Outpatient Management of Congestive Heart Failure For the Primary Physician

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"It is much more important to know what sort of patient has a disease than what sort of disease a patient has."

Sir William Osler

Objectives of Talk

- 1. Identify reasons patients with heart failure decompensate and require hospital readmission
- 2. Identify strategies for effectively managing patients in the outpatient environment
- 3. Identify evidence-based therapies and evidence-based doses of those therapies for management of heart failure due to systolic dysfunction
- 4. Identify strategies for management of heart failure with normal ejection fraction

Definition of Congestive Heart Failure

A syndrome including **circulatory congestion** or **inadequate tissue perfusion** due to **abnormal heart function** and **associated neurohormonal abnormalities**

Pathophysiology of Heart Failure

How it gets that way

Pathophysiology of Congestive Heart Failure

- Myocardial damage
  - Ischemia, infarction (CAD)
  - Hypertension
  - Viral
  - Idiopathic
- Remodeling
  - Catecholamines
  - Renin-Angiotensin-Aldosterone System
  - Cytokines
  - Endothelin

Causes of Heart Failure (Italian Registry)

- Ischemic heart disease — 40 percent
- Dilated cardiomyopathy — 32 percent
- Primary valvular heart disease — 12 percent
- Hypertensive heart disease — 11 percent
- Other — 5 percent

Classification Systems for CHF

Classification of CHF

- May be defined in terms of:
  - Affected ventricle(s) – Right and/or Left
  - Primary manifestation – Congestion or Hypoperfusion
  - Relative Cardiac output – Low output or High output (e.g. thyrotoxicosis)
  - Ventricular function – Low ejection fraction ("Systolic Dysfunction") or Preserved ejection fraction ("HFNEF = Heart Failure with Normal Ejection Fraction")
  - Acute versus Chronic – ADHF (Acute Decompensated Heart Failure) vs Chronic Stable Congestive Heart Failure

Significance of CHF Classification

- Evidence base only exists for certain forms of congestive heart failure
- The evidence base is in evolution
- Understanding the pathophysiology of CHF enables us to understand what forms of therapy might be effective

New York Heart Association Functional Classifications

- Class I - symptoms of heart failure only at levels that would limit normal individuals
- Class II - symptoms of heart failure with ordinary exertion
- Class III - symptoms of heart failure on less than ordinary exertion
- Class IV - symptoms of heart failure at rest

Stages of Heart Failure

Heart failure develops over time in symptomatic and asymptomatic phases. Each phase can be targeted with specific treatments to reduce morbidity and mortality. The stages of heart failure development described below are excerpted from Hunt, SA, Baker, DW, Chin, MH, ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, ACC/AHA Practice Guidelines, 2001.

Stage A Heart Failure Patients

Patients at high risk of developing heart failure (HF) because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.

Stage B Heart Failure Patients

Patients who have developed structural heart disease that is strongly associated with the development of heart failure (HF) but who have never shown signs or symptoms of HF.

Stage C Heart Failure Patients

Patients who have current or prior symptoms of heart failure associated with underlying structural heart disease

Stage D Heart Failure Patients

Patients with advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy and who require the specialized interventions

Why do patients decompensate?

- Failure to take medications
  - Fear of or perception of side effects
  - Can't afford
  - Not on formulary
  - Not motivated to take
- Excess sodium in diet
- Worsening heart disease
- Worsening renal function

Strategies for Management of CHF

- Based on first "decongesting" the patient
- Then managing the underlying cardiac pathophysiologic abnormalities
  - For primary myocardial disease, the abnormalities are generally due to damage to the myocardium based on adverse effects of the neurohormonal response to ventricular failure – the very responses which are adaptive short-term become deleterious long-term
  - For valvular, pericardial and endomyocardial disease, the treatment is that of the underlying anatomical abnormality

Treatment of Acute Decompensated Heart Failure

Treatment of ADHF

(Acute Decompensated Heart Failure)

- Evidence-base is not robust
- The principles are relieving congestion and augmenting perfusion
- While one might expect that positive inotropic agents would be beneficial in this condition, a host of inotropic agents have failed to show long-term benefit, or have actually resulted in increased mortality
- Beta Blockers, one of the cornerstones of therapy for chronic heart failure, are contraindicated in ADHF

Role of Loop Diuretics in ADHF

Loop diuretics relieve symptoms of dyspnea and edema, but may cause:

Electrolyte abnormalities

Activation of RAAS and SNS

Diuretic resistance

Structural changes in distal tubule

Worsening renal function. (Furosemide lowers GFR by ~ 15%)

? Increased mortality

DOSE-HF study compared high and low dose loop diuretic, as continuous infusion or q12h i.v. bolus – showed no difference in outcome short-term

Ultrafiltration for ADHF

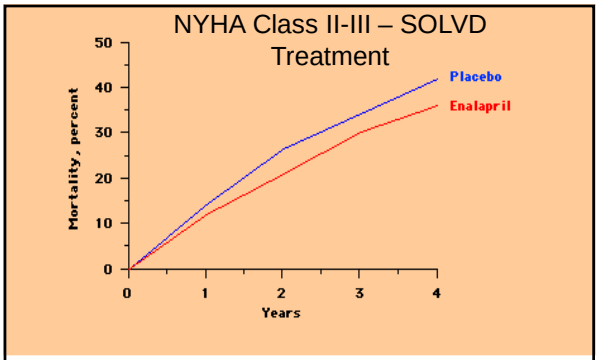
- Ultrafiltration, also called aquapheresis, a form of hemodialysis which allows removal of fluid that is isotonic with plasma. Simplified veno-venous ultrafiltraton device, with very small extracorporeal blood, minimizes hemodynamic shifts, and hypotension.
- UNLOAD trial published in 2007, showed that early ultrafiltration resulted in greater weight loss, greater fluid loss, and no difference in renal function. Rehospitalization in UNLOAD was less in UF group vs diuretic group. (JACC, 2007; 49;675-683)
- UF patients had less activation of RAAS and Catecholamine systems.

Treatment of Heart Failure due to Systolic Dysfunction

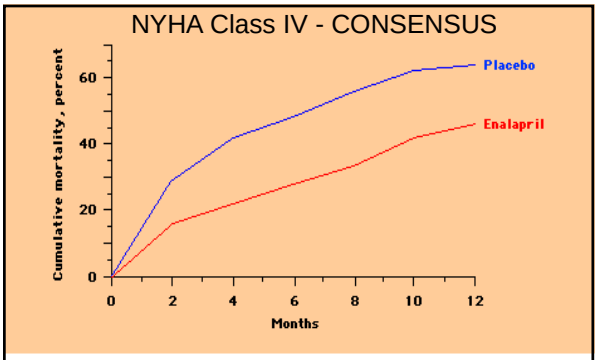
Evidence-based Therapies for Heart Failure due to Systolic Dysfunction

- This is the most robust evidence-based treatment for heart failure
- ACE-I or ARB for Heart Failure with LVSD
- Beta blocker for HF with LVSD (only 3 approved: carvedilol, metoprolol and bisoprolol)
- Aldosterone antagonists for patients with HF in NYHA Class IV or Class III with Myocardial Infarction
- Add Digoxin for patients who remain symptomatic
- The combination of Isosorbide Dinitrate and Hydralazine has a survival benefit in African-Americans

ACE-Inhibitor and/or ARB in Heart Failure with Systolic Dysfunction



ACE inhibitor improves survival in moderate CHF Enalapril, compared to placebo, decreases patient mortality in NYHA class II and III heart failure (p = 0.0036). (Data from The SOLVD Investigators, N Engl J Med 1991; 325:293.)



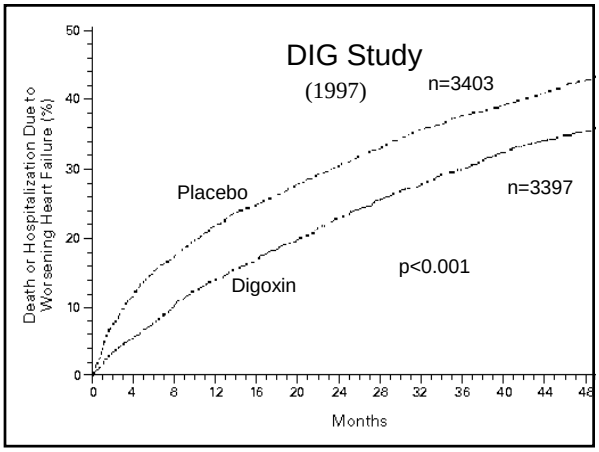
ACE inhibitor improves survival in advanced CHF Decreased mortality in patients with advanced NYHA class III or IV heart failure after treatment with enalapril compared to placebo (p = 0.003). (Data from The CONSENSUS Trial Study Group, N Engl J Med 1987; 316:1429.)

Results of CHARM (Candesartan Heart failure Assessment

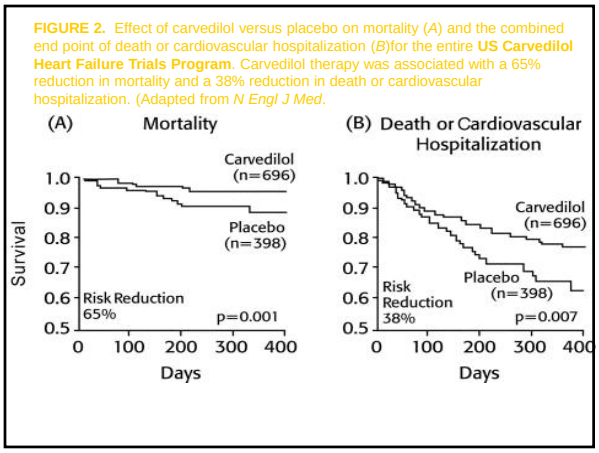
of Reduction in Mortality and morbidity) Studies

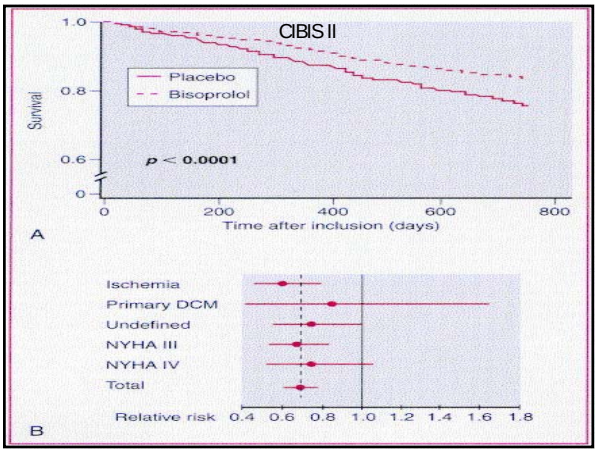
- CHARM-Alternative (ACE-Intolerant Patients): Use of candesartan resulted in a 23% (*P* < .001) relative risk reduction in cardiovascular death or heart failure hospitalization
- CHARM-Added (Addition of candesartan to an ACE-I in patients with EF<40%: Patients taking candesartan had a 15% lower risk of cardiovascular mortality (*P* = .005). Symptoms of heart failure as assessed by NYHA functional class were also improved (*P* < .001)

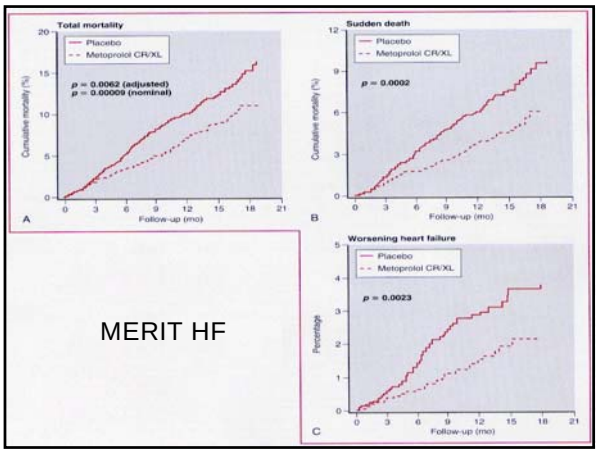
Digoxin in Heart Failure



Beta Blockers in Heart Failure





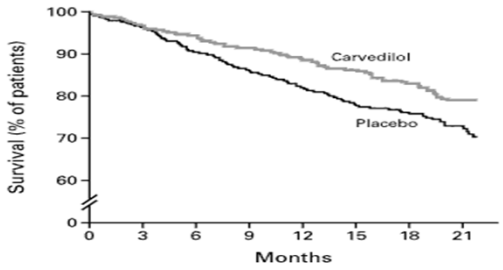


MERIT HF

COPERNICUS (Addition of Carvedilol to an ACE-I in pts. With Post-MI LVD):

Kaplan–Meier Analysis of Time to Death in the Placebo Group and the Carvedilol Group.

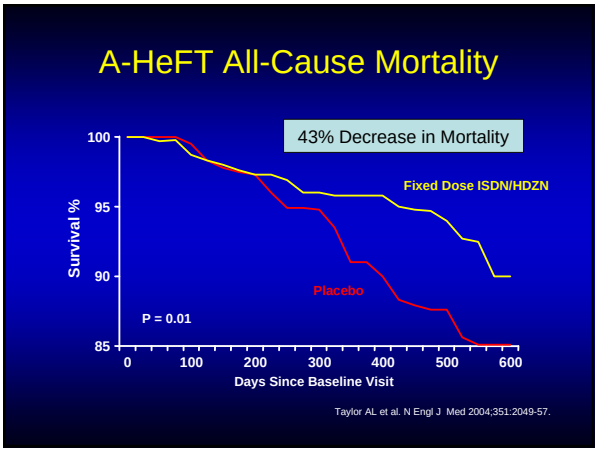
P=0.0014



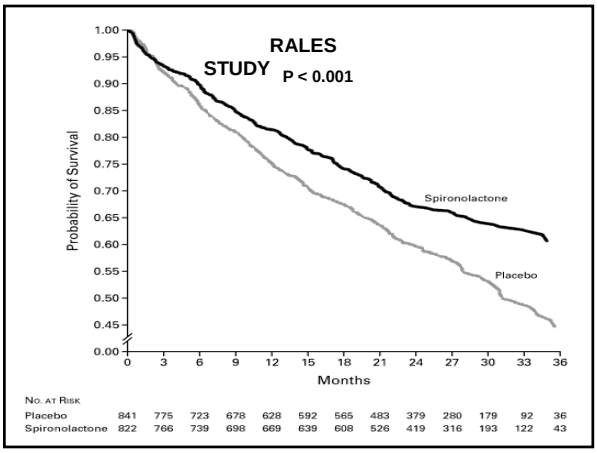
No. of Patients at Risk

Placebo	1133	937	703	580	446	286	183	114
Carvedilol	1156	947	733	620	479	321	208	142

Fixed-dose Hydralazine and ISDN in Heart Failure

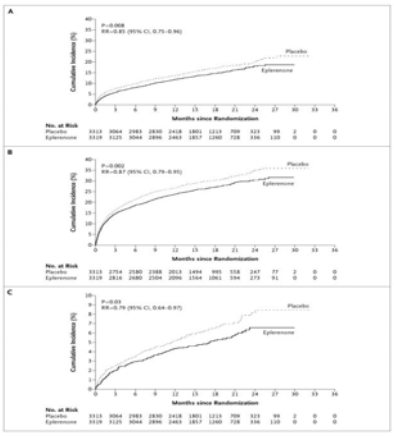


Aldosterone Antagonists in Heart Failure



No. at Risk

Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43



EPHESUS RESULTS

Kaplan-Meier Estimates of the Rate of Death from Any Cause (Panel A), the Rate of Death from Cardiovascular Causes or Hospitalization for Cardiovascular Events (Panel B), and the Rate of Sudden Death from Cardiac Causes (Panel C)

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Heart Failure with Normal Ejection Fraction (HFNEF)

Current Therapies for HFNEF

- Terminology has evolved: Previously: Diastolic dysfunction; heart failure with normal systolic function
- Now recognized to be a condition with both diastolic (compliance) abnormalities and with abnormalities of conformational change (twisting abnormalities – left ventricular deformation) but with normal ejection fraction
- Present therapies are not “evidence-based”

Current Therapies for HFNEF (continued)

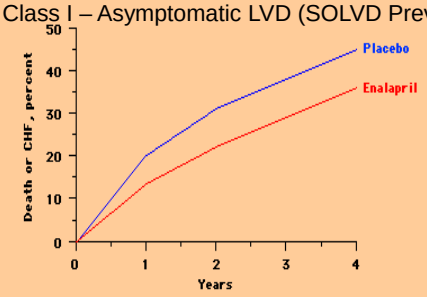
- Patients with HFNEF tend to be older than those with Systolic Dysfunction, tend to be female more commonly, and tend to have more hypertension
- Hypertension is principal target for HFNEF
- From I-PRESERVE Study (NEJM, 359:2456, December 4, 2008 , Irbesartan NOT superior to placebo for death or CV hospitalization

Treatment of Asymptomatic Left Ventricular Dysfunction (ALVD)

Evidence-based Therapies for Asymptomatic Left Ventricular Dysfunction (ALVD)

- Just as with Heart Failure with Systolic Dysfunction, an extensive evidence-base exists for ALVD
- ACE-I or ARB have a combined death or CHF benefit
- Among patients with asymptomatic left ventricular dysfunction treated with ACE inhibitors, beta blockers appear to reduce mortality and the rate of progression to symptomatic heart failure

Class I – Asymptomatic LVD (SOLVD Prevention)



Enalapril improves outcome in asymptomatic LV dysfunction In the SOLVD prevention trial of 4228 patients (83 percent post-MI) with asymptomatic left ventricular dysfunction, prophylactic administration of enalapril reduced the probability of death or congestive heart failure (p<0.001). (Data from The SOLVD Investigators, N Engl J Med 1992; 327:685.)

Clinical Trials in Patients With Asymptomatic LVSD

Study	Patient Population (n)	Treatment	Average Duration, mo	Relative Mortality Risk Reduction	Sudden Death Risk Reduction	Death Due to Worsening HF Risk Reduction
ß-Blockers						
Retrospective analysis of SOLVD Prevention[24]	Asymptomatic LVSD (4228; 1015 patients	ß-Blockers vs no ß-blockers plus enalapril	37.4	23% (P<0.01)	28% (P<0.05)	29% (P<0.05)
Post hoc analysis of SAVE[25]	Asymptomatic LVSD (2231; 789 patients	ß-Blockers vs no ß-blockers plus captopril	42	43% (P<0.001)	NR	32% (P<0.001)
ANZ[26]	HF (415); asymptomatic	Carvedilol vs placebo	19	36%* (P=0.02)	10% (P=NS)	8% (P=NS)
CAPRICORN[27]	Post-AMI LVSD (1959); asymptomatic	Carvedilol vs placebo (including ACE inhibitor)	15.6	23% (P=0.03)	26% (P=0.098)	40% (P=0.083)

Questions?

Device Therapy for CHF

Cardiac Resynchronization Therapy

- In Heart Failure, synchronization of contraction of the right and left ventricles can result in substantially improved performance
- This is accomplished by biventricular pacing, coupled to atrial pacing (to optimize A-V intervals)

Cardiac Resynchronization Therapy

- From **MADIT-CRT** (N Engl J Med; published at www.nejm.org on September 1, 2009, 10.1056/NEJMoa0906431) , In Minimally symptomatic cardiac patients (NYHA I or II) with decreased EF and wide QRS, CRT-D reduced mortality or HF events (which ever comes first) when compared with ICD-only therapy by 41%.
- CRT may improve LV twist in some patients with CHF with Systolic dysfunction who will later improve LV end-systolic volume as well

Left Ventricular Assist Devices

- Implanted devices with external power source, which can be worn by patients with advanced HF
- Used both as bridge to cardiac transplantation and as "destination therapy"

Applying this to your patient

- CHF, like diabetes, COPD and hypertension, is a chronic disorder which is rarely cured but can be effectively managed with application of evidence-based therapies
- Critical role of education in the management of patients with CHF
- Critical role of careful monitoring of patients and actively engaging them in their mangement

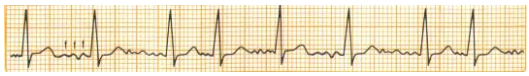
Conclusions

- Important to understand classification and pathophysiology of congestive heart failure
- Treatment of Acute Decompensated Heart Failure evolving, but evidence-base not strong
- Treatment of Chronic Heart Failure due to Systolic Dysfunction has strong evidence base, favoring use of ACE-I/ARB, Beta Blocker, and sometimes digoxin, spironolactone, and/or hydralazine/ISDN

Conclusions (continued)

- Little data concerning effective treatment of HFNEF
- Good evidence base for treatment of ASLVD: again ACE-I/ARB and Beta Blocker
- Critical role of recognizing causes of decompensation and working with patient to anticipate and prevent them

Questions?



Atrial Fibrillation: An update

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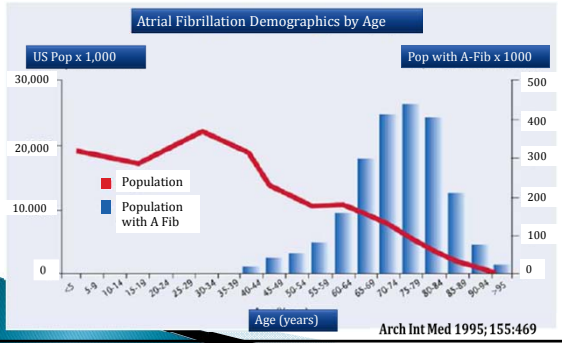
Atrial Fibrillation

- "Supraventricular tachyarrythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function"
  from ACC/AHA Practice Guidelines
- Most common arrhythmia seen in clinical practice

Prevalence increases with age
- 1% < 60 year olds
- 8% > older than 80 years



Clinical Significance of A-Fib

Loss of atrial synchronous mechanical activity

Irregular rapid Ventricular response

Impaired diastolic filling → +/- Ischemia

Cardiomyopathy

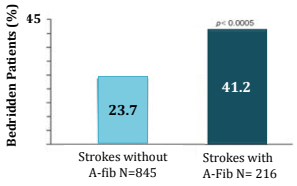
Cardiac Output + Risk for Thromboembolic event

Increased Morbidity and Mortality

Atrial Fibrillation Poses a Risk for Thromboembolism

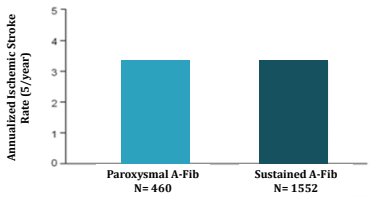
- ~ 5% per year risk for ischemic stroke
- It accounts for ~ 15% of all strokes, but they tend to be larger and more devastating than other embolic sources

Severity of Ischemic strokes in patients with and without A Fib



Neuroepidemiology 2003; 22:118

Risk of ischemic stroke in patients with paroxysmal and permanent A-fib



J Am Coll Cardiol 2000: 35; 183

Causes of Atrial Fibrillation

- **Cardiac**
  - Long standing HTN
  - MI
  - Heart Failure
  - Cardiothoracic surgery
  - Pericarditis
  - Myocarditis
  - Congenital Heart disease
  - Valvular disease
  - Associated with WPW syndrome
  - Infiltrative diseases (e.g., Amyloid heart disease)
- **Non cardiac**
  - Pulmonary Emboli
  - Pneumonia
  - Cor pulmonale
  - Sleep apnea
  - Hyperthyroidism
  - Alcoholism
  - Drug abuse

Persistent A-fib Leads to Atrial Remodeling

- Atrial remodeling results in:
  - Patchy fibrosis, leads to abnormal conduction pathways
  - Fatty infiltration of SA node
  - Atrial fiber hypertrophy leads to dilatation and enlargement

A "critical mass" of atrial tissue appears to be an important factor in maintaining A-fib

Factors Affecting Persistent A-fib

- Electrical remodeling: "critical atrial mass"
- Duration of A-fib
  - Cardioversion (pharmacological or electrical) is more successful when a-fib is < 24 hrs
  - The longer A-fib lasts, the less the chance to return and maintain sinus rhythm

Clinical Presentation and Evaluation

- Asymptomatic
- Non specific symptoms
- Palpitations, Chest pain, dyspnea, fatigue, lightheadedness, syncope
- Heart failure
- Stroke
- Cardiac collapse requiring emergency treatment
- History and Physical Exam
- Assess cardiovascular stability
- Obtain an EKG, provide oxygen if needed
- Labs: CBC diff, Chem panel, TSH, free T-4, Cardiac enzymes
- Chest X-ray
- Echocardiogram

Evaluation of Patients with A-fib

Additional Tests:

- Holter or Event Monitor
- TEE in patients in whom cardioversion is being considered
- Treadmill or Stress Test
- Electrophysiology Studies (EPS)

Management of A-fib

- Cardioversion can be achieved electrically or pharmacologically
  - The risk for thrombosis is the same
  - It can be done safely if A-fib is < 48 hrs duration
  - If A-fib is > 48 hrs, anticoagulate for at least 3 weeks prior to and 4 weeks after cardioversion
- **DC Cardioversion should be performed emergent if patient is hemodynamicaly unstable**

Management of A-fib

Three critical questions to answer:

1. To restore and maintain sinus rhythm?
2. To allow A-fib to continue but achieve ventricular rate control?
3. How to best prevent thrombosis?

The answer to these questions depend on patient's condition, risk/benefit analysis of options and the patient's preferences

Rate vs. Rhythm control: Which is best?

- The latest recommendations come from the AFFIRM and the RACE trials, both published NEJM, Dec 2002
- Patient were assigned to either rate control or rhythm control
- End points:
  - Death from CV events
  - HF
  - Thromboembolic events
  - Bleeding
  - Implantation of pacemakers
  - Severe drug adverse side effects
  - Hospitalization

Findings of RACE and AFFIRM trials: Rhythm Control No Better than Rate Control

- The number of deaths in rate controlled groups were lower than rhythm controlled, but not statistically significant
- The risk of thromboembolic events was the same in both groups
- Drugs used to control rate are safer than those used to control rhythm
- Patients in rhythm control group had more hospitalizations due to CV events and serious drug side effects

Rate Control in A-fib

For the majority of patients it is recommended to:

- Control rate rather than rhythm and provide long term anticoagulation
  - Ventricular rate of < 80 beats/min at rest and < 110 beats/min during exercise
  - β-Blockers (BB) or Calcium channel blockers (CCB) Diltiazem or Verapamil are the first line therapy
  - Digoxin is useful when BB or CCB are not tolerated, or use in combination

Importance of Rate Control

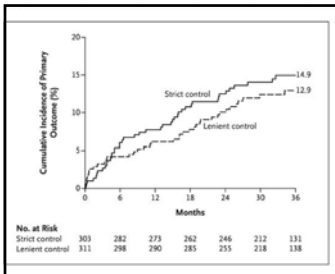
Decreasing the ventricular response rate:

- Improves diastolic filling and coronary perfusion
- Decreases myocardial energy demand
- Prevents tachycardia-mediated cardiomyopathy

Lenient Ventricular Rate Control

- RACE II Study
  - 614 patients with permanent atrial fibrillation were randomized to either
    - lenient rate-control strategy (resting heart rate <110 beats per minute) or
    - a strict rate-control strategy (resting heart rate <80 beats per minute and heart rate during moderate exercise <110 beats per minute)

- Van Gelder et al.; RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. NEJM 2010;362(15):1363-1373



The primary outcomes:

- Composite of death from CV causes
- Hospitalization due to HF, stroke, syst embolism, bleeding, and life-threatening arrhythmic events

Outcome:
Lenient rate control, ventricular rate of less than 110 beats/min at rest, was not inferior to strict rate control in preventing cardiac death, heart failure, stroke, and life-threatening arrhythmias

What about Rhythm Control?

- Antiarrhythmic drugs carry significant potential for serious side effects
- Have inconsistent efficacy of drugs
- Their long term efficacy is limited

Choosing Antiarrhythmic drug is challenging:

- It depends on the patient's cardiac condition

It is best to co-manage patients on antiarrhythmic drugs with a cardiologist

Drugs to Maintain Sinus Rhythm

- Flecainide
- Propafenone
- Dofetilide

} For patients minimal or no heart ds

- Ibutilide
- Amiodarone
- Sotalol
- Dronedarone

} Prefer for patients with CAD, CHF

Anticoagulation

- It decreases the risk of thromboembolism
- Most patients should be anticoagulated, unless the risk exceeds its benefits
- Warfarin and ASA are the most widely used agents and their used depend on the risk profile of patients
- Dabigatran approved by the FDA Nov, 2010
- and…. many more under study

Estimating Patient's Risk for Stroke

- $CHADS_2$ is a validated scoring system which assess patient's risks for stroke
- Each risk factor counts for 1 point, except for Stroke or TIA which account for 2 points each
- $CHADS_2$ is the acronym for the following risk factors:
  - **C**= Congestive HF
  - **H**= HTN (syst or diast)
  - **A**= age 75 or older
  - **D** =Diabetes
  - **S** = h/o stroke or TIA

- **$CHADS_2$ is not perfect**
- **It doe not include CAD**
- **It does not adjust for gender**
  - **Females have higher risk for thromboembolism than males**

$CHADS_2$ Score Continued

- According to the American College of Chest Physicians, patients at low risk can be treated with ASA, those at high risk with Warfarin and those with moderate risk can use either drug
  - Warfarin dose is adjusted to target INR level
  - Aspirin dose is 81 to 325 mg daily

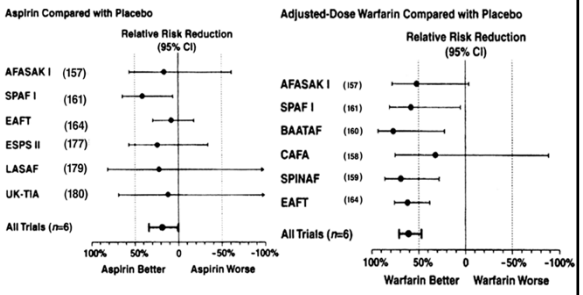
Risk of Stroke Stratified by $CHADS_2$ Score

$CHADS_2$ Score	Adjusted Stroke Rate * (95%CI)	Risk Level	Recommended therapy
0	1.9 (1.2-3.0)	Low	Aspirin 81-325 mg daily
1	2.8 (2.0-3.8)	Low	
2	4.0 (31-5.1)	Intermediate	Warfarin Target INR 2.0-3.0
3	5.9 (4.6- 7.3)	Intermediate	
4	8.5 (6.3- 11.1)	High	Warfarin Target INR 2.0-3.0
5	12.5 (8.2- 17.5)	High	
6	18.2 (10.5-27.4)	High	

* Adjusted Stroke Rate is the expected stroke rate per 100 patient-year

Adapted from ref 15, Snow V et al. Ann Int Med 2003:139:1009-1017

What is best? Aspirin or Warfarin?



Bottom line: both warfarin and aspirin are better than placebo, but warfarin is superior to aspirin

How to Assess the Risk of Bleeding?

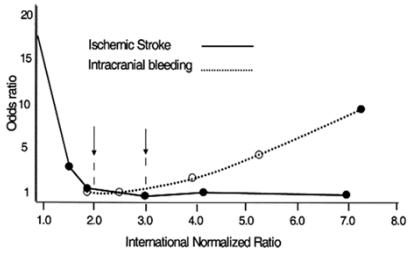
- Outpatient Bleeding Risk Index, OBRI, is a validated tool that helps assess the risk of bleeding for patients on Coumadin
- Four parameters are considered, each given 1 point
  - 1. Age > 65
  - 2. H/o hemorrhagic stroke
  - 3. h/o GI bleed
  - 4. One or more of the following: Recent MI; Severe anemia (Htc < 30); DM; and Renal impairment (Cr > 1.5 mg/dL)

OBRI scores: Risk of major bleeding per year

- Zero: low risk ~ 3 %/ yr
- Score 1-2. Intermediate, ~ 12%/yr
- Score 3-4 High Risk, ~ 48%/yr

- OBRI does not include
  - Risk for falls
  - Alcoholism
  - Other bleeding disorders

Few things to remember about Warfarin

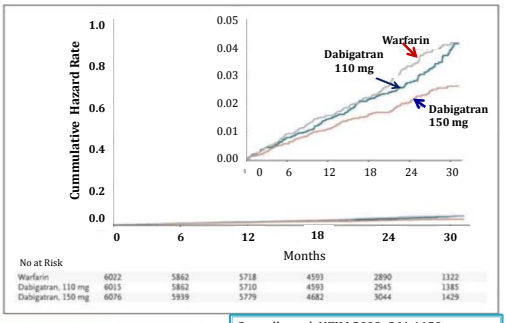


- Target Goal: INR 2.0 to 3.0 for most patients
- Target Goal: INR 2.5 to 3.5 for patients with rheumatic heart disease, persistent thrombus on trans-esophageal echo or for those with prosthetic valves

Dabigatran: Direct thrombin inhibitor

- Dabigatran Etexilate is a pro-drug, rapidly converted into dabigatran. Half life 12-17hrs
- FDA approved for the prevention of stroke and systemic embolism in patients with non-valvular A-fib
- Fixed dose: Oral 150 mg bid and 75 mg bid in impaired kidney function, GFR < 30 ml/min
- Predictable anticoagulant effect
- No need for routine coagulation monitoring
- No interaction with food of CYP450 system

RE-LY Trial: Cumulative Hazard Rates for the Stroke or Systemic Embolism



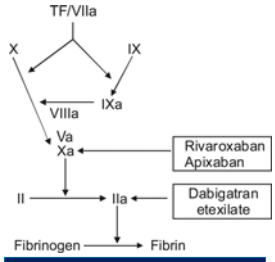
Connolly et al, NEJM 2009; 361:1139

Dabigatran

Advantages	Disadvantages
▸ Superior to warfarin in stroke prevention in patients with A-fib ▸ Anticoagulation effect in 30 to 60 min with a predictable response ▸ Fewer drug interactions than warfarin ▸ No need for frequent office visits	▸ Increased the risk of MI ▸ Increased risk of GI bleed in elderly patients ▸ Increasing concern for adverse outcomes in trauma patients ◦ No practical way to assess level of anticoagulation ◦ No quick reversal ▸ High Cost ◦ 150 mg $ 246 for 60 caps

New agents for anticoagulation

- **Apixaban. Aristotle Trial:**
  - ↓ stroke and syst embolism by 21%
  - ↓ major bleeding by 31%
  - ↓ mortality by 11%
- **Rivaroxaban: ROCKET AF** Clinical Trials
  - Non-inferior to warfarin for the prevention of stroke or systemic embolism.
  - Less ICH and fatal bleeding



Eikelboom, et al Circulation 2007
A Replacement for Warfarin: The Search Continues

When to Refer to Cardiology?

- It depends on your level of comfort and experience

However, must consider when patients
- Need rhythm control
- Serious cardiac disease
- Need for
  - EPS, Ablation therapy
  - Pacemaker
  - Surgical treatment

Other Therapies for Atrial Fibrillation

Non-Pharmacological Treatment of A-Fib

- Radiofrequency Ablation
- Surgery: Maze procedure

} Disrupt the initiation and conduction of electrical activity of arrhythmogenic foci

- Surgery: Left Atrial Appendage (LAA) Ligation
- Pacemaker
- Defibrillators

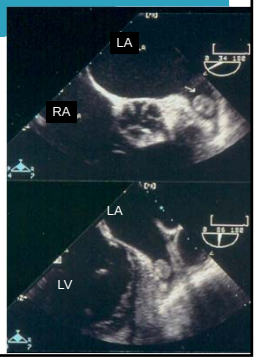
} Electric override of arrhythmogenic impulses

Surgical Treatment of A-fib

- The "Maze" procedure: Incisions made in both atria to isolate and interrupt the multiple reentrant circuits
  - Radial approach: Incisions done in an attempt to maintain physiologic activation of atria
  - "Corridor" surgery: Isolation of SA node to create an electrical "corridor" to activate the AV node
- Still, limited long term data available of risk/benefits

Surgical Treatment to Prevent Thrombosis
LAA occlusion or ligation

- Most thrombi in non-valvular A-fib come from the LAA
- LAA ligation is done during cardiac surgery
- No large studies available yet
- Percutaneous procedures are being studied; early results were promising

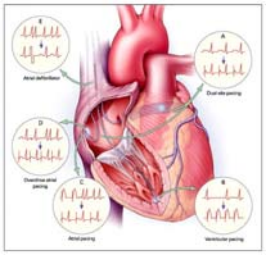


Radioablation Therapy

- EPS studies identified specific foci in the atria which serves as triggers of A-fib
  - Foci at or near the pulmonary veins
  - Other foci: Cristae terminalis and coronary sinus
- Ablation of these foci has cured A-fib
  - Still, these studies are small and of short follow up
  - End points regarding thrombosis were confounded by LAA obliteration
- AV nodal ablation and pacemaker
- No long term data on risk/benefits

Pacemakers

- Override abnormal electrical signals
- Type of pacer depends on patient's condition
  - Dual chamber pacer maintain AV synchrony
    - Improve symptoms and quality of life
- Cardiac resynchronization
- Defibrillators/Pacer devices



In Summary

- Assess hemodynamic stability
- History, PE, labs, imaging studies
- Treat underlying cause(s) and comorbid conditions
- Control Rate. First line drugs: BB and CCB
  - Vent rate at rest < 80 bpm
  - Vent rate during exercise < 110 bpm
  - But….perhaps no need for strict control
- Anticoagulation: Assess risks/benefits: OBRI vs. $CHADS_2$
  - Warfarin vs. ASA vs. Dabigatran

In Summary

- Refer to Cardiologist
  - Antiarrhythmic therapy
  - Persistent, poorly tolerated A-fib
  - Complex cardiac disease
  - Need for ablation, surgical tx, pacemaker or defibrillators
- Remember Immunizations: Pneumovax and Flu vaccine

Thank you

Questions?

UPDATE IN TRAVEL MEDICINE 2012

David N. Spees, M.D.

June 22, 2012

Credentials

- Am Soc of Tropical Med and Hygiene (ASTMH)
  - Certificate of Knowledge in Clinical Tropical Medicine and Travelers' Health (CTropMed®)
    - Member since 1984
- International Society of Travel Medicine (ISTM)
  - Certificate of Knowledge in Travel Health (CTH)
    - Founding Member 1991
- Overseas experience
  - Kinshasa, Democratic Republic of Congo-2 years
  - Cairo, Egypt- 2 years
  - Cambridge, England- 1 year

Lecture Map

1. Vaccines
2. Insect repellants
3. Malaria prophylaxis
4. Traveler's Diarrhea
5. Immunocompromise and vaccines

Vaccines

What is the most common vaccine-preventable disease in travelers?

1. Hepatitis A

OR

2. Influenza

Vaccine Preventable Perils

- Hepatitis A
  - "Most common vaccine –preventable infection acquired during travel" HIIT 2012 (Yellow Book)
  - Non-immune Traveler's risk= 1-10/1,000/month

Influenza

- "**Most preventable** infection among travelers to subtropical and tropical countries."
- "occur primarily outside the domestic epidemic season."
  - CID 2005: 40(1 May)
- Keep your vaccine to give to travelers (usually expires 6/30/xx)

Indications for Typhoid Vaccine

- CDC: "Where there is increased risk of exposure", it is "common in most parts of the world except in industrialized countries"
- Travel to Asia, Africa, and Latin America

Typhoid Vaccines

- Vivotif™-**Oral, Live, Attenuated Ty21a Vaccine**
  - One cap qod for 4 doses
  - Booster q5yrs
- Typhim Vi™-**Vi Capsular Polysaccharide Vaccine**
  - 0.5ml IM
  - Booster q2yrs

Practical Advice for Typhoid Vaccine

Not evidence based

- 2 weeks of potential exposure in next 2 years for Typhim™ and 5 years for the Vivotif™
- IM for short lead time and PO for longer lead time

Typhoid: Live oral Ty21a

(Risk 3-30/100,000/month)

- Do not take at the same time as an antibiotic (it's a live bacterial vaccine)
- Nor with hot beverage or alcohol
- Do take on empty stomach
- If 4 dose schedule interrupted, must be restarted

Measles Vaccine

- New Countries with measles outbreaks
  - France (14,000 cases in 2011) and Europe (26,000 in 2011)
  - New Zealand
- Usual areas of risk
  - Asia, Southeast Asia, the South Pacific, and Africa
- CDC says: Be up-to-date…regardless of any travel plans

Measles "Up-to-Date"

- 1. Physician or laboratory-diagnosed measles or a positive antibody test
- 2. Were born in the United States before 1957
- 3. Have had 2 doses of MMR vaccine
  - -2 dose schedule (school age and college dose) started 1989

Measles Review

Therefore those born between 1957 - ~1985 and went to college before 1989

Or born between 1956 - ~1985 and did not go to college

- Need MMR # 2

Who else needs Measles Vaccine?

- 6m-18 months old (not counted if given between 6-12 mon)
- 18m-5yrs: 2nd MMR if >28 days since the 1st
-

Yellow Fever

- Contraindicated
  - thymectomy or thymus disease, e.g. Myasthenia gravis
  - CD-4 count <200
  - Breastfeeding
- Increased risk of complications for persons >60 years old

Polio

- New country with polio- China
- Usual: India, Pakistan, Afghanistan, and most of Central Africa
- One booster dose after age 18 for travelers to countries with cases

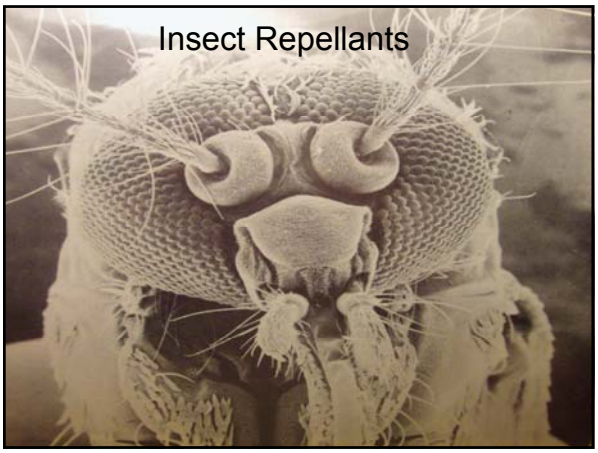
Hepatitis B

- Acceptable accelerated schedule
  - Months 0, 1, 4
- Other schedules
  - Months 0, 1, 2, 12
    - As good as months 0, 1, 6
  - 0, 7, 28 days, booster at 6-12 months

Encephalitis, Japanese B

- Check Yellow Book at
  - www.cdc.gov/travel

Insect Repellants



Insect Repellants

- Conventional Repellants
  - Picaridin
  - DEET
- Biopesticide Repellants
  - Oil of lemon eucalyptus or PMD
    - From natural materials
  - IR3535
- Recommend 10%-50% conc. CDC/repellents

Picaridin (7 years of use)

(Natrapel 8 hour…, Sawyer…, Repel…)

- Advantages (as opposed to DEET)
  - Odorless and Non-sticky
  - Less likely to irritate skin
  - No damage to fabrics/plastics
  - "Less irritating if sprayed in the child's eyes"
- Disadvantages
  - Not available in California and NY
  - (but can get through the internet)

Picaridin (for malaria protection?)

Medical Letter: "It's long term safety is less well established." (no reports of oral ingestion)

CDC **recommends Picaridin for the prevention of insect bites**

No AAP opinion

Oil of lemon eucalyptus

(p-menthane 3,8-diol or PMD)

Repel (various), Citrapel (various), Cutter Lemon Eucalyptus (all 30-40%)

- "30% PMD protection from biting for 6 hours." http://cfpub.epa.gov/oppref/insect/index.cfm
- "PMD (and DEET) have 90-100% protection for 5-6 hours." Med Vet Entomol. 2000

- EPA warning: "may not want to apply to hands." Not for children <3 y.o.
- AAP: "much less effective"
- CDC: Not recommended

IR3535

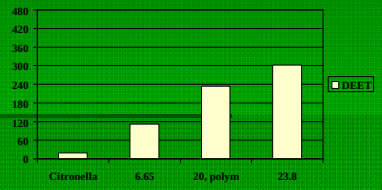
Skin So Soft Bug (various), Bullfrog Mosquito (various), Sawyer (various)

- 15-20 % lasts 8 hours
- CDC: Not recommended

Oil of Citronella

No longer recommended

- Oil of Citronella's duration of protection is from 1-60 minutes **NEJM 2002; 347:16**



DEET

- 56 years of use
- Used by 200 million persons/year EPA, 1980
- EPA classifies it as a non-health concern
- AAP OK with ≤30% in children

Permethrin

- 33 years of use
- Effective against mosquitoes, ticks, mites and other insects
- Lasts through washings (concentration dependent)
- Repellent and insecticide
- Use on clothing, blankets, PJ's…

DEET plus Permethrin

AIM, 1998

- 33% polymer-based DEET & Permethrin impregnated clothing
- 8 hour exposure
- Results:
- Treated: 1 bite/hour
- Controls: 108 bites/hour
- Conclusion: 99.9% protection

Malaria: Insect Avoidance

ERB=B

- Long sleeves and long pants
- DEET 20-30%, polymerized or controlled release (up to 50% in adults)
  - Second line: Picaridin 20%
- Permethrin on clothes

Dengue – "Break bone fever"

- Endemic in most tropical and subtropical areas of the world
- In US travelers: 30% Caribbean, 21% Pacific Islands, 17% Asia, 15% Central Amer., 15% South Amer., 2% Africa
- Competent vectors reside in the U.S.A.

Malaria Prophylaxis

Malaria Prophylaxis?

- Factors to consider
  - Risk of malaria vs. risk of prophylaxis
    - Little high quality nor timely data
    - Risks of exposure are underestimated and risks of prophylaxis are overestimated
- Variables:
  - Location
  - Type exposure
  - Length of exposure
  - Season

Prophylaxis of Chloroquine-resistant Plasmodium falciparum (EBR=A)

75-95% protective

1. Atovaquone/proguanil (Malarone™)
2. Doxycycline
3. Mefloquine (Lariam™)

Malarone (atovaquone/proguanil)

- DOC in most cases
- Adult and pediatric strengths
- Expensive if >14 days of malarious exposure
- Side effects ~ placebo
- No neuropsychiatric adverse effects
- FDA approved for maximum 6 months

Doxycycline

- Most frequent 2nd choice
- Sun sensitization an issue
- Send Candida vaginitis treatment in women
- Does not prophylaxis against diarrhea
- Probably good for Leptospirosis prophylaxis in freshwater exposures

Mefloquine

- Medication Guide states:
  - "2. Lariam can rarely cause serious mental problems in some patients.
    - …people taking Lariam occasionally experience severe anxiety, feelings that people are against them, hallucinations,…depression, unusual behavior, or feeling disoriented. There have been reports that in some patients these side effects continue after Lariam is stopped. Some patients think about killing themselves…"
      - Roche Laboratories Inc., 2003
- 5% with neuropsychiatric effects stop it
- Pregnancy Category B (EBR=C)

Primaquine (for prophylaxis of P. vivax)

- Reserved for those unable to take any other recommended regimen OR to areas with predominant Plasmodium vivax
- Document normal G6PD level!
- 30 mg base (2 x 15. mg tabs) daily with food, starting 2 days before exposure, daily during exposure, and for 7 days after leaving malarious area
- Consider consulting the Malaria Hotline (**770-488-7788**)

Primaquine as Prophylaxis in Chloroquine-sensitive areas

- Eliminates the dormant phase (hypnozoites) of P. vivax which can cause malaria weeks, months or years later
- 35% of malaria cases in USA were >2 months after return
- 81% of these were P. vivax

ASTMH 85(6), 2011

- (or use Chloroquine weekly)
- Currently: nationwide shortage

Primaquine can be first line in Chloroquine sensitive areas

P. vivax ≥90%

- Argentina, SA
- Belize
- Bolivia
- Costa Rica
- Ecuador, SA
- El Salvador
- Guatemala
- Honduras
- Mexico
- Nicaragua
- Panama
- Paraguay, SA

Primaquine as Terminal Prophylaxis

- After prolonged exposure (months)
- Give at end of malarone/doxy/mefloquine
- Assure G6PD is normal
- 30mg base (15mg X 2 tabs) daily for 14 days

http://www.cdc.gov/malaria/

CDC Malaria Map Application

Traveler's Diarrhea

Traveler's Diarrhea

- Basic Principle: Cook it, Boil it, Peel it, or Forget it
- Problem: Even persons that strictly follow guidelines develop the diarrhea.
- Why? Epidemiologically shown that Flies are transmitters of Campylobacter EID, Vol.11:3
- Flies carry E. coli on their feet Appl. Environ Microbiol. 2004 Dec;70(12)

Traveler's Diarrhea-Facts

- 85 % of Campylobacter in Thailand resistant to fluoroquinolones
- Quinolone-resistant Campylobacter is spreading in SE Asia and Indian subcontinent
- 80% of TD caused by enterotoxigenic E. coli
- 40% = Average rate of TD to high risk regions
- 82% report improvement with self-treatment

TD-Evidence Based Recommendations (EBR)

- Level A – Consistent, good quality patient oriented evidence
  - 1) Antibiotics (usually a quinolone) should be used to reduce the duration and severity
  - 2) Loperamide can be used with an antibiotic for adults with TD
- Level B – Inconsistent or limited quality patient oriented evidence
  - Traveler's should avoid high-risk foods and eating behaviors

TD-Prophylaxis

EBR – Level C (consensus of experts)

"Prophylaxis should not be used extensively"

- Consider for AIDS, Cancer, Immunosuppressed
- Best choice
- Rifaximin (Xifaxan™) – 200 mg TID

Rifaximin

Advantages
- Well tolerated
- Not absorbed

Disadvantages
- Expensive
- TID dosing

- Adverse Effects
  - Abd distension <2%
  - Diarrhea <2%
  - Stomach pain <2%

Probiotics and TD

- Intestinal bacteria that promote health by stimulating optimal mucosal immune responses.
- Shortens viral diarrhea by **0.7** and by **1.2** days in antibiotic-associated diarrhea (peds) Ped Infect Dis J, 2005
- Mixed results when used for prevention
  - Study A – No effect on overall rate
  - Study B – Controls = 40%, Lactobacillus gg – 24%
  - Study C – For misc. destinations: Controls = 7.4% vs. 3.9% in probiotic group

TD – Bottom line :-)

- Loperamide - 2 after 1st diarrheal stool, & 1 after next few
- Ciprofloxacin
  - 500 mg X 2, if continues 500 BID x 3days
    - Nausea 2.5%, Diarrhea 1.6%, vomiting 1% = 5.1%
- Levofloxacin
  - 500 mg daily x 3 days
    - Nausea 0.6%, vomiting 0.4%, stop rate = 3.4%
- Azithromycin
  - 2nd line for adults
  - 1st line for children

Thailand, India and SE Asia
Azithromycin

- 1000 mg once
- or
- 500 mg daily x 3

- in children - 10 mg/kg x 3 days

Azithromycin-Adverse Effects

1000 mg once
- -diarrhea 7%
- nausea 5%
- Abd pain 5%
- vomiting 2%
- = 19%

500 mg daily x 3
- diarrhea 5%
- nausea 3%
- Abd pain 3%
- =11%

Immunocompromise and vaccines

Immunocompromise and Vaccines
Steroid Therapy

- Live Viral vaccines are OK if:
  - Less than 2 weeks
  - Topical, inhaled, short acting alternate day, intra-articular, intra-bursa or tendon
- NOT OK if:
  - ≥ 20 mg prednisone/day
  - ≥ 2 mg/kg/day
- WAIT ≥3 months if on steroids > 2 weeks

Immunocompromise and Vaccines
Immunobiologicals

- Anti-TNF agents
  - Entanercept (Enbrel™),
  - Infiximab (Remicade™)
  - adalimumab (Humira™),
  - certolizumab (Cimzia™), Golimumab (Simponi™),…
- Interleukin-# receptor inhibitors
  - Anakinra (Kineret™)
  - Tocilizumab (Actemra™)
- selective costimulation modulators
  - Abatacept (Orencia™)
- Pyrimidine synthesis inhibitor
  - Leflunomide (Arava™)

Immunocompromise and Vaccines
Immunobiologicals

- INACTIVATED vaccines: (Tdap, Hep A, B, mengin, HPV, Pneum)
  - Best- At least 2 weeks before
    - or >3 months after therapy stopped
  - Already on Rx- Acceptable to give
- LIVE vaccines
  - MMR- 6 weeks before
  - Varicella and Zoster- "1-3" months before (Pick 3m)
  - Live influenza- Avoid
  - Yellow Fever and Oral Typhoid- Avoid

Immunomodulators & Vaccines
Specifically Varicella

- LIVE Viral Vaccines are RISKY if:
  - Methotrexate ≥0.4mg/kg/week
  - Azathioprine ≥3.0 mg /kg/day (Immuran™)
  - 6-mercaptopurine ≥1.5 mg/kg/day
  - Assume same for MMR and Yellow Fever

Immunocompromise and Vaccines
Chemotherapy

- How long after ChemoRx before live vaccines?
  - 3 months
    - (MMR, Varicella, Yellow Fever)

Immunocompromise and Vaccines
Solid Organ Transplants

- How long after transplant before inactivated vaccines?
  - Typically 6 to 12 months
    - (Hep A, B, Tdap, Mening, rabies, Typhim, Flu, IPV, Pneumo)
- How Long before giving live viral vaccines?
  - Avoid

Immunocompromise and Vaccines
Stem Cell Transplants

- How long before Hep A, B, Typhim, Mening, Rabies?
  - –1 year (however, best to wait 2 years)
- How long before MMR vaccine?
  - –2 years
    - Unless Graft vs. Host disease or still on immunosuppressives
- How long before YF and Varicella vaccines?
  - –Avoid

Resources

- www.CDC.gov/travel
- www.istm.org (Inter. Society Travel Med)
- www.immunize.org
- Travel and Tropical Medicine, Jong & McMullen, 4th ed., 2008

Fibromyalgia and Myofascial Care

Bill H. McCarberg, MD
Kaiser Permanente San Diego
Adjunct Assistant Clinical Professor
University of California, San Diego
President Western Pain Society

Is Fibromyalgia Real?

- Condition which lends itself to questioning
  - Nonspecific symptoms, no definite testing, psychologic comorbidities are common
- Disease of the month
  - Systemic yeast, Epstein Bar Virus, Lyme disease, lupus
- Science
  - fMRI, HPA axis, genetics, biochemical markers
- Diagnosis
- Treatment

Mechanistic Characterization of Pain

Peripheral (nociceptive)	Neuropathic	Central (non-nociceptive)
Primarily due to inflammation or mechanical damage in periphery	Damage or entrapment of peripheral nerves	Primarily due to a central disturbance in pain processing
NSAID, opioid responsive	Responds to both peripheral and central pharmacological therapy	Tricyclic, neuroactive compounds most effective
Responds to procedures		Behavioral factors more prominent
Behavioral factors minor		Examples
Examples		Fibromyalgia
Osteoarthritis		Irritable bowel syndrome
Rheumatoid arthritis		Tension headache
Cancer pain		Idiopathic low back pain

Paradigm Shift in Fibromyalgia

American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Psychologic and behavioral factors nearly always present and negative

- Chronic widespread pain
- Tenderness in ≥11 of 18 tender points
- Final common pathway
- Part of a larger continuum
- Many somatic symptoms, diffuse tenderness
- Psychologic and behavioral factors play roles in some individuals

Controversial areas – clinical significance still unclear

- Role of inflammation
  - Elevated levels of certain cytokines
  - Emerging role of glial cells in pain makes attractive link
- Role of dysautonomia and hypothalamic pituitary adrenal axis changes
  - Many are epiphenomena and due to co-morbidities
  - Others may be diatheses
- Chiari malformation/cervical stenosis

"Stressors" Capable of Triggering These Illnesses (Supported by Case-Control Studies[1,2])

- Early life stressors[3]
  - Children born in 1958 who had experienced a motor traffic accident or who were institutionalized were 1.5 – 2X more likely to have chronic widespread pain 42 years later
- Peripheral pain syndromes (e.g. RA, SLE, osteoarthritis)[4]
- Physical trauma (automobile accidents)[5]
- Certain catastrophic events (war but not natural disasters)[6]
- Infections
- Psychological stress/distress

1. Clauw and Chrousos. *Neuroimmunomodulation.* 1997;4:134-53. 2. McLean and Clauw. *Med Hypotheses.* 2004;63:653-8.
3. Jones et al. ACR Meeting. 2007. 4. Clauw et al. JCR. 1997.
5. McBeth. ACR Meeting. 2006. 6. Clauw et al. J Occup Environ Med. 2003;45:1040-8.

Genetics of Fibromyalgia

- Familial predisposition[1]
  - Most recent work by Arnold, et al suggests >8 odds ratio (OR) for first-degree relatives, and much less familial aggregation (OR 2) with major mood disorders
  - Much stronger with bipolarity, obsessive compulsive disorder
- Genes that may be involved
  - 5-HT2A receptor polymorphism T/T phenotype[2]
  - Serotonin transporter[3]
  - Dopamine D4 receptor exon III repeat polymorphism[4]
  - COMT (catecholamine o-methyl transferase)[5]

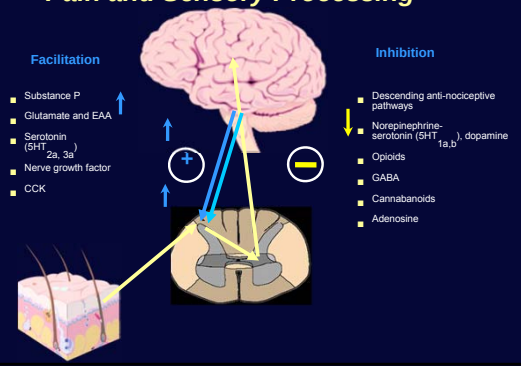
1. Arnold et al. *Arthritis Rheum.* 2004;50:944-52. 2. Bondy et al. *Neurobiol Dis.* 1999;6:433-9.
3. Offenbaecher et al. *Arthritis Rheum.* 1999;42:2482-8. 4. Buskila et al. *Mol Psychiatry.* 2004;9:730-1.
5. Gursoy et al. *Rheumatol Int.* 2003;23:104-7.

Conditions Characterized by Widespread Secondary Hyperalgesia / Allodynia

- Fibromyalgia
- Temporomandibular disorder[1,2]
- Headache (tension > migraine)[3,4]
- Idiopathic low back pain[5,6]
- Vulvodynia/vulvar vestibulitis[7]
- Whiplash associated disorder[8]
- IBS[9,10]

1. Maixner et al. *Pain.* 1995;63:341-51. 2. Kashima et al. *Cranio.* 1999;17:241-246.
3. Langemark et al. *Arch Neurol.* 1993;50:1161-4. 4. Buchgreitz et al. *Pain.* 2006;123:19-27.
5. Giesecke et al. *Arthritis Rheum.* 2004;50:613-23. 6. Giesbrecht and Battie. *Phys Ther.* 2005;85:1085-92.
7. Giesecke et al. *Obstet Gynecol.* 2004;104:126-33. 8. Lemming et al. *Clin J Pain.* 2005;21:412-21.
9. Whitehead et al. *Gastroenterology.* 1990;98:338-40. 10. Mertz et al. *Gastroenterology.* 1995;109:40-52.

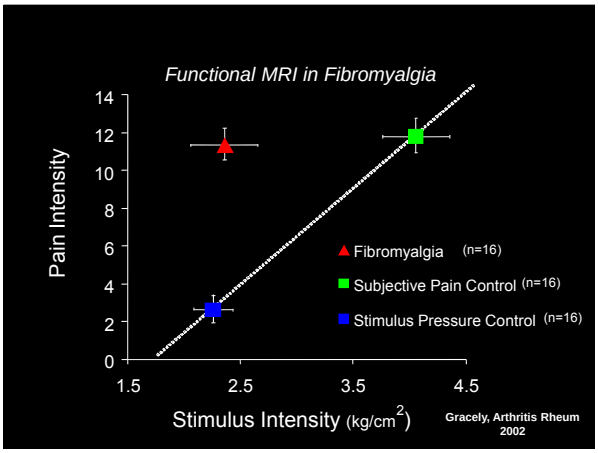
Supraspinal Influences on Pain and Sensory Processing

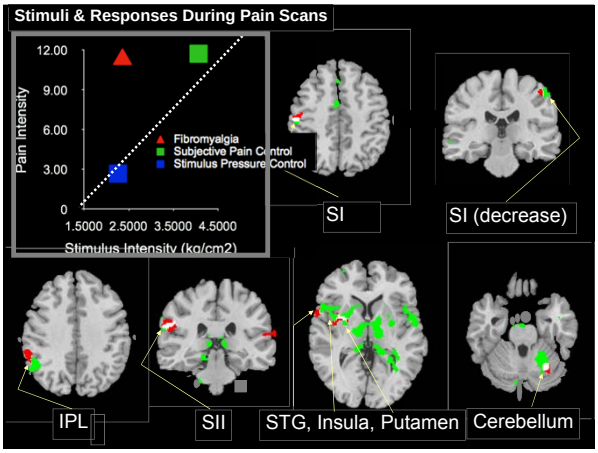


fMRI of Evoked Pressure Pain in Fibromyalgia and Related Conditions

- Is there objective evidence of augmented pain processing in fibromyalgia?[1]
- Role of depression in pain processing in FM[2]
- Role of cognitive factors in pain processing in FM
  - Locus of control
  - Catastrophizing[3]
- fMRI changes of augmented central processing of pain also seen in idiopathic low back pain[4]

1. Gracely et al. *Arthritis Rheum.* 2002;46:1333-43. 2. Giesecke et al. *Arthritis Rheum.* 2003;48:2916-22.
3. Gracely et al. *Brain.* 2004;127:835-43. 4. Giesecke et al. *Arthritis Rheum.* 2004;50:613-23.





There is a Deficiency of Descending Analgesic Activity in FM:[1,2] Which one?

Opioids

- Normal or high levels of CSF enkephalins[3]
- Never been administered in RCT but most feel that opioids are ineffective or marginally effective
- Harris recently used PET to show decreased mu opioid receptor binding in FM[4]

Noradrenergic/Serotonergic

- Low levels of biogenic monoamines in CSF in FM[5]
- Nearly any class of drug that raises both serotonin and norepinephrine has demonstrated efficacy in FM

1. Kosek and Hansson. *Pain*. 1997;70:41-51. 2. Julien et al. *Pain*. 2005;114:295-302.
3. Baranauk et al. *BMC Musculoskelet Disord*. 2004;5:48. 4. Harris et al. *J Neurosci*. 2007;27:10000-6.
5. Russell et al. *Arthritis Rheum*. 1992;35:550-6.

Fibromyalgia? The History

- Pain
  - Current and lifetime history of widespread pain
  - The more widespread, the more likely it is fibromyalgia
  - "I hurt all over"
  - Pain felt in any area of musculoskeletal and non-musculoskeletal regions
  - Often "unpredictable", worsened by stress
  - Often accompanied by stiffness, non-dermatomal paresthesias

Fibromyalgia? The History

- Other somatic symptoms
  - Fatigue
    - Not made better by rest or exercise
  - Memory difficulties
    - Difficulty with memory and concentration
  - Insomnia and sleep disturbances
  - Co-morbid syndromes
    - Irritable bowel
    - Interstitial cystitis
    - Headache
    - TMJ/TMD

Diagnostic Work-up

- Intensity of evaluation depends largely on history
  - If symptoms acute or sub-acute extensive evaluation necessary
  - If symptoms have lasted for many years and history is classic virtually no work-up is necessary
- Laboratory evaluation at some point in illness
  - ESR, CRP
  - CBC and chemistry profile
  - TSH, Vitamin D
  - Avoid serological studies e.g. ANA, RF

Treatment of Fibromyalgia and Other Central Pain Syndromes

Pharmacological Therapies

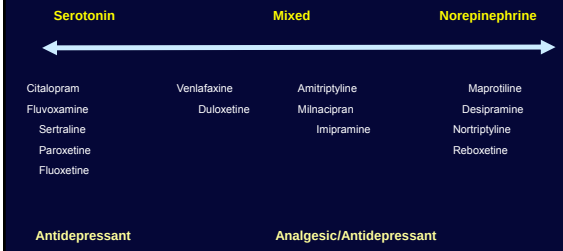
Strong Evidence	▪ Dual reuptake inhibitors such as ▪ Tricyclic compounds (amitriptyline, cyclobenzaprine) ▪ SNRIs and NSRIs (milnacipran, duloxetine, venlafaxine?) ▪ Anticonvulsants (e.g., pregabalin, gabapentin)
Modest Evidence	▪ Tramadol ▪ Selective serotonin reuptake inhibitors (SSRIs) ▪ Gamma hydroxybutyrate ▪ Dopamine agonists
Weak Evidence	▪ Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe)
No Evidence	▪ Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, guanifenesin

Modified from Goldenberg et al. *JAMA*. 2004;292:2388-95.

Careful with Opioids

- Multiple studies show they are ineffective
- Psychologic comorbidities may lead to more abuse, dependence
- Most fibromyalgia expert use opioids in selected cases

Relative Activity on Serotonin and Norepinephrine Reuptake Among Antidepressants



Fishbain et al. *Pain Med.* 2000;1:310-6.

Nonpharmacological Therapies

Strong Evidence	Education Aerobic exercise Cognitive behavior therapy
Modest Evidence	Strength training Hypnotherapy, biofeedback, balneotherapy
Weak Evidence	Acupuncture, chiropractic, manual and massage therapy, electrotherapy, ultrasound
No Evidence	Tender (trigger) point injections, flexibility exercise

Goldenberg et al. *JAMA.* 2004;292:2388-95.

Symptoms of Pain, Fatigue, etc.

- Nociceptive processes (damage or inflammation of tissues)
- Disordered sensory processing

Functional Consequences of Symptoms

- Increased Distress
- Decreased activity
- Isolation
- Poor sleep
- Maladaptive illness behaviors

Dually Focused Treatment

- *Pharmacological therapies to improve* ***symptoms***
- Nonpharmacological therapies to address **dysfunction**

Clauw and Crofford. *Best Pract Res Clin Rheumatol.* 2003;17:685-701.

Exercise

- Aerobic exercise nearly universally beneficial; tolerance, compliance, adherence are biggest issues
- To maximize benefits
  - Begin several months after pharmacologic therapy
  - Begin with low-impact exercises; avoid strength training until late
  - Both physician and patient should consider this as a “drug”
- Less evidence supporting strengthening, stretching

Cognitive Behavioral Therapy

- A program designed to teach patients techniques to reduce their symptoms, to increase coping strategies, and to identify and eliminate maladaptive illness behaviors
- Shown to be effective for nearly any chronic medical illness
- Not all CBT is created equally; very dependent on content, therapist and program

Self help program highlights

- Program features 10 topics or "Steps":
  - Understanding Fibromyalgia
  - Being Active
  - Sleep
  - Relaxation
  - Time for You
  - Setting Goals
  - Pacing Yourself
  - Thinking Differently
  - Communicating
  - Fibro Fog

Recommended Approach

- Education
- Identify and treat "peripheral" pain generators
- For patients who need or want medications, start with low doses of mixed tricyclic antidepressants (amitriptyline, cyclobenzaprine); start low, go slow
- If patient has depression, memory problems, fatigue as most prominent symptoms
  - Add mixed reuptake inhibitor (eg, duloxetine, milnacipran, venlafaxine) or SSRI (may need high doses)
- If patient has sleep disturbance as most prominent symptom
  - Use pregabalin or gabapentin first, give higher % of dose at night

Clauw and Crofford. *Best Pract Res Clin Rheumatol.* 2003;17:685-701.

