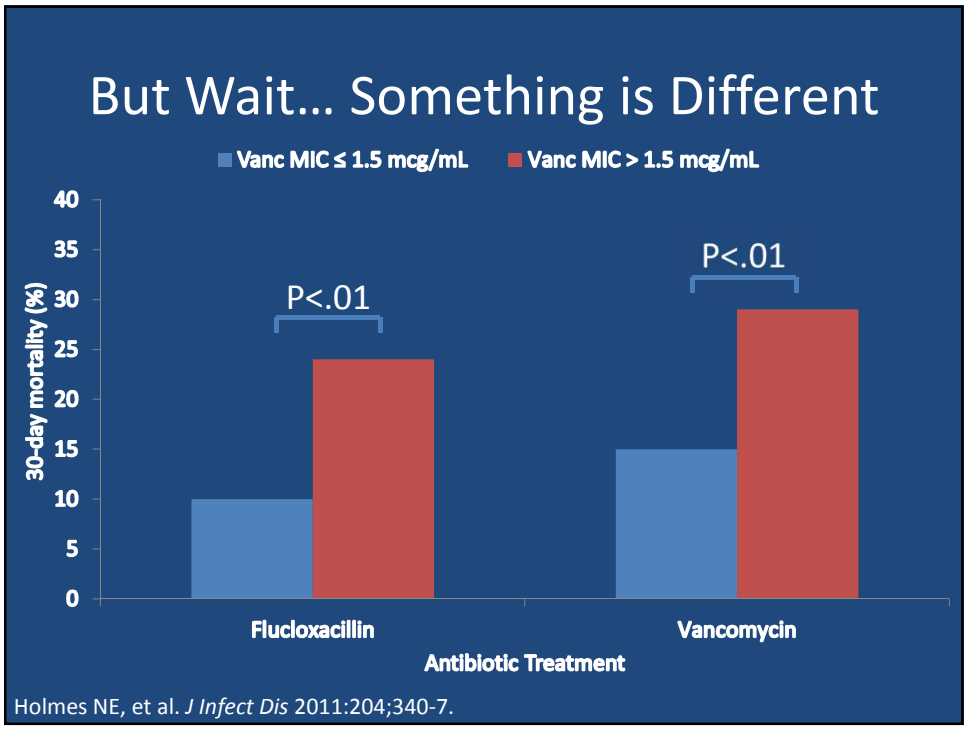
A Whole Bunch of *S. aureus* Bacteremia Patients

- Prospective study from Jan 07-Nov 08
- 8 hospitals in Australia & New Zealand
- 532 patients
- Impact of vancomycin MIC on 30d mortality
- Previous smaller retrospective studies suggest higher vancomycin MIC = worse outcome.

Holmes NE, et al. *J Infect Dis* 2011:204;340-7.



Holmes NE, et al. *J Infect Dis* 2011:204;340-7.



Holmes NE, et al. *J Infect Dis* 2011:204;340-7.

The Take Home

- High vanc MICs (>1.5) for *S. aureus* = problem
- Even in MSSA treated with flucloxacillin!
- So… Vanco AUC/MIC not really the problem?
- Switching based on vanc MIC not necessary?
- Switching usually = Big $$$

Holmes NE, et al. *J Infect Dis* 2011:204;340-7.
Holland TL & Fowler VG. *J Infect Dis* 2011;204:329-31.

"Vancomycin's long reign as first-line therapy for serious MRSA infections may be in its twilight, but there is still no proven heir to the throne."

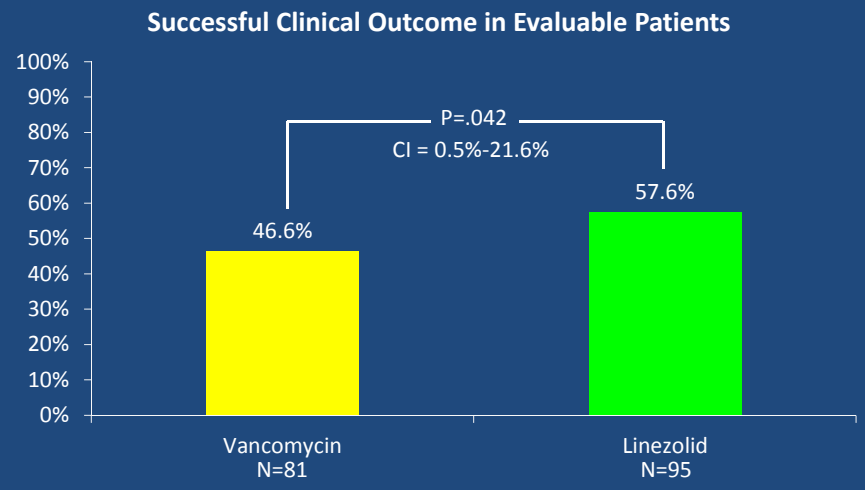
Thomas L. Holland & Vance G. Fowler Jr.
Journal of Infectious Diseases
2011:204;329-31

Linezolid vs Vanco for Culture Proven MRSA Pneumonia

- Phase 4 randomized double blind
- 156 worldwide centers- 90 U.S., 28 E.U.
- 1:1 Randomization
- 1225 patients enrolled over 4 years
- 448 culture positive for MRSA
- 348 patients evaluable, 2/3 on the vent each arm
- Vanco 15mg/kg Q12h vs Linezolid 600mg Q12h

Kunkel M, et al. IDSA 2010 Abstract LB-49
Pfizer Medical Information Request: ZEPHyR trial (1001 Study)

Linezolid vs Vanco for Culture Proven MRSA Pneumonia: Outcomes



Kunkel M, et al. IDSA 2010 Abstract LB-49
Pfizer Medical Information Request: ZEPHyR trial (1001 Study)

Other Information

- Benefit consistent across multiple subgroups
  - Bacteremic pneumonia
  - Patients on the vent
- Vancomycin troughs
  - Day 3 mean = 14, median = 12.3
  - Day 6 mean = 17
- No apparent benefit to higher vanco troughs
- More nephrotoxicity in vanco arm (7.2% vs 3.8%)
- No mortality benefit (17%V vs 15.7%L)

Kunkel M, et al. IDSA 2010 Abstract LB-49
Pfizer Medical Information Request: ZEPHyR trial (1001 Study)

Higher Doses of Daptomycin?

