Updates in Therapeutics® 2013:

The Pharmacotherapy Preparatory Review & Recertification Course
Pediatrics

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Conflict of Interest Disclosure

- The speaker, Kirsten Ohler, has no real or potential conflicts of interest related to the subject matter in this presentation.

Agenda

Discuss the pharmacological management of the following pediatric disease states:

- Pediatric and neonatal sepsis/meningitis
- Respiratory syncytial virus (RSV)
- Otitis media
- Immunizations
- Pediatric seizure disorders
- Attention deficit hyperactivity disorder (ADHD)

Case 1

Neonate born at 36 week's gestational age develops respiratory distress, hypotension, and mottling at 5 hours of life. Witnessed seizure in the NICU. Mother is GBS positive; three doses of penicillin given before delivery

Best empiric antibiotic regimen?

a. Vancomycin
b. Ampicillin + gentamicin
c. Ampicillin + ceftriaxone
d. Ceftazidime + gentamicin

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Sepsis/Meningitis - Pathogens

Age	Organism
0 - 1 month	Group B β Streptococcus, E. coli, Listeria, viral, nosocomial
1 - 3 months	Neonatal pathogens, H. influenzae, N. meningitidis, Strep pneumoniae
3 mo - 12 yr	H. influenzae, N. meningitidis, Strep pneumoniae
> 12 yr	N. meningitidis, Strep pneumoniae

Page 1- 5

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Page 1-5

Case 2

Culture results reveal gram negative rods in the cerebral spinal fluid.

Which recommendation regarding antibiotic prophylaxis is best?

a. 5-month old stepsister is at high risk and should receive rifampin
b. The patient should receive rifampin to eliminate nasal carriage
c. Antibiotic prophylaxis is not indicated
d. All close contacts should receive rifampin

Page 1-6

Chemoprophylaxis

- Purpose: prevent the spread of *Haemophilus influenzae* and *Neisseria meningitidis*
- High risk groups: household contacts, nursery or child care center contacts, direct contact with patient's secretions
- Drug of choice: rifampin

Page 1-6

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Case 3

6-year-old boy presents to the ED with fever, altered mental status & petechiae. No trauma. Tox screen negative. Elevated WBC with a left shift. Cultures are pending.

Best empiric antibiotic regimen?

a. Ampicillin + gentamicin
b. Cefuroxime
c. Ceftriaxone + vancomycin
d. Rifampin

Page 1-6

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Page 1-6

Case 4

You are screening babies during RSV season for risk factors associated with the development of severe RSV infection.

Which is the best recommendation regarding the use of palivizumab for RSV prophylaxis?

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Case 4

Palivizumab should NOT be prescribed for:

a. A 34 weeks' gestation baby with a cyanotic congenital heart defect

b. A 21-day-old, 31 weeks' gestation baby, only child, non-smoking parents, will not attend day care

c. A 5-month-old, 29 weeks' gestation infant, history of CLD, no O_2 or meds

d. An 18-month-old, 26 weeks' gestation infant history of CLD, no O_2 or meds in past 8 mo

Respiratory Syncytial Virus

- Risk Factors
  - premature birth
  - chronic lung disease (CLD)
  - cyanotic or complicated congenital heart disease
  - immunodeficiency
  - airway abnormalities
  - other: low socioeconomic status, passive smoking, day care, siblings

Page 1-7

Respiratory Syncytial Virus

AAP guidelines for palivizumab use

Gestational Age (weeks)	Age at Start of RSV Season (months)	Other Criteria	Maximal Doses
≤ 28	< 12		5
29–31+ 6 days	< 6		5
32–34 + 6 days	< 3	At least one of the following: • day care attendance • sibling < 5 years of age	3
Any	< 24	Chronic lung disease requiring medical therapy within past 6 months	5
Any	< 24	Hemodynamically significant congenital heart disease	5
Any	< 12	Congenital abnormalities of airway or neuromuscular disease	5

Page 1-8

Case 4

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Case 5

18-month-old with history of premature birth and CLD is admitted to the PICU with respiratory distress requiring intubation, fever, and a 3-day history of cold-like symptoms. A nasal swab is positive for respiratory syncytial virus.

Page 1-8

Case 5

Which is the best intervention?

a. Palivizumab
b. Corticosteroids
c. Cefuroxime
d. Intravenous fluids and supportive care

Case 6

A 5-month-old infant, born at term, healthy is treated for her first case of otitis media with amoxicillin 45 mg/kg/day for 7 days. Follow-up exam shows fullness of middle ear, cloudy TM. Afebrile and eating well.

Best treatment recommendation?

a. No antibiotics are warranted at this time
b. High-dose (90 mg/kg/day) amoxicillin x 7 days
c. Decongestant & antihistamine daily
d. Azithromycin

Page 1-10

Otitis Media

- Common pathogens
  - viral
  - *Streptococcus pneumoniae*
  - nontypeable *Haemophilus influenzae*
  - *Moraxella catarrhalis*

Page 1-9

Otitis Media

- Treatment Principles
  - clinical resolution in a significant # of cases
  - immediate antibiotics if bulging TM
  - if > 2 years old, may delay antibiotics if NO bulging TM and no severe systemic symptoms
    - 6mo – 2yrs, may differ if symptoms mild & OM uncertain
  - antibiotics not needed for OM w/ effusion
  - persistence of middle ear fluid is likely

Pages 1-9 & 1-10

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Page 1-10

Case 7

4-year-old boy diagnosed with 4th case of otitis media in 12 months. No evidence of hearing loss or delayed language skills.

Which of the following is the best intervention?

a. Long-term antibiotic prophylaxis
b. Tympanostomy tubes
c. High-dose amoxicillin and ensuring he is up-to-date on pneumococcal and influenza vaccines
d. No antibiotic therapy is warranted

Page 1-11

Case 8

1-year-old boy with history of Kawasaki disease treated 4 months ago with IVIG. At well-child check-up, due for MMR and varicella. Mother has several concerns regarding immunizations.

Best reason to defer administration of vaccines?

a. Association between MMR & autism
b. Allergic reaction to MMR if patient has egg allergy
c. Many concurrent vaccines can overload immune system
d. Decreased vaccine efficacy because of previous IVIG administration

Page 1-11

Immunizations

- Barriers to routine immunization
  - contraindications
    - anaphylactic reaction to the vaccine
    - acute moderate – severe febrile illness
    - immunodeficiency, pregnancy, recent IVIG
    - encephalopathy w/in 7 days of previous DTaP
  - misconceptions regarding contraindications
    - mild acute illness, current antibiotics, etc.

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Immunizations

- Special populations
  - Preterm infants
    - immunize based on chronologic age
  - Immunocompromised children
    - no live vaccines
  - Patients receiving corticosteroids
    - recommendations depend on steroid dose / duration
  - Patients who recently received IVIG
    - affects live vaccines (ex. MMR, varicella)
    - recommendations depend on indication / dose of IVIG
  - HIV-infected patients
    - recommendations depend on degree of immunocompromise

Page 1-14

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For which of the following patients would it be best to recommend deferring immunizations?

a. 12-month-old boy who recently completed a cycle chemotherapy for ALL
b. 6-month-old girl on amoxicillin for otitis media
c. 12-month-old, HIV-positive boy with CD4 >1000
d. 12-year-old girl completing a prednisone "burst" (1 mg/kg/day) for asthma exacerbation

Page 1-14

Immunizations

- Recent changes to the routine schedule
  - 7-valent conjugated pneumococcal vaccine (PCV-7) replaced with 13-valent product (PCV-13)
  - Human papilloma virus (HPV) vaccine indicated for males 9-26 years for prevention of genital warts

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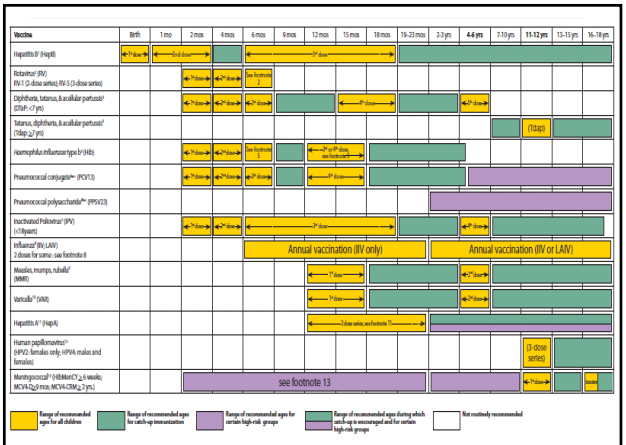

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Page 1-14

Case 10

14-year-old moderately obese girl complains of erythematous pruritic rash. She was started on oxcarbazepine three weeks ago for partial seizures. Sexually active ± contraception.

Which of the following is the best intervention?

a. Change to carbamazepine
b. Change to levetiracetam
c. Change to valproic acid
d. No change in therapy is necessary

Page 1-18

Pediatric Seizures

Seizure type	Drugs of Choice	Alternatives
Partial	VPA, CBZ, PHT	PB, Gabapentin, Lamotrigine, Tiagabine, Topiramate, Oxcarbazepine, Zonisamide, Levetiracetam
Generalized		
Tonic-clonic	VPA, CBZ, PHT	Lamotrigine, Topiramate, Zonisamide, Levetiracetam
Myoclonic	VPA	Topiramate, Zonisamide, Levetiracetam
Absence	Ethosuximide, VPA	Lamotrigine, Zonisamide, Levetiracetam
Lennox-Gastaut	VPA, Topiramate, Lamotrigine	Felbamate, Zonisamide
Infantile spasms	ACTH	Lamotrigine, tiagabine, topiramate, VPA, zonisamide

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Pediatric Seizures

Rash
- Carbamazepine
- Oxcarbazepine
- Lamotrigine
- Phenytoin
- Phenobarbital
- Zonisamide

Menstrual irregularities
- Valproic acid

Weight gain
- Valproic acid
- Gabapentin

Weight loss
- Topiramate
- Zonisamide

Cognitive/CNS effects
- Phenobarbital
- Topiramate
- Levetiracetam

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Page 1-18

Case 11

9-year-old boy is newly diagnosed with ADHD symptoms at home and school.