Recommended Approach - II

- Consider – sodium oxybate, naltrexone
- For additional analgesic effect, add tramadol, tizanidine, opioids
- For sleep, if patient doesn't tolerate TCA, use zolpidem, zaleplon, trazodone
- Aggressively introduce non-pharmacological therapies

Clauw and Crofford. *Best Pract Res Clin Rheumatol.* 2003;17:685-701.

Conclusions

- Fibromyalgia and other "idiopathic" pain syndromes have strong neurobiological underpinnings
- These are likely polygenic disorders characterized by pain and sensory amplification
- There is evidence of increased levels of pro-nociceptive neurotransmitters (e.g. Subtance P, glutamate) and decreased levels of anti-nociceptive neurotransmittters (e.g. serotonin, norepinephrine)
- The condition can be easily diagnosed in clinical practice based primarily on the patient history

Treatment of Obesity: 2011

Ken Fujioka, MD
Scripps Clinic Research
La Jolla, California USA

Disclosures

- Advisory Board: Novo Nordisk, Orexigen, Allergen
- Consultant: Abbott, Lilly, Enteromedics, Jenny Craig
- Speaker : Abbott, Merck
- When the Grants are running low will work the senior circuit for Chippendales

Average family practitioner sees 20 pts per day then he or she will see

Select the most correct answer

A. 6 obese and one morbidly obese pt

B. 4 obese pts and no morbidly obese pts

- C. Family practice doctors that see kids will see a lot less obesity
  - (less than 3 a day)
- D. A FP that specializes in Women's health will see over 10
  - Half of these women will think they are obese but are are simply overweight

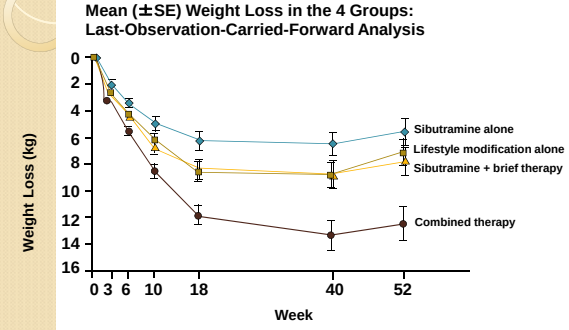
ARS How often does the primary care doctor see an obese pt on a daily basis

- Correct answer is about 6 per day and one to two morbidly obese patients
- Obesity is very common
- Even in La Jolla California land of the rich and beautiful the Family practice docs will see at least 20% obese and one morbidly obese patient per day
  - Tanja Crockett Obesity Research Sept 2012

ARS Question: expected wt loss from diet and lifestyle changes

- How much weight loss can you expect if you have a patient diet, change their lifestyle
- 0% to 5%
- 5% to 10%
- 10% to 15%
- 15% to 20%
- 20% to 25%

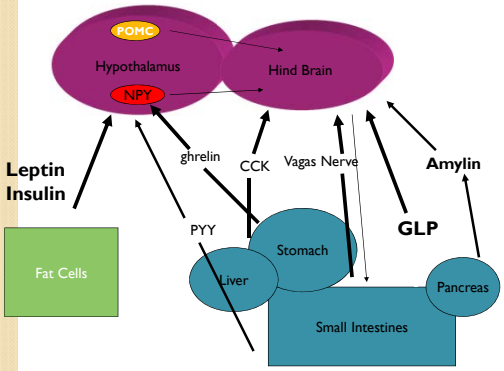
Lifestyle Modification and Pharmacotherapy for Obesity



Wadden TA, et al. *N Engl J Med.* 2005;353(20):2111-2120.

So why is weight loss so difficult

- Once a patient gains weight
  - For whatever reason
- That patient will have an increased number of fat cells
  - Jules Hirsch late 1980s
- The hormones controlling weight will adapt to a starved state forever
  - Sumithran P. NEJM 365;17;2011
- The patient's metabolic rate will drop lower than expected and stay reduced
  - Rosemnaum M,Leibel RL Int J Obesity 2010



Fujioka K. San Diego Geriatric Surfing weekly 2011 Senior Spring Swimsuit Issue

What does this mean for the practicing physician

- Expect a 5% to 10% as success
  - The patient will not be happy with this as they are expecting 30%
- There are huge benefits to this amount of weight loss
  - Blood sugar
  - Blood pressure
  - Sleep apnea
  - Many good things
    - Fujioka K Diabetes, obesity and Metabolism 2010

Treatment options and expected weight loss

Treatment	% weight loss
Diet, Exercise and Lifestyle modification	5–10%
Medications	5–10%
Medications with Diet, Exercise and Lifestyle	10–15%
Bariatric surgery	20–35%

Handbook of Obesity treatment Chapter 37 Weight loss Clinics: Range of capabilities, benefits, risks, and costs; Editor George Bray:2008
Fujioka K, Lee MW. Pharmacologic Treatment options for obesity: Current and Potential medications. Nutrition Clin Prac. 2007 Vol. 22#1pp50-54
Hofso et al. European Journal of Endocrinology. 163735-45, 2010

Case: 38 year old borderline Diabetic Hispanic obese female with PCO

- Referred by the primary care physician because of fasting glucose of 119
- Besides starting metformin what diet will you prescribe?
  - ADA 1800 calorie diet
    - (the RD wants this one)
  - Low glycemic diet
    - (Women's health magazines want this one)
  - HCG diet
    - (the patient wants this one)

Choosing a Diet

- Might there be a better diet for this group of patients ?
  - PCO
  - Metabolic syndrome
  - Early type two Obese Diabetics
- What do they all have in common
- Insulin resistance

CALERIE Trial:

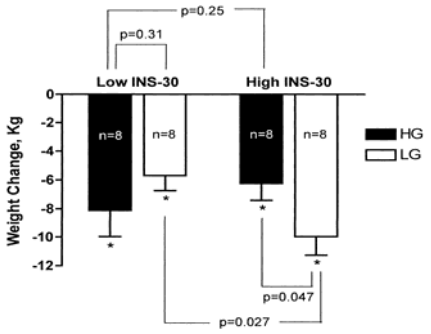
low carbohydrate vs. high carbohydrate diets

- 34 overweight patients tested for insulin resistance
  - Half were insulin resistant (high insulin)
  - Half were insulin sensitive (low insulin)
- Randomized for 24 weeks:
  - 30% caloric restricted diet
  - Average of 2000 kcals per day

A low-glycemic load diet facilitates greater weight loss in overweight adults with high insulin secretion
But not in overweight adults with low insulin secretion in the CALERIE trial. Diabetes Care 2005;28:2939-2941

CALERIE trial: randomized to one of two diets

- High Carbohydrate diet
  - 60% carbohydrate, 20% protein, 20% fat
  - mean estimated daily glycemic index of 86
    - glycemic load of 116 g/1,000 kcals
  - 15 g fiber/1,000 kcal
- Low Carbohydrate diet
  - 40% carbohydrate, 30% protein, 30% fat
  - mean estimated daily glycemic index of 53
    - glycemic load of 45 g/1,000 kcals
  - 15 g giber/1,000 kcal



A low-glycemic load diet facilitates greater weight loss in overweight adults with high insulin secretion
But not in overweight adults with low insulin secretion in the CALERIE trial. Diabetes Care 2005;28:2939-2941

Conclusions: CALERIE study

- In healthy overweight patients with insulin resistance there was more weight loss in the patient assigned to the low-glycemic load diet
- There are papers that will have different conclusions *

Published studies looking at weight loss on a low carbohydrate diets in insulin resistant patients

Pitas study	Yes
Baba study	Yes
Cornier study	Yes
Plodkowski	Yes
Ebbeling study	Yes
McLaughlin	No
McLaughlin	No

- Lee & Fujioka Diabetes Obesity Metabolism 2011;13:204-206

ARS: We now need to prescribe an exercise routine

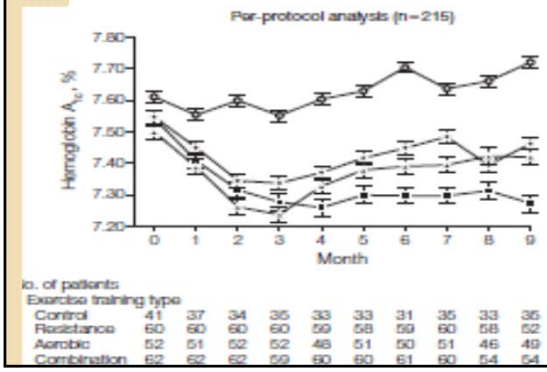
- Which exercise prescription will you give to the patient
- 1. Cardio or Aerobic training
- 2. Resistance training
- 3. Both Resistance training and Aerobic

Exercise and weight loss

- What do you tell your patient ?
  - Aerobic or Cardiovascular training (walking)
  - Resistance training (weight lifting)
  - Combination of both (cardio and resistance)
  - Church TS, Blair SN, Cocreham S, et al Effects of Aerobic and Resistance Training on HbA1c in pts with Type 2 DM. JAMA 2010;304(20):2253-62

Aerobic or Resistance Training

- Randomized 262 pts with type 2 DM to
  - Placebo group stretching and relaxation
  - 3 days of Resistance training
  - Aerobic exercise
  - Combination of resistance and aerobic
- Exercise prescriptions standardized to:
  - 150 minutes per week (all were of equal time requirements)
  - Moderate intensity 10 to 12 kcal/kg of body weight
  - Exercise intensity of 50% to 80%
  - All sessions supervised
- 9 month exercise program



Weight loss: Resistance vs. Aerobic

	Control	Resistance	Aerobic	Combination
Body wt.	+ 0.4	-0.3	- 0.8	-1.5*
(Fat mass)	(+ 0.1)	(- 1.4)**	(- 0.6)	(- 1.7)**

* Statistically significant from control and resistance group
** Statistically significant from the control group
Above values in Kilograms

Take home Message on Exercise

- In obese diabetics
  - And more than likely obese non diabetics
- A Combination of Resistance training and Aerobic training of at least 3 hours per week are needed for weight loss

Three medications that recently went before the FDA for approval

- Lorcaserin
  - Arena
- Qnexa
  - Vivus
- Contrave
  - Orexigen

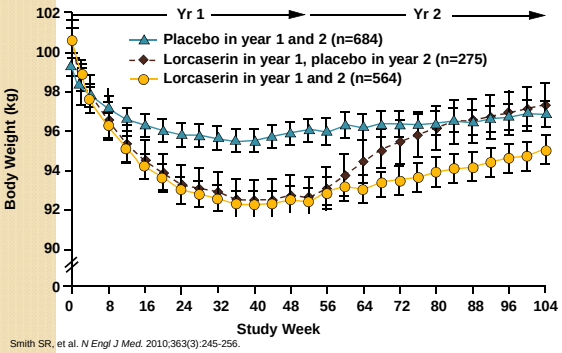
Lorcacerin

- Serotonin Agonist
- Increases Satiety
- Well known biologic system
- Recent positive vote by FDA advisory panel (18-4-1)
- **Arena (developed and own the drug) and Eisai (has the U.S. marketing rights)**

Lorcaserin (FDA briefing documents)

- Selective 5HT2c (serotonin) receptor ag New PDUFA 27 June 2012
- Percent weight loss -5.8 (-2.5 placebo)
  - -3.3 placebo subtracted
  - 5% responder rates = 47% vs 23% for pbo
- Heart rate -1.9 (pbo -0.3)
- SBP: -1.7 (pbo -1.1)
  DBP: -1.5 (pbo -1.0))

Lorcaserin: Body Weight Over Years 1 & 2



Smith SR, et al. *N Engl J Med.* 2010;363(3):245-256.

Locacerin

- Will have to deal with the history of Phen-fen and thickened heart valves
- If one looks at the science of heart valve thickening with phen-fen it appeared that the problem was all fenfluramine and not the addition of phentermine
- Locacerin did rather extensive trials looking at heart valves and locacerin
- Valvulopathy: HR 1.07 95% CI [0.74; 1.55]

Lorcaserin: Where will it fit

- 5.8% weight loss (Placebo 2.5%)
- This system is well known
  - drug appears to be very safe
- Will be useful in patients with cardiovascular disease
  - Example Strokes or status post MIs

Qnexa

- Combination of Phentermine and Topiramate
- Very good efficacy (close to 10% wt loss)
- How does it work ?
  - Phentermine: increases epinipherrine and nor-epi
    Topiramate: unknown

FDA Decision Qnexa

- Vivus pharmaceutical
- Qnexa: combination of Phentermine and Topiramate
- Advisory committee votes 10 to 6 against approval Oct. 28, 2010
- the FDA declines approval
  - Main reason: "safety risks" and potential for birth defects
- February 2012 2nd FDA advisory committee votes 20-2 for approval

56 week data of changes in Blood Pressure and Heart rate on phentermine/topiramate

		Placebo	3.75/23	7.5/46		15/92	
Wt change	%	-1.5		-4.7	-8.2		-10.4
SBP, mm Hg	-2.3		-3.3	-5.2		-5.2	
DBP, mm Hg	-1.9		-0.9	-3.3		-2.9	
Pulse	0.0		+1.3	+0.6		+1.6	

- Expect the company to do a post approval cardiovascular outcomes study because of effect on heart rate

Q-nexa FDA advisory Panel 2-22-12

- topiramate monotherapy exposure in pregnancy associated with a two- to five-fold increased prevalence of oral clefts
- Labeling stating that the drug is in Pregnancy Category X
- Distribution of Qnexa only through 10 certified mail-order pharmacies
  - agree to training of their pharmacists
  - submitting to internal audits

Risk mitigation strategy for Qnexa

- Targeted education programs aimed at providers and patients, including a brochure on contraception and recommendations for monthly pregnancy testing
- Development of a pregnancy registry to track pregnancy outcomes

FDA Decision: Contrave

- Orexigen Pharmaceutical
- Contrave: a combination of Bupropion and Naltrexone
- Advisory committee votes 13 to 7 **for approval**
- and the FDA declines approval
  - Main reason: "Cardiovascular problems"
    - LA times February 1, 2011

Contrave

- % weight loss -6.7% (pbo -2.5)
  - Pacebo subtracted -4.2 %
- 5% responders 48 vs 16 for pbo
- Cardiovascular effects:
- BPM +0.1 (pbo -1.0)
- SBP: -0.9 (pbo -2.3)
  DBP: -1.1 (pbo -1.5)

Communication from Office of New Drug development to Orexigen

- Written correspondence detailing requirements for a Cardiovascular outcomes trial
  - Enroll a population of obese pts with an estimated background rate of 1.0-1.5% annual risk of a Major Cardiovascular event
  - The upper bound of the 95% confidence interval should exclude a hazard ratio of
    - 2.0 at interim analyses (87 events)
    - 1.4 at final analyses
    - ≤10,000 pts, and ≤ 2 years to interim analysis
      - Sept 20, 2011 press release

ARS: Diet Sodas Good or Bad

- "Doc is it ok for me to drink diet colas for my weight loss program
- A. No, it will cause rebound weight gain
- B. No, you might as well drink a regular soda
- C. No, you would do just as well or better to drink water
- C. Yes, and it has been shown to help with weight loss (more than drinking water)

Choice study for weight loss

Choose Healthy Options Consciously Everyday (CHOICE)

- compared the replacement of caloric beverages for 6 months with
- Water
- Diet beverages
- Controls
  - designed to equate treatment contact time
  - and attention, monthly weigh-ins, and weekly monitoring
  - Choose Healthy Options Consciously Every day Am J Clin Nutr 2012;95:555-63

CHOICE Results

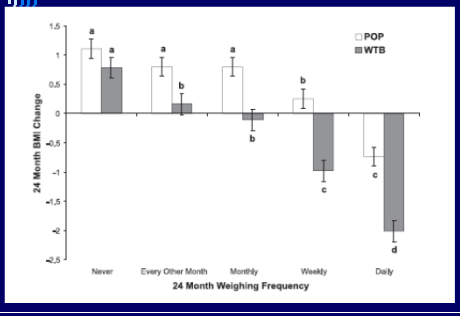
- 2.5% in the Diet Beverage group
- 2.0% in the Water group
- 1.8% in the Control group

- Statistically the Diet Beverage group had more pts lose at least 5% of their weight
- Take home is if you can get your pt to drink diet sodas or water they will lose 2.5 to 2.0 percent of their weight

ARS: how often should your patient weigh themselves ?

- A. Never
- B. Once a month
- C. Once a week
- D. Every day

RELATION OF SELF-WEIGHING TO WEIGHT LOSS



Source: Linde et al. *Ann Behav Med.* 2005;30(3):210–216

The End

Special thanks to the staff for putting up with my travel and not getting things in on time

HCG Treatment for obesity

- Injections of human chorionic HCG have been claimed to aid in:
  - reducing hunger
  - affecting mood
  - localized (spot) reduction.

- West J Med 127:461-463, Dec 1977
- Human Chorionic Gonadotropin
- (HCG) in the Treatment of Obesity
- A Critical Assessment of the Simeons Method
- FRANK L. GREENWAY, MD, and GEORGE A. BRAY, MD, Torrance, California

Double blind placebo controlled HCG study

- Placed both groups on a 500 kcal per day diet
- received daily injections of HCG or placebo
- Rated hunger and mood
- Did anthropomorphic measurements

Double blind trial of HCG for weight loss: Bray and Greenway

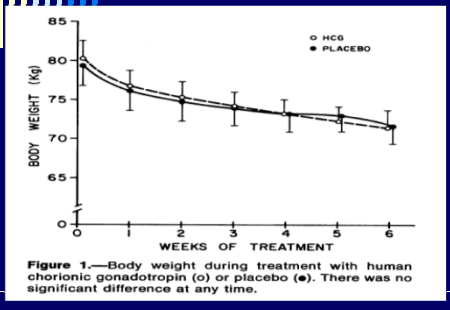


Figure 1.—Body weight during treatment with human chorionic gonadotropin (o) or placebo (●). There was no significant difference at any time.

Double blind trial of HCG for weight loss: Bray and Greenway

- No difference in weight loss
- No difference in mood
- No difference in the fat loss or location of fat loss

Screening for Prostate Cancer: A Dilemma with a History

Alfred O. Berg, MD, MPH
Professor, UW Family Medicine
Former Chair, USPSTF

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Case

- Warren Buffett (age 81) was recently screened with PSA, biopsied, and is now scheduled for RT for prostate cancer in July. Comment?

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Disclosures

- No financial conflicts
- No off-label recommendations
- No speakers' bureaus
- No consulting
- No legal work

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Objectives — 1

- Understand the significance of prostate cancer in the U.S. and the history of screening guidelines for prostate cancer
- Understand the recent changes in evidence about screening for prostate cancer

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Objectives — 2

- Understand changes in guidelines from the U.S. Preventive Services Task Force, the American Cancer Society, and the American Urological Association
- Understand different approaches to screening that clinicians might take in their own practice

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Prostate Cancer Basics

- Highly prevalent
  - 33% of men between ages 40-60 have microscopic cancer cells
  - 75% of men over age 80
  - 16% of men will get a diagnosis of prostate cancer in their lifetime
- Modest mortality
  - 2.8% of men die from prostate cancer
  - Most men who die are over age 75
  - 95% alive after 12 years without treatment

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Cancer Screening Model

- Cancer happens
- It grows
- It spreads
- It kills

- Therefore: detect and treat it early

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Early History — 1975

- First systematic review
- Screening for prostate cancer
- Reviewed the only available screening test: digital rectal exam
- "do not recommend screening"

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Early History — 1979

- Canadian Task Force on the Periodic Health Examination
- "poor evidence" for prostate cancer screening (DRE)

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US Preventive Services Task Force

- **USPSTF I: 1984 — 1989**
  - 20 members — MDs, allied health
  - First *Guide* published in 1989
- **USPSTF II: 1990 — 1995**
  - 10 members — all primary care MDs
  - Second *Guide* published in 1995
- **USPSTF III: 1998 — present**
  - 16 members — interdisciplinary
  - Multiple products beginning April, 2001
  - Prostate cancer addressed in 2002,2008,2012

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Potential Benefits of Screening

- Improved prognosis
- Permits less radical treatment
- Reassurance from negative results
- Saves resources

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Potential Harms of Screening

- Hazards intrinsic to the tests
- Labeling
- Adverse effects of unnecessary treatment
- False-positives: anxiety, follow-up tests
- False-negatives: false reassurance
- Diverts resources

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1989

- USPSTF — insufficient evidence for DRE; transrectal ultrasound and serum tumor markers not recommended
- ACS – annual DRE
- NCI – annual DRE
- CTF – recommend against screening

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Interventions Not Routinely Recommended for Older Adults 1989 USPSTF

- Screening for prostate cancer
- Screening for breast cancer under age 50
- Screening for dementia
- Screening for osteoporosis
- Screening for diabetes
- Screening chest X-ray
- Screening ECG
- Screening urinalysis

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1996

- USPSTF – DRE, PSA, TRUS not recommended (D)
- ACS, AUA, ACR
  annual DRE age 40;
  PSA age 50
- CTF – recommend against screening
- OTA – evidence inconclusive

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USPSTF 2002 - 2008

- 2002
  insufficient evidence (I)
  NYT: "*Task Force Softens Stance*"
- 2008
  insufficient evidence for men under age 75 (I)
  recommend against for men over age 75 (D)

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2012

- ACS – ". . . men [should] have a chance to make an informed decision with their health care provider about whether to be screened for prostate cancer."
- AUA – screen "well informed men" (policy is under review)
- CTF — not currently under review
- USPSTF – D

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USPSTF Grades

Certainty of Net Benefit	Magnitude of Net Benefit (Benefit Minus Harms)			
	Substantial	Moderate	Small	Zero/Negative
High	**A**	**B**	**C**	**D**
Moderate	**B**	**B**	**C**	**D**
Low	**I Statement**			

Do: A & B recommend routinely
Depends: C recommend individual decision
Don't do: D recommend against
Don't know: I insufficient evidence

USPSTF Prostate Cancer Screening – Final May 2012

- **The USPSTF recommends against PSA-based screening for prostate cancer.**
  Grade: D recommendation
- Applies to men without symptoms suspicious for prostate cancer, regardless of age, race, or family history.
- Did not evaluate the use of the PSA test as part of a diagnostic strategy in men with symptoms suspicious for prostate cancer.

What Changed?

- Grade
  Changed from **I** statement to **D** recommendation
  - From shared decision-making to recommend against screening
- Why?
  - New evidence regarding benefits and harms
  - Five new clinical trials of screening and prostate cancer mortality

Evidence on Mortality

- 5 Clinical Trials
  - 1 poor quality
  - Focus on 2 large trials in USA and Europe
- Results
  - ERSPC: 0.06% decrease in deaths of men 50-74 (in 2 of 7 countries only)
  - PLCO: 0.03% increase in deaths
  - Combined: no effect

Also Updated

- Natural history data
- Ecological data
- Harms of treatments

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Benefits per 10,000 Screened

- Between 0 and 6 fewer deaths from prostate cancer over about 10 years (NNS ~ 1,444 to prevent one death
- No improvement in all-cause mortality

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Harms per 10,000 Screened

- 1,000-1,200 will be biopsied
- 1,100 will be diagnosed with prostate cancer
- 90% of those diagnosed will be treated (next slide)

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Harms per 10,000 Treated

- 50 deaths within 1 month of surgery
- 100-700 men with serious surgical complications (e.g. cardiac, DVT)
- 2,000-3,000 with incontinence, impotence, or both
- *Overall averages about 500 serious harms per 10,000 screened*

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"A 3% lifetime risk of prostate cancer death means that 97% of men have to be informed about a test that cannot help them—it can only harm them. And the benefit only accrues to a small fraction of those destined to die of the disease."

– *Gil Welch, JAMA December 2012*

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Critique of Earlier Draft

- Trials flawed
- New data from PLCO 1/12
  - After 13 years still no benefit
- Ecological data - inconclusive
- CISNET Modeling
  - Maximum possible benefit a 20% mortality reduction (from 2.80% to 2.24%)

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What's Next?

- ACS, AUA, ACPM, AAFP, and ACP expected to update within the next 12 months
- Don't expect much new

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Clinical Advice

- Do not order a PSA without informing your patients (PSA should never be "routine")
- You must be willing to discuss potential benefits and harms
- Focus should be on systems to facilitate decision-making

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- Prostate cancer is a serious health problem that affects thousands of men and their families. But before getting a PSA test, all men deserve to know what the science tells us about PSA screening: there is a very small potential benefit and significant potential harms. We encourage clinicians to consider this evidence and not screen their patients with a PSA test unless the individual being screened understands what is known about PSA screening and makes the personal decision that even a small possibility of benefit outweighs the known risk of harms.

— *Michael LeFevre, USPSTF Co-Chair*

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Conflict of Interest and Bias

- Common and often not transparent
- Financial conflicts include clinical
- Disclosure not an adequate remedy
- Balance or exclude them?
- 2011 IOM recommendations for systematic reviews and guidelines set a high bar

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Quote of the Month 10/11

- "We in medicine need to look into our soul and we need to learn the truth. If your income is dependent on you not understanding something, it is very easy not to understand something."

  - Otis Brawley, ACS Chief Medical Officer

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- "Screening is cheap and effective advertising and a moneymaker. For every 1,000 men we screen at the mall, 145 have an abnormal screen, and 135 come to us for evaluation. Fees easily cover the cost of screening."

  - hospital exec quoted by Otis Brawley

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What about Warren Buffett?

- ACS, AUA, USPSTF all agree that men in their 80's should *not* be routinely screened (average life expectancy < 10 years)
- Alarms stockholders about something that is unlikely to matter
- Moral: Great wealth does not guarantee great medical advice

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Why the USPSTF got it wrong

Christopher J. Kane MD
Professor of Surgery, Chief of Urology
C Lowell and JoEllen Parsons Chair in Urology

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USPSTF

- Gives prostate cancer screening a D grade.
- The definite evidence of harm far outweighs the unproven benefit of PSA screening
- 8,000 comments received concerning the recommendation in the first 30 days (comment period).

Why?

- The randomized trials of PSA screening show little improvement in mortality at a high cost of treatment
- PSA is a poor screening test with poor specificity so many men get prostate biopsies and worry and don't have cancer
- Many men who are treated had bad side effects, surgical complications, erectile dysfunction and incontinence and don't benefit from treatment

Recent studies

Screening revisited:

•PLCO (Prostate, Lung, Colorectal and Ovary) - Andriole GL, Crawford ED, Grubb RL, et al.: Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009, 360:1310–1319.

•ERSPC (European Randomized Screening for Prostate Cancer) - Schroder FH, Hugosson J, Roobol MJ, et al.: Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009, 360:1320–1328

Screening

PLCO:

•Randomization 50-74 yo men from 1993-2001

- •38,350 men to intervention vs 38,355 to control
- •Screening: Annual PSA (6 yrs) and DRE (4 yrs)
- •Control: NO screening
- •Follow for ≥ 13 years

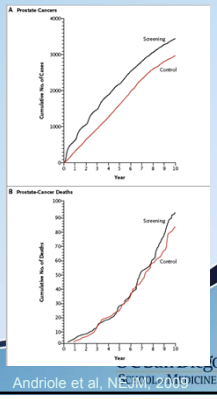
•Goal: whether or not screening reduces *Prostate Cancer Mortality*

Screening

PLCO:

•Findings after median 11.5 yrs

- •Prostate Ca diagnosis:
  - •Screened-9% vs Control-7.8%
- •Prostate Ca Mortality:
  - •Screened-0.24% vs Control-0.21%



Andriole et al, NEJM, 2009

PLCO Contamination:

- Flaws:
  - Assumed that 10% with prev screening in control arm would continue
  - In actuality, Control Arm,
    - 44% of men in each arm had ≥1 PSA test before randomization
    - During trial, 52% had undergone PSA screening and 46% with DRE
  - Controls:
    - Only 15% decreased diagnosis
    - 93% of cancers were asymptomatic, organ-confined
  - Follow-up was 11.5 years from randomization, NOT treatment

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Screening

ERSPC:

- 162,243 men 55-69 yo randomized from 1991-2003
- Median follow-up - 9 years
- Screening:
  - Did NOT require annual PSA – only 2.1 tests averaged over course of study
  - DRE variable, but usually only if equivocal PSA

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ERSPC:

- Prostate Cancer diagnosis: Screened-8.2% vs Control-4.8
- Death from prostate cancer: screened arm RR was 0.80 (95% CI 0.67–0.95; P=0.01)
  - Curves began to diverge at 7-8 years
- NNS to prevent 1 death=1410; NNT=48

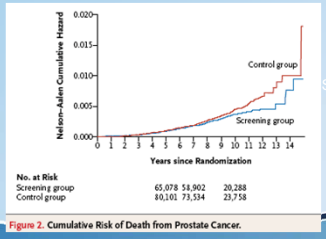

Figure 2. Cumulative Risk of Death from Prostate Cancer.

Schroder et al, NEJM, 2009

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Screening - Newer data

Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja

- 20,000 men aged 50-64 yrs
- Screened every 2 years
- Followed median 14 years
- Screened:
  - Prostate cancer diagnosed: Screened-12.7% vs Control-8.2%
  - Prostate cancer death: Screened-0.5% vs Control-0.9%
    - RR Reduction = 0.56 (95%CI, 0.39-0.82, p=0.002)
      - *Compared to ERSPC = 0.8*

Hugosson et al, Lancet Oncol, 2010

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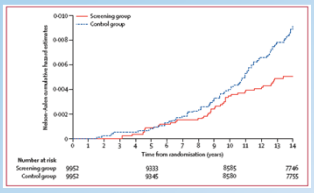
Screening - Newer data



- Younger patients – more likely to have incurable cancer at first screen
- Lower PSA threshold for biopsy (2.5-3 vs 4) and more frequent screening (2 vs 4 yrs)
- Lower contamination (3% vs 44%)
- ***Longer follow-up with improved RR***
- NNS = 293 and NNT = 12 to prevent 1 Death
  - Not significantly different from Breast or Colorectal cancer

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The NEW ENGLAND JOURNAL of MEDICINE

MARCH 15, 2012

Prostate-Cancer Mortality at 11 Years of Follow-up

- Now with 11 years of follow-up, the relative reduction in the risk of death from prostate cancer is 21% (RR 0.79, 95% CI 0.68-.91 p=0.001), 29% after adjustment for noncompliance.
- NNS now 1055, NNT 37.

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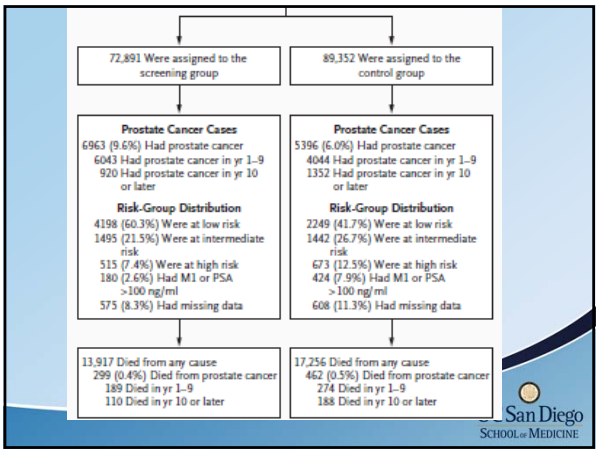


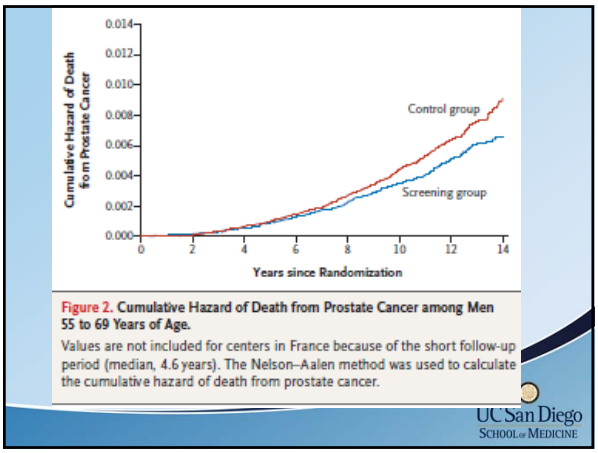


Figure 2. Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.

Values are not included for centers in France because of the short follow-up period (median, 4.6 years). The Nelson–Aalen method was used to calculate the cumulative hazard of death from prostate cancer.

So in what ways were they wrong?

- There is strong evidence that radical prostatectomy saves lives over observation (38% prostate cancer mortality reduction, 25% all cause mortality reduction) at 15 years (Bill-Axelson NEJM 2011; 364:1708-17)
- Diagnostic procedures to detect prostate cancer are common in both screened and unscreened populations, they just occur later in unscreened men.

May 12, 2011

The NEW ENGLAND JOURNAL of MEDICINE

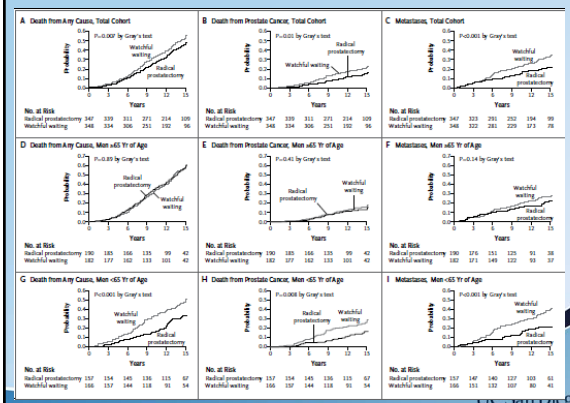
ORIGINAL ARTICLE

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Mirja Ruutu, M.D., Ph.D., Hans Garmo, Ph.D., Jennifer R. Stark, Sc.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D., Stefan Bratell, M.D., Ph.D., Anders Spångberg, M.D., Ph.D., Juni Palmgren, Ph.D., Gunnar Steineck, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D., for the SPCG-4 Investigators*

RP vs. WW

- 1989-1999 695 men with newly diagnosed prostate cancer randomized between RP and WW
- Median followup 12.8 years
- RR of death in surgery arm 0.62 (95% 0.44-0.87 p=0.01)
- Survival benefit was confined to men under 65
- NNT to prevent 1 death was 15, 7 for men under 65



Bill-Axelson, A et al. N Engl J Med 2011

- The task force minimized the burden of living with advanced cancer and primarily looked at survival (bone mets, obstruction, fractures etc…)
- The task force did not adequately consider at risk populations (AA and FH men)
- The task force minimized the epidemiologic data that since PSA testing began in the 1990's there has been a 40% reduction in prostate cancer mortality and 75% reduction in presentation with advanced disease.

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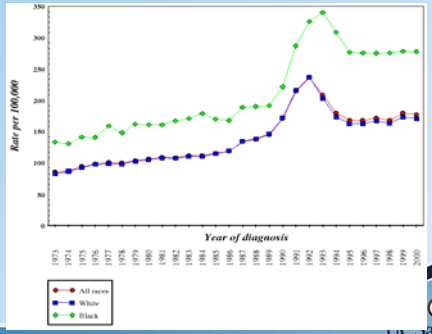
US Age Adjusted Incidence



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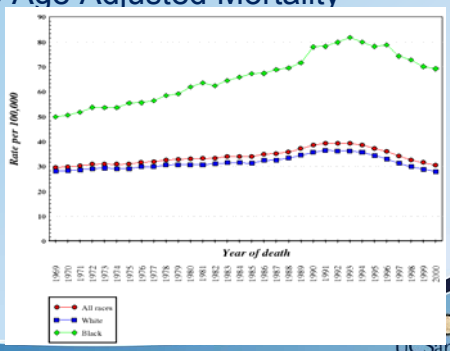
US Age Adjusted Mortality



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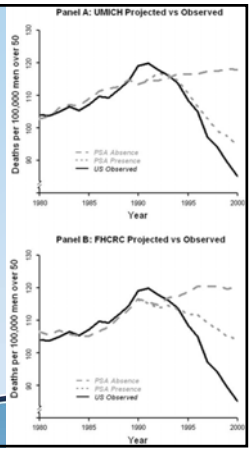
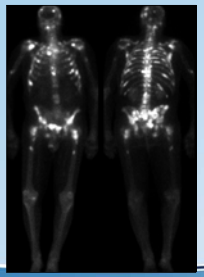
Defining the proportion of mortality reduction from PSA screening and early detection

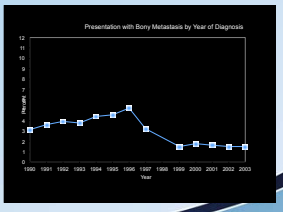
- Two models generated to determine the proportion of decline in mortality from early detection vs. improved treatment
- 45-70% mortality reduction from early detection

Etzioni et al Cancer Causes Control. 2008 Mar;19(2):175-81.



Stage Evolution





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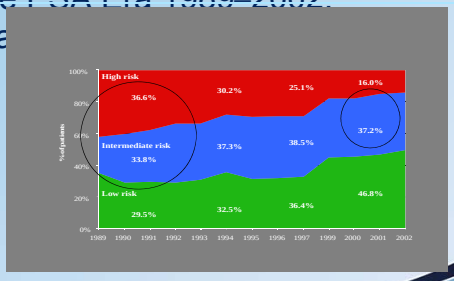
Changes in Risk Stratification in the PSA Era 1989–2002: Ca



Cooperberg MR, et al. J Urol. 2003 Dec;170(6 Pt 2):S21-5.
Copyright Lippincott Williams & Wilkins 2003.

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So how do we answer the screening concerns?

- Improve the specificity of PSA
- Stop screening men who are unlikely to benefit
- Diminish overtreatment by offering active surveillance more than currently

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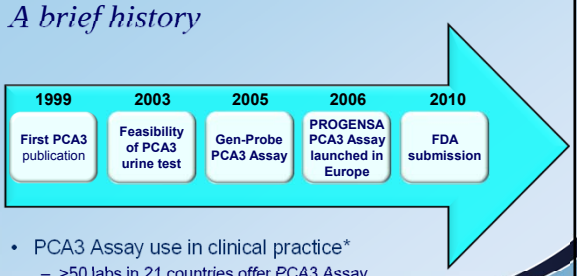
Prostate Cancer Gene 3 (PCA3)
A brief history



- PCA3 Assay use in clinical practice*
  - >50 labs in 21 countries offer PCA3 Assay
  - Worldwide, ~185,000 tests performed to date
  - www.PCA3.org run by European clinicians

*The PCA3 Assay is not FDA - approved

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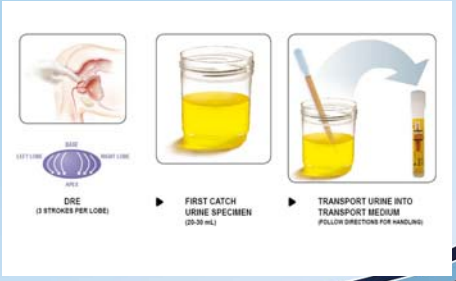
PCA3 Molecular Urine Test
Specimen Processing



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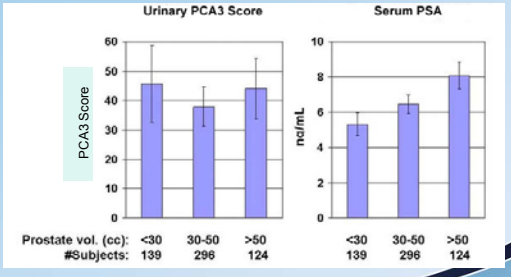
PCA3 Score is independent of prostate size



Source: Deras/Aubin, et al. (2008) J. Urol. 179: 1587

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Repeat biopsy dilemma

- The fear that prostate cancer may have been missed at first biopsy often leads to repeat biopsies
  - The majority (~80%) of repeat biopsies are negative
  - Biopsy is costly and can be associated with considerable anxiety, discomfort, pain and other complications
  - The incidence of resistant post-biopsy infections is rising
- Clinicians and patients must decide on a repeat biopsy based on the associated risks and benefits
- Clear unmet need for more accurate methods to:
  - supplement PSA for guiding repeat biopsy decisions
  - reduce the number of unnecessary biopsies (~5 men are biopsied per cancer diagnosed)

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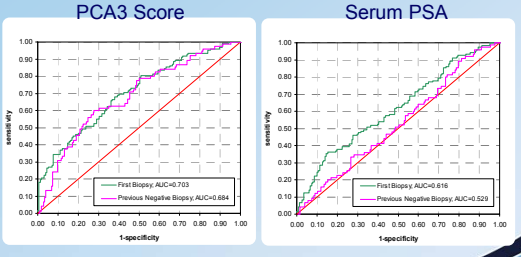
PCA3 utility for predicting repeat biopsy outcome



Source: Deras/Aubin, et al. (2008) J. Urol. 179: 1587

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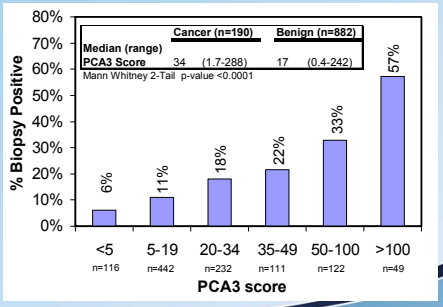
PCA3 in the GSK REDUCE Trial (placebo arm, n=1072)
Men with previous negative biopsy and elevated serum PSA



Source: Aubin et al. (2010) J. of Urology 184(5):1947

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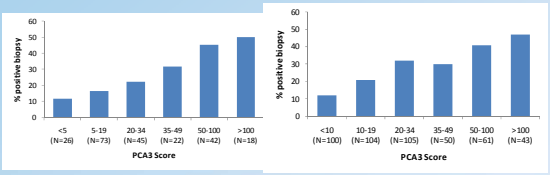
PCA3 correlates with likelihood of positive repeat biopsy
North American and European multi-center studies



North American Study
Marks et al (2007) Urol. 69:532

European Study
Haese et al (2008) Eur. Urol. 54:1081

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PCA3 complements the existing standard of care
GSK REDUCE trial placebo arm (repeat biopsy population)

Marker	ROC AUC (95% CI)
Serum PSA	0.612 (0.570, 0.655)
Percent free PSA	0.637 (0.593, 0.681)
PCA3 Score	0.693 (0.649, 0.736)
Predictive Model*	0.717 (0.675, 0.759)
Predictive Model* + PCA3 Score	0.753 (0.712, 0.793)

* Age, family history, prostate volume, serum PSA, %free PSA

Source: Aubin et al. (2010) J. of Urology 184(5):1947

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Risk Stratification

- PSA
- Clinical Stage
- Gleason Grade
- Number and extent of positive biopsies
- PSA velocity/ PSA kinetics
- Obesity

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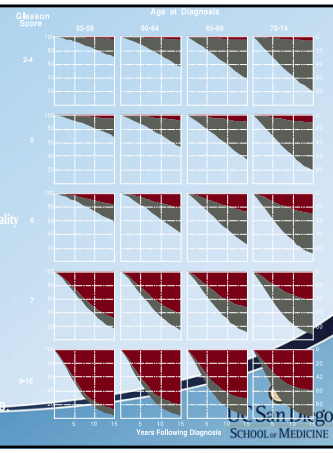
Analysis of Men Age 55–74 at Diagnosis: Conservative Rx Localized CAP

Gleason score	Prostate cancer mortality at 15 years
2–4	4%–7%
5	6%–11%
6	18%–30%
7	42%–70%
8–10	60%–87%



Albertsen PC. JAMA. 1998;280:975-980.
Copyrighted 1998, American Medical Association.

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UCSF CAPRA

Cooperberg et al J Urol June 2005

Variable	Level	Points	N	% of cohort	% fail
PSA	2.1-6	0	721	50	9
	6.1-10	1	453	31	14
	10.1-20	2	209	15	28
	20.1-30	3	36	3	33
	>30	4	20	1	55
Gleason	1-3/1-3	0	1068	74	12
	1-3/4-5	1	239	17	20
	4-5/1-5	3	132	9	28
T-stage	T1/T2	0	1410	98	14
	T3a	1	29	2	21
% pos bx	<34%	0	911	63	10
	≥34%	1	528	37	23
Age	<50	0	51	4	6
	>50	1	1388	96	15

Score calculated by totaling each characteristic, range 0-10

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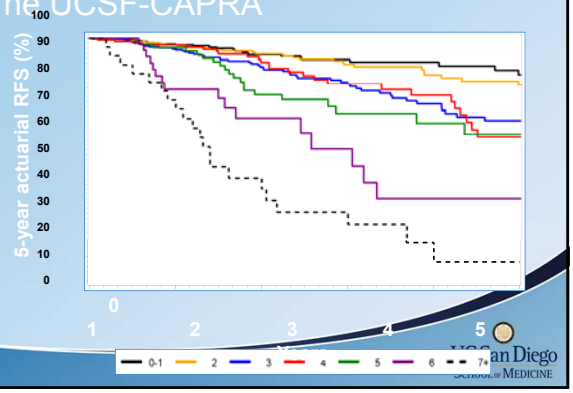
C

The UCSF-CAPRA



Clinically Indolent Disease

How to define an "insignificant tumor"?

- Clinical stage T1c
- PSA density < 0.15ng/ml/cm^3

And absence of

- Any Gleason pattern 4 or 5
- > 3 cores involved
- > 50% of core involved
- In a 12 core Bx

Epstein. JAMA 2004;291:1368

Active Surveillance

- Advantages
  - Avoids risk from surgery or radiation therapy
  - Decreased cost
- Disadvantages
  - Inaccurate staging/grading may put patient at risk for metastases
  - Stress
  - Side effects from repeat biopsy

Do Nothing?!

• 331 patients with a median follow-up period of 84 months (range 24–132 months)

•101 patients (31%) came off active surveillance because criteria for intervention were fulfilled,

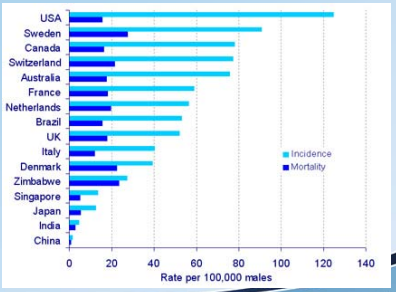
•32 patients (10%) received radical treatment although they did not fulfill the criteria for intervention

•The overall survival was 85% and the disease-specific survival was 99%

•Three patients died of prostate cancer

Klotz et al Nat Clinic Pract Uro Mar 2008

Prostate Cancer Incidence Mortality Rates by Country



Summary

- PSA is an imperfect screening test. High sensitivity but low specificity
- PSA screening does save lives
- Younger men and those at increased risk of prostate cancer benefit the most
- We currently have methods of improving the specificity of screening
- We should stop screening men unlikely to benefit
- We should offer active surveillance to low risk men

Summary

- To discourage PSA screening for all men is irresponsible
- The USPSTF methodology is severely flawed
- Lets thoughtfully move forward with prostate cancer detection and treatment that keeps faith with the patients at risk for the second leading cancer killer of American Men

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UROLOGY.UCSD.EDU HEALTH.UCSD.EDU RCHSD.ORG

Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level ≤ 4.0 ng per Milliliter

–14.9% of these cancers had Gleason 7 or higher

–Prostate cancer prevalence:
- •PSA ≤ 0.5 ng/mL 6.6%
- •PSA 0.6 – 1.0 ng/mL 10.1%
- •PSA 1.1 – 2.0 ng/mL 17.0%
- •PSA 2.1 – 3.0 ng/mL 23.9%
- •PSA 3.1 – 4.0 ng/mL 26.9%

–High grade cancer prevalence:
- •PSA ≤ 0.5 ng/mL 12.5%
- •PSA 3.1 – 4.0 ng/mL 25.0%

Thompson et al NEJM 2004

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Melanoma, or Not!

Charles Miller M.D.
Dermatologist, Kaiser Permanente
San Diego, CA (pic from Cabrillo Point)

Background: Skin Cancer in the US

- >1 million skin cancers per year
- 1 in 5 people in the US will get a skin cancer in their lifetime
- 96% of these are non-melanoma skin cancers (BCC/SCC)

Skin Cancer Prevention

1 in 5 Americans will get Skin Cancer

Approximately 95% not fatal

Almost 5% ARE fatal

Background: Malignant Melanoma

- The incidence of Melanoma is rising faster than for any other cancer (6%/year 1950-90)
  - This leads to a doubling every 10-15 years

Lifetime risk of Invasive Melanoma in the US

2010 : 1 in 57 develop Invasive Melanoma

Background: Melanoma

- More than 12,000 deaths in US last year from skin cancer--8800 due to Melanoma
- Melanoma is the most common cancer killer in women age 30-35
- Responsible for more years of life lost /cancer than any other adult malignancy except testicular cancer

2011 : 70,000 invasive cases Melanoma in U.S.

2011 : 53,360 Melanoma In-Situ (stage 0)

Risk of any Melanoma: 2011

- 1 in 33 Caucasian Americans
- 1 in 500 in Latino Americans
- 1 in 1000 in African Americans
  - But: 300% increased incidence of Stage 3 or 4 disease at detection in African Americans.

Risk Factors: Clinical Characteristics

- Fair complexion
  - freckles, red/blond hair, blue eyes
- Large number of moles
- Clinically atypical moles
- Family history of melanoma
- Sunburns in childhood / amount of sun in childhood

Diagnosis and Staging

Table 2. AJCC 2002 Revised Melanoma Staging

STAGE	HISTOLOGICAL FEATURES/TNM Classification	OVERALL SURVIVAL: 1-Year	5-Yr	10-Yr
0	Intraepithelial/in situ melanoma (TisN0M0)		100%	100%
IA	≤ 1 mm without ulceration and Clark Level II/III (T1aN0M0)		95%	88%
IB	≤ 1 mm with ulceration or level IV/V (T1bN0M0)		91%	83%
	1.01–2 mm without ulceration (T2aN0M0)		89%	79%
IIA	1.01–2 mm with ulceration (T2bN0M0)		77%	64%
	2.01–4 mm without ulceration (T3aN0M0)		79%	64%
IIB	2.01–4 mm with ulceration (T3bN0M0)		63%	51%
	> 4 mm without ulceration (T4aN0M0)		67%	54%
IIC	> 4 mm with ulceration (T4bN0M0)		45%	32%
IIIA	Single regional nodal micrometastasis, nonulcerated primary (T1-4aN1aM0)		69%	63%
	2–3 microscopic regional nodes, nonulcerated primary (T1-4aN2aM0)		63%	57%
IIIB	Single regional nodal micrometastasis, ulcerated primary (T1-4bN1aM0)		53%	38%
	2–3 microscopic regional nodes, ulcerated primary (T1-4bN2aM0)		50%	36%
	Single regional nodal macrometastasis, nonulcerated primary (T1-4aN1bM0)		59%	48%
	2–3 macroscopic regional nodes, nonulcerated primary (T1-4aN2bM0)		46%	39%
	In-transit met(s)/satellite lesion(s) *without* metastatic lymph nodes (T1-4a/bN2cM0)		30-50%	
IIIC	Single macroscopic regional node, ulcerated primary (T1-4bN1bM0)		29%	24%
	2–3 macroscopic regional nodes, ulcerated primary (T1-4bN2bM0)		24%	15%
	4 or more metastatic nodes, matted nodes/gross extracapsular extension, or in-transit met(s)/satellite(s) *and* metastatic nodes (anyTN3M0)		27%	18%
IV	Distant skin, subcutaneous, or nodal mets with normal LDH (anyTanyNM1a)	59%	19%	16%
	Lung mets with normal LDH (anyTanyNM1b)	57%	7%	3%
	All other visceral mets with normal LDH or any distant mets with increased LDH (anyTanyNM1c)	41%	9%	6%

Adapted with permission from Balch et al. Final Version of the American Joint Committee on Cancer Staging System for Cutaneous Melanoma. J Clin Oncol 2001; 19:3635–3648. Lippincott Williams & Wilkins. ©

Clinical Characteristics: ABCDE Rules

- A: Asymmetry in shape of a mole
  Appearance of a new mole
- B: Borders that are notched or irregular
  Bleeding
- C: Color of a mole is variable or changing
  Concern of patient regarding a mole
- D: Diameter exceeding 6mm
- E: Evolution (meaning change)
  - Enlarging
  - Elevated

ABCDE Rules Review

Treatment

- Early detection and removal of melanoma is the best treatment

What's more important that knowing what is melanoma?

What' s not Melanoma?

Seborrheic Keratosis
(barnacle, age spot, wisdom spot)

Seborrheic Keratosis

Seborrheic Keratosis, SK

Benign Nevi

Hemangioma

Dermatofibroma

Sunscreens

Prevention

- Protective clothing including Hats!
- Teach and use good habits in childhood
- Properly use sunscreens
  - with SPF 30 or greater
    - True – not much more protection than with SPF 15, but no one uses enough of SPF15 to get SPF 15 protection – so use SPF 30
- Self skin exams every 1-3 months
- Avoid the sun when possible
- No tanning booths!

Prevention: Sunscreens
The Pros

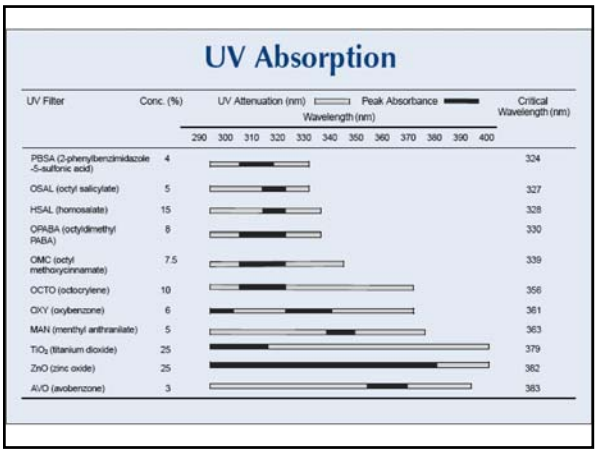
- Universally accepted that UV light plays a major role in skin cancer
- Sunscreens proven to reduce the risk for BCC/SCC

•and Cons

- Decreased Vitamin D
- 10-20 minutes 3 times per week
- or supplement

Quick answer to: What sunscreen should I wear, Doc?

- My answer is:
  - Any sunscreen with an SPF 30 or higher that has Zinc in it.
  - or Avobenzone“
  - Or Parsol 1789
  - Or Mexoryl
- Why? you may ask.



Sunscreen

- If you look at the previous graph, the black bars illustrate the best protection for a given ingredient. Zinc covers nearly the entire spectrum.
- Why SPF 30 when 15 is enough.
  - Well – for one, you need to use a baseball size amount for a waist up application. No one uses that much (not even your Dermatologist).

I think

“SPF 30 with Zinc”

is a statement I can live with, patients can remember, and hopefully, they will follow.

Skin Cancer Prevention =

Wrinkle Prevention

Twin Studies

Skin Cancer Prevention

Minimize Sun Exposure

- UVA
- UVB

Hats | Clothing | Shade | Sunglasses

Skin Cancer Prevention

Sunscreen
- SPF = UVB protection
- Stars = UVA protection

SPF 30+ with Zinc

Zinc or Titanium or Avobenzone or Octocrylene

Skin Cancer Prevention

New Sunscreen Labeling rules

July 2012:

1. SPF 30 +
2. Broad Spectrum
3. Water Resistant 80 minutes

Skin Cancer Prevention

2 million cases of skin cancer this year in U.S.

1.6 million cases of Basal Cell Carcinoma

300,000 cases of Squamous Cell Carcinoma

Almost 100,000 cases of Melanoma

Millions of cases of AKs

Actinic Keratosis - AK's

- 1-5mm scaly or rough red papules
- Pre-cancerous (low conversion rate)
- Easier to feel them than see them
  - Rub finger over skin
- AK Treatment
  - Freeze with LN2
  - 2mm halo
  - Repeat for thicker lesions

Skin Cancer Prevention Early Detection!!

A: **Asymmetry in shape of a mole**
Appearance of a new mole
B: **Borders that are notched**
Bleeding
C: **Color of a mole is variable**
Color of a mole is changing
D: **Diameter exceeding 6mm**
E: **Evolution (meaning change)**
+ Enlarging
+ Elevated

Skin Cancer Prevention

What Sunscreen should I buy?

SPF 30+ with Zinc

1. SPF 30 +
2. Broad Spectrum
3. Water Resistant 80 minutes

Skin Cancer Prevention

WHY?

Skin Cancer Prevention

- No Tanning Beds
- Sunscreen: SPF 30+ Broad Spectrum 80 min in water
- Oral Vitamin D 1000-2000 IU/Day
- ABCDE Rules
- Don't Smoke
- Minimize unprotected direct sun exposure

Dementia Update 2012

John Daly, MD
Clinical Professor, UCSD
Program Director, UCSD Geriatrics Fellowship
Medical Director, SOCARE

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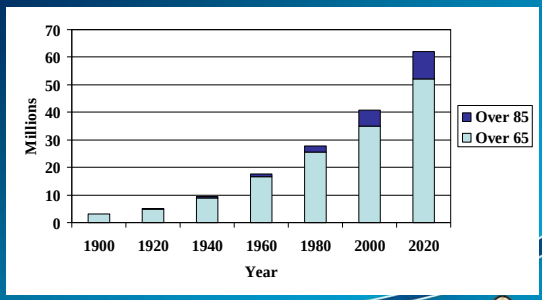
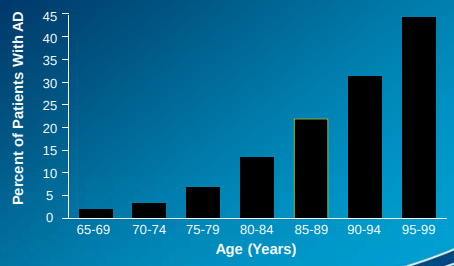
Number of persons over 65 in US



Prevalence of Alzheimer's Disease with Increasing Age



Adapted from Ritchie K, Kildea D. *Lancet*. 1995;346:931-934.

Early History

- Dementia (Latin: Demens)
  - Without Mind
- 2000 BC (Egypt): Memory Loss Related to Aging
- 200 AD: Galen wrote about cerebral dysfunction
- Middle Ages: Not focused upon much
- 1700s: Philippe Pinel likely coined "dementia"
- 1700s: Jean Esquirol - **Des Maladies Mentales**
  - Causes: Age, syphilis, mercury, wine, masturbation, and menstrual disorders.

Boller and Forbes. J Neuro Sci 1998

Throughout Literature

…Last scene of all that ends this strange eventful history, is second childishness and mere oblivion; Sans teeth, sans eyes, sans taste, sans every-thing

Shakespeare. **As You Like It**. 1600

What is dementia?

- "Insanity with loss of intellectual power due to brain disease or injury" Oxford Dictionary

The 3 requirements for dementia diagnosis

- Cognitive impairment involving two or more cognitive areas (memory, language, visual spatial skills, executive function, apraxia……)
- Functional decline from a previous higher functional level.
- Impairments not due to delirium

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Dementia or Delirium?

Know the difference

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DSM IV Criteria for Dementia

- Memory impairment and at least one of the following:
  Apraxia, agnosia, aphasia or executive function impairment
  - Deficit in two or more areas of cognition
- Impairments must be severe enough to cause impairment in social or occupational function and must be a decline from a prior higher level in function
- Diagnosis should NOT be made for deficits occurring exclusively during the course of an episode of delirium

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DSM IV Criteria for Delirium

- Disturbance in consciousness with reduced ability to focus, sustain or shift attention
- Change in cognition
- Disturbance develops over a short period and tends to fluctuate unpredictably
- History, PE or lab results indicate disturbance caused by consequence of medical condition, intoxication, medication or mixed causes

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What's the Difference?

Unrecognized delirium leads to increased morbidity and mortality because of failure to treat the underlying cause

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Pearls of Geriatric Assessment

- With advancing age, the specificity and sensitivity of the typical signs and symptoms of disease decline
- Any alteration of homeostasis in an elderly individual is likely to produce abnormalities of mental status and cognition (i.e. delirium)

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Delirium and Mortality

- 6-month mortality of elderly patients admitted to post acute care facility
  - With delirium: 25.0%
  - With sub-syndrome delirium: 18.3%
  - Without delirium: 5.7%

(Marcantonio et al. JAGS #6,June 2005:963-9)

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Dementia vs. Delirium

- Dementia
  - Insidious onset
  - Chronic course
  - Attention usually normal
  - Few motor signs
  - Usually no autonomic signs
- Delirium
  - Onset acute or sub-acute
  - Fluctuating course
  - Impaired attention
  - Often hyperactive or hypoactive
  - Increased sympathetic activity common
  - Triggering event/drug may be apparent

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What is *Normal* Brain Aging?

- The presence of Alzheimer's disease pathology over age 85 is 50%
- Since there has been no test for pre-symptomatic Alzheimer's disease, how much of the age-related difference seen in memory testing is due to effects of early or undetected Alzheimer's disease?

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Criteria for Diagnosis of Mild Cognitive Impairment (MCI)

- Cognitive complaint
- Normal activities of daily living
- Normal general cognitive function
- Abnormal testing in one or more cognitive areas for age and educational level
- Not demented

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Recognizing Dementia

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Ten Warning Signs of Dementia

- Memory problems that affect job
- Difficulty with familiar tasks
- Language problems
- Disorientation to time and place
- Judgment problems
- Problems with abstract thinking
- Misplacing things
- Changes in mood or behavior
- Changes in personality
- Loss of initiative

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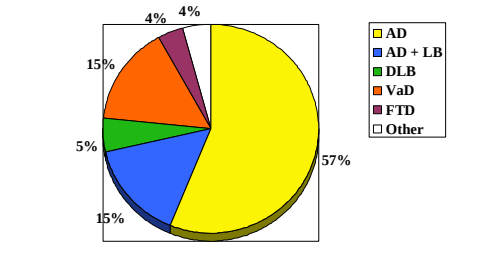
Etiologies of Dementia



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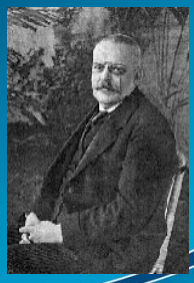
Alzheimer's Disease

- First described in 1906 by Dr. Alois Alzheimer
- Initial case report was a 51-year-old woman with a progressive dementia
- She died at age 56 and at autopsy, he described the plaques and tangles that are the hallmark of AD



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A Curious Case

- 51 year old woman brought in by her husband for 8 months of worsening behavioral changes
  - Strong feelings of jealously towards her husband
  - Memory impairment and disorientation
  - Inability to manage household or to cook
  - Gets lost in familiar places; fearful of friends
- On exam
  - Disoriented with rapid forgetting
  - When asked to write her name, writes "Mrs." then forgets the rest.
  - Speech has paraphrasic errors

Maurer et al. Lancet 1997

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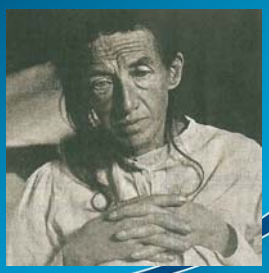
Auguste Deter (1901)

- Interested Alzheimer because she was young
- Progressively worsened
- Died of sepsis 4.5 years later (decubitus ulcer)
- Genetics:
  - ApoE3 homozygote
  - No APP mutations
  - Suspect she had a Presenilin 2 mutation



Yu, et al. Arch Neurol 2010

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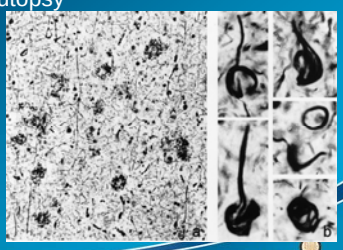
Alzheimer's Most Famous Case

- Kept records of her hospital course
- Performed an Autopsy
- Sections from frontal, parietal and occipital cortex (no hippocampus or entorhinal cortex)



Yu, et al. Arch Neurol 2010

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Classification of Dementia 1906-1976

- Prior to 1976, dementia was classified as either senile or "pre-senile" dementia
- Senile dementia was considered to be an expected consequence of aging
- "Pre-senile" dementia was attributed to Alzheimer's disease, which was believed to be a relatively rare condition causing dementia in younger people

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Senile Dementia and Alzheimer's Disease

In his landmark article in 1976, Dr. Robert Katzman demonstrated that the majority of senile dementia was, in fact, Alzheimer's disease

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NINCDS-ADRDA Criteria for Probable AD (1984 Clinical Criteria)

- Dementia by clinical exam and confirmed by cognitive testing
- Deficits in two or more areas of cognition
- Progressive worsening
- No disturbance of consciousness
- Onset after age 40; usually after 65
- Absence of systemic disorder or other brain disease that could cause changes

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The Diagnosis of Probable AD is Supported by:

- Progressive deterioration of specific cognitive functions:
  - Aphasia - language
  - Apraxia - impairment in learned motor skills
  - Agnosia - alterations in perception
- Impaired ADLs and altered behavior patterns
- Family history, especially if confirmed by neuropathology
- Normal LP and EEG
- Evidence of cerebral atrophy on CT

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Features that Make Diagnosis of Alzheimer's Disease Unlikely

- Sudden onset, rapid progression
- Early occurrence of: gait disturbance, seizures or behavioral changes
- Focal neurological findings
- Early evidence of extrapyramidal symptoms
- Other medical disorder severe enough to account for memory loss or other symptoms

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Dementia with Lewy Bodies

- Lewy Body Dementia
- Lewy Body Variant of Alzheimer's Disease
- Cortical Lewy Body Disease
- Diffuse Lewy Body Disease

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Criteria for Probable Dementia with Lewy Bodies

- Progressive cognitive decline sufficient to interfere with usual social or occupational function
- At least two of following:
  - Fluctuating cognition with alterations of alertness or attention
  - Recurrent visual hallucinations
  - Spontaneous motor features of Parkinsonism

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Adverse Drug Reactions in Dementia with Lewy Bodies

- Antipsychotics
  - Severe EPS reactions
  - Neuroleptic malignant syndrome
- Dopaminergic Agents: Carbidopa/Levodopa
  - Hallucinations and psychosis
- Memantine?
  - There are several case reports of increased hallucinations and agitation in Lewy body dementia patients treated with memantine

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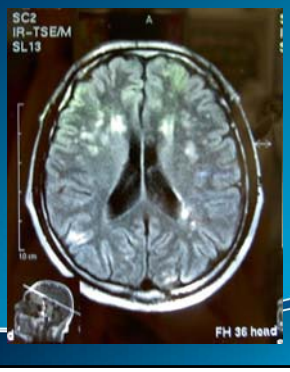
Vascular Dementia



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NINDS-AIREN Criteria for Probable Vascular Dementia

- Dementia
- Cerebral vascular disease defined by:
  - Focal signs of stoke on neurologic exam
  - Evidence of relevant cerebral vascular disease:
    - Multiple large vessel infarcts
    - Single strategically placed infarct (angular gyrus, thalamus, basal forebrain, PCA or ACA territories)
    - Multiple basal ganglia or white matter lacunes or extensive periventricular white matter lesions
- A relationship between the two:
  - Within 3 months of stroke
  - Abrupt deterioration and stepwise progression

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Features that Make the Diagnosis of Vascular Dementia Unlikely

- Early onset of memory problems, progressive worsening of memory and other cognitive deficits in absence of corresponding focal lesion on imaging
- Absence of focal neurological signs other than cognitive deficits
- Absence of any cerebrovascular lesions on brain imaging

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Frontotemporal Dementia

- Group of related diseases involving degeneration of the frontal and temporal lobes of the brain
- These areas are involved in decision making, behavioral control, emotion and language
- It is the most common of the early onset dementias

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Variants of Frontotemporal dementia

- Behavioral variant
  - Pick's disease or frontovariant FTD
  - Affects social skills, personal conduct, emotions and self awareness
  - About 60 % of FTD
- Semantic variant
  - Temporal variant FTD
  - Deficit is in meaning of language and not production of speech
- Primary progressive aphasia
  - Progressive loss of ability to produce language
  - Represents about 20% of FTD

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Clinical Diagnostic Features of Frontotemporal Dementia

Core Diagnostic Features

- Behavioral disorder:
  - insidious onset, slow progression
  - loss of personal and social awareness
  - disinhibition, hyperorality, loss of insight
- Affective symptoms:
  - depression; delusions; apathy; lack of empathy
- Speech disorder:
  - progressive reduction of speech
  - stereotypy of speech; echolalia, perseveration; late mutism
- Investigations:
  - normal EEG
  - frontal or temporal volume loss on imaging
  - profound frontal system dysfunction on neuropsychological testing

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Diagnostic Features of Frontotemporal Dementia

- Supportive diagnostic features
  - Onset before age 65
  - Positive family history 1st degree relative
  - Bulbar palsy, muscle wasting, fasciculations
- Diagnostic exclusion features
  - Abrupt onset with seizure activity
  - Early severe amnesia, spatial disorientation, apraxia
  - Cerebellar ataxia
  - Early severe pathological EEG

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Summary of the four common dementias

Alzheimer's Disease	Dementia with Lewy bodies	Fronto-temporal dementia	Vascular dementia
Memory loss is prominent	Parkinsonism Hallucination Visual spatial prblems	Behavior changes Language disturbance	Evidence of strokes Memory loss is not prominent
Amyloid Tau-p	Lewy bodies	Tau	Strokes on imaging

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The Diagnostic Evaluation of Dementia

- Medical history and physical
- Neurological evaluation
- Cognitive testing
- Brain imaging
- Laboratory tests
- Psychiatric evaluation

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Evidence Supports the Following Tests in Routine Dementia Evaluation

- CBC
- Electrolytes
- Metabolic panel
- Thyroid function tests
- B-12 level
- Depression screening
- MRI or CT structural brain image

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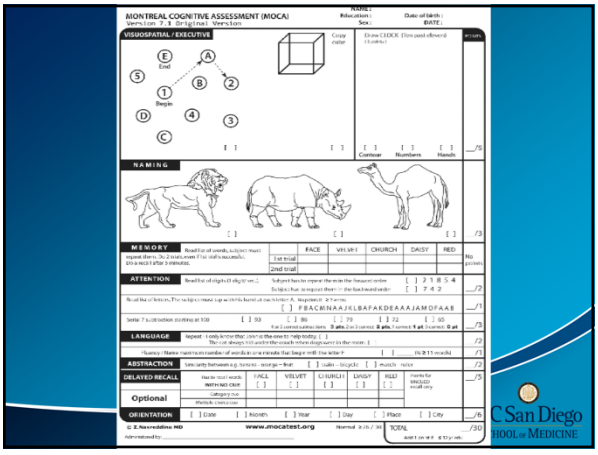

Issues to Cover at Diagnosis

- Effect of disease
- Disease progression
- Ability to perform daily tasks
- Available medications
- Difficult behaviors
- Where to find help and services
- Caregiver information
- Financial and legal planning issues
- Driving

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The Multidisciplinary Team – Essential Components

- Medical team
- Social work
- Case management
- Patient resources
- Family
- Community

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Recommendations

- Need to be presented face-to-face as well as in a clear written format
- Need to be *discussed* with the patient, family and caregivers with *adequate* time for questions and clarification
- Need to be pertinent to the individual's living situation and available resources

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Why Screen for Early Dementia?