- "Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (B-III)."[1]
- "High-dose daptomycin (10 mg/kg/day), if the isolate is susceptible…"[1]

	Daptomycin SD (≤6mg/kg/d)	Daptomycin HD (>6mg/kg/d)	P-value
Clinical Success	16/22 (73%)	29/31 (94)	0.05
Microbiological Success	13/19 (68)	27/29 (93)	<0.05

**Table adapted from ref 2

1. Liu C, et al. *Clin Infect Dis* 2011;52:1-38.
2. Bassetti M, et al. *Int J of Antimicrob Agents* 2010;36:459–461

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Ceftaroline

- Skin-skin structure infections compared to vancomycin
  - MRSA: n = 152 ceftaroline; n = 122 vancomycin
  - MRSA response rate: 93.4% ceftaroline vs 94.3% vancomycin
- Community-acquired pneumonia
  - 1 case of MRSA
  - MSSA: n = 25 ceftaroline; n = 30 ceftriaxone
  - Response rates for MSSA = ceftriaxone

Corey GR, et al. *Clin Infect Dis.* 2010;51(6):641-650.
File TM, et al. *Clin Infect Dis.* 2010;51(12):1395-1405.

Ceftaroline: Rabbit Model of Endocarditis

Regimen	Mean log_{10} cfu/g of vegetation	# of sterile vegetations/total
Control	8.99 ±0.47	0/10
Ceftaroline 40mg/kg-bid	2.45 ±0.14	10/10
Ceftaroline 20mg/kg-bid	3.14 ±1.38	8/10
Ceftaroline 5mg/kg-bid	5.26 ±2.73	3/9
Teicoplanin 20mg/kg-bid	3.07±0.66	6/10

40 mg/kg bid regimen appears to approximate 600mg BID in humans.
Ceftaroline MIC of isolate used to perform experiment = 1mg/L

Jacqueline C, et al. *J Antimicrob Chemother* 2010;65(10):2264-2265.
Ceftaroline [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc; 2010.

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And Finally…A Few Tidbits

Antibiotic Stewardship: The Elephant in the Room

- Skin and soft tissue infections
- A couple of recent studies
- High volume
- Vanco + Pip/Tazo
- Its not a diabetic foot infection!

Jenkins TC, et al. *Clin Infect Dis* 2010;51:895–903
Jeng, A. et al. *Medicine* 2010;89:217-26

Future Directions - Procalcitonin

- The best thing to happen to antibiotic stewardship in the next 10 years?
- Multiple studies
- Promising results
- A way to shorten lengths of therapy
- Again though… the almighty dollar

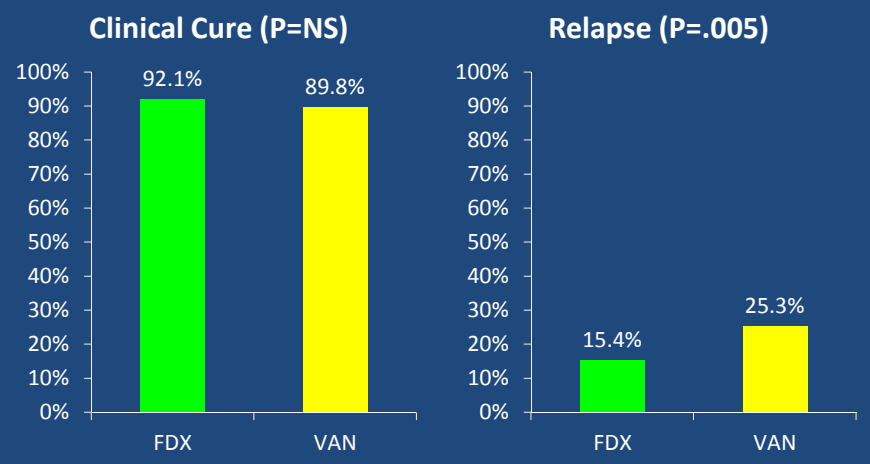
Hayashi Y & Paterson DL. *Clin Infect Dis* 2011;52:1232–40.

Fidaxomicin (FDX) vs Vanco for CDI

- 629 patients
- All patients with symptoms and toxin + stools
- VAN 125mg PO QID or FDX 200mg PO BID X10d
- Primary endpoint = clinical cure
- Secondary endpoints = relapse rates & global cure (clinical cure + no relapse)

Louie T, et al. *NEJM* 2011;364:422-31.

Results



Louie T, et al. *NEJM* 2011;364:422-31.

Why was Fidaxomicin Associated with Fewer Relapses?

- 85 patients serially evaluated during and after TX
- Serial stool cultures on day 4, 10, 14, 21, 28, 42
- Both drugs smashed *C. difficile*
- Vancomycin more damaging to normal gut flora
- Fidaxomicin relatively gut flora sparing
  - 3-4 logs less damage to other gut anaerobes on day 10, 14, 21, and 28

Louie T, et al. IDSA 2010 Abstract 1418

Conclusions

- Gram negatives – pick your SSRI and hang on tight
- MRSA – New drugs, new options, continued challenges
- Stewardship opportunities abound
- C. diff – fewer relapses but…

Texas Society of Health-System Pharmacists

Texas Legislative Update on Pharmacy Issues

The 2011 Texas Legislative Session

★

The Pharmacy Agenda

Texas Society of Health-System Pharmacists

Who Represents Pharmacy in Texas

✓Texas Society of Health System Pharmacists

✓Texas Federation of Drug Stores

✓Texas Pharmacy Association

(Texas Pharmacy Business Council)

Texas Society of Health-System Pharmacists

Texas Pharmacy Practice Coalition "Shoulder-to-Shoulder"

Texas Society of Health-System Pharmacists

2011 Legislative Update From the institutional view….

Shields Legislative Associates

Texas Society of Health-System Pharmacists

The Big Ticket Items….