Best recommendation for initial drug regimen?

a. Methylphenidate OROS (Concerta®) once daily
b. Methylphenidate IR (Ritalin®) twice daily given four hours apart
c. Guanfacine at bedtime
d. D-methylphenidate (Focalin®) twice daily given four hours apart

Page 1-19

Drug Therapy for ADHD

- Stimulants
  - Methylphenidate-containing products
  - Amphetamine-containing products
- Non-stimulants

Pages 1-19 – 1-22

Drug Therapy for ADHD

- Methylphenidate-containing products
  - duration of effect
    - short = Ritalin and Focalin
    - intermediate = Metadate ER and Ritalin SR
    - long = Concerta, Metadate CD, Ritalin LA
  - side effects
    - insomnia, loss of appetite, headache, may exacerbate tics

Pages 1-19 – 1-21

Drug Therapy for ADHD

- Amphetamine-containing products
  - duration of effect
    - Adderall vs. Adderall XR
  - side effects
    - insomnia, loss of appetite, nervousness, exacerbation of hypertension and tics
    - potential association with sudden cardiac death

Pages 1-20 & 1-22

Drug Therapy for ADHD

- Non-stimulant medications
  - Atomoxetine (Strattera)
    - potential association with severe liver injury
    - does not exacerbate tics
  - Clonidine
    - more effective for hyperactivity than inattention
    - lessens the severity of tics
    - sedation
  - Guanfacine
    - ↓ sedation and ↑ duration than clonidine

Page 1-20 & 1-22

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Page 1-19

Case 12

The patient is started on methylphenidate OROS (Concerta®); symptoms well-controlled, but complaining of insomnia.

Best modification to treatment regimen?

a. Administer Concerta later in day
b. Change to methylphenidate modified release (Metadate CD) once a day.
c. Change to methylphenidate patch
d. Change to atomoxetine at bedtime

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Questions

2013 Updates in Therapeutics:

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Geriatrics

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Kaiser Permanente Colorado

Conflict of Interest Disclosure

- The speaker, Jennifer Dugan, has no real or potential conflicts of interest related to the subject matter in this presentation.

Patient Case 1

NH is an 85 yo woman in a nursing facility.

- Type 2 DM, HTN, moderate dementia due to CVA, s/p hip fracture.
- Glyburide 10 mg/d, lisinopril 10 mg/d, metformin 500 mg BID, donepezil 10 mg/d, aspirin 81 mg/d, MVI, zolpidem 5 mg QHS PRN, Meclizine 12.5 mg TID PRN, bowel regimen

Handout Page 1-39; Answer Page 1-65

Patient Case # 1cont.

Which functional assessment is most important to evaluate?

A. **IADLS**

B. **Depression**

C. **Gait and balance**

D. **Pressure sores**

Handout Page 1-39; Answer Page 1-65

Patient Case # 2

Labs for NH include fasting glucose 90 mg/dL, sodium 138 mEq/L, potassium 4.5 mEq/L, chloride 102 mEq/L, CO2 25 mEq/L, blood urea nitrogen 30 mg/dL, SCr 1.8 mg/dL, and TSH 4.0 mU/L. **Which pharmacokinetic parameter is most likely to be changed in N.H.?**

A. **Oral absorption**

B. **Distribution**

C. **Metabolism**

D. **Renal excretion**

Handout Page 1-39; Answer Page 1-64

Physiologic Changes in the Elderly Pearls

- Absorption from transdermal patches may be reduced if insufficient subcutaneous fat
- Distribution may be increased for highly protein-bound meds
- Metabolism impacts benzodiazepine choices
- Elimination is not just about Serum Creatinine

Patient Case # 3

Based on your assessment of age- and disease-related changes in N.H., which is best to address first?

A. **Diabetes management**

B. **Alzheimer disease treatment**

C. **Hypertension treatment**

D. **Stroke prevention**

Handout Page 1-39; Answer Page 1-64

N.H. meds

- Glyburide 10 mg/day
- Lisinopril 10 mg/day
- Metformin 500 mg BID
- Donepezil 10 mg/day
- Aspirin 81 mg/day
- MVI

Patient Case # 4

To maintain and improve function in N.H., which intervention is best to implement?

A. Add a calcium and vitamin D supplement

B. Add simvastatin 10 mg/day

C. Add warfarin

D. Assess for incontinence and treat with anticholinergic agents

Handout Page 1-40; Answer Page 1-64

Common Drug Related Problems in Elderly

- Overuse
- Underuse
  - ACE inhibitors in CHF, anticoagulation in A fib, drug therapy post MI, untreated depression
- Medication Adherence
  - Intentional nonadherence related to perceived overmedication, ADRs, cost
- Use of inappropriate medications
- Adverse drug events

Patient Case # 5

An 85-year-old woman seen for dementia. MMSE is 24/30. PMH: Parkinson disease, hypothyroidism, and OA. Independent in ADLs.
Meds: carbidopa/levodopa CR, trihexyphenidyl, celecoxib, levothyroxine, docusate, and bisacodyl.
Which medication change is best to consider first?

A. Add donepezil 5 mg/day.

B. Slow dosage reduction of carbidopa/levodopa.

C. Slow dosage reduction and discontinue trihexyphenidyl.

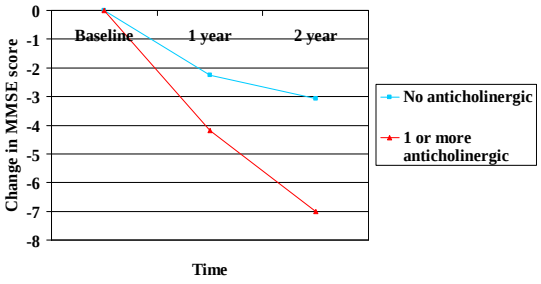
D. Replace celecoxib with acetaminophen.

Handout Page 1-42; Answer Page 1-64

Potentially Inappropriate Medications

- Common offenders
  - Diphenhydramine
  - Long Acting Benzos (Diazepam, Chlordiazepoxide)
  - Skeletal Muscle Relaxants
  - Amitriptyline, Doxepin, Imipramine
  - GI antispasmodics and other anticholinergics
  - Indomethacin, Piroxicam
  - Promethazine
  - Butalbital compounds
  - Z-drugs (zolpidem, zalepolon, eszopiclone)

Change in MMSE scores over time for pts receiving AChEIs



Lu C-J, Tune LE. Am J Geriatr Psychiatry 2003; 11(4): 458-461.

Treating Adverse Effects with New Med

- Watch for prescribing cascade:
  - Metoclopramide →Parkinsonian sxs → Levodopa
  - Donepezil → Incontinence → Oxybutynin
  - Diphenhydramine → Urinary Retention → Terazosin
  - Dihydropyridine CCB → Edema → Furosemide

Patient Case # 6

An 87-year-old man with Alzheimer disease is on rivastigmine 6 mg 2 times/day. His family notes improvement in his functional ability but reports that he is experiencing nausea and vomiting that seem related to rivastigmine.

Which is the best recommendation at this time?

A. Advise the patient to take his drug with an antacid.

B. Add prochlorperazine 25 mg by rectal suppository with each rivastigmine dose.

C. Discontinue rivastigmine and initiate memantine 5 mg twice daily.

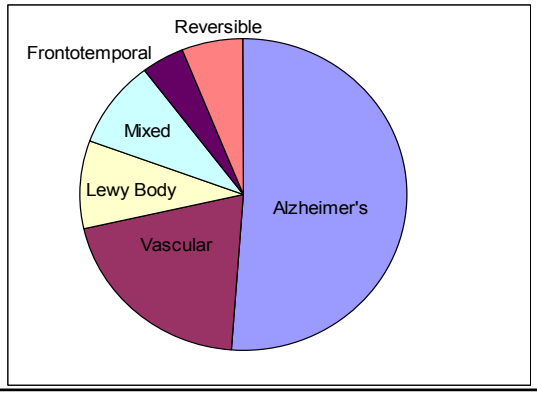
D. Change rivastigmine to the daily patch that delivers 9.5 mg/day.

Handout Page 1-44; Answer Page 1-64

Symptoms of Dementia

- Functional disability
- Cognitive impairments
- Behavioral and psychological symptoms

Prevalence of Types of Dementia



Differentiating Dementias

Diagnosis	Key Symptoms
Dementia with Lewy bodies	Visual hallucinations, Parkinsonian sx, fluctuating alertness
Vascular Dementia	Acute onset, stepwise deterioration, focal neurologic signs
Alzheimer's Disease	Slow onset, progressive decline

Delirium

- **Disturbance of consciousness and difficulty with attention**
- **Change in cognition (eg, memory deficit, disorientation, language disturbance, perceptual disturbance)**
- **The disturbance develops over a short period (usually hours to days) and tends to fluctuate during the course of the day.**
- **Evidence from the history, physical examination, or laboratory findings is present that indicates the disturbance is caused by a direct physiologic consequence of a general medical condition, an intoxicating substance, medication use, or more than one cause.**

Adapted from: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. 4th ed. Washington, DC: American Psychiatric Association; 2000.

Therapy for Dementia

- Acetylcholinesterase Inhibitors
  - Donepezil
  - Galantamine
  - Rivastigmine
- Memantine
- Efficacy and Safety Pearls

GI effects from AChEIs

	Donepezil	Galantamine	Rivastigmine po	Rivastigmine patch
Nausea	19%	24%	47%	7%
Vomiting	8%	13%	31%	6%
Diarrhea	15%	12%	19%	6%

Patient Case # 7

RA is 75 yo woman with Alzheimer disease on donepezil 10 mg/day for 3 years. MMSE 21/30→ 17/30. RA is at home with husband- can't do IADLs but can do ADLs with cueing .

Which is the next best course of action?

A. Change her treatment from donepezil to rivastigmine.

B. Stop donepezil.

C. Add memantine 5 mg/day.

D. Add vitamin E 400 units 2 times/day.

Handout Page 1-45; Answer Page 1-64

Evaluating Efficacy

- Evaluate patient in 3-6 months to determine need for continued treatment
- Utilize caregiver reports, MMSE/SLUMS, and/or ADLs
- No change or mild improvement at 6 months→continue treatment
- Continued decline on therapy → consider discontinuation or changing medication
- 4 points/year is average decline without treatment

Patient Case # 8

87-yo woman in dementia unit. PMH: AD, PD, OA, requiring total assistance with bathing and dressing and help with feeding. Meds: donepezil 10 mg/day, memantine 10 mg 2 times/day, carbidopa/levodopa 25/100 mg 4 times/day, oxybutynin extended release 5 mg/day, and MVI. MMSE score is 5/30, and GDS is 4/15. Patient crying out "Help me, help me." Which one of the following additional assessment tools is most necessary in assessing this patient?