- Allows the individual a chance to plan for the future, while decision-making capacity exists
- Safety issues
  - Medication compliance
  - Driving
  - Neglect and abuse
  - Wandering
- Can disease course can be modified?

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The Primary Care Physician's Role in Care of Patient's with Dementia

- Recognition of symptoms
- Accurate diagnosis
- Documentation of diagnosis
- Development of a care plan and referral to appropriate social support services
- Follow-up assessment and care
- Appropriate use of prescription medications

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Which patients need referral to neurologist or other dementia specialist?

- Sudden onset, rapid progression.
- Age of onset less than 60
- Any focal neurologic findings
- Marked behavior change or language disturbance at onset
- Seizures
- Movement disorder or Parkinsonism
- If it "doesn't feel right"

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Patients you may wish to refer to a multidiscipline dementia center

- Mild cognitive impairment or early stage disease
- Patients with poor social support systems or at risk living conditions
- Individuals who express an interest in research or clinical trials
- If you are feeling overwhelmed by the patient's care needs

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Resources the primary care physician must have to care for the patient with dementia

- Access to neuropsychological testing
- Social worker with dementia care experience
- Access to care management services
- A knowledge of community support systems in your area (ex: Alzheimer's Association)

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ACP and AAFP Evidence Review for Dementia Treatment

- RCTs: Modified Jadad score 3 or above
  - Donepezil - 24 studies: 2 moderate to severe, 1 severe
  - Galantamine - 10 studies: all mild to moderate
  - Rivastigmine - 9 studies: 1 moderate, none severe
  - Memantine - 5 studies: 2 mild to moderate, 2 moderate to severe, 1 severe

Raina et al Ann Intern Med 2008; 148:379-397

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Summary of ACP and AAFP Guidelines for Dementia Treatment

- Clinicians should base the decision to initiate cholinesterase inhibitor or memantine on individual assessment
  - Weak recommendation, moderate quality evidence
- Choice should be based on tolerability, adverse effects, ease of use and cost
  - Weak recommendation, low quality evidence

Qaseem et al Annals Internal Medicine March 4, 2008

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New Diagnostic Modalities

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Earlier Identification of Disease

- The pathophysiology of Alzheimer's Disease develops years to perhaps decades prior to detectable cognitive dysfunction
- Can these changes be detected in asymptomatic individuals?
- Are there "surrogate-markers" for early disease?
  - Biomarkers in CSF or blood
  - Advanced imaging technologies

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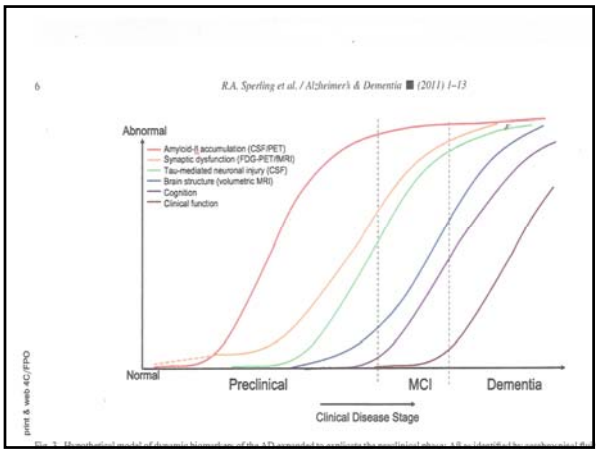

New Alzheimer's Disease Guidelines and Criteria

- Notable difference from 1984 NINCDS-ADRDA includes formulation of 3 AD stages and inclusion of biomarkers
- Broad consensus that the use of biomarkers must be validated and standardized before routine clinical application

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Three Stages of Alzheimer's Disease

- Pre-clinical
  - Pathophysiological changes in the brain, but cognitively normal
- Mild cognitive impairment (MCI) due to AD
  - Clinical and research criteria
- Dementia due to Alzheimer's Disease
  - Probable
  - Possible
  - Probable with evidence of AD pathophysiology

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Preclinical Alzheimer's Disease: Biomarkers and Advanced Imaging

Measures of:

A-beta accumulation:
- CSF A-beta 42
- PET image with amyloid tracer

Neuronal injury:
- CSF tau/p-tau
- FDG-PET/fMRI
- sMRI

Solely for research:

This is a conceptual model and not meant to imply that all individuals with early AD pathology will progress to AD dementia

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MCI with AD Pathology

• Clinical Core – Change in cognition over time consistent with AD – Impairment in 1 or more cognitive domains – Independent function – Not demented	Criteria can be used in clinical setting
• Research criteria – Incorporates biomarkers and advanced imaging	Research only: Prior to use in community, biomarker criteria and standardization must occur

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Dementia due to Alzheimer's Disease

• Probable AD – Core clinical criteria	Retains framework of 1984 NINCDS-ADRDA criteria
• Possible AD – Atypical course – Mixed etiology	Previous possible AD should be reevaluated with updated criteria
• Probable AD with AD pathology – Biomarkers – Advanced imaging	Not recommended for routine AD diagnosis; may increase certainty in AD diagnosis

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Amyloid Imaging

- Florbetapir (Amyvid: Eli-Lilly Avid)
  - 18F tracer that labels amyloid on PET scan
  - In January 2011, the FDA Peripheral and Central Nervous System Drugs advisory board voted approval, if a clinical trial can confirm that doctors can read the scans properly.

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CSF Markers for Alzheimer's Disease

- CSF levels of tau and A-beta 42 have been shown to accurately predict which MCI patients will progress to AD
  - Significantly elevated tau levels and lower A-beta 42 levels in CSF are highly sensitive and specific for Alzheimer's pathology

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Volumetric MRI

- The finding of a hippocampal volume two standard deviations below normal and a inferior lateral ventricle volume greater than two standard deviations above normal is strongly predictive of progression to AD in patients with MCI

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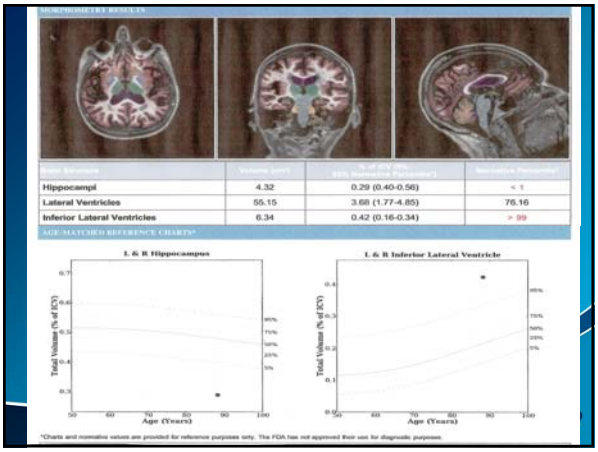

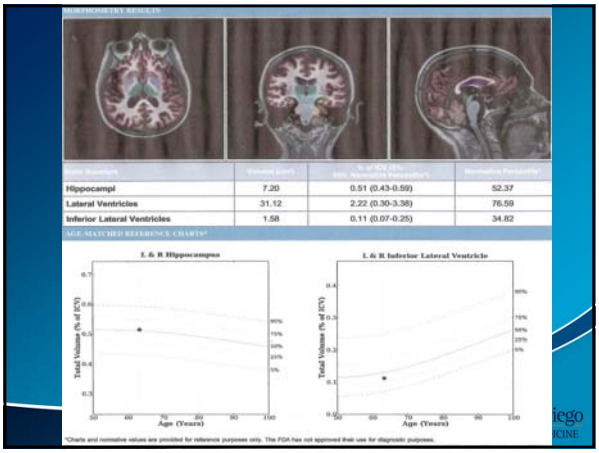

Dementia is……

- Loss of memory and other cognitive functions
- A decline in the ability to perform usual daily tasks
- Changes in behavior and personality
- Loss of ability for self care and self determination

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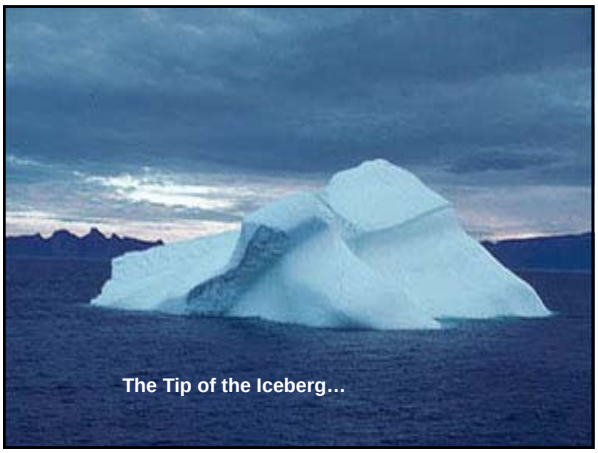
There are approximately
5.4 million individuals
in the U.S. today
with the diagnosis
of Alzheimer's Disease



University of California, San Diego
Shiley-Marcos
Alzheimer's Disease
Research Center

8950 Villa La Jolla Drive, Suite C-129
La Jolla, CA, 92037
Phone: (858) 622-5800
Fax: (858) 622-1017
http://adrc.ucsd.edu

SOCARE

- Team provides comprehensive initial evaluation and social assessment
- Referral for: imaging, neuropsychological testing, geriatric psychiatry or neurology, as indicated
- A final conference with patient and family to present diagnosis, recommendations and education about community resources

SOCARE Contact Information

Clinic Office
(619) 471-3833

The San Diego and Imperial County Alzheimer's Association

858 492-4400

- Services available include:
  - Education for patients and caregivers
  - Support groups
  - Crisis help line
  - Safe return program
  - And many, many more

Other Resources

- Southern Care Givers Resource Center
  - 858 268-4432
- Glenner Memory Care Centers
  - 800 736-6674

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Collaborative Care Model of Mental Health Care

Kurt Lindeman, M.D.
June 23, 2012

Conflict on Interest

- none

Lecture Objectives

- At the conclusion of this presentation, the learner will be able to:
  - Understand the significance of mental health issues in the primary care setting.
  - Describe the various aspects of collaborative care models used to manage mental health care in the primary care setting.
  - Take initial steps to implement collaborative care models in their own practice.

Mental health in the primary care setting.

Mental health in the primary care setting.

- The combined lifetime prevalence of all mental health disorders is 57.4% (Kessler, 2005)
- Approximately half of all mental health care services are provided solely by Primary Care providers. (deGruy, 1996)

Mental health in the primary care setting.

- Psychiatric Diagnoses have been found in *42.5% of patients in a Primary Care Office (Ansseau, 2004)
- Estimates as high as 50-70% of patients in Primary Care have psychological symptoms affecting their medical condition (Gatchel, 2003)

Mental health in the primary care setting.

- The most commonly detected disorders include
  - Mood Disorders 31% - depression and dysthymia
  - Anxiety disorders 19% - generalized anxiety
  - Somatoform disorders 18%
  - Substance dependence 10%
  - (Ansseau, 2004)

Mental health in the primary care setting.

- Approximately half of the patients with a psychiatric disorder were not recognized as having a mental illness by there primary care physician. (Higgens, 1994)

Mental health in the primary care setting.

- "The bidirectional relationship between the effects of depression/anxiety and medical illnesses creates a vicious cycle of medical, mental health, and behavioral concerns that can negatively affect the course of illness." (Beachum, 2012)
  - Decreased quality of life
  - Decline in activities of daily living
  - Poor adherence
  - Decreased health related behaviors
  - Increased use of services
  - Increased morbidity and mortality (Katon, 2003)

Mental health in the primary care setting.

- 30,000 people die of suicide each year
- 650,000 attempts!
- Suicide is related to physical health
  - 32% will have had a medical visit in the preceding 6 months
  - Physical health is noted as an important contributing factor in 11-51% of attempts
- (Kaplan and Saddock, 2003)

Mental health in the primary care setting.

- Treatment of depression after screening can improve outcomes.
- However the USPSTF recommends against screening unless you have staff-assisted care support in place.
- Screening alone does not lead to improved outcomes.
- (Phillips, 2011)

Collaborative Care Models

Collaborative Care Models

- Collaborative Care offers a seamless, multidisciplinary approach to patient care.
- It is a collaborative approach to care that occurs entirely within the primary care clinic.
- It involves the partnership of multiple specialties in patient care — including physicians, nurses, and behavioral health professionals.
- (Beachum, 2012)

Collaborative Care Models

- "It is evident that there is no single approach to integrating or coordinating services. However, there are critical success factors that vary depending on program goals, populations, the role and type of implementer among others." (RWJ Foundation, 2007)
- There is "no uniform definition of integration."

Collaborative Care Models

- Blount suggests analyzing a program according to the following categories
  - Location of services:
    - Coordination – referrals to outside services
    - Collocation – services within the same building
    - Integration – services in the same place, working in partnership
  - Targeted or non-targeted patient population
  - Specified or unspecified Behavioral Health services
  - Small scale or extensive implementation
  - Open or protocolized treatment strategies

Collaborative Care Models

- Properly organized models should impact
  - Access to services
  - Clinical outcome
  - Maintained improvement
  - Improved adherence
  - Patient and provider satisfaction
  - Cost effectiveness
- (Blount, 2003)

Collaborative Care Models

- RWJF echoes Blount in asserting
  - Service integration can mean different things and may take on many forms … the path toward integration varies depending on the goals, the resources, and the system reach of the implementer.

Collaborative Care Models

- RWJF continued…
- Commonalities between programs include
  - All programs appeared to be vested in a shared belief that treating the whole person is paramount.
  - Existence of a conceptual framework
  - Improved communication tools and processes
  - Screening tools
  - Collaboration in determining clinic approach
  - Identifying funding mechanisms
  - Establishing sustainability

Collaborative Care Models

- Evidence suggests that Collaborative Care:
  - Reduces barriers to access and forestalls progression of illnesses
  - Improves efficiency as much as 200–300% in achieving positive health outcomes
  - Increases patient and PCP satisfaction
  - Fewer appointment cancellations
  - Higher adherence to medical recommendations
- (Beachum, 2012)

Collaborative Care Models

- IMPACT Model
- Improving Mood-Promoting Access to Collaborative Treatment
- It is a collaborative model of depression treatment in primary care.
- Impact-UW.org

Collaborative Care Models

- The five most essential elements of IMPACT are:
  - Collaborative Care
  - Depression Care managers
  - Designated Psychiatrist
  - Outcome measurement
  - Stepped Care
- (Impact-uw.org)

Collaborative Care Models

- Collaborative care is the cornerstone of the IMPACT model and functions in two main ways:
  - The patient's primary care physician works with a care manager and the patient to develop and implement a personalized treatment plan
  - Care manager and primary care provider consult with psychiatrist to change treatment plans if patients do not improve
- (impact-uw.org)

Collaborative Care Models

- Depression Care Manager: This may be a nurse, social worker or psychologist and may be supported by a medical assistant or other paraprofessional. The care manager:
  - Educates the patient about depression
  - Supports antidepressant therapy if prescribed
  - Coaches patients in behavioral activation
  - Offers a brief course of counseling
  - Monitors depression symptoms for treatment response
  - Completes a relapse prevention plan
  - (impact-uw.org)

Collaborative Care Models

- Designated Psychiatrist:
  - Consults to the care manager and primary care physician on the care of patients who do not respond to treatments as expected
- (impact-uw.org)

Collaborative Care Models

- Outcome measurement:
  - IMPACT care managers measure depressive symptoms at the start of a patient's treatment and regularly thereafter.
  - The PHQ-9 is an effective measurement tool.
    - (Impact-uw.org)

Collaborative Care Models

- Stepped care:
  - Treatment adjusted based on clinical outcomes and according to an evidence-based algorithm
  - Aim for a 50 percent reduction in symptoms within 10-12 weeks
  - If patient is not significantly improved at 10-12 weeks, change the plan with help from the psychiatrist
- (impact-uw.org)

Collaborative Care Models

- "The IMPACT collaborative care model appears to be feasible and significantly more effective than usual care for depression in a wide range of primary care practices."
- At 12 months, 45% of intervention patients had a 50% or greater reduction in depression symptoms from baseline compared with 19% of usual care participants.
- (Unutzer, Jama 2002)

Collaborative Care Models

- "These findings are consistent with a substantial body of evidence for collaborative care for depression that has emerged over the past 10 years."
- A meta-analysis of the evidence for collaborative depression care was published by Gilbody, et al in the Archives of Internal Medicine in 2006. They examined 37 randomized controlled trials with 12,355 total patients. They concluded, "Sufficient randomized evidence had emerged … to demonstrate the effectiveness of collaborative care."
- (impact-uw.org)

Implementation

Implementation

- There are many ways to improve the provision of mental health care in your practice.
  - Educate yourself
  - Increase communication with patients and providers
  - Collocation
  - Collaboration
  - Start a Collaborative Care program
  - Wellness programs

Implementation

- Educate yourself
  - Learn the DSM criteria for the common diagnoses
  - Learn the common medications
  - Learn the screening questions
  - Learn the co-morbidities
  - Take a class, CME, online certifications, etc…

Implementation

- Educate yourself - Learn outside resources
  - Do you know how to refer to mental health services?
  - What resources do you have in your system, how do patients find resources on their own?
  - What resources are available in the community?
    - Access and Crisis Line, 211, couples, groups, substances, housing, food, clothing, shelter, fun organizations
  - Do you have social workers in your clinic?

Implementation

- Communicate with patients and providers
  - Start asking your patients about mental health care
  - Ask your patients about their mental health care providers and other resources
  - Communicate with your patients mental health care providers
  - Start decreasing stigma amongst patients

Implementation

- Collocation
  - Can your clinic relocate it's mental health providers to the same space in which you work?
  - Once you're close it's easy to start talking
  - You'll likely capture more patients this way
  - Decrease stigma amongst patients and providers

Implementation

- Collaboration
  - If you're already using the same work-space as your mental health providers, start talking to them. Set time to meet. Have lunch together.

Implementation

- Start a program
  - What exactly are you targeting? What population, what condition?
  - How are you going to find these pts?
  - What service are you going to offer them?
  - Where is this service located?
  - How are you going to communicated with those service providers?
  - Are you going to share a treatment plan?
  - Are you going to make a protocol?
  - Who is going to follow the treatment plan, progress and protocol?
  - Do you have specialist help?
  - Will it be accessible?
  - How are you going to fund this?
  - Will it be cost effective?

Implementation

- Wellness programs
  - Lots of things that are good for your health are also good for your mental health.
  - Connecting mental health patients with wellness programs may improve their health*.
  - This may also foster a team approach to provide holistic services for their health.

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Collaborative Care Model of Mental Health Care

- Questions?

PHARMACOTHERAPY for SMOKING CESSATION

Sarah McBane, PharmD, CDE, BCPS

June 23, 2012

TOBACCO DEPENDENCE: A 2-PART PROBLEM

Tobacco Dependence

Physiological	Behavioral
The addiction to nicotine	The habit of using tobacco
↓ Treatment	↓ Treatment
Medications for cessation	Behavior change program

Treatment should address the physiological **and** the behavioral aspects of dependence.

Objectives

1. List several health risks associated with chronic tobacco use
2. Describe dosing and usage of pharmacologic agents used in tobacco cessation
3. Compare the efficacy of the various pharmacologic aids for cessation
4. Identify the five components of comprehensive tobacco cessation counseling

CLINICAL PRACTICE GUIDELINE for TREATING TOBACCO USE and DEPENDENCE

- Update released May 2008
- Sponsored by the U.S. Department of Health and Human Services, Public Heath Service with:
  - Agency for Healthcare Research and Quality
  - National Heart, Lung, & Blood Institute
  - National Institute on Drug Abuse
  - Centers for Disease Control and Prevention
  - National Cancer Institute

www.surgeongeneral.gov/tobacco/

HANDOUT

ANNUAL U.S. DEATHS ATTRIBUTABLE to SMOKING, 2000–2004

		Percent of all smoking-attributable deaths
Cardiovascular diseases	128,497	29%
Lung cancer	125,522	28%
Respiratory diseases	103,338	23%
Second-hand smoke	49,400	11%
Cancers other than lung	35,326	8%
Other	1,512	<1%

TOTAL: 443,595 deaths annually

Centers for Disease Control and Prevention (CDC). (2008). *MMWR* 57:1226-1228.

METHODS for QUITTING

- Nonpharmacologic
  - Counseling and other non-drug approaches
- Pharmacologic
  - FDA-approved medications

Counseling and medications are both effective, but the combination of counseling and medication is more effective than either alone.

Fiore et al. (2008). *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline.* Rockville, MD: USDHHS, PHS, May 2008.

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PHARMACOLOGIC METHODS: FIRST-LINE THERAPIES

Three general classes of FDA-approved drugs for smoking cessation:

- Nicotine replacement therapy (NRT)
  - Nicotine gum, patch, lozenge, nasal spray, inhaler
- Psychotropics
  - Sustained-release bupropion
- Partial nicotinic receptor agonist
  - Varenicline

NICOTINE GUM

Nicorette (GlaxoSmithKline); generics

- Resin complex
  - Nicotine
  - Polacrilin
- Sugar-free chewing gum base
- Contains buffering agents to enhance buccal absorption of nicotine
- Available: 2 mg, 4 mg; original, cinnamon, fruit, mint (various), and orange flavors

NRT: RATIONALE for USE

- Reduces physical withdrawal from nicotine
- Eliminates the immediate, reinforcing effects of nicotine that is rapidly absorbed via tobacco smoke
- Allows patient to focus on behavioral and psychological aspects of tobacco cessation

NRT products approximately doubles quit rates.

NICOTINE GUM: DOSING

Dosage based on current smoking patterns:

If patient smokes	Recommended strength
≥25 cigarettes/day	4 mg
<25 cigarettes/day	2 mg

Recommended Usage Schedule for Nicotine Gum		
Weeks 1–6	Weeks 7–9	Weeks 10–12
1 piece q 1–2 h	1 piece q 2–4 h	1 piece q 4–8 h

DO NOT USE MORE THAN 24 PIECES PER DAY.

NRT: PRODUCTS

Polacrilex gum
- Nicorette (OTC)
- Generic nicotine gum (OTC)

Lozenge
- Nicorette Lozenge (OTC)
- Nicorette Mini Lozenge (OTC)
- Generic nicotine lozenge (OTC)

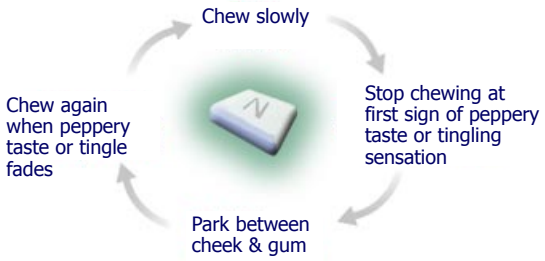
Transdermal patch
- NicoDerm CQ (OTC)
- Generic nicotine patches (OTC, Rx)

Nasal spray
- Nicotrol NS (Rx)

Inhaler
- Nicotrol (Rx)

Patients should stop using all forms of tobacco upon initiation of the NRT regimen.

NICOTINE GUM: CHEWING TECHNIQUE SUMMARY



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NICOTINE GUM: ADDITIONAL PATIENT EDUCATION

- To improve chances of quitting, use at least nine pieces of gum daily
- The effectiveness of nicotine gum may be reduced by some foods and beverages:
  - Coffee
  - Juices
  - Wine
  - Soft drinks

Do NOT eat or drink for 15 minutes BEFORE or while using nicotine gum.

NICOTINE LOZENGE

Nicorette Lozenge and Nicorette Mini Lozenge (GlaxoSmithKline); generics

- Nicotine polacrilex formulation
  - Delivers ~25% more nicotine than equivalent gum dose
- Sugar-free mint, cherry flavors
- Contains buffering agents to enhance buccal absorption of nicotine
- Available: 2 mg, 4 mg

NICOTINE GUM: ADD'L PATIENT EDUCATION (cont'd)

- Chewing gum will *not* provide same rapid satisfaction that smoking provides
- Chewing gum too rapidly can cause excessive release of nicotine, resulting in adverse effects
- May stick to dental work

NICOTINE LOZENGE: DOSING

First cigarette smoked	Recommended strength
Within 30 min of awakening	4 mg
After 30 min of awakening	2 mg

Recommended Usage Schedule for the Nicotine Lozenge

Weeks 1–6	Weeks 7–9	Weeks 10–12
1 lozenge q 1–2 h	1 lozenge q 2–4 h	1 lozenge q 4–8 h

DO NOT USE MORE THAN 20 LOZENGES PER DAY.

NICOTINE GUM: SUMMARY

ADVANTAGES

- Might satisfy oral cravings.
- Might delay weight gain (4-mg strength).
- Patients can titrate therapy to manage withdrawal symptoms.
- A variety of flavors are available.

DISADVANTAGES

- Need for frequent dosing can compromise compliance.
- Might be problematic for patients with significant dental work.
- Patients must use proper chewing technique to minimize adverse effects.
- Gum chewing might not be socially acceptable.

NICOTINE LOZENGE: DIRECTIONS for USE

- Use according to recommended dosing schedule
- Place in mouth and allow to dissolve slowly (nicotine release may cause warm, tingling sensation)
- Do not chew or swallow lozenge.
- Occasionally rotate to different areas of the mouth.
- Standard lozenges will dissolve completely in about 20–30 minutes; Nicorette Mini lozenge will dissolve in 10 minutes.

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NICOTINE LOZENGE: ADDITIONAL PATIENT EDUCATION

- To improve chances of quitting, use at least nine lozenges daily during the first 6 weeks
- The lozenge will *not* provide the same rapid satisfaction that smoking provides
- The effectiveness of the nicotine lozenge may be reduced by some foods and beverages:
  - Coffee
  - Juices
  - Wine
  - Soft drinks

Do NOT eat or drink for 15 minutes BEFORE or while using the nicotine lozenge.

TRANSDERMAL NICOTINE PATCH: DOSING

Product	Light Smoker	Heavy Smoker
NicoDerm CQ	**≤10 cigarettes/day** Step 2 (14 mg x 6 weeks) Step 3 (7 mg x 2 weeks)	**>10 cigarettes/day** Step 1 (21 mg x 6 weeks) Step 2 (14 mg x 2 weeks) Step 3 (7 mg x 2 weeks)
Generic (formerly Habitrol)	**≤10 cigarettes/day** Step 2 (14 mg x 6 weeks) Step 3 (7 mg x 2 weeks)	**>10 cigarettes/day** Step 1 (21 mg x 4 weeks) Step 2 (14 mg x 2 weeks) Step 3 (7 mg x 2 weeks)

NICOTINE LOZENGE: SUMMARY

ADVANTAGES

- Might satisfy oral cravings.
- Might delay weight gain (4-mg strength).
- Easy to use and conceal.
- Patients can titrate therapy to manage withdrawal symptoms.
- Several flavors are available.

DISADVANTAGES

- Need for frequent dosing can compromise compliance
- Gastrointestinal side effects (nausea, hiccups, and heartburn) may be bothersome.

TRANSDERMAL NICOTINE PATCH: ADDITIONAL PATIENT EDUCATION

- Water will not harm the nicotine patch if it is applied correctly; patients may bathe, swim, shower, or exercise while wearing the patch
- Do *not* cut patches to adjust dose
  - Nicotine may evaporate from cut edges

- Keep new and used patches out of the reach of children and pets
- Remove patch before MRI procedures

TRANSDERMAL NICOTINE PATCH
NicoDerm CQ (GlaxoSmithKline); generic

- Nicotine is well absorbed across the skin
- Delivery to systemic circulation avoids hepatic first-pass metabolism
- Plasma nicotine levels are lower and fluctuate less than with smoking

TRANSDERMAL NICOTINE PATCH: ADD'L PATIENT EDUCATION (cont'd)

- Side effects to expect in first hour:
  - Mild itching
  - Burning
  - Tingling
- Additional possible side effects:
  - Vivid dreams or sleep disturbances
  - Headache

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TRANSDERMAL NICOTINE PATCH: SUMMARY

ADVANTAGES

- Provides consistent nicotine levels.
- Easy to use and conceal.
- Once daily dosing associated with fewer compliance problems.

DISADVANTAGES

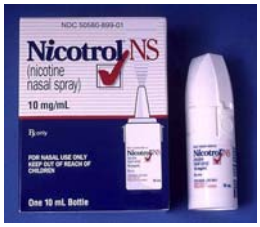
- Patients cannot titrate the dose to acutely manage withdrawal symptoms.
- Allergic reactions to the adhesive may occur.
- Patients with dermatologic conditions should not use the patch.

NICOTINE NASAL SPRAY: ADDITIONAL PATIENT EDUCATION

- What to expect (first week):
  - Hot peppery feeling in back of throat or nose
  - Sneezing
  - Coughing
  - Watery eyes
  - Runny nose
- Side effects should lessen over a few days
  - Regular use during the first week will help in development of tolerance to the irritant effects of the spray

NICOTINE NASAL SPRAY
Nicotrol NS (Pfizer)

- Aqueous solution of nicotine in a 10-ml spray bottle
- Each metered dose actuation delivers
  - 50 mcL spray
  - 0.5 mg nicotine
- ~100 doses/bottle
- Rapid absorption across nasal mucosa



NICOTINE NASAL SPRAY: SUMMARY

ADVANTAGES

- Patients can easily titrate therapy to rapidly manage withdrawal symptoms.

DISADVANTAGES

- Need for frequent dosing can compromise compliance.
- Nasal/throat irritation may be bothersome.
- Higher dependence potential.
- Patients with chronic nasal disorders or severe reactive airway disease should not use the spray.

NICOTINE NASAL SPRAY: DOSING & ADMINISTRATION

- One dose = 1 mg nicotine (2 sprays, one 0.5 mg spray in **each** nostril)
- Start with 1–2 doses per hour
- Increase prn to *maximum* dosage of 5 doses per hour or 40 mg (80 sprays; ~½ bottle) daily
- For best results, patients should use at least 8 doses daily for the first 6–8 weeks
- Termination:
  - Gradual tapering over an additional 4–6 weeks

NICOTINE INHALER
Nicotrol Inhaler (Pfizer)

- Nicotine inhalation system consists of:
  - Mouthpiece
  - Cartridge with porous plug containing 10 mg nicotine and 1 mg menthol
- Delivers 4 mg nicotine vapor, absorbed across buccal mucosa

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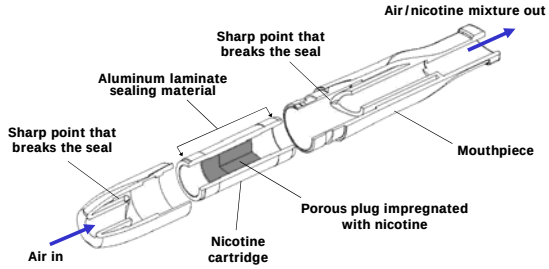
NICOTINE INHALER: DOSING

- Start with at least 6 cartridges/day during the first 3-6 weeks of treatment
  - Increase prn to *maximum* of 16 cartridges/day
  - In general, use 1 cartridge every 1-2 hours
- Recommended duration of therapy is 3 months
- Gradually reduce daily dosage over the following 6–12 weeks

NICOTINE INHALER: DIRECTIONS for USE (cont'd)

- During inhalation, nicotine is vaporized and absorbed across oropharyngeal mucosa
- Inhale into back of throat or puff in short breaths
- Nicotine in cartridges is depleted after about 20 minutes of active puffing
  - Cartridge does *not* have to be used all at once
  - Open cartridge retains potency for 24 hours
- Mouthpiece is reusable; clean regularly with mild detergent

NICOTINE INHALER: SCHEMATIC DIAGRAM



Reprinted with permission from Schneider et al. (2001). *Clinical Pharmacokinetics* 40:661–684. Adis International, Inc.

NICOTINE INHALER: ADDITIONAL PATIENT EDUCATION

- Side effects associated with the nicotine inhaler include:
  - Mild irritation of the mouth or throat
  - Cough
  - Headache
  - Rhinitis
  - Dyspepsia
- Severity generally rated as mild, and frequency of symptoms declined with continued use

NICOTINE INHALER: DIRECTIONS for USE (cont'd)

- Put top on mouthpiece and align marks to close
- Press down firmly to break top seal of cartridge
- Twist top to misalign marks and secure unit

NICOTINE INHALER: ADD'L PATIENT EDUCATION (cont'd)

- The inhaler may not be as effective in very cold (<59°F) temperatures—delivery of nicotine vapor may be compromised
- Use the inhaler longer and more often at first to help control cravings (best results are achieved with frequent continuous puffing over 20 minutes)
- Effectiveness of the nicotine inhaler may be reduced by some foods and beverages

Do NOT eat or drink for 15 minutes BEFORE or while using the nicotine inhaler.

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NICOTINE INHALER: SUMMARY

ADVANTAGES

- Patients can easily titrate therapy to manage withdrawal symptoms.
- The inhaler mimics the hand-to-mouth ritual of smoking.

DISADVANTAGES

- Need for frequent dosing can compromise compliance.
- Initial throat or mouth irritation can be bothersome.
- Cartridges should not be stored in very warm conditions or used in very cold conditions.
- Patients with underlying bronchospastic disease must use the inhaler with caution.

BUPROPION SR: DOSING

Patients should begin therapy 1 to 2 weeks PRIOR to their quit date to ensure that therapeutic plasma levels of the drug are achieved.

Initial treatment

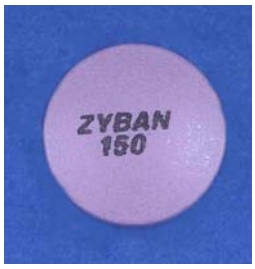
- 150 mg po q AM x 3 days

Then…

- 150 mg po bid
- Duration, 7–12 weeks

BUPROPION SR
Zyban (GlaxoSmithKline); generic

- Nonnicotine cessation aid
- Sustained-release antidepressant
- Affects DA and NE
  - ↓ craving for cigarettes
  - ↓ symptoms of nicotine withdrawal



BUPROPION: ADVERSE EFFECTS

Common side effects include the following:

- Insomnia (avoid bedtime dosing)
- Dry mouth

Less common but reported effects:

- Tremor
- Skin rash

BUPROPION: CONTRAINDICATIONS and WARNINGS

- Contraindications: seizures, MAOI use, eating disorders
- Warning: Neuropsychiatric symptoms and suicide risk
- Precaution: concern for seizures, cirrhosis

Patients should stop bupropion and contact a health care provider immediately if agitation, hostility, depressed mood or changes in thinking or behavior (including suicidal ideation) are observed

BUPROPION: ADDITIONAL PATIENT EDUCATION

- Dose tapering not necessary when discontinuing treatment
- If no significant progress toward abstinence by seventh week, therapy is unlikely to be effective
  - Discontinue treatment
  - Reevaluate and restart at later date

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BUPROPION SR: SUMMARY

ADVANTAGES

- Easy to use oral formulation.
- Twice daily dosing might reduce compliance problems.
- Might delay weight gain
- Bupropion might be beneficial for patients with depression.

DISADVANTAGES

- The seizure risk is increased.
- Several contraindications and precautions preclude use in some patients.

VARENICLINE: DOSING

Patients should begin therapy 1 week PRIOR to their quit date. The dose is gradually increased to minimize treatment-related nausea and insomnia.

	Treatment Day	Dose
Initial dose titration	Day 1 to day 3	0.5 mg qd
	Day 4 to day 7	0.5 mg bid
	Day 8 to end of treatment*	1 mg bid

* Up to 12 weeks

VARENICLINE Chantix (Pfizer)

- Nonnicotine cessation aid
- Partial nicotinic receptor agonist
  - ↓ symptoms of nicotine withdrawal
  - Blocks dopaminergic reward pathway

VARENICLINE: ADVERSE EFFECTS

- Common (≥5% and 2-fold higher than placebo)
  - Nausea
  - Sleep disturbances (insomnia, abnormal dreams)
  - Constipation
  - Flatulence
  - Vomiting

VARENICLINE: WARNINGS and PRECAUTIONS

- Neuropsychiatric Symptoms and suicide risk
- Cardiovascular adverse events in patients with existing cardiovascular disease
- Serious skin reactions
- Nausea

Patients should stop varenicline and contact a health care provider immediately if agitation, hostility, depressed mood or changes in thinking or behavior (including suicidal ideation) are observed

VARENICLINE: SUMMARY

ADVANTAGES

- Easy to use oral formulation.
- Twice daily dosing might reduce compliance problems.
- Offers a new mechanism of action for persons who have failed other agents.

DISADVANTAGES

- May induce nausea in up to one third of patients.
- Post-marketing surveillance data indicate potential for neuropsychiatric symptoms.

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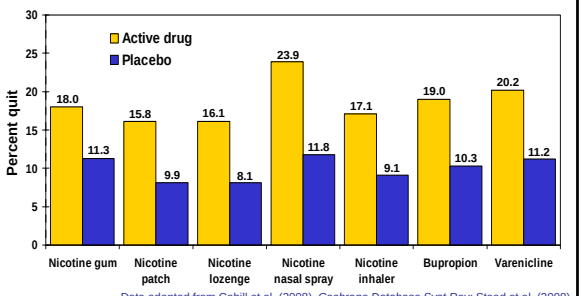
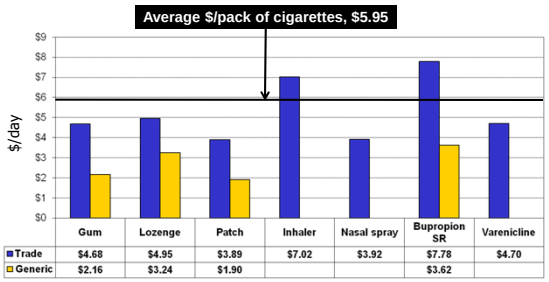
LONG-TERM (≥6 month) QUIT RATES for AVAILABLE CESSATION MEDICATIONS



Data adapted from Cahill et al. (2008). *Cochrane Database Syst Rev;* Stead et al. (2008). *Cochrane Database Syst Rev;* Hughes et al. (2007). *Cochrane Database Syst Rev*

COMPARATIVE DAILY COSTS of PHARMACOTHERAPY



	Gum	Lozenge	Patch	Inhaler	Nasal spray	Bupropion SR	Varenicline
Trade	$4.68	$4.95	$3.89	$7.02	$3.92	$7.78	$4.70
Generic	$2.16	$3.24	$1.90			$3.62	

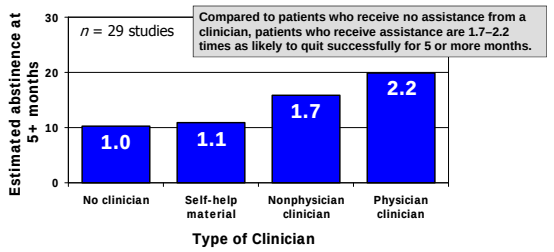
COMBINATION PHARMACOTHERAPY

Regimens with enough evidence to be 'recommended' first-line

- **Combination NRT**
  - Long-acting formulation (patch)
    - Produces relatively constant levels of nicotine
  - **PLUS**
  - Short-acting formulation (gum, inhaler, nasal spray)
    - Allows for acute dose titration as needed for nicotine withdrawal symptoms
- **Bupropion SR + Nicotine Patch**

EFFECTS of CLINICIAN INTERVENTIONS

With help from a clinician, the odds of quitting approximately doubles.



Fiore et al. (2008). *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline.* Rockville, MD: USDHHS, PHS, May 2008.

COMPLIANCE IS KEY to QUITTING

- Promote compliance with prescribed regimens.
- Use according to dosing schedule, NOT as needed.
- Consider telling the patient:
  - "When you use a cessation product it is important to read all the directions thoroughly before using the product. The products work best in alleviating withdrawal symptoms when used correctly, and according to the recommended dosing schedule."

The 5 A's

ASK	about tobacco USE
ADVISE	tobacco users to QUIT
ASSESS	READINESS to make a quit attempt
ASSIST	with the QUIT ATTEMPT
ARRANGE	FOLLOW-UP care

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The 5 A's (cont'd)

- ARRANGE follow-up care

Number of sessions	Estimated quit rate*
0 to 1	12.4%
2 to 3	16.3%
4 to 8	20.9%
More than 8	24.7%

* 5 months (or more) postcessation

Provide assistance throughout the quit attempt.

Fiore et al. (2008). *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline*. Rockville, MD: USDHHS, PHS, May 2008.

BRIEF COUNSELING: ASK, ADVISE, REFER (cont'd)

- Brief interventions have been shown to be effective
- In the absence of time or expertise:
  - Ask, advise, and refer to other resources, such as local group programs or the toll-free quitline **1-800-QUIT-NOW or 1 800 – NO-BUTTS**

This brief intervention can be achieved in less than 1 minute.

PHARMACOTHERAPY for SMOKING CESSATION

Sarah McBane, PharmD, CDE, BCPS

June 23, 2012

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Prescription Drug Abuse/Misuse in the Primary Care Setting

Nathan A Painter, PharmD, CDE
Assistant Clinical Professor
UCSD Skaggs School of Pharmacy

Ambulatory Care Pharmacist
UCSD Family Medicine Clinics

Outline

1. Discuss the high prevalence of prescription drug misuse and associated etiologic and social factors.
2. Discuss the balance to treat chronic pain, while identifying and treating addiction should it occur.
3. Apply best practices in the treatment of chronic pain with opioids
4. List warning signs of opioid misuse and discuss how a clinician might respond.

What Prescriptions Drugs Get Abused?

- Opioids: hydrocodone (Vicodin), oxycodone (Oxycontin)
- Anxiolytics: benzodiazepines (Xanax, Valium), barbiturates (butalbital, Fiorecet)
- Stimulants: amphetamine (Adderall), methylphenidate (Ritalin)

Epidemiology of Prescription Drug Misuse and Abuse

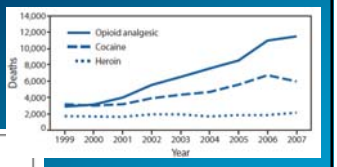
- National
  - Nearly 1 in 5 teens (19% or 4.5 million) have used prescription drugs to get high.
  - 1 in 10 teens (10% or 2.4 million) reported using cough medicine to get high.
  - 7 of the top 10 drugs abused by 12th graders are prescription drugs or OTC medications.
  - 2007 MTF – 1 in 10 seniors used Vicodin and over 5% used OxyContin
- California
  - Prescription drug use is accelerating
  - Prescription drug use exceed all other drugs other than marijuana

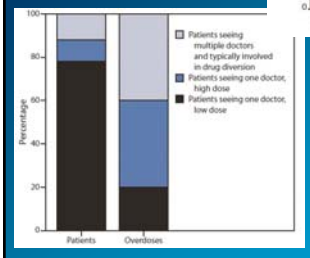
Non-medical Use: National Survey on Drug-Use and Health (in thousands)

Results from the 2006 NSDUH: National Findings. http://oas.samhsa.gov/nsduh/2k6nsduh/2k6Results.pdf

	Lifetime		Past Year		Past Month	
	2006	2007	2006	2007	2006	2007
Nonmedical Use of Psychotherapeutics	50,965	50,412	16,482	16,280	7,095	6,895
Pain Relievers	33,472	33,060	12,649	12,466	5,220	5,174
OxyContin®	4,098	4,354	1,323	1,422	276	369
Tranquilizers	21,303	20,208	5,058	5,282	1,766	1,835
Stimulants	22,468	21,654	3,761	2,998	1,385	1,053
Methamphetamine	14,206	13,065	1,889	1,343	731	529
Sedatives	8,822	8,396	926	864	385	346

Prescription Drug Overdose





MMWR. 1/2012. 61(1).
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm?s_cid=mm6101a3_w

Epidemiology of Prescription Drug Misuse and Abuse

- It is generally believed that the broad availability of prescription drugs (e.g., via the medicine cabinet, the Internet, and physicians) and misperceptions about their safety make prescription medications particularly prone to abuse.
- Among those who abuse prescription drugs, high rates of other risky behaviors, including abuse of other drugs and alcohol, have also been reported (another good reason to be doing urine tox screens in your clinic.

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Major Findings on PDM

- Pain relievers are most widely used of all prescription drugs across all populations.
- PDM is closely associated with age – percentage rates increase among youth as they get older – peaking in their late teens (18-20) falling off after 20.
- Older adults exhibit lower rates of misuse – however because there are more of them, results in greater overall use.
- Whites are predominately the users of prescription drugs (approximately 75%).
- Young females (12-17) use slightly more than young males. This changes as they get older.

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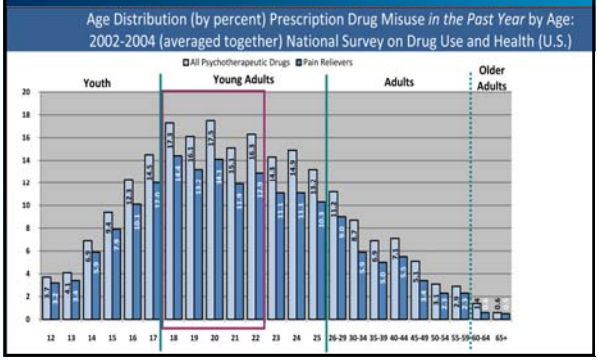
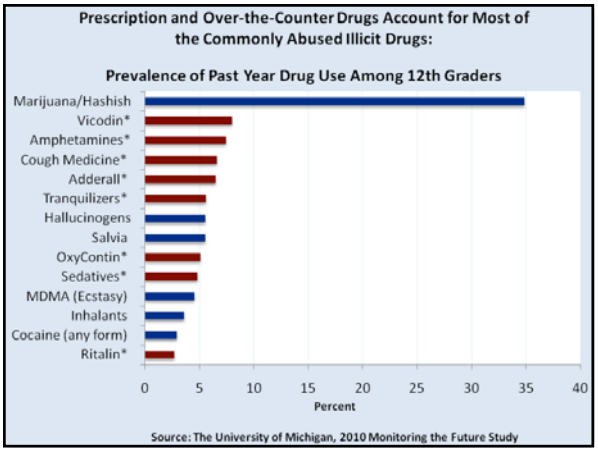
Major Findings on PDM





Youth Misconceptions

- 40% believe prescription drugs are “safer” than illicit.
- 30% believe there’s “nothing wrong” using prescription drugs.
- 29% believe they are not addictive
- 55% believe there is no harm in using prescription drugs

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Where are they getting them?

- From 2007 NSDUH:
  - 56.5% got them from someone they know
  - 18.1% obtained them from a physician
  - 4.1% purchased them from a “dealer”
  - .5% bought them on the Internet
- From 2005 PATS Survey:
  - 60% of teens say they are easy to obtain from parents medicine cabinet
  - 50% from other peoples prescriptions
  - More than 50% of teens said “they are available everywhere”
- Another Survey:
  - 1 in 4 kids with a legitimate prescription had been approached by others.

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Substance Abuse and Mental Health Services Administration Survey 2009-2010

- The homes of relatives or friends as key sources for people to start misusing powerful painkillers
- Drugs left in home medicine cabinets are prime targets for prescription drug abuse
- Among first-time or occasional users of prescription pain killers, most received them from family or friends.
- Among chronic abusers of pain relievers, 41% obtained pills for free or without asking from friends or relatives, while 26% got a prescription

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CURES

- Consider use of the California Prescription Monitoring Program to check history of patient's prescriptions for controlled substances (http://ag.ca.gov/bne/cures.php)
- In order to obtain access to the PDMP system Prescribers and Pharmacists must first register with CURES by submitting an application form electronically at https://pmp.doj.ca.gov/pmpreg/.
- To obtain a CURES report complete form available at: http://ag.ca.gov/bne/pdfs/BNE1176.pdf

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Opioid Drugs and Risk Evaluation and Mitigation Strategies (REMS)

- On May 16, 2011, the FDA met with members of the Industry Working Group (IWG) and other sponsors of Long Acting and Extended Release opioid drugs. The purpose of the meeting was to discuss the next steps in implementing A Risk Evaluation and Mitigation Strategy (REMS) for these products through a single shared system. Topics discussed included:
- 1) Prescriber training
- 2) Medication Guides
- 3) REMS assessment plan
- 4) Administrative requirements

http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm
http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163655.htm

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White House Office of National Drug Control Policy

- Mandatory prescriber education
  - Public/private partnership to develop an educational campaign directed at parents and patients
- Prescription drug monitoring programs
  - CURES
- Proper medication disposal
- Law enforcement agencies
  - Decrease prescription drug diversion and abuse
  - Pill mills
  - Doctor shopping

http://www.whitehouse.gov/ondcp/2012-national-drug-control-strategy

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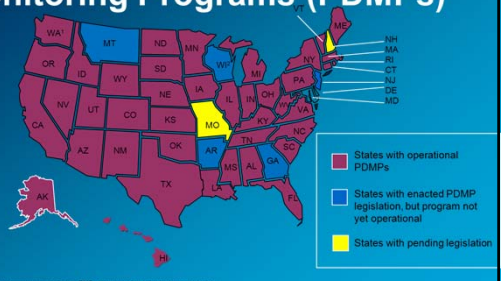
Status of State Prescription Drug Monitoring Programs (PDMPs)



*Washington has temporarily suspended its PMP operations due to budgetary constraints.
†Legislation has been proposed in Wisconsin that, if passed, would establish a PDMP.

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Prescription Drug Misuse from a Healthcare Provider's Perspective

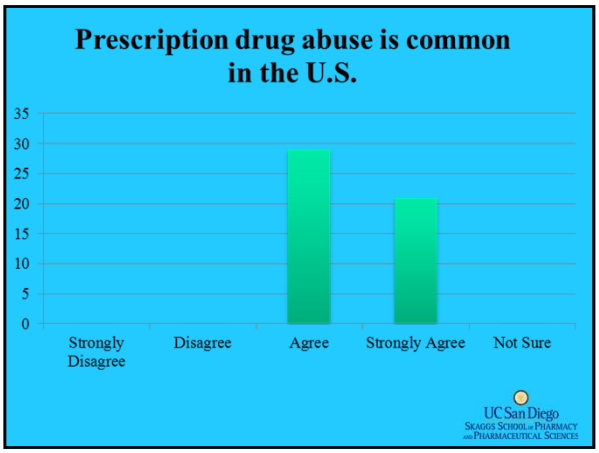
To determine whether prescribers are aware of the prevalence of prescription drug misuse

To evaluate healthcare providers' knowledge of current prescription drug misuse statistics

To assess whether prescribers are able to recognize the signs of prescription drug misuse

Jacqueline Hovhanessian, PS4, Marina Zotova, PS4

UC San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences


Prescription drug abuse is common in the U.S.
35
30
25
20
15
10
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Strongly Disagree
Disagree
Agree
Strongly Agree
Not Sure
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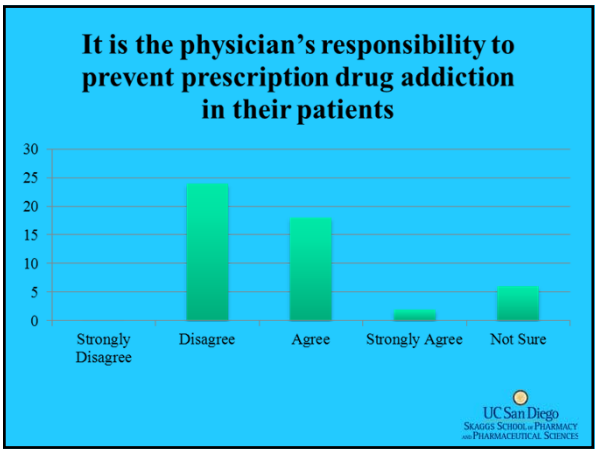
It is the physician's responsibility to prevent prescription drug addiction in their patients
30
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Strongly Disagree
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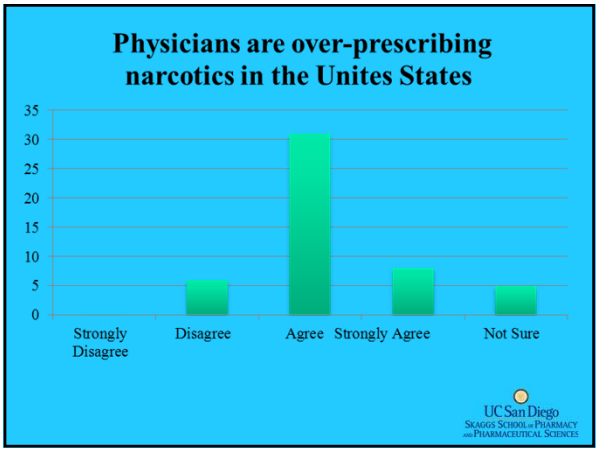
UC San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences


Physicians are over-prescribing narcotics in the Unites States
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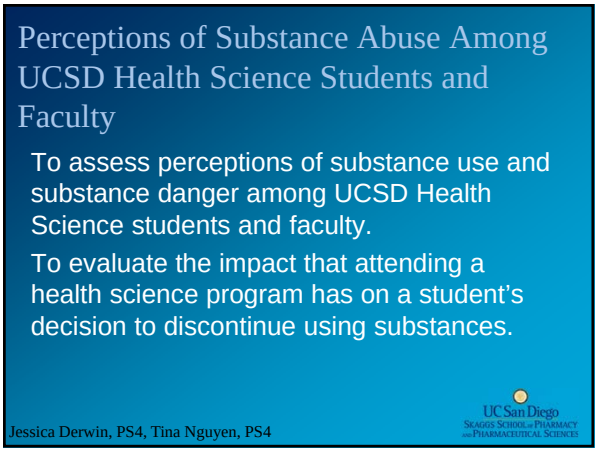
Strongly Disagree
Disagree
Agree
Strongly Agree
Not Sure
UC San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences


Perceptions of Substance Abuse Among UCSD Health Science Students and Faculty
To assess perceptions of substance use and substance danger among UCSD Health Science students and faculty.
To evaluate the impact that attending a health science program has on a student's decision to discontinue using substances.
Jessica Derwin, PS4, Tina Nguyen, PS4
UC San Diego
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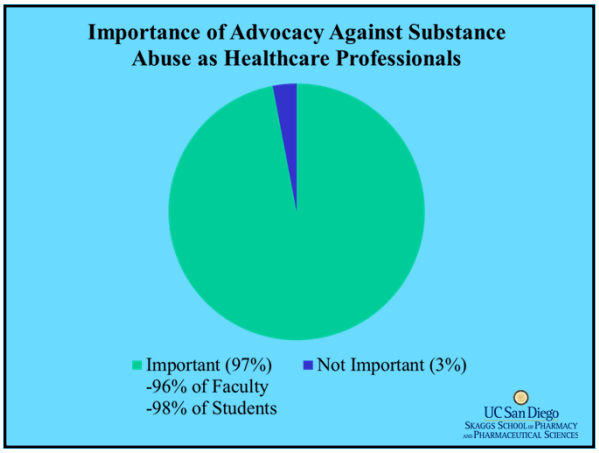
Importance of Advocacy Against Substance Abuse as Healthcare Professionals
Important (97%)
-96% of Faculty
-98% of Students
Not Important (3%)
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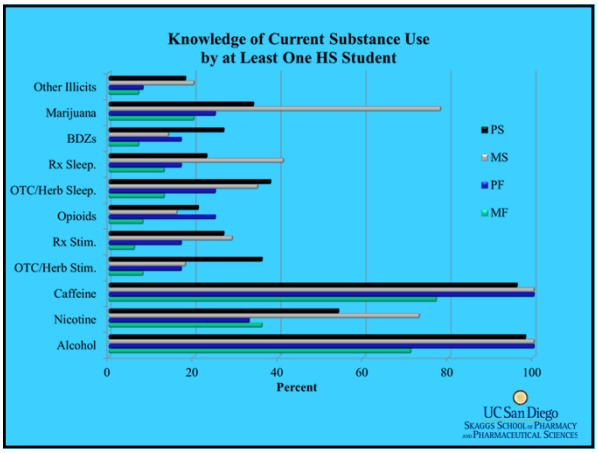
Knowledge of Current Substance Use by at Least One HS Student
Other Illicits
Marijuana
BDZs
Rx Sleep.
OTC/Herb Sleep.
Opioids
Rx Stim.
OTC/Herb Stim.
Caffeine
Nicotine
Alcohol
PS
MS
PF
MF
0
20
40
60
80
100
Percent
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Opioid Agreement/Contract

- Have a Treatment Plan/Informed Consent (documentation of risk/benefit) on the chart (DGIM has a Treatment Agreement that can be used)
- Treatment Agreement (use for those at high risk for abuse/addiction)
  - One physician/one pharmacy
  - Frequent visits
  - Drug screening
  - Agreement to return for pill count when asked to do so
  - Number/frequency of all refills
  - Reason for discontinuation (violation of agreement, misuse of medication, abuse of other substances)
- Example: http://www.painedu.org

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Informed Consent

SPECIFIC RISKS OF THE TREATMENT (long-term opioid use):

- Side effects (short and long term)
- Physical dependence, tolerance
- Risk of drug interactions or combinations (respiratory depression)
- Risk of unintentional or intentional misuse (abuse, addiction, death)
- Legal responsibilities (disposing, sharing, selling)

Paterick et al., 2008

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Drug Screening

Purpose

- Evidence of therapeutic adherence
- Evidence of non-use of illicit drugs

Results of study from pain medicine practice (n=122)

- 22% of patients had aberrant medication taking behaviors
- 21% of patients had NO aberrant behaviors BUT had abnormal urine drug test

Therefore, aberrant behavior and urine drug test monitoring are both important.

Katz et al. Clinical J of Pain, 2002.

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Other Strategies

- Pill counts should be part of management
- Should be done by licensed personnel only
- May be most useful early in treatment and can be combined with urine toxicology at a nursing or pharmacist visit (no MD visit needed)

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Pain Assessment

- Periodic review:
  - Evidence of analgesia
  - Treat side effects
  - Enhanced social/employment functioning
  - Overall improved quality of life
  - Family assessment
  - Unsatisfactory: review other options
- You can always get a consultation:
  - Pain specialists
  - Psychiatrist (co-occurring mental illness is common)
  - Addiction specialist

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Risks/Concerns of Chronic Opioid Therapy

- "Causing Addiction" in persons without abuse or dependence history with opioids
- "Feeding" an existing addiction
- Causing a relapse in a patient in stable remission
- Diversion of medication by a patient with or without pain

None of these risks are adequately quantified for any patient population, but they are not negligible

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Aberrant Medication-Taking Behavior

Red Flags

- Deterioration in functioning at work or socially
- Illegal activities – selling, forging, buying from nonmedical sources
- Injection or snorting medication
- Multiple episodes of "lost" or "stolen" scripts
- Resistance to change therapy despite adverse effects
- Refusal to comply with random drug screens
- Concurrent abuse of alcohol or illicit drugs
- Use of multiple physicians and pharmacies

Aberrant Medication-Taking Behavior

Yellow Flags

- Complaints about need for more medication
- Drug hoarding
- Requesting specific pain medications
- Openly acquiring similar medications from other providers
- Occasional unsanctioned dose escalation
- Nonadherence to other recommendations for pain therapy

Approaching Patient with Aberrant Medication-Taking Behavior

- Take non-judgmental stance
- Use open-ended questions
- State your concerns about the behavior
- Examine the patient for signs of flexibility
  - Is the patient more focused on specific opioid or pain relief?
- Approach as if they have a relative contraindication to controlled drugs (if not absolute contraindication)
- Take pressure off yourself by referring to clinic policies

Passik & Kirsh, 2005

Substance Use Disorder Treatment

- Therapeutic Options:
- Combination of medication treatment plus psychosocial/psychotherapeutic interventions:
  - Inpatient (usually detoxification; short term pharmacotherapy) followed by:
    - Residential
    - Intensive outpatient
    - Individual/Group Drug Counseling
    - +/- Maintenance pharmacotherapy
- Know the options in your community

Conclusions

- Prescription drug misuse/abuse and associated addiction increasing
- Consider non-opioid treatment options for chronic pain
- If chronic opioids are to be used:
  - Treatment Agreement/Informed Consent
  - Good documentation of treatment plan and responses
  - Get releases at outset for other treatment providers, family member(s) important to therapy
- Know the options for referral in your community

QUESTIONS?

- DEA Drug Take Back Initiative
  - http://www.deadiversion.usdoj.gov/drug_disposal/takeback/
- CURES
  - http://ag.ca.gov/bne/cures.php

References

- Monitoring the Future, 2007.
- 2005 & 2006 National Survey on Drug Use and Health: National Findings," SAMHSA, September 2006 & 2007.
- Office of National Drug Control Policy (ONDCP) www.ondcp.gov
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- Principles of Addiction Medicine, Ries R etal (eds), pp 99-112, 2009.
- Textbook of Substance Abuse Treatment, Gallanter M, Kleber H, pp 215-235, 2008.

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Concussion
Mild Traumatic Brain Injury (mTBI)

David E.J. Bazzo, M.D. FAAFP, CAQSM
Professor of Family Medicine
UCSD School of Medicine

PreTest

A direct blow to the head is needed to diagnose concussion?

1. True
2. False

Loss of consciousness is needed to diagnose a concussion?

1. True
2. False

Currently in California, if a high school athlete suffers a mild concussion, but his/her evaluation is unremarkable, they may return to sport:

1. Next day for practice or game
2. Next week for practice or game
3. After physician evaluation with written release
4. Whenever the patient feels ready to return
5. Whenever the coach or trainer feel that the athlete is ready

New 3T functional MRI can tell you when a player may return to play

1. True
2. False

Concussion symptoms may take several hours to present after the onset of injury

1. True
2. False

LOC with concussion confers a worse prognosis?

1. True
2. False

Seizure immediately after concussion confers a worse prognosis?