- ✓Huge Budget Shortfall
- ✓ 38 New Legislators
- ✓ Redistricting

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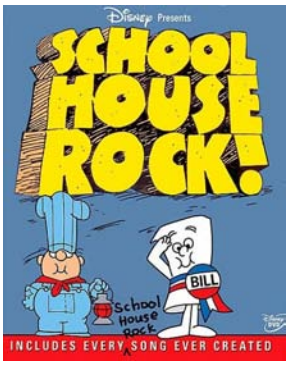
The Legislature is in Session….



The BIG Pharmacy Issues for 2011 were….

Texas Society of Health-System Pharmacists

For retail pharmacy its all about $$$$….

Medicaid

- ✓ Medicaid Managed Care
- ✓ Dispensing Fee Cuts
- ✓ Actual Acquisition Costs

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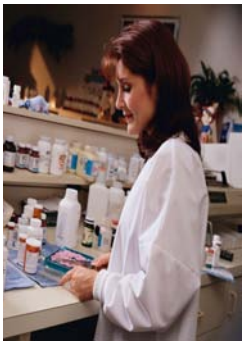
Pharmacy Practice Issues….



- ✓ Doctor Dispensing
  - SB 546 – Dispensing of all drugs
  - HB 915 – ANP's dispensing
  - SB 1750 – PA's Sch. II in Hospitals
  - SB 1081 – Derm's aesthetic drugs

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Pharmacy Practice Issues….

- ✓ Prescription Monitoring Program
  - SB 1273 – Eliminate DPS# + NPI
- ✓ Immunizations by RPh
  - HB 2666 – Middle School Age
- ✓ Accelerated Refills
  - HB 2096 – 90 day for maintenance drugs

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Pharmacy Practice Issues….

- ✓ Generic Drug Substitution
  - SB 1756 – Can't sub. "tamper resistent"
- ✓ E-Prescribing
  - SB 594 – Sch. II's – like federal rules
- ✓ Photo ID for Control. Substances
  - HB 3041 – Pain clinic problems

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Pharmacy Practice Issues….

- ✓ Privacy of Patient Information
  - SB 622 – Broader than HIPAA
- ✓ Pharmacy Tech. on TSBP
  - SB 1262 – Adds 1 Tech & 1 Public
- ✓ Consolidation of Health Bds.
  - HB 4326 – Umbrella Licensing Board

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Texas State Board of Pharmacy...

- ✓ No-Show Issues….
  - Pharmacist service in small hospitals
  - Legal Immigration status
  - Legible prescriptions – Medical errors
  - Pharmacist - relief services
  - Technician training
  - Display of Pharmacists license

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Chain Pharmacy Issues…

✓More No-Shows

- Drug take-back programs
- Eliminate Technician Ratios

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Time to invest in your profession…

The most regulated profession on Earth… is under attack

Get involved NOW !!!

Texas Society of Health-System Pharmacists

2012 Election Update






** Plus 4 new Congressional Seats…

Texas Society of Health-System Pharmacists

The Domino Effect….

….. Movin on up !!!

- *Perry → Pres, VP*
- *Dewhurst → U.S. Senate*
- *Abbott, Patterson, Combs → Lt. Gov.*
- *6 House members → Texas Senate*
- *5 House members → Congress*

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Next November…. ???

Will Texans Still be looking for "More Change"

Texas Society of Health-System Pharmacists

This Time Next Year….

…Imagine the number of new legislators

OMG !!! – As of today

3-6 new State Senators

and

22 – 36 New House Members

New Drug Update

Leroy C. Knodel, Pharm.D.
Associate Professor, Department of Surgery
UT Health Science Center San Antonio
Clinical Associate Professor
College of Pharmacy, UT Austin

"This is a test. For the next 60 seconds, this presenter will conduct a test of the Audience Response System. This is only a test."

- **Which of the following drugs will NOT come off patent between now and the end of 2012?**

A. Viagra
B. Lipitor
C. Lexapro
D. Singulair
E. Plavix
F. Provigil
G. Zyprexa

"This is a test. For the next 60 seconds, this presenter will conduct a test of the Audience Response System. This is only a test."

- **Which of the following drugs will NOT come off patent between now and the end of 2012?**

Viagra

NOTE: One of the original patents for Viagra is set to expire in 2012, but in a recent court ruling against Teva, generic versions of Viagra cannot be marketed until 2019

Other Notable Drugs with Patent Expirations in 2012

(U.S. sales > $250 million/year)

- **Levaquin®**
- **Avapro®**
- **Avalide®**
- **Seroquel®**
- **Avandia®**
- **Clarinex®**
- **Lunesta®**
- **Lovenox®**
- **Diovan®**
- **Geodon®**

Ticagrelor (Brilinta®) – AstraZeneca

Major Summary Points

- **INDICATION – reduction of thrombotic cardiovascular events in pts with ACS**
  - Non-ST elevation and ST elevation MI
  - Unstable angina
- **Studied in combination with aspirin; ASA doses > 100 mg decrease efficacy**
- **FDA Advisory Committee recommended approval in July, 2010**

Acute Coronary Syndrome

- **Affects more than 1.4 Americans annually**
- **Comprised of heart attacks & unstable angina**
- **Usually due to coronary artery disease**
- **In the U.S., it is estimated that in 2009**
  - 785,000 people will have a new MI
  - 470,000 people will have a recurrent MI

Percutaneous Coronary Intervention (PCI)

- **Use to treat stenotic coronary arteries; less invasive than coronary artery bypass surgery (CABG)**
  - CABG superior in multi-vessel disease
- **Procedure**
  - Inflation of balloon within the stenotic artery
  - Usually performed in concert with other procedures such as the placement of stents
- **PCI with stents - ↓ symptoms of CAD, ↓ cardiac ischemia**
  - ↓ mortality due to CAD primarily in patients treated for acute heart attack (vs. thrombolytics)