A. Brief Psychiatric Rating Scale

B. Functional Assessment Staging

C. An evaluation of incontinence

D. Framingham Risk Assessment

Handout Page 1-48; Answer Page 1-64

Patient Case # 9

87-yo woman in dementia unit. PMH: AD, PD, OA, requiring total assistance with bathing and dressing and help with feeding. Meds: donepezil 10 mg/day, memantine 10 mg 2 times/day, carbidopa/levodopa 25/100 mg 4 times/day, oxybutynin extended release 5 mg/day, and MVI. MMSE score is 5/30, and GDS is 4/15.

Which one of the following changes would be best to reduce inappropriate medications?

A. Change carbidopa/levodopa to a continuous release formulation.

B. Discontinue oxybutynin

C. Discontinue memantine

D. Reduce dose of donepezil

Handout Page 1-48; Answer Page 1-65

Patient Case # 10

This same patient (MMSE 5/30, GDS 4/15) is medically assessed, and reversible causes of her hyper-vocalization are ruled out. **Which one of the following represents the best approach to treating her behavioral symptoms?**

A. Implement a behavioral approach

B. Add valproic acid

C. Add quetiapine

D. Add citalopram

Handout Page 1-48; Answer Page 1-65

General Approach to Behaviors in Dementia

- Define target agitated behavior
- Consider contributing causes
- Address ALL causes
- Non-pharmacologic measures
- Pharmacologic interventions

Lyketsos et al, Am J Geriatr Psychiatry July 2006;14:7

Examples of Non-pharmacologic Interventions

Behavior	Causes	Management
Agitation	Discomfort, pain	Assess/manage pain, constipation, infection
	Physical illness (UTI)	Evaluate medically, treat
	Overstimulation-noise, TV, people, etc	Reduce noise, stress; limit TV, crowding
Paranoia	Forgot where placed object	Offer to help find; have more than one of same object
	Misinterpreting actions or words	Do not argue or try to reason, do not take personally, distract
	Change in environment	Familiarize, reassure, set routine
Insomnia	Depression	Treat with antidepressant
	Less need for sleep	Later bedtime, more exercise

Adapted from Sutor B et al. Mayo Clin Proc. 2001;76:540-550

When should we consider pharmacologic treatment of BPSD?

- Behavior is dangerous, distressing, damaging to social relationships and persistent

AND

- Has not responded to comprehensive non-pharmacologic treatment plan, including removal of possibly offending drugs

OR

- Requires emergency treatment to allow proper investigation of underlying problems

Pharmacologic Treatment

- Cochrane review suggests best evidence is with risperidone and olanzapine for psychosis and aggression
- Start at low doses
- Use quetiapine if patient has comorbid Parkinson's disease or Lewy Body Dementia
- Use for shortest duration possible
- Adverse effects include increased mortality; recent cohort study* suggests worse with haloperidol, less with quetiapine

*BMJ 2012;344:e977

Patient Case #11

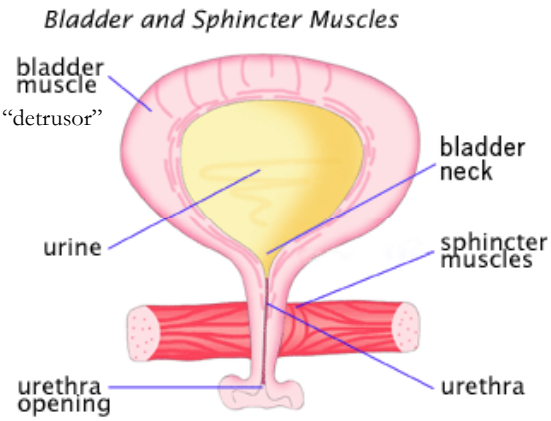
A 75-year-old woman reports urinary urgency, frequency, and loss of urine when she cannot make it to the bathroom in time. She wears a pad at night that she changes 2 or 3 times. PMH: Alzheimer disease (MMSE 23), osteoarthritis, and hypothyroidism.

UA negative, exam WNL, PVR normal.

Which of the following interventions would be best?

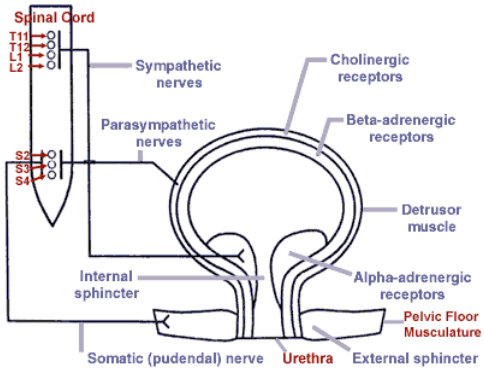
A. Bethanechol
B. Pelvic floor muscle exercises plus estrogen vaginal cream
C. Darifenacin
D. Oxybutynin

Handout Page 1-53; Answer Page 1-65



Normal Urination

- STORAGE - under sympathetic control
  - → inhibition of detrusor contraction
  - → increase sphincter contraction
- URINATION - under parasympathetic control
  - → induces detrusor contraction
  - → induces sphincter relaxation
- Urethral sphincter:
  - proximal smooth muscle contracts via sympathetic stimulation
  - distal urethral striated muscle via cholinergic stimulation



Types of Urinary Incontinence

- **Functional**
- **Urge (Bladder overactivity)**
- **Stress (Urethral underactivity)**
- **Overflow (Urethral overactivity/Bladder underactivity)**
- **Mixed**

Nonpharmacologic Interventions

- Pelvic floor exercises (Kegel exercises)
- Bladder training
- Biofeedback
- Scheduled/Timed Voiding
- Avoid aspartame, spicy/citrus foods, caffeine, carbonated beverages
- Pessaries/bladder neck support prostheses

Treatment of UI

- Functional
  - Assist with functional disabilities
  - Scheduled bathroom visits
  - Bedside commode
  - Stop precipitating drugs
- Urge
  - Nonpharmacologic interventions
  - Anticholinergics (generally equivalent efficacy)
  - Beta 3 agonist (Mirabegron)

Anticholinergic Adverse Effects

Drug	Dry mouth %	Constipation %	Dizziness%
Oxybutynin	88	32	38
Oxy ER/XL	68	9	11
Oxy TDS	10	5	4
Oxy gel	8	1	3
Tolterodine	50, 39	10, 10	4, 3
Fesoterodine	99	14	2
Trospium	33	11	?
Solifenacin	34	19	1
Darifenacin	59	28	0

Treatment of overactive bladder in women. AHRQ Publication No. 09-E017. 8/09

Miragebron

- Beta-3 receptor activation relaxes detrusor smooth muscle during the storage phase
  - End result: Increased bladder capacity
- No efficacy benefit over antimuscarinics but low anticholinergic effects
- Dose-related activity on beta-1 receptors lead to CV side effects
- In clinical trials: Solabegron

Treatment of UI

- **Stress**
  - **Kegel exercises, pessaries, surgery**
  - **Consider stopping precipitating medications**
    - **Alpha-1 blockers, methlydopa, ACE inhibitors**
  - **Vaginal estrogens?**
  - **Alpha agonists?**
  - **Duloxetine?**
- **Overflow**
  - **Consider stopping precipitating medications**
    - **Alpha agonists, beta-blockers, TCAs, anticholinergics, CCBs, diuretics, muscle relaxants**
  - **Treatment of BPH**
  - **Cholinergic stimulation?**

Patient Case #12

A.W. is an 85-year-old man who presents to his physician with LUTS. A digital rectal examination confirms the diagnosis of BPH. Ultrasound shows prostate volume is 31 g. A.W.'s score on the AUASI is 15. His BP is 118/70 sitting, 102/62 standing.

Which of the following interventions would be best?

A. Terazosin

B. Finasteride

C. Tamsulosin

D. Finasteride plus tamsulosin

Handout Page 1-55; Answer Page 1-65

BPH

- Alpha Blockers
- Alpha Reductase Inhibitors
- Combination Therapy
  - May be needed in men with LUTS, a larger prostate size (>40g), and an elevated PSA

Patient Case #13

WF is an 85-year-old man with pain from hip OA. He also has hypertension, coronary artery disease, and BPH. For his OA, W.F. has been taking acetaminophen 650 mg 3 times/day. W.F. reports that acetaminophen helps, but he still experiences pain that limits his ability to walk. **Which of the following interventions would be best?**

A. Change the analgesic to celecoxib

B. Add hydrocodone

C. Change the analgesic to ibuprofen

D. Add glucosamine

Handout Page 1-58; Answer Page 1-65

Osteoarthritis

- Nonpharmacologic Treatment
- Acetaminophen dosing
- NSAIDs vs Opioids
- Preventing adverse effects
- Glucosamine

Patient Case #14

F.A. is a 55 yo woman with RA. Diagnosed 1 year ago, she began therapy with methotrexate, and she is presently receiving 15 mg every week, folic acid 2 mg/day, ibuprofen 800 mg 3 times/day, and omeprazole 20 mg/day. Today F.A. reports a recurrence of her symptoms. Radiographic evaluation of her hand joints shows progression of joint space narrowing and bone erosion.

Which of the following interventions would be best?

A. Administer etanercept

B. Switch to hydroxychloroquine

C. Add prednisone bridge therapy

D. Change to leflunomide

Handout Page 1-59; Answer Page 1-65

Rheumatoid Arthritis

- DMARDs first line
  - MTX
  - Hydroxychloroquine
  - Sulfasalazine
  - Leflunomide
- Biologic Treatments
- NSAIDs and Corticosteroids
  - Short term
  - No effect on disease progression

Questions

- ?????

2013 Updates in Therapeutics:
The Pharmacotherapy Preparatory Course
Gastrointestinal Disorders

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Conflict of Interest Disclosures

Dr. Hemstreet has no conflicts to disclose.

Learning Objectives

1. Review and apply national guideline treatment strategies for the following gastrointestinal (GI) disorders: gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), ulcerative colitis, Crohn's disease, viral hepatitis, chronic liver disease, upper GI bleeding, constipation, diarrhea, irritable bowel syndrome (IBS), nausea, vomiting, pancreatitis, prevention of stress related mucosal disease (SRMD).
2. Recommend appropriate pharmacologic and nonpharmacologic interventions for the treatment of GERD.
3. Differentiate between clinical signs, symptoms, risk factors, and treatment of both *Helicobacter pylori* and nonsteroidal anti-inflammatory drug (NSAID)-associated PUD.

Learning Objectives

4. Discuss the role of pharmacologic intervention in the treatment of nonvariceal upper GI bleeding.
5. Review the clinical differences in signs, symptoms, and treatment of Crohn's disease and ulcerative colitis.
6. Identify the common manifestations of chronic liver disease and their treatment.
7. Review the treatment of both acute and chronic viral hepatitis.