1. True
2. False

During the weekend of 10/17/10 in NFL
A record **22 Concussions** were recorded

For each single concussion in the NFL..
Over 5,000 happen to high school kids

- 1.2 million high school football players yearly
- 140,000 - 250,000 high school football concussions each year
- Up to 47% of all high school football players have experienced a concussion - 35% have had more than one

And no one know how many happen to our youngest athletes

The numbers

- Over 15 Million kids play contact sports each year in the U.S. alone
- The CDC estimates that more than 3.8 million sports brain injuries occur every year
- The vast majority of them go undetected, unreported and unmanaged – estimates 80%. Particularly in girls soccer and basketball
- Pediatric emergency room visits for sports concussion have tripled over the last decade

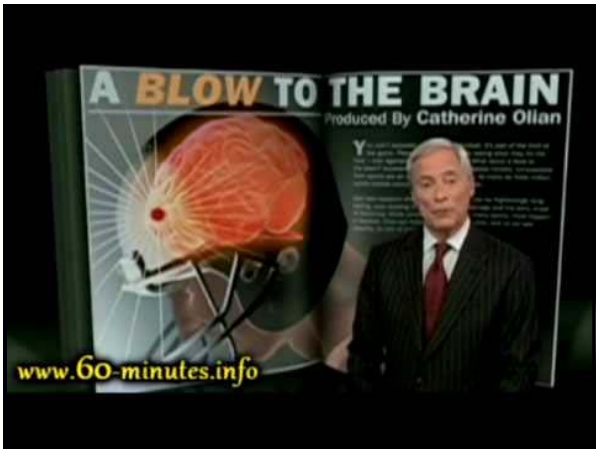
The problem

- 32 (44?) states have passed sports concussion laws and National legislation is on its way
- Estimated that 40% of players return sooner than they should

Epidemiology in Children and Adolescents

- 500,000 ER visits/year resulting in 95,000 hospitalizations/year
- 90% of these are "minor", but 7,000 children die each year of head trauma and 29,000 cases of permanent disability yearly
- Main causes: MVA's, falls, assaults, bike accidents and trauma related to sports

Symptom Checker, Harvard Medical School, Harvard Health Decision Guide, 2007



Video links

- Second impact syndrome – NY Times
  - http://video.nytimes.com/video/2007/09/15/sports/1194817092469/high-school-football-s-hidden-danger.html
- High school football – ESPN Outside the Lines
  - http://www.youtube.com/watch?v=du_giQ96ddk
- CNN – Sanjay Gupta program on concussion

Definition of Mild Traumatic Brain Injury

A disturbance in brain function caused by direct or indirect force to the head

A dysfunction of brain metabolism rather than a structural injury or damage to the brain

Mild traumatic brain injury(MTBI) is controversially used interchangeably with the term concussion

McCrory et. al., Concensus statement on concussion in sport: the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. J Athl Train. 2009;44(4):434-448

US Dept. HHS, CDC, Heads Up: Facts for Physicians about MTBI, 2006

Definition

- Results in rapid onset of short –lived impairment of neurologic function that resolves spontaneously
- Symptoms largely reflect a functional disturbance rather than a structural injury
- May or may not involve loss of consciousness
- Resolution of symptoms typically follows a sequential course but in some cases symptoms may be prolonged
- No abnormality on standard structural neuroimaging studies

3rd International conference on concussion in sports, Zurich, Nov. 2008

Glasgow Coma Scale

Glasgow coma scale

		Score
Eye opening	spontaneously	4
	to speech	3
	to pain	2
	none	1
Verbal response	orientated	5
	confused	4
	inappropriate	3
	incomprehensible	2
	none	1
Motor response	obeys commands	6
	localises to pain	5
	withdraws from pain	4
	flexion to pain	3
	extension to pain	2
	none	1
Maximum score		15

Traumatic Brain Injury (TBI)

- A broad term used to describe a spectrum of brain injuries resulting from trauma
- Severe TBI : GCS = 3-8
- Moderate TBI : GCS = 9-12
- Mild TBI : GCS = 13-15

Signs and Symptoms of Acute Concussion

- Physical
- Cognitive
- Emotional
- Sleep Related

3rd International Conference on concussion in sports, Zurich, Nov. 2008

Physical Signs and Symptoms of Acute Concussion

- Headache
- Nausea/vomiting
- Balance problems
- Visual problems
- Fatigue
- Sensitivity to light or noise
- "Dazed" or "Stunned"

US Dept. HHS, CDC, Heads Up: Facts for Physicians About MTBI, 2006

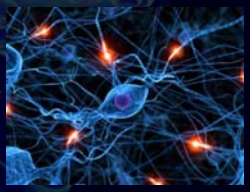
Cognitive Signs and Symptoms of Acute Concussion

- Feeling mentally "foggy" or slowed down
- Difficulty concentrating or remembering
- Forgetful of recent information (amnesia)
- Confused about recent events
- Answers questions slowly
- Repeats questions(perseverates)

US Dept. HHS, CDC, Heads Up: Facts for Physicians About MTBI, 2006

Emotional Signs and Symptoms of Acute Concussion

- Irritability
- Sadness
- Hyper-emotional
- Nervousness
- Anxiety



US Dept. HHS, CDC, Heads Up: Facts for Physicians About MTBI, 2006

Sleep Related Signs and Symptoms of Acute Concussion

- Drowsiness
- Hyper- or Hyposomnolence
- Difficulty falling asleep

US Dept. HHS, CDC, Heads Up: Facts for Physicians About MTBI, 2006

Differential Diagnosis

- Heat illness
- Exertional migraine
- Sleep disorder

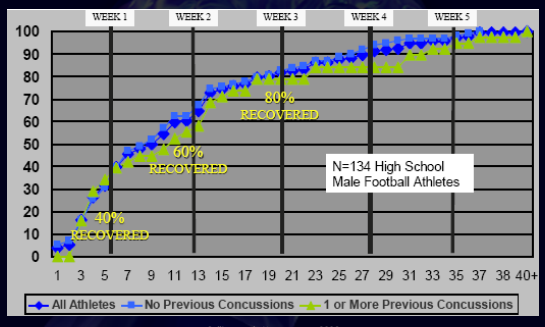
- For concussion, need a temporal relationship of injury to symptoms

Variable concussion recovery rates by age

Author	Sample Size	Population	Test Utilized	Total days cognitive resolution	Total day symptom resolution
Lovell at al. 2005	95	Professional (NFL)	Paper and pencil NP	1 day	1 day
Guskiewicz et al. 2003	94	College	Balance BESS	3-5 days	7 days
Lovell, Collins et. al. 2008	208	High School	Computer NP 2	26 day	17 days

presented at 2011 AMSSM by Collins

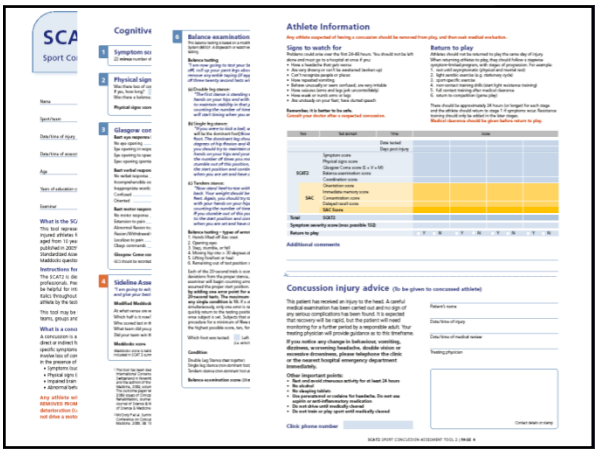
Recovery time in concussed high school athletes



Collins et. al.; Neurosurgery 2006

Office Tools and Techniques for Evaluation

- Thorough history: signs, symptoms, previous head injuries
- Head and neck exam
- Focused neurological exam(including mental status, gait and balance assessment) –Balance Error Scoring System(BESS)
- SAC(Standardized Assessment of Concussion) or SCAT2(Sport Concussion Assessment Tool)

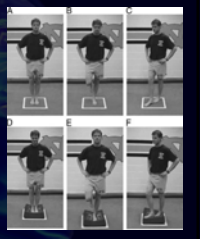


Evaluation

- SAC(Standardized Assessment of Concussion) or SCAT2(Sport Concussion Assessment Tool)
- Standard orientation questions are unreliable (person, place and time)
- Serial monitoring for first few hours – observing carefully for signs of deterioration

SCAT2 Balance Examination

- Double leg stance
- Single leg stance
- Tandem stance
- Error types
  1. Hands lifted off iliac crest
  2. Opening eyes
  3. Step, stumble or fall
  4. Moving hip into >30 degrees abduction
  5. Lifting forefoot or heel
  6. Remaining out of test position for > 5 seconds



NCAA.ORG has the BESS and SCAT2 demonstration video

Return to Play Guidelines

- Any player with signs of concussion should be removed from play
- Player should be closely monitored for the next few hours
- Medical evaluation with frequent follow up
- Return to play follows a medically supervised stepwise process

Return to Play Guidelines

- "When in doubt, sit them out"
- New California Interscholastic Federation(CIF) guideline requires a licensed physician(MD or DO) to provide written release prior to returning to play
- Zurich Guidelines (November 2008) provide a structured return to play protocol
- Athletes must be asymptomatic at rest, with cognition and when physically active before returning to play

Return to Play Guidelines

Recommendations

1. Any athlete who is suspected to have suffered a concussion should be removed from participation until he or she is evaluated by a physician with training in the evaluation and management of sports concussions
2. No athlete should be allowed to participate in sports if he or she is still experiencing symptoms from a concussion.
3. Following a concussion, a neurologist or physician with proper training should be consulted prior to clearing the athlete for return to participation.
4. A certified athletic trainer should be present at all sporting events, including practices, where athletes are at risk for concussion.
5. Education efforts should be maximized to improve the understanding of concussion by all athletes, parents, and coaches.

Position Statement History

Approved by the AAN Sports Neurology Section, Practice Committee, and Board of Directors
October 2010 (AAN Policy 2010-36).

Prevention

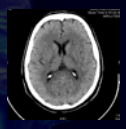
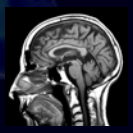
- Headgear - "risk compensation"
- Mouth guards
- Rule Changes
- Education – public, players, athletic trainers, coaches, parents


Neuroimaging

- In general, structural imaging provides little benefit in concussion evaluation
- Should be used if suspicion of an intracerebral structural lesion exists: i.e. prolonged disturbance of consciousness, focal neurologic deficit or worsening symptoms

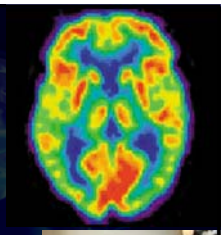
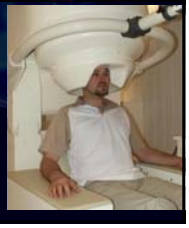

Neuroimaging

- Non-contrast CT – test of choice for intracranial hemorrhage during the first 24-48 hours after injury
- CT best modality for detecting skull fractures
- After 48 hours MRI may be more appropriate (able to detect cerebral contusions, petechial hemorrhage and white matter lesions)

Neuroimaging

- Functional Imaging(Functional MRI)- can measure metabolic and hemodynamic changes in the brain
- Other functional modalities such as PET, MRS, SPECT and MEG(Magnetic Encephalogram) with DTI (Diffusion Tensor Imaging) are promising and still being developed

Neuropsychological Testing

- Measures reaction time, memory and other neurocognitive functions
- Useful because cognitive recovery will usually be delayed until after clinical symptom resolution
- Can assist with return to play clinical decision making
- Done when the athlete is asymptomatic
- Can be used for pre-participation screening with high risk sports

Neuropsychological Testing

- Computer based - ImPACT, CogSport, ANAM, Headminder, CNS Vital Signs
- Written based – usually requires a neuropsychologist to interpret and administer
- Several other types in development and available, e.g. – King-Devick test, Military Acute Concussion Evaluation(MACE)

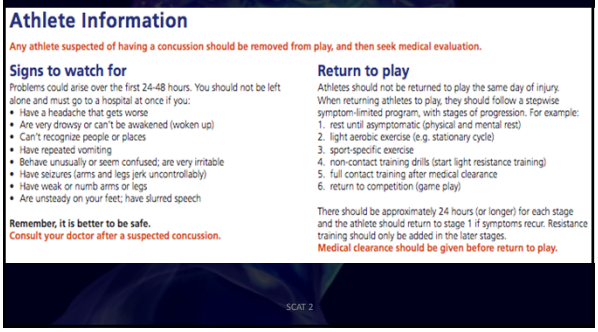
Treatment

- Rest
- Rest
- More rest – both physical and cognitive
- Education – patients/players, coaches, parents and teachers
- Most concussions resolve(80-90%) within a relatively short time period(7-10 days)

Rehabilitation

- Cognitive rehabilitation
  - Progression of cognitive tasks
- Vestibular rehabilitation
  - Balance training

Patient Instructions



Athlete Information

Any athlete suspected of having a concussion should be removed from play, and then seek medical evaluation.

Signs to watch for

Problems could arise over the first 24-48 hours. You should not be left alone and must go to a hospital at once if you:

- Have a headache that gets worse
- Are very drowsy or can't be awakened (woken up)
- Can't recognize people or places
- Have repeated vomiting
- Behave unusually or seem confused; are very irritable
- Have seizures (arms and legs jerk uncontrollably)
- Have weak or numb arms or legs
- Are unsteady on your feet; have slurred speech

Remember, it is better to be safe.
Consult your doctor after a suspected concussion.

Return to play

Athletes should not be returned to play the same day of injury. When returning athletes to play, they should follow a stepwise symptom-limited program, with stages of progression. For example:

1. rest until asymptomatic (physical and mental rest)
2. light aerobic exercise (e.g. stationary cycle)
3. sport-specific exercise
4. non-contact training drills (start light resistance training)
5. full contact training after medical clearance
6. return to competition (game play)

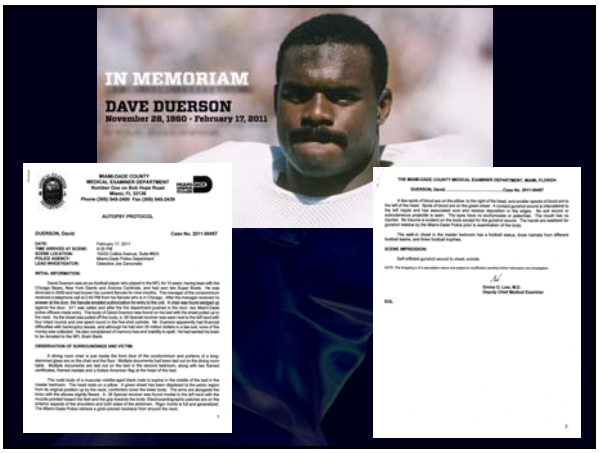
There should be approximately 24 hours (or longer) for each stage and the athlete should return to stage 1 if symptoms recur. Resistance training should only be added in the later stages.
Medical clearance should be given before return to play.

SCAT 2

Chronic Traumatic Brain Injury

- Post-Concussion Syndrome – small number usually 10-20% of all concussions
- Second Impact Syndrome(SIS) - controversial
- Chronic Traumatic Encephalopathy(CTE) – NFL Football Brain Registry – also referred to as "dementia pugilistica", some cases can mimic ALS
- Long term psychiatric effects – much more significant than previously believed

Long term symptoms

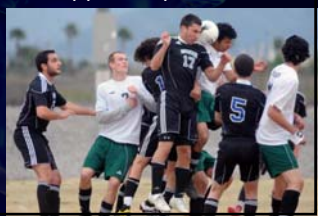


Summary

- MTBI/Concussions are a common everyday occurrence frequently seen by primary care providers – "Take it seriously…bruising the brain is a big deal" (Dr. Dave Baron 1/5/11)
- Guidelines and tools are available to help in the management of these cases
- There is a tremendous need to improve our knowledge base and understanding of these injuries
- Whenever possible…"Play it safer"

Case 1 - Soccer

- 16 yo male high school soccer player
- While heading ball hit head with other player
- Rubbed head ,continued to play for last few minutes of game without apparent problem (per Mom)
- No LOC



Case 1 – Soccer (cont)

- That night, tried to study for math test (usually his best subject) noted lights bothered his eyes and dull headache where hit head
- Difficulty concentrating while studying
- Denied nausea/vomiting or visual changes but felt "tired"
- Brought to clinic the next day for evaluation
- PE: scalp soft tissue contusion at site of impact, no pupillary abnormalities, normal speech, orientation, gait, gross cranial nerve evaluation and gross motor functioning.

What additional evaluation should be done to assess for concussion?

1. Questionnaire about symptoms
2. Computer based neuropsych testing
3. Balance testing
4. 1 and 2
5. 2 and 3
6. All of the above

Would head imaging be warranted at this time? If so which imaging :

1. Skull radiograph
2. CT Scan
3. MRI
4. No Imaging warranted

The patient wants to know when he can play soccer again. What do you tell him?

1. The next day
2. One week
3. One month
4. When released by a physician
5. Can't return to play

Case 1 – Soccer (cont)

- Additional assessment performed
  - SCAT2 positive symptom score
  - Positive slight balance problem on BESS
- A: Concussion
- P: No imaging indicated
  - Managed with cognitive and physical rest
  - Re-evaluated 72 hours later
- Outcome: Symptoms improved - Graded return to exercise initiated - Resumed soccer one week post injury -No recurrence of symptoms

Case 2 - Skateboarder

- 19 yo ♀ collegiate tennis player
- 2/20/11 fell from skateboard and hit back of head
- 2/22/11 seen by training staff with c/o left sided neck pain, HA, sleepy, hard to concentrate, sensitive to light
- PMH: No hx concussion

Case 2 – Skateboarder (cont)

- 2/24/11 initial physician visit:
  - Lightheaded, headache began DOI and not changed
  - no balance problem, no weakness
- O: nl except TTP L paraspinal cervical muscles
- A: Concussion
- P: Rest from physical and mental activity
  - Close f/u for sx change

Would you image this patient?

1. Yes with skull x-ray
2. Yes with CT Scan
3. Yes with MRI
4. Yes with other imaging
5. No

Case 2 – Skateboarder (cont)

- We opted:
  - If sx worse proceed with imaging, low threshold
- 2/25/11 (4 days after injury)
- Symptoms got worse – to ED
  - CT Scan – punctate hemorrhage , repeat scan 6 hours later, no change
  - D/C'd with f/u
- 3/2/11
- S: Still HA, light sensitivity, sleepy, gets confused easily
  - No vision change, normal hearing, balance
- O: no new findings
- A: Concussion
- P: No activity
  - Weekly exams

Would you repeat any imaging?

1. Yes, CT Scan
2. Yes, MRI
3. Yes, other imaging
4. No

Case 2 – Skateboarder (cont)

- Repeat imaging with MRI
- 3/7 reviewed image cavernous hemangioma
  - Continued to have problems studying
- 3/9/11 (17 days post injury)
  - sx worse, bad HA, arms and legs feel weaker, tingling, numbness on both that last for hours. Studying making things worse, decreased appetite, nausea, no vomiting
- TO ED
  - Recommended MRI w/contrast, including GRE sequences.
- Pt went home for spring break, saw her neurologist thought to be hemangioma with no need for further w/u, nl exam
- 3/30/11
- Better, no HA, N/V/Dizzy, nl energy, sleeping well

25 STEPS: HOW TO SET UP A STUDENT-RUN FREE CLINIC PROJECT

1. Identify a core group of interested students.
2. Identify a faculty advisor/ champion who will help to build credibility and
. support from your institution and help to ensure adequate clinical supervision for all activities.
3. Find a community partner who is already serving the underserved in a community setting- e.g. school, church, neighborhood program, meal program. Meet with the partner and begin to establish a trusted relationship. From the beginning, help your fellow health professional students and team understand that we, as health professionals , are guests in the community partner's setting. Thus, if something is needed, whether an electrical outlet, or a copy machine, or keys to a certain door, that we are in this long term partnership together and the elements of trust and mutual respectare essential to a successful long term project.
4. Establish a legal relationship between the university and the site so that for the purpose of health professional education, the site becomes an extension of the university. Complete a memorandum of understanding and/ or affiliation agreement. This may take several months and will involve the legal/ contracting team from both partners. The legal contracting team at your university will know how to set these up. Your faculty champion can help you with this step.
5. Identify what permits you will need for certain activities and arrange for County or state permits as needed including environmental waste hauling(how you will get rid of your medical waste) , CLIA waiver(so you can do simple on-site labs) , and others, e.g. a permit to use an x-ray unit for dental services, etc.
6. Contact local preceptors, community faculty, and faculty if they would be willing to volunteer (from once a month to once every 3 months), in addition to the core faculty advisor(s) It is important to establish liability and malpractice coverage for all aspects of your free clinic project. Community physicians who would like to volunteer will be appointed as community/ voluntary faculty at your health professions school. Refer to Item 4. Also, you will need to ensure that all your health professional student and community volunteers have a legal status at your program. Thus, if a medical student is enrolled, they will be covered because they are supervised by a member of faculty and there is an affiliation agreement in place. If you have a community member who would like to volunteer their services, they can sign up as a free clinic project volunteer and complete your paperwork for volunteering, You never want to burden your community partner. Ensuring that liability structures are established is key. It may feel onerous, but in the long run, there is a feeling of safety and both community partner and institutional trust that is established because it is recognized that these structures are in place.
8. Start small, perhaps one evening a week at a local community program.

9. If possible, arrange for elective credit for the medical/ health professional students. At UCSD, first and second year medical students who want to work in the free clinic must take a required elective course, Community Advocacy, which introduces them to the free clinic project, and includes philosophy, approach, skills, and opportunities for reflection as well as their first clinical experiences . Students who continue to be involved receive further elective credit. Fourth year medical students can complete a clerkship in underserved or family medicine that gives them extensive experience at the free clinic project and, with supervision, the opportunity to learn to be , clinical coaches/ teachers to the first and second years
10. Initial basic supplies can usually be donated from a local practice, or the faculty practice. Pharmaceuticals initially can be donated, and also one can use the Patient Assistance Programs which provide free prescription medications for specific patients. . The $4 programs at many stores, such as Target, can also be used. Beginning to provide medications this way requires no additional input of funds. Soon, develop a basic formulary using generics, and a mechanism to use the Patient Assistance Programs, and a wish list formulary for samples and purchased medications, so that patients are not being constantly switched from medicine to medicine. Approach your university, local labs, purchasing cooperatives such as Council Connections, and other resources to achieve affordable lab services. Medical specialty clinics can be developed as well by involving medical students as specialty managers and specialist faculty as attendings.
11. Faculty may consider writing a HRSA medical student education grant to fund some faculty teaching time, especially for program supervision. AAMC grants for student community service grants, and other small grants can also be written. Local foundations may be interested in your project. Over time, approach your university for core infrastructure funding as foundations prefer to match core funding.
12. Empower your students, encouraging them, with guidance and supervision, to develop patient charts, history forms, data collection methods, an intake system, environmental waste permits, lab arrangements, social resource consultations, health education, fund-raising..."whatever it takes" to provide excellent, high quality care.
13. Allow some of these questions to surface over time, as the clinic evolves, questions and issues will emerge, that the students will then address, e.g. patient flow, quality assurance. Develop a mechanism to follow up during the week, to check lab results, etc. It is essential to have patient contact information for each patient, even it is the street corner where a patient usually sleeps, and/ or their best friend's cell phone. Explain to patients that labs can only be drawn, if you have a way to find them if needed. Reinforce the approach that high quality care, one patient at a time, is the most important role you can play. Given that the need in the nation is

almost infinite, student-run free clinic projects cannot address this larger need. But, one patient at a time, you can provide safe, legal, high quality thorough integrated health care.

14. Develop a mission statement and a clinic philosophy, that is reinforced and adhered to, e.g. our approach includes showing respect to all patients, taking time with them and establishing trust, so over time, some of their deeper problems and issues can be addressed. Always show respect to all patients, colleagues, fellow students, custodians. Our philosophy consists of four tenets: Empowerment, a Humanistic approach, a Transdisciplinary Model, and the Community as Teacher.
15. In our program, patients are seen by a pair of medical students, preclinical and clinical. Other students, including pharmacy students, social work interns, acupuncture students, and interpreters, ; the clinical student acts as the coach. The students then present to the attending and the attending comes to see the patient, then the chart is written and signed off by both students and the attending. All patient care must be directly supervised by clinical attendings.
16. Develop strong social resource and case management activities at the clinic so that those patients who are eligible for access through Medi-Cal, Medicare, Medicaid, County Programs, or SCHIP/ Healthy Families are assisted with access and are able to have a medical home. Develop an approach that integrates assessment for the Social Determinants of Health(SDH) into your history, essentially evolving the Social history into a Social Determinants of Health history. Encourage and reinforce thorough social histories and treatment/ intervention Plans that include addressing the SDH. In our setting, all patients who are eligible for government supported programs are referred for care. Free clinic projects should serve people who are not eligible for any access or who are unable to achieve access, thus, those 'who fall through the cracks.' Your program can become part of the "safety net" for the safety net.
17. Develop mechanisms to follow outcomes. A clinical database and/ or Electronic Health Record can be be developed to measure patient outcomes and compile patient statistics. The Quality of Well Being Scale is used to measure outcomes. Other measures are the SF-12, SF-36, SF-1, and the PHQ-9(which is used for depression).
18. In the summer, students can also volunteer and receive credit and, with funding, several students can be hired to help build the infrastructure of the clinic. These students can work on improving the clinic infrastructure, look at the clinic as a whole, brainstorm its current needs, then set goals, assign tasks, and meet weekly to review objectives and achievements.
19. Students may do community projects and occasional research projects One must be careful of research in a free clinic setting- patients are very grateful and are a "vulnerable population". Also, trust building is very important. If your clinic is seen too much as all about research, it may be

hard to build trust. Nonetheless, research which helps to address the needs of the community and the clinic, and uses a Community Oriented Primary Care Research model, which involves the community at ALL steps.

20. As each site grows and becomes stronger, new sites are developed or new resources at existing sites are developed. Overall, growing deeper and stronger in terms of quality at one site is more important than developing many sites.
21. Reach out to other professions, lawyers, pharmacists, social workers, acupuncturists, nurses, dentists, and other integrative health professionals to develop collaborations to create a transdisicplinary model to address patient needs. Eventually, pharmacy faculty and students, dental faculty and students, social work faculty and students, law school faculty and students, acupuncture faculty and students, nursing faculty and students, and others, all will work side by side with the patient at the center.
22. Involve community members as much as you can, roles include liaison, outreach, promotoras, teachers for the students. Have the student see the community as their teacher and learn from community members how best to address concerns or take the next step. Consider starting empowerment groups for the patients/ clients, and involve them in creating and receiving health education and health maintenance activities. The concept of the promotora, the wise woman(person) from the community, who helps build trust to the community and brings wisdom from the community is key to the success of these projects.
23. Maintain very high professional standards, confidentiality, and quality of care, safety, not "poverty" or "half-care" because it's the "free clinic". As a society, we are underserving this population, thus inherent in the term underserved is a 'right to health care."
24. Avoid hierarchical structures among the student leaders. Everyone has a leadership role; everyone works both administratively and clinically, expect a high level of maturity, responsibility, and ownership and most of all, humility. No task is too small. The clinic leaders are the ones who also take out the garbage.
25. Practice regular reflection activities, "learning circles", build community among everyone at the sites, learn from our mistakes, follow up, and model respectful communication, empathy, congruence, and positive regard. Practice thoroughness, conscientiousness, and compassion.

'UCSD Student Run Free Clinic Project What It's All About'

Ellen Beck, MD

http://meded.ucsd.edu/freeclinic/

Objectives

By the end of this presentation, the learner will:

- Have an improved understanding of health care disparities in San Diego
- Gain knowledge of the history of the UCSD Student-Run Free Clinic Project and how it addresses health care needs of uninsured patients
- Be able to initiate or participate in similar projects in other areas where health care disparities exist

Access to Care

- More than 50 million without access to health care
- More than 108 million without access to dental care
- Health care costs are the most common cause of personal bankruptcy in the country, even for those with health insurance

Health care is county by county

- Federal Health Care, e.g. Medicare
- State programs
- County-responsibility to care for the indigent and those without access to care

Health care is County by County

- San Francisco-Universal access to care through Healthy San Francisco
- San Diego---health care desert
- CMS-less than 1200 a month
  - disease that can lead to your death
  - sign a lien against your future property

Health Care Programs

- LIHP Low Income Health Program 133% of Federal Poverty Level($892) --no previous diagnosis, no lien
- Children-Medi-Cal, Healthy Families, Child Health Initiative(not here)
- Mammograms and Every Woman counts
- "Cancer lottery"

Underserved Care

- Maintain very high professional standards, confidentiality, and quality of care, safety, not "poverty" or "half-care" because it's the "free clinic". As a society, we are underserving this population, thus inherent in the term underserved is a 'right to health care."

My own background

- McGill University
- Worked in remote areas in northern Canada
- Department of Community Health-Elderly services, education, community programs, mental health services
- Directed a clerkship for McGill in primary care and geriatrics
- 1987 came to San Diego
- My parents and my patients were my greatest teachers

UCSD Student-Run Free Clinic Project

- Founded in 1997
- Committed Community Partners, passionate students, faculty and community volunteers
- 4 sites
- Community Partners:
- 2 “social justice” churches, already serving the underserved
- 2 inner city elementary schools

Free Clinic Project

- 2000 patients-1000 core medical patients and 1000 others,
- “safety net” for the safety net, San Diego-very limited safety net, many fall through the cracks
- No other resources
- Provide continuous, comprehensive high quality health care to people without access to care

Population

- 51% Latino, 30% Caucasian, 9% African-American,7% Asian, 4% other or not stated
- Now 69% Latino, 12% Caucasian,
- All ages: majority from 21-65
- 25% street homeless
- 51% women, 49% male,
- 85% with chronic illness: Hypertension, Hyperlipidemia, Diabetes, Asthma, Depression

All do not qualify for and/or cannot afford access to care

Core philosophy

- Empowerment
- Humanistic
- Trans-disciplinary
- Community as Teacher

- Taught, modeled, and expected throughout all activities

Empowerment

- Create an environment in which the other: individual, family, community take charge of their life and achieve joy and wellbeing

Esperanza Empowerment Group Member 3 years

"When I first came to the group, I was carrying a lot, and I let everything out. I cried a lot and since then, everybody in the group has helped me to think, to defend myself, to move forward without fear. Everything I hear here, I share with my family and they also are changing. I was in the hospital recently and they gave me a lot of support. I want this group to continue and want to invite a lot of people so that they also can listen and learn not to have fear and to move forward. This is my home and I want to share it with everybody."

Irma Empowerment group member 4 years

…Before coming to this group, I did not know how to control my temper and I did not know how to speak with my children or my husband. Now I feel like a different person. I know how to control my temper. I know how to speak to my children. Now I know how to get along with myself better. Before, I didn't value myself. I didn't take time for myself. I feel much better about myself. Thanks to all of you….For me, this group is like a family, something beautiful that happened in my life, this experience, this support….Ojala! I wish I can continue to come and to share."

Humanistic

- Rogerian person-centered approach
- Empathy
- Congruence: Self-awareness
- Positive Regard: Respect

Transdisciplinary

- All fields working together with the patient at the center
- Dispel hierarchies and existing stereotypes and inter-professional prejudices

"Culturally Humble" (Tervalon)

Students/Trainees- UCSD Medical Students

- 105 first year-complete required elective
- 70 first and second year, each quarter-elective
- Some third year-continuity site and selectives
- 80 fourth year four week clerkship either in Family Medicine or Underserved Medicine

Student perceived self-efficacy with the underserved pre-post first free clinic elective

- N=431 medical students who took elective between 2001-2001
- Students' perception of self-efficacy with care of the homeless, minority families, and women and children all improved (all p<0.001).
- Attitudes towards the care of the homeless and minority families improved (p<0.001, p=0.0283 respectively).
- Students reported an increase in interest in primary care, as well as increased interest in working with the underserved (both p<0.001).

Yoon, R., Johnson, M., Smith, S., Beck, E. Independent Study Project, 2009

Students learn to teach

What we do

- Teach the philosophy: through examples, role modeling, weekly reflection sessions, community building, didactics that include topics such as health promotion, health education, and working with interpreters, social resources

All care and services are supervised by licensed professionals

- Volunteers!!!!!! THANK YOU!!!
- Family Doctors, Specialists, Pharmacists, Dentists, Nurses, Lawyers, Community Members, Students…..
- All of our clinical leadership team and many of our volunteers were once students with us and have returned to be faculty supervisors

Transdisciplinary

- Pharmacy students-all first year, many third and fourth year
- Pre-dental students
- Acupuncture students: Pacific College of Oriental Medicine
- Social Work Interns: San Diego School of Social Work
- Law Students: California Western School of Law

182 Diabetic Patients
Process outcomes

- Had the following test within the last year

Blood Pressure	100%
HA1C	99%
LDL	93%
TG	88%
HDL	88%
Microalbumin	80%

Marrone, L., Smith, S., Johnson, MJ, Beck, E Independent Study Project, UCSD 2010

182 Diabetic Patients
Intermediate Outcomes

- LDL <100 70%
- LDL <130 86%
- BP <130/80 46%
- BP<140/90 77%
- Mean HA1C 8.26%

Marrone, L., Smith, S., Johnson, MJ, Beck, E Independent Study Project, UCSD 2010

LABS

- Contract with Quest Labs
- Affordable labs

Pharmacy

- Patient Assistance Programs
- $1.7 million each year in free meds, not samples
- Website
- In San Diego, 211

Dental Care

- Greatest unmet medical need in the nation---over 108 million
- Toothless leads to joblessness
- Cost Prohibiitive
- Medical-dental link—all dental diseases are infections, affects diabetes, etc.
- When a patient's sugar is out of control…..

Acupuncture and integrative approaches

- Pacific College of Oriental Medicine

Specialty and Hospital Services

- Specialty clinics, 17 different specialties, faculty and community volunteers supervise students in care
- Former students are now our volunteer dermatologist, orthopedist
- Collaborate with Project Access for specialty procedures and treatments

Hospitalization---huge unmet need

- No county hospital
- Hospitals are required by law to stabilize the emergent patient, but there is no law that they can't bill
- All hospitals have charity programs, but patients often don't know how to access them
- Need for ombudsman to help with bills
- Need for intense case management

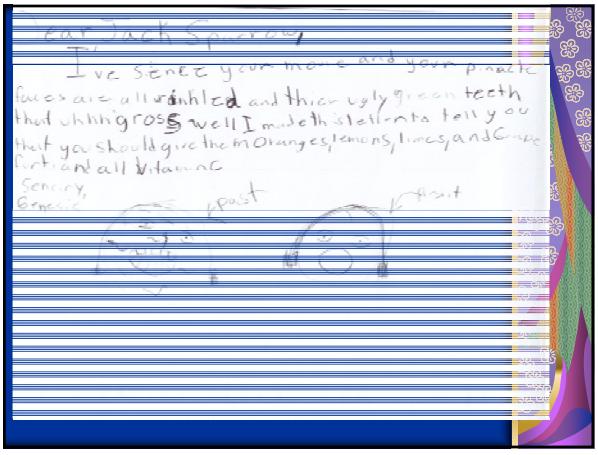
Social and Legal Services

- Benefits of Intensive Case Management
- Social Determinants of Health History
- Students work with Social Workers
- Also, free legal clinic: California Western School of Law
- Resource: Center for Health Education and Advocacy(Legal Aid)

Comprehensive Wellness Program

- Inner City Elementary School-Golden Avenue Elementary in Lemon Grove
- Children-Wellness Teachers-components of wellness, physical and emotional, creativity, expression, meaning
  Junior Health Promoters
- Parents-Access to Healthcare and Education and Classes
- Teachers-Professional Renewal
- Environment-Gardens, Murals, Learning environment

Golden Avenue Elementary
Blue Bandaid Brigade---
Youth Health Promoters



What we do at the Free Clinic Project

- Teach Back method: Pretend that you are the doctor and I am the patient, or let's switch roles, and please teach me what I have just taught you.
- Barriers Reduction: Identify what barriers are preventing someone from taking charge of their life and their health, and with them, help to reduce those barriers
- Personal prescriptions: Sources of stress and Sources of Strength

Other factors That Affect Health

- Fear: Working with clients to address their fears-teaching fear management tools
- Trust: Being 'trust bridges', Helping people build trust
- Stigma: Address concepts of stigma and how to overcome it
- Knowledge: Classes, sharing knowledge, adult education model

Promotoras

Introduce students to the clinic promotoras, explain and value the importance of their role

They come to the medical school to teach the students

They are available during clinic to help problem solve and consult.

They co-facilitate the empowerment group.

New Program

- San Diego workforce Partnership
- Create work experience for entry level health professionals from underserved backgrounds
- E.g. Pharmacy tech, dental assistant, Medical Assistants, LVN, etc.

Fellowship in Underserved Health Care

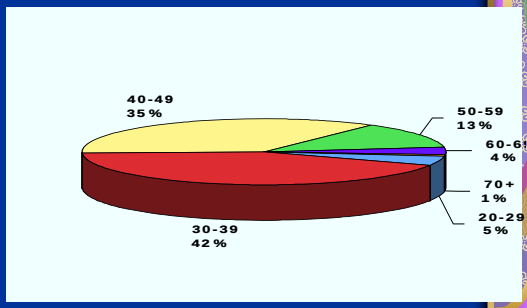
- 1-2 year Fellowship in Underserved Health Care
- Medicine, then expanded to Dentistry, Acupuncture, now Pharmacy, hopefully mental health, law, nursing
- Help direct the free clinic project and complete a project and training
- 6 medical fellows, 5 were previously student leaders at the free clinic project, now they have returned to be the role models and clinic directors, supervising all aspects of care
- 2 dental fellows
- All now work with the underserved

National Faculty Development Addressing Health Needs of the Underserved

- 135 faculty
- 30 states
- 25% from underrepresented minorities in the health professions

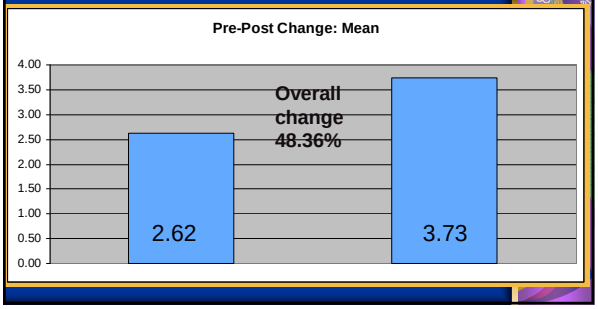
3 areas of focus:
faculty development skills
community partnerships and programs
personal and professional renewal

Faculty Development Program Age Range of Participants

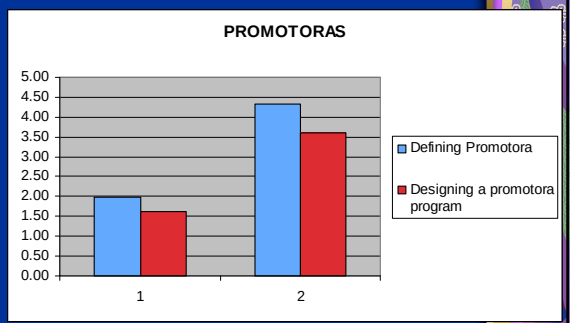


Faculty Development Program Outcomes: Pre-post Change

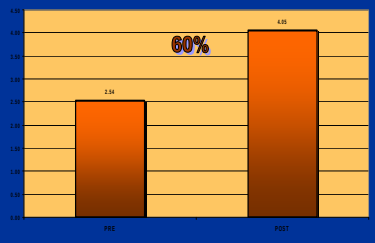
in overall confidence in being able to demonstrate your proficiency in the following skills
N: 40 of 49 participants of the 2003, 2005, 2006, 200



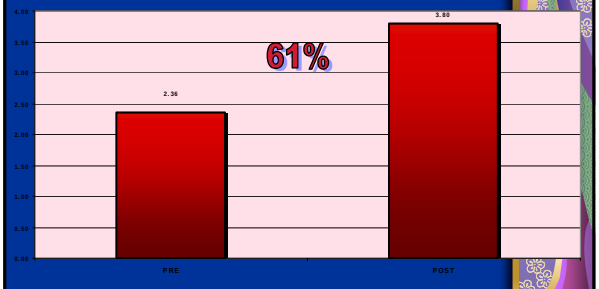
Defining Promotora 118% Designing a Promotora Program 123%

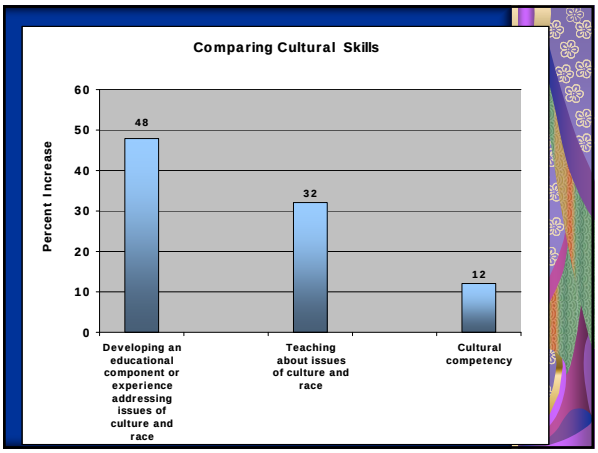


Designing student curricula related to underserved communities



Designing a student or resident-run free clinic project





2003: Outcomes after first 53 participants

- 7 new or improved student-run free clinic projects
- 19 new student curricula
- 30 new resident curricula
- 21 PI or co-investigator for a grant
- 35 new leadership roles

What we have learned

- Ownership
- Coaching and role modeling
- Orientation re philosophy and specific expectations
- Teaching students to be teachers
- Showing the students that the patients and community are truly the teachers
- Directly related to patient care
- Group reflection that starts and ends a session and in class, related to patient care

What lessons have we learned

- Ownership: If the students feel directly involved in care and education, they will take responsibility
- Involve community members in the training, the teaching and the role modeling
- Role Models, supervisors that have lived and can teach the philosophy
- Philosophy that is transmitted, practiced and expected

What Can YOU do

- Remain intact/martyrs die
- Learn the programs in your county
- For children
- For women
- For cancer
- Think social determinants
- Ask for help(social work, 211, county)

If you want to get involved

Emails lightstreams@gmail.com or ebeck@ucsd.edu

Our volunteer coordinator is Anne Crane acrane@ucsd.edu

Handout: 25 steps for starting a student run free clinic project

Website: http://meded.ucsd.edu/freeclinic/

Please come visit!

Review of Objectives

- Have an improved understanding of health care disparities in San Diego
- Gain knowledge of the history of the UCSD Student-Run Free Clinic Project and how it addresses health care needs of uninsured patients
- Be able to initiate or participate in similar projects in other areas where health care disparities exist

Gandhi, Marley, Rumi, King, Aristotle, Chavez, Hillel Rule of life

- Gandhi Be the change you wish to see in the world.
- Marley Emancipate yourself from mental slavery. Only you can free your mind
- Rumi Don't move the way fear moves you.
- King Injustice anywhere is a threat to justice everywhere
- Aristotle There are infinite needs in the world. Find one of your great passions and match it to that need.
- Chavez Si, se puede.
- Hillel If I am not for myself, who will be for me? If I am only for myself, what am I? If not now, when?

New Frontiers in Type 2 Diabetes Mellitus Management: Introducing the Role of the Kidney as a Therapeutic Target

This activity is jointly sponsored by New Jersey Academy of Family Physicians and Consensus Medical Communications.

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- No Disclosures

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Content Development Faculty Disclosures

- Timothy Bailey, MD, CPI, FACE, FACP, has reported grants/research support from Animas, Bayer, BD, Boehringer Ingelheim, Corcept, Bristol Myers Squibb, Dexcom, GlaxoSmithKline, Halozyme, Lifescan, Lilly, Medtronic, Merck, Novo Nordisk, Resmed, Roche, Sanofi-Aventis, and Xoma. He has received consulting and speaking honoraria from Roche, Sanofi-Aventis, Novo Nordisk, Amylin, and BD
- Jaime Davison, MD, has reported grants/research support from Bristol Myers Squibb, Astra Zeneca, Novo Nordisk, Merck, Eli Lilly and Co., Roche, Janssen, and Lifescan
- Ruby Halper-Erkkila, MD, has no financial relationships to disclose
- Edward J. Schwager, MD, FAAFP, has no financial relationships to disclose

Pre-Test

For T2DM patients with no cardiovascular disease, what is your maximum target A1C?

1. < 6%
2. ≤ 6.5%
3. < 7%
4. ≤ 7.5%
5. < 8%

The primary mechanism of lowering glucose by SGLT2 drugs is:

1. Increasing insulin secretion
2. Decreasing hepatic glucose production
3. Preventing renal glucose reabsorption
4. Improving insulin sensitivity
5. Increasing glucose update

Potential benefits of the SGLT2 inhibitors in addition to glucose lowering include:

1. Blood pressure lowering
2. Reduction in LDL-C
3. Weight loss
4. Blood pressure lowering + weight loss
5. All of the above

Objectives

- Identify the challenges and barriers to goal achievement in patients with T2DM and implement appropriate solutions
- Utilize guidelines to appropriately set targets to help patients reach glycated hemoglobin (A1C) goals
- Distinguish the unique differences between available pharmacotherapeutic options and discuss the clinical implications of these differences on appropriate patient selection
- Describe the pharmacology and rationale for the use of SGLT2 inhibitors and explore their potential role in T2DM patients

Case Study: James

- James, a 63-year-old man, presents for a follow-up visit. He has diabetes, which was diagnosed about 4 years ago, hypertension, hyperlipidemia, paroxysmal atrial fibrillation, patent foramen ovale, and coronary artery disease with a non-obstructive lesion at the right coronary artery at cath
- James admits to not exercising and feels he has "put on a few pounds"
- Social history: Non-smoker, no alcohol use, office executive

Case Study James: Current Medications

- Metformin 1000 mg po twice a day
- Lisinopril 20 mg po daily
- Diltiazem ER 120 mg po daily
- Simvastatin 40 mg po daily
- Dabigatran 150 mg po twice a day
- ASA 81 mg po daily

Case Study James: Lab Results and Physical Exam

- Lab results
  - FPG 223 mg/dL
  - BUN 10 mg/dL
  - Cr 0.96 mg/dL
  - GFR 99 mL/min
  - Urine microalb: Neg
  - Tchol 133 mg/dL
  - TG 110 mg/dL
  - HDL 38 mg/dL
  - LDL 73 mg/dL
- A1C

Baseline (4 years ago)	7.4%
After 3 months of metformin	6.4%
6 months ago	6.9%
Most recent	7.6%

- Physical exam
  - Height 67 inches
  - Weight 195 lbs
  - BMI 30.5 kg/m^2
  - BP 128/78 mm Hg

Number of Americans With Diabetes Rises to Nearly 26 Million

- 8.3% of total population
  - 90%-95% have T2DM

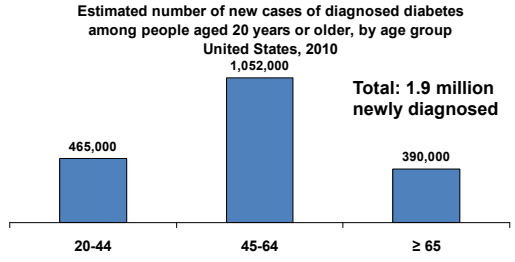
33% by 2050

- 1.9 million new cases each year in people aged > 20 years
- 79 million Americans aged > 20 years have prediabetes
- Seventh leading cause of death in United States
- Leading cause of kidney failure, non-traumatic lower-limb amputations, and blindness in US adults
- Diabetes costs: $174 billion annually

The epidemic continues…

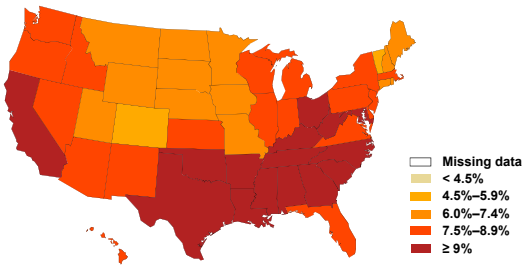
Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA.
Centers for Disease Control and Prevention. http://www.cdc.gov/media/releases/2011/p0126_diabetes.html. Accessed March 23, 2012.

Newly Diagnosed Diabetics: 55% Are 45-64 Years Old



Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed March 23, 2012.

Age-Adjusted Percentage of US Adults Who Had Diagnosed Diabetes: 2009

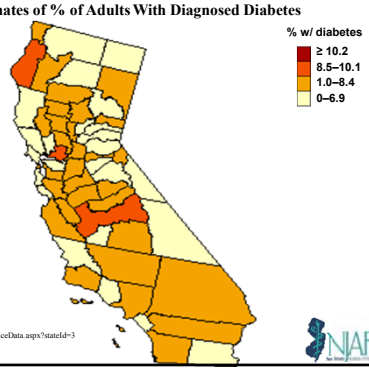


Centers for Disease Control and Prevention. Division of Diabetes Translation. National Diabetes Surveillance System. http://www.cdc.gov/diabetes/statistics. Accessed April 3, 2012.

Adults With Diagnosed Diabetes in Your State

2008 Age-Adjusted Estimates of % of Adults With Diagnosed Diabetes

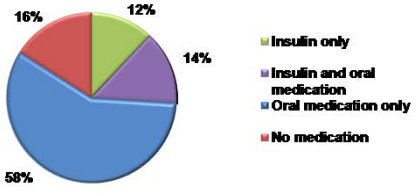
California



Centers for Disease Control and Prevention. http://apps.nccd.cdc.gov/DDT_STRS2/CountyPrevalenceData.aspx?stateId=34&Mode=DBT. Accessed March 23, 2012.

16% of Patients Diagnosed With Diabetes Do Not Take Any Medications

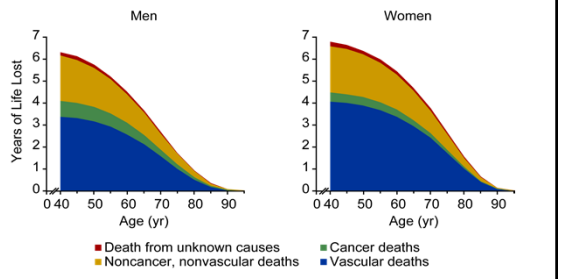
US Adults With Diagnosed Diabetes – Treatment With Insulin or Other Medications



2007–2009 National Health Interview Survey

Centers for Disease Control and Prevention. National Diabetes Fact Sheet: National estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services.
US Department of Health and Health Services, National Institutes of Health, and National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics, 2011. Published February 2011.

Estimated Future Years of Life Lost Owing to Diabetes



The Emerging Risk Factors Collaboration

Adapted from Seshasai SR, et al. *N Engl J Med.* 2011;364(9):829-841.

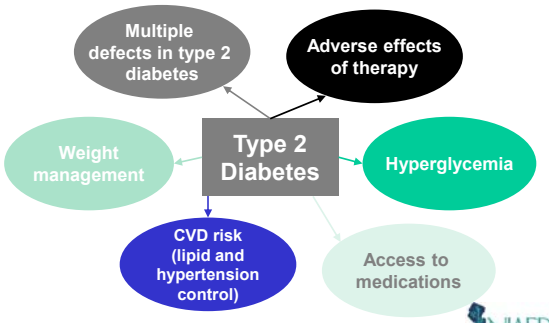
Prevent/Delay T2DM

- Significantly decrease rate of onset with lifestyle modification or metformin
  - Lifestyle intervention: 34% reduction at 10 years in DPPOS[1]
  - Metformin: Less effective than lifestyle intervention in DPP and DPPOS (18%) but may be cost-saving over a 10-year period[2]
- ADA recommendations[3]: Considered in those with IGT, IFG, or an A1C of 5.7%-6.4%
  - Weight loss: 7% of BW
  - Increasing physical activity to at least 150 min/week of moderate activity (walking)
  - Metformin: Especially for those with BMI > 35 kg/m^2, age < 60 years, and women with prior GDM
  - Annual monitoring for the development of diabetes

DPP=diabetes prevention program; DPPOS=diabetes prevention program outcomes study

1. Knowler WC, et al. *Lancet.* 2009;374(9702):1677-1686.
2. Herman WH, et al. Presented at: 71st Scientific Sessions of the American Diabetes Association; June 24-28, 2011; San Diego, California. Abstract 136-LBOR.
3. *Diabetes Care.* 2012;35(Suppl 1):S11-S63.

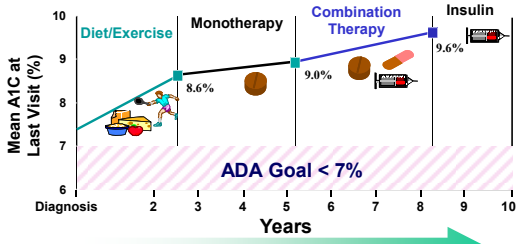
Challenges in Diabetes Care



Adapted from International Diabetes Center, Minneapolis, MN. © 2005 All rights reserved.

JF2

The Paradigm of Treatment: Treat to Failure



Diabetes progression

At insulin initiation, the average patient had:

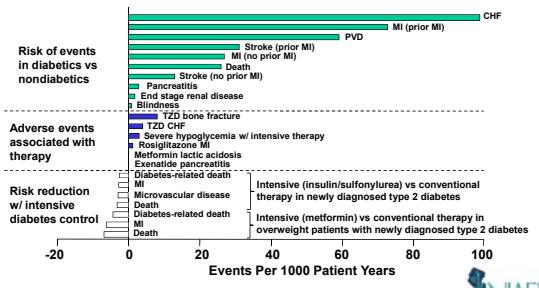
- 5 years with A1C > 8%
- 10 years with A1C > 7%

The progressive nature of T2DM ultimately overwhelms medications

Adapted from Brown JB, et al. *Diabetes Care.* 2004;27(7):1535-1540.

Established Benefits of Glycemic Control

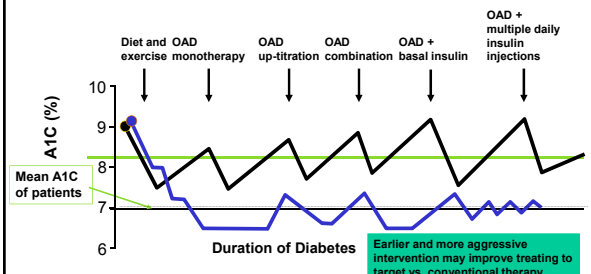
- Overall, glucose-lowering agents have a favorable risk-benefit profile



Bergenstal RM, et al. *Am J Med.* 2010;123(4):374.e 9-18. Copyright © 2010, Elsevier.

JF3

Do Not Delay Initiating Pharmacologic Treatment or Intensifying Therapy When Not at Goal



Earlier and more aggressive intervention may improve treating to target vs. conventional therapy

OAD=oral anti-diabetic

Adapted from Del Prato, et al. *Int J Clin Pract.* 2005;59:1345-1355.

Slide 22

JF2 Faculty: This is an updated slide per Dr Bailey's comment
Jennifer Frederick, 5/8/2012

Slide 24

JF3 Faculty: new slide per Dr Bailey
Jennifer Frederick, 4/26/2012

Treatment Goals

A1C: ADA	**< 7%***
A1C: AACE	**≤ 6.5%**
Blood pressure	**< 130/80 mm Hg**
LDL	**< 100 mg/dL****
Triglycerides	**< 150 mg/dL**
HDL	**> 40 mg/dL men** **> 50 mg/dL women**
Apolipoprotein	**< 80 highest risk;** **< 90 high risk**
Weight loss	**Reduce weight by at least 5%-10%; avoid weight gain**

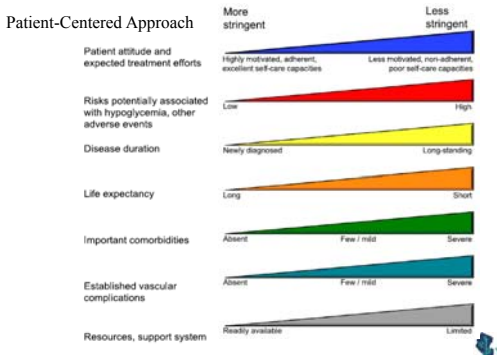
- Individualize glycemic targets
  - Using clinical characteristics: age, duration of disease, comorbidities, hypoglycemia
- Clinical impact of cardiovascular outcome trials
- ACCORD, ADVANCE, VADT

* More stringent A1C goal (< 6.5%) for select individuals (long life expectancy, no significant CVD, short duration of diabetes)
**< 70 mg/dL with overt CVD

Diabetes Care. 2012;35(Suppl 1):S11-S63.
Rodbard HW, et al. *Endocr Pract*. 2009;15(6):540-559.
Handelsman Y, et al. *Endocr Pract*. 2011;17 Suppl 2:1-53.

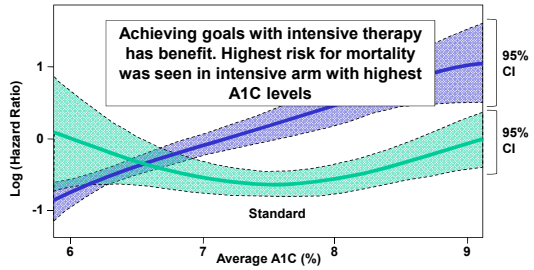
JF4

Determining Glycemic Targets



Ismail-Beigi F, et al. *Ann Intern Med*. 2011;154(8):554-559.
Inzucchi SE, et al. *Diabetes Care*. 2012. Copyright © 2012 American Diabetes Association.

Clinical Implications of Intensive Glycemic Control Trials

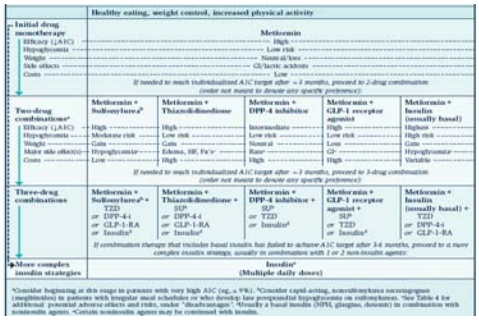


Riddle MC, et al. *Diabetes Care*. 2010;33(5):983-990. Copyright © 2010 American Diabetes Association.
Diabetes Care. 2012;35(Suppl 1):S11-S63.
Genuth S, Ismail-Beigi F. *J Clin Endocrinol Metab*. 2012;97(1):41-48.

Case Study James

- Summary:
  - 63 years old
  - History of T2DM on metformin
  - A1C 7.6%
  - GFR: 99 mL/min
  - BMI: 30.5 kg/m^2 – Has gained about 15 lbs, not exercising
  - Hx of CAD
- What is the optimal A1C goal for this patient?
  1. ≤ 6.5%
  2. < 7.0%
  3. 7.1%–7.5%

2012 ADA/EASD Treatment Algorithm for Type 2 Diabetes: Patient-Centered Approach



Inzucchi SE, et al. *Diabetes Care*. 2012. Copyright © 2012 American Diabetes Association.

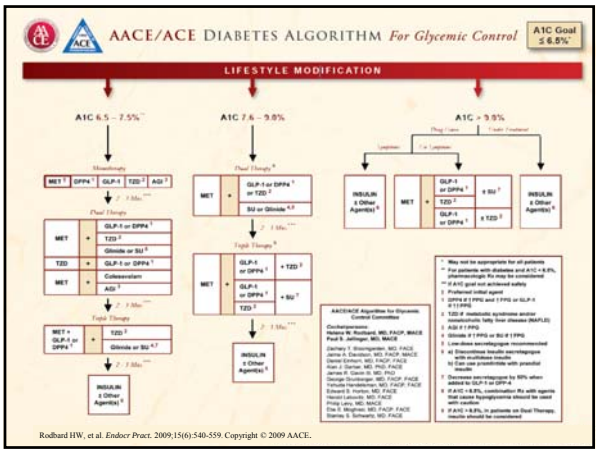
2012 ADA/EASD Treatment Algorithm for Type 2 Diabetes: Key Points

- Individualize glycemic targets and glucose-lowering therapies
- Diet, exercise, and education remain the foundation
- Metformin is the optimal first-line drug (unless contraindications)
- After metformin, combination therapy with 1-2 orals or injectables
  - (Aim to minimize side effects where possible)
- Ultimately, many patients will require insulin alone or in combination
- Focus on the patient: his/her preferences, needs, and values
- Comprehensive CV risk reduction must be major focus

Inzucchi SE, et al. *Diabetes Care*. 2012.

Slide 26

JF4 Faculty: Switched out figure with one in the new ADA/EASD reference.
Jennifer Frederick, 4/23/2012

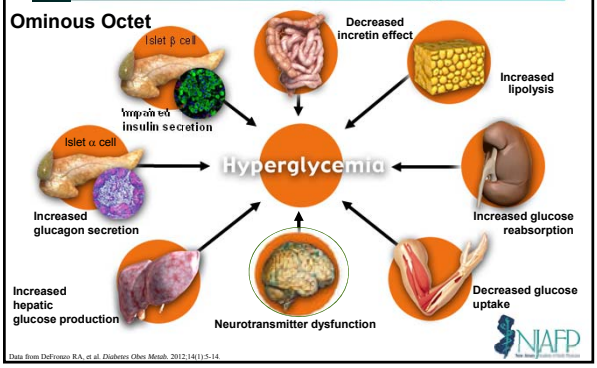


Case Study James

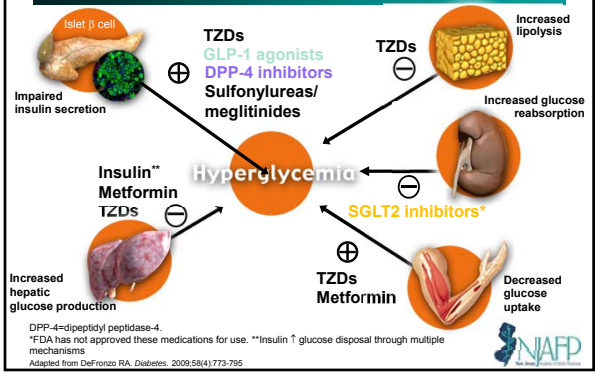
- What would you do next to manage his diabetes?
  1. Refer to diabetic education
  2. Re-educate on lifestyle changes, continue monotherapy, and ask to see back in office in 3 months
  3. Re-educate on lifestyle changes and begin dual therapy
  4. Re-educate on lifestyle changes and begin triple therapy

Assessing Options in Modern T2DM Management—Implications for Clinical Practice

Pathophysiology of T2DM: An Evolving Concept



Treatment of T2DM: A Sound Approach Based Upon Pathophysiology



Kidneys Play an Important Role in Handling of Glucose

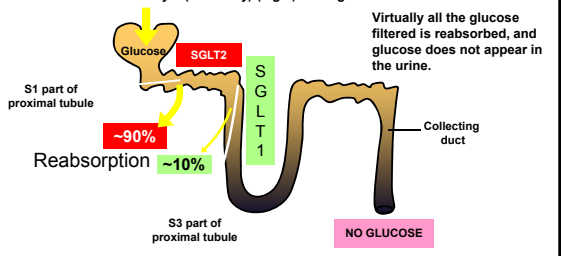
Total glucose stored in body	~450 g
Glucose utilization	~250 g/day
Brain	~125 g/day
Rest of body	~125 g/day
Glucose in Western diet	180 g/day
Glucose production (gluconeogenesis + glycogenolysis)	~70 g/day
Renal glucose filtration and reabsorption	~180 g/day

Data from Wright EM, et al. J Intern Med. 2007;261(1):32-43.

SGLT2 Is the Major Transporter for Renal Glucose Reabsorption

Volume of plasma kidneys filter/day = 180 L
Normal glucose concentration = 1000 mg/L

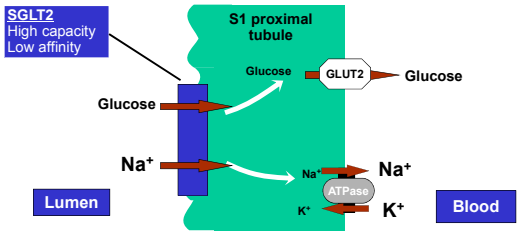
Glucose filtered/day = (180 L/day) (1 g/L) = 180 g



SGLT = Sodium-glucose cotransporter

Wright EM. *Am J Physiol Renal Physiol.* 2001;280(1):F10-F18. Thorens B. *Am J Physiol.* 1996;270(4 Pt 1):G541-G553 .

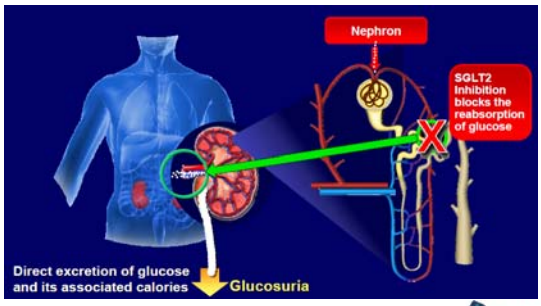
SGLT2 Mediates Glucose Transport in the Renal Proximal Tubule



SGLT2 transporter mediates 90% of renal glucose reabsorption

Adapted from Bakris GL, et al. *Kidney Int.* 2009;75(12):1272-1277.

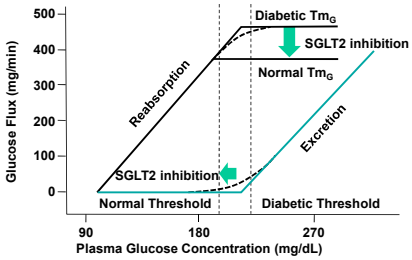
SGLT2 Inhibition Lowers Blood Glucose Levels by Acting on the Kidney Where Glucose Is Reabsorbed



Jennings A, et al. Presented at: Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Bristol-Myers Squibb, AstraZeneca. July 19, 2011.

Renal Glucose Handling Before and After SGLT2 Inhibition

Inhibition of SGLT2 transport 'resets' the system



SGLT2 inhibitors reduce Tm$_G$ for glucose reabsorption, lowering the glucose excretion threshold—bringing the glucose reabsorption threshold closer to normal (arrows).

Tm$_G$ = maximal transport rate for glucose

DeFronzo RA, et al. *Diabetes Obes Metab.* 2012;14(1):5-14. Copyright © 2012 Blackwell Publishing Ltd.

Rationale for SGLT2 Inhibitors

- SGLT2 is responsible for 90% of renal glucose reabsorption
  - Potentially lower blood glucose levels due to increased renal excretion of glucose
  - Potential weight loss due to urine loss of the calories from glucose
- Phlorizin: 'Prototype' SGLT inhibitor–non-selective inhibitor of SGLT; derived from apple bark, stimulated urinary glucose excretion
- Mutations in SGLT2 transporter are benign
  - Familial renal glucosuria (FRG)

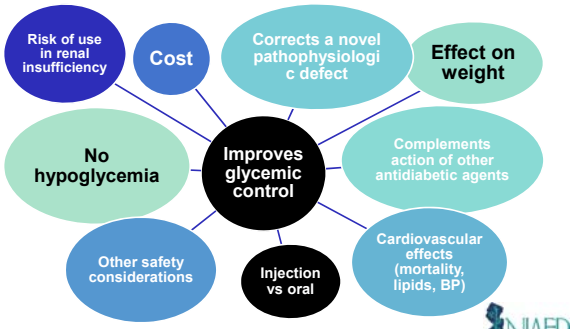
DeFronzo RA, et al. *Diabetes Obes Metab.* 2012;14(1):5-14.
White JR. *Clinical Diabetes.* 2010;28(1):5-10.

Case Study James:
Current Therapy Metformin 1000 mg po Twice a Day

- What treatment change would you recommend next for this patient?

1. Do nothing
2. Add SU
3. Add TZD
4. Add GLP-1 agonist
5. Add DPP-4 inhibitor
6. Add alpha-glucosidase inhibitor
7. Add basal insulin

Individualizing Therapy: Factors to Consider



Case Study James: Current A1C 7.6% What Do the Guidelines Recommend?

A1C 7.6%-9.0%

Dual Therapy[7]

MET + GLP-1 or DPP-4[1] / or TZD[2] / SU or glinide[3,4]

→ *2-3 Mos.****

Triple Therapy[8]

MET + GLP-1 or DPP-4[1] + TZD[2] / GLP-1 or DPP-4[1] + SU[6] / TZD[2]

*2-3 Mos.****

Insulin ± other agent(s)[5]

AACE/ACE Diabetes Algorithm

*** If A1C goal not achieved safely
1 DPP-4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG
2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
3 Glinide if ↑ PPG or SU if ↑ FPG
4 Low-dose secretagogue recommended
5 a) Discontinue insulin secretagogue with multidose insulin; b) Can use pramlintide with prandial insulin
6 Decrease secretagogue by 50% when added to GLP-1 or DPP-4
7 If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution
8 If A1C > 8.5%, in patients on dual therapy, insulin should be considered

Adapted from Rodbard HW, et al. *Endocr Pract.* 2009;15(6):540-559. Copyright © 2009 AACE.

JF7

Case Study James: Current A1C 7.6% What Do the Guidelines Recommend? Recommendations to Avoid Weight Gain

ADA/EASD 2012 Diabetes Algorithm

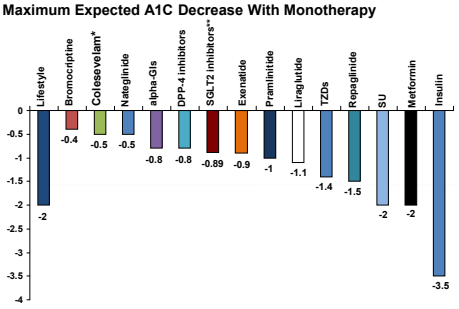
	Healthy eating, weight control, increased physical activity	
Initial drug monotherapy	Metformin	
Efficacy (↓A1C)	High	
Hypoglycemia	Low risk	
Weight	Neutral/loss	
Side effects	GI/lactic acidosis	
Costs	Low	
	If needed to reach individualized A1C target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference)	
Two-drug combinations*	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist
Efficacy (↓A1C)	Intermediate	High
Hypoglycemia	Low risk	Low risk
Weight	Neutral	Loss
Major side effect(s)	Rare	GI
Costs	High	High

*Consider beginning at this stage in patients with very high A1C (eg, ≥ 9%). †See Table 4 for additional potential adverse effects and risks, under "disadvantages".

Inzucchi SE, et al. *Diabetes Care*. 2012;supplementary data. Copyright © 2012 American Diabetes Association.