Myocardial Infarction

- **Classification of MIs based on ECG**
  - ST-elevation MI (STEMI)
    - Usually complete occlusion of coronary artery
    - Treatment: PCI/stent insertion or thrombolytics
  - Non-ST-elevation MI (NSTEMI)
    - Usually a sudden narrowing of coronary artery
    - Treatment: anticoagulants & antiplatelet agents; PCI commonly performed at some point during hospitalization

Ticagrelor – Major Summary Points

- **Antiplatelet agent that acts on $P2Y_{12}$ class of ADP receptors on platelets**
- **Platelet Inhibition and Patient Outcomes (PLATO) trial**
  - 18,624 patients randomized; 43 countries including the U.S. (< 8% of subjects from U.S.)
  - **Results** discordant for U.S. and non-U.S. subjects (greater use of high-dose ASA in U.S. subjects compared to low-dose ASA use in rest of world???) --- "North American Anomaly"

Ticagrelor – Major Summary Points

- **PLATO Trial – ASA Use by Subjects**

	ASA > 100 mg	ASA > 300 mg
U.S. Participants	57%	54%
Non-U.S. Participants	8%	2%

PLATO Trial Results

	Ticagrelor versus Clopidogrel
CV death, MI, or Stroke	16% reduction
MI	16% reduction
CV Death	21% reduction
Stroke	Non-Significant Difference
Life-Threatening Bleeding	Non-Significant Difference

Ticagrelor – Major Summary Points

- **Black box warning**
  - Like other antiplatelet agents, can cause significant, sometimes fatal, bleeding
  - Doses of ASA > 100 mg ↓ effectiveness & should be avoided; use with ASA 75-100 mg/day

Ticagrelor – Major Summary Points

- **Most AEs not significantly different from clopidogrel**
- **Dyspnea (13.8% vs. 7.8% for clopidogrel)**
  - Including exertional dyspnea, dyspnea at rest, nocturnal dyspnea, paroxysmal nocturnal dyspnea
  - Mild-to-moderate
  - Generally resolves with continued treatment

Ticagrelor – Major Summary Points

- **Drug interactions**
  - Ticagrelor is metabolized by CYP3A4 (primarily) and to a lesser extent by CYP3A5; avoid use with
    - Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin)
    - Strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, dexamethasone)

Ticagrelor – Major Summary Points

- **Drug interactions**
  - Ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of P-gp transporter
    - ↑ simvastatin and lovastatin concentrations
    - Do NOT exceed 40 mg/day of either statin
- **Dosage & administration**
  - Initial dose/loading dose
    - 180 mg (two 90 mg tablets) as a loading dose PLUS aspirin (usually 325 mg) as a loading dose
  - Maintenance dose
    - 90 mg twice daily PLUS aspirin 75-100 mg daily

Comparison of Clopidogrel, Prasugrel, & Ticagrelor

	Plavix® Clopidogrel	Effient® Prasugrel	Brilinta® Ticagrelor
Prodrug	Yes	Yes	No
Platelet Inhibition	Irreversible	Irreversible	Reversible
Dosing Frequency	Once daily	Once daily	Twice daily
Fatal & Life-threat-ening Bleeding	+	++	+
ASA Dosage Recommendation	75-325 mg	75-325 mg	75-100 mg

Audience Response Time

- Should the FDA have approved Brilinta®, without requiring AstraZeneca to perform a postmarketing study to prove that it actually works in Americans?

A. _ell NO! What idiot would approve a drug before it is proven to be effective in the people who will be using it?

B. YES! It would be "brilliant" decision and not that inconsistent with other decisions sometimes coming out of Washington D.C.

C. I really don't know, but would be interested in what Lindsay Lohan thinks, since she is out of jail now

Dabigatran Etexilate (Pradaxa® – BI)

Major Summary Points

- **INDICATION – to ↓ the risk of thrombo-embolic stroke & systemic embolism in patients with non-valvular atrial fibrillation**
- **Available in Canada since 2008 for prevention of thromboembolism in patients undergoing hip or knee replacement**

Atrial Fibrillation

- **Most common cardiac arrhythmia**
- **Frequently becomes chronic and associated with small ↑ in risk of death**
- **Depending on presence of other risk factors, risk of stroke can be 7X greater in AF patients**
- **Non-valvular atrial fibrillation**
  - Seen in 5% of persons over age of 65
  - Seen in 10% of persons over age of 75
- **Frequently asymptomatic, but can cause dizziness, fainting, chest pain, and CHF**

Dabigatran – Major Summary Points

- **Competitive, direct thrombin (factor IIa) inhibitor**
  - Inhibits clot-bound thrombin
  - Inhibits circulating thrombin
  - ↓ thrombin-stimulated platelet aggregation
- **Advantages over warfarin**
  - Anticoagulant effect is less variable
  - Monitoring is not required
- **Disadvantages compared to warfarin**
  - No antidote, but is dialyzable

Dabigatran – Major Summary Points (cont)

- **Prodrug - rapid oral absorption on empty stomach; peak serum concentrations:**
  - 1 hour (fasting)
  - 3 hours (high fat meal)
- **No hepatic metabolism; eliminated primarily in urine**
- **Half-life is approximately 12-17 hours**

Dabigatran – Major Summary Points (cont)

- **RELY Trial**
  - 18,113 AF patients (mean age 71) at risk of stroke
  - Treated for median of 2 years with dabigatran (110 or 150 mg BID) or warfarin (INR of 2-3)
  - About 20% of patients on ASA

Stroke or Systemic Embolism (per year)

Warfarin	Dabigatran 110 mg	Dabigatran 150 mg
1.71%*	1.54%	1.11%*

Dabigatran – Major Summary Points (cont)

- **Adverse effects**
  - Bleeding (17%)
  - Major bleeding (RELY Trial)

Warfarin	Dabigatran 110 mg	Dabigatran 150 mg
3.57%*	2.87%*	3.32%

  - Management of bleeding
    - No antidote
    - Fresh frozen plasma, red blood cells, etc.
    - Hemodialysis