Learning Objectives

8. Recognize pertinent information for educating patients and prescribers regarding the appropriate use of pharmacologic agents for various GI disorders.
9. Recommend appropriate pharmacologic and nonpharmacologic interventions for diarrhea and constipation.
10. Review recommendations for the treatment and prevention of nausea and vomiting.

Learning Objectives

11. Discuss the clinical and treatment differences between acute and chronic pancreatitis.
12. Discuss the role of pharmacologic intervention in the treatment of IBS.
13. Understand commonly encountered statistical tests and concepts using GI disorders as examples.

Patient Case # 1

- HPI: 55 year old man with 8 month history of GERD symptoms 4-5 days/week. Prescriber wishes to initiate esomeprazole 20 mg/day.
- PMH: GERD, MI, HF, Hypothyroidism
- MEDS: Ranitidine + Calcium Carbonate, Metoprolol, Furosemide, Lisinopril, Aspirin

Handout Page 14; Answer Page 70

Patient Case # 1

- Which one of the following baseline tests is best to perform in this patient today before initiating his esomeprazole therapy?

A. Peripheral bone mineral density screening.
B. Serum magnesium.
C. Serum potassium.
D. Chest radiograph.

Handout Page 14; Answer Page 70

Treatment of GERD

- Nonpharmacologic/Lifestyle modifications
  - Targeted
- Antacids
- Acid suppression (as needed or scheduled)
  - Proton Pump Inhibitors
  - Histamine-2 Receptor Antagonists
- Promotility Agents
- Proper patient education
- Surgical intervention

PPI Safety Concerns

Adverse Effect	Prevention and Management
Risk of Fracture (Hip, wrist, spine)	• Re-evaluate need • Limit dose and duration • Ensuring adequate Calcium and Vitamin D • BMD screening if at risk for low bone mass • Weight bearing Exercise
Hypomagnesemia	• Re-evaluate need • Limit dose and duration • Consider baseline testing (diuretics, digoxin) • Supplementation
Clostridium difficile associated diarrhea	• Re-evaluate need •Limit dose and duration • Evaluate for *C. difficile* if patient receiving PPI has diarrhea that is not improving. Have patients report diarrhea. •Report cases to Medwatch

Patient Case # 2

- HPI: 68 year old female with heme positive stools anemia and abdominal pain. Use of OTC ketoprofen for 2 months.
- PMH: Type 2 DM, Peripheral neuropathy, Hypertension
- MEDS: metformin, aspirin, gabapentin, lisinopril
- Diagnostics: endoscopy reveals 1 cm gastric ulcer with an intact clot, *H. pylori* negative via CLO Test

Handout Page 19; Answer Page 70

Patient Case # 2

- Which one of the following treatments is best for this patient's ulcer?

A. Ranitidine 150 mg 2 times/day for 4 weeks
B. Lansoprazole 30 mg 2 times/day plus amoxicillin 1000 mg 2 times/day plus clarithromycin 500 mg 2 times/day for 10 days.
C. Lansoprazole 30 mg/day for 8 weeks
D. Misoprostol 200 mcg 4 times/day for 8 weeks.

Handout Page 19; Answer Page 70

Peptic Ulcer Disease (PUD)

- Classification
  - Duodenal ulcer
  - Gastric ulcer
- Etiologies
  - *Helicobacter pylori* (carcinogen)
  - NSAIDs
- Symptoms
  - Epigastric pain, nausea, anorexia, belching
  - May be temporally related to food intake

NSAID Associated PUD

- NSAIDs have topical and systemic adverse GI effects
  - COX-2 vs. COX-1 effects
- Risk Factors
  - Age >60, History of PUD +/- complications
  - Corticosteroids, anticoagulants, low dose aspirin
- Contributing factors
  - *H. pylori*, Smoking, CVD, RA, SSRIs

Management of NSAID-Associated PUD

- Remove and reevaluate need for NSAID and/or aspirin
  - Test for *H. pylori* and treat if positive
- Acid suppression
  - PPI for 8-12 weeks
- Misoprostol
- COX-2 Inhibitors
  - Cardiovascular risks
  - Use with aspirin

Patient Case #3

- HPI: 42 year old male with sharp epigastric pain for 6 weeks. Pain is worse with eating and is present approximately 5 days per week. Some relief with OTC antacids.
- MEDS: antacids as needed
- Allergies: Penicillin (severe rash)
- UBT for *H. pylori* is positive

Handout Page 19; Answer Page 70

Patient Case #3

- Which one of the following treatments for *H. pylori* is best?

A. Amoxicillin, clarithromycin, omeprazole for 10 days
B. Cephalexin, clarithromycin, omeprazole for 10 days
C. Bismuth, tetracycline, metronidazole, omeprazole for 14 days
D. Levofloxacin, metronidazole, omeprazole for 10 days

Handout Page 19; Answer Page 70

Diagnosis of *H. pylori*

- Invasive testing (endoscopic)
  - Histology
  - Rapid urease (affected by antisecretory agents)
  - Culture
- Non-invasive testing
  - Serologic (IgG)
  - Urea breath test (affected by antisecretory agents)
  - Fecal antigen (affected by antisecretory agents)

Treatment of *H. pylori*

- Triple therapy
  - PPI + amoxicillin or metronidazole + clarithromycin
  - 10-14 days of treatment (14 preferred)
  - Efficacy affected by previous macrolide exposure
- Quadruple Therapy
  - PPI + Bismuth + Metronidazole + Tetracycline
  - 1st line, PCN allergy, previous macrolide exposure, failure of triple therapy
  - 10-14 days of treatment

Patient Case #4

- HPI: 35 year old male with ulcerative colitis (pancolitis). Experiences 5-6 bloody bowel movements per day when prednisone is reduced to less than 40mg/day.
- MEDS: Balsalazide 6.75 g/day x 2 years, prednisone 40 mg/day x 1 year

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Patient Case #4

- What would be an appropriate modification of his drug regimen at this time?

A. Change balsalazide to sulfasalazine 6g/day
B. Initiate therapy with methotrexate IM weekly
C. Initiate infliximab and taper prednisone
D. Add mesalamine suppository daily

Handout Page 32; Answer Page

Clinical Findings	Ulcerative Colitis	Crohn's Disease
Bowel Involvement	Rectum/Colon	Mouth to Anus
Perianal Involvement	No	Yes
Depth	Superficial	Submucosa/deeper
Pattern of inflammation	Continuous	Patchy
Histology	Crypt abscesses	Granulomas
Fistula, perforation, or Strictures	No	Yes
Toxic megacolon	Yes	No
Colorectal cancer	Yes	Uncommon
Malnutrition	Rare	Yes
Pseudopolyps	Common	Fairly Common

Drug Treatment Options

- 5-Aminosalicylates
  - Sulfasalazine
  - Mesalamine
  - Olsalazine
  - Balsalazide
- Antibiotics
  - Metronidazole
  - Ciprofloxacin
- Corticosteroids
- Immunomodulators
  - Azathioprine
  - 6-Mercaptopurine
  - Methotrexate
  - Cyclosporine
  - Tacrolimus
- Biologics
  - Infliximab
  - Adalimumab
  - Certolizumab
  - Natalizumab

Approach to the Treatment of IBD

1. Indentify disease: UC vs. CD
2. Severity: Active (mild to fulminant) or remission
3. Determine extent and location of disease
4. Pick drug(s) based on
   - Onset of action
   - Formulation (Oral, Topical, Parenteral)
   - Effectiveness
   - Potential adverse effects or contraindications

IBD Treatment Guidelines

Severity	UC	Crohn's
Mild-Moderate	Aminosalicylate	Aminosalicylate or Budesonide (ileal)
Moderate to Severe	Infliximab OR Azathioprine/6-MP +/- Corticosteroid (short-term)	TNF-α inhibitor OR Azathioprine/6-MP OR Methotrexate +/- Corticosteroid (short-term) Natalizumab (last line)

Key Safety Concerns in IBD

Drug(s)	Adverse Effects
TNF-alpha antagonists	• Risk of infection (screen for TB and Viral hepatitis) • Risk of Heart Failure and/or exacerbation • Hepatosplenic T-cell lymphoma when used with azathioprine or 6-MP in young male patients • Antibody formation
Antimotility agents	• Risk of toxic megacolon in active disease
Azathioprine/6MP	• Bone marrow suppression, pancreatitis, hypersensitivity • Need to check TPMT activity
Methotrexate	• Bone marrow suppression, pulmonary and hepatic toxicity
Corticosteroids	• Adrenal suppression, metabolic effects, infection
Natalizumab	• Progressive mutilfocal leukoencephalopathy

Patient Case #5

- HPI: 25 year old woman with Crohn's disease. Presents with a 2 day history of crampy abdominal pain, fever, fatigue, and 10-12 bloody stools per day.
- MEDS: Pentasa 250mg #4 caps 2 times/day
- PMH: Crohn's Disease x 5 years
- Vitals: Temp 101F, HR=110, RR=18, BP = 118/68

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Patient Case #5

- Which of the following therapeutic choices is best?

Increase dose of Pentasa to 4 grams/day

Cyclosporine 4 mg/hr continuous infusion

Surgery consult for immediate colectomy

Hydrocortisone 100 mg IV q 8 hours

Handout Page 32; Answer Page 71

Patient Case #6

- HPI: 47 year old woman with nausea, abdominal pain, fever. Abdominal distention with tenderness and shifting dullness.
- PMH: Cirrhosis (Class C)
- MEDS: Furosemide, spironolactone
- Diagnostics: Paracentesis (albumin 0.9 g/dl, WBC 1000/mm^3), Scr 1.2 mg/dl, BUN 37 mg/dl, AST IU/ml, ALT 20 IU/ml, Albumin 2.5 g/dl, T bili 3.2 mg/dl

Handout Page 39; Answer Page 71

Patient Case #6

- Which recommendation is best at this time for treatment of this patient's hepatic encephalopathy?