Relative A1C Reduction Ability

Maximum Expected A1C Decrease With Monotherapy



*Colesevelam has not been studied as monotherapy. **SGLT2 inhibitors are not FDA approved.

Nathan DM, et al. *Diabetes Care*. 2009;32(1):193-203. Welchol [package insert]. Parsippany, New Jersey: Daiichi Sankyo, Inc.; 2011. Cycloset [package insert]. Tiverton, Rhode Island: VeroScience, LLC; 2010. Victoza [package insert]. Bagsvaerd, Denmark: Novo Nordisk A/S; 2012. Byetta [package insert]. San Diego, CA: Amylin Pharmaceuticals, Inc.; 2011. Jennings A, et al. Presented at: Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Bristol-Myers Squibb, AstraZeneca. July 19, 2011.

EP1

T2DM: Therapeutic Landscape (Non-insulin) 2012

Agent (examples)	Advantages	Disadvantages	Cost
SUs (glyburide, glipizide, glimepiride)	Extensive experience, well tolerated, ↓CV events/mortality, ↓ microvascular risk	Hypo, wt gain, β-cell exhaust/ low durability	$
Glinides (repaglinide, nateglinide)	↓PPG, dosing flexibility	Hypo, wt gain, β-cell exhaust, dose frequency	$ $ $
Biguanides (metformin)	Extensive experience, wt loss, no hypo, ↓ CV events/mortality	GI, lactic acidosis (rare) B12 deficiency Contraindications: CKD, acidosis, hypoxia, dehydration	$
TZDs (pioglitazone osiglitazone*)	No hypo, β-cell preserv/ durability, ↓TG (pio), ↑HDL-C, ↓BP ?, ↓CVD events (pio)	Wt gain, edema/HF bone fxs, ? ↑ bladder cancer (pio), ↑LDL-C (rosi), ? ↑CVD/MI (rosi)	$ $ $
α-GIs (acarbose, miglitol)	No hypo, ↓PPG, nonsystemic, ? ↓CVD	Modest A1C efficacy, GI, dose frequency	$ $

*Prescribing highly restricted in US

Diabetes Care. 2012;35(Suppl 1):S11-S63.
Rodbard HW, et al. *Endocr Pract*. 2009;15(6):540-559.
Inzucchi SE, et al. *Diabetes Care*. 2012.

EP2

T2DM: Therapeutic Landscape (Non-insulin) 2012 (cont.)

Agent (examples)	Advantages	Disadvantages	Cost
GLP-1 receptor agonists (exenatide, liraglutide)	No hypo, wt loss, ? β-cell preserv, ? CV benefits	GI, injections, training requirements, ? acute pancreatitis, thyroid tumors* (animals)	$ $ $
Amylinomimetics (pramlintide)	Wt loss, ↓PPG	GI, injections, dose frequency, hypo (unless ↓ insulin), modest A1C efficacy	$ $ $
DPP-4 inhibitors (sitagliptin, linagliptin, saxagliptin)	Well tolerated, no hypo, wt neutral	Modest A1C efficacy, Urticaria/angioedema, ? pancreatitis	$ $ $
Bile acid sequestrants (colesevelam)	No hypo; ↓LDL-C	Modest A1C efficacy, ↑TG, constipation, interference w/ absorption of other meds	$ $ $
D2 agonists (bromocriptine)	No hypo, ? ↓CVD events	Nausea, dizziness, fatigue, rhinitis, modest A1C efficacy	$ $

*C-cell hyperplasia/medullary thyroid tumors

Diabetes Care. 2012;35(Suppl 1):S11-S63.
Rodbard HW, et al. *Endocr Pract*. 2009;15(6):540-559.
Inzucchi SE, et al. *Diabetes Care*. 2012.

Slide 45

JF7 Faculty - added in new slide based on the new ADA/EASD recommendations.
Jennifer Frederick, 4/24/2012

Slide 47

EP1 Faculty: minor updates to tables based on Table 1 of the ADA/EASD 2012 Diabetes Care reference.
Emily Pahl, 5/2/2012

Slide 48

EP2 Faculty: minor updates to tables based on Table 1 of the ADA/EASD 2012 Diabetes Care reference.
Emily Pahl, 5/2/2012

Risks and Benefits of Current Medications

	Metformin (MET)	DPP4 Inhibitor	GLP-1 Agonist (Incretin Mimetic)	Sulfonylurea (SU)	Glinide™	Thiazolidinedione (TZD)	Colesevelam	Alpha-glucosidase inhibitor (AGI)	Insulin	Pramlintide
MEDICATIONS*										
BENEFITS										
Postprandial glucose (PPG) - lowering	MILD	MODERATE	MODERATE TO MARKED	MODERATE	MODERATE	MILD	MILD	MODERATE	MODERATE TO MARKED	MODERATE TO MARKED
Fasting glucose (FPG) - lowering	MODERATE	MILD	MILD	MODERATE	MILD	MODERATE	MILD	NEUTRAL	MODERATE TO MARKED	MILD
Nonalcoholic fatty liver disease (NAFLD)	MILD	NEUTRAL	MILD	NEUTRAL	NEUTRAL	MODERATE	NEUTRAL	NEUTRAL	NEUTRAL	NEUTRAL
RISKS										
Hypoglycemia	NEUTRAL	NEUTRAL	NEUTRAL	MODERATE	MILD	NEUTRAL	NEUTRAL	NEUTRAL	MODERATE TO SEVERE	NEUTRAL
Gastrointestinal Symptoms	MODERATE	NEUTRAL	MODERATE	NEUTRAL	NEUTRAL	NEUTRAL	MODERATE	MODERATE	NEUTRAL	MODERATE
Risk of use in renal insufficiency	SEVERE	REDUCE DOSAGE	MODERATE	MODERATE	NEUTRAL	MILD	NEUTRAL	NEUTRAL	MODERATE	UNKNOWN
Contraindicated in Liver Failure or Predisposition to Lactic Acidosis	SEVERE	NEUTRAL	NEUTRAL	MODERATE	MODERATE	MODERATE	NEUTRAL	NEUTRAL	NEUTRAL	NEUTRAL
Heart failure / Edema	USE WITH CAUTION IN CHF	NEUTRAL	NEUTRAL	NEUTRAL	NEUTRAL	MILD / MODERATE CONTRA-INDICATED IN CLASS 3,4 CHF	NEUTRAL	NEUTRAL	NEUTRAL UNLESS WITH TZD	NEUTRAL
Weight Gain	BENEFIT	NEUTRAL	BENEFIT	MILD	MILD	MODERATE	NEUTRAL	NEUTRAL	MILD TO MODERATE	BENEFIT
Fractures	NEUTRAL	NEUTRAL	NEUTRAL	NEUTRAL	NEUTRAL	MODERATE	NEUTRAL	NEUTRAL	NEUTRAL	NEUTRAL
Drug-Drug interactions	NEUTRAL	NEUTRAL	NEUTRAL	MODERATE	MODERATE	NEUTRAL	NEUTRAL	NEUTRAL	NEUTRAL	NEUTRAL

Rodbard HW, et al. *Endocr Pract.* 2009;15(6):540-559. Copyright © 2009 AACE.

Case Study James: Current Therapy Metformin 1000 mg po Twice/Day

- What treatment change would you recommend next for this patient?
  1. Do nothing
  2. Add SU
  3. Add TZD
  4. Add GLP-1 agonist
  5. Add DPP-4 inhibitor
  6. Add α-glucosidase inhibitor
  7. Add basal insulin

Case Study James

- If SGLT2 inhibitors were available, would it be a good therapeutic option in this patient?

Review of Emerging Data on SGLT2 Inhibitors

Clinical Evidence for SGLT2 Inhibition in Diabetes

- SGLT2 inhibition:
  - Novel mechanism of action independent of insulin
  - Results in glucosuria and a decrease in A1C, FPG,[1,2] and PPG[3]
  - Decreases FPG, evident within 1 week[1,2]
  - Is effective as monotherapy and as add-on to other oral agents and insulin
  - Is associated with weight loss and a decrease in BP
- Hypoglycemia generally is not different from placebo

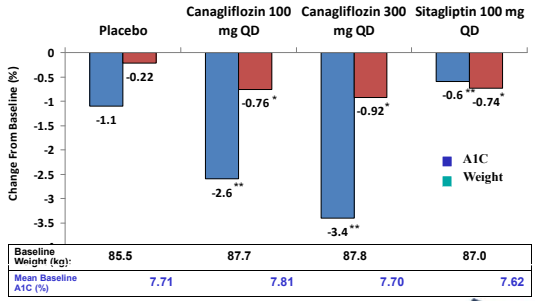
1. Ferrannini E, et al. *Diabetes Care.* 2010;33(10):2217-2224.
2. Bailey CJ, et al. *Lancet.* 2010;375(9733):2223-2233.
3. Wilding JP, et al. *Diabetes Care.* 2009;32(9):1656-6162.

SGLT2 Inhibitors in Development

- NDA submitted
  - Dapagliflozin (BMS-512148)
    - FDA response letter January 12, 2012
    - Additional clinical data to assess benefit-risk profile requested
- Phase III
  - Canagliflozin (JNJ-28431754)
  - Empagliflozin (BI 10773)
  - Ipragliflozin (ASP-1941)
- Several other agents in phase II

Bristol-Myers Squibb. http://www.bms.com/news/press_releases/pages/default.aspx. Published January 19, 2012. Accessed March 29, 2012.
Chao EC, Henry RR. *Nat Rev Drug Discov.* 2010.

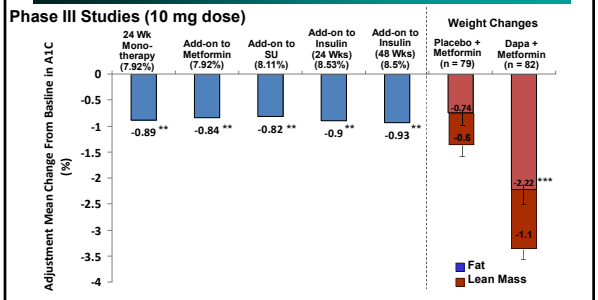
Canagliflozin: A1C and Weight Changes at Week 12



P ≤ 0.001 vs. placebo. ** *P* ≤ 0.01. Phase IIb study. Patients on background metformin. Canagliflozin is not FDA approved

Rosenstock J, et al. Presented at: 46th Annual Meeting of the European Association for the Study of Diabetes; September 20-24, 2010; Stockholm, Sweden. Abstract 873.

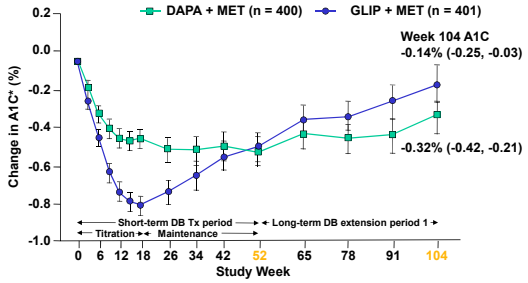
Dapagliflozin*: Reductions in A1C and Weight Changes



Dapagliflozin is not FDA approved; $^{**}P \leq 0.0001$; $^{***}P < 0.0001$ vs placebo

Bristol-Myers Squibb, AstraZeneca. Background document dapagliflozin: US Food & Drug Administration endocrinologic & metabolic advisory committee. Published June 13, 2011. Jennings A, et al. Presented at: Endocrinologic and Metabolic Drugs Advisory Committee Meeting. Bristol-Myers Squibb, AstraZeneca. July 19, 2011.
Bolinder J, et al. *J Clin Endocrinol Metab.* 2012;97(3):1020-1031.

Durability in Glycemic Efficacy Seen in 2-Year Trial vs. SU



DAPA=Dapagliflozin; Dapagliflozin is not FDA approved.

Nauck M, et al. Presented at: 71st Scientific Sessions of the American Diabetes Association; June 24-28, 2011; San Diego, California. Abstract 40-LB.

Potential Safety Considerations With SGLT2 Inhibitors

- Evidence reveals
  - Urinary track infections
  - Genital infections
- Questions
  - Breast and bladder cancer?
  - Intravascular volume depletion due to osmotic diuresis?
  - Drug-drug interactions?
  - Nephrotoxicity?
- Evidence does not demonstrate
  - Electrolyte imbalance
  - Increased risk for hypoglycemia
  - Nocturia

Perspectives on SGLT2 Inhibition

Potential Advantages	Concerns
• Once-daily administration	• Polyuria
• Decreases both FPG and PPG	• Diuretic effect
• Weight loss (50 g urine glucose = 200 kcal/day)	– Hypotension
• Low risk of hypoglycemia	– Dehydration
• Blood pressure lowering	– Hypovolemia
• Effect independent of insulin secretion or insulin resistance	• Electrolyte disturbances
• Use with any other Rx-T1D, T2D, ? pre-diabetes	• Bacterial urinary tract infections
	• Fungal genital infections
	• Unexpected effects-not yet known

Summary

- Diabetes rates continue to increase
- Treat patients early and aggressive
  - Achieving A1C goals with intensive therapy has benefit
  - Glycemic goals should be individualized
  - Lifestyle changes + metformin
  - Monitor and titrate pharmacological therapy
- New therapeutic target
  - Kidney makes an important contribution to normal glucose homeostasis
  - SGLT2 plays a critical role in glucose reabsorption and could be an important treatment target in diabetes

Post-Test

For T2DM patients with no cardiovascular disease, what is your maximum target A1C?

1. < 6%
2. ≤ 6.5%
3. < 7%
4. ≤ 7.5%
5. < 8%

The primary mechanism of lowering glucose by SGLT2 drugs is:

1. Increasing insulin secretion
2. Decreasing hepatic glucose production
3. Preventing renal glucose reabsorption
4. Improving insulin sensitivity
5. Increasing glucose update

Potential benefits of the SGLT2 inhibitors in addition to glucose lowering include:

1. Blood pressure lowering
2. Reduction in LDL-C
3. Weight loss
4. Blood pressure lowering + weight loss
5. All of the above

Autism Update

San Diego
Academy of
Family Practice

June 23, 2012

Stephen Camarata, PhD,

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John F. Kennedy Center for Research on Human Development

Vanderbilt University School of Medicine

Professor,

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Collaborators: Mark Wolery, PhD, Ann Kaiser, PhD, Sasha Key, PhD Mark Wallace, PhD, John Gore, PhD, Paul Yoder, PhD, Michelle Robinson, OTL, Mary Camarata, CCC-SLP, Joi Mitchell, CCC-SLP, Terrie Gibson, PhD, Jessica Ambrose, CCC-SLP, Amy Warren, Heather Gillum, PhD

Robert Koegel, PhD & Lynn Koegel, PhD
UCSB Koegel Autism Insititute

Support: NIDCD, Institute for Educational Sciences (IES), Scottish Rite of Nashville, TN

Presentation Outline

- What is Autism today?
- What is ASD today?
- The Problem of Spontaneous Recovery in ASD
- Treatment Perspectives: Questionable Practices
- Treatment Perspectives: Evidence Based Practices

Diagnostic Challenge: Identifying Children with Autism and Autism Spectrum Disorders

ASD is NOT Autism

- "About 1 in 88 children has been identified with an autism spectrum disorder (ASD) according to estimates from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network."
- "ASDs are almost 5 times more common among boys (1 in 54) than among girls (1 in 252)."

CDC Press Release April 19, 2012

Does this Mean that 1 in 55 Boys will Grow up as “Rainmen?”

Does this Mean that 1 in 55 Boys will Grow up as “Rainmen?”

From CDC Report

“The proposed revised diagnostic criteria for Autism Spectrum Disorder would combine three subgroups currently under the DSM-IV-TR heading of Pervasive Developmental Disorders into one category and might require a child to display more pronounced symptoms to receive a diagnosis.”

And…

- "The pooled Relative Risk was 1.95(p \ 0.001) showing that AD diagnostic stability was [significantly] higher than PDD-NOS. When diagnosed before 36 months PDD-NOS bore a 3-year stability rate of 35%." Rondeau et al 2010 (JADD)
- Note: The stability of AS was greater than 90%!

So…

- ASD stability: less than 35%
- Autism stability: greater than 90%

Finally…

- prevalence estimates are13 per 10,000 for AD and 20.8 per 10,000 for PDD-NOS (Fombonne 2005).
- But, all of these were pooled into "ASD" for the CDC estimates

.

Bottom Line

- Autism and Autism Spectrum are on the rise!
- Rate is likely to "decrease" under new criteria, but that won't mean society is "curing" ASD
- ASD that is not "classic autism" has a relatively high recovery rate, in some cases WITHOUT intervention

For Intervention

- Untreated recovery creates culture of "superstitious" cures
- If a 24 month old isn't using words, but has typical comprehension and no speech disorders
- The untreated "recovery" rate ranges from 50% to 70%

Kanner

He opposed "habit to dilute the original concept of infantile autism by diagnosing it in many disparate conditions which show one or another isolated symptom" of autism.

"Almost overnight, the country seemed to be populated by a multitude of autistic children," he said.

Kanner, L. (1965). Infantile Autism and the Schizophrenias. Behavioral Science, Vol. 10, p. 413

ASD (PDD-NOS, ASPERGER) versus PDD-Autism

- Treatment Challenge: Clinical Trials With a Heterogeneous Condition, and in the case of some ASD, LOW STABILITY
- Clinicians want to help!
- Need for fair comparison groups

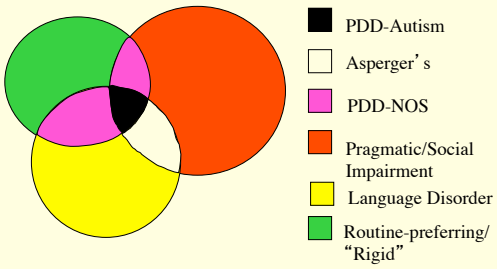
The Lancet, June 2010

- "At the same time, today's study exemplifies the complexity of attempting to detect change in samples of young children with such a heterogeneous condition. There are very few positive published trials in autism, for behavioural interventions, traditional pharmaco- therapy, or complementary/alternative therapies."

What Is Autism?

Why Does this Matter?

The domains of ASD (Folstein)



The Role of Speech and Language in Differential Diagnosis of Developmental Disabilities

DSM Diagnostic Process

Language Related
Conditions in Toddlers

Delayed Onset of Language

- Nonclinical
- Speech Disorder
- Language Disorder
  - Expressive
  - Mixed Expressive-Receptive
- Phonological Disorder
- Pervasive Developmental Disorder (Includes Autism, PDD-NOS, Asperger)
- Cognitive Impairment (Mental Retardation)

PDD-AUTISM

- Qualitative Impairment in Social Interaction
- Qualitative Impairment in Communication
- Restrictive/Repetitive and Stereotyped Behavior
- Delays or Abnormal Functioning (onset prior to 3) in: Social Interaction, Language, Symbolic Play

PDD-NOS

- Meets basic PDD criteria
- Does NOT fit into another PDD category OR into another DSM-IV category (e.g. mixed expressive-receptive language disorder)
- Displays some of the characteristics of Autism, but not all
- Example: Language Disorder PLUS stereotopy, but is social verabally and nonverbally
- A Broad, not well defined category
- Slated for Removal in DSM-V

Note: Mixed Expressive/ Receptive Language Disorder

- Lack of Verbal Social Interaction
- Lack of Verbal Communication
- Use of Routines to Compensate for Reduced Comprehension
- Will often Receive "ASD" score on ADOS and CARS-2

Nonclinical Late Talking

- Language Growth without Intervention (Whitehurst et al. 1992; Paul, 1996; Law, 2002)
- Early Strength in Analytical Abilities
- Dominance of Spatial-Analytical Skills
- Nonverbal Cognitive Abilities in typical range
- No Other Conditions (e.g. phonological disorder, receptive language disorder)

Asperger Syndrome

- Meets the broad PDD classification
- Normal Grammar
- ***Not late talking***
- Normal Broad Cognitive Abilities
- Displays behavioral and some social characteristics of Autism
- Slated for Removal in DSM-V

Vaccines, Autism and Treatment

CNN January 5, 2011

- **Retracted autism study an 'elaborate fraud,' British journal finds**

"I do believe sadly it's going to take some diseases coming back to realize that we need to change and develop vaccines that are safe. If the vaccine companies are not listening to us, it's their f___ing fault that the diseases are coming back." http://www.time.com/time/health/article/0,8599,1888718,00.html#ixzz1qFAZnfv9.

Into this void: Autism "Treatments"

- Example: Secretin
- Example: Defeat Autism Now (DAN)
- Example: Facilitated Communication

Secretin

- Digestive Hormone
- Promoted as "Cure" for Autism
- Clinical Trial Discontinued Early

DAN

DAN

- Chelation as "detox" for mercury in vaccines (thimerisol removed from vaccines more than decade ago)
- Vitamins (B12 and EFA)
- Gluten Free Diet
- Patient Resource: Defeating Autism: a Damaging Delusion (Fitzpatrick, 2008)

Facilitated Communication

- Augmentative Communication with Facilitator
- Hailed as "Breakthrough"
- False Charges of Abuse
- Scientific Studies Showed Hoax/Facilitator Source of Message

Still Practiced
Autism National Committee

- The benefit of FCT in leading to FC as an acceptable and valid form of AAC has been established…
- *www.autcom.org/articles/PPFC.pdf (2008)*

Interactive Metronome

- Marketed as a treatment for autism
- Focuses on "tapping" and "rhythm" as treatment
- Use beats and hand or foot sensor
- Does not address core autism symptoms

Hyperbaric Therapy

- Hyperbaric Chamber
- Infuse oxygen into neural system
- Claim: Increases “myelin”
- No Evidence

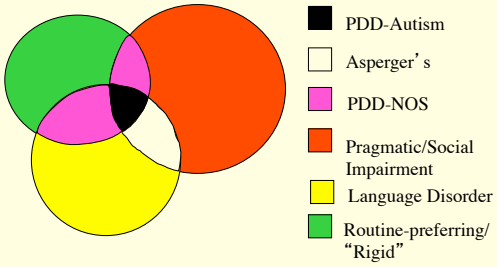
What Does Work?

- No Magic Bullets
- No Autism Drug, but medication can target specific symptoms such as anxiety, hyperactivity (individualized)
- Behavioral Intervention (individualized)
- Hard work in a supportive, positive setting (such as Glenwood!)

Matching Children to Treatments

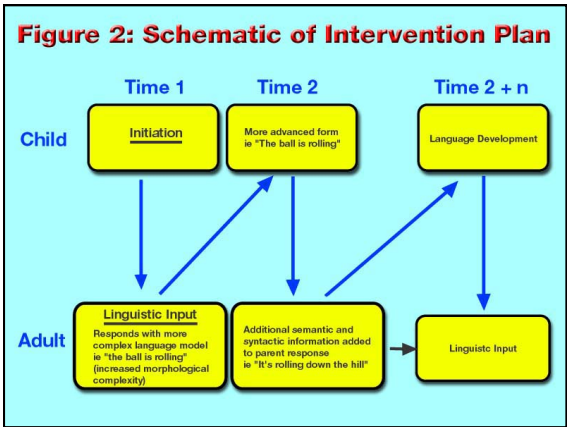
No one treatment will apply to all children

The domains of ASD (Folstein)



Pivotal Response Training

- Koegel and Koegel
- Approach rather than didactic "package"
- See Koegel, Koegel & Camarata, JADD 2011



Diagnostic Process: What is Interfering with Transactions?

Potential Breakdowns

- Attention
- Memory
- Rate of Learning
- Social Interaction
- Hyperactivity
- Motor Skills
- Sensory Skills (e.g. Hearing)

Research Goal: Discovering Which Treatments Are Needed to Gain Access to Learning Transactions

Treatment Process: What Should be Taught for a Child to Access Transactions?

What Level of Support is Needed for a Child to Learn?

Figure 1: Schematic of Intervention Plan

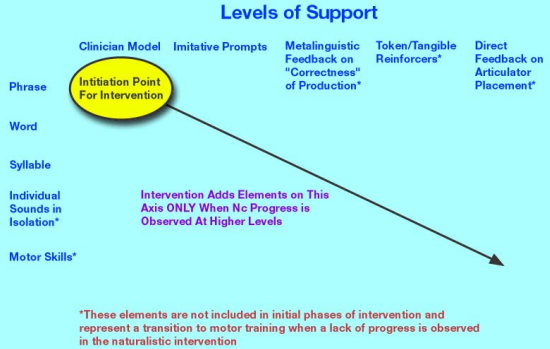
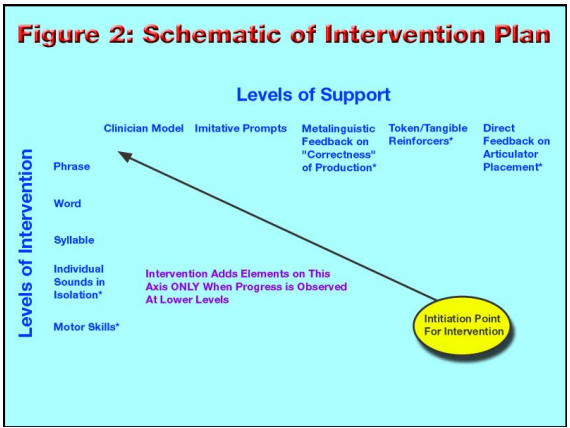


Figure 2: Schematic of Intervention Plan



Sensory Integration Study

- Weighted Vests
- Deep Pressure
- Swinging
- Trampoline
- Brushing
- Auditory Integration

Note

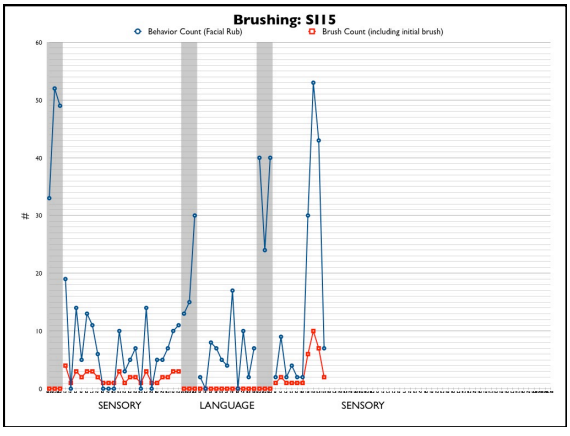
- Weighted Vest Discontinued
- Meta Analysis in Literature Showed No Benefit for Weighted Vest
- Weighted Vest Proponents Now Need to Provide Evidence to Support Implementation

Important Considerations

Exercise increases learning (jogging, swimming)

Many Sensory Activities are FUN and motivating

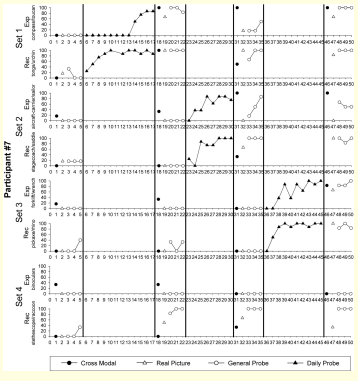
Is it engagement or sensory processing?

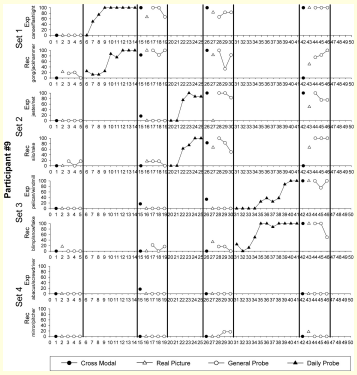


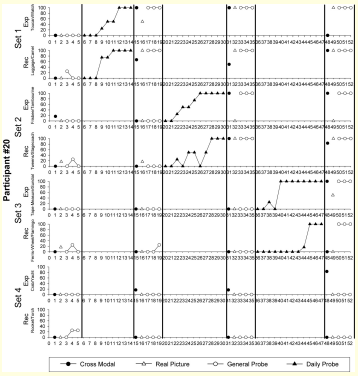
Why is Receptive Language Important in Autism?

Implications

- Social Skills
- Overselectivity (Camarata et al 2009)
- Behavior Regulation
- Impact on "Stores of Acquired Knowledge"
- Lack of Intervention Studies (Focus on Expressive Skills with assumption of Cross-Modal Generalization)




Participant #9
Set 1
Set 2
Set 3
Set 4
Cross Modal
Real Picture
General Probe
Daily Probe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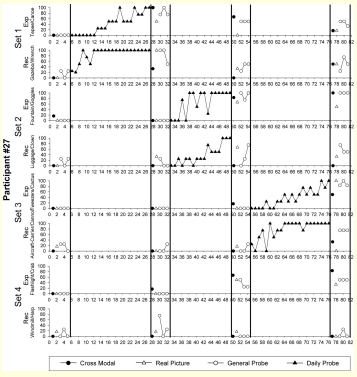
Set 2
Set 3
Set 4
Cross Modal
Real Picture
General Probe
Daily Probe

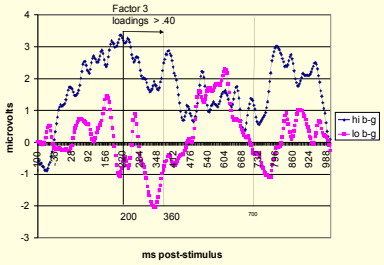

Participant #27
Set 1
Set 2
Set 3
Set 4
Cross Modal
Real Picture
General Probe
Daily Probe

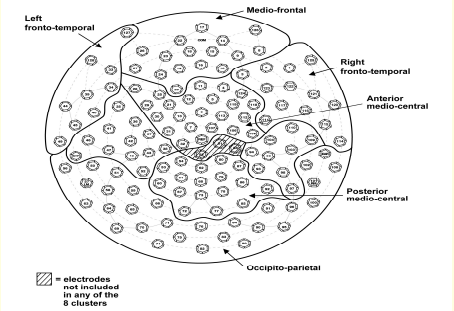
Preliminary Conclusions

- Teaching Words results in Word Learning
- Limited Cross Modal Generalization
- Expressive Does NOT Automatically Generalize to Receptive and Vice Versa

Neuro-Imaging

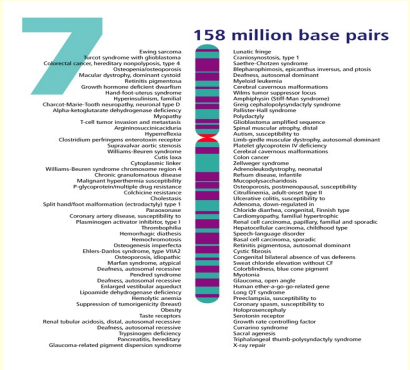
- Does Auditory Processing Efficiency Predict Response to Language Intervention?
- Interactive
- Didactic
- Hypothesis: Relatively better APE will be associated with higher growth in Interactive





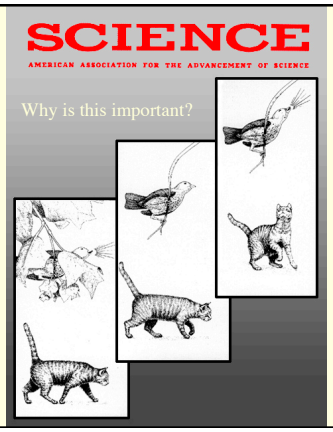
Genetics

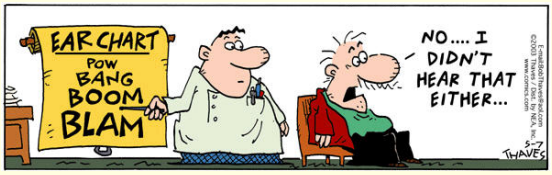
- Are there genes or combinations of genes that predict:
- 1. Assignment to ASD severity categories (current studies collapse all into "ASD")
- 2. Response to Treatments (e.g., as in pharmacological studies)



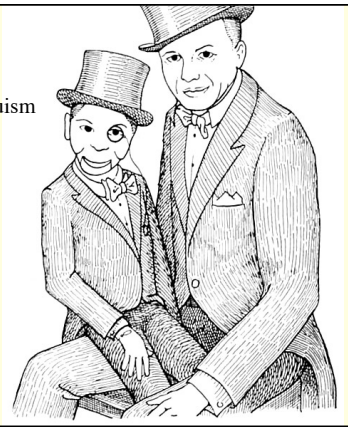
Multisensory Processing

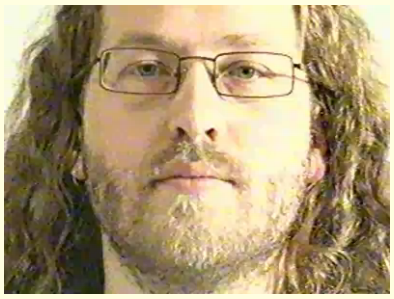
- Not Sensory Integration
- Not "Sensory Processing Disorder"



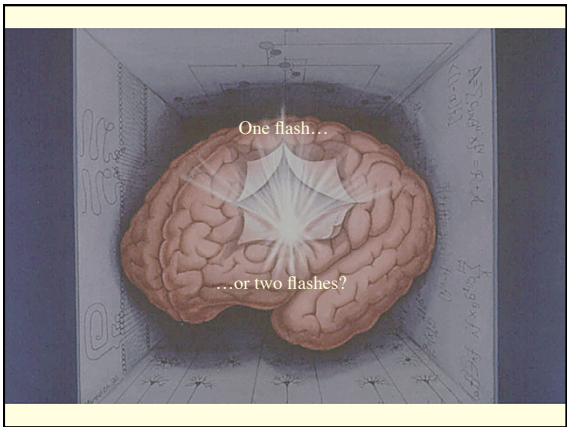


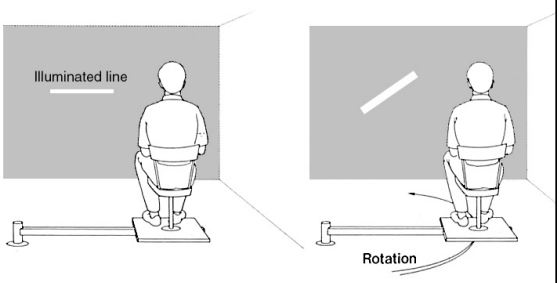
Ventriloquism





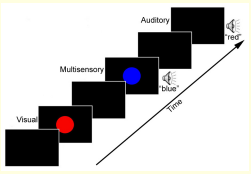
The McGurk Effect

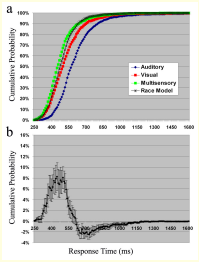


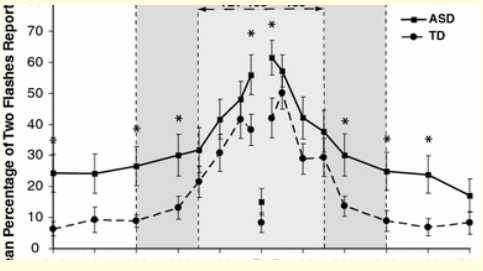


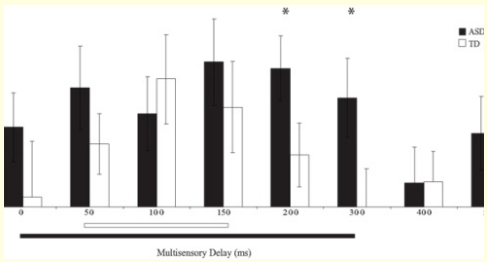
Vestibular influences on vision

Multisensory facilitation (i.e., speeding) of target (object) identification









Implications

- Asynchronous Auditory and Visual Inputs
- Impact of APE?
- Impact on Comprehension?
- Does SIT impact this asynchrony?

IUD Insertion Workshop

Marianne McKennett, MD
San Diego Academy
June 24, 2012

IUD Insertion Techniques

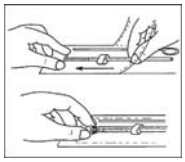
Paragard – Copper
Mirena - Progestin

IUD Insertion

- At any time during menstrual cycle
- Patient Selection
- Documentation
  - Negative pregnancy test on day of insertion
  - Pelvic exam
  - Negative test for gonorrhea and chlamydia
- Routine antibiotics unnecessary, including for endocarditis prophylaxis
- Risks, benefits, alternatives discussion
- NSAID one hour prior

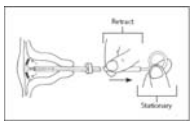
Copper IUD Insertion

- Bimanual exam to determine position of uterus
- Fold arms of IUD into insertion tube
- Place speculum
- Cleanse cervix with antiseptic
- Place tenaculum



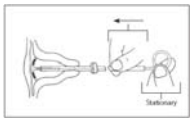
Copper IUD Insertion

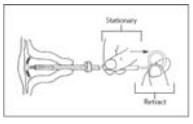
- Sound uterus- 6 to 9 cm adequate
- Align flange with IUD arms and set distance
- Place white inserter rod into insertion tube
- Insert IUD until flange is against cervical os
- Pull inserter tube back, keeping rod stable



Copper IUD Insertion

- Advance inserter tube slowly
- Remove inserter rod, tube and tenaculum
- Cut string to 3cm





Mirena IUD Insertion

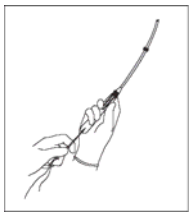
- Bimanual exam to determine position of uterus
- Insert speculum
- Cleanse cervix with antiseptic
- Place tenaculum
- Sound uterus

Mirena IUD Insertion

- With sterile gloves, release threads from slider
- Position slider at top
- Ensure arms are horizontal

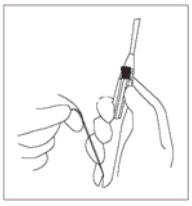
Mirena IUD Insertion

- Pull on threads to draw IUD into insertion tube



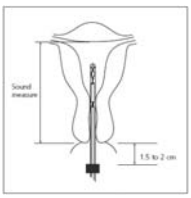
Mirena IUD Insertion

- Fix threads tightly in the cleft at the end of the handle



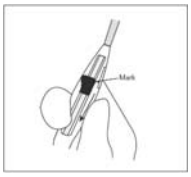
Mirena IUD Insertion

- Set flange to depth measured by the sound
- Insert IUD, holding slider firmly at top of handle
- Advance until flange is 1.5 to 2 cm from os



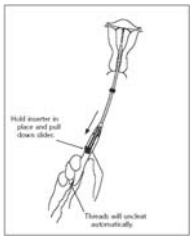
Mirena IUD Insertion

- To release arms of IUD, pull slider back to raised horizontal line on the handle
- Advance inserter until flange against cervix



Mirena IUD Insertion

- Release IUD by pulling slider all the way down, holding inserter in place
- Threads will release
- Remove inserter
- Cut threads to 2-3cm



IUD: Patient Education

- Additional non-hormonal contraception if IUD placed during luteal phase – after Day 5 LMP (condoms x one week)
- Verify position of IUD after each menstruation
- Call MD if unable to locate strings
- Follow-up appointment after next menstruation
- Cramping common – relief with nsaid's

IUD Troubleshooting

- IUD threads missing?
  - Pregnancy test
  - Cytobrush
  - Radiography or ultrasonography
- Positive pregnancy test?
  - Must rule out ectopic (1/1000 person years)
  - Increased risk of SAB and preterm delivery
  - Remove IUD if strings visible and pregnancy early
- Cervical dysplasia
  - Colposcopy ok, remove for excisional procedure

IUD Removal

- Grasp threads at cervical os with ring forceps and apply traction
- Can't see strings?
  - Try cytobrush
  - Try colposcope for magnification
  - Try special IUD hook to find strings
- If resistance is met, abandon removal

Knee Exam, Injection and Common Problems

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University of California, San Diego

Lee P. Ralph, M.D.
Physician and Partner
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and Family Health Center

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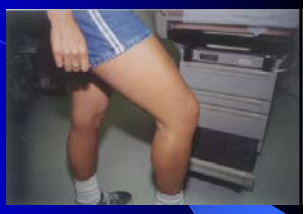
Staff Physician
Smart Center, MCAS Miramar

Introduction

- Functional evaluation of the knee
- Functional anatomy
- Examination
- Injection techniques
- Common Problems

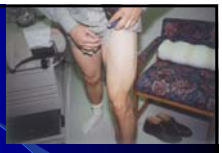
Anatomy

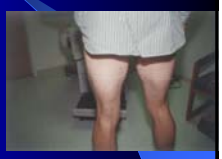
- External anatomy
  - Skin
  - Deformities

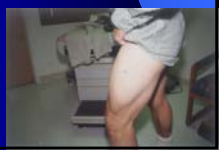


External anatomy

- Muscles
  - Quadriceps
    - Quad tendon, Patellar tendon
  - Hamstring
  - Lateral band

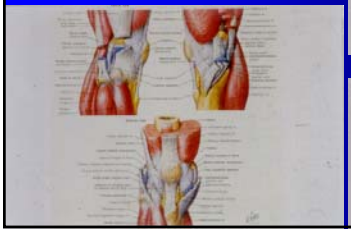


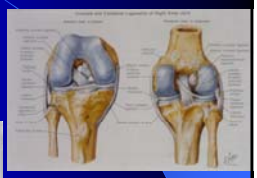


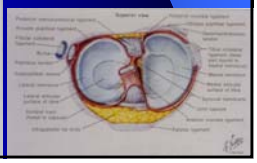


Anatomy

- Muscles
- Bones
  - -Patella
  - -Tibia
  - -Fibula
  - -Femur
- Ligaments
  - MCL
  - LCL
  - -ACL
  - -PCL
- Meniscus
  - -Medial
  - -Lateral

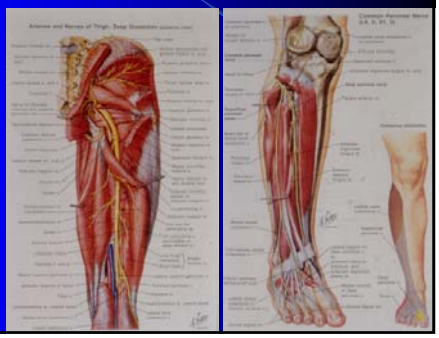






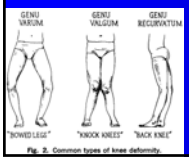
Nerves and Vessels

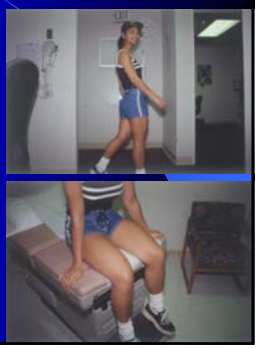
- Vessels
  - Popliteal
- Nerves
  - Tibial
  - Peroneal
  - Sural



Exam

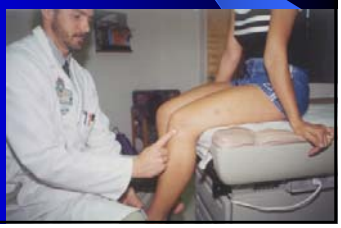
- Inspection
  - Gait
  - Deformity
    - Skin
    - Muscles
    - Bones
    - Effusion





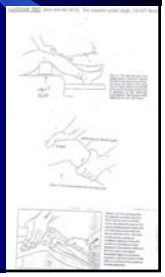
Exam

- Palpation (Sitting)
  - Tibia / Patella
  - Joint Line
  - Ligaments / Tendons

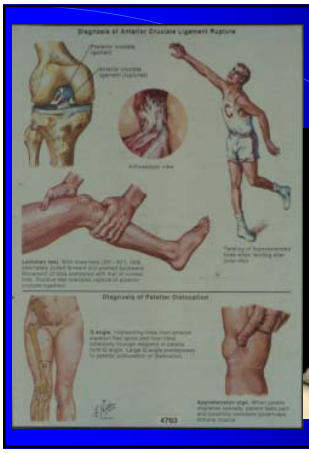


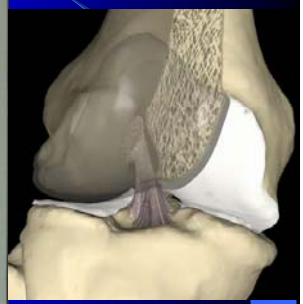
- Range of motion (prone)
  - Extension (heel height difference)
  - Flexion (distance from buttocks)

- Ligaments (tested in 30^{o} flexion)
  - ACL
    - Lachman's
      - vs. Anterior Drawer 90^{0}
    - Pivot shift



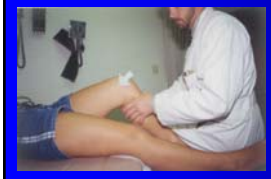
ACL

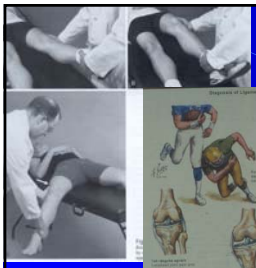


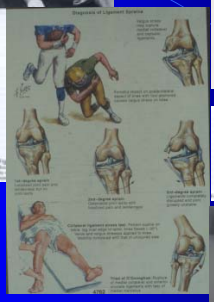


PCL - Quad Active test

Drawer Test / Sag Sign

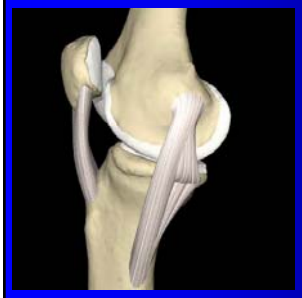


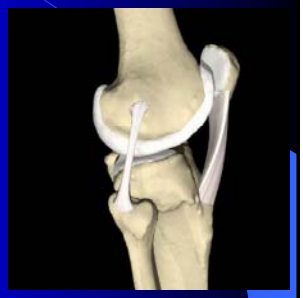


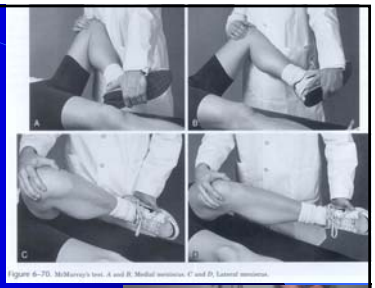


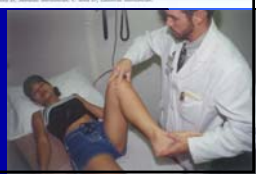
- Ligaments
  - MCL
    - (Valgus stress)
  - LCL
    - (Varus Stress)

MCL LCL



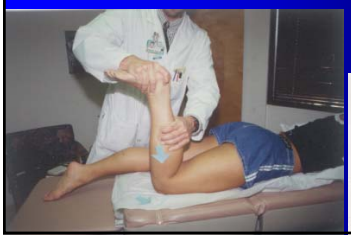


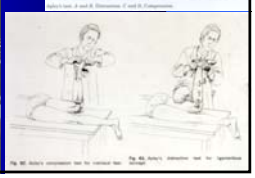




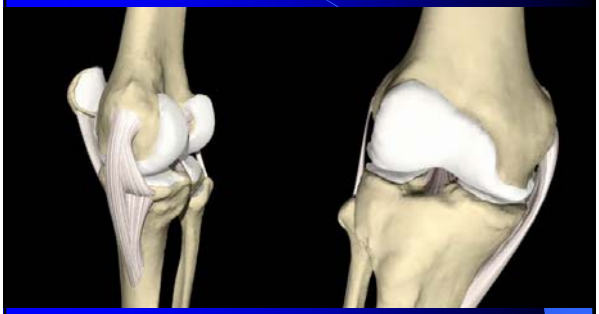
- Meniscus
  - Joint line ttp
  - McMurray's

- Meniscus
  - Apley's
    - compression / distraction

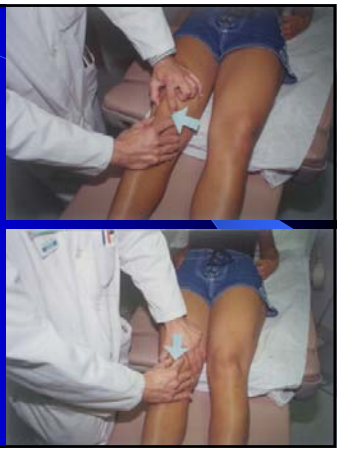




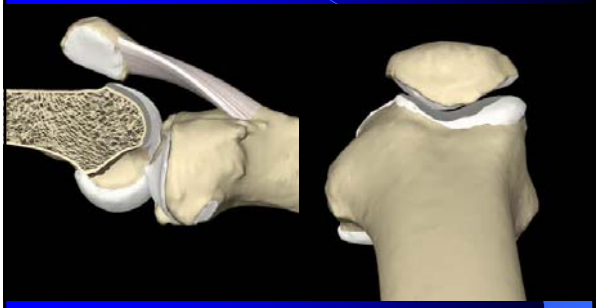
Meniscus Forces



- Patella
  - Mobility / tracking
  - Crepitus
  - Apprehension
  - Grind
  - Inhibition

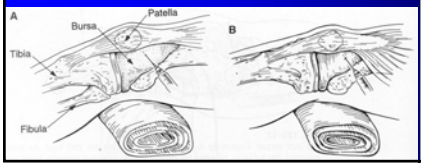


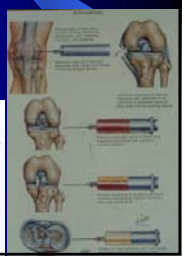
Patellar Motion

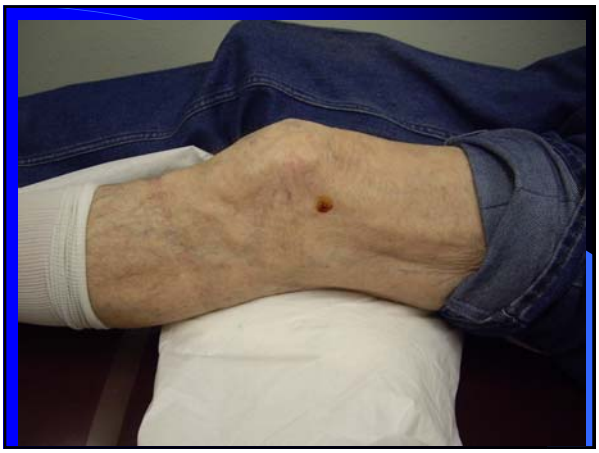


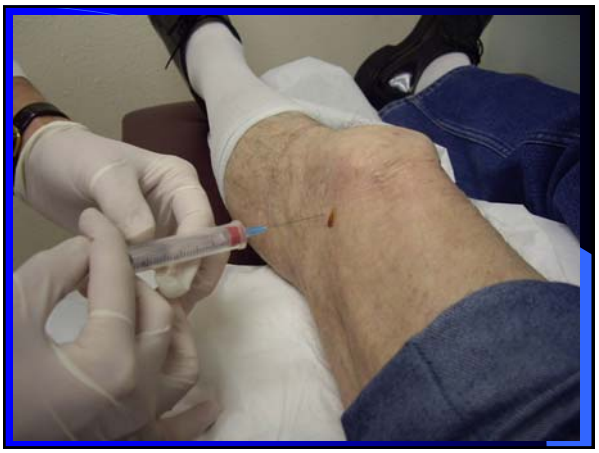
Injection

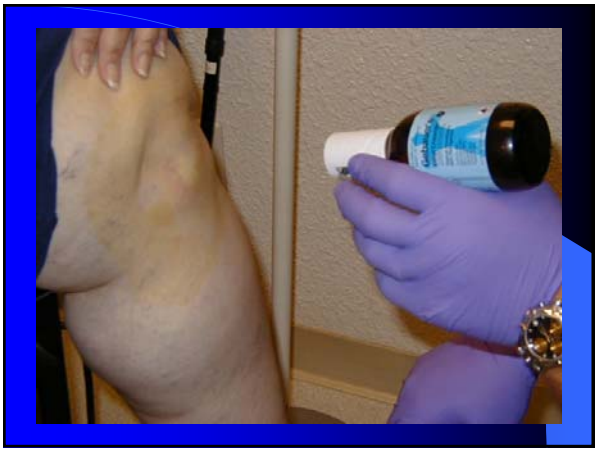
- Approaches
  - Medial (Inferior, Superior)
  - ***Lateral*** (Inferior, ***Superior***)
  - Suprapatellar

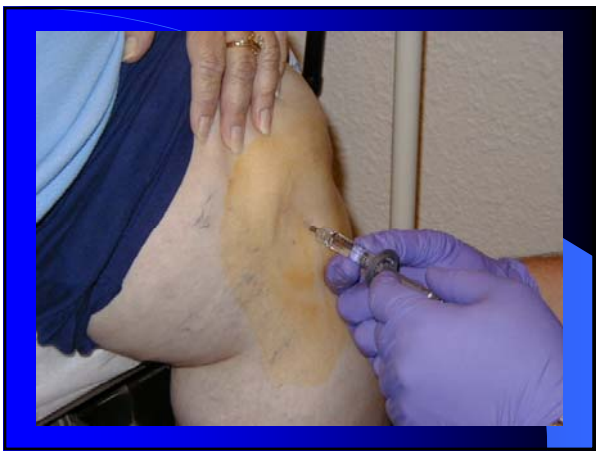


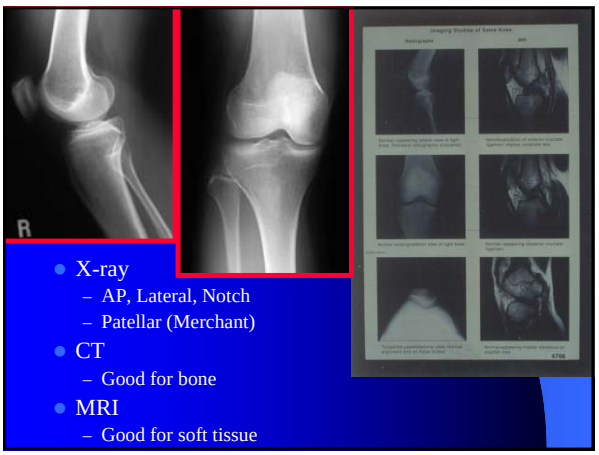











R
X-ray
AP, Lateral, Notch
Patellar (Merchant)
CT
Good for bone
MRI
Good for soft tissue

Shoulder Exam, Injection and Common Problems

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University of California, San Diego

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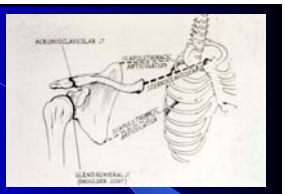
Physician and Partner
San Diego Sports Medicine
and Family Health Center

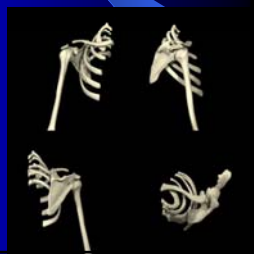
Introduction

- Functionally evaluate the shoulder
- Functional Anatomy
- Examination
- Injection Techniques

Anatomy

- Bones
- Joints, Articulation





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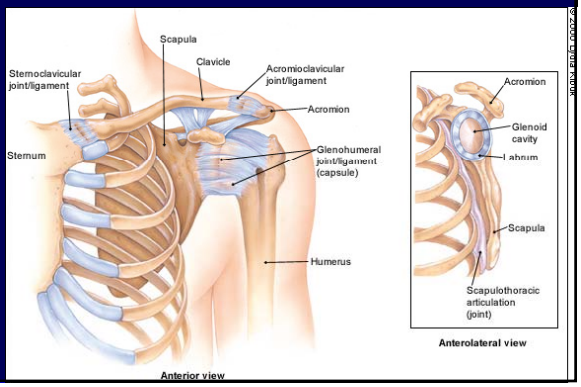
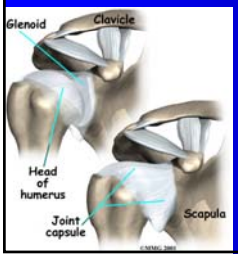


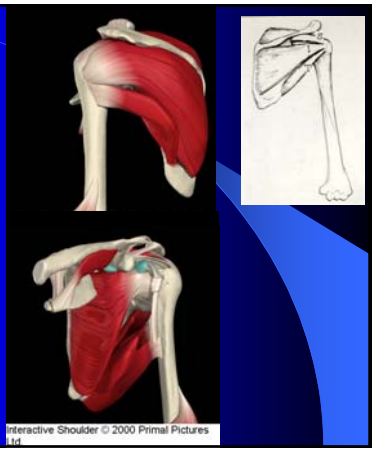
- Capsule
  - Anterior displacement
  - Inferior displacement
  - Posterior displacement

Anatomy



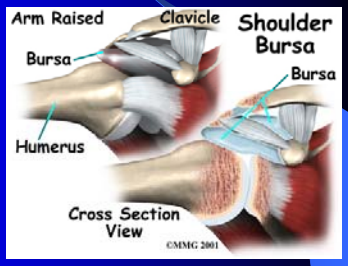
Anatomy

- Rotator cuff
  - Supraspinatus
    -elevation
  - Infraspinatus
    -external rotation
  - Teres minor
  - Subscapularis
    -internal rotation



Anatomy

- Subacromial space is bordered by the coracoid process, acromion and coracoacromial ligament

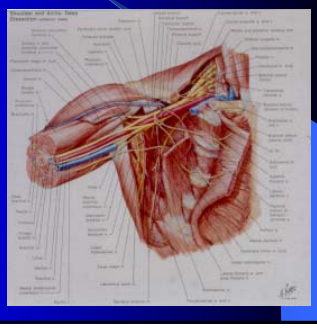


- Contents:
  - Subacromial bursa
  - Supraspinatus tendon
  - Tendon of the long head of the biceps

http://www.orthogastonia.com

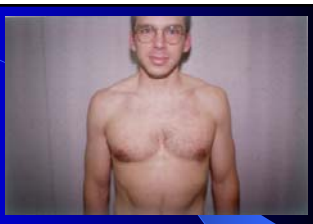
Anatomy

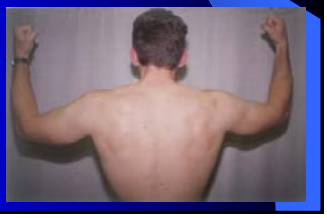
- Nerves
- Vasculature



Examination

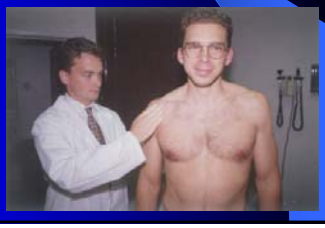
- Observation
  - Deformity
  - Musculature
  - Skin





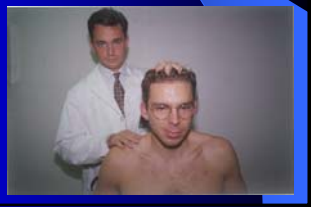
Examination

- Palpation
  - "Know your anatomy"
    - Bony
    - Rotator Cuff
    - Joint
    - Pulses



Examination

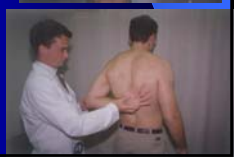
- Range of Motion / Muscle testing
  - Cervical
    - Atlantoaxial compression - Spurling's test



ROM

- Shoulder
  - Passive / Active
    - Elevation (drop arm test) — Supraspinatus
    - E.R. (90º ABD) — Infraspinatus / teres minor
    - I.R. (Spinal Level) — Subscapularis





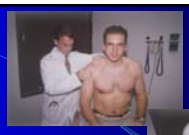
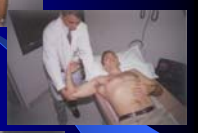
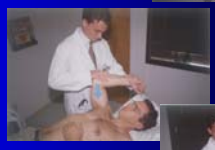
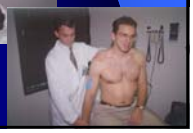
Examination

- Strength
  - Empty can (drop arm test)
  - External Rotation
  - Gerber liftoff



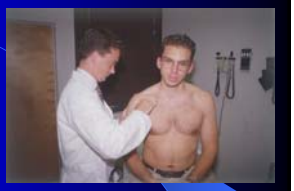
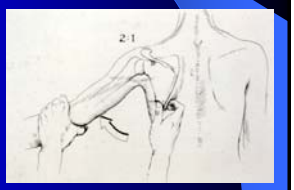
Examination

- Stability
  - Glenohumeral
    - Anterior
      - Load Shift
      - Apprehension / relocation
    - Posterior
      - Load Shift
      - Apprehension
    - Inferior
      - Sulcus sign

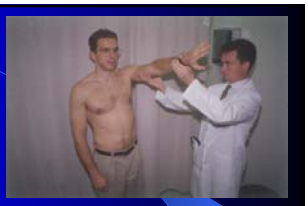
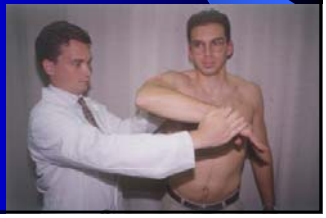
Examination

- Stability
  - AC Joint
    - Inferior humeral displacement
    - Distal clavicle motion
  - Sternoclavicular
    - Medial clavicle motion
  - Scapulothoracic
    - normal rhythm 2:1 ratio

Examination

- Impingement Signs
  - Forward flexion, pronated forearm
  - 90º forward flexion, internal rotation
- Scarf Test


Examination

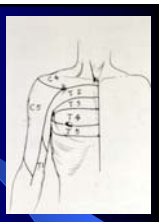
- Labrum tests
  - Clunk test (akin to McMurray's test for knee)
  - Crank test (160º, bent, loaded elbow; IR,ER)

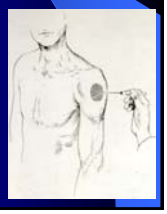

Examination

- Biceps notch
  - Speed's test (straight arm, sup., 60º resist flex)
  - Yergeson's (flex elbow, sup. wrist against reistance, arm to side & elbow at 90º)

Examination

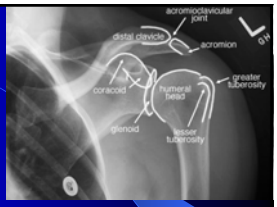
- Neurologic: Reflexes
  - Biceps C_5
  - Brachioradialis C_6
  - Triceps C_7
- Sensation
  - Dermatomes C_4, C_5, T_2
  - Axillary nerve dislocations





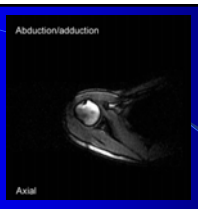
Radiograph

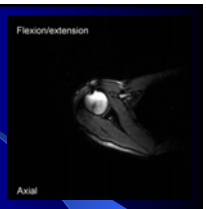
- X-ray
  - Internal / External Rotation
  - True Anterior / Posterior
  - Transcapular "Y" view - dislocation
  - Axillary Lateral - dislocation
  - Outlet view - acromium type
  - West Point view - instability - glenoid
  - Stryker Notch view - instability - Hill-Sachs

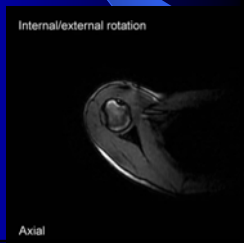


Radiograph

- Arthrograms
  - Good for full thickness RC tear
  - Capsular volume (laxity)
  - Some labral tears
- CT
  - Good for bone
- MRI
  - Good for tissue (rotator cuff)

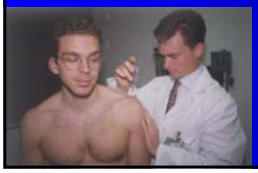


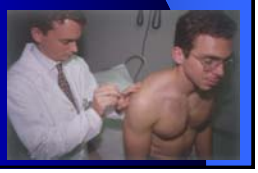




Injection

- Subacromial
  - Posterolateral approach vs others
- Acromioclavicular
- Glenohumeral





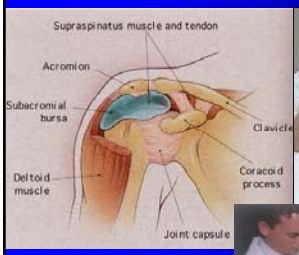
Shoulder Injections Indications

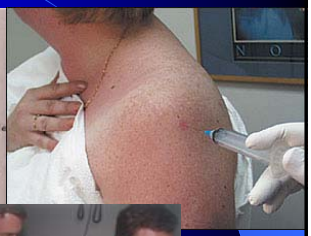
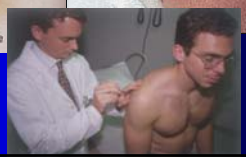
- Subacromial bursa:
  - Subacromial bursitis
  - Rotator cuff impingement
  - Rotator cuff tendinosis
  - Adhesive capsulitis
- Glenohumeral Joint:
  - Osteoarthritis
  - Adhesive capsulitis
  - Rheumatoid arthritis
- Acromioclavicular joint:
  - OA
  - Osteolysis of the distal clavicle

Subacromial Bursa Injection

- Three approaches
  - Anterior - not recommended
  - Lateral
  - Posterolateral

Subacromial Bursa Injection



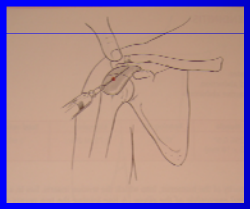
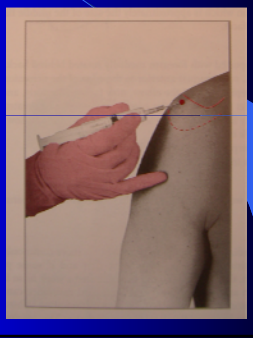



Subacromial Bursa Injection

- *Lateral approach*
  - The lateral edge of the acromion is palpated. The needle is inserted at the mid-point of the acromion and angled slightly upwards under the acromion to full length

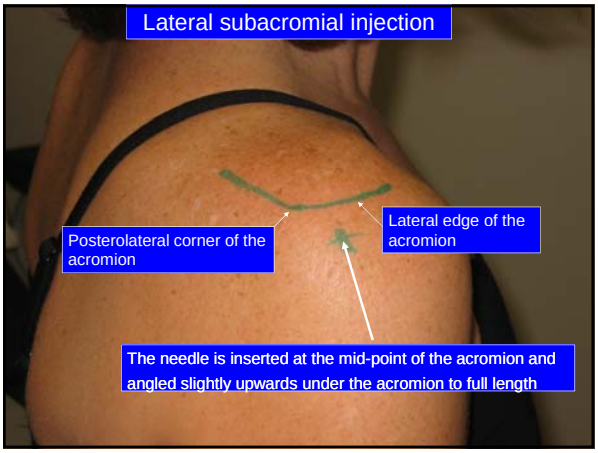
Subacromial Bursa Injection

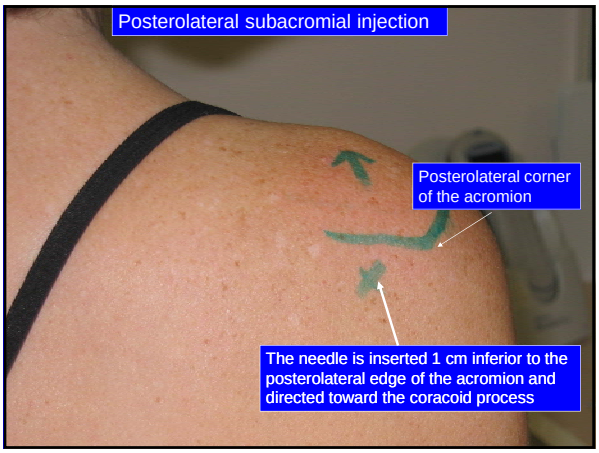
Lateral approach

Subacromial Bursa Injection

- *Posterolateral approach*
  - The distal, lateral, and posterior edges of the acromion are palpated. The needle is inserted just inferior to the posterolateral edge of the acromion. The needle is directed toward the opposite nipple. (coracoid) The material should flow freely into the space without any resistance or significant discomfort to the patient.