Dabigatran – Major Summary Points (cont)

- **Adverse effects (cont)**
  - **Hemorrhagic stroke (RELY Trial)**

Warfarin	Dabigatran 110 mg	Dabigatran 150 mg
0.38%*	0.10%*	0.12%*

  - **Gastrointestinal**
    - Risk of major GI bleeding significantly higher with dabigatran vs. warfarin (1.6% vs. 1.1%)
    - Dyspepsia and gastritis
      - Take with food
      - H2-receptor antagonist or PPI

Dabigatran – Major Summary Points (cont)

- **Adverse effects – bleeding events (per 100 patient-years) in RELY Trial**
  - Intracranial hemorrhage – 0.3 (vs. 0.8 with warfarin)*
  - Life-threatening bleed – 1.5 (vs. 1.9 with warfarin)*
  - Major bleed – 3.4 (vs. 3.6 with warfarin)
  - Any bleed – 16.6 (vs. 18.4 with warfarin)*
- **Discontinuation rates associated with AEs**
  - Dabigatran – 21%
  - Warfarin – 16%

Dabigatran – Adverse Effects (cont)

- **Drug interactions**
  - Dabigatran is a substrate for p-glycoprotein (P-gp) transporter
    - P-gp inducers (e.g., rifampin, St John's wort)
      - ↓ dabigatran concentrations
      - Avoid concomitant use
    - P-gp inhibitors (e.g. ketoconazole, clarithromycin)
      - ↑ dabigatran concentrations
      - No dosage adjustment required
  - Precaution - medications that ↑ bleeding risk (e.g., antiplatelet agents, chronic NSAID use , heparin)

Dabigatran – Major Summary Points (cont)

- **Dosage – based on renal function**
  - CrCl > 30 mL/min – 150 mg BID
  - CrCl 15-30 mL/min – 75 mg BID
- **Take with food or on empty stomach**
- **Missed dose – take as soon as possible unless it is less than 6 hrs before next dose**
- **Capsules – do not chew, crush or empty**
- **Keep in original container; capsules must be used within 60 days after opening***

*FDA. Pradaxa (dabigatran etexilate mesylate) capsules: Special storage and handling requirements. March 29, 2011). http://www.fda.gov/Drugs/DrugSafety/ucm248746.htm

Dabigatran – Major Summary Points (cont)

- **Conversion from warfarin**
  - Stop warfarin
  - When INR is < 2, start dabigatran
- **Guidelines provided in the PI for**
  - Conversion from dabigatran to warfarin
  - Switching from dabigatran to parenteral anticoagulant
  - Switching from parenteral anticoagulant to dabigatran
- **Patients having surgery/invasive procedures**
  - CrCl ≥ 50 mL/min – d/c dabigatran 2 days prior
  - CrCl < 50 mL/min – d/c dabigatran 3-5 days prior

Dabigatran – Miscellaneous Considerations

- **Warfarin underused in clinical practice**
  - INR monitoring & dose adjustments
  - Drug-drug and drug-food interactions
- **Dabigatran**
  - Reaches steady-state in 2-3 days
  - Fixed doses, but requires BID dosing
  - No antidote for quick or temporary reversal
  - Higher rate of GI bleeding compared to warfarin
  - Long-term safety data not available
  - Combination therapy with antiplatelet agents
  - Cost-effectiveness data

Audience Response Time

Which of the following is FALSE regarding dabigatran (Pradaxa®)?

A. Monitoring is not required
B. Initial dosage is based on renal function
C. Is more effective than warfarin in preventing thromboembolic stroke in patients with non-valvular atrial fibrillation
D. Has a higher discontinuation rate than warfarin
E. Is more likely to cause life-threatening bleeding than warfarin

Audience Response Time

Which of the following is FALSE regarding dabigatran (Pradaxa®)?

A. Monitoring is not required
B. Initial dosage is based on renal function
C. Is more effective than warfarin in preventing thromboembolic stroke in patients with non-valvular atrial fibrillation
D. Has a higher discontinuation rate than warfarin
E. Is more likely to cause life-threatening bleeding than warfarin

Rivaroxaban (Xarelto® – Janssen)

Major Summary Points

- **INDICATION – prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery**
- **Future indications**
  - prevention of stroke and systemic embolism in non-valvular atrial fibrillation (at FDA)
  - treatment and long-term prevention of venous thromboembolism
  - secondary prevention of cardiovascular events in patients with acute coronary syndrome

Rivaroxaban – Major Summary Points

- **Once-daily, factor Xa inhibitor**
- **Second oral anticoagulant approved by FDA in last 9 months**
  - Dabigatran(Pradaxa®) Indication
    - to ↓ the risk of thromboembolic stroke & systemic embolism in patients with non-valvular atrial AF
  - Rivaroxaban Indication
    - prophylaxis of DVT which may lead to PE in patients undergoing knee or hip replacement

Rivaroxaban – Major Summary Points

- **Primary competition is enoxaparin (Lovenox®)**
  - Superior efficacy in hip/knee replacement
  - Bleeding rates not significantly different
  - Oral versus subcutaneous injection
    - Improved compliance???
- **Atrial fibrillation (off-label)**

	Efficacy*	Bleeding*
Rivaroxaban	Same (?)	Same (?)
Dabigatran	Superior	Similar
Apixaban	Superior	Less

*Compared to warfarin

Rivaroxaban – Major Summary Points

RECORD 1 Trial – Total Hip Replacement

	Rivaroxaban	Enoxaparin
Total VTEs	1.1%	3.9%
Major VTEs	0.2%	2.1%

RECORD 2 Trial – Total Hip Replacement

	Rivaroxaban	Enoxaparin
Total VTEs	2%	8.4%
Major VTEs	0.7%	4.8%

Rivaroxaban – Major Summary Points

RECORD 3 Trial – Total Knee Replacement

	Rivaroxaban	Enoxaparin
Total VTEs	9.7%	18.8%
Major VTEs	1.0%	2.5%

Rivaroxaban – Major Summary Points

- **Metabolized via CYP3A4/5 & CYP2J2; also by hydrolysis**
- **Drug interactions**
  - Combined P-gp & strong CYP3A4 inhibitors

