WORKING THROUGH SHORTAGES OF PARENTERAL NUTRITION COMPONENTS

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PHARMACY PRACTICE
UNIVERSITY OF THE INCARNATE WORD

FEIK SCHOOL OF PHARMACY

There's a drug shortage. I'm thinking of replacing your meds with eight hours a day before & after meals!
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

Food and Drug Administration (FDA)
American Society of Health-System Pharmacists (ASHP)
American Society of Parenteral and Enteral Nutrition (A.S.P.E.N.)
Manufacturers
Institute for safe medication practices (ISMP)
A.S.P.E.N., members and other clinicians

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, Cyanocobalamin (vit. B12)
  • Monthly: Folic acid 0.6mg
• Do not use pediatric products for this population


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)

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

**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


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**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 and symptoms of magnesium deficiency
  • EKG changes
  • Arrhythmias
  • 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:
- 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

Jeanne D. Waggener, R.Ph. – President – Waco
Alice G. Mendoza, R.Ph. – Vice President – Kingsville
Dennis F. Wiesner, R.Ph. – Treasurer – Austin
Buford T. Abeldt, Sr., R.Ph. – Lufkin
Phyllis A. Stine – Abilene
W. Benjamin Fry, R.Ph., FIACP, FACA – San Benito
L. Suzan Kedron, Dallas
Joyce Tipton, R.Ph., MBA – Houston
Charles F. Wetherbee – Boerne
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**

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.

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.

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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
Changes to Class A Rules
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**

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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."

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
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.
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.

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
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.
§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:

- 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 practitioner’s standard of practice allows that practitioner to authorize a prescription under such circumstances.

Reasons to suspect that a prescription may have been authorized without a valid patient-practitioner relationship, or in violation of the practitioner’s 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;

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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.
Texas Administrative Code

EXAMINING BOARDS

PAIN MANAGEMENT

RULE 377.3

Guidelines

(a) The Texas Medical Board will use these guidelines to assess a physician's treatment of pain.

1. Evaluation of the patient

   A physician is responsible for obtaining a medical history and physical examination that includes a problem-focused exam specific to the chief presenting complaint of the patient.

   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 causing diseases and conditions;
   (iv) the effect of the pain on physical and psychological function;
   (v) any history and present use of substance abuse, and
   (vi) the presence of one or more recognized medical indications for the use of a dangerous or scheduled drug.

(b) Treatment plan for chronic pain. The physician is responsible for a written treatment plan that is documented in the medical record. The medical record should include:

   (i) how the modification relates to the chief presenting complaint of chronic pain;
   (ii) dosage and frequency of any drugs prescribed;
   (iii) further testing and diagnostic evaluations to be ordered;
   (iv) other treatments that are planned or considered;
   (v) periodic reviews planned, and
   (vi) objectives that will be used to determine treatment success, such as pain relief and improved physical and psychological function.

(c) Discussed 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, person designated by the patient, or with management of the patient's medical record. The discussion should be documented in the medical record. This record should be maintained in the medical record or a separate electronic record in compliance with federal and state laws.
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.”
<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>City</th>
<th>State</th>
<th>Zip</th>
<th>Phone</th>
<th>Board Action</th>
<th>Revised Date</th>
<th>Outcome</th>
<th>Board of Pharmacy Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. John Smith</td>
<td>123 Main St</td>
<td>Austin</td>
<td>TX</td>
<td>78701</td>
<td>(555) 555-1234</td>
<td>Revoked</td>
<td>10/1/2011</td>
<td>Outcome A</td>
<td>Licensure Suspended</td>
</tr>
<tr>
<td>Dr. Jane Doe</td>
<td>456 Market St</td>
<td>Dallas</td>
<td>TX</td>
<td>75201</td>
<td>(666) 666-7890</td>
<td>Revoked</td>
<td>10/1/2011</td>
<td>Outcome B</td>
<td>Licensure Suspended</td>
</tr>
</tbody>
</table>

*Note: This list is in alphabetical order by last name of the clinic's licensed physicians. Use the search bar to find the name of the physician. A link to search for an individual is located at the end of this list.*

*Texas State Board of Pharmacy 10/1/2011*
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.
Recent Disciplinary Notifications

August 1, 2011
- Board temporarily suspends pharmacy license of Trigirl Asadpoo, A.D.P.A.
- Board temporarily suspends pharmacy license of Alfredo Sepulveda, A.D.P.A.
- Board temporarily suspends pharmacy license of Kristin Reynolds, A.D.P.A.