GH Joint Injection

- *Anterior Approach*
  - The needle should be placed just medial to the head of the humerus and 1 cm lateral to the coracoid process. The needle is directed posteriorly and slightly superiorly and laterally. If the needle hits against bone, it should at a slightly differen

GH Joint Injections

- *Posterior Approach.* The needle should be inserted 1 to 2 cm inferior to the posterolateral corner of the acromion and directed anteriorly. An assistant pulling down on the arm and externally rotating the shoulder helps to open up the joint space.

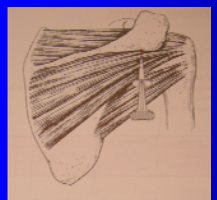
** Only attempt a GH joint injection if you have seen it done and feel very comfortable

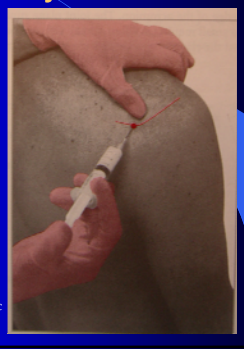
GH Joint Injection

- *Anterior Approach*
  - The needle should be placed just medial to the head of the humerus and 1 cm lateral to the coracoid process. The needle is directed posteriorly and slightly superiorly and laterally. If the needle hits against bone, it should at a slightly differen

GH Joint Injections

Posterior Approach





Saunders, S. Injection Techniques in Orthopaedic and Sports Medicine. 2nd edition. WB Saunders. 2002.

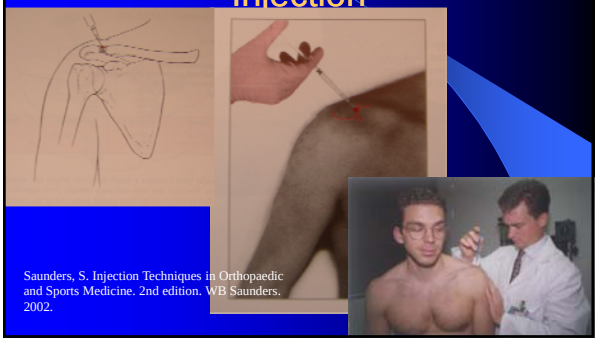
Acromioclavicular Joint Injection

- The AC joint lies about one thumb's width medial to the lateral edge of the acromion
- The joint line runs obliquely medially at approximately a 20 degree angle

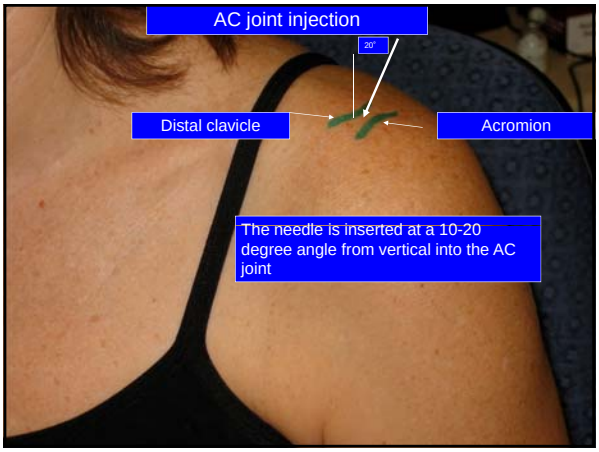
Acromioclavicular Joint Injection

- The AC joint lies about one thumb's width medial to the lateral edge of the acromion
- The joint line runs obliquely medially at approximately a 20 degree angle

Acromioclavicular Joint Injection



Saunders, S. Injection Techniques in Orthopaedic and Sports Medicine. 2nd edition. WB Saunders. 2002.



Acromioclavicular Joint Injection

http://www.fpnotebook.com/OrthoShoulderInjectAC.jpg

http://www.aafp.org/afp/20030315/1271.html

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Depression SAM Preparation
San Diego Academy of Family Physicians
Annual Scientific Assembly
Timothy Munzing, MD - 2012

Learning Objectives
- Review the MC-Family Medicine SAM process
- List risk factors for depression
- Discuss various depression screening tools
- Explain depression management strategies
- Family Medicine & Primary Care:

The Cost to Society
- Major health problem in the U.S.
- 18 million office visits/yr
- 100 million prescriptions/yr
- "Clinical paradox" -- only 1 of 3 patients accurately diagnosed
- Economic costs: $44 billion/yr

Incidence/Prevalence
- Lifetime prevalence: 17 % (10 – 20%)
- 8 million cases of major depressive disorder per year
- Antidepressants are among the most commonly prescribed medications in the U.S.

Risk Factors
- Age: peak age of onset 20-40 yrs
- Gender: female 2 X
- Family history: 1.5 to 3 X
- Stressful life events
- Marital status: divorced, separated, widowed, married vs unmarried?
- Personal history of depression
  - 1 episode - 50% relapse
  - 2 episodes - 75%
  - 3 episodes - 90%
- Postpartum: up to 1 in 10
- Chronic medical illness

Recognition
- Depression: DSM-IV
  5 of 9 Required
- Depressed mood*
- Loss of interest or pleasure*
- Change in sleep
- Change in appetite/ weight

- Low energy/ fatigue
- Psychomotor agitation/ slowing
- Low self-esteem or guilt
- Poor concentration
- Thoughts of suicide or death

Presenting Complaints in Patients with Depression
- "I think I need hormones"
- "My husband thinks I need hormones."
- My wife made the appointment for me"
- "I need a 'check up'" (in a younger male)
- "I need something for stress."

U.S. Preventive Services Task Force
(Screen only when support available to ensure accurate diagnosis, effective treatment and follow-up)

Screening instruments:
- Beck Depression Inventory
- Zung Self-Depression Scale
- Patient Health Questionnaire (PHQ-9)
  - Simultaneous assessment of both DSM-IV depression criteria and symptom severity, and is useful for follow-up
  - Lowest rate of false-positives (highest positive predictive value) in primary care use of instruments for depression
- Center for Epidemiologic Study Depression Screen (CES-D)

2 questions to ask:
- *Over the past 2 weeks have you ever felt down, depressed, or hopeless?*
- *Over the past 2 weeks, have you felt little pleasure or interest in doing things?*
- *Sensitivity 96%* *Specificity 57%*

Depression: Differential Dx
- Adjustment disorder
- Grief and bereavement
- Substance abuse
- Mood disorder due to medications or medical illness
- Dementia/ dementia syndrome
- Other co-morbid psychiatric disorders

Depression: Diagnostic Considerations Once the diagnosis is made:
- Suicide assessment: 4-6 % MDD
- Bipolar depression
- Psychotic depression
- Substance abuse

- Seasonal depression
- Concomitant medical illness
- Concomitant psychiatric illness
- Concomitant medications

Perimenapausal Depression
- Life stress is a stronger predictor of depression during midlife than is menopause
- The loss of ovarian function during menopause is not a major risk factor for the development of depression
- Hormone therapy has not been shown to be an effective treatment for depression in perimenopausal women

Depression and the Elderly
- Patients who are elderly when their first episode of depression occurs have a relatively high likelihood of developing chronic or recurring depression
- Physicians are less likely to correctly diagnose depression in elderly patients than in younger patients
- Treatment of depression in the elderly is more important than in younger patients because the depression is generally more severe
- Strongest risk factor in elderly – death of a spouse

Depression and High Medical Care Utilization
- In patients classified as high utilizers, the incidence of current or past major depressive disorder is twice that of other patients
- High utilizers often have ill defined medical conditions
- Depressed patients classified as high utilizers have worse rates of medical resource utilization compared to those of non-depressed high utilizers

Suicide Risk Factors
- Hopelessness
- Caucasian Race
- Male
- Advanced Age
- Living Alone
- Family History
- Prior Suicide Attempts
- Substance Abuse
- General Medical Illness
- Psychosis
- Ways and Means

Depression and Suicide Attempts
- Men successfully commit suicide at a higher rate than women
- Patients hospitalized for suicidality have a markedly increased lifetime risk of suicide compared to patients managed in an outpatient setting

- Patients with depressive disorders have suicide prevalence rates higher to those of the general population
- Depressed cigarette smokers attempt suicide more frequently than depressed nonsmokers
- Increased subjective assessment of depression by the patient is associated with an increased risk for a suicide attempt

Depression: R/O Bipolar

- *"Have you ever had 4 continuous days when you were feeling so good, high, or "hyper" that other people thought you were not your normal self or you got into trouble?"*
- *"Have you experienced 4 continuous days that you were so irritable that you found yourself shouting at people or starting fights or arguments?"*
- The mean age of onset for major depressive disorder is between the ages of 25 and 35
- The age of onset of bipolar disorder is 6 years earlier on average than the onset of major depressive disorder

Dysthymic disorder

- Dysthymic disorder is less prevalent than major depressive disorder in primary care settings
- Psychiatric comorbidity is common in patients with dysthymic disorder
- Dysthymic disorder is no less likely than major depressive disorder to lead to significant functional impairment

Depression and General Medical Conditions

- Chronic medical illness is a risk factor for major depressive disorder
- Depression is a significant side effect of a wide range of medications used to treat medical illnesses
- Depression can adversely affect the doctor-patient relationship
- Patients with aversive symptoms such as pain are at increased risk for developing depressive disorders
- Patients with depression may exhibit an increase in maladaptive interpersonal behaviors, making collaboration with the physician more difficult
- Patients with depression have higher rates of adverse health-risk behaviors when compared to non-depressed patients
- The medical cost of a chronic medical illness is increased by comorbid depression

Depression and Myocardial Infarction

- Depression has not been shown to be an etiologic factor in the development of ischemic heart disease
- The depression will most likely not resolve as the patient recovers from the myocardial infarction
- Major depression is a significant predictor of short-term mortality from ischemic heart disease

- Major depression is a significant predictor of long-term mortality from ischemic heart disease
- Psychosocial interventions have been shown to be effective in improving depression in myocardial infarction survivors

Comorbid depression and coronary artery disease (CAD)
- Patients with CAD and comorbid depression have a twofold to threefold increased risk of future cardiac events when compared to non-depressed controls
- Comorbid depression is associated with greater platelet activation
- Possible Mechanisms
  - abnormalities in platelet aggregation
  - cardiac rhythm disturbances
  - reduced compliance with medical recommendations

Depression and Diabetes
- The presence of type 1 or type 2 diabetes doubles the likelihood of comorbid depression in adults
- In patients with comorbid depression and diabetes mellitus, the level of dietary compliance is inversely related to the severity of depressive symptoms
- Health care costs for patients with diabetes mellitus and comorbid depression are higher than the health care costs of non-depressed diabetic patients

Depression with Alcohol and Drug Abuse
- Symptoms that resemble primary mood and anxiety disorders can result from alcohol and substance intoxication and withdrawal
- Treatment for mood and anxiety disorders in patients with substance use disorders should not be withheld pending a period of sobriety

Screening Pregnant and Post-Partum Patients
- The onset of postpartum depression frequently occurs before the patient is seen for a routine 6-week postpartum visit
- Screening for depression in post-partum patients is effective
- Significant dysphoria that arises more than 2 weeks after delivery should raise a strong suspicion for depression

General Management Issues
Components of practice redesign that have been shown in studies to contribute to improved outcomes in patients with depression include:
- Patient self-management support
- A functioning interface to mental health specialists that ensures access for consultation, shared management, and referral
- Case management that functions to ensure that patients are monitored regularly for treatment adherence, status of their illness, and needed changes in treatment

Depression Management

- Pharmacotherapy
- Talk Therapy
- Exercise
- Psychotherapy and antidepressant medication are equally effective in patients with mild depression
- Combining psychotherapy with antidepressant medication is likely to be more beneficial than either treatment alone in patients with severe depression

Components of successful depression disease management programs

- A system to track patients with depression
- Patient education strategies
- The use of nurses or other care coordinators to help maintain contact with and educate patients
- Collaboration with mental health professionals

Depression Management

- Pharmacotherapy:- 50 – 70% effective
- Proven effectiveness in patients with Major Depressive Disorder
- Dysthymia

Antidepressant Therapy Equally Effective

- SSRI's
- Cyclics: tricyclics and tetracyclics (maprotiline, amoxapine)
- MAOI: phenelzine (Nardil), tranylcypromine (Parnate), isocarboxacid (Marplan)
- Dopamine antagonists (Bupropion)
- SNRI's (Venlafaxine)

Specific Medication Selection Factors:

- prior response to agent
- anticipated side effects
- concomitant illness
- potential for drug interactions
- family history of response
- patient desire
- cost

SSRIs

- 1st line therapy -- ease in prescribing and superior side effect profile
- Fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram
- Side effects: nausea*, H/A, insomnia*, anxiety/agitation*, sedation, sexual dysfunction (desire, arousal, orgasm) * *May resolve themselves after 10-14 days*

TCAs

- 2nd line therapy
- Side effects: anticholinergic (dry mouth, constipation, urinary retention, blurred vision, confusion & hallucination risk in elderly); orthostatic hypotension; antihistamine (sedation, weight gain); *less a problem with desipramine & nortriptyline*
- Low therapeutic index

Depression: Guide to Use of Antidepressants

- Start at low initial dose, titrate up to target dose over 5 to 10 days
- At 4 weeks, if no or partial response and side effects tolerable, increase dose; if side effects intolerable or no response, switch AD or add adjunctive Rx
- Full therapeutic effect may not be evident for 4 to 6 weeks

Depression: Treatment Strategy

- Treat a minimum of 6 to 8 months after recovery
- Follow-up visits every 1 to 3 months
- When stopping, taper over 2-3 months; if relapse, treat 3 to 6 more months

Depression: Long-Term Treatment

- Multiple episodes – more than 3
- Recurrence within one yr of Rx
- Double depression (MDD+ dysthymia)
- Onset after 60 yrs
- Co-morbid anxiety or substance abuse
- Co-morbid medical disorders worsened by depression

Post-Partum Depression Treatment

- Tricyclic antidepressants can cause anticholinergic effects in the breastfed newborn
- The risk-benefit decision regarding whether to use an antidepressant in a breastfeeding woman rests almost entirely on the severity of the depression and the need for medication, rather than on any known risks to the infant

Early 3rd Trimester Major Depression Treatment

- If she takes an SSRI, her baby might develop a syndrome consisting of irritability, abnormal crying, tachypnea, thermal instability, and poor muscle tone
- There is a small but significant risk of a withdrawal syndrome in newborns if serotonergic antidepressants are taken during the third trimester of pregnancy
- SSRI use in the third trimester has been linked to the development of persistent pulmonary hypertension of the newborn

Paroxetine (Paxil) and pregnancy

- Paroxetine use during pregnancy has been linked to an increased risk of congenital heart malformations
- Paroxetine use in pregnancy has been linked to an increased risk for cleft palate

- Euthymic women who discontinue antidepressant therapy during pregnancy have a fivefold higher risk of relapse over the course of pregnancy compared with women who continue their antidepressant

Perimenopausal female - moderate to severe major depressive disorder
- First line treatment options
- Fluoxetine (Prozac)
- Nortriptyline (Pamelor)
- Venlafaxine (Effexor)
- Desipramine (Norpramin)

Treatment in Elderly
- In mild to moderate depression, the effectiveness of antidepressant medication is roughly equal to that of short-term, focused psychologic therapies
- In general, tricyclic antidepressants have a higher dropout rate than serotonergic agents
- Tricyclic antidepressants should generally not be used in elderly patients because of the higher side-effect related dropout rate compared to serotonergic agents
- Suicide risk is higher in elderly patients when depression is untreated, compared to the risk in untreated younger patients with depression

MAO Treatment of Major Depression
- MAOIs may be more effective than tricyclic antidepressants in patients with atypical symptoms of major depression (hypersomnia, increased appetite)
- MAOIs may precipitate hypertensive crisis when combined with certain foods or medications
- MAOIs are not safe to use in combination with SSRIs
- Partial remission after 8 weeks of treatment – options include:

SSRI Discontinuation Syndrome
- Dysphoria
- Fatigue
- Difficulty concentrating
- Anxiety
- Insomnia
- “Electric shock” sensation in his legs
- “Rushing sensations” in one’s head
- Fluoxetine (Prozac) can be stopped without risk of discontinuation syndrome

St Johns Wort
- May be effective in milder forms of major depression
- No more effective than placebo in patients with severe major depression
- Better tolerated than prescription antidepressants
- May reduce the efficacy of combined oral contraceptives

Bipolar II Characteristics with Depression

- Lability of mood
- A tendency to engage in intense fantasy or daydreaming
- Social anxiety
- A high energy level

Bipolar Treatment

- Lithium
- Olanzapine (Zyprexa)
- Lamotrigine (Lamictal)
- Aripiprazole (Abilify)

Obstacles to Attaining Remission

- Patients and clinicians are satisfied with partial improvement in symptoms (ie, response but not remission)
- Treatments may not be well tolerated
- Under-dosing
- Failure to recognize residual symptoms
- Continued psychosocial stressors

Depression Rx: ECT

- Effective, safe, life-saving
- Consider if:
- Profound vegetative symptoms
- Psychosis
- Rapid physical decline
- Resistance to multiple. medications
- History of prior response to ECT

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Knowledge Assessment Questions: Depression

Note: The order in which these questions are listed is the order in which they will be presented the first time through the Knowledge Assessment. On subsequent visits to the assessment, the questions will be presented in groups organized by competency (content area).

1. A 36-year-old female consults you because of a depressed mood, trouble sleeping, and decreased appetite for 3 weeks. She has no previous history of depression, but her mother is being treated successfully for depression, and urged her to see you. The patient is in a supportive marriage and is functioning well at work. She denies anhedonia, guilt, psychomotor retardation or agitation, trouble concentrating, decreased energy, and suicidal thoughts.

   Appropriate management options at this time include which of the following? (Mark all that are true.)

   - ○ Sertraline (Zoloft)
   - ○ Paroxetine (Paxil)
   - ○ Cognitive-behavioral therapy
   - ○ Observation only

Ackermann RT, Williams JW Jr: Rational treatment choices for non-major depressions in primary care: An evidence-based review. *J Gen Intern Med* 2002;17(4):293-301. 2) Katon W, Robinson P, Von Korff M, et al: A multifaceted intervention to improve treatment of depression in primary care. *Arch Gen Psychiatry* 1996;53(10):924-932.

Last Modified 02/06

2. A 55-year-old male is showing signs of major depressive disorder after a myocardial infarction. True statements regarding this situation include which of the following? (Mark all that are true.)

   - ○ Depression has been shown to be an etiologic factor in the development of ischemic heart disease

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- ○ The depression will most likely resolve as the patient recovers from the myocardial infarction
- ○ Major depression is a significant predictor of short-term mortality from ischemic heart disease
- ○ Major depression is a significant predictor of long-term mortality from ischemic heart disease
- ○ Psychosocial interventions have been shown to be effective in improving depression in myocardial infarction survivors

Berkman LF, Blumenthal J, Burg M, et al: Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA* 2003;289(23):3106-3116. 2) Guck TP, Kavan MG, Elsasser GN, et al: Assessment and treatment of depression following myocardial infarction. *Am Fam Physician* 2001;64(4):641-648. 3) Bush DE, Ziegelstein RC, Patel UV, et al: Post-myocardial infarction depression. Evidence Report/Technology Assessment no 123, Agency for Healthcare Research and Quality, AHRQ pub no 05-E018-2, 2005. 4) Lichtman JH, Bigger JT Jr, Blumenthal JA, et al: Depression and coronary heart disease: Recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. *Circulation* 2008;118(17):1768-1775. 5) Whooley MA: Depression and cardiovascular disease: Healing the broken-hearted. *JAMA* 2006;295(24):2874-2881.

Last Modified 02/07

3. In a patient diagnosed with major depression, which of the following would support the use of long-term maintenance antidepressant medication? (Mark all that are true.)
   - ○ A positive family history for depression in a first degree relative
   - ○ Three lifetime recurrences
   - ○ Occurrence of the first episode during adolescence
   - ○ Occurrence of the first episode during young adulthood
   - ○ Occurrence of the first episode at age 70 years or greater

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Reynolds CF III, Dew MA, Pollock BG, et al: Maintenance treatment of major depression in old age. *N Engl J Med* 2006;354(11):1130-1138. 2) Glick ID, Suppes T, DeBattista C, et al: Psychopharmacologic treatment strategies for depression, bipolar disorder, and schizophrenia. *Ann Intern Med* 2001;134(1):47-60.

Last Modified 02/07

4. Which one of the following is true regarding perimenopausal depression?

   A) The loss of ovarian function during menopause is a major risk factor for the development of depression

   B) Hormone therapy has been shown to be an effective treatment for depression in perimenopausal women

   C) Life stress is a stronger predictor of depression during midlife than is menopause

   D) The incidence of depression in women peaks during the perimenopausal years

National Institutes of Health: National Institutes of Health State-of-the-Science Conference statement: Management of menopause-related symptoms. *Ann Intern Med* 2005;142(12 Pt 1):1003-1013. 2) *Depression in Primary Care: Detection and Diagnosis. Volume 1. Detection and Diagnosis*. Clinical Guideline No. 5, AHCPR Publication No. 93-0550. April 1993.

Last Modified 02/07

5. A 32-year-old female informs you that she and her husband have decided to have a child. She was diagnosed with major depression 3 months ago, but it has been well controlled with paroxetine (Paxil). She had a previous episode of major depression 10 years ago that also responded to paroxetine. She asks what effect antidepressant use would have on her pregnancy.

   Accurate advice would include which of the following? (Mark all that are true.)

   ○ Pregnancy has been shown to have a salutary effect on major depressive disorder

   ○ Paroxetine use during pregnancy has been linked to an increased risk

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of congenital heart malformations

- ○ Paroxetine use in pregnancy has been linked to an increased risk for cleft palate

- ○ SSRI use during the first trimester of pregnancy is associated with a higher risk of persistent pulmonary hypertension in the newborn

- ○ Euthymic women who discontinue antidepressant therapy during pregnancy have a fivefold higher risk of relapse over the course of pregnancy compared with women who continue their antidepressant

Cohen LS, Altshuler LL, Harlow BL, et al: Relapse of major depression during pregnancy in women who maintain or discontinue treatment. *JAMA* 2006;295(5):499-507. 2) Louik C, Lin AE, Werler MM, et al: First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med* 2007;356(26):2675-2683. 3) Alwan S, Reefhuis J, Rasmussen SA, et al: Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 2007;356(26):2684-2692. 4) Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al: Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354(6):579-587.

Last Modified 04/08

6. True statements regarding the prevalence and nature of depression in the elderly include which of the following? (Mark all that are true.)

   - ○ Depression is roughly two to three times more common in the elderly than in younger patients

   - ○ Physicians are more likely to correctly diagnose depression in elderly patients than in younger patients

   - ○ Treatment of depression in the elderly is less important than in younger patients because the depression is generally less severe

   - ○ Patients who are elderly when their first episode of depression occurs have a relatively high likelihood of developing chronic or recurring depression

Birrer RB, Vemuri SP: Depression in later life: A diagnostic and therapeutic challenge. *Am Fam Physician* 2004;69(10):2375-2382.

Last Modified 02/06

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7. Agents approved by the FDA for maintenance therapy in patients with bipolar disorder include which of the following? (Mark all that are true.)

   ○ Lithium

   ○ Divalproex (Depakote)

   ○ Olanzapine (Zyprexa)

   ○ Lamotrigine (Lamictal)

   ○ Aripiprazole (Abilify)

   ○ Bupropion (Wellbutrin)

Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002;159(4 suppl):1-50.

Last Modified 02/06

8. A 33-year-old male presents with signs and symptoms of depression and a history of daily heavy alcohol and polysubstance abuse for the past 5 years. Which one of the following is true in this situation?

   A) Symptoms that resemble primary mood and anxiety disorders can result from alcohol and substance intoxication and withdrawal

   B) This patient has an organic mood disorder secondary to alcohol dependence

   C) Carbamazepine is the appropriate first-line medication to treat withdrawal symptoms in this patient

   D) Treatment for mood and anxiety disorders in patients with substance use disorders should be withheld pending a period of sobriety

Grant BF, Stinson FS, Dawson DA, et al: Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2004;61(8):807-816.

Last Modified 02/06

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9. You are considering starting a program in which you screen all pregnant women for depression during their pregnancy and then immediately after delivery. Which of the following should be taken into account in such a program? (Mark all that are true.)

   - ○ The onset of postpartum depression frequently occurs before the patient is seen for a routine 6-week postpartum visit
   - ○ Screening questionnaires for depression during pregnancy have low sensitivity and high specificity
   - ○ The "baby blues" are so common during the first few weeks after delivery that screening for postpartum depression during that time would not be effective
   - ○ Significant dysphoria that arises more than 2 weeks after delivery should raise a strong suspicion for depression
   - ○ "Baby blues" commonly persist for several weeks after delivery

Austin MP, Lumley J: Antenatal screening for postnatal depression: A systematic review. *Acta Psychiatr Scand* 2003;107(1):10-17. *Internet access is not available for this reference. The publisher has granted permission to post the article in a downloadable format, but posting the document in a manageable size significantly reduced the quality of the reproduction. We have provided a brief summary of the article for your use in completing the knowledge assessment, and have also provided a low-resolution downloadable version of the article. If a better version becomes available, we will replace the current versions.* 2) Epperson CN: Postpartum major depression: Detection and treatment. *Am Fam Physician* 1999;59(8):2247-2256.

Last Modified 02/06

10. True statements regarding the relationship between depression and high utilization of medical care include which of the following? (Mark all that are true.)

   - ○ Depressed patients classified as high utilizers commonly present with defined medical conditions
   - ○ In patients classified as high utilizers, the incidence of current or past major depressive disorder is twice that of other patients

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- ○ The prevalence of defined medical conditions is higher among high utilizers who are classified as being depressed, compared to those who are classified as non depressed

- ○ Depressed patients classified as high utilizers have rates of medical resource utilization similar to those of nondepressed high utilizers

Savageau JA, McLoughlin M, Ursan A, et al: Characteristics of frequent attenders at a community health center. *J Am Board Fam Med* 2006;19(3):265-275.

Last Modified 02/06

11. A 32-year-old male who was successfully treated for major depressive disorder with paroxetine (Paxil) for the past 10 months chooses to stop his medication. Within a week he develops symptoms of dysphoria, fatigue, difficulty concentrating, anxiety, and insomnia. In addition, he also complains of an "electric shock" sensation in his legs and "rushing sensations" in his head.

    Which one of the following is the most likely diagnosis?

    A) Recurrence of major depressive disorder

    B) Dysthymic disorder

    C) SSRI discontinuation syndrome

    D) Bipolar disorder

Warner CH, Bobo GW, Warner C, et al: Antidepressant discontinuation syndrome. *Am Fam Physician* 2006;74(3):449-456.

Last Modified 02/07

12. A 28-year-old female with severe major depression has achieved partial symptom remission with SSRIs but complains of persistent diarrhea and loss of libido. She asks you about using St. John's wort to treat her depression.

    Appropriate advice would include which of the following? (Mark all that are true.)

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- ○ St. John's wort may be effective in milder forms of major depression
- ○ St. John's wort is more effective than placebo in patients with severe major depression
- ○ St. John's wort is better tolerated than prescription antidepressants
- ○ The combination of St. John's wort and SSRIs is safe and effective for major depression
- ○ St. John's wort may reduce the efficacy of combined oral contraceptives

Linde K, Mulrow CD, Berner M, et al: St. John's wort for depression. *Cochrane Database Syst Rev* 2005;(2):CD000448. 2) Shelton RC, Keller MB, Gelenberg A, et al: Effectiveness of St. John's wort in major depression: A randomized controlled trial. *JAMA* 2001(15);285:1978-1986. 3) Szegedi A, Kohnen R , Dienel A, et al: Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): Randomised controlled double blind non-inferiority trial versus paroxetine. *BMJ* 2005;330(7490):503-507. 4) Markowitz JS, Donovan JL, DeVane CL, et al: Effect of St. John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *JAMA* 2003;290(11):1500-1504.

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13. Patients in primary care settings may present with depressive symptoms that do not meet the full criteria for a DSM-IV Axis I depressive disorder. These symptom clusters are referred to as subsyndromal depressive symptoms.

    Which of the following are true regarding these symptoms? (Mark all that are true.)

    - ○ In primary-care settings, patients with subsyndromal depressive symptoms are less prevalent than those who meet the full criteria for DSM-IV Axis I mood and anxiety disorders
    - ○ The disability scale scores of patients with subsyndromal depressive symptoms are equivalent to scores of patients with no psychiatric symptoms
    - ○ Psychotherapy is the most appropriate treatment modality for patients with subsyndromal depressive disorders

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- ○ Many patients with subsyndromal depressive symptoms also meet the criteria for other DSM-IV Axis I psychiatric disorders

Olfson A, Broadhead WE, Weissman MM, et al: Subthreshold psychiatric symptoms in a primary care group practice. *Arch Gen Psychiatry* 1996;53(10):880-886. 2) Judd LL, Paulus MP, Wells KB, et al: Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. *Am J Psychiatry* 1996;153(11):1411-1417. *Internet access is not available for this reference. The publisher has granted permission to post the article in a downloadable format, but posting the document in a manageable size significantly reduced the quality of the reproduction. We have provided a brief summary of the article for your use in completing the knowledge assessment, and have also provided a low-resolution downloadable version of the article. If a better version becomes available, we will replace the current versions.*

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14. You diagnose postpartum depression in a 28-year-old woman 3 weeks after delivery. She is breastfeeding.

    When making decisions about her treatment, which of the following statements would be true? (Mark all that are true.)

    - ○ SSRIs can be used safely, but only at a lower dosage and for a shorter length of time than is typical in women who are not breastfeeding

    - ○ Tricyclic antidepressants can cause anticholinergic effects in the breastfed newborn

    - ○ The greatest risk for behavioral or clinical side effects in the breastfed newborn whose mother is taking an antidepressant is at 3-4 months of age

    - ○ The risk-benefit decision regarding whether to use an antidepressant in a breastfeeding woman rests almost entirely on the severity of the depression and the need for medication, rather than on any known risks to the infant

Wisner KL, Perel JM, Findling RL: Antidepressant treatment during breast-feeding. *Am J Psychiatry* 1996;153(9):1132-1137. *Internet access is not available for this reference. The publisher has granted permission to post the article in a downloadable format, but posting the document in a manageable size significantly reduced the quality of the reproduction. We have provided a brief summary of the article for your use in completing the knowledge assessment, and have also provided a low-resolution downloadable version of the article. If a better version*

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becomes available, we will replace the current versions. 2) Wisner KL, Gelenberg AJ, Leonard H, et al: Pharmacologic treatment of depression during pregnancy. *JAMA* 1999;282(13):1264-1269.

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15. Which one of the following is true regarding the effectiveness of antidepressants for treating major depression?

    A) SSRIs are the most effective class of antidepressants

    B) Tricyclic antidepressants (TCAs) are the most effective class of antidepressants

    C) Serotonin-noradrenalin reuptake inhibitors (SNRIs) such as venlafaxine are the most effective class of antidepressants

    D) Dopamine antagonists (DAs) such as bupropion (Wellbutrin) are the most effective class of antidepressants

    E) SSRIs, SNRIs, and DAs are more effective than TCAs

    F) All classes of antidepressants are equally effective

Treatment of Depression—Newer Pharmacotherapies. Evidence Report/Technology Assessment no 7, USDHHS, Agency for Health Care Policy and Research, AHCPR pub no 99-E014, 1999. 2) MacGillivray S, Arroll B, Hatcher S, et al: Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: Systematic review and meta-analysis. *BMJ* 2003;327(7409):289. 3) Gartlehner G, Gaynes BN, Hansen RA, et al: Comparative benefits and harms of second-generation antidepressants: Background paper for the American College of Physicians. *Ann Intern Med* 2008;149(10):734-750.

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16. The lifetime prevalence of major depressive disorder in the general population is

    A) 2%–5%

    B) 5%–10%

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C) 10%–20%

D) 20%–30%

Kessler RC, Berglund P, Demler O, et al: The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003;289(23):3095-3105.

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17. You are treating a 53-year-old female for her first episode of major depression. After 6 weeks of treatment with antidepressants, all depressive symptoms have resolved.

    Evidence suggests that the TOTAL length of treatment with antidepressants for this patient should be AT LEAST

    A) 3 months

    B) 6 months

    C) 12 months

    D) 18 months

Geddes JR, Carney SM, Davies C, et al: Relapse prevention with antidepressant drug treatment in depressive disorders: A systematic review. *Lancet* 2003;361(9358):653-661.

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18. True statements regarding dysthymic disorder include which of the following? (Mark all that are true.)

    ○ Dysthymic disorder is less prevalent than major depressive disorder in primary care settings

    ○ Psychiatric comorbidity is uncommon in patients with dysthymic disorder

    ○ Dysthymic disorder is less likely than major depressive disorder to lead to significant functional impairment

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○ Dysthymic disorder usually results from the stress of chronic medical conditions

Steiner M, Bell B, Browne G, et al: Prevalence of dysthymic disorder in primary care. *J Affect Dis* 1999;54(3):303-308. 2) Spitzer RL, Williams JB, Kroenke K, et al: Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA* 1994;272(22):1749-1756.

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19. Which one of the following is true regarding the relationship between stressful life events and the onset of major depressive disorder?

A) The genetically influenced traits that predispose patients to major depressive disorder have a protective effect on the response to stressful events

B) Stressful life events are associated with the onset of major depressive disorder

C) Stressful life events play a minimal role in the onset of major depressive disorder

Kendler KS, Karkowski LM, Prescott CA: Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry* 1999;156(6):837-841.

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20. Which one of the following does the U.S. Preventive Services Task Force currently recommend with regard to depression screening in adults?

A) No recommendation either for or against routine screening for depression in primary care

B) Screening only for adults with risk factors for depression, such as a positive family history, or when there is clinical suspicion

C) Screening only when staff-assisted depression care supports are in place to ensure accurate diagnosis, effective treatment, and follow-up

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D) Screening in all primary care practices because it is highly effective

US Preventive Services Task Force: Screening for depression in adults. Agency for Healthcare Research and Quality, 2009. 2) US Preventive Services Task Force: Major depressive disorder in children and adolescents. Agency for Healthcare Research and Quality, 2009. 3) O'Connor EA, Whitlock EP, Beil TL, et al: Screening for depression in adult patients in primary care settings: A systematic evidence review. *Ann Intern Med* 2009;151(11):793-803.

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21. A 54-year-old female has multiple complaints that she attributes to "getting old," including insomnia, weight gain, irritability, trouble concentrating, and "memory loss." She has had these symptoms for 3 months. Her past history includes a 10-year history of hypertension, which is well controlled with atenolol (Tenormin), 25 mg daily. Her vital signs are unremarkable, and a physical examination is remarkable only for mild obesity and a midline hysterectomy scar. Her TSH level is normal. After an appropriate diagnostic interview, you diagnose major depressive disorder of mild intensity. She is not suicidal and is not abusing alcohol.

    Appropriate treatment options at this point include which of the following? (Mark all that are true.)

    ○ Stopping the atenolol and rechecking the patient's symptoms in 2–4 weeks

    ○ Psychotherapy alone

    ○ Antidepressant medication alone

    ○ Benzodiazepines

Gerstman BB, Jolson HM, Bauer M, et al: The incidence of depression in new users of β-blockers and selected antihypertensives. *J Clin Epidemiol* 1996;49(7):809-815. 2) Ko DT, Hebert PR, Coffey CS, et al: Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002;288(3):351-357. 3) Casacalenda N, Perry JC, Looper K: Remission in major depressive disorder: A comparison of pharmacotherapy, psychotherapy, and control conditions. *Am J Psychiatry* 2002;159(8):1354-1360.

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22. True statements regarding comorbid depression and coronary artery disease (CAD) include which of the following? (Mark all that are true.)

- ○ Patients with CAD have a prevalence of major depressive disorder in the range of 40%–50%
- ○ Patients with CAD and comorbid depression have a twofold to threefold increased risk of future cardiac events when compared to nondepressed controls
- ○ Independent of other risk factors in patients initially free of CAD, the relative risk for the development of CAD conferred by depression is 3.5–4.0
- ○ The prevalence of major depressive disorder is inversely related to elevations in LDL-cholesterol
- ○ Comorbid depression is associated with greater platelet activation

Rudisch B, Nemeroff CB: Epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry* 2003;54(3):227-240. 2) Whooley MA: Depression and cardiovascular disease: Healing the broken-hearted. *JAMA* 2006;295(24):2874-2881. 3) Lichtman JH, Bigger JT Jr, Blumenthal JA, et al: Depression and coronary heart disease: Recommendations for screening, referral, and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. *Circulation* 2008;118(17):1768-1775.

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23. You are considering starting a depression disease management program in your practice. According to the literature, components of successful depression disease management programs include which of the following? (Mark all that are true.)

- ○ A system to track patients with depression
- ○ Patient education strategies
- ○ The use of nurses or other care coordinators to help maintain contact with and educate patients

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- ○ Collaboration with mental health professionals

- ○ Screening all adult patients in the practice for major depression at least once every 5 years

Gilbody S, Whitty P, Grimshaw J, et al: Educational and organizational interventions to improve the management of depression in primary care: A systematic review. *JAMA* 2003;289(23):3145-3151. 2) Dietrich AJ, Oxman TE, Williams JW Jr, et al: Going to scale: Re-engineering systems for primary care treatment of depression. *Ann Fam Med* 2004;2(4):301-304. 3) Pignone MP, Gaynes BN, Rushton JL, et al: Screening for Depression. Systematic Evidence Review, no 6. Agency for Healthcare Research and Quality, 2002, pub no AHRQ02-S002. 4) O'Connor EA, Whitlock EP, Beil TL, et al: Screening for depression in adult patients in primary care settings: A systematic evidence review. *Ann Intern Med* 2009;151(11):793-803. 5) Oxman TE, Dietrich AJ, Williams JW Jr, et al: A three-component model for reengineering systems for the treatment of depression in primary care. *Psychosomatics* 2002;43(6):441-450.

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24. True statements regarding the relationship between diabetes mellitus and depression include which of the following? (Mark all that are true.)

- ○ The presence of type 1 or type 2 diabetes doubles the likelihood of comorbid depression in adults

- ○ In patients with comorbid depression and diabetes mellitus, the level of dietary compliance is inversely related to the severity of depressive symptoms

- ○ Depression is associated with hyperglycemia in patients with type 1 diabetes, but not in those with type 2 diabetes

- ○ Health care costs for patients with diabetes mellitus and comorbid depression are similar to the health care costs of nondepressed diabetic patients

Lustman PJ, Anderson RJ, Freedland KE, et al: Depression and poor glycemic control: A meta-analytic review of the literature. *Diabetes Care* 2000;23(7):934-942. 2) Anderson RJ, Freedland KE, Clouse RE, et al: The prevalence of comorbid depression in adults with diabetes: A meta-analysis. *Diabetes Care* 2001;24(6):1069-1078. 3) Ciechanowski PS, Katon WJ, Russo JE: Depression and diabetes: Impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med* 2000;160(21):3278-3285.

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25. Both physical and psychological stress are related to the pathophysiology of mood disorders. True statements regarding this process include which of the following? (Mark all that are true.)

- ○ The response to both physical and psychologic stress is mediated in part by the hypothalamic-pituitary-adrenocortical system
- ○ Acute psychologic stress leads to a decrease in corticotropin-releasing factor, adrenocorticotropic hormone (ACTH), and cortisol levels
- ○ Successful treatment of depression leads to a reversal of abnormalities in the hypothalamic-pituitary-adrenal system
- ○ The dexamethasone suppression test is a useful clinical test for the presence of major depressive disorder

Holsboer F: Stress, hypercortisolism and corticosteroid receptors in depression: Implications for therapy. *J Affect Dis* 2001;62(1-2):77-91. *Internet access is not available for this reference. The publisher has granted permission to post the article in a downloadable format, but posting the document in a manageable size significantly reduced the quality of the reproduction. We have provided a brief summary of the article for your use in completing the knowledge assessment, and have also provided a low-resolution downloadable version of the article. If a better version becomes available, we will replace the current versions.*

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26. After a complete evaluation of a 76-year-old woman with depression, you decide she needs to be treated. Her depression is moderately severe, and she has no other significant medical problems.

    True statements regarding her treatment include which of the following? (Mark all that are true.)

- ○ In mild to moderate depression, the effectiveness of antidepressant medication is roughly equal to that of short-term, focused psychologic therapies
- ○ Serotonergic antidepressants are significantly more effective than tricyclic antidepressants for moderate to severe major depression

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- ○ In general, tricyclic antidepressants have a higher dropout rate than serotonergic agents

- ○ Tricyclic antidepressants should generally not be used in elderly patients because of the higher side-effect related dropout rate compared to serotonergic agents

- ○ Newer serotonergic agents should generally be avoided in the elderly because of the risk of drug interactions with the many medications usually taken by elderly patients

McCusker J, Cole M, Keller E, et al: Effectiveness of treatments of depression in older ambulatory patients. *Arch Intern Med* 1998;158(7):705-712. 2) Anderson IM, Tomenson BM: Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: A meta-analysis. *BMJ* 1995;310(6992): 1433-1438. 3) Birrer RB, Vemuri SP: Depression in later life: A diagnostic and therapeutic challenge. *Am Fam Physician* 2004;69(10):2375-2382.

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27. Depression may affect the management of general medical illness for which of the following reasons? (Mark all that are true.)

- ○ Patients with aversive symptoms such as pain are at increased risk for developing depressive disorders

- ○ Patients with depression may exhibit an increase in maladaptive interpersonal behaviors, making collaboration with the physician more difficult

- ○ Patients with depression have higher rates of adverse health-risk behaviors when compared to nondepressed patients

- ○ The medical cost of a chronic medical illness is reduced by comorbid depression

Katon WJ: Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry* 2003;54(3);216-226.

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28. When used at full therapeutic doses, which one of the following

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antidepressant medications can be discontinued without tapering in adults, with a low risk of side effects?

A) Nortriptyline (Pamelor)

B) Desipramine (Norpramin)

C) Paroxetine (Paxil)

D) Fluoxetine (Prozac)

E) Sertraline (Zoloft)

Depression clinical practice guidelines. Kaiser Permanente Care Management Institute, 2006. 2) Judge R, Parry MG, Quail D, et al: Discontinuation symptoms: Comparison of brief interruption in fluoxetine and paroxetine treatment. *Int Clin Psychopharmacol* 2002;17(5):217-225. 3) Zajecka J, Fawcett J, Amsterdam J, et al: Safety of abrupt discontinuation of fluoxetine: A randomized, placebo-controlled study. *J Clin Psychopharmacol* 1998;18(3):193-197. 4) Rosenbaum JF, Fava M, Hoog SL: Selective serotonin reuptake inhibitor discontinuation syndrome: A randomized clinical trial. *Biol Psychiatry* 1998;44(2):77-87.

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29. A 68-year-old male with diabetes mellitus and hypertension has a past history of major depressive disorder but has not been depressed recently. He and his wife ask you about the possibility that his depression may return and become a significant problem.

    Which of the following would be accurate advice when discussing their concerns? (Mark all that are true.)

    ○ Depression is a normal part of the aging process and does not require treatment at this man's age

    ○ Depression that occurred more than 20 years ago does not increase the patient's risk for a recurrence now

    ○ Suicide risk is higher in elderly patients when depression is untreated, compared to the risk in untreated younger patients with depression

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- ○ Depression secondary to a chronic medical illness, such as myocardial infarction or diabetes mellitus, rarely requires treatment with an antidepressant and will remit as the chronic medical disease improves

Birrer RB, Vemuri SP: Depression in later life: A diagnostic and therapeutic challenge. *Am Fam Physician* 2004;69(10):2375-2382. 2) Fiske A, Wetherell JL, Gatz M: Depression in older adults. *Annu Rev Clin Psychol* 2009;5:363-89.

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30. A trial of antidepressant discontinuation would be appropriate for which of the following? (Mark all that are true.)

- ○ A 42-year-old male with a first lifetime episode of major depression who has taken medication for 4 months and is now asymptomatic

- ○ A 35-year-old female with a first lifetime episode of major depression who has taken medication for 12 months and is now asymptomatic

- ○ A 28-year-old female with generalized anxiety disorder and her third lifetime episode of major depression who has taken medication for 6 months and is now asymptomatic

- ○ A 64-year-old female with her third lifetime episode of major depression who has taken medication for 12 months and is now asymptomatic

Trivedi MH, Kleiber BA: Algorithm for the treatment of chronic depression. *J Clin Psychiatry* 2001;62(suppl 6):22-29.

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31. True statements regarding epidemiologic factors related to bipolar disorder and major depressive disorder include which of the following? (Mark all that are true.)

- ○ The lifetime prevalence rate for major depressive disorder is approximately twice that of bipolar disorder

- ○ The mean age of onset for major depressive disorder is between the

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ages of 25 and 35

- ○ The age of onset of bipolar disorder is 6 years earlier on average than the onset of major depressive disorder

- ○ Bipolar disorder is approximately twice as common in females as in males

Hirschfeld RM, Cass AR, Holt DC, et al: Screening for bipolar disorder in patients treated for depression in a family medicine clinic. *J Am Board Fam Pract* 2005;18(4):233-239. 2) Das AK, Olfson M, Gameroff MJ, et al: Screening for bipolar disorder in a primary care practice. *JAMA* 2005;293(8):956-963. 3) Weissman MM, Bland RC, Canino GJ, et al: Cross-national epidemiology of major depression and bipolar disorder. *JAMA* 1996;276(4):293-299.

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32. Which one of the following instruments allows simultaneous assessment of both DSM-IV depression criteria and symptom severity, and is useful for follow-up?

A) The nine-item Patient Health Questionnaire (PHQ-9)

B) The Beck Depression Inventory (BDI)

C) The Center for Epidemiologic Studies Depression Screen (CES-D)

D) The Zung Depression Scale (ZDS)

E) The Primary Care Evaluation of Mental Disorders (PRIME-MD)

Williams JW Jr, Noel PH, Cordes JA, et al: Is this patient clinically depressed? *JAMA* 2002;287(9):1160-1170. 2) Nease DE Jr, Maloin JM: Depression screening: A practical strategy. *J Fam Pract* 2003;52(2):118-124. 3) Ebell MH: Screening instruments for depression. *Am Fam Physician* 2008;78(2):244-246. 4) Dejesus RS, Vickers KS, Melin GJ, Williams MD: A system-based approach to depression management in primary care using the Patient Health Questionnaire-9. *Mayo Clin Proc* 2007;82(11):1395-1402.

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33. True statements regarding the treatment of major depression in adults include which of the following? (Mark all that are true.)

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- ○ Psychotherapy and antidepressant medication are equally effective in patients with mild depression
- ○ Psychotherapy is more effective than antidepressant medication for severe depression
- ○ Combining psychotherapy and antidepressant medication in patients with mild to moderate depression is significantly more cost-effective than either treatment alone
- ○ Interpersonal therapy (IPT) is the most effective form of psychotherapy
- ○ Combining psychotherapy with antidepressant medication is likely to be more beneficial than either treatment alone in patients with severe depression

Casacalenda N, Perry JC, Looper K: Remission in major depressive disorder: A comparison of pharmacotherapy, psychotherapy, and control conditions. *Am J Psychiatry* 2002;159(8):1354-1360. 2) Thase ME, Greenhouse JB, Frank E, et al: Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Arch Gen Psychiatry* 1997;54(11):1009-1015. *Internet access is not available for this reference. The publisher has granted permission to post the article in a downloadable format, but posting the document in a manageable size significantly reduced the quality of the reproduction. We have provided a brief summary of the article for your use in completing the knowledge assessment, and have also provided a low-resolution downloadable version of the article. If a better version becomes available, we will replace the current versions.* 3) Keller MB, McCullough JP, Klein DN, et al: A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000;342(20):1462-1470. 4) De Jonghe F, Kool S, van Aalst G, et al: Combining psychotherapy and antidepressants in the treatment of depression. *J Affect Disord* 2001;64(2-3):217-229.

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34. Indications for electroconvulsive therapy (ECT) for major depression include which of the following? (Mark all that are true.)

- ○ Bipolar depression
- ○ Profound vegetative symptoms
- ○ Suicidal ideation

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- ○ Psychosis
- ○ Resistance to multiple trials of pharmacotherapy

UK ECT Review Group: The efficacy and safety of electroconvulsive therapy in depressive disorders: A systematic review and meta-analysis. *Lancet* 2003;361(9360):799-808.

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35. A 38-year-old male presents with panic attacks, and asks for refills of alprazolam (Xanax) prescribed by another physician. Previous treatment attempts with SSRIs approved for panic disorder have not been helpful, often triggering severe agitation and insomnia. Additional history taking reveals that he began to have problems with anxiety in late childhood. He has had a number of impairing depressive episodes and these demonstrate a marked seasonal pattern with increased severity during the winter months. His mother was hospitalized on at least one occasion for a psychotic mania.

    You continue to explore the patient's history. If found, which one of the following would be most specific for confirming your suspicions of bipolar disorder?

    A) Symptomatic improvement on divalproex (Depakote)

    B) A full sibling with a confirmed diagnosis of bipolar I disorder

    C) A first degree relative with mania responsive to lithium

    D) A hypomanic episode

Akiskal HS, Maser JD, Zeller PJ, et al: Switching from 'unipolar' to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry* 1995;52(2):114-123. 2) Piver A, Yatham LN, Lam RW: Bipolar spectrum disorders. New perspectives. *Can Fam Physician* 2002;48:896-904.

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36. True statements regarding antidepressants and suicide include which of the following? (Mark all that are true.)

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- ○ Tricyclic antidepressants (TCAs) are more lethal in overdose than SSRIs
- ○ Suicide rates are higher with TCAs than with SSRIs
- ○ Selective norepinephrine reuptake inhibitors (SNRIs) are less likely than SSRIs to be associated with suicidal thoughts in adolescents
- ○ SSRIs have been shown to lead to more suicide attempts in adolescents than placebo

Depression clinical practice guidelines. Kaiser Permanente Care Management Institute, 2006. 2) Buckley NA, McManus PR: Fatal toxicity of serotoninergic and other antidepressant drugs: Analysis of United Kingdom mortality data. *BMJ* 2002;325(7376):1332-1333. 3) Jick SS, Dean AD, Jick H: Antidepressants and suicide. *BMJ* 1995;310(6974):215-218.

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37. Which of the following disorders will respond to a medication that has its primary action on the serotonin and/or norepinephrine neurotransmitter systems? (Mark all that are true.)
    - ○ Dysthymic disorder
    - ○ Fibromyalgia
    - ○ Schizophrenia
    - ○ Irritable bowel syndrome
    - ○ Attention deficit/hyperactivity disorder

Hudson JI, Mangweth B, Pope HG Jr, et al: Family study of affective spectrum disorder. *Arch Gen Psychiatry* 2003;60(2):170-177.

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38. Appropriate advice for patients when first prescribing antidepressants for major depression includes which of the following? (Mark all that are true.)
    - ○ Antidepressants should be stopped as soon as any side effects are

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noted

- ○ Antidepressant side effects such as nausea, anxiety, and dry mouth are likely to persist for 6–12 weeks

- ○ Antidepressants should be continued even after symptoms of depression have resolved

- ○ If the full effect of medication has not been reached after 4 weeks, a medication change will be necessary

Lin EHB, Von Korff M, Katon W, et al: The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care* 1995;33(1):67-74. 2) Bull SA, Hu XH, Hunkeler EM, et al: Discontinuation of use and switching of antidepressants: Influence of patient-physician communication. *JAMA* 2002;288(11):1403-1409. 3) Trivedi MH, Rush AJ, Wisniewski SR, et al: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *Am J Psychiatry* 2006;163(1):28–40.

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39. You have made a diagnosis of severe depression in a 30-year-old woman who is early in the third trimester of her first pregnancy. Which of the following would be accurate advice regarding the risk of taking antidepressants during the remainder of her pregnancy? (Mark all that are true.)

    - ○ If she takes an SSRI, her baby might develop a syndrome consisting of irritability, abnormal crying, tachypnea, thermal instability, and poor muscle tone

    - ○ If she takes an SSRI her baby is likely to be slightly larger than babies born to mothers who did not take antidepressants

    - ○ She should stop any antidepressant a few weeks before her anticipated due date to prevent a neonatal withdrawal syndrome

    - ○ There is a small but significant risk of a withdrawal syndrome in newborns if serotonergic antidepressants are taken during the third trimester of pregnancy

    - ○ SSRI use in the third trimester has been linked to the development

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of persistent pulmonary hypertension of the newborn

Moses-Kolko EL, Bogen D, Perel J, et al: Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: Literature review and implications for clinical applications. *JAMA* 2005;293(19):2372-2383. 2) Huntington J, Zantop V: Antidepressant medications in pregnancy. *Am Fam Physician* 2004;70(11):2195-2196. 3) Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al: Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354(6):579-587.

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40. Which one of the following is true regarding the Beck Depression Inventory (BDI), the Zung Depression Scale (ZDS), the Center for Epidemiologic Studies Depression screen (CES-D), and the nine-item Patient Health Questionnaire (PHQ-9)?

    A) They can be performed by the patient alone, and take 5 minutes or less

    B) They can be performed by the patient alone, and take 10 minutes or more

    C) They must be administered by a trained or lay interviewer, and take 5 minutes or less

    D) They must be administered by a trained or lay interviewer, and take 10 minutes or more

Williams JW Jr, Noel PH, Cordes JA, et al: Is this patient clinically depressed? *JAMA* 2002;287(9):1160-1170. 2) Nease DE Jr, Maloin JM: Depression screening: A practical strategy. *J Fam Pract* 2003;52(2):118-124. 3) Kroenke K, Spitzer RL, Williams JB: The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med* 2001;16(9):606-613.

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41. Atypical antipsychotics include drugs such as clozapine (Clozaril), risperidone (Risperdal), and olanzapine (Zyprexa). True statements regarding the association between the atypical antipsychotics and treatment-emergent hyperglycemia or diabetes mellitus include which of the following? (Mark all that are true.)

    ○ Preexisting risk factors for type 2 diabetes mellitus are thought to be

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a risk factor for this phenomenon

- ○ Weight gain is always an associated phenomenon
- ○ Patients on atypical antipsychotics should be monitored at 6, 12, and 18 months for evidence of worsening glycemic control
- ○ Based on available data, olanzapine and clozapine are associated with the highest risk for treatment-associated hyperglycemia
- ○ Preexisting diabetes mellitus is a contraindication to the use of atypical antipsychotics

American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity: Consensus development conference on antipsychotic agents and obesity and diabetes. *Diabetes Care* 2004;27(2):596-601.

Last Modified 02/06

42. A 43-year-old perimenopausal female has moderate to severe major depressive disorder. Appropriate first-line medications include which of the following? (Mark all that are true.)

- ○ Fluoxetine (Prozac)
- ○ Nortriptyline (Pamelor)
- ○ Venlafaxine (Effexor)
- ○ Desipramine (Norpramin)
- ○ St. John's wort

Linde K, Mulrow CD, Berner M, et al: St. John's wort for depression. *Cochrane Database Syst Rev* 2005;(2):CD000448. 2) Shelton RC, Keller MB, Gelenberg A, et al: Effectiveness of St. John's wort in major depression: A randomized controlled trial. *JAMA* 2001(15);285:1978-1986.

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43. Temperament characteristics associated with a bipolar II outcome in patients initially presenting with an episode of major depression include

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which of the following? (Mark all that are true.)

- ○ Lability of mood
- ○ Excessive use of denial as an ego defense
- ○ A tendency to engage in intense fantasy or daydreaming
- ○ Social anxiety
- ○ A high energy level

Akiskal HS, Maser JD, Zeller PJ, et al: Switching from 'unipolar' to bipolar II. An 11-year prospective study of clinical and temperamental predictors in 559 patients. *Arch Gen Psychiatry* 1995;52(2):114-123.

Last Modified 02/06

44. A 45-year-old female presents during the month of May with a severe major depression. She is tearful and expresses thoughts of hopelessness. She admits to thinking about suicide from time to time, but agrees to a "no-harm" contract. There are adequate psychosocial supports in place to allow outpatient treatment to proceed.

    True statements regarding this situation include which of the following? (Mark all that are true.)

    - ○ Her risk of suicide will likely decrease during the first week of antidepressant treatment
    - ○ Her suicide risk is lowered by her presentation in the spring
    - ○ The "no-harm" contract allows the next follow-up visit to be scheduled in 3–4 weeks
    - ○ A family history of suicide would increase her risk for a suicide attempt

Kessler RC, Borges G, Walters EE: Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry* 1999;56(7):617-626.

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45. You prescribe antidepressants for a 37-year-old female for major depression of moderate severity. When you see her 8 weeks later for a follow-up visit she is sleeping better, concentrating better at work, and not overeating as much as she was. However, she is still fatigued and has poor self-esteem, has not resumed her social activities, and feels "a little" depressed. You administer a standardized depression questionnaire, and conclude the patient has achieved partial remission. Laboratory findings are normal.

At this point, appropriate treatment options include which of the following? (Mark all that are true.)

- ○ Maintain the current medication dosage and see her back in 4 weeks
- ○ Increase the dosage of her medication
- ○ Change medications
- ○ Stop treatment and refer to specialty behavioral health care
- ○ Recommend adjunct psychotherapy
- ○ Augment with another medication

Hirschfeld RM, Dunner DL, Keitner G, et al: Does psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone, psychotherapy, and their combination. *Biol Psychiatry* 2002;51(2):123-133. 2) Keller MB, McCullough JP, Klein DN, et al: A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000;342(20):1462-1470. 3) Depression clinical practice guidelines. Kaiser Permanente Care Management Institute, 2006. 4) Trivedi MH, Rush AJ, Wisniewski SR, et al: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *Am J Psychiatry* 2006;163(1):28–40. 5) Trivedi MH, Fava M, Wisniewski SR, et al: Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 2006;354(12):1243-1252. 6) Nierenberg AA, Fava M, Trivedi MH, et al: A comparison of lithium and T3 augmentation following two failed medication treatments for depression: A STAR*D report. *Am J Psychiatry* 2006;163(9):1519–1530.

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46. Deficiencies in which of the following neurotransmitters have been linked to the development of depression? (Mark all that are true.)

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- ○ Dopamine
- ○ Norepinephrine
- ○ Acetylcholine
- ○ Serotonin
- ○ Histamine

Mann JJ: The medical management of depression. *N Engl J Med* 2005;353(17):1819-1834.

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47. True statements regarding the relationship of depression to general medical illness include which of the following? (Mark all that are true.)

- ○ Chronic medical illness is a risk factor for major depressive disorder
- ○ Depression is a significant side effect of a wide range of medications used to treat medical illnesses
- ○ Patients with neurologic illnesses have a low baseline prevalence of major depressive disorder
- ○ Rheumatoid factor has been found to have a major direct pathophysiologic effect on the brain, which can lead to secondary depression
- ○ Depression can adversely affect the doctor-patient relationship

Katon WJ: Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry* 2003;54(3);216-226.

Last Modified 02/07

48. True statements regarding monoamine oxidase inhibitors (MAOIs) include which of the following? (Mark all that are true.)

- ○ MAOIs are more effective than SSRIs for patients with typical symptoms of major depression (insomnia, decreased appetite)

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- ○ MAOIs may be more effective than tricyclic antidepressants in patients with atypical symptoms of major depression (hypersomnia, increased appetite)

- ○ MAOIs may precipitate hypertensive crisis when combined with certain foods or medications

- ○ MAOIs are safe to use in combination with SSRIs

Williams JW Jr, Mulrow CD, Chiquette E, et al: A systematic review of newer pharmacotherapies for depression in adults: Evidence report summary. *Ann Intern Med* 2000;132(9):743-756. 2) Thase ME, Trivedi MH, Rush AJ: MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology* 1995;12(3):185-219.

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49. Primary care patients with medical disorders may suffer from comorbid subsyndromal depressive disorders, as well as comorbid full-criteria DSM-IV Axis I depressive disorders. True statements regarding these patients include which of the following? (Mark all that are true.)

- ○ Patients with comorbid depressive disorders have significantly higher baseline health care costs than patients without depressive disorders

- ○ Patients with comorbid depressive disorders have health care costs similar to those of patients without these comorbidities when severity of medical illness is factored in

- ○ Both major depressive disorder and subsyndromal depression are associated with significant functional impairment in primary care settings

- ○ Subsyndromal depression is less prevalent than full-criteria major depressive disorder in primary care settings

Williams JW, Kerber CA, Mulrow CD, et al: Depressive disorders in primary care: Prevalence, functional disability, and identification. *J Gen Intern Med* 1995;10(1):7-12. 2) Simon G, Ormel J, VonKorff M, et al: Health care costs associated with depressive and anxiety disorders in primary care. *Am J Psychiatry* 1995;152(3):352-357. *Internet access is not available for this reference. The publisher has granted permission to post the article in a downloadable format, but posting the document in a manageable size significantly reduced the quality of the reproduction. We have provided a brief summary of the article for your use in completing the knowledge assessment, and have also provided a low-resolution downloadable version of the*

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article. If a better version becomes available, we will replace the current versions.

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50. Components of practice redesign that have been shown in studies to contribute to improved outcomes in patients with depression include which of the following? (Mark all that are true.)

    ○ Patient self-management support

    ○ Dissemination of guideline binders

    ○ A functioning interface to mental health specialists that ensures access for consultation, shared management, and referral

    ○ Physician attendance at CME programs

    ○ Case management that functions to ensure that patients are monitored regularly for treatment adherence, status of their illness, and needed changes in treatment

Oxman TE, Dietrich AJ, Williams JW Jr, et al: A three-component model for reengineering systems for the treatment of depression in primary care. *Psychosomatics* 2002;43(6):441-450. 2) Dietrich AJ, Oxman TE, Burns MR, et al: Application of a depression management office system in community practice: A demonstration. *J Am Board Fam Pract* 2003;16(2):107-114. 3) Gilbody S, Whitty P, Grimshaw J, et al: Educational and organizational interventions to improve the management of depression in primary care: A systematic review. *JAMA* 2003;289(23):3145-3151. 4) O'Connor EA, Whitlock EP, Beil TL, et al: Screening for depression in adult patients in primary care settings: A systematic evidence review. *Ann Intern Med* 2009;151(11):793-803. 5) Lee PW, Dietrich AJ, Oxman TE, et al: Sustainable impact of a primary care depression intervention. *J Am Board Fam Med* 2007;20(5):427-433.

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51. A 24-year-old female presents to your office complaining of symptoms of depression and generalized anxiety. During an episode of severe depression as a teenager, she attempted suicide by acetaminophen overdose. In the past, another physician made a diagnosis of social phobia and prescribed paroxetine (Paxil). After taking the paroxetine for 3 days, she experienced an episode of elation, decreased need for sleep, racing thoughts, and increased activity, including a spending spree totaling several thousand dollars.

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Which one of the following would be the most appropriate medication choice for her current depression?

A) Olanzapine/fluoxetine (Symbyax)

B) Venlafaxine extended release (Effexor XR)

C) Sertraline (Zoloft)

D) Clomipramine (Anafranil)

E) Divalproex (Depakote)

Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002;159(4 suppl):1-50. 2) Tohen M, Vieta E, Calabrese J, et al: Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003;60(11):1079-1088.

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52. A 27-year-old female presents to your office as a new patient. She has a history of major depressive disorder and irritable bowel syndrome. At present she is not under treatment and her depression is moderately severe. She has a family history of obsessive-compulsive disorder, major depressive disorder, migraine headaches, and fibromyalgia.

Which of the following would apply to this patient? (Mark all that are true.)

○ The clustering of diagnoses in the patient's family probably has an underlying biologic basis mediated by serotonin

○ Abnormalities in the cholinergic neurotransmitter system have been implicated in the primary pathophysiology of both of the patient's diagnoses

○ The primary cause of this patient's major depressive disorder is learned or modeled behavior

○ In this patient, a course of interpersonal psychotherapy is indicated prior to starting a trial of antidepressant medication

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Hudson JI, Mangweth B, Pope HG Jr, et al: Family study of affective spectrum disorder. *Arch Gen Psychiatry* 2003;60(2):170-177.

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53. True statements regarding major depressive disorder include which of the following? (Mark all that are true.)

    ○ Patients with major depressive disorder have high levels of psychiatric comorbidity

    ○ The mean duration of an episode of untreated major depression is 8 weeks

    ○ Over 50% of non-institutionalized patients with major depressive disorder receive appropriate evidence-based treatment

    ○ The risk of developing major depressive disorder is highest in the preteen years

Kessler RC, Berglund P, Demler O, et al: The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003;289(23):3095-3105.

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54. A 21-year-old female is diagnosed with common migraine headaches. She has a history of recurrent major depression well controlled with citalopram (Celexa).

    Which one of the following medications used for the treatment of migraine would increase her risk of developing serotonin syndrome?

    A) Propranolol (Inderal)

    B) Topiramate (Topamax)

    C) Naproxen

    D) Sumatriptan (Imitrex)

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FDA Alert [7/2006]: Potentially life-threatening serotonin syndrome with combined use of SSRIs or SNRIs and triptan medications. 2) Boyer EW, Shannon M: The serotonin syndrome. *N Engl J Med* 2005;352(11):1112-1120.

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55. Which one of the following is the strongest risk factor for the development of major depression in the elderly?

    A) A personal history of major depression

    B) The onset of a new chronic disease

    C) The death of a spouse

    D) A marked decrease in the independent activities of daily living (IADL) score

Schoevers RA, Beekman ATF, Deeg DJ, et al: Risk factors for depression in later life; Results of a prospective community based study (AMSTEL). *J Affect Disord* 2000;59(2):127-137.

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56. A 28-year-old female presents with the onset of sadness and tearfulness over the past month. Questioning reveals that her husband is annoyed with her for not wanting to go out like she used to. She is also having difficulty sleeping despite feeling tired almost constantly, has almost stopped eating due to lack of interest, and is feeling guilty over letting her family down because of her tiredness. You diagnose acute major depressive disorder and begin medication after discussing treatment options with the patient.

    Which one of the following would be most appropriate for monitoring the patient's condition during the acute phase of the depression?

    A) Scheduling office visits with you at all monitoring points to ensure adequate assessment of response

    B) A visit or phone call by your staff at 1 week to ask general questions about adherence and side effects

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C) Phone calls by a staff member that include assessment of the patient's progress with a standardized depression assessment instrument

D) Required referral to a central case management service to assess the patient's progress

E) An agreement with the patient that she should call in at intervals of 2, 4, and 6 weeks to let your nurse know how she is doing

Oxman TE, Dietrich AJ, Williams JW Jr, et al: A three-component model for reengineering systems for the treatment of depression in primary care. *Psychosomatics* 2002;43(6):441-450.

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57. Possible mechanisms implicated in the relationship between depression and increased cardiovascular morbidity and mortality include

○ increased heart rate variability

○ increased ratio of parasympathetic to sympathetic tone

○ abnormalities in platelet aggregation

○ cardiac rhythm disturbances

○ reduced compliance with medical recommendations

Joynt KE, Whellan DJ, O'Connor CM: Depression and cardiovascular disease: Mechanisms of interaction. *Biol Psychiatry* 2003;54(3):248-261. 2) O'Connor CM, Gurbel PA, Serebruany VL: Depression and ischemic heart disease. *Am Heart J* 2000;140(4 suppl):S63-S69. *Internet access is not available for this reference. The publisher has granted permission to post the article in a downloadable format, but posting the document in a manageable size significantly reduced the quality of the reproduction. We have provided a brief summary of the article for your use in completing the knowledge assessment, and have also provided a low-resolution downloadable version of the article. If a better version becomes available, we will replace the current versions.* 3) Ziegelstein RC: Depression in patients recovering from myocardial infarction. *JAMA* 2001;286(13):1621-1627.