	Rivaroxaban AUC	Rivaroxaban Cmax
Ketoconazole	↑ 160%	↑ 70%
Ritonavir	↑ 150%	↑ 60%

Avoid use with **strong** CYP3A4 inhibitors; moderate inhibitors do not appear to significantly ↑ risk of bleeding

Rivaroxaban – Major Summary Points

- **Drug interactions**
  - Renal impairment **PLUS** combined P-gp & weak or moderate CYP3A4 inhibitors
    - Examples - erythromycin, azithromycin, diltiazem, verapamil, quinidine, amiodarone, felodipine
    - ↑ risk of bleeding
    - **"use Xarelto® in this situation only if the potential benefit justifies the potential risk"**

Rivaroxaban – Major Summary Points

- **Drug interactions**
  - Combined P-gp & strong CYP3A4 inducers
    - Examples – rifampicin, carbamazepine, phenytoin, rifampin, St. John's wort
    - ↓ rivaroxaban efficacy
    - Consider increasing rivaroxaban dose

Rivaroxaban – Major Summary Points

- **Drug interactions**
  - Anticoagulants - ↑ risk of bleeding
    - avoid concomitant administration
  - NSAIDs/Aspirin
    - Risk of bleeding may be ↑
    - Patients treated with the combination should be assessed for signs/symptoms of blood loss
  - Clopidogrel - ↑ risk of bleeding
    - Avoid concomitant use unless benefit outweighs the ↑ bleeding risk

Rivaroxaban – Major Summary Points

- **Dosage and Administration**
  - 10 mg once daily (with or without food)
  - Total hip replacement
    - Recommended duration of treatment – 35 days
  - Total knee replacement
    - Recommended duration of treatment – 12 days
  - GI feeding tubes
    - Crushed tablet can be given via feeding tube
    - Confirm gastric placement of feeding tube

Fidaxomicin (Dificid® – Optimer)

Major Summary Points

- **INDICATION – treatment of *Clostridium difficile*-associated diarrhea in adults**
- **Company assessing whether prophylaxis is a viable marketplace for fidaxomicin**
- **Macrolide antibacterial with minimal systemic absorption**
  - No known drug interactions
  - Most common AEs are GI (e.g., nausea, vomiting)

Clostridium difficile

- **Anaerobic gram-positive bacteria**
- **Is rampant in hospitals & nursing homes**
- **Spreads mainly from unwashed hands to a variety of surfaces (bed rails, remote controls, sinks, telephones, stethoscopes)**
- **Produces spores that can persist for weeks or months on virtually any surface**
- **Spores are resistant to killing by alcohol**
- **Produces toxins that attack intestinal lining**

Clostridium difficile Infection

- **Most common hospital-acquired diarrhea**
- **Infects 500,000 people in the U.S. each year**
  - 30,000 deaths; up to 1% must have colectomy
- **Accounts for 15%-20% of antibiotic-associated diarrhea cases**
- **Up to 25% of diarrhea cases respond to d/c of antibiotic therapy alone**
- **Concerns**
  - Incidence of CD diarrhea rising
  - Newer, more virulent strains being seen

Clostridium difficile Infection (cont)

- **Risk factors for infection**
  - Recent broad spectrum antibiotic use, multiple antibiotic use, or prolonged antibiotic use
  - 65 years of age or older
  - Current or recent hospitalization
  - Resident of nursing home
  - Serious underlying disease states or compromised immune system
  - Abdominal surgery or GI procedure
  - Colon diseases (inflammatory bowel disease)
  - Previous *C. difficile* infection

Clostridium difficile Infection (cont)

- **Complications**
  - Dehydration
  - Kidney failure
  - Bowel perforation
  - Toxic megacolon
  - Death
- **Treatment**
  - Mild to moderate infection - metronidazole
  - More severe symptoms - vancomycin
  - Probiotics (e.g., *Saccharomyces boulardii*)
  - Surgery

Fidaxomicin – Major Summary Points (cont)

- **Clinical trials resulting in FDA approval**

Clinical Response Rates at the End of Therapy

	Trial 1	Trial 2
Fidaxomicin	88%	88%
Vancomycin	86%	87%

Sustained Response Rates at 25 Days Post-Therapy

	Trial 1	Trial 2
Fidaxomicin	70%	72%
Vancomycin	57%	57%

Fidaxomicin – Major Summary Points (cont)

- **Dosage and Administration**
  - 200 mg twice daily for 10 days (~ $2,800)
- **Cost of standard vancomycin dosage regimen for C. difficile is ~$1000-$1500**
- **Issue: Should fidaxomicin replace vancomycin as first-line therapy for severe cases of *C. difficile*-associated diarrhea?**

Linagliptin (Tradjenta® – BI & Lilly)

Major Summary Points

- **INDICATION – adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus**
  - Monotherapy or combination therapy
- **Dipetidyl peptidase-4 (DPP-4) inhibitor (works only when blood glucose is elevated)**
  - ↑ insulin secretion (beta cells of pancreas)
  - ↓ hepatic glucose production (alpha and beta cells)

Comparison with Sitagliptin (Januvia®) and Saxagliptin (Onglyza®)

- **Efficacy in ↓ A1C appears similar (~ 0.6-0.8%)**
  - Other agents (i.e., metformin, glitazones, insulin, and sulfonylureas) are more effective in lowering A1C
- **More likely to be used in combination therapy**
- **NOT associated with weight gain**
- **Only 1 dosage strength – no dosage modification required in renal impairment**
- **Saxagliptin has more drug interactions (CYP 3A4/5) than either sitagliptin or linagliptin**

Linagliptin – Major Summary Points (cont)

- **Majority of linagliptin (~ 90%) is excreted unchanged**
- **Drug Interactions**
  - Strong inducers of P-glycoprotein or CYP3A4 enzymes MAY ↓ linagliptin efficacy
  - Rifampin - ↓ linagliptin concentrations