A. Intravenous albumin
B. Intravenous vancomycin plus tobramycin
C. Intravenous cefotaxime plus albumin
D. Oral trimethoprim/sulfamethoxazole DS daily

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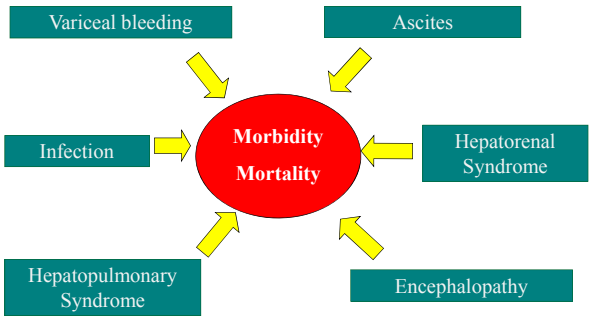
Complications of Cirrhosis



Spontaneous Bacterial Peritonitis

- Definition: Primary infection of the ascitic fluid
- Pathogens
  - Enteric gram negatives
  - Streptococci
- Clinical features
  - Fever, abdominal pain, AMS, vomiting
  - High risk of hepatorenal syndrome, increased mortality
  - Ascitic fluid PMN > 250 mm^3

SBP Treatment and Prevention

- Treatment: 3rd gen Cephalosporin + albumin
- Primary Prevention
  - During setting of an acute GI bleed
  - Ascitic fluid protein < 1.5 g/dl + Scr > 1.2 mg/dl or BUN > 25 mg/dl or Na < 130 mEq/L, or CP > 9 with bilirubin > 3 mg/dl
- Secondary Prevention: any patient with prior episode
- Hospital: Ceftriaxone/Cefotaxime, Fluoroquinolone
- Outpatient: TMP/SMX, Norfloxacin/ciprofloxacin

Patient Case #7

- HPI: 36 year old female with 36 hours of hematemesis, fatigue, dizziness, black tarry stools.
- PMH: Cirrhosis, alcohol abuse, MI (2 years ago)
- Diagnostics: EGD several large esophageal varices that are banded.

Handout Page 39; Answer Page 71

Patient Case #7

- In addition to the endoscopic band ligation which of the pharmacologic interventions is best?

A. Nadolol 20mg orally once a day x 3 days
B. Vasopressin continuous infusion x 2 days
C. Octreotide 50 ug bolus, then 50 ug/hr for 5 days
D. Pantoprazole 80mg bolus, then 8mg/hr x 72 hours

Handout Page 39; Answer Page 71

Variceal Bleeding

- Varices: Collateral vessels formed secondary to increased resistance to blood flow within the liver
- Bleeding risk
  - 25-35% of patient with cirrhosis
  - 30-50% mortality per bleed
- High recurrence rate
  - ~70% within first month of bleed

Treatment of Variceal Bleeding

- Stabilization + IV fluids
- Endoscopic interventions
  - Sclerotherapy
  - Band ligation
- Medical Management
  - Vasopressin + nitroglycerin
  - Octreotide x 3-5 days
  - Antibiotics (3rd Gen Ceph or Fluoroquinolone)

Prevention of Variceal Bleeding

- Pharmacologic +/- endoscopic
- Primary prevention
  - Small varices + high bleeding risk
  - Medium/Large varices
  - Non selective beta blockers
- Secondary prevention
  - All patients with history of bleeding
  - Non selective beta blockers
  - Endoscopic (band ligation)

Patient Case #8

- HPI: 45-year old woman with history of IVDA. Diagnosed 8 months ago with HBV. Treatment naive. No ascites or encephalopathy.
- Diagnostics:
  - AST 650 IU/ml, ALT 850 IU/ml
  - HBSAg (+), HBeAg (+), YMDD mutation
  - HBV DNA 107, 000 IU/ml
  - Biopsy: severe necroinflammation/bridging fibrosis

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Patient Case #8

- What is the most appropriate course of action at this time?

A. No treatment; Recheck HBV DNA in 6 months
B. Initiate PEG-IFN + ribavirin
C. Initiate lamivudine 100 mg/day
D. Initiate tenofovir 300 mg/day

Handout Page 53; Answer Page 71

Hepatitis B

- DNA Virus, Genotypes A-H
- Transmission
  - Parenteral, bodily fluids, sexual contact, perinatal
- Detect via serologies, symptoms, LFTs
  - Patients with active disease will be HBsAg (+)
- Treat patients with chronic disease (> 6 months)
  - > 2 x ALT, HBV DNA > 20,000 IU/ml

Chronic Hepatitis B Treatment

- Need to distinguish if HBV:
  - is HBeAg positive or negative
  - Harbors the "YMDD mutation" of the DNA polymerase
- Difficult patient populations
  - Decompensated liver disease
  - Co-infection
  - Treatment experienced

Summary of HBV Treatment Recommendations

HBV Population	Preferred Treatment Options	Duration	Comments
HBeAg positive	Entecavir and tenofovir are preferred oral agents Use of the other oral reverse transcriptase inhibitors is possible but not preferred	Minimum of 1 year	Preferred if contraindications or nonresponse to INFα
	INFα PEG-INFα	16 weeks 48 weeks	If contraindication or no response, use entecavir and tenofovir
HBeAg negative	Entecavir and tenofovir are preferred oral agents Use of the other oral reverse transcriptase inhibitors is possible but not preferred	> 1 year	Preferred if contraindications or no response to INFα
	INFα PEG-INFα	≥ 1 year	If contraindication or nonresponse, use entecavir and tenofovir

Nucleoside Analog Adverse Effects

- Class effects
  - Rebound hepatitis upon discontinuation
  - GI Effects (N/V/D/Abdominal pain)
  - HIV resistance
  - Lactic Acidosis (rare)
  - Reductions in bone mineral density
- Nephrotoxicity (adefovir)
- Telbivudine
  - Elevations in CK
  - Peripheral neuropathy
- Renally dose all medications

Patient Case #9

- HPI: 38 year old male with chronic hepatitis C (genotype 1b) currently undergoing treatment Evaluated at 12 week follow up appointment after starting treatment.
- MEDS: Pegylated interferon + ribavirin
- NKDA
- LABS:
  - AST 350 IU/ml, ALT 420 IU/ml
  - HCV RNA 850,000 IU/ml
  - SCr 1 mg/dl, Hb 12 g/dl, WBC 12 x 10^3

Handout Page 53; Answer Page 72

Patient Case #9

- What is the most appropriate course of action at this time?

A. Reassess in 12 months
B. Initiate tenofovir
C. Inititate PEG-INF and ribavirin
D. Inititate PEG-INF, ribavirin, and telaprevir

Handout Page 53; Answer Page 72

Hepatitis C

- RNA Virus
  - Genotypes 1-6 (1-3 most common is US)
    - Several subtypes
  - Genotype 1 most resistant to drug treatment
  - Transfusion, IV drug abuse, transplant
- Major cause of chronic liver disease
  - 60-80% progression following acute infection
  - #1 reason for transplant

Treatment of Chronic Hepatitis C

- First line:
  - Genotype 1 :Pegylated interferon + ribavirin + telaprevir OR boceprevir
  - Genotypes 2 and 3 :Pegylated interferon + ribavirin
- Pegylated Interferon Dosing:
  - Pegasys: 180ug SQ Weekly
  - Peg Intron: 1-1.5 ug/kg/week SQ
- Ribavirin orally in 2 divided doses:
  - Dose differs based on genotype, weight, and interferon product

Direct Acting Antivirals (DAAs)

	Telapravir (Incivek®)	Boceprevir (Victrelis®)
FDA Approved indication	• Chronic HCV therapy (genotype 1) in combination with PEG-INf alfa and ribavirin in patients with compensated liver disease • Not studied in Child-Pugh class B or C	• chronic HCV genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (≥18 years of age) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

Direct Acting Antivirals (DAAs)

	Telapravir (Incivek®)	Boceprevir (Victrelis®)
Dose	• 750 mg three times daily for 12 weeks plus PEG-INF followed by PEG-INF and ribavirin x 12 weeks if undetectable HCV RNA at week 4 and 12. • 375 mg tablets • Give doses 7-9 hours apart; give with meal that has at least 20 g fat ingested 20 minutes prior • Take missed doses if within 4 hours	• 800 mg orally three times daily starting after 4 weeks of PEG-INF and ribavirin • 200 mg capsules • Give doses 7-9 hours apart; give with meal or light snack • Take missed doses if within 2 hours

DAA Safety

- Both contraindicated in pregnancy and in male partners of pregnant women
- Telaprevir
  - Rash (up to 56%) maculopapular/eczematous
  - DRESS, Stevens Johnson Syndrome
  - Anemia, pruritis, nausea
- Boceprevir
  - Anemia, neutropenia, fatigue, dysgeusia

DAA Drug Interactions

- **Both are potent CYP 3A4/5 inhibitors**
- **Several CYP3A4 substrates or inducers are contraindicated**

Telaprevir	Boceprevir
Alfuzosin	Alfuzosin
Rifampin	Rifampin
Dihydroergotamine,ergonovine, ergotamine,methylergonovine	Dihydroergotamine,ergonovine, ergotamine,methylergonovine
Cisapride St. John's Wort Pimozide Tadalafil, sildenafil Oral triazolam or midazolam	Cisapride St. John's Wort Pimozide Drosperinone
Atorvastatin, lovastatin, simvastatin	lovastatin, simvastatin Carbamazepine, phenytoin, phenobarbital

DAA Drug Interactions

- **May narrow therapeutic index drugs must be adjusted**
- **Must check prescribing information**

- Antiarrthymics (amiodarone, fleicanide, profafenone)
- Digoxin
- Warafin
- Bosentan
- Azole antifungals
- Colchicine
- Clarithromycin
- Rifabutin
- DHP calcium channel blockers
- Dexamethasone
- Inhaled budesonide and fluticasone
- Methadone
- Cyclosporine/tacrolimus

HCV Monitoring

Parameter	Definition
Rapid Virological Response (RVR)	Negative HCV RNA at week 4 of treatment
Early Virological Response (EVR)	> 2 log decline in HCV RNA compared to baseline or negative HCV RNA at 12 weeks
End of Treatment Response (ETR)	Negative HCV RNA at the end of a 24 or 48 week course depending on genotype
Sustained Virological Response (SVR)	Negative HCV RNA 24 weeks after finishing treatment

Chronic Hepatitis C Treatment Duration

- Genotype 1:
  - It depends…..
- Genotypes 2 and 3: 24 weeks

Chronic Hepatitis C Treatment Duration

Regimen	Patient Group	HCV RNA Week 4	HCV RNA Week 8	Recommendation
PEG-INF+ Ribavirin + Boceprevir	Previously untreated	Undetectable	Undetectable	Continue all 3 drugs for 28 weeks total
		Detectable	Undetectable	1. Continue all 3 drugs for a total of 36 weeks. 2. Then continue PEG-INF and ribavirin for through week 48
	Previous partial responders or relapsers	Undetectable	Undetectable	Continue all 3 drugs for 36 weeks total
		Detectable	Undetectable	1. Continue all 3 drugs for a total of 36 weeks. 2. Then continue PEG-INF and ribavirin for through week 48
	Patients with HCV RNA > 100 IU/ml at week 12 or detectable HCV RNA at week 24	NA	NA	1. Discontinue all 3 drugs