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58. Which one of the following best describes bipolar II disorder?

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A) A history of one or more periods of impairing manic symptoms lasting at least 4 days

B) Recurrent periods of hypomania with at least one episode of major depression

C) Alternating periods of hypomania and minor depression

D) A history of at least one episode of acute mania

E) Recurrent major depression refractory to adequate trials of at least 3 antidepressants from different pharmacologic classes

Parker G: Bipolar disorder: Assessment and management. *Aust Fam Physician* 2007;36(4):240-243.

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59. True statements regarding suicide attempts among patients with a major depressive episode include which of the following? (Mark all that are true.)

○ Women successfully commit suicide at a higher rate than men

○ Patients hospitalized for suicidality have a markedly increased lifetime risk of suicide compared to patients managed in an outpatient setting

○ Patients with depressive disorders have suicide prevalence rates similar to those of the general population

○ Depressed cigarette smokers attempt suicide more frequently than depressed nonsmokers

○ Increased subjective assessment of depression by the patient is associated with an increased risk for a suicide attempt

Bostwick JM, Pankratz VS: Affective disorders and suicide risk: A reexamination. *Am J Psychiatry* 2000;157(12):1925-1932. 2) Oquendo MA, Galfalvy H, Russo S, et al: Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. *Am J Psychiatry* 2004;161(8):1433-1441.

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60. Which one of the following screening instruments for depression has the lowest rate of false-positives (highest positive predictive value) in primary care use?

A) The nine-item Patient Health Questionnaire (PHQ-9)

B) The Beck Depression Inventory (BDI)

C) The Center for Epidemiologic Studies Depression Screen (CES-D)

D) The Zung Depression Scale (ZDS)

E) The Primary Care Evaluation of Mental Disorders (PRIME-MD)

Williams JW Jr, Noel PH, Cordes JA, et al: Is this patient clinically depressed? *JAMA* 2002;287(9):1160-1170. 2) Nease DE Jr, Maloin JM: Depression screening: A practical strategy. *J Fam Pract* 2003;52(2):118-124. 3) Kroenke K, Spitzer RL, Williams JB: The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med* 2001;16(9):606-613.

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PRECONCEPTION HEALTH CARE ALL THE TIME

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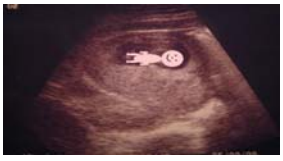
INTRODUCTION

- Why focus on Preconception Care?
- Obstacles to Preconception Care
- Available Evidence
- Preconception Care
  - Actively planning pregnancy
  - Unsure
  - Do not desire pregnancy

Preconception health care is actually Periconception health care



WHY FOCUS ON PRECONCEPTION CARE?

- Benefits for women who choose to participate
- Family Physicians have many opportunities for preconception care

OBSTACLES

- **Patient:**
- Lack of knowledge/understanding of goals of preconception care
- Even before planned pregnancies, most have not had discussions about preconception health care
- Most discussions are started by the patient
- Unplanned pregnancy (up to 50% in the US)
- Lack of access: women at highest risk often have less access to care
- Cultural differences

OBSTACLES

- Provider:
- Lack of evidence – what works?
- Poor reimbursement (?)
- - is this care cost-effective?
- Limited time in primary care visits
- Lack of training

WHAT IS SUPPORTED BY EVIDENCE?

- Rubella immunization
- Alcohol use
- Reduction of congenital anomalies (folic acid)
- Smoking
- Obesity
- Diabetic women
- Medications/Teratogens
- Hypothyroidism

CASE #1

Case #1 – 28 y/o G0, here for her annual exam. She has no chronic medical issues. She is currently taking oral contraceptives but is planning on trying to get pregnant in a few months. Is there anything that she needs to do?

RUBELLA

- Congenital rubella syndrome still occurs
- Most of these women had missed opportunities for screening/vaccination
- Women with equivocal or negative tests should be revaccinated after pregnancy
- Special attention to women born in other countries
- Recommend waiting one month after vaccination before attempting pregnancy

ALCOHOL USE

- Prospective cohort study 992 women, 2012
- Fetal alcohol syndrome seen with alcohol exposures in all trimesters
  - Strongest association second half of first trimester
  - No evidence of a "safe" threshold

ALCOHOL USE

- Cochrane review 2009
  - Pre-pregnancy health promotion was associated with lower rates of binge drinking (RR 1.24)

RECOMMENDATION

- **The USPSTF recommends screening and behavioral counseling interventions to reduce alcohol misuse by adults, including pregnant women, in primary care settings**
- **Brief behavioral counseling associated with small to moderate reductions in alcohol consumption (Level B)**

NEURAL TUBE DEFECTS (NTD)

- Periconceptional folic acid decreases occurrent NTD, RR 0.28 (95% CI 0.13-0.58)
- Number needed to treat 847
- Not associated with increased rate of conception
- Does not affect rates of miscarriage, ectopic, stillbirth
- Increase in multiple births – most likely from confounding from IVF

OTHER MALFORMATIONS

- GU malformations
  - Women using multivitamins (with folic acid) during first trimester had 85% decreased risk of having a child with GU malformation (OR 0.15, 95% CI 0.05-0.43)
- Cleft lip/palate
  - Women taking at least 0.4 mg folic acid day had OR 0.61 (0.39-0.96) for child with cleft lip +/- cleft palate

FOLIC ACID

- Dose for primary prevention is 0.4 to 0.8 mg one month before conception through first 2-3 months of pregnancy
- Current fortification levels are 0.14 mg per 100 grams whole grain
  - has decreased prevalence of NTDs by 26%

Folic Acid Knowledge

Age	Aware	Knowledge	Taking supplement
18-24	61	6	30
25-34	87	12	47
35-45	89	16	40

MMWR, 2008

INCREASING FOLIC ACID CONSUMPTION

- Canfield, 2002
  - Women with a history of a child with NTD were more likely to use folic acid prior to subsequent pregnancies if counseled about its benefits
- deWeerd, 2002
  - In women who planned a pregnancy and had preconception care, counseling about folic acid increased folic acid intake

RECOMMENDATIONS

- **Maternal folic acid intake decreases incidence of neural tube defects in their infants (LOE A)**
- **Maternal folic acid intake decreases genitourinary and cleft-lip malformations in their infants (LOE B)**
- **Education about folic acid increases vitamin use in motivated women (LOE A)**

CASE #2

M.A. is a 22yo woman who comes in to establish care. She smokes 10 cigarettes per day and would like to quit, but is concerned about weight gain. Her BMI is 31. She is sexually active with her boyfriend. They use condoms for contraception. What is your advice?

SMOKING IN PREGNANCY

Accounts for 5% of perinatal deaths, 20-30% of low birth weights and 15% of preterm births

PRE-CONCEPTION RISKS OF SMOKING

- Twice as likely to experience delay to conception
  - OR at 12 months of failing to achieve a pregnancy in a smoker 1.54 (1.19-2.01)
- 30% higher odds of having infertility

SMOKING IN PREGNANCY

- Pregnancy Risk Assessment Monitoring System (PRAMS) 2008
  - 23.0% smoking 3 months prior to pregnancy
  - 12.8% smoking during last 3 months of pregnancy
  - 17.6% smoking postpartum

PREGNANCY HEALTH RISKS OF SMOKING

- Spontaneous abortion OR 1.8 (1.3-2.6)
- Abruption OR 1.65 (1.44-1.91)
- Previa OR 1.58 (1.04-2.9)
- Stillbirth OR 2.0 (1.4-2.9)
- PPROM – 2 times more likely
- Prematurity – 30% higher risk
- Low birth weight - on average weigh 200 grams less
  - 5% decreased body weight per pack per day smoked

INFANT SEQUELAE OF MATERNAL SMOKING DURING PREGNANCY

- Infant Mortality all causes OR 1.8 (1.3-2.6)
- Infant Mortality from respiratory causes (excluding conditions of prematurity) OR 3.8
- Decreased weight, length and HC at birth
  - at 5 years of age, full catch up in weight, partial in length, no catch up in HC

INFANT SEQUELAE OF MATERNAL SMOKING DURING PREGNANCY

- Anal atresia OR 1.4
- Congenital urinary tract anomalies OR 2.3
- Oral Cleft RR 1.34 (1.16-1.54)
- Omphalocele/gastroschisis Prevalence Ratio (PR) 1.37
- Clubfoot PR 1.62
- Polydactyly/syndactyly PR 1.33
- Septal congenital heart defects (ASD, VSD) OR 1.44 (light smoker) to 2.06 (heavy smoker)

INFANT SEQUELAE OF MATERNAL SMOKING DURING PREGNANCY

SIDS (Sudden Infant Death Syndrome)

- Tushar 2006
- OR 3.5 (1.4-8.7)
- 20.7% of SIDS cases from 1997-2000 could have been prevented if all women had stopped smoking
- 61.3% of SIDS cases in children born to women who smoked during pregnancy were the result of smoking

CHILDHOOD SEQUELAE OF MATERNAL SMOKING DURING PREGNANCY

- Increased rates of ODD and conduct disorder
- ADHD – OR 2.39
- Studies evaluating cognition, speech delay and school achievement show negative trends but are not as robust
- Asthma – OR 1.8 (controlled for second hand smoke)

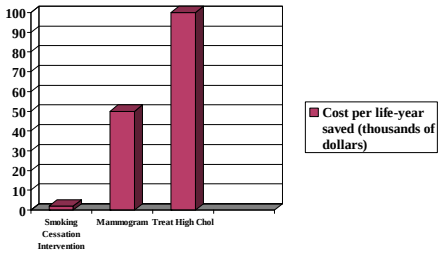
SMOKING CESSATION

- Pregnancy Specific Self-Help Material
- Meta-analysis 2008
  - OR 1.9 (1.2-2.9)
  - Abstinence rates usual care 8.6% increased to 15.0% with materials

SMOKING CESSATION

- Psychosocial Interventions – Fiore 2008
- Meta-analysis of routine care/brief intervention versus more intense psychosocial interventions
- OR quitting smoking 1.8 (1.4-2.3)
  - abstinence rates 13.3% intervention groups versus 7.6%

COST-EFFECTIVENESS OF SMOKING CESSATION IN PREGNANCY



Information from Marks JS. A cost-benefit/cost-effectiveness analysis of smoking cessation for Pregnant women. Am J Prev Med. Vol 6:282-289, 1990.

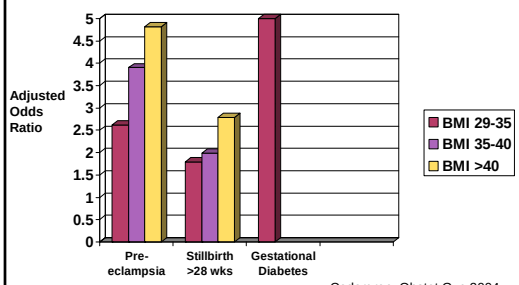
RECOMMENDATIONS

- **Brief physician counseling is effective in reducing smoking in non-pregnant patients (LOE A)**
- **Minimal pregnancy specific interventions improve quit rates in women who smoke during pregnancy (LOE A)**

OBESITY

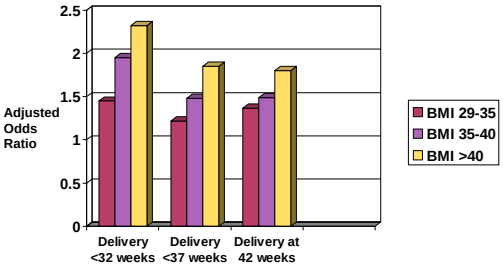
- 29% of women age 20-39 are obese

ANTENATAL COMPLICATIONS BY DEGREE OF MATERNAL OBESITY



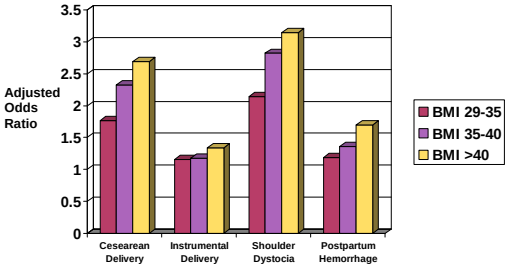
Cedergren, Obstet Gyn 2004
Baeten, Am J Public Health 2001

ANTENATAL COMPLICATIONS BY DEGREE OF MATERNAL OBESITY



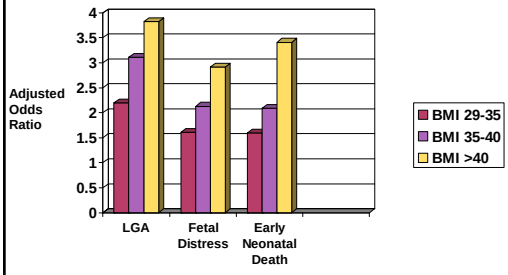
Cedergren, Obstet Gyn 2004

LABOR AND DELIVERY COMPLICATIONS BY DEGREE OF MATERNAL OBESITY



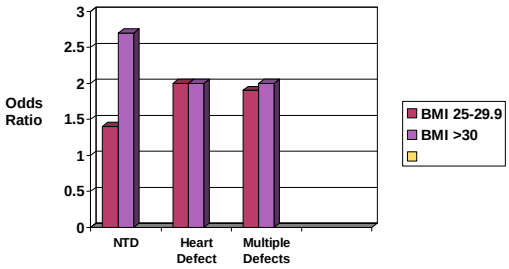
Cedergren, Obstet Gyn 2004

NEONATAL OUTCOMES BY DEGREE OF MATERNAL OBESITY



Cedergren, Obstet Gyn 2004

MATERNAL BMI AND BIRTH DEFECTS



Watkins ML, Peds 2003

RECOMMENDATIONS

- **USPTFS - intensive counseling and behavioral interventions in obese adults results in weight loss (up to 6% body weight) (LOE B)**
- **ACOG recommends preconception counseling for obese women, including information about maternal and fetal risks in pregnancy (LOE C)**

CASE #3

T.M. is a new patient who comes in for a well-woman exam. She is 33 and has had type 2 diabetes for the past 4 years. She has a 10yo and 8yo from a previous marriage. She is on glyburide and metformin. She is newly remarried and trying to get pregnant. Her hemoglobin A1c is 8.2.

DIABETES

- Decreased fertility
- Increased risk of SAB
- Increased risk of fetal malformations
  - Common anomalies: heart defects, sacral agenesis, GU malformations
  - Anomalies occur before 8 weeks gestation
  - Risk is decreased with better glycemic control

DIABETES

DARE (Database of Abstracts of Reviews of Effectiveness) meta-analysis of 14 cohort studies, compared 1192 diabetic women with pre-conception care vs. 1439 women usual care

- Pooled data showed 2.1% rate of congenital anomalies in pre-conception care group vs. 6.5%
  - NNT 23

PRE-CONCEPTION CARE FOR WOMEN WITH DIABETES

- Discuss risks of congenital anomalies, SAB, other pregnancy complications
- Use contraception until blood glucose is optimized
- Diabetic education, dietary education
- Generally switch to insulin, but can continue metformin/glyburide until pregnant
- Stop ACE-I, statins
- Goal Hga1c <7.0

RECOMMENDATIONS

- **Discuss reproductive health plans with women who have diabetes (LOE C)**
- **intensive pre-conception interventions in women with diabetes reduces the risk of congenital anomalies (LOE A)**

CASE #4

- **30 y/o G2P0 who comes in for regular medication check. She takes valproic acid (Depakote) for a seizure disorder and has been well controlled on that medication. She is single but partnered and using OCPs for birth control, but she admits not taking pills consistently.**

EPILEPSY

- Lower fertility in women with epilepsy
- BUT, combination hormone contraceptives are less effective
- Higher rates of fetal malformations and lower cognitive function due to meds (not epilepsy itself)
- Some evidence that pre-conception care decreases fetal anomalies, but more studies needed

PRE-CONCEPTION EPILEPSY CARE

- Being seizure free for 9 months prior to pregnancy associated with high likelihood of remaining seizure free during pregnancy (84-92%)
- Very well-controlled patients may be able to go off meds, discuss with neurologist
- Aim for monotherapy
- Avoid carbamazepine, valproate, phenytoin
  - newer meds are probably less teratogenic
  - Supplement with 4 mg folic acid

MEDICATIONS

- Isotretinoin (Accutane)
- Paroxetine (Paxil)
- ACE Inhibitors
- Statins
- Methotrexate
- Warfarin - up to 25% will have fetal warfarin syndrome if taken from weeks 6-9 of pregnancy

RECOMMENDATIONS

- **Women who are seizure free prior to pregnancy are more likely to be seizure free during pregnancy (LOE B)**
- **Certain medications should be "red flags" in women of reproductive age (LOE C)**
- **Consider changing medications vs. recommending more effective methods of contraception (LOE C)**

CASE #5

- **27 y/o G1P1 who is here for her annual exam. She is planning on becoming pregnant again. Her previous pregnancy resulted in a preterm delivery at 34 weeks, and she wants to know what she can do to prevent this in a future pregnancy. Her only medication is levothyroxine**.

THYROID DISORDERS IN PREGNANCY

- Overt hypothyroidism
  - elevated TSH, low free T4
- Subclinical hypothyroidism
  - elevated TSH, normal free T4
- Hypothyroxinemia
  - normal TSH, low free T4

HYPOTHYROIDISM IN PREGNANCY

- Prevalence 1.4%, 2004
- Untreated hypothyroidism
  - Higher rates of SAB, abruption, PET, IUGR, low birth weight, PTL and fetal death
  - Associated with poor cognitive development in offspring

HYPOTHYROIDISM IN PREGNANCY

- Most of the increased need is in early first trimester (as early as 4 weeks)
- Recommend that women take 2 extra doses per week as soon as they find out they're pregnant, and check TSH ASAP
- Most studies show that average increased dose is 50-100 ug/day

SUBCLINICAL HYPOTHYROIDISM AND HYPOTHYROXINEMIA IN PREGNANCY

- Subclinical hypothyroidism (high TSH, normal free T4)
  - 2 large studies - no changes in pregnancy outcomes
- Hypothyroxinemia (normal TSH, low free T4)
  - one large study – no changes
  - another large study – increased rates of preterm labor, macrosomia, gestational diabetes

HYPOTHYROXINEMIA AND PEDIATRIC OUTCOMES

- significantly lower Neonatal Behavioral Scores ate 3 weeks of age
- significantly lower scores on Bayley Neurodevelopmental Scale at 10 months of age

SUBCLINICAL HYPOTHYROIDISM AND PEDIATRIC OUTCOMES

- 15% women with subclinical hypothyroidism versus 5% controls had children with IQ<85 at 7-9 years old

RECOMMENDATIONS

- **In women with established hypothyroidism, maintaining euthyroid levels during pregnancy improves pregnancy outcomes and decreases neurodevelopmental delays in offspring (LOE B)**
- **ACOG does not recommend routine screening for thyroid abnormalities in pregnant women (LOE I)**

PERICONCEPTION CARE THREE CATEGORIES OF WOMEN

1. Actively planning pregnancy
2. Unsure
3. Do not desire pregnancy

ACTIVELY PLANNING PREGNANCY

- Schedule for comprehensive preconception evaluation

COMPREHENSIVE PRECONCEPTION VISIT

- same as a first prenatal visit – including history, physical, and labs
- Prenatal labs: HIV, hepatitis B, syphilis, rubella, hematocrit, Pap test, PPD (if indicated), gonorrhea/chlamydia testing, blood type and antibodies

COMPREHENSIVE PRECONCEPTION VISIT

- Genetic counseling if needed
  - Screen for cystic fibrosis, sickle cell trait, thalassemia
- Update immunizations
  - Rubella, varicella, Tdap
- Prescribe multivitamins with folic acid

COMPREHENSIVE PRECONCEPTION VISIT

- Discuss conditions/exposures that are supported by evidence
  - Rubella immunization
  - Alcohol use
  - Reduction of congenital anomalies (folic acid)
  - Smoking
  - Obesity
  - Diabetes
  - Medications/Teratogens
  - Hypothyroidism

UNSURE

- Using less effective contraception or unreliable contraception users
- Clarify reasons for ambivalence
- Use Five Minute Intervention

FIVE MINUTE INTERVENTION

- How to Screen:
  - "What are you using for birth control?"
  - "Are you thinking about having a baby in the future?"

FIVE MINUTE INTERVENTION

- When to use:
  - Negative pregnancy test
  - Health maintenance visit
  - Postpartum visit
  - Screen the mother at well child visit
  - Special attention (red flags): diabetes, medications, previous poor pregnancy outcome

FIVE MINUTE INTERVENTION

- Brief discussion
  - Vitamins with folic acid
  - Smoking cessation
  - Review meds and chronic medical conditions for red flags
  - Routine immunizations: rubella, varicella, hepatitis B, Tdap
  - www.familydoctor.org
    - "Things to Think About Before You're Pregnant"

DO NOT DESIRE PREGNANCY

- Emphasize effective contraception and planned pregnancy
- Emergency contraception
  - Discuss and make available

CODING/BILLING

- Comprehensive preconception care visit
  - can bill as gyn prev med exam
- Preconception care for specific issues
  - bill under the disease (i.e. diabetes)
- Pure preconception care
  - use procreative management V26.89
  - bill based on counseling time

SUMMARY

- Prescribe folic acid for all women of child-bearing age
- Assist women with smoking cessation and weight loss
- Pay special attention to women with medical health issues or medications that can impact pregnancy
- Best strategy may be to decrease unintended pregnancy

QUESTIONS

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Contraception Update

Marianne McKennett, M.D.
San Diego Academy
June 24, 2012

Learning Objectives

- Be able to collaborate with patient to select the best option for her and partner
- Know benefits and risks of current contraceptives
- Understand options and benefits of Long-Acting Reversible Contraception (LARC)
- Be able to use the "Quick Start" method

Case #1

- 17 y/o G1 P0 never sexually active here with boyfriend to begin birth control.
- Issues:
  - Does she need a pap smear?
  - Any concerns specific to adolescent
  - When to start?
  - Emergency Contraception?

Case #2

- 24 y/o G1P1 female at 6 weeks postpartum, breastfeeding.
- Issues:
  - Hormonal contraception and breastfeeding

Case #3

- 35 y/o G2 P2 female not sure whether she wants to be pregnant again, not ready for permanent method.
- Issues:
  - Smoking
  - Cardiovascular risks

Epidemiology

- 49% of pregnancies in U.S. are unintended (3 million preg/year)
- 1.2 million abortions per year
- 10 million U.S. women use OCP's
- 100 million women worldwide
- 5/100 women get pregnant with typical use
- 1/100 women with perfect use

Combination Hormonal Contraceptives

Combination Estrogen-Progesterone

- Estrogen content
  - 20-50 micrograms of ethinyl estradiol
  - Now 20-35 micrograms
- Progestational Agents
  - Norgestrel – First Generation
  - Levonorgestrel – Second Generation
  - Desogestrel – Third Generation
  - Drospirenone – Fourth Generation

Combination OCPs: Third generation progestins

- Desogestrel and norgestimate: Desogen, Ortho-Cept, Ortho-Cyclen, Ortho Tri-Cyclen
- Developed in 1990s
- Reduce androgenic and metabolic side effects
- Decreased effect on blood glucose, insulin concentrations and lipid profile
- Reduce acne and hirsutism, do not adversely affect weight or BP
- Better tolerated because of lack of cycle control (i.e., breakthrough bleeding, spotting and amenorrhea)

Types of Progestin in Combination Estrogen-Progestin Oral Contraceptives Marketed in the United States or Mentioned in Studies of Types of Progestin and Cardiovascular Disease

Petitti, D. B. N Engl J Med 2003;349:1443-1450

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Non-Contraceptive Benefits

- Ovarian Cancer
  - 50% decrease in OCP users
- Endometrial Cancer
  - Progestin suppresses proliferation
- Acne
  - Decrease free testosterone
- Menstrual Disorders
  - Decrease severity of DUB

Risk Considerations

- Arterial Risks
  - Estrogen consideration
  - MI
  - Stroke
- Venous Thromboembolic Disease
  - Progesterone
  - VTE
  - Cerebral Venous Thrombosis

Myocardial Infarction/CVA

- Initial concern with older formulations
- RR 1-1.1 in pooled analysis of case-control studies in U.S.
- MICA study reported RR 1.4
- Differences due to increased # smokers and undiagnosed htn in later study
- Risk increased in women who SMOKE or have HTN

Age-Specific Estimates of the Excess Rates of Myocardial Infarction, Ischemic Stroke, and Venous Thromboembolism Attributable to the Use of Low-Estrogen Oral Contraceptives and Pregnancy-Related Mortality

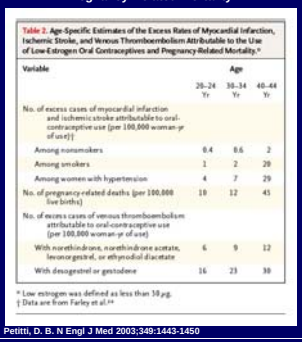

Table 2. Age-Specific Estimates of the Excess Rates of Myocardial Infarction, Ischemic Stroke, and Venous Thromboembolism Attributable to the Use of Low-Estrogen Oral Contraceptives and Pregnancy-Related Mortality.*

Variable	Age 20–24 Yr	Age 30–34 Yr	Age 40–44 Yr
No. of excess cases of myocardial infarction and ischemic stroke attributable to oral-contraceptive use (per 100,000 woman-yr of use)†			
Among nonsmokers	0.4	0.6	2
Among smokers	1	2	20
Among women with hypertension	4	7	29
No. of pregnancy-related deaths (per 100,000 live births)	10	12	45
No. of excess cases of venous thromboembolism attributable to oral-contraceptive use (per 100,000 woman-yr of use)			
With norethindrone, norethindrone acetate, levonorgestrel, or ethynodiol diacetate	6	9	12
With desogestrel or gestodene	16	23	30

* Low estrogen was defined as less than 50 μg.
† Data are from Farley et al.[44]

Petitti, D. B. N Engl J Med 2003;349:1443-1450

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Venous Thromboembolism

- Risk increased 3-4 x in OCP users
- Risk increased 1.5-1.8 x with desogestrel or gestodene compared to levonorgestrel
- Alesse, Triphasil, Nordette, Mirena
- Increased risk Thrombophilia

Patient Concerns

- Weight Gain
  - EBM shows no causal relationship
  - Both groups gain weight!
  - <1#/6months related to OCP's
- Breastfeeding
  - Concern re: decreased milk supply
  - Need to wait until at least 6 wks pp
  - 3 weeks pp re: risk of VTE

Summary of Guidelines for the Use of Combination Estrogen-Progestin Oral Contraceptives in Women with Characteristics That Might Increase the Risk of Adverse Effects

Table 3. Summary of Guidelines for the Use of Combination Estrogen–Progestin Oral Contraceptives in Women with Characteristics That Might Increase the Risk of Adverse Effects.*

Variable	ACOG Guidelines	WHO Guidelines
Smoker, <35 yr of age		
<15 cigarettes/day	Risk unacceptable	Risk usually outweighs benefit
≥15 cigarettes/day	Risk unacceptable	Risk unacceptable
Hypertension		
Blood pressure controlled	Risk acceptable; no definitive data on effect of blood-pressure control	Risk usually outweighs benefit if systolic blood pressure is 140–159 mm Hg and diastolic blood pressure is 90–99 mm Hg
Blood pressure uncontrolled	Risk unacceptable; no definitive data on effect of uncontrolled blood pressure	Risk unacceptable if systolic blood pressure is ≥160 mm Hg or diastolic blood pressure is ≥100 mm Hg
History of stroke, ischemic heart disease, or venous thromboembolism	Risk unacceptable	Risk unacceptable
Diabetes	Risk acceptable if no other cardiovascular risk factors and no end-organ damage	Benefit outweighs risk if no end-organ damage and diabetes is of ≤20 yr duration
Hypercholesterolemia	Risk acceptable if LDL cholesterol ≤160 mg/dl and no other cardiovascular risk factors	Benefit–risk ratio is dependent on the presence or absence of other cardiovascular risk factors
Multiple cardiovascular risk factors	Not addressed	Risk usually outweighs benefit or risk unacceptable, depending on risk factors
Migraine headache		
Age ≥35 yr	Risk usually outweighs benefit	Risk usually outweighs benefit
Focal symptoms	Risk unacceptable	Risk unacceptable
Breast cancer		
Current disease	Risk unacceptable	Risk unacceptable
Past disease, no active disease for 5 yr	Risk unacceptable	Risk usually outweighs benefit
Family history of breast or ovarian cancer	Risk acceptable	Risk acceptable

* The American College of Obstetricians and Gynecologists (ACOG) guidelines recommend the use of formulations containing less than 50 μg of ethinyl estradiol with the "lowest progestin dose," without mention of the type of progestin. The World Health Organization (WHO) guidelines pertain explicitly to formulations containing 50 μg or less of ethinyl estradiol and do not mention the dose or type of progestin. To convert values for low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.0259.

Petitti D. N Engl J Med 2003;349:1443-1450

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Yasmin and Yaz

- 30 mcg ethinyl estradiol
- 3 mg drospirenone
- Spironolactone analog with antimineralocorticoid activity
- No androgen effect
- Theoretical concern re: elevated K
- Theoretical decrease in bloating, wt gain, bp reduction

Extended Oral Contraceptive

- 30 mcg ethinyl estradiol
- 150 mcg levonorgestrel
- 84 consecutive days
- 7 days non-hormone pills
- Dispensed as 3 month supply
- "Seasonale", "Seasonique"
- Now LO-formulation

Contraceptive Patch

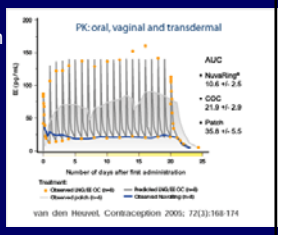
- 0.75 mg of ethinyl estradiol
- Norelgestromin (norgestimate)
- Pharmacokinetics
  - Design 20 microgms/150 microgms
  - Systemic exposure 60% higher than OCP users taking a 35 microgram pill
- 90 kg weight limit

Combination Hormonal Patch: Ortho Evra

- Perfect use failure rate 0.3%. Typical use rate unknown
- Appropriate use
  - Applied weekly for 3 weeks
  - One patch-free week for withdrawal bleed
  - Recommended application sites: upper arm, buttocks, lower abdomen, upper torso (excluding the breasts)

Vaginal Contraceptive Ring: NuvaRing

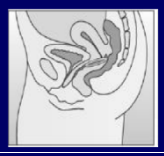
- 99% effective
- Mechanism of action
- Avoids first-pass metabolism and GI interference
- Lower hormonal dose
- Uniform hormone concentration



Vaginal Ring - NuvaRing

- Ethinyl estradiol at rate of 15 mcgms/day
- Etonogestrel 120 mcgms per day
- Three weeks in/ one week out
- Can be out of vagina only 3 hours before back-up contraception needed

  Back-up x 7 days



EBM: Patch vs Ring vs OCP's

- Cochrane Review-moderate quality
- Is there a difference in effectiveness or safety?
- Contraceptive effectiveness similar
- Vaginal ring users are more satisfied
- Is there more risk of VTE with patch?
  - VTE events in study were too low to reach a definite conclusion about safety profiles

Combined Contraception Shot

- 25 mg medroxyprogesterone
- 5 mg estradiol cypionate
- Monthly
- Approved by FDA but not available in US
- Available in Mexico

Progestin - Only Methods

Progestin Only

- OCP's
- Implants
- Depo-Provera
  - 150 mg medroxyprogesterone
- Mirena
  - Releases 20 mcg levonorgestrel per day
  - 5 years of efficacy
  - Oligomenorrhea
  - Maintains estradiol levels

Implanon / Nexplanon

- Differs from Norplant
  - 1 rod instead of 6
  - Less androgenic progesterone
    - 3-keto desogestrel instead of levonorgestrel
  - Higher rate of amenorrhea - unscheduled bleeding
- Designed for 3 years of use
- Initial hormone release 67µg/day, decreases to 30 µg/day after 2 years
- Concentrations that inhibit ovulation within 8 hours of insert, steady state at 4 months
- Rapidly reversible, prompt return to fertility
- Unscheduled bleeding, headache, weight change are common complaints

Depo-Provera – Bone Density

- 25% of users have estrogen in menopausal range
- Some users decrease bone density 7%
- Regain lost bone within 2 yrs
- 2 year use threshold
- Women > 40 y/o -? Time to regain
- Younger women - ? Affect peak density

Intrauterine Devices

- History
  - World-wide is most popular nonpermanent
  - 2-10% of US women
  - Decreased use in 1980's –Dalkon Shield
- Copper-releasing Mirena
- Progestin-releasing ParaGard
- Mechanism of action
- Contraceptive effects reversible after removal

IUD Patient Selection

- Ideal candidate: parous woman in mutually monogamous relationship without hx of PID
- Nulliparous women
  - Yes
  - More challenging insertion
  - Higher risk expulsion
  - Higher failure rates

Hormone-releasing IUD

- 99.9% effective (5)
- $300 to $400 every 5 years
- Mechanism of action
  - 52mg levonorgestrel released at rate of 20mcg/day
  - Thickens cervical mucus
  - May stop ovulation
  - Thins uterine lining
- Good for 5 years

Hormone-releasing IUD

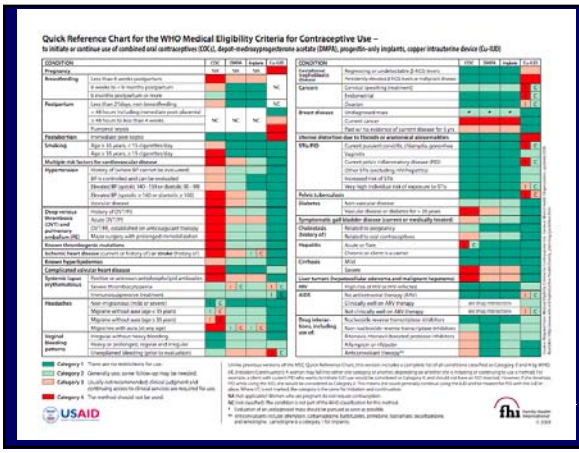
- Advantages
  - Typically reduces menorrhagia and dysmenorrhea
  - 20 % amenorrhea at 1 year (5)
  - Estradiol levels maintained so no increased risk of osteopenia (5)
  - Lower risk of PID than with copper IUD
- Disadvantages/Adverse events
  - Possible spotting/irregular bleeding during first 6 months post-insertion
  - Cramping
  - Amenorrhea, acne, depression, weight gain, decreased libido, headache
  - Perforation
  - Expulsion

Copper IUD

- 99.2% effective (5)
- $250 to $300 every 10 years
- Mechanism of action
  - Copper ions interfere with sperm mobility
  - Incites foreign body reaction that creates spermicidal environment
  - Barium sulfate makes it radiopaque
- Good for 10 years

Copper IUD: Pros and Cons

- Advantages
  - No hormone-related side effects
  - May provide protection against endometrial cancer (5)
  - Emergency contraception
- Disadvantages/Adverse events
  - Increase in menstrual blood loss, dysmenorrhea, anemia
  - Cramping
  - Perforation
  - Expulsion



Emergency Contraception

- 1970's Yuzpe Method-OCP's 100 mcg ethinyl estradiol and 1 mg norgestrel
- 2 tablets Q 12 hrs x 2 doses (Ovral)
- Progestin-only "Plan B"
- Levonorgestrel 0.75 mg Q12 hrs x 2 or 1.5 mg x 1
- Reduces risk of pregnancy to 1% if given within 72 hrs unprotected intercourse
- Advanced provision recommended

Emergency Contraception

- Plan B can be given as single dose (1.5mg)
- Copper IUD within 5 days of intercourse
- Mifepristone 10 mg po (not in US)
- Mechanism of Action hormonal EC
  - May delay ovulation
  - May interfere with fertilization
  - Does NOT interfere with implanted preg

Types of Emergency Contraception

Table 1. Types of Emergency Contraception.

Class	Dose	Brands Available in the United States
Combined oral contraceptives	100 μg of ethinyl estradiol and 0.3 mg of levonorgestrel twice 12 hr apart	Preven (Gynétics) Ovral (Wyeth)*
Progestin-only oral contraceptives	1.5 mg of levonorgestrel once or 0.75 mg twice 12 hr apart	Plan B (Women's Capital Corporation)
Copper T intrauterine device	—	ParaGard T 380A (Ortho-McNeil)
Antiprogestins	10 mg of mifepristone	None at this dose

* Other hormonal contraceptives that are effective for emergency contraception, along with the doses and instructions for use, are listed at http://www.not-2-late.com.

Westhoff C. N Engl J Med 2003;349:1830-1835

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Timing of emergency contraception

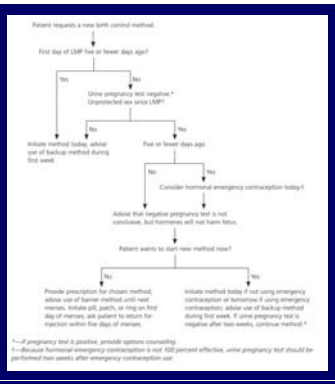
Quick Start Method

Same-Day Contraception Start

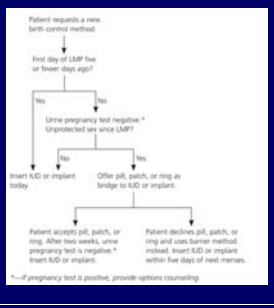
- EBM- Cochrane Review 2008
- 5 RCT of immediate start vs conventional start for hormonal contraception (n = 2,427)
- Medroxyprogesterone injection decreases unintended pregnancies
- Exposure to OCP's in early pregnancy is NOT harmful to growing fetus

Principles of Same Day Start Non-implantable Hormonal

- Negative pregnancy test in office
- Method can be started any day of menstrual cycle
- Barrier method x 7 days for women who are not in the first 5 days of cycle
- Emergency contraception offered if >5days LMP and unprotected sex
- F/U for urine pregnancy test in 2 weeks



"Quick Start" IUD or Implant



Adolescent Services

- Minor consent for services – Age 12 y/o
- "Quick Start" regimen
  - Initiate method right away
  - If starts OCP's, Nuvaring, Patch after Day 6, use condoms x 7 days and consider EC
  - Pregnancy test if 10 days post ovulation
- IUC's – can be considered
- GC/CT screening-annually, use urine

Adolescent Concerns

- DMPA
  - Concern re: decreased bone mineral density
- Lowest dose Combo OCP's
  - 20 mcg ethinyl estradiol (Alesse)
- Prevention of Bone Loss
  - Wt bearing exercise, adequate intake of calcium and Vit D, no Tobacco or ETOH

Long Acting Reversible Contraception (LARC)

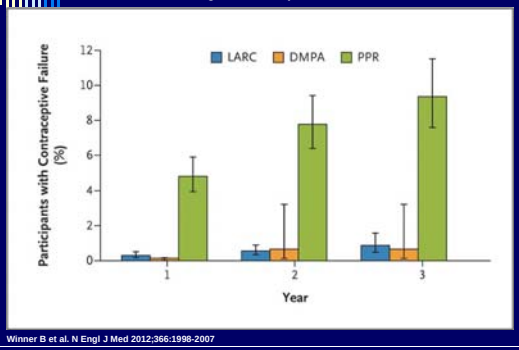
LARC Methods

- Intrauterine Devices
  - Progesterone-containing Mirena
  - Copper -containing Paragard
- Subdermal Implants
  - Implanon
  - Nexplanon
  - etonorgestrel

Prospective Study PROTECT

- 7486 participants
- IUD, Implant, DMPA, Pill, Patch or Ring
- 334 unintended pregnancies
- Failure rate 4.55/100 user years PPR
- Failure rate 0.27/100 user years LARC
- PPR users - age <21 yrs had 2x failure rate compared to those >21 years

Cumulative Percentage of Participants Who Had a Contraceptive Failure at 1, 2, or 3 Years, According to Contraceptive Method.



Winner B et al. N Engl J Med 2012;366:1998-2007

The NEW ENGLAND JOURNAL of MEDICINE

Patient Cases

- Adolescent
- Post Partum
- 35 y/o female

Case #1

- 17 y/o G1 P0 never sexually active here with boyfriend to begin birth control.
- Issues:
  - Does she need a pap smear?
  - Any concerns specific to adolescent
  - When to start?
  - Emergency Contraception?

Case #2

- 24 y/o G1P1 female at 6 weeks postpartum, breastfeeding.
- Issues:
  - Hormonal contraception and breastfeeding

Case #3

- 35 y/o G2 P2 female not sure whether she wants to be pregnant again, not ready for permanent method.
- Issues:
  - Smoking
  - Cardiovascular risks

19 y/o G1P1 requests Mirena

- LMP 3 days ago
- Used Micronor (progesterone-only ocp's) but stopped weeks ago
- 3 months post partum
- How would you proceed?

23 y/o G1P1 requests Paragard

- 4 months post partum
- 7 days LMP
- Sexual intercourse yesterday
- GC/Chlam neg 2 months pp
- How would you proceed?

References

- Winner, B et al. Effectiveness of Long-Acting Reversible Contraception. NEJM 2012; 366: 1998-2007.
- Westhoff, C. Emergency Contraception. NEJM 2003; 349: 1830-5.
- Petitti, D. Combination Estrogen-Progestin Oral Contraceptives. NEJM 2003; 349: 1443-50.
- Lesnewski, R., Prine, L. Initiating Hormonal Contraception. Am Fam Physician 2006; 74: 105-12.
- MMWR July 2011. Update to CDC's U.S. Medical Eligibility Criteria for Contraceptive Use 2010

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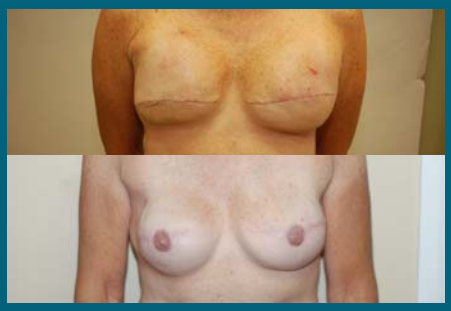

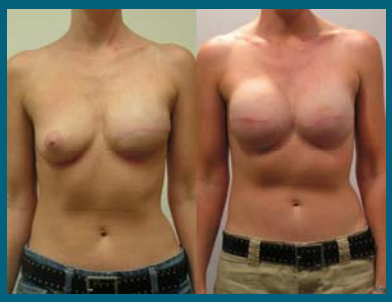

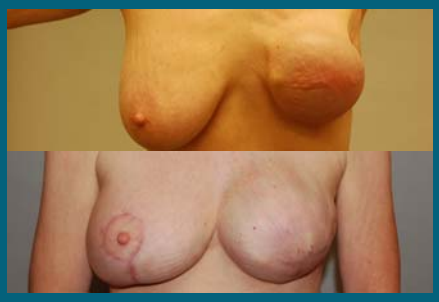

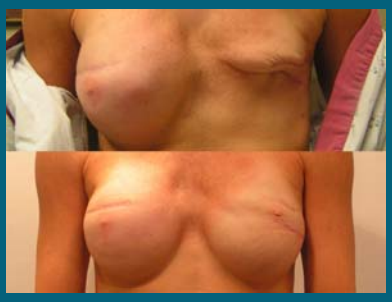

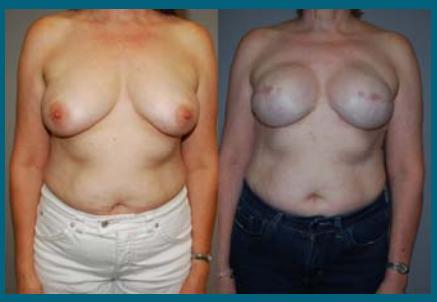

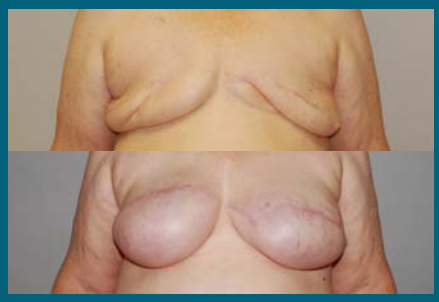

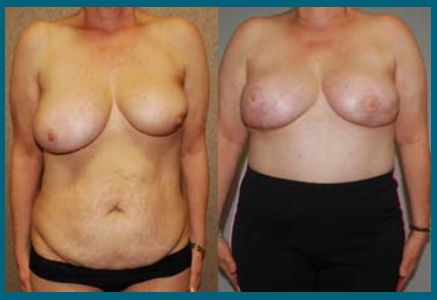

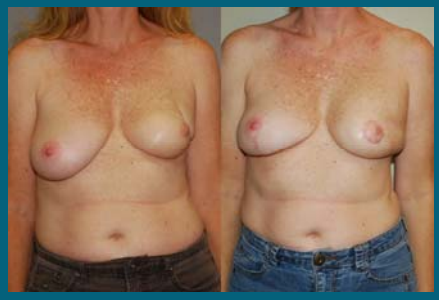

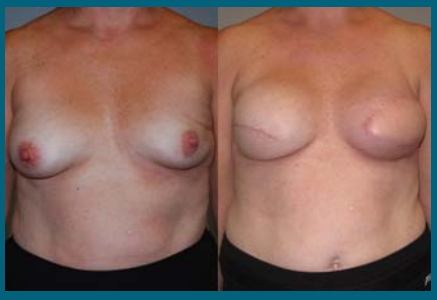

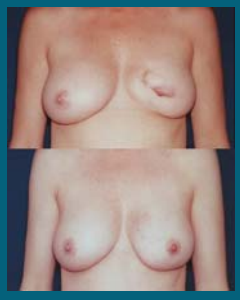

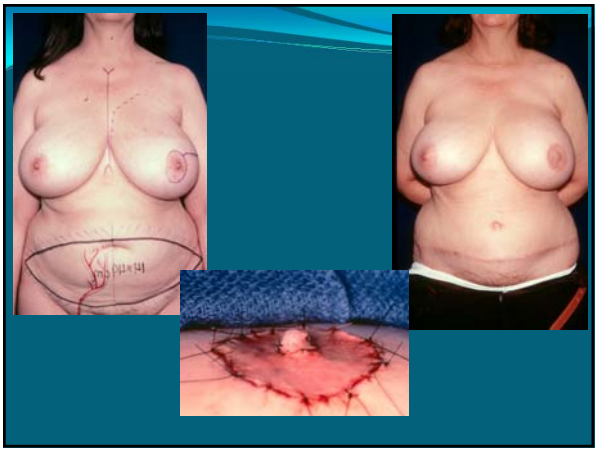

Suspicious Breast Mass

Elizabeth Revesz, MD
Breast Surgeon
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Objectives

1. Understand the significance of breast cancer in the U.S.
2. Have improved knowledge of the diagnostic approach to suspicious breast masses
3. Gain insights into the surgical approach to diagnosis and management of breast masses

the significance of breast cancer in the U.S.

Trends in 5-Year Relative Survival Rates* (%)

by Year of Diagnosis,

United States, 1975 to 2006

	ALL RACES		
	1975 TO 1977	1984 TO 1986	1999 TO 2006
All sites	50	54	68†
Brain	24	29	36†
Breast (female)	75	79	90†
Colon	52	59	66†
Esophagus	5	10	19†
Hodgkin lymphoma	74	80	87†
Melanoma of the	83	87	93†
Non-Hodgkin lymphoma	48	53	69†
Prostate	69	76	100†
Pancreas	3	3	6†
Ovary	37	40	45†
Testis	83	93	96†
Rectum	49	57	69†
Lung & bronchus	13	13	16†
Thyroid	93	94	97†

†The difference in rates between 1975-1977 and 1999-2006 is statistically significant (p<0.05).

Breast Cancer

- **2008 Estimates based on SEERs data**
  - Estimated 182,460 new cases of breast cancer
  - Currently there are over 2 million women living in the US who have been diagnosed with and treated for breast cancer.
  - Estimated 40,480 would die of breast cancer
  - From 2004-2008, the median age at diagnosis for cancer of the breast was 61 years of age

Surveillance Epidemiology and End Results
providing information on cancer statistics to help reduce the burden of this disease on the U.S. population
http://seer.cancer.gov/statfacts

- One person is diagnosed with breast cancer every 3 minutes
- One person dies of breast cancer every 14 minutes
- People over the age of 50 account for 75% of breast cancer cases

Joan McLaughlin WOMEN'S CENTER FOR HEALTH AND HEALING

the diagnostic approach to suspicious breast masses

www.pph.org/women

Joan McLaughlin WOMEN'S CENTER FOR HEALTH AND HEALING

H&P

- History:
  - When- was it discovered
  - Who- was this found by patient or by another physician
  - How- self exam, accidentally, trauma
  - Any previous history

(Medical and surgical history should be obtained as well it can play a role)

www.pph.org/women

Joan McLaughlin WOMEN'S CENTER FOR HEALTH AND HEALING

Risk Factors

- Female gender
- Caucasian
- Age 50 or older
- Having personal history of breast or ovarian cancer
- Abnormal breast biopsies
- First degree relatives (mother, father, sister, child) with breast cancer
- A mutation in the BRCA1 or BRCA2 gene
- Early menstrual periods (before age 12)
- Late menopause (after age 55)
- Never pregnant or first pregnancy after age 30
- Radiation exposure of the chest
- Alcohol consumption
- Obesity and lack of exercise
- Hormone replacement therapy

www.pph.org/women

Joan McLaughlin WOMEN'S CENTER FOR HEALTH AND HEALING

Physical exam

- Breast exam:
  - Visual inspection:
    - Sitting up – arms resting in lap
    - Sitting up- arms raised above head
  - Palpation:
    - Full breast exam sitting up
    - Axillary exam sitting up
    - Full breast exam supine with arm raised above the head

www.pph.org/women

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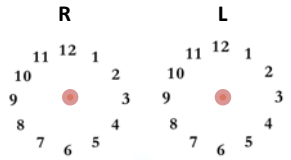
Physical exam

- Symmetry
- Describing the mass:
  - Side
  - Size
  - O'clock/ Quadrant
  - Distance
  - Consistency: firm, rubbery, smooth, multi-lobed, fluctuating
  - Skin: dimpling, color change
  - Relationship: fixed, movable, attached to skin or chest wall
  - Nipple: discharge, flaky, ulcerated, inverted



www.pph.org/women

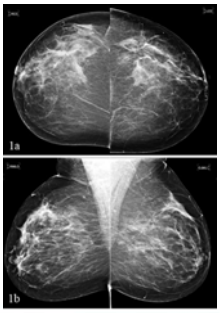
Joan McLaughlin WOMEN'S CENTER FOR HEALTH AND HEALING

Imaging

- Diagnostic mammogram
- Ultrasound
  - The order should contain the description and the location of the palpable mass
  - Include a very short history and risk factors
  - The more the radiologist knows the better their understanding of what they are looking at.

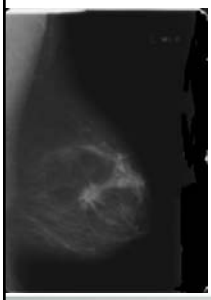
www.pph.org/women

Screening Mammogram

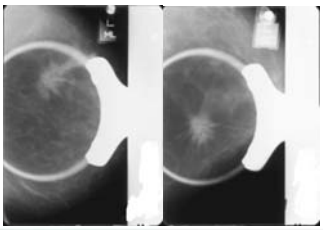


- Two views
- Detects changes in density
- Detects calcifications

Mammogram Diagnostic

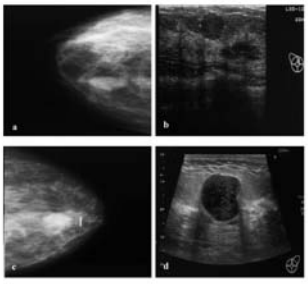


- Multiple views
- Spot compression
- Magnification



Ultrasound

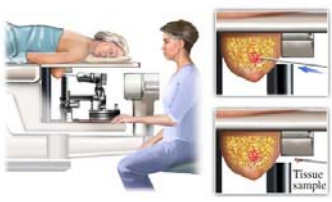
- Not a screening test
- Used to further evaluate a palpable mass or a mammographic finding

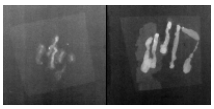


the surgical approach to diagnosis of breast masses

- If the mass remains suspicious a core needle biopsy is recommended.
- This should be done under image guidance:
  - Stereotactic or Ultrasound
- The only times surgical biopsy is acceptable is:
  - mass cannot be adequately sampled via core needle
  - Non-concordance
  - Patient cannot tolerate the procedure

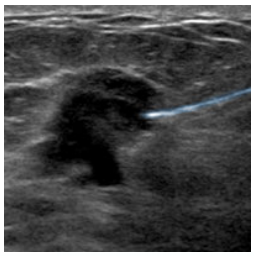
Biopsy

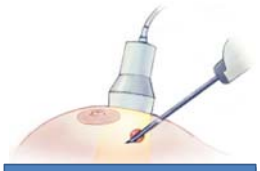




Stereotactic core needle biopsy

Biopsy





Ultrasound guided core needle biopsy

the surgical approach to management of breast masses

Breast Conserving Therapy ~ Mastectomy (BCT)

NSABP B-06:

Fisher B, et al. NEJM 2002;347(16):1233-1241

	Lumpectomy	Lumpectomy + XRT	Mastectomy
LR	39.2%	14.3%	5%
DFS	45%	46%	49%
OS	46%	46%	47%

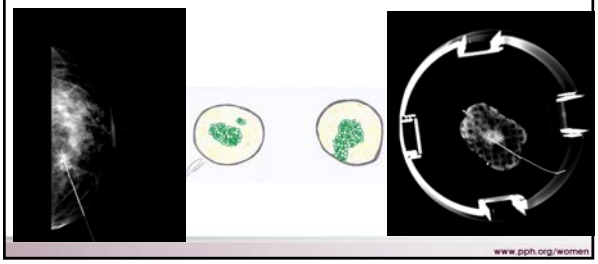
Milan Study:

Veronesi U, et al. NEJM 2002;347(16):1227-1232

	Quadrantectomy + XRT	Mastectomy
LR	8.8%	2.3%
Death rate	41.7%	41.2%

BCT

- Lumpectomy, segmental mastectomy, quadrantectomy
- Palpation guided or needle localization
- Requires negative margins
- Post operative radiation



Contraindications to BCT

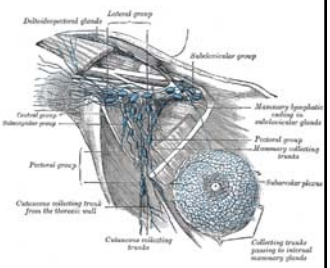
- Pregnancy
- Previous mantle radiation
- Inflammatory breast cancer
- Large tumor to breast ratio
  - Neoadjuvant therapy
- Multicentric disease
- Pts without access or the ability to have radiation

Sentinel Lymph Node

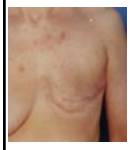
- Technechium 99 sulfur colloid and Lymphozuryn
- Not necessary for most DCIS
- 1-3 sentinel nodes are removed
- If > 2 sentinel nodes are positive, completion axillary dissection is recommended.

Axillary Dissection

- removal of additional lymph nodes
- risk of lymphedema approximately 15-20%, compared to sentinel node biopsy which has 1-2% risk of lymphedema.



Mastectomy



- Simple mastectomy
  - Surgical removal of the breast and the extra skin
  - The end result is a flat chest.
- Skin sparing mastectomy
  - Surgical removal of the breast with the nipple and areolar complex. Immediate reconstruction is necessary.
- Nipple sparing mastectomy
  - Surgical removal of the breast leaves nipple and areola and the skin, immediate reconstruction is necessary. Strict requirements need to be met to ensure a good outcome.

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Thank you

The Z-11 trial

- Prospective randomized trial
- T1 and T2 clinically node negative breast cancer, with <3 positive sentinel nodes, treated with breast conserving surgery, and whole breast irradiation. > 3 positive nodes had ALND.
- After a 6.3-year follow-up
- ALND had 0.4% recurrence rates
- SLN BX had 0.9% recurrence rates
- No significant difference at preventing recurrence or improving survival between the two groups.

- These findings hold true only for patients that fit the protocol of the trial.

Giuliano et. al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg. **2010** Sep;252(3):426-32; discussion 432-3.

- BCT
  - Chance of recurrence without radiation is 40%
  - Chance or recurrence with radiation is 5%
  - Risk of developing a new cancer in either breast is 15-20%
- Mastectomy
  - Chance of recurrence is 5%
  - Risk of developing a new cancer is 2-5%
  - Skin sparing mastectomy
  - Nipple sparing mastectomy

Lipid Management in the CKD Patient:

A Patient-Centered Approach to Care

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Disclosures

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Overview

- Incidence of CKD is increasing
- CVD is very common in patients with CKD and CKD patients often have major lipid abnormalities
- Many clinicians, however, are reluctant to treat CKD patients aggressively

This program will review:

- Staging and epidemiology of CKD
- Epidemiology of CVD in the CKD population
- Characteristics of dyslipidemia found in CKD patients
- Evidence concerning treatment of dyslipidemia
- Results of the SHARP clinical trial

Harper et.al. Managing Dyslipidemia in Chronic Kidney Disease. *J Am Coll Card.* 2008;51(25)2375-2384.

Learning Objectives

At the conclusion of this program the learner should be able to:

1. Review the role of GFR and urine albumin in screening for CKD
2. Discuss risk factors that contribute to CKD
3. Explain the pathophysiology of dyslipidemia in CKD
4. Discuss the importance of LDL reduction in patients with CKD
5. Discuss the pharmacologic and non-pharmacologic options for treating dyslipidemia in patients with CKD
6. Employ a patient-centered approach in treating patients with dyslipidemia in CKD

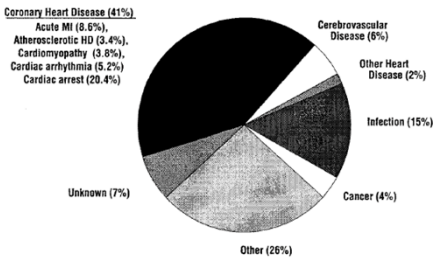
Pop Quiz

Q: What is the leading cause of death for patients with CKD?

a. Renal failure
b. Cardiovascular disease
c. Infection
d. Cerebrovascular disease

Pop Quiz

Answer: Cardiovascular Disease



K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. *American Journal of Kidney Diseases, Vol 41, No 4, Suppl 3 (April), 2003: pp S11-S21*

Definition of Chronic Kidney Disease

Either present for at least 3 months:

- GFR <60 mL/min/1.73m^2
- Evidence of structural kidney damage, e.g. microalbuminuria/proteinuria, polycystic kidney disease, etc.

K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. *American Journal of Kidney Diseases, Vol 41, No 4, Suppl 3 (April), 2003: pp S11-S21*

Epidemiology of Chronic Kidney Disease

Prevalence of CKD is rising:
•16.8% of US population aged 20 and older (NHANES 2004) up from 14.5% (1988-1994)

Most CKD is stages 1-3
•97.6% of those with CKD are in stages 1-3, with 2.3% in stages 4-5.

Prevalence rises with age:
•20 – 39 yrs. = 8.5%
•40-59 yrs. = 12.6%
•≥60 yrs. = 39.4%

No significant gender difference

Saydah S, et al. Prevalence of Chronic Kidney Disease and Associated Risk Factors — United States, 1999—2004. MMWR March 2, 2007;56(08):161-165.

Epidemiology of Chronic Kidney Disease

Modest racial differences:
•White = 16.1%
• Black = 19.9%
• Mexican-American = 18.7%

Prevalence strongly correlated with diabetes, CVD, and hypertension:
• Diabetes: 40.2%
• CVD: 28.2%
• Hypertension: 24.6%

Modest correlation with obesity: 19.8%

Saydah S, et al. Prevalence of Chronic Kidney Disease and Associated Risk Factors — United States, 1999—2004. MMWR March 2, 2007;56(08):161-165.

Case Study

Mr. Clark: 53-year-old African-American male

PMH: type-2 diabetes, "borderline" hypertension, hypercholesterolemia

No medications

Social history: non-smoker, moderate alcohol, sedentary, sales job with extensive travel

Family history: maternal hypertension, paternal hypertension, DM2 ESRD/HD.

Temperature: 98.1

Pulse: 85

BP: 146/88

BMI: 32

Exam: WNL

What tests would you order?

Case Study

Lab tests ordered (fasting):

•CBC
•BMP
•AST/ALT
•Hgb A1c
•Lipid Profile
•TSH
•Microalbumin
•Baseline EKG

Assessing Kidney Function

- Serum creatinine level alone is an inadequate measure of kidney function/dysfunction
- K/DOQI guidelines recommend:
  - ✓ All individuals should be assessed for risk of CKD as part of routine health care
  - ✓ GFR should be calculated (either MDRD or CKD-EPI equations)
  - ✓ Proteinuria may be assessed with urine dipsticks, but for adults at high risk for CKD, albumin should be measured since this is a more sensitive measure of kidney damage

National Kidney Foundation. *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39:S1-S266,* 2002 (suppl 1).

Stages of Kidney Disease

Stage	Description	GFR
1	Kidney damage with normal or elevated GFR (indicated byalbuminuria)	≥ 90
2	Kidney damage with mild GFR reduction	60-89
3	Moderate reduction in GFR	30-59
4	Severe reduction in GFR	15-29
5	Kidney failure (ESRD)	< 15 or dialysis

K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. *American Journal of Kidney Diseases, Vol 41, No 4, Suppl 3 (April), 2003: pp S11-S21*

Risk Factors for Chronic Kidney Disease

- Diabetes
- Hypertension
- Age 60 years or older
- Racial or ethnic minorities
- Exposure to known nephrotoxins
- Low income or education level
- Autoimmune disease
- Systemic infection
- Urinary tract infections
- Nephrolithiasis
- Neoplasia
- Family history of kidney disease
- Recovery from acute kidney injury
- Reduction in kidney mass
- Low birth weight

National Kidney Foundation. *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39:S1-S266,* 2002 (suppl 1).

Lipid Abnormalities Associated with CKD

Dyslipidemia associated with decreased GFR includes:

- Profound dysregulation of lipoprotein metabolism
- Development in early stages of CKD
- ↓ HDL
- ↑ Triglyceride-rich lipoproteins
- Significant atherogenic potential

Harper et.al. Managing Dyslipidemia in Chronic Kidney Disease. *J Am Coll Card.* 2008;51(25)2375-2384.

Lipid Abnormalities Associated with CKD

But in CKD a different cardiovascular pathology also emerges:

- Vascular stiffness
- Vascular calcification
- Structural heart disease
- Sympathetic overactivity

Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998; 32 (suppl 3): S112–19.

Case Study

Mr. Clark's lab results come back with the following values:

Cr: 2.0 mg/dL
GFR: 47.9 mL/min/1.73m^2
Glu: 257 mg/dL
$A1_c$: 9.7%
Urine albumin: 123 mg/g
Total cholesterol: 203 mg/dL
LDL: 134 mg/dL
TG: 190 mg/dL
HDL: 31 mg/dL

What is your assessment of Mr. Clark's medical problems?

Case Study

Mr. Clark's Medical Problems:

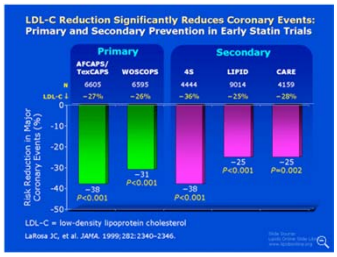
- Stage 3 CKD
- Uncontrolled DM
- Uncontrolled HTN
- Multiple risk factors for CVD

Prescription:

- Therapeutic lifestyle changes
- ACE or ARB for hypertension
- Tx diabetes, avoiding metformin
- Work up etiology of CKD: rule out SLE, HIV, syphilis, hepatitis, multiple myeloma
- After hypertension and diabetes are nominally controlled, initiate statin with target LDL of less than 100

Statins For CKD Lipid Management

Statins clearly lower the risk of major coronary events in the non-CKD population.



LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA*. 1999;282:2340-2346.

Statins For CKD Lipid Management

Question: Are statins effective for CKD patients and, in particular, patients with more severe (non-atherogenic) CVD?

First attempts to answer involved sub-group analysis and meta-analysis of previous statin trials. Results were difficult to interpret:

- Some evidence for reduction of CV events, regardless of CKD stage, but no reduction in mortality
- Some data suggested benefit of statins only for CKD patients with pre-existing CVD

SHARP trial designed to clarify these data

Kanbay M, et a. Statin treatment for dyslipidemia in chronic kidney disease and renal transplantation: a review of the evidence. *J Nephrology*. 2009;22:598-609.

SHARP Trial

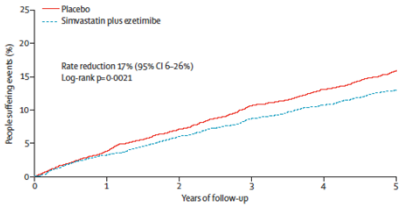
Methods:

- Randomized, double-blind
- N = 9270 (3023 on dialysis and 6247 not)
- Patients assigned to simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo.
- Primary endpoint: non-fatal MI, coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure

Baigent C et.al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. *Lancet*. Published online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3.

SHARP Trial

Results:



Baigent C et.al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. *Lancet*. Published online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3.

SHARP Trial

- No increase in risk of myopathy, liver and biliary disorders, cancer, or non-vascular mortality
- No substantial effect on kidney disease progression
- Similar proportional reductions in all subgroups (including among dialysis and non-dialysis patients)

Baigent C et.al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. *Lancet*. Published online June 9, 2011 DOI:10.1016/S0140-6736(11)60739-3.

Guidelines For Lipid Management in CKD Patients

SHARP affirms existing NKF-K/DOQI guidelines for the management of lipids in patients with CKD

1. All adults and teens with CKD should be evaluated for dyslipidemia
2. Assessment should include a complete fasting lipid profile with total cholesterol, LDL, HDL, and triglycerides

K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. *American Journal of Kidney Diseases, Vol 41, No 4, Suppl 3 (April), 2003: pp S11-S21*

Guidelines For Lipid Management in CKD Patients

3. CKD patients with dyslipidemia should be evaluated for remediable, secondary causes
   - ✓ Uncontrolled DM
   - ✓ Nephrotic-range proteinuria
   - ✓ Uncontrolled hypothyroidism
4. Initiate therapeutic lifestyle changes in all patients with lifestyle-related risk factors regardless of lipid levels:
   - ✓ Modify diet to reduce cholesterol and saturated fats
   - ✓ Increase fiber intake
   - ✓ Weight reduction
   - ✓ Increase physical activity

K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. *American Journal of Kidney Diseases, Vol 41, No 4, Suppl 3 (April), 2003: pp S11-S21*

Guidelines For Lipid Management in CKD Patients

5. Dyslipidemia treatment varies according to lipid levels

Table 25. The Management of Dyslipidemias in Adults with Chronic Kidney Disease.

Dyslipidemia	Goal	Initiate	Increase	Alternative
TG ≥500 mg/dL	TG <500 mg/dL	TLC	TLC + Fibrate or Niacin	Fibrate or Niacin
LDL 100-129 mg/dL	LDL <100 mg/dL	TLC	TLC + low dose Statin	Bile acid seq. or Niacin
LDL ≥130 mg/dL	LDL <100 mg/dL	TLC + low dose Statin	TLC + max. dose Statin	Bile acid seq. or Niacin
TG ≥200 mg/dL and non-HDL ≥130 mg/dL	Non-HDL <130 mg/dL	TLC + low dose Statin	TLC + max. dose Statin	Fibrate or Niacin

K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. *American Journal of Kidney Diseases, Vol 41, No 4, Suppl 3 (April), 2003: pp S11-S21*

Statin Dosing

NCEP suggests more intensive statin therapy:

- Treat according to global CVD risk level, not just lipid values
- Achieve at least a 30% to 40% reduction in LDL-C
- May need combination therapy to achieve goals

Grundy SM, Cleeman JI, Merz CN, et al, for the National Heart, Lung and Blood Institute, the American College of Cardiology Foundation, and the American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110:227-239.