Linagliptin – Major Summary Points (cont)

- **Dosage and administration**
  - Recommended dose – 5 mg once daily (with or without food)
  - NO dosage modification required in renal or hepatic impairment

Roflumilast (Daliresp® – Forest)

Major Summary Points

- **INDICATION – treatment to ↓ the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis & a history of exacerbations**
- **MOA – orally administered selective phosphodiesterase-4 (PDE4) inhibitor**
  - antiinflammatory effects (NOT a bronchodilator)

Chronic Obstructive Pulmonary Disease

- **12 million in the U.S. have the diagnosis; 4th leading cause of death**
- **Primary forms:**
  - Chronic bronchitis (long-term cough with mucus)
  - Emphysema
- **Common symptoms: cough, dyspnea, fatigue, frequent respiratory infections, wheezing**
- **Treatment**
  - Inhaled bronchodilators
  - Inhaled steroids
  - Antibiotics during exacerbations
  - Oxygen

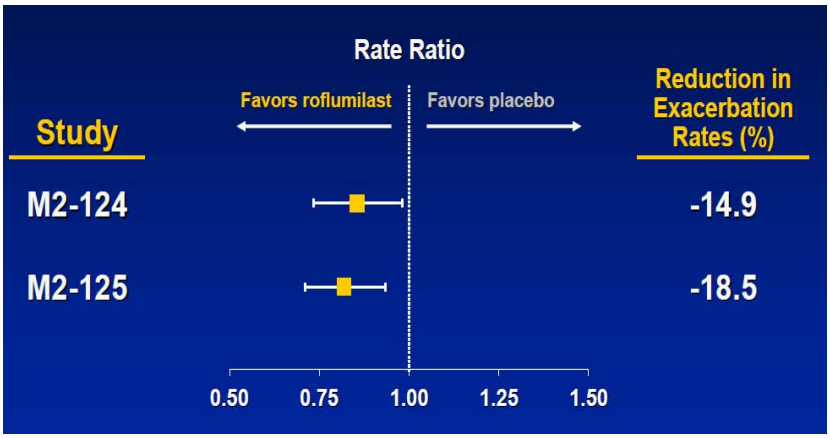
Roflumilast – Major Summary Points

- **Metabolism**
  - Metabolized to roflumilast N-oxide by CYP3A4 & CYP1A2
  - Both parent and metabolite are active
- **Drug Interactions**
  - Strong **CYP3A4 & CYP1A2 inducers** (e.g., rifampicin, carbamazepine, phenytoin) may ↓ therapeutic effectiveness
  - Strong **CYP3A4 inhibitors** or **dual inhibitors of CYP3A4 & CYP1A2** (e.g., erythromycin, ketoconazole, fluvox-amine, cimetidine) may ↑ roflumilast concentrations and may ↑ adverse reactions

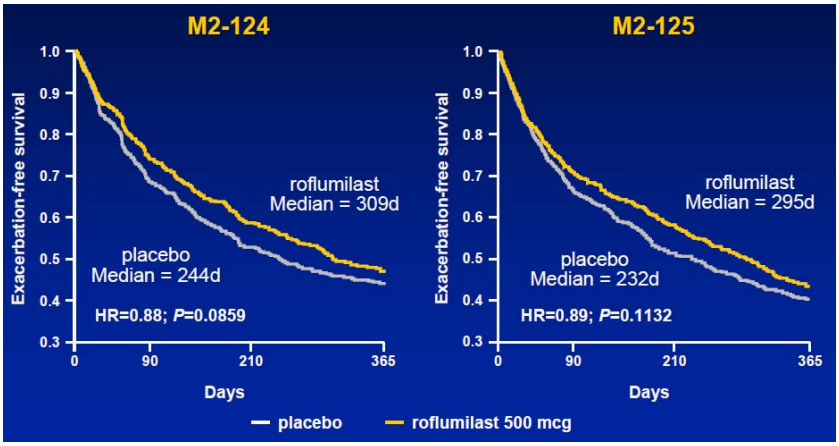
Roflumilast – Major Summary Points

- **Approval based on two Phase 3 clinical studies**
  - > 1,500 patients with COPD associated with chronic bronchitis who had experienced at least 1 exacerbation in previous 12 months
- **Used primarily as add-on therapy (combination with inhaled corticosteroids, short-acting beta-agonists, short-and long-acting anti-muscarinics) in most trials**
- **Current therapies - 4-25% ↓ in exacerbations**
- **Efficacy**
  - **Improving FEV1** – less than with tiotropium or salmeterol plus fluticasone (???)
  - **Preventing Exacerbations** – better than salmeterol, fluticasone, and tiotropium (???)

Reduction in Rate of Moderate or Severe Exacerbation



Time to First Moderate or Severe Exacerbation



Roflumilast – Major Summary Points

- **Approved by FDA despite Advisory Committee vote of 10 to 5 against approval**
  - Concerns about AEs and modest ↑ in lung function

	Roflumilast (%)	Placebo
Diarrhea	9.5	2.7
Weight Loss	7.5	2.1
Nausea	4.7	1.4
Headache	4.4	2.1
Back Pain	3.2	2.2
Insomnia	2.4	1.0
Dizziness	2.1	1.1
Decreased Appetite	2.1	0.4

Roflumilast – Major Summary Points

- **Psychiatric AEs (insomnia, anxiety, depression)**
  - Roflumilast (5.9%)
  - Placebo (3.3%)
- **Suicidal ideation and behavior reported**
- **High discontinuation rate**
  - Roflumilast (14.8%)
  - Placebo (9.9%)

Roflumilast – Major Summary Points

- **Weight Loss (overall)**
  - Roflumilast (7.5%)
  - Placebo (2.1%)
- **Moderate Weight Loss (5-10% of body weight)**
  - Roflumilast (20%)
  - Placebo (7%)
- **Severe Weight Loss (>10% of body weight)**
  - Roflumilast (7%)
  - Placebo (2%)

Roflumilast – Major Summary Points

- **Contraindicated in moderate to severe hepatic impairment**
- **NOT a bronchodilator – do not use for treating acute bronchospasm**
- **Dosage and administration**
  - 500 mcg tablet once daily (with or without food)

Audience Response Time

Which of the following is TRUE regarding roflumilast in the treatment of COPD?