Chronic Hepatitis C Treatment Duration

	Patient Group	HCV RNA Week 4	HCV RNA Week 12	Recommendation
PEG-INF + Ribavirin + Telaprevir	Treatment naive or prior relapse	Undetectable	Undetectable	1. Continue all 3 drugs for 12 weeks 2. Then treat with PEG-INF and ribavirin for an additional 12 weeks (24 weeks total)
		Detectable (1000 IU/ml or less)	Detectable (1000 IU/ml or less)	1. Continue all 3 drugs for 12 weeks 2. Then treat with PEG-INF and ribavirin for an additional 36 weeks (48 weeks total)
	All patients	≥1000 IU/ml	≥1000 IU/ml	1. Discontinue all 3 drugs at week 12
	Detectable HCV RNA at 24 weeks	NA	NA	1. Discontinue PEG-INF and ribavirin

Patient Case #10

- HPI: 55 year old man with chronic alcohol abuse and chronic pancreatitis. Steatorrhea and weight loss (now 135 lb)
- LABS: Albumin 2.1 g/dl, Fecal fat 20g/day
- Medications: morphine CR, oxycodone IR as needed

Handout Page 67; Answer Page 72

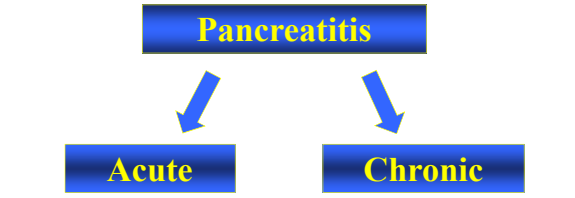
Patient Case #10

- What is the best course of action for this patient?

A. Increase morphine CR to 60 mg twice daily
B. Initiate dronabinol to improve appetite
C. Initiate pancrelipase 30,000 units/meal
D. Add a multivitamin to his regimen

Handout Page 67; Answer Page 72

Overview



- Mild-Severe Inflammation
- Generally reversible exocrine and/or endocrine function
- Rarely progresses to chronic
- Pain, N/V, sepsis, organ dysfunction

- Longstanding pancreatic injury
- Fibrosis/destruction of tissue
- Irreversible exocrine and/or endocrine function
- Pain, steatorrhea, malnutrition, diabetes

Acute Pancreatitis

- Largely supportive Care
- Pain management
- Antiemetics
- Nutritional support
  - Enteral
  - Hyperglycemia
- Antibiotics
  - Infection, abscess, or necrosis

Chronic Pancreatitis

Complication	Targeted Therapies	Comments
Pain	Narcotic +/ non-narcotic therapies Pancreatic enzymes	• Acetaminophen and/or NSAIDs • Long acting narcotic preparations + IR breakthrough • Caution with acetaminophen and narcotics if alcohol use is continued
Maldigeston and Malabsorption	Pancreatic enzymes Fat soluble vitamins	• Start around 30,000-40,000 lipase units per meal; ½ dose for snacks • Do not crush or chew • Max 2500 u/kg/dose; 10,000 u/kg/day • Titrate to steatorrhea + weight gain • Porcine based so avoid if pork allergy • ADEK
Diabetes	Insulin	• Long acting + short acting • Oral intake may be variable

Patient Case #11

- HPI: 32-year-old woman with crampy abdominal pain, bloating and constipation for 6 months. Not food related. Diagnosed with IBS-C.
- LABS: within normal limits
- Medications and allergies: none

Handout Page 67; Answer Page 72

Patient Case #11

A. Which of the following therapeutic interventions is best for this patient?

B. Amitriptyline 50 mg/day
C. Senna 2 tablets twice daily
D. Tegaserod 6 mg twice daily
D. Lubiprostone 8 mcg twice daily

Handout Page 67; Answer Page 72

Irritable bowel syndrome

- Categories
  - Diarrhea Predominant (IBS-D)
  - Constipation Predominant (IBS-C)
  - Mixed Pattern (IBS-M)
- Features
  - Change in frequency and/or stool appearance
  - Pain, bloating, Relief with defecation
- Target main symptoms and comorbidities

Therapies	Comments
Hyoscyamine, dicyclomine	• Target pain due to spasm and also treat diarrhea • Initial or adjunctive therapy for IBS-D or IBS-M
Tricyclic antidepressants	• Target pain and diarrhea • Generally reserved for IBS-D • Low doses
SSRIs, SNRIs	• Target pain and often have promotility action in IBS-D • Can also treat comorbid depression and anxiety
Lubiprostone	• Indicated for IBS-C in women > 18 years • Main adverse effect is nausea, more expensive option
Loperamide	• Adjunctive for IBS-D, but does not treat pain
Probiotics	• Some potential improvement in global symptoms and pain
Alosetron	• Indicted for IBS-D in women > 18 years failing other therapies • Must be enrolled in prescribing program • Risk of ischemic colitis
Tegaserod	• Indication: IBS-C; available on emergency use only due to CV risk
Rifaximin	• Some data to support improvement in bloating

Patient Case #12

- HPI: 30-year-old pregnant woman (14 weeks) with myalgias, watery diarrhea (4-5), vomiting x 1.
- LABS: influenza (-), WBC 8000 x 10^3
- Medications: prenatal vitamin
- Allergies: none

Handout Page 67; Answer Page 72

Patient Case #12

- What is the most appropriate course of action at this time for this patients diarrhea?

A. Loperamide
B. Bismuth subsalicylate
C. Lactase
D. Pyridoxine

Handout Page 67; Answer Page 72

Management of Diarrhea

- Remove correct underlying cause
  - Identify drug-induced causes
- Rehydration
  - ORS
  - Parenteral
- Dietary modification

Antidiarreheal Preparations

Therapies	Comments
Loperamide	• OTC and prescription products, tablet and liquid • OTC indicated in age > 6 • Pregnancy category B
Opioids (diphenoxylate, tincture of opium)	• Generally reserved for more severe cases • Increased risk of CNS adverse effects

Bismuth subsalicylate	• OTC tablet and liquid preparations
	• Avoid:
	  • Patients < 12 years of age
	  • Pregnancy
	  • Salicylate allergy
	  • Signs/symptoms of bleeding or mucous
	• Stool and tongue discoloration
	• Chelation interactions

Lactase	• Suspected or diagnosed lactose intolerance
Probiotics	• Data in AAD, IBD, IBS, radiation induced

THE END

Updates in Therapeutics® 2013: The Pharmacotherapy Preparatory Review & Recertification Course
Biostatistics: A Refresher

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Page 1-145

Conflict of Interest Disclosures

No conflicts of interest to disclose related to this presentation

Outline

- Purpose: What this is and isn't
- Introduction: What do I need to know?
- Variables
- Descriptive statistics
- Inferential statistics
- Hypothesis testing
- Statistical tests
- Decision errors

Statistics

- ..collecting, classifying, summarizing, and analyzing data (demystifying?)
- Tools for quantifying clinical and laboratory data in a meaningful way
- Assists in determining whether/how much a treatment or procedure affects a group
- Why pharmacists need to know statistics?
  - Hopefully obvious to this group
  - More importantly: WHAT do I need to know

Page 1-148

What do you need to know?

- Descriptive statistics/simple statistics
  - Mean, median, frequency, SD, range, CI
- Chi-square; Fisher exact test
- t-test(s)
- Kaplan Meier, Cox proportional hazards
- Analysis of variance
- Correlation
- Regression (linear, multiple, logistic, other)
- Multivariate analysis
- Wilcoxon rank sum test (non-parametric)

Pages 1-148-9

Summarized from: *JAMA* 2007; 298:1010-22

Statistics: WHY do you need to know it?

- Domain 2: Retrieval, Generation, Interpretation, and Dissemination of Knowledge in Pharmacotherapy (25%)
  - Interpret biomedical literature with respect to study design and methodology, statistical analysis, and significance of reported data and conclusions.
  - Knowledge of biostatistical methods, clinical and statistical significance, research hypothesis generation, research design and methodology, and protocol and proposal development

Page 1-148

Types of Variables/Data
Discrete variables

- Can only take a limited number of values within a given range
  - Nominal: Classified into groups in an unordered manner and with no indication of relative severity
    - Sex (M/F), mortality (yes/no), disease state (present/absent)
  - Ordinal: Ranked in a specific order but with no consistent level of magnitude of difference between ranks
    - NYHA functional class: I, II, III, IV
- COMMON ERROR:
  - Use of means (SDs) with ordinal data.

Page 1-149

Types of Variables/Data
Continuous Variables

- Counting variables, can take on any value within a given range
- Interval Scaled: Data ranked in a specific order with a consistent change in magnitude between units; the zero point is arbitrary
  - degrees Fahrenheit
- Ratio Scaled: Like "interval" but with an absolute zero
  - degrees Kelvin, pulse, BP, time, distance

Page 1-149

Types of Statistics

- Descriptive Statistics
  - Used to summarize and describe data that are collected or generated in research studies.
  - This is done both visually and numerically
- Inferential Statistics
  - Conclusions or generalizations made about a population (large group) from the study of a sample of that population

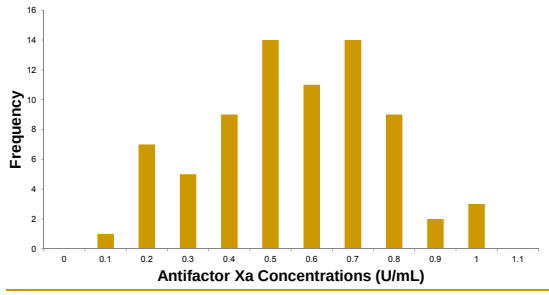
Pages 1-149-51

Types of Statistics: Descriptive statistics

- Visual methods of describing data
  - Frequency distribution
  - Histogram
  - Scatter plot

Pages 1-149-50

Types of Statistics: Descriptive statistics
Histogram



Descriptive statistics: Numerical methods
Measures of Central Tendency

- Mean
  - Used only for continuous and normally distributed data
  - Very sensitive to outliers (tends toward the tail)
  - Most commonly used/well-understood
- Median (a.k.a 50th percentile)
  - Midpoint of the values when placed in order from highest to lowest. Half above and below.
  - Used for ordinal or continuous data (especially for skewed populations)
  - Insensitive to outliers

Page 1-150

Descriptive statistics: Numerical methods
Measures of Central Tendency

- Mode
  - Most common value in a distribution
  - Used for nominal, ordinal, or continuous data
  - Data may have > one mode (bimodal, trimodal)
  - Describes meaningful distributions with a large range of values

Page 1-150

Measures of Data Spread and Variability
Standard Deviation

- Measure of the variability about the mean
- Applied to continuous data that are ~normally distributed or transformed to be
- Empirical rule: 68% within ±1 SD, 95% within ±2 SD, and 99% within ±3 SD
- Coefficient of variation (CV) relates the mean to the SD
  - (SD/mean × 100%)
- Variance = SD^2

Page 1-150

Measures of Data Spread and Variability
Range

- Difference between the smallest and largest
- Applied to "parametric" and "non-parametric"
- Easy to compute
- Size of range is very sensitive to outliers
- Often reported as the actual value rather than the difference between the two extreme values

Page 1-150

Measures of Data Spread and Variability
Percentiles

- Point in a distribution which a value is larger than some percentage of the other values
- 75th percentile: 75% of the values are smaller
- Does not assume the population has a normal or any other distribution
- IQR: percentile that describes the middle 50%, encompasses the 25th–75th percentile.