July 13, 2011
- Board temporarily suspends pharmacy license of Shannan Thrapp, A.D.P.A.
- Board temporarily suspends pharmacy license of Robyn Edge, Pharmacy

May 9, 2011
- Board temporarily suspends pharmacy license of Ruby Ogun, Pharmacist, R.Ph.
- Board temporarily suspends pharmacy license for Medium H.

All Licensees/Registrants
### Fee Reductions (Effective 12/1/2011)

<table>
<thead>
<tr>
<th>Licensee/Registrant</th>
<th>Current Fee</th>
<th>Fee on 12/1/2011</th>
<th>Difference</th>
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<tbody>
<tr>
<td>Pharmacists</td>
<td>$306</td>
<td>$223</td>
<td>- $83</td>
</tr>
<tr>
<td>Pharmacies</td>
<td>$479</td>
<td>$396</td>
<td>- $83</td>
</tr>
<tr>
<td>Pharmacy Technicians</td>
<td>$80</td>
<td>$62</td>
<td>- $18</td>
</tr>
<tr>
<td>Technician Trainees</td>
<td>$53</td>
<td>$42</td>
<td>- $11</td>
</tr>
</tbody>
</table>
New TSBP Regulatory Database System

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

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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!
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 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

    0  2   4   6   8   10
    No Hurt Hurts Little Bit Hurts Little More Hurts Even More Hurts Whole Lot Hurts Worst

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

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

- Alkalining 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
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,1 John S. Bradley,1 John E. Edwards, Jr.,1 David Gilbert,1 Louis B. Rice,11 Michael Scheld,11 Brad Spellberg,12 and John Bartlett1

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


Mechanisms of Resistance

Increasing Numbers of CTX-M ESBLs

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>Proportion susceptible*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>32</td>
<td>0%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>32</td>
<td>3%</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>&gt;64; &gt;64</td>
<td>0%</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&gt;256; &gt;256</td>
<td>0%</td>
</tr>
<tr>
<td>Ceftazidine</td>
<td>&gt;256; &gt;256</td>
<td>0%</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>&gt;64; &gt;64</td>
<td>0%</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt;64; &gt;64</td>
<td>11%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>8; 8</td>
<td>8%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;32; &gt;32</td>
<td>3%</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;32; &gt;32</td>
<td>0%</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&gt;64; &gt;64</td>
<td>0%</td>
</tr>
<tr>
<td>Minocycline</td>
<td>16; 32</td>
<td>0%</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>1; 4</td>
<td>64%</td>
</tr>
<tr>
<td>Colistin</td>
<td>0.5; 8</td>
<td>89%†</td>
</tr>
</tbody>
</table>

*Proportion susceptible is calculated as the percentage of isolates with MIC values ≤ the breakpoint.

Carbageddon 2

- 3 urine isolates from different states, including *K. pneumoniae*, *E.coli* and *Enterobacter cloacae*, were + for bla\textsubscript{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

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…


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?

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.

Yet Again a Vanc MIC of >1.5 is Bad

P<.001

But Wait… Something is Different

P<.01

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 $$$


“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

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)

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

<table>
<thead>
<tr>
<th></th>
<th>Daptomycin SD (≤6mg/kg/d)</th>
<th>Daptomycin HD (&gt;6mg/kg/d)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Success</td>
<td>16/22 (73%)</td>
<td>29/31 (94%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Microbiological</td>
<td>13/19 (68%)</td>
<td>27/29 (93%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Success</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Table adapted from ref 2**
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


Ceftaroline: Rabbit Model of Endocarditis

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

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

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
- It's not a diabetic foot infection!

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


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)

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 Legislative Update on Pharmacy Issues

The 2011 Texas Legislative Session
★
The Pharmacy Agenda

Who Represents Pharmacy in Texas

- Texas Society of Health System Pharmacists
- Texas Federation of Drug Stores
- Texas Pharmacy Association
  (Texas Pharmacy Business Council)
Texas Pharmacy Practice Coalition
“Shoulder-to-Shoulder”

2011 Legislative Update
From the institutional view....
The Big Ticket Items….

✓ Huge Budget Shortfall
✓ 38 New Legislators
✓ Redistricting

The Legislature is in Session….

The BIG Pharmacy Issues for 2011 were….
For retail pharmacy it's all about $$$. . . .

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

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
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

Pharmacy Practice Issues….

- Generic Drug Substitution
  - SB 1756 – Can’t sub. “tamper resistant”

- E-Prescribing
  - SB 594 – Sch. II’s – like federal rules

- Photo ID for Control. Substances
  - HB 3041 – Pain clinic problems
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

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
Chain Pharmacy Issues…

- More No-Shows
  - Drug take-back programs
  - Eliminate Technician Ratios

Time to invest in your profession…

The most regulated profession on Earth… is under attack

Get involved NOW !!!
2012 Election Update

** Plus 4 new Congressional Seats…

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
Next November.... ???