A. It is a potent bronchodilator and anti-inflammatory

B. It is more effective than salmeterol plus fluticasone in improving FEV1

C. It is most commonly used as monotherapy

D. Is reported to cause weight loss in 7.5% of treated patients

Audience Response Time

Which of the following is TRUE regarding roflumilast in the treatment of COPD?

A. **It is a potent bronchodilator and anti-inflammatory**

B. **It is more effective than salmeterol plus fluticasone in improving FEV1**

C. **It is most commonly used as monotherapy**

D. **Is reported to cause weight loss in 7.5% of treated patients**

Ipilimumab (Yervoy® – Bristol-Myers Squibb)

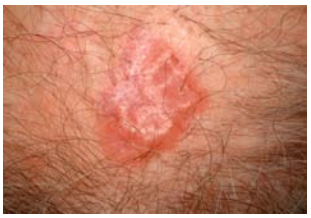
Major Summary Points

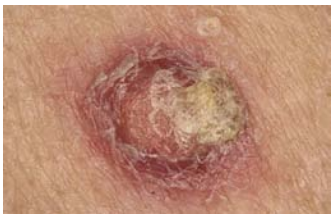
- **INDICATION – treatment of unresectable or metastatic melanoma**
- **MOA – recombinant, human monoclonal antibody**
  - Targeted T cell antibody
  - Shown to augment T-cell activation & prolif-eration, resulting in antitumor immune responses
- **Activity is NOT specific against particular tumor**

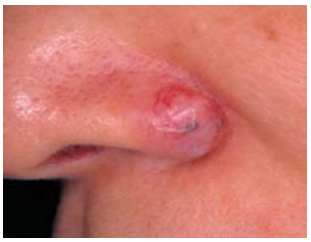
Melanoma

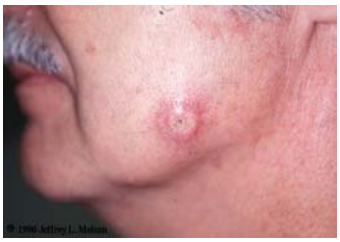
- 3rd most common skin cancer behind basal cell and squamous cell
- Develops in the melanocytes of the skin
- 6th most common cancer in U.S.; responsible for 75% of all skin cancer deaths
- Number of cases in U.S. ↑ faster than any other cancer
- Median age at diagnosis 59 years
- Usually starts as single lesion and can spread via lymph nodes throughout body

Basal Cell & Squamous Skin Cancer





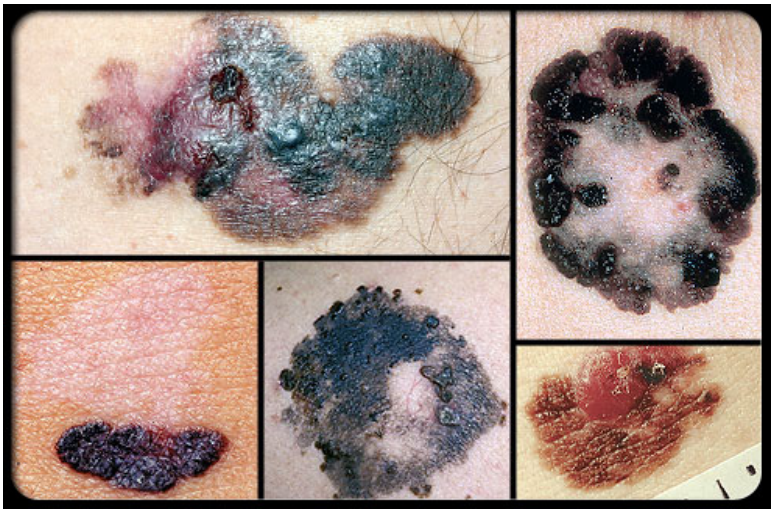




Basal Cell Skin Cancer

Squamous Skin Cancer

Malignant Melanoma



Melanoma

- **Five-Year Survival**
  - Localized to skin(98%)
  - Spread only to lymph nodes (65%)
  - Spread to other organs (15%)
- **Racial Disparity (cases per 100,000 males)**
  - Whites (27)
  - Hispanics (4.5)
  - American Indians/Alaska Natives (4.1)
  - African Americans (1)

Ipilimumab – Major Summary Points (cont)

- **Primary clinical trial used for FDA approval**
  - 676 patients with unresectable or metastatic melanoma previously treated

	Median Survival (months)
Ipilimumab 3 mg/kg + gp 100 vaccine	10
Ipilimumab 3 mg/kg	10.1
gp 100 vaccine	6.4

Hodi FS, et al. N Engl J Med 2010;363:779-81.

Ipilimumab – Major Summary Points (cont)

- **Warnings/Precautions**
  - Severe and fatal immune-mediated reactions are reported (12.9% of treated patients)

Enterocolitis	Dermatitis
Neuropathies	Endocrinopathies
Hepatitis	

  - Grade 3 or 4 reactions seen in 10-15%
    - Required drug d/c and steroids
    - Not all patients responded
    - In some pts, improvement not seen for several wks

Ipilimumab – Major Summary Points (cont)

- **Drug interactions – no studies conducted**
- **Dosage and administration**
  - 3 mg/kg IV over 90 minutes
  - Dosed every 3 weeks for 4 doses
  - Dosage modifications based on AEs included in PI
- **Complete course of therapy is ~$120,000**

Ipilimumab – Major Summary Points (cont)

- **Recently completed study also shows survival benefit in newly diagnosed patients**
- **BMS also trying to identify a biomarker for patients more likely to respond**
- **Also being studied in prostate cancer, pancreatic cancer, and metastatic brain cancer associated with lung cancer (NSC)**
- **Maintenance dosing for melanoma being studied at 10 mg/kg**

Conclusions & Your Questions