Pages 1-150-1

Example: Pharm.D. students were asked the following questions…..

	2006 (n=119)	2007 (n=127)	2008 (n=134)
The examination questions in this course were appropriate to the material that was covered			
Mean (SD)	2.48 (1.08)	3.80 (0.91)	4.04 (0.82)
Median (IQR)	2.0 (2.0-3.0)	4.0 (3.0-4.0)	4.0 (4.0-5.0)
I understand the importance of this course to the profession of Pharmacy			
Mean (SD)	3.51 (1.08)	3.57 (0.92)	3.90 (0.90)
Median (IQR)	4.0 (3.0-4.0)	4.0 (3.0-4.0)	4.0 (4.0-4.0)

1=S. Disagree; 2=Disagree; 3=Neutral; 4=Agree; 5=S. Agree

Curr Pharm Teach Learn 2010; 2:171-9

Measures of Data Spread and Variability
Summary

- Measures of central tendency should be presented along with measures of variability
- What measures of central tendency should be presented with…
  - Continuous, interval scaled data?
  - Ordinal data?
- What measures of spread and variability should be presented with…
  - Means?
  - Medians?

Pages 1-149-51

Dataset
HDL-cholesterol example

- 20 HDL concentrations measured as part of a clinical study…..

64	60	59	65	64	62	54
54	68	67	79	55	48	65
59	65	87	49	46	46	

- Calculate the mean, median, and mode of the above data set.
- Calculate the range, SD and SEM
- Evaluate the visual presentation of the data

Pages 1-149-51

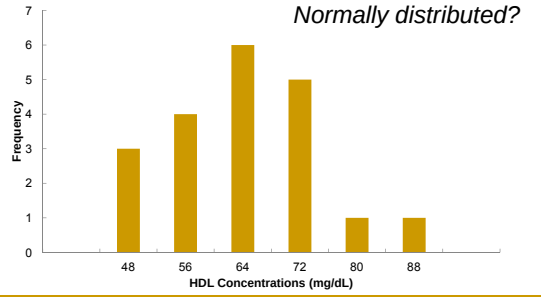
Dataset
HDL-cholesterol example

Measure of Central Tendency	Mean 60.8	Median 61	Mode 65
Measure of Spread	SD 10.4	Range 41 (46-87)	IQR (54-65)

- SEM: 2.3
- Evaluate the visual presentation of the data…..

Pages 1-149-51

HDL-cholesterol example
Grouped Histogram



Inferential statistics

- Conclusions made about a population from a study of a sample of that population
- Choosing/evaluating statistical methods depends on the type of data used
- Educated statement about an unknown population is commonly referred to as an inference
- Statistical inference can be made by estimation or hypothesis testing

Page 1-151

Population Distributions
Discrete

- Binomial distribution
- Poisson distribution

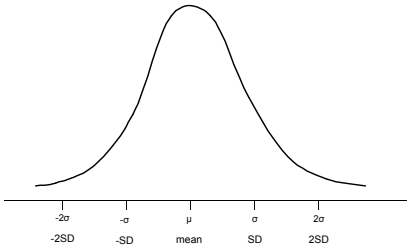
Page 1-151

Population Distributions
Normal (Gaussian) Distribution

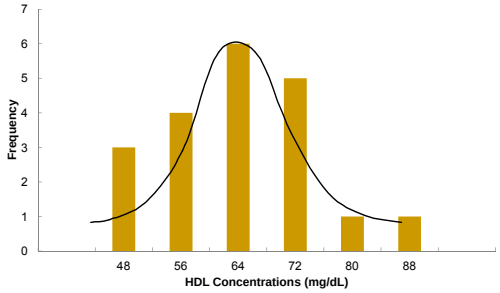
- Most common model for population distributions
- Symmetric or “bell-shaped”
- Important landmarks
  - μ: Population mean is equal to zero.
  - σ: Population SD is equal to 1.
  - x and s represent the sample mean and SD.

Pages 1-151-2

Population Distributions
Normal (Gaussian) Distribution



HDL-cholesterol example
Grouped Histogram



Normal (Gaussian) Distribution
How do we assess?

- Frequency distribution and histograms
- Median ~ mean (most practical and easiest to use)
  - HDL Example: 61 vs. 60.8 mg/dL
  - Formal test: Kolmogorov–Smirnov test
  - Challenging to evaluate when you are reading a paper
- Mean/SD define a normal distribution…….. termed *parametric*

Pages 1-151-2

Normal (Gaussian) Distribution
Estimation and sampling variability

- Separate samples from a population will give different estimates
- Distribution of means approximates a normal distribution.
  - Mean of this "distribution of means" = μ (pop mean)
  - SD of means is estimated by the SEM.
  - 95% of the sample means lie within ±2 SEM of μ
- Distribution of means from these random samples is ~ normal regardless of the underlying population distribution

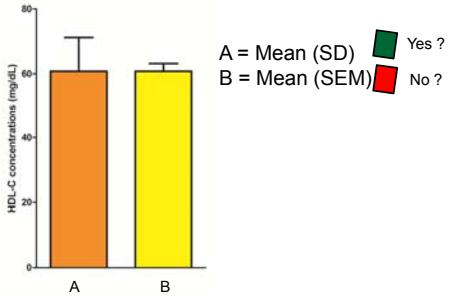
Pages 1-151-2

Normal (Gaussian) Distribution
Standard Error of the Mean (SEM)

- SEM = SD/sqrt(n)
- <u>The SEM quantifies uncertainty in the estimate of the mean, not variability in the sample.</u>
- Why is all of this worth knowing about the difference between the SEM and SD?
  - Application: 95% CI is ~ mean ± 2 ● SEM
  - Deception?

Page 1-152

Dataset: HDL-cholesterol example
SD or SEM?



Confidence Intervals

- 95% CIs are the most commonly reported CIs
  - In repeated samples, 95% of all CIs include true population value.
  - Why are 95% CIs most often reported?
- Assume a baseline birth weight in a group with a mean ± SD of 1.18 ± 0.4 kg
  - 95% CI ~ mean ± 1.96 × SEM (or 2 × SEM)
  - What is the 95% CI? (1.07, 1.29)
- SD, SEM, and CIs are often used interchangeably (incorrectly)

Pages 1-152-3

CI's Instead of Standard Hypothesis Testing?

- Hypothesis testing and calculation of p-values tell us whether there is (or is not), a statistically significant difference, but nothing about the magnitude
- CI's
  - Help to determine the importance of a finding and its application
  - Provide an idea of the magnitude of the difference
  - Difference between two continuous variables:
    - CI that includes 0 (no diff) is not statistically significant ($p \geq 0.05$)
    - There is no need to show both the 95% CI and the p-value
  - CI's for OR and RR are evaluated differently

Page 1-153

Hypothesis Testing

- Null hypothesis (H_0):
  - No difference between comparator groups (Tx A = Tx B)
- Alternative hypothesis (H_a):
  - States that there is a difference (Tx A ≠ Tx B)
- Results of "hypothesis testing" will indicate whether there is enough "evidence" to reject H_0
  - H_0 is "rejected"= statistically significant (SS) difference
  - H_0 is "not rejected" = no SS difference
  - We are not concluding that the treatments are equal.

Pages 1-153-4

Statistical Tests and Choosing a Statistical Test

- Dependent on:
  - Type of data (nominal, ordinal, continuous)
  - Distribution of data (normal, etc.)
  - Study design (parallel, crossover, etc.)
  - Presence of confounding variables
  - One-tailed versus two-tailed
- Parametric vs. nonparametric tests

Page 1-154

Parametric vs. Non-parametric

- Parametric tests assume…
  - Data being investigated have an underlying ~normal distribution
  - Data are continuous
  - Data being investigated have variances that are ~ equal
- Nonparametric tests…
  - Data are not normally distributed
  - Data do not meet other criteria (discrete data)

Page 1-154

Parametric Tests
Student's t-test

- One-sample test:
  - Compares the mean of the study sample with the population mean

Group 1 Mean	Known population mean

Pages 1-154-5

Parametric Tests
Student's t-test(s)

- Two-sample, independent samples, or unpaired test:
  - Compares the means of two independent samples.

Group 1	Group 2

Page 1-155

Parametric Tests
Student's t-test(s)

- Two-sample, independent samples, or unpaired test:
  - Equal variance test
    - Rule of thumb for variances: Ratio of larger to smaller variance is greater than 2, we conclude variances are different
    - Formal test for differences in variances: F test
    - Adjustments can be made for cases of unequal variance.
  - Unequal variance test
    - Correction employed to account for variances

Page 1-155

Parametric Tests
Student's t-test(s)

- Two-sample, independent samples, or unpaired test:
  - Equal variance test
    - Rule of thumb for variances: Ratio of larger to smaller variance is greater than 2, we conclude variances are different
    - Formal test for differences in variances: F test
    - Adjustments can be made for cases of unequal variance.
  - Unequal variance test
    - Correction employed to account for variances

Page 1-155

Parametric Tests
Student's t-test(s)

- Paired test: Compares the mean difference of paired or matched samples. This is a related samples test.