Will Texans Still be looking for “More Change”

This Time Next Year....

...Imagine the number of new legislators
OMG !!! – As of today

YOU’RE FIRED!

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 $\text{P2Y}_{12}$ 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”

<table>
<thead>
<tr>
<th></th>
<th>ASA &gt; 100 mg</th>
<th>ASA &gt; 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Participants</td>
<td>57%</td>
<td>54%</td>
</tr>
<tr>
<td>Non-U.S. Participants</td>
<td>8%</td>
<td>2%</td>
</tr>
</tbody>
</table>
PLATO Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor versus Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, or Stroke</td>
<td>16% reduction</td>
</tr>
<tr>
<td>MI</td>
<td>16% reduction</td>
</tr>
<tr>
<td>CV Death</td>
<td>21% reduction</td>
</tr>
<tr>
<td>Stroke</td>
<td>Non-Significant Difference</td>
</tr>
<tr>
<td>Life-Threatening Bleeding</td>
<td>Non-Significant Difference</td>
</tr>
</tbody>
</table>

Ticagrelor – Major Summary Points

- **Black box warning**
  - Like other antiplatelet agents, can cause significant, sometimes fatal, bleeding
  - Doses of ASA $> 100$ mg $\downarrow$ 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

<table>
<thead>
<tr>
<th></th>
<th>Plavix® Clopidogrel</th>
<th>Effient® Prasugrel</th>
<th>Brilinta® Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Platelet Inhibition</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Dosing Frequency</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Fatal &amp; Life-threat-</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>ening Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA Dosage</td>
<td>75-325 mg</td>
<td>75-325 mg</td>
<td>75-100 mg</td>
</tr>
<tr>
<td>Recommendation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

---

I think it .......
I believe .......

Could I get back to you after my next parole hearing?
Dabigatran Etexilate (Pradaxa® – BI)

Major Summary Points

• INDICATION – to ↓ the risk of thromboembolic 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)**

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1.71%*</td>
<td>1.54%</td>
<td>1.11%*</td>
</tr>
</tbody>
</table>

Dabigatran – Major Summary Points (cont)

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

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>3.57%*</td>
<td>2.87%*</td>
<td>3.32%</td>
</tr>
</tbody>
</table>

- 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)

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.38%*</td>
<td>0.10%*</td>
<td>0.12%*</td>
</tr>
</tbody>
</table>

  – 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*

### 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
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)

<table>
<thead>
<tr>
<th></th>
<th>Efficacy*</th>
<th>Bleeding*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>Same (?)</td>
<td>Same (?)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Superior</td>
<td>Similar</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Superior</td>
<td>Less</td>
</tr>
</tbody>
</table>

*Compared to warfarin

---

Rivaroxaban – Major Summary Points

RECORD 1 Trial – Total Hip Replacement

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTEs</td>
<td>1.1%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Major VTEs</td>
<td>0.2%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

RECORD 2 Trial – Total Hip Replacement

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTEs</td>
<td>2%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Major VTEs</td>
<td>0.7%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>
Rivaroxaban – Major Summary Points

RECORD 3 Trial – Total Knee Replacement

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTEs</td>
<td>9.7%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Major VTEs</td>
<td>1.0%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Rivaroxaban – Major Summary Points

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

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban AUC</th>
<th>Rivaroxaban Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>↑ 160%</td>
<td>↑ 70%</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>↑ 150%</td>
<td>↑ 60%</td>
</tr>
</tbody>
</table>

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”

• 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

**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 (Dairesp® – 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Rate Ratio</th>
<th>Reduction in Exacerbation Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2-124</td>
<td>0.87</td>
<td>-14.9</td>
</tr>
<tr>
<td>M2-125</td>
<td>0.82</td>
<td>-18.5</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Roflumilast (%)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>9.5</td>
<td>2.7</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>7.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Headache</td>
<td>4.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>2.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>
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 & proliferation, 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

- 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

<table>
<thead>
<tr>
<th>Arme</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab 3 mg/kg + gp 100 vaccine</td>
<td>10</td>
</tr>
<tr>
<td>Ipilimumab 3 mg/kg</td>
<td>10.1</td>
</tr>
<tr>
<td>gp 100 vaccine</td>
<td>6.4</td>
</tr>
</tbody>
</table>


Ipilimumab – Major Summary Points (cont)

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

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterocolitis</td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td></td>
</tr>
<tr>
<td>Neuropathies</td>
<td></td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td></td>
</tr>
</tbody>
</table>

- 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