Group 1	
Measurement 1	Measurement 2

Page 1-155

Parametric Tests
Student's t-test(s)

- COMMON ERROR:
  - Use of multiple t-tests to compare more than two groups

Page 1-155

Parametric Tests
Analysis of Variance (ANOVA)

- One-way (single factor) ANOVA:
  - Compares the means of ≥3 groups
    - Independent samples test

Young	Group 1	Group 2	Group 3

- Two-way (two factor) ANOVA:
  - Additional factor added

Young	Group 1	Group 2	Group 3
Elderly	Group 1	Group 2	Group 3

Page 1-155

Parametric Tests
Analysis of Variance (ANOVA)

- Repeated Measures ANOVA:
  - Related samples test, extension of paired t-test

	Related Measurements		
Young (Group 1)	Measurement 1	Measurement 2	Measurement 3

Page 1-155

Parametric Tests
Post-hoc tests

- Remember multiple t-test error
- Maintains appropriate α-error rate
- Determine which groups actually differ
- Conducted if ANOVA statistically significant
- Post hoc tests (examples):
  - Tukey HSD (Honestly Significant Difference),
  - Bonferroni
  - Scheffe
  - Newman-Keuls

Page 1-155

Non-Parametric Tests

- Tests for ordinal data or continuous data (that do not meet appropriate assumptions for parametric tests)
- Tests for independent samples
  - Wilcoxon rank sum and Mann-Whitney U-test
    - Compares 2 independent samples (independent samples t-test)
  - Kruskal-Wallis one-way ANOVA by ranks
    - Compares $\geq$ 3 independent groups (one-way ANOVA)
    - Post hoc testing

Pages 1-155-6

Non-Parametric Tests

- Tests for related or paired samples
  - Sign test and Wilcoxon signed rank test: Compares 2 matched or paired samples (paired t-test)
  - Friedman ANOVA by ranks: Compares $\geq$3 matched/ paired groups

Pages 1-155-6

Non-Parametric Tests
Nominal Data

- Chi-square (χ^2) test: Compares expected and observed proportions between $\geq$2 groups
  - Test of independence
  - Test of goodness of fit
- Fisher exact test: Use of Chi-square test for small groups (cells) containing <5 observations
- McNemar: Paired samples
- Mantel-Haenszel: Controls for the influence of confounders

Page 1-156

Choosing the Most Appropriate Statistical Test: Example

Group	Baseline LDL (mg/dL)	p-value Baseline	Final LDL (mg/dL)	p-value Final
Rosuvastatin (n=25)	152 ± 5	> 0.05	138 ± 7	> 0.05
Simvastatin (n=25)	151 ± 4		135 ± 5	

Page 1-156

Choosing the Most Appropriate Statistical Test: Example

	Rosuvastatin (n=25)	Simvastatin (n=25)
Men/Women	12/13	10/15
Smokers	10	13
Baseline LDL-C (mg/dL)	152 ± 5	151 ± 4

- Which is the appropriate statistical test to determine baseline differences in:
  - Sex distribution?
  - Low-density lipoprotein cholesterol?
  - Percentage of smokers and nonsmokers?

Page 1-156

Appropriate test to determine baseline differences in….

- 1. Sex distribution?
  2. Low-density lipoprotein cholesterol?
  3. Percentage of smokers and nonsmokers?

A. Wilcoxon signed rank test
B. Chi-square test
C. ANOVA
D. Two-sample t-test

Choosing the Most Appropriate Statistical Test: Example

	Rosuvastatin (n=25)	Simvastatin (n=25)
Baseline LDL (mg/dL)	152 ± 5	151 ± 4
Final LDL (mg/dL)	138 ± 7	135 ± 5
Δ LDL (mg/dL)	14 ± 6	16 ± 5

- Which is the appropriate statistical test to determine:
  - The effect of rosuvastatin on LDL-C
  - The primary end point: 3-month change in LDL-C
- The authors concluded that rosuvastatin is similar to simvastatin. What else would you like to know?

Page 1-156

Appropriate test to determine

- Effect of rosuvastatin on LDL-C
- Primary end point: 3-month change in LDL-C

A. Wilcoxon signed rank test
B. Chi-square test
C. ANOVA
D. Two-sample t-test

Decision Errors
Type I Error

- Probability of making Type I error = significance level (α)
  - Convention is to set the α to 0.05
  - 5.0% of the time, we will conclude there is a SS difference when actually one does not exist.
  - Calculated chance that a type I error has occurred is called the "p-value."
  - Lower p-value does not suggest more importance, only SS difference and less likely attributable to chance

Page 1-157

Decision Errors
Type II error

- Type II Error:
  - Convention: 0.10-0.20
  - Concluding that no difference exists when one truly does (not rejecting H_0 when it should be rejected)

Page 1-157

Decision Errors
Power (1-β)

- Ability to detect differences between groups if one actually exists
- Dependent on the following factors:
  - Predetermined α
  - Sample size
  - Size of the difference between the outcomes you wish to detect
  - Variability of the data that are being measured
- Power is decreased by….
  - As above and…
  - Poor study design
  - Incorrect statistical tests (use of nonparametric tests when parametric tests are appropriate)

Page 1-157

Decision Errors: Statistical power analysis and sample size calculation

- Should be performed in all studies a priori
- Necessary components for estimating appropriate sample size
  - Acceptable type II error rate (usually 0.10–0.20)
  - Observed difference in predicted study outcomes that is clinically significant
  - Expected variability in above
  - Acceptable type I error rate (usually 0.05)

Page 1-157

Statistical significance versus clinical significance

- Size of the p-value is not related to the importance of the result.
- Statistically significant not necessarily clinically significant
- Lack of statistical significance does not mean results are not important.
- With nonsignificant findings consider… sample size, estimated power, and observed variability

Page 1-158

Correlation and Regression Introduction

- Correlation examines the strength of the association between two variables.
  - It does not necessarily assume that one variable is useful in predicting the other.
- Regression examines the ability of one or more variables to predict another variable.

Pages 1-158-60

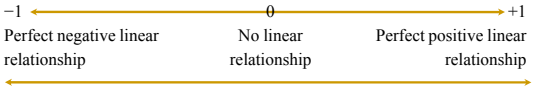
Correlation
Pearson Correlation

- "Strength" of the relationship between two variables that are..
  - normally distributed
  - ratio or interval scaled
  - linearly related
- Often referred to as the degree of association between the two variables
- Does not necessarily imply that one variable is dependent on the other

Pages 1-158-60

Correlation Coefficient

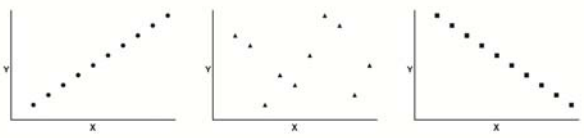
- Pearson correlation coefficient (r) ranges from −1 to +1 and can take any value in between….



- Hypothesis testing is performed to determine whether the correlation coefficient is different from zero. This test is highly influenced by sample size
- Spearman Rank Correlation: Nonparametric test that does not assume a normal distribution or continuous data. Can be used for ordinal data or nonnormally distributed continuous data

Pages 1-158-60

Correlation Coefficient



1
Perfect positive linear relationship

0
No linear relationship

-1
Perfect negative linear relationship

Correlation Pearls

- Closer r is to 1 (either + or −), the more highly correlated the two variables
- No consistent interpretation of the value of r
- Pay more attention to the magnitude of the correlation than to the p-value
- VIEW the relationship between the two variables

Pages 1-158-60

Regression

- Statistical technique related to correlation
- There are many different types
  - Simple linear regression:
    - continuous outcome (dependent) variable
    - continuous independent (causative) variable
- Two main purposes of regression:
  - Development of prediction model
  - Accuracy of prediction

Pages 1-159-60

Regression

- Development of prediction model
  - Making predictions of the dependent variable from the independent variable
  - $Y = mx + b$ (dependent variable = slope × independent variable + intercept)

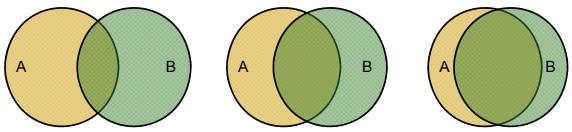
Pages 1-159-60

Regression

- Accuracy of prediction: How well the independent variable predicts the dependent variable.
  - Determines the extent of variability in the dependent variable that can be explained by the independent variable.
  - Coefficient of determination (r^2) describes this relationship. Values of r^2 can range between 0 and 1.
  - An r^2 of 0.80: 80% of the variability in *Y* is "explained" by the variability in *X*.
- Statistical tests associated with regression

Pages 1-159-60

Coefficient of determination (r^2)



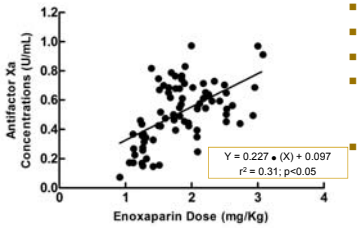
$r^2 \sim 0.25$ $r^2 \sim 0.5$ $r^2 \sim 0.80$

Types of Regression

- Simple linear regression
- Multiple linear regression
- Simple logistic regression
- Multiple logistic regression
- Nonlinear regression
- Polynomial regression

Page 1-159

Regression Example



What you should know…

- Slope and intercept?
- Required assumptions?
- r^2 interpretation?
- Predict antifactor Xa concentrations at doses of 2 and 3.75 mg/kg
- What does the p<0.05 value indicate?

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Survival Analysis

- Studies the time between entry in a study and some event (e.g., death, myocardial infarction)
  - Censoring makes survival methods unique
  - Subjects do not enter the study at the same time

Pages 1-160-1

Survival Analysis

- Kaplan-Meier method
  - Uses survival times to estimate the proportion of people who would survive a length of time
- Log-Rank Test
  - Compare the survival distributions ≥ 2 groups
- Cox proportional hazards model
  - Evaluate the impact of covariates on survival in two or more groups
  - Allows calculation of a hazard ratio (and CI)

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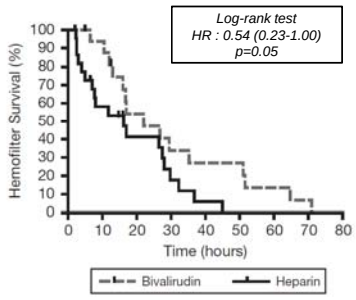
Survival Analysis
Kaplan-Meier method



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Pharmacotherapy 2010; 30:1117-26

Survival Analysis
Cox proportional hazards model

- Most popular method to evaluate the impact of covariates
  - Investigates several variables at a time
  - Actual method of construction/calculation is complex
  - Compares survival in two or more groups after adjusting for other variables
  - Allows calculation of a hazard ratio (and CI)

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