Statin Dosing

Daily doses of currently-available statins required for a 30% - 40% LDL-C reduction

- 40 mg lovastatin
- 40 mg pravastatin
- 40-80 mg fluvastatin
- 20-40 mg simvastatin
- 10 mg atorvastatin
- 5-10 mg rosuvastatin

Note: dose adjustments for renal function are not required because statins are hepatically metabolized

Grundy SM, Cleeman JI, Merz CN, et al, for the National Heart, Lung and Blood Institute, the American College of Cardiology Foundation, and the American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110:227-239.

Clinical Practice Tips Related to Statins

- Statins are relatively safe
- Baseline creatine phosphokinase level
- Re-check lipids 6 – 12 weeks from initiation
- Once target LDL is achieved, test annually
- Be aware of potential polypharmacy hazards
- Consider different statin or “holiday” period for myalgias without CPK elevation
- Side effects vary—don’t give up on statins at first sign of side effects!

Expert Panel Meeting June 6, 2011, Nashville TN.

Other Pharmacotherapeutic Options

Ezetimibe

•Used safely with simvastatin in CKD (SHARP trial)

Fibrates

•Consider for CKD patients if TG levels are persistently above 500 mg/dL

Niacin

•Recent NHLBI trial stopped early because no benefit was seen when added to atorvastatin; small increased risk of ischemic stroke in the high-dose niacin arm

Fish oil

•No trial data showing improved outcomes, but may have other benefits

Expert Panel Meeting June 6, 2011, Nashville TN.
NIH News. NIH stops clinical trial on combination cholesterol treatment. Press release. May 26, 2011.

Case Study

Mr. Clark returns in 12 weeks for follow-up tests, which reveal the following:

GFR: 46.2 mL/min/1.73m^2
Glu: 195 mg/dL
Urine albumin: 125 mg/g
Total cholesterol: 186 mg/dL
LDL: 119 mg/dL
TG: 185 mg/dL
HDL: 30 mg/dL

How would you proceed?

Case Study

Mr. Clark returns in 12 weeks for follow-up tests, which reveal the following:

GFR: 46.2 mL/min/1.73m^2
Glu: 195 mg/dL
Urine albumin: 125 mg/g
Total cholesterol: 186 mg/dL
LDL: 119 mg/dL
TG: 185 mg/dL
HDL: 30 mg/dL

Upon questioning, Mr. Clark admits he has not been taking the statin regularly because he thinks it is causing muscle soreness and pain—though he also has been trying to exercise more, so the soreness may be unrelated to the statin.

Case Study

Clinical strategy:

- Switch to another statin
- Trial off stain then restart
- Support continuing TLC

Guideline Comparison

The 2 most widely-used guidelines for lipid management differ in some key ways.

NKF-K/DOQI Guidelines	Adult Treatment Panel III Guidelines
1. CKD patients should be considered to be in the highest risk category.	1. CKD patients are not managed differently from other patients.
2. Evaluation of dyslipidemias should occur at presentation with CKD, after a change status, and annually.	2. Evaluation of dyslipidemias should occur every 5 years.
3. Drug therapy should be used for LDL 100-129 mg/dL after 3 months of TLC.	3. Drug therapy is considered optional for LDL 100-129 mg/dL.
4. Initial drug therapy for high LDL should be with a statin.	4. Initial drug therapy for high LDL should be with a statin, bile acid sequestrant, or nicotinic acid.
5. Recommendations are made for patients <20 years old.	5. No recommendations are made for patients <20 years old.
6. Fibrates may be used in Stage 5 CKD a) for patients with triglycerides ≥500 mg/dL; and b) for patients with triglycerides ≥200 mg/dL with non-HDL cholesterol ≥130 mg/dL, who do not tolerate statins.	6. Fibrates are contraindicated in Stage 5 CKD.
7. Gemfibrozil may be the fibrate of choice for treatment of high triglycerides in patients with CKD.	7. No preferences are indicated for which a fibrate should be used to treat hypertriglyceridemia.

K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. *American Journal of Kidney Diseases, Vol 41, No 4, Suppl 3 (April), 2003: pp S11-S21*

Patient-Centered Care

Suggestions for improving patient care:

- ✓ Ask patients about the non-medical aspects of their lives
- ✓ Provide culturally-specific educational materials written or produced at an appropriate reading level (typically 7th grade)
- ✓ Explore patient beliefs about their illnesses and possible treatments
- ✓ Consider adopting the "medical home" model of health care delivery

Providing culturally competent, patient-centered care

- Physicians can improve their own communication skills and "cultural competence"
- Expert Panel suggestion: physicians bring mindful reflection and creativity to every encounter with a patient
- Clinical care should be patient-centered and tailored to each individual within the context of his or her family and community.

Case Study

Mr. Clark returns in 2 months for $A1_c$ and other labs with the following results:

BP: 126/70
GFR: 46.0 mL/min/1.73m^2
Glu: 182 mg/dL
$A1_c$: 7.1%
Urine albumin: 110 mg/g
Total cholesterol: 173 mg/dL
LDL: 104 mg/dL
TG: 173 mg/dL
HDL: 34 mg/dL

What is your interpretation?

Case Study

Mr. Clark has made significant progress.
•HTN: controlled
•DM Type 2: markedly improved
•Dyslipidemia: His LDL is nearly at goal, HDL and TG not yet optimal
•Stage 3 CKD: stable

Thoughts/Plans:
•Although TG and HDL are not optimal, neither a fibrate nor niacin is indicated
•TLC and/or titration of statin to achieve LDL goal
•Blood sugar levels are better, but consider additional TLC and/or combination therapy to lower $A1_c$ further
•Continue patient-centered approach, supporting TLC with referrals as needed
•Schedule follow-up visit in 3-6 mo.

Conclusions

- Roughly 1 of every 6 US adults has CKD
- Bulk of CKD is in stages 1-3
- Hypertension & diabetes major contributing risk factors
- CV disease accounts for roughly half of CKD mortality
- Family physicians can address this problem
- Assessment must include eGFR and tests for proteinuria—preferably urine albumin

Conclusions

- Focus on lowering LDL with TLC and statin or statin combination therapy
- SHARP demonstrated 17% reduction in CV events in CKD population
- More intense lipid management in CKD patients has the potential to significantly reduce CV morbidity

Discussion

Pertussis Vaccine Update
What is all the Whoop about?

Mark H. Sawyer, MD
University of California, San Diego
Rady Children's Hospital San Diego

Disclosures

- **I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial products or services discussed in this CME activity.**
- **I will discuss the off-label use of Tdap vaccine for seniors and pregnant women**

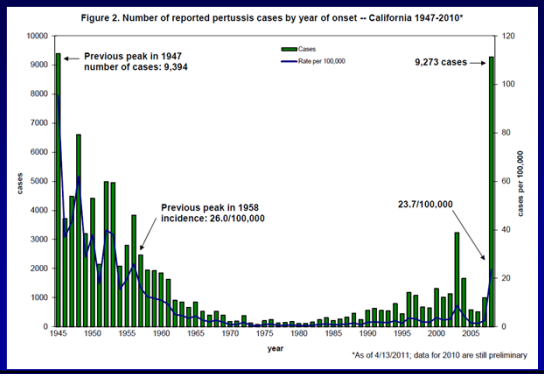
Questions you hear about pertussis immunization

- Why are we seeing so much pertussis?
  - ✓Does vaccine immunity wane quickly?
  - ✓Was DTP a better vaccine than DTaP?
- How are we doing with DTaP and Tdap vaccine coverage?
- What happened to the interval between prior Td and Tdap?
- Is Tdap vaccine safe in pregnancy?
- Can we immunize the elderly?
- Do we need a Tdap booster?

Objectives

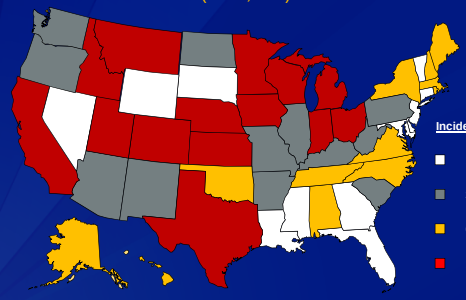
- List three reasons why pertussis remains so prevalent
- Describe current pertussis vaccine coverage levels
- Explain the rationale for removing a minimum interval between Td and Tdap
- Describe the current CDC recommendations for use of Tdap in pregnant women and seniors

California 2010: Highest number of pertussis cases in 63 years



Annual incidence by State, 2010

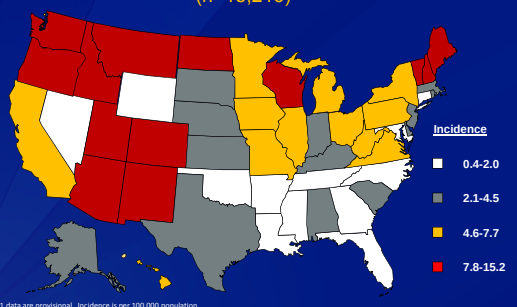
2010* incidence 9.0
(n-27,555)



Incidence is per 100,000 population
Source : CDC National Notifiable Disease Surveillance System, *2010 data accessed July 22, 2011
CDC Wonder Population Estimates (Vintage 2009) ; Courtesy of Tom Clark, MD

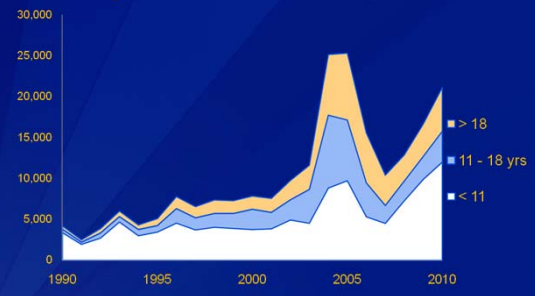
Annual incidence by State, 2011*

2011 incidence 5.0
(n=15,216)



*2011 data are provisional. Incidence is per 100,000 population
Source : CDC National Notifiable Disease Surveillance System, 2011
CDC Wonder Population Estimates (Vintage 2009) ; Courtesy of Tom Clark, MD

U.S. Reported Pertussis Cases, 1990-2010*



*2010 data are provisional.
CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service

Reported pertussis-related deaths by age-groups, U.S., 1980-2009

Age-group	1980-1989[1]	1990-1999[1]	2000-2009[2]
0-1 month	38	68	152
2-3 month	11	16	23
4-5 month	5	5	2
6-11 month	7	4	1
1-4 years	13	2	2
5-10 years	1	6	3
11-18 years	0	0	3
>18 years	1	2	8
Total	77*	103	194

* Includes one case with unknown age
[1] Vitek CR et al. Pediatr Infect Dis J 2003; 22(7):628-34.
[2] National Notifiable Diseases Surveillance System, CDC, 2009

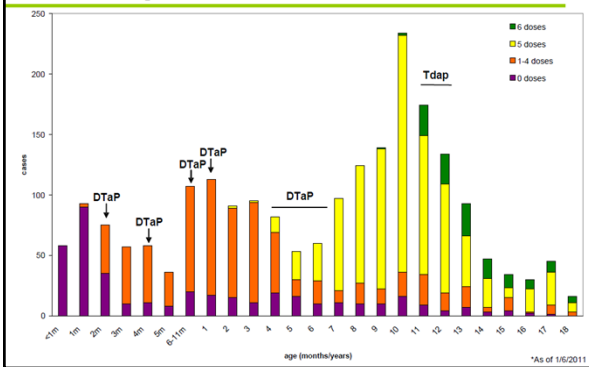
Questions you hear about pertussis immunization

- **Why are we seeing so much pertussis?**
  - ✓ **Does vaccine immunity wane quickly?**
  - ✓ **Was DTP a better vaccine than DTaP?**
- How are we doing with DTaP and Tdap vaccine coverage?
- What happened to the interval between prior Td and Tdap?
- Is Tdap vaccine safe in pregnancy?
- Can we immunize the elderly?
- Do we need a Tdap booster?

Reasons for outbreaks of Pertussis

- Pertussis is very contagious
- People who have pertussis can be contagious for up to 3 weeks
- Pertussis is difficult for doctors to recognize and diagnose
- Even after someone begins treatment for pertussis they are contagious for up to 5 days
- Immunity from prior vaccination or disease wanes over time so people become susceptible again.

Number of reported pertussis cases aged 0-18 years -- California 2010-2011*



*As of 1/6/2011

Overall VE & Duration of Protection Estimates

Model *	Case (n)	Control (n)	VE, %	95% CI
Overall VE, All Ages				
0 dose	53	19	Ref	--
5 doses	629	1,997	88.7	79.4 – 93.8
Time since 5th dose				
0 doses	53	19	Ref	--
< 12 months	19	354	98.1	96.1 – 99.1
12 – 23 months	51	391	95.3	91.2 – 97.5
24 – 35 months	79	366	92.3	86.6 – 95.5
36 – 47 months	108	304	87.3	76.2 – 93.2
48 – 59 months	141	294	82.8	68.7 – 90.6
60+ months	231	288	71.2	45.8 – 84.8

* Accounting for clustering by county and provider

Questions you hear about pertussis immunization

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- **How are we doing with DTaP and Tdap vaccine coverage?**
- What happened to the interval between prior Td and Tdap?
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- Do we need a Tdap booster?

Have you received a Tdap immunization?

- **1) Yes**
- **2) No**
- **3) Don't know**
- **4) I don't want to tell you**

Pertussis Vaccine Coverage Rate Data

Population	Coverage Level	Source
DTaP 19-35 months	84.4±1.0	NIS Infant 2010
Tdap, teens 13-17 years	68.7 (67.5-69.8)	NIS Teen 2010
Tdap, adults 19-64 years	6.6 (6.1-7.2)	NHIS 2009

http://www.cdc.gov/vaccines/stats-surv/default.htm , downloaded 9-24-2011

Questions you hear about pertussis immunization

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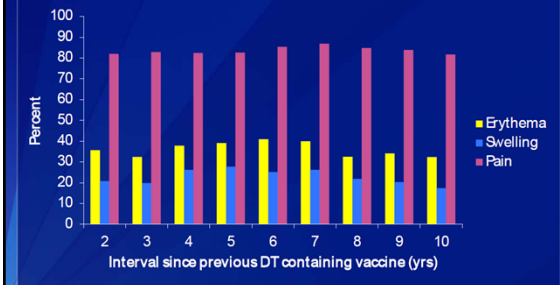
  - ✓Was DTP a better vaccine than DTaP?
- How are we doing with DTaP and Tdap vaccine coverage?
- **What happened to the interval between prior Td and Tdap?**
- Is Tdap vaccine safe in pregnancy?
- Can we immunize the elderly?
- Do we need a Tdap booster?

Percent of reported solicited adverse events in the 14 days after immunization with Tdap



Halperin SA, et. al. How soon after a prior tetanus-diphtheria vaccination can one give adult formulation tetanus-diphtheria-acellular pertussis vaccine? Pediatr Infect Dis J. 2006 25(3):195-200.

ACIP Tdap Recommendations

- Adolescents or adults who have not received a dose of Tdap or for whom vaccine status is unknown should be immunized as soon as feasible. Tdap can be administered regardless of interval since the last tetanus or diphtheria containing vaccine.

MMWR January 14, 2011/60(01);13-15

Questions you hear about pertussis immunization

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- **Is Tdap vaccine safe in pregnancy?**
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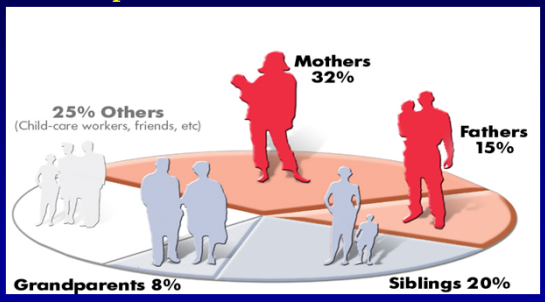
Tdap vaccine during pregnancy

Parents are the most common source of pertussis infection in infants



Bisgard, K. *PIDJ.* 2004;23:985-9. n=264 cases

Tdap during pregnancy?

- Move mother's dose to the 3rd trimester
  - Protect infant against transmission from mother (similar to postpartum)
  - Likely benefit -- direct immunity to infant through maternal antibodies[1]

[1] Healy et al 2004; Van Savage et al 1990; Gall et. Al. 2011; Leuridan, et al. 2008; Shakib et al 2010.

6

Garret R. Beeler Asay, presentation to ACIP 2011

Tdap during pregnancy The questions

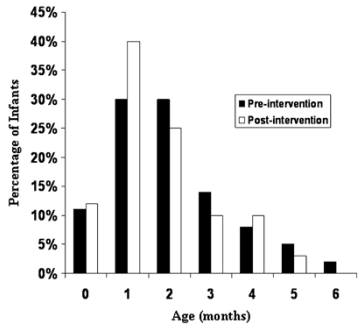
- Will other strategies work?
- Is the vaccine safe?
- Will maternal immunization blunt the infants subsequent response to DTaP?

Other vaccination strategies to protect infants from pertussis

Timing of Vaccination	Pros	Cons
Infant birth dose	• Protection for newborn (delayed)	• No vaccine in pipeline • Effect on immune response to primary DTaP series unknown
Before pregnancy	• Protection for mother • Possible immunity for newborn through transplacental transfer	• Duration of protection of Tdap is unknown
Postpartum (cocooning)	• Protection for mother (delayed) • Herd immunity (if other family members vaccinated) • Effectively implemented strategy	• No active transfer of immunity to newborn • Difficult to vaccinate other family members • No data on effectiveness • Programmatic challenges

Jennifer Liang, CDC Pertussis Workgroup

Pertussis-infected infants by age (in months) and intervention period.



Castagnini L A et al. Clin Infect Dis. 2012;54:78-84

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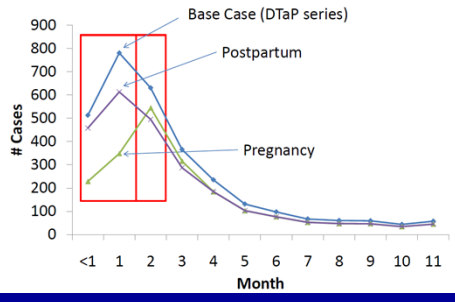
Clinical Infectious Diseases

Tdap safety during pregnancy

Data Source	Observations
General experience with inactivated vaccines including Td	n=millions. No pregnancy related adverse events observed
Vaccine manufacturer pregnancy registries	n=hundreds; no signal to suggest pregnancy related adverse events
VAERS data over 6 years	n=hundreds/thousands. No signal to suggest pregnancy related adverse events
Specific clinical trials	n=hundreds. No adverse events

Postpartum vs. Pregnancy



18

Garret R. Beeler Asay, presentation to ACIP 2011

What about "blunting"?

- Transplacental antibody may interfere with active antibody production following primary DTaP dose [1]
- Mixed evidence for blunting from acellular vaccine

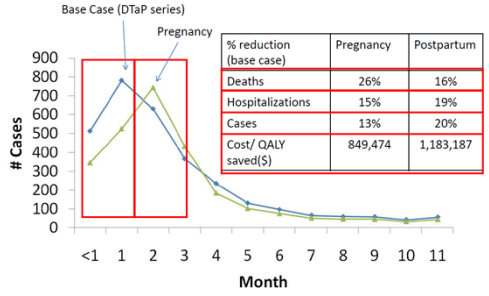
[1]Belloni (2003); Englund et al (1995); Halasa (2008); Van Savage (1990); Wood (2010)

7

Garret R. Beeler Asay, presentation to ACIP 2011

Worst Case Scenario

***50%** increase in risk of disease (months 3,4) & **20%** maternal antibody effectiveness*



% reduction (base case)	Pregnancy	Postpartum
Deaths	26%	16%
Hospitalizations	15%	19%
Cases	13%	20%
Cost/ QALY saved($)	849,474	1,183,187

28

Garret R. Beeler Asay, presentation to ACIP 2011

ACIP Tdap Recommendations During Pregnancy

- Women's health care providers should implement a Tdap vaccination program for pregnant women who previously have not received Tdap. Tdap should be administered during pregnancy, preferably during the third or late second trimester*. Alternatively, if not administered during pregnancy, Tdap should be administered immediately postpartum.

* After 20 weeks gestation

MMWR October 21, 2011 / 60(41);1424-1426

Cocooning Recommendation

- Adolescents and adults who have or who anticipate having close contact with an infant aged less than 12 months (e.g., parents, siblings, grandparents, child-care providers and healthcare providers) and who previously have not received Tdap should receive a single dose of Tdap.

Questions you hear about pertussis immunization

- Why are we seeing so much pertussis?
  - ✓Does vaccine immunity wane quickly?
  - ✓Was DTP a better vaccine than DTaP?
- How are we doing with DTaP and Tdap vaccine coverage?
- What happened to the interval between prior Td and Tdap?
- Is Tdap vaccine safe in pregnancy?
- **Can we immunize the elderly?**
- Do we need a Tdap booster?

Tdap in those >64 years of age

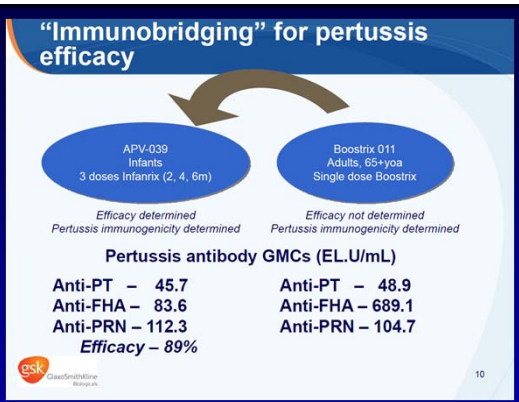
Courtesy of Tami Skoff

"Grandparent care"

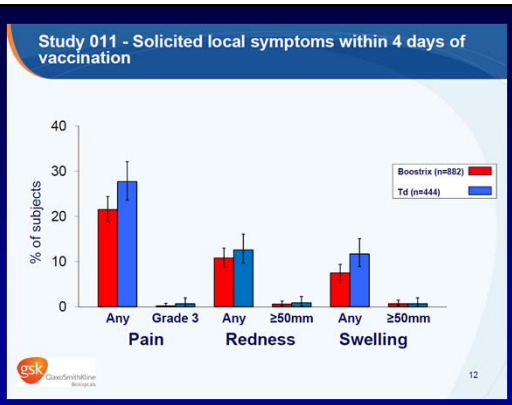
- 29.5% working mothers have grandparent provide childcare for children <5 years of age.[1]
- 35.2% (432/1229) of children (0-3 years) received grandparent care during at least one 3-month period.[2]

[1] Laughlin L. 2010. Who's Minding the Kids? Child Care Arrangements: Spring 2005 and Summer 2006. Current Population Reports, P70-121. U.S. Census Bureau, Washington DC. 2005.
[2] Vandell, DL, et al. 2004. Variations in Child Care by Grandparents During the First Three Years. J Marriage and Family. 66.

"Immunobridging" for pertussis efficacy



GSK presentation to ACIP 2010



GSK presentation to ACIP 2010

Tdap recommendations >64 years of age

- ACIP recommends that adults aged 65 years and older ~~who have or who anticipate having close contact with an infant less than 12 months of age and~~ who previously have not received Tdap should receive a single dose of Tdap . Tdap can be administered regardless of interval since the last Td. Either Tdap vaccine product may be used.

MMWR January 14, 2011/60(01);13-15; provisionally updated by ACIP February 2012

Questions you hear about pertussis immunization

- Why are we seeing so much pertussis?
  - ✓Does vaccine immunity wane quickly?
  - ✓Was DTP a better vaccine than DTaP?
- How are we doing with DTaP and Tdap vaccine coverage?
- What happened to the interval between prior Td and Tdap?
- Is Tdap vaccine safe in pregnancy?
- Can we immunize the elderly?
- **Do we need a Tdap booster?**

Tdap Booster

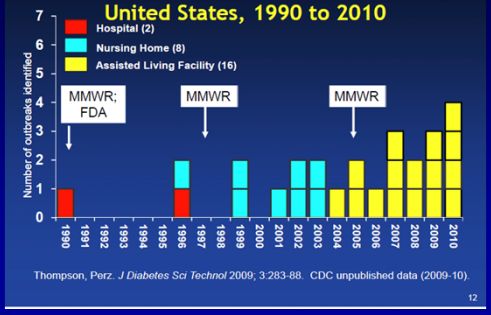
- Tdap boosters will certainly be needed based on waning immunity
- Interval between Tdap vaccines uncertain
- Growing experience in Canada, Australia, and other countries with a 10 year interval
- Limited experience with a 5 year interval
- Stay tuned….

Tdap Recommendations CDC/AAP/AAFP/ACOG/ACP

- **Routine use at 11-12 years of age**
- **Replace Td for all ages 11 and above**
- **Special focus on adults in contact with young infants**
  - ✓**Pregnant women**
  - ✓**Health care workers**
  - ✓**Parents and siblings**
  - ✓**Grandparents (including those >64 years of age)**
- **No minimum interval from prior Td**

Do adults with diabetes really need a hepatitis B vaccine?

Outbreaks of Hepatitis B Virus Infection associated with Blood Glucose Monitoring United States, 1990 to 2010



Thompson, Perz. *J Diabetes Sci Technol* 2009; 3:283-88. CDC unpublished data (2009-10).

12

Adjusted Odds* of Acute Hepatitis B among Persons with Diabetes: Multivariate Analyses

Parameter	Adjusted OR (95% CI)
Diabetes (no "Other HBV risk factor" present)	1.89 (1.40 - 2.57)
Diabetes ("Other HBV risk factor" present)	1.10 (0.57 – 2.11)

*Controlling for age, gender, race/ethnicity

No observations deleted based on DF Beta results

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ACIP Recommendation

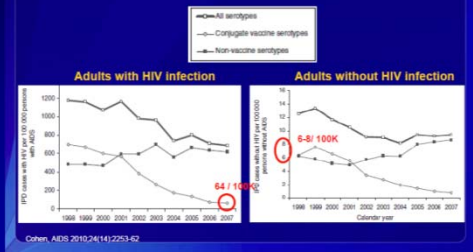
- Hepatitis B vaccination should be administered to unvaccinated adults with diabetes mellitus who are aged 19 through 59 years
- Hepatitis B vaccination may be administered at the discretion of the treating clinician to unvaccinated adults with diabetes mellitus who are aged ≥60 years

MMWR **December 23, 2011 / 60(50);1709-1711**

Pneumococcal conjugate vaccine-PCV13

Should we be using this vaccine in adults?

Trends in IPD rates among adults 18-64 yrs old with & without HIV-infection, before and after PCV7 introduction, 1998-2007



Cohen. AIDS 2010;24(14):2253-62

Efficacy of PCV7 in HIV Infected Adults, Malawi

- Double-blind, randomized, placebo-controlled clinical efficacy trial (n=496)
- HIV-infected adolescents and adults who had recovered from documented IPD
- Two doses of PCV7 given 4 weeks apart

Vaccine	Endpoint	Vaccine Efficacy (95% CI)
PCV7	Vaccine serotype IPD	74% (30%, 90%)
	All cause pneumonia* (includes IPD cases)	25% (-19%, 53%)

French *NEJM* 2010;362(9):812-822

27

PCV13 in adults

- Possible recommendations this year for use in immunocompromised adults
- Probably 1-2 years before ACIP recommends broader use in adults with other risk factors for pneumococcal disease

Summary

- Large outbreaks of pertussis occurred across the United States in 2010 and 2011
- Vaccination is the best way to interrupt the spread of pertussis
- CDC has expanded the groups of people who should receive pertussis vaccine
- We need to all work together to prevent spread of pertussis to young babies.
- New uses of hepatitis B vaccine and conjugated pneumococcal vaccine in adults

Measles and Measles Immunization Update

Mark H. Sawyer, MD
Professor of Clinical Pediatrics
UCSD School of Medicine
Rady Children's Hospital San Diego

Objectives

- Describe the status of measles outbreaks in the U.S.
- List the clinical features of measles
- Identify the factors that predispose to an outbreak of measles
- Describe the relationship between rising concerns about vaccine safety and measles outbreaks

Disclosures

- "On the wagon" for 4 years
  - No industry support
  - No honoraria
  - No dinners
  - I have thrown away my pharmaceutical company pens
- No off-label use discussed today

Once upon a time a boy went for a ride on an _____.

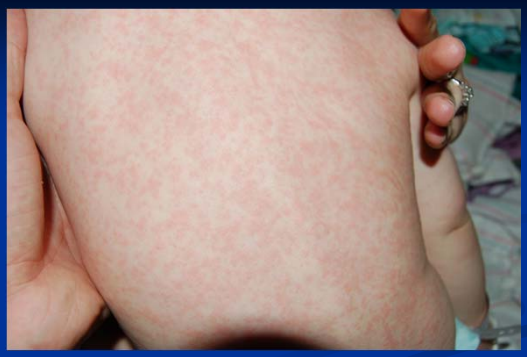
He went on a long, long ride to _____.

In Switzerland there was lots and lots of snow and the boy got to play with lots of _____.

The boy was exposed to someone in the _____.

After a while the boy got back on an _____

and came home to ___ ____.



Soon the boy didn't feel so good and he had a _____.

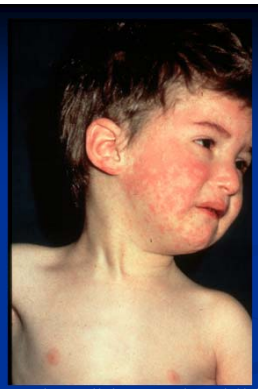
So he went to the _____.

At the doctor's he had to wait in the ____ ___.

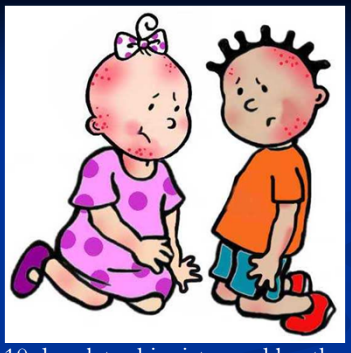
with some other ___ ___.

He also came to _____ _____.

After a few days he felt better
so he went back to ____.



The test they did at Rady Children's
showed he had the _____.

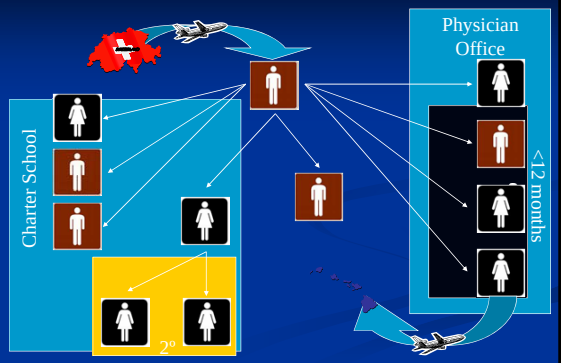


10 days later his sister and brother
also had the _____.

Now many other children living in ___ ____ have the measles.

THE END

San Diego Measles Outbreak



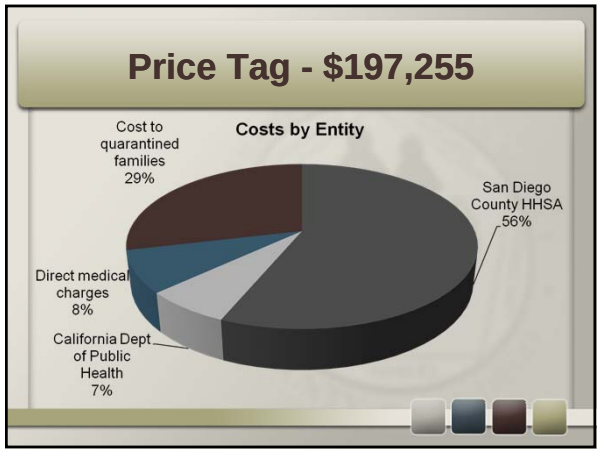
Measles Outbreak San Diego 2008

- Sites of known close exposure
  - Homes (2 confirmed)
  - Doctor's office (3 confirmed, 1 possible)
  - 1 Emergency room
  - 2 Elementary schools (4 confirmed, 2 possible)
  - 2 Pre-schools
  - 1 swim class
- Sites of possible exposure
  - 2 grocery stores
  - 1 fast food restaurant
  - 1 pizza restaurant
  - 1 large entertainment venue

Measles Outbreak San Diego-Impact

- Over 60 children on home quarantine for up to 21 days (including one in Hawaii)
- Nursery school class and swim class canceled
- Over 300 person-hours expended at San Diego HHSA
- 2 CDC staff and 2 State DHS staff traveling to San Diego to help

Price Tag - $197,255

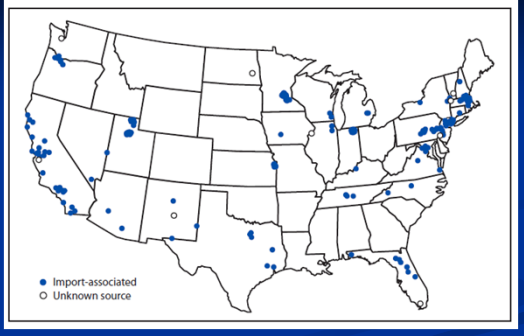


Measles is rare in the U.S.

- San Diego: 25 cases in 15 years before 2008
  - No more than 4 in one year since 1992
- United States: an average of 60 cases per year; 222 cases in 2011/17 separate outbreaks
- But not elsewhere…
  - France - over 13,957 cases
  - Spain - 1,637 cases
  - Italy - over 4,300 cases
  - Germany - 1,480 cases
  - England and Wales - 854 cases
  - Quebec, Canada - 742 cases

http://www.cdc.gov/measles/

FIGURE 1. Origin of reported measles cases (N = 222) — United States, 2011



MMWR 2012; 61(15):253-257

TABLE. Countries where imported measles was acquired, by World Health Organization (WHO) region, number of cases (n = 72), and genotype — United States, 2011

WHO region	No. of cases	Country	No. of cases	Genotype identified*
African	4	Ethiopia	1	B3
		Kenya	2	B3 (2)
		Nigeria	1	B3
Americas	2	Canada	1	
		Dominican Republic†	1	D4
Eastern Mediterranean	3	Jordan	1	D4
		Pakistan	2	
European	33	Bulgaria	1	
		France	13	D4 (5), G3
		France/Germany/Spain§	1	
		France/Italy§	1	D4
		France/Italy/Spain/Germany§	1	
		France/Spain/United Kingdom§	1	
		France/United Kingdom§	1	D4
		Italy	4	D4 (3)
		Poland	1	
		Romania	1	D4
		Romania/Hungary§	2	D4 (2)
		Spain	1	
		United Kingdom	5	D4 (3)
South-East Asia	19	Bangladesh	1	
		India	16	D4, D8 (5)
		Indonesia	2	
Western Pacific	11	China	2	H1
		Malaysia	2	D9 (2)
		Philippines	6	D9 (4)
		Philippines/Vietnam/ Singapore/Malaysia§	1	

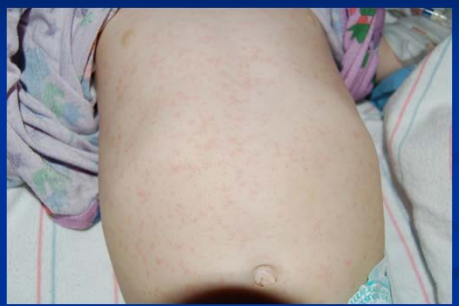
MMWR 2012; 61(15):253-257

Why is this happening?

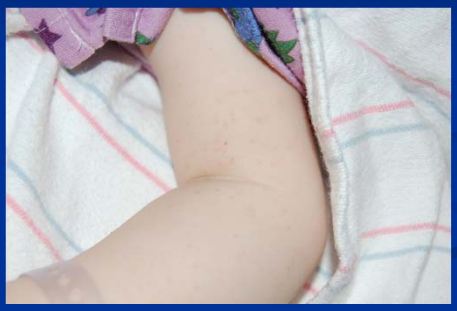
- Measles is rare in the U.S. so it is not expected and may not be recognized

This is measles

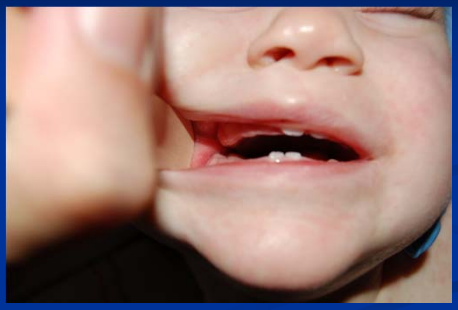
This is measles



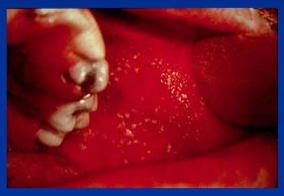
This is measles

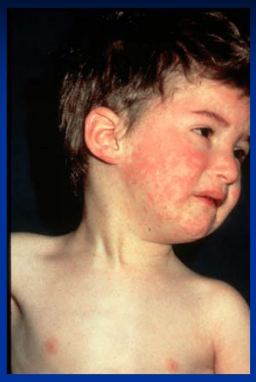


This is measles-Koplik spots



Koplik spots





This is Measley!

WHEN YOU SEE RASH….

GET A TRAVEL HISTORY

Measles
Typical presentation

- Prodrome of 2-4 days: high fever followed by the 3 C's (cough, coryza, conjunctivitis)
- Rash begins on the face and travels down and out lasting 5-6 days
- Koplik spots appear on the buccal mucosa 1-2 days before the rash and can last several days
- Affected children are usually very irritable with decreased oral intake
- Fever abates abruptly as rash is beginning to fade

Measles
The numbers

- Average incubation period from exposure to rash is 12-14 days
  - Minimum: 7 days
  - Maximum: 18 days
- Contagious for 4 days before the rash to 4 days after (a total of 9 days)
- Quarantine period: 21 days after last exposure

Measles Diagnosis

- IgM and IgG serology
  - 75% IgM positive by day 3 of rash
  - Almost 100% positive by day 5
- Virus can be recovered from oropharyngeal swab and urine by culture

Why is this happening?

- Measles is rare in the U.S.
- Measles is very contagious: >90% attack rate in households

Measles is very contagious
Minneapolis Metrodome

An Outbreak of Measles at an International Sporting Event with Airborne Transmission in a Domed Stadium

Kristen R. Ehresmann, Craig W. Hedberg, Mary Beth Grimm, Cheryl A. Norton, Kristine L. MacDonald, and Michael T. Osterholm

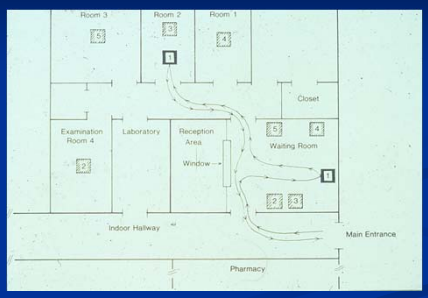
Acute Disease Epidemiology Section and Acute Disease Prevention Services Section, Minnesota Department of Health, Minneapolis

- 1991 International Special Olympics Games
- Index case an athlete from Argentina
- 16 outbreak-associated cases
- 2 cases whose only exposure was sitting in the upper deck >30 m above the athletes
- Airflow goes from floor to upper deck to support the dome

Ehresmann KR, J Infect Dis 1995;171:679

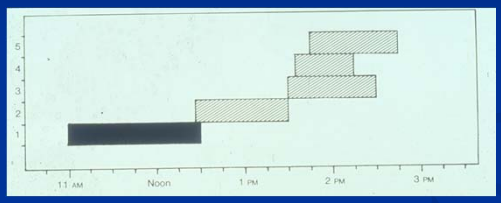
Measles is very contagious
Healthcare settings

Measles is very contagious



Remington PL, JAMA 1985; 253:1574

Measles is very contagious
Remains in the air for 2 hours



Remington PL, JAMA 1985; 253:1574

Isolation of potential patients is crucial to control the outbreak

- Instruct patients to call the office before coming if they have been exposed to measles or suspect measles
- Screen patients prior to them sitting in waiting room
- Designated exam room for suspect cases-leave vacant for 2 hours between patients
- Instruct suspect patients to remain at home throughout the incubation period

Why is this happening?

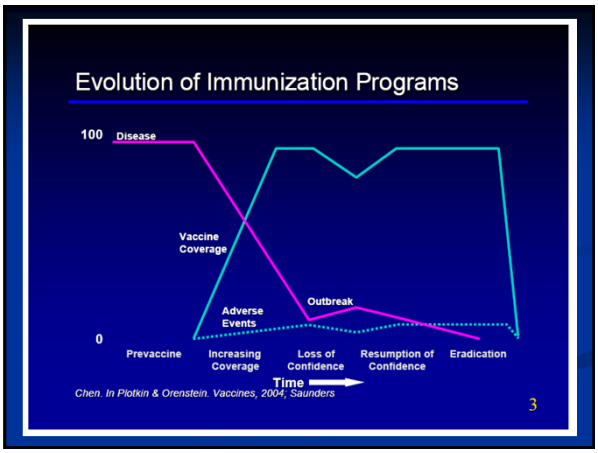
- Measles is rare in the U.S.
- Measles is very contagious: >90% attack rate in households
- Our society is highly mobile

Our society is very mobile

Tiger Woods played golf in San Diego on January 27 and in Dubai on January 29, 2008

Why is this happening?

- Measles is rare in the U.S.
- Measles is very contagious: >90% attack rate in households
- Our society is highly mobile
- Elimination of vaccine-preventable diseases leads to rising concerns about vaccine safety



Why is this happening?

- Measles is rare in the U.S.
- Measles is very contagious: >90% attack rate in households
- Our society is highly mobile
- Elimination of vaccine-preventable diseases leads to rising concerns about vaccine safety
- In public opinion, emotion trumps science

Factors that have increased concern

- Distrust
  - ✓Industry
  - ✓Government
  - ✓Doctors
- Uncertainty
- Rapid increase in the number of vaccines
- Inaccurate information on the Internet
- Media/Celebrities

Know Your Source!

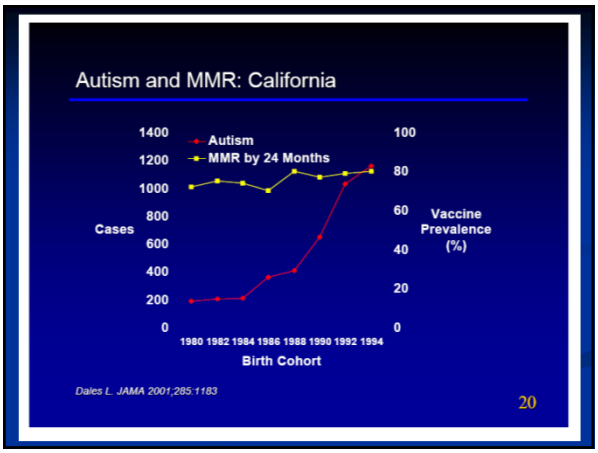
"On the Internet, nobody knows you're a dog."

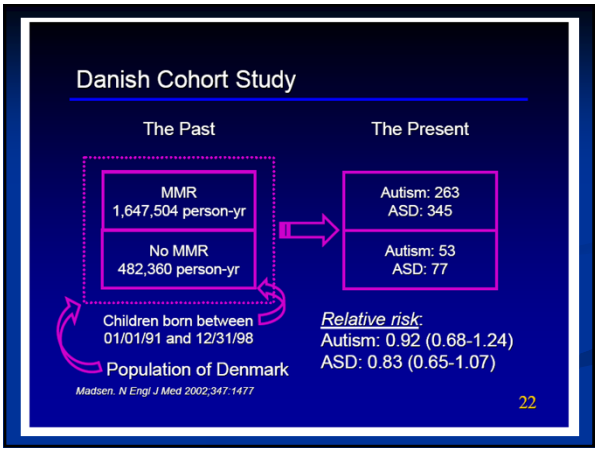
Peter Steiner,
The New Yorker Magazine, vol. 69 (LXIX) no. 20. July 5, 1993, pg. 61

Falsehood flies and the truth comes limping after so that when men come to be undeceived it is too late. The jest is over and the tale has had its effect

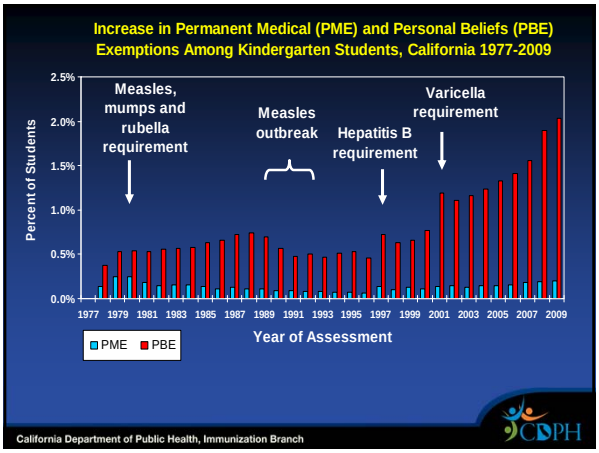
Jonathan Swift, The Examiner Nov. 9, 1710

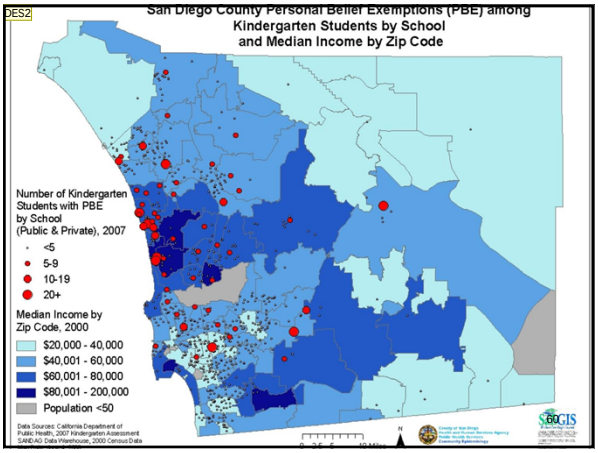
The Truth Comes Limping After…





The Tale Has Had It's Effect….





Slide 60

DES2 We didn't have the chance to recreate this map with the correct points. Perhaps just make the point on the previous slide about correlation with income. Also, only for non-charter public schools was the correlation with higher median income significant. That's probably due to charter and private schools drawing students from a larger area from where the school is located.
David E Sugerman, 2/1/2009

Measles Vaccine

- 2-5% do not respond to the first dose
- 99% respond after two doses
- Many people born before 1985 have only had one dose
- Two doses of vaccine are recommended for adults who:
  - Attend college
  - Travel internationally
  - Are healthcare workers

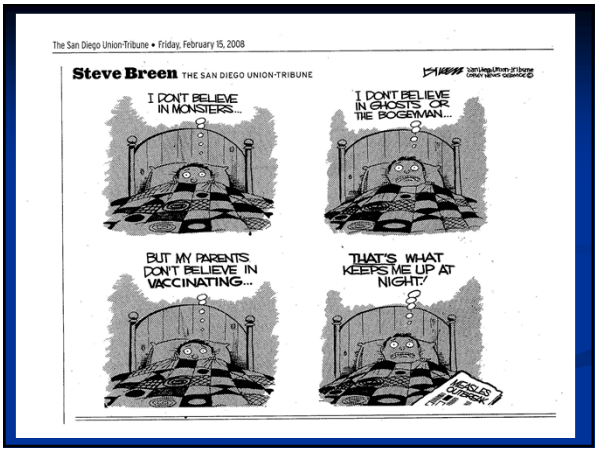
Travel Vaccine Recommendations

- Individuals older than 6 months be protected from measles and receive MMR vaccine, if needed, prior to departure.
- Infants 6 through 11 months old should receive 1 dose of MMR vaccine before departure.†
- Children 12 months of age or older should have documentation of 2 doses of MMR vaccine (separated by at least 28 days).
- Teenagers and adults without evidence of measles immunity should have documentation of 2 appropriately spaced doses of MMR vaccine.

Summary

- Measles outbreaks continue to occur throughout the United States
- Almost all cases are related to foreign travel-take a travel history
- Isolate your patients immediately if you think measles
- We have to continue to educate families about the risks measles disease and benefits of vaccination

63



Resources

NNII (www.immunizationinfo.org)
VEC (www.vaccine.chop.edu)
IAC (www.immunize.org)
CDC/NIP (www.cdc.gov/nip)
AAP (www.aap.org)
AAFP (www.aafp.org/)
IVS (www.vaccinesafety.edu)
Vaccine Page (www.vaccines.org)
Every Child by Two (www.ecbt.org)

Outpatient Management of Congestive Heart Failure For the Primary Physician

David J. Shaw, M.D., M.B.A.

"It is much more important to know what sort of patient has a disease than what sort of disease a patient has."

Sir William Osler

Objectives of Talk

- 1. Identify reasons patients with heart failure decompensate and require hospital readmission
- 2. Identify strategies for effectively managing patients in the outpatient environment
- 3. Identify evidence-based therapies and evidence-based doses of those therapies for management of heart failure due to systolic dysfunction
- 4. Identify strategies for management of heart failure with normal ejection fraction

Definition of Congestive Heart Failure

A syndrome including **circulatory congestion** or **inadequate tissue perfusion** due to **abnormal heart function** and **associated neurohormonal abnormalities**

Pathophysiology of Heart Failure

How it gets that way

Pathophysiology of Congestive Heart Failure

- Myocardial damage
  - Ischemia, infarction (CAD)
  - Hypertension
  - Viral
  - Idiopathic
- Remodeling
  - Catecholamines
  - Renin-Angiotensin-Aldosterone System
  - Cytokines
  - Endothelin

Causes of Heart Failure (Italian Registry)

- Ischemic heart disease — 40 percent
- Dilated cardiomyopathy — 32 percent
- Primary valvular heart disease — 12 percent
- Hypertensive heart disease — 11 percent
- Other — 5 percent

Classification Systems for CHF

Classification of CHF

- May be defined in terms of:
  - Affected ventricle(s) – Right and/or Left
  - Primary manifestation – Congestion or Hypoperfusion
  - Relative Cardiac output – Low output or High output (e.g. thyrotoxicosis)
  - Ventricular function – Low ejection fraction ("Systolic Dysfunction") or Preserved ejection fraction ("HFNEF = Heart Failure with Normal Ejection Fraction")
  - Acute versus Chronic – ADHF (Acute Decompensated Heart Failure) vs Chronic Stable Congestive Heart Failure

Significance of CHF Classification

- Evidence base only exists for certain forms of congestive heart failure
- The evidence base is in evolution
- Understanding the pathophysiology of CHF enables us to understand what forms of therapy might be effective

New York Heart Association Functional Classifications

- Class I - symptoms of heart failure only at levels that would limit normal individuals
- Class II - symptoms of heart failure with ordinary exertion
- Class III - symptoms of heart failure on less than ordinary exertion
- Class IV - symptoms of heart failure at rest

Stages of Heart Failure

Heart failure develops over time in symptomatic and asymptomatic phases. Each phase can be targeted with specific treatments to reduce morbidity and mortality. The stages of heart failure development described below are excerpted from Hunt, SA, Baker, DW, Chin, MH, ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, ACC/AHA Practice Guidelines, 2001.

Stage A Heart Failure Patients

Patients at high risk of developing heart failure (HF) because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.

Stage B Heart Failure Patients

Patients who have developed structural heart disease that is strongly associated with the development of heart failure (HF) but who have never shown signs or symptoms of HF.

Stage C Heart Failure Patients

Patients who have current or prior symptoms of heart failure associated with underlying structural heart disease

Stage D Heart Failure Patients

Patients with advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy and who require the specialized interventions

Why do patients decompensate?

- Failure to take medications
  - Fear of or perception of side effects
  - Can't afford
  - Not on formulary
  - Not motivated to take
- Excess sodium in diet
- Worsening heart disease
- Worsening renal function

Strategies for Management of CHF

- Based on first "decongesting" the patient
- Then managing the underlying cardiac pathophysiologic abnormalities
  - For primary myocardial disease, the abnormalities are generally due to damage to the myocardium based on adverse effects of the neurohormonal response to ventricular failure – the very responses which are adaptive short-term become deleterious long-term
  - For valvular, pericardial and endomyocardial disease, the treatment is that of the underlying anatomical abnormality

Treatment of Acute Decompensated Heart Failure

Treatment of ADHF

(Acute Decompensated Heart Failure)

- Evidence-base is not robust
- The principles are relieving congestion and augmenting perfusion
- While one might expect that positive inotropic agents would be beneficial in this condition, a host of inotropic agents have failed to show long-term benefit, or have actually resulted in increased mortality
- Beta Blockers, one of the cornerstones of therapy for chronic heart failure, are contraindicated in ADHF

Role of Loop Diuretics in ADHF

Loop diuretics relieve symptoms of dyspnea and edema, but may cause:

Electrolyte abnormalities

Activation of RAAS and SNS

Diuretic resistance

Structural changes in distal tubule

Worsening renal function. (Furosemide lowers GFR by ~ 15%)

? Increased mortality

DOSE-HF study compared high and low dose loop diuretic, as continuous infusion or q12h i.v. bolus – showed no difference in outcome short-term

Ultrafiltration for ADHF

- Ultrafiltration, also called aquapheresis, a form of hemodialysis which allows removal of fluid that is isotonic with plasma. Simplified veno-venous ultrafiltraton device, with very small extracorporeal blood, minimizes hemodynamic shifts, and hypotension.
- UNLOAD trial published in 2007, showed that early ultrafiltration resulted in greater weight loss, greater fluid loss, and no difference in renal function. Rehospitalization in UNLOAD was less in UF group vs diuretic group. (JACC, 2007; 49;675-683)
- UF patients had less activation of RAAS and Catecholamine systems.

Treatment of Heart Failure due to Systolic Dysfunction

Audience Response #1

Choose three correct answers from the following list

Three **Evidence-based** Therapies for Heart Failure with Systolic Dysfunction are:

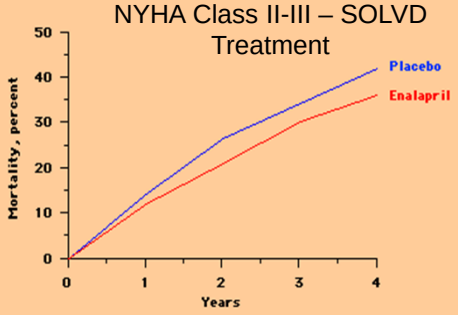
1. Angiotensin receptor blocker
2. Atenolol
3. Hydralazine/Isosorbide dinitrate
4. Spironolactone
5. Furosemide

Evidence-based Therapies for Heart Failure due to Systolic Dysfunction

- This is the most robust evidence-based treatment for heart failure
- ACE-I or ARB for Heart Failure with LVSD
- Beta blocker for HF with LVSD (only 3 approved: carvedilol, metoprolol and bisoprolol)
- Aldosterone antagonists for patients with HF in NYHA Class IV or Class III with Myocardial Infarction
- Add Digoxin for patients who remain symptomatic
- The combination of Isosorbide Dinitrate and Hydralazine has a survival benefit in African-Americans

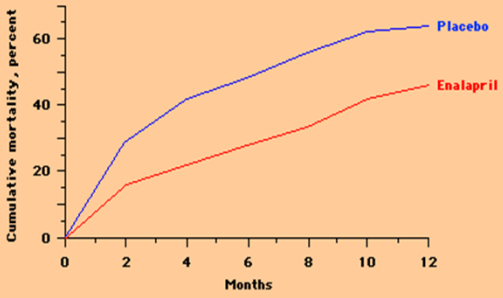
ACE-Inhibitor and/or ARB in Heart Failure with Systolic Dysfunction

NYHA Class II-III – SOLVD Treatment



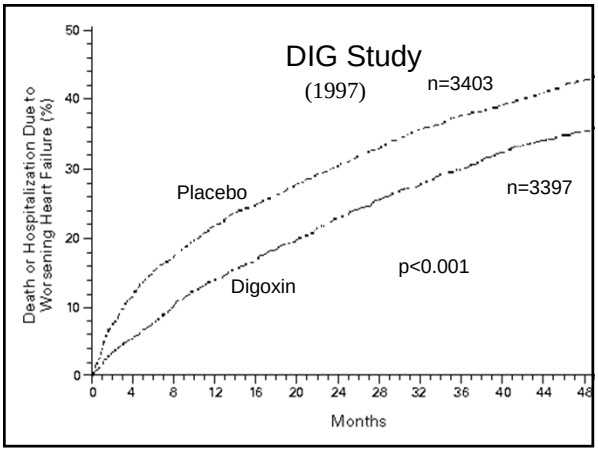
ACE inhibitor improves survival in moderate CHF Enalapril, compared to placebo, decreases patient mortality in NYHA class II and III heart failure (p = 0.0036). (Data from The SOLVD Investigators, N Engl J Med 1991; 325:293.)

NYHA Class IV - CONSENSUS



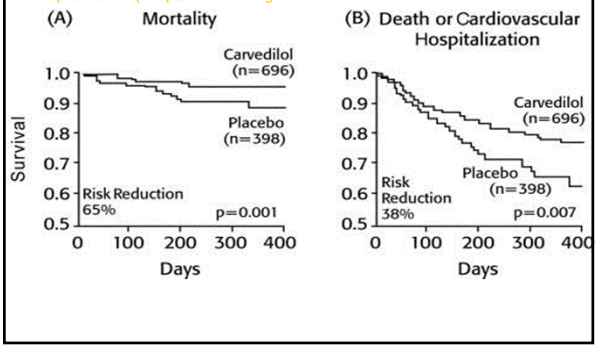
ACE inhibitor improves survival in advanced CHF Decreased mortality in patients with advanced NYHA class III or IV heart failure after treatment with enalapril compared to placebo (p = 0.003). (Data from The CONSENSUS Trial Study Group, N Engl J Med 1987; 316:1429.)

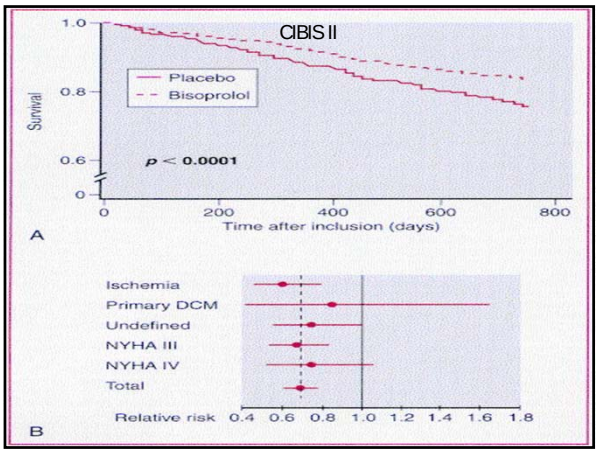
Digoxin in Heart Failure

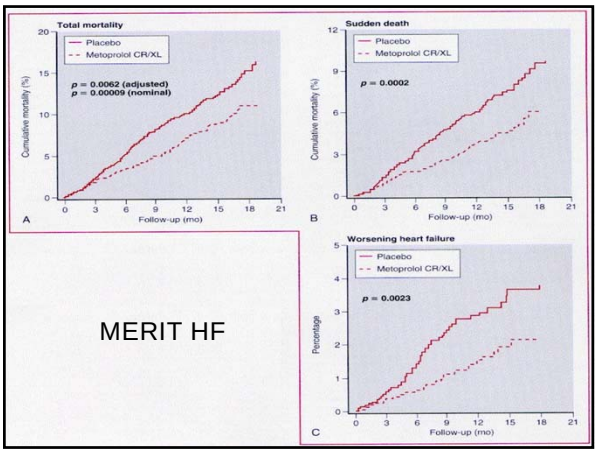


Beta Blockers in Heart Failure

FIGURE 2. Effect of carvedilol versus placebo on mortality (*A*) and the combined end point of death or cardiovascular hospitalization (*B*)for the entire **US Carvedilol Heart Failure Trials Program**. Carvedilol therapy was associated with a 65% reduction in mortality and a 38% reduction in death or cardiovascular hospitalization. (Adapted from *N Engl J Med.*

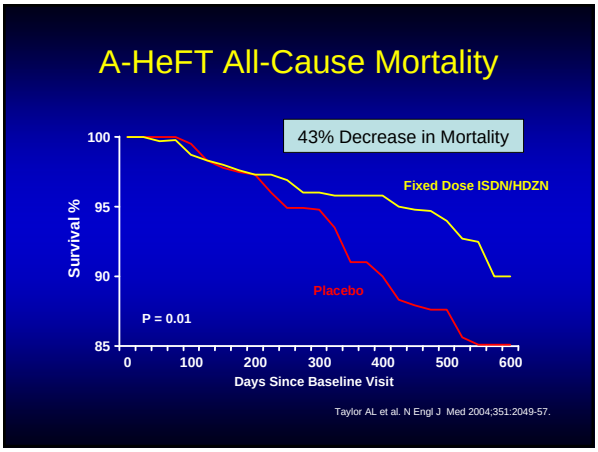




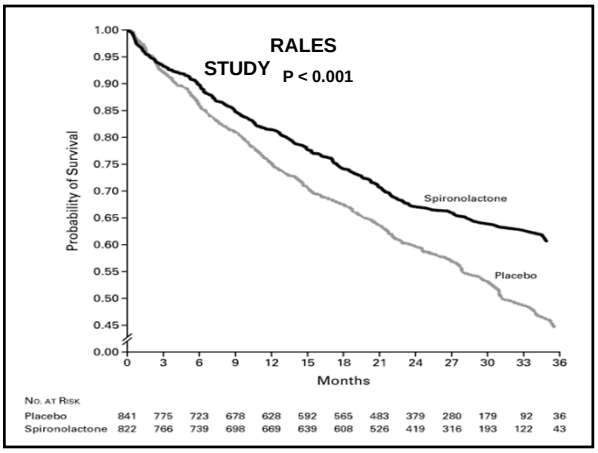


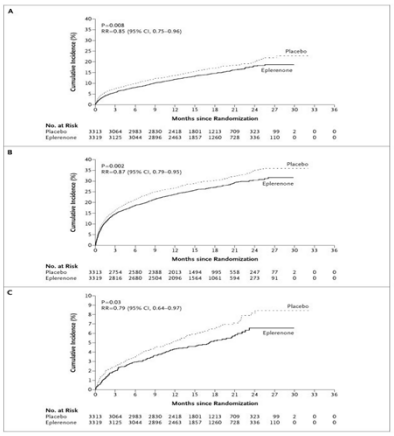
MERIT HF

Fixed-dose Hydralazine and ISDN in Heart Failure



Aldosterone Antagonists in Heart Failure





EPHESUS RESULTS

Kaplan-Meier Estimates of the Rate of Death from Any Cause (Panel A), the Rate of Death from Cardiovascular Causes or Hospitalization for Cardiovascular Events (Panel B), and the Rate of Sudden Death from Cardiac Causes (Panel C)

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Heart Failure with Normal Ejection Fraction (HFNEF)

Current Therapies for HFNEF

- Terminology has evolved: Previously: Diastolic dysfunction; heart failure with normal systolic function
- Now recognized to be a condition with both diastolic (compliance) abnormalities and with abnormalities of conformational change (twisting abnormalities – left ventricular deformation) but with normal ejection fraction
- Present therapies are not “evidence-based”

Current Therapies for HFNEF (continued)

- Patients with HFNEF tend to be older than those with Systolic Dysfunction, tend to be female more commonly, and tend to have more hypertension
- Hypertension is principal target for HFNEF

Treatment of Asymptomatic Left Ventricular Dysfunction (ALVD)

Audience Response #2

Choose two correct answers from the following list

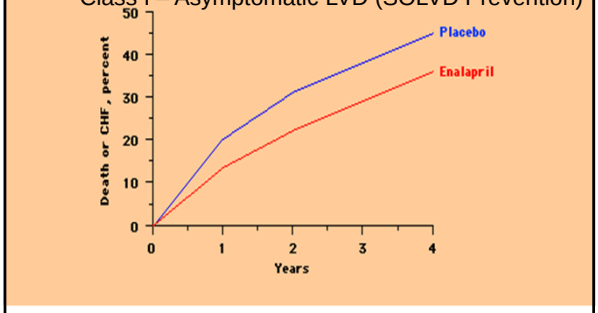
Two **evidence-based** therapies for asymptomatic left ventricular dysfunction are:

1. Metoprolol
2. Eplerenone
3. Lisinopril
4. Digoxin
5. Amlodipine

Evidence-based Therapies for Asymptomatic Left Ventricular Dysfunction (ALVD)

- Just as with Heart Failure with Systolic Dysfunction, an extensive evidence-base exists for ALVD
- ACE-I or ARB have a combined death or CHF benefit
- Among patients with asymptomatic left ventricular dysfunction treated with ACE inhibitors, beta blockers appear to reduce mortality and the rate of progression to symptomatic heart failure

Class I – Asymptomatic LVD (SOLVD Prevention)



Enalapril improves outcome in asymptomatic LV dysfunction In the SOLVD prevention trial of 4228 patients (83 percent post-MI) with asymptomatic left ventricular dysfunction, prophylactic administration of enalapril reduced the probability of death or congestive heart failure (p<0.001). (Data from The SOLVD Investigators, N Engl J Med 1992; 327:685.)

Clinical Trials in Patients With Asymptomatic LVSD

Study	Patient Population (n)	Treatment	Average Duration, mo	Relative Mortality Risk Reduction	Sudden Death Risk Reduction	Death Due to Worsening HF Risk Reduction
ß-Blockers						
Retrospective analysis of SOLVD Prevention[24]	Asymptomatic LVSD (4228; 1015 patients	ß-Blockers vs no ß-blockers plus enalapril	37.4	23% (P<0.01)	28% (P<0.05)	29% (P<0.05)
Post hoc analysis of SAVE[25]	Asymptomatic LVSD (2231; 789 patients	ß-Blockers vs no ß-blockers plus captopril	42	43% (P<0.001)	NR	32% (P<0.001)
ANZ[26]	HF (415); asymptomatic	Carvedilol vs placebo	19	36% (P=0.02)	10% (P=NS)	8% (P=NS)
CAPRICORN[27]	Post-AMI LVSD (1959); asymptomatic	Carvedilol vs placebo (including ACE inhibitor)	15.6	23% (P=0.03)	26% (P=0.098)	40% (P=0.083)

Evidence-based Doses of Heart Failure Medications

Evidence-based doses of Heart Failure Medications - I

ACE Inhibitors Indicated in Asymptomatic Left Ventricular Dysfunction (ALVD) and CHF with EF < 40% in NYHA Class I-IV

ACE Inhibitor Goals	Initial Dose	Target Dose	Maximum Dose
benazepril (Lotensin)	5-10 mg daily	20-40 mg. daily	80 mg. daily
captopril (Capoten)	6.25-25 mg. 3/day	50-100 mg. tid	150 mg. 3/day
enalapril (Vasotec)	2.5-5 mg. 2/day	10 mg. 2/day	20 mg. 2/day
fosinopril (Monopril)	10 mg. daily	20-40 mg. daily	80 mg. daily
lisinopril (Zestril/Prinivil)	2.5-10 mg. daily	20-40 mg. daily	80 mg. daily
moexipril (Univasc)		15-30 mg. daily	60 mg. daily
quinapril (Accupril)	2.5-10 mg. daily	20-40 mg. daily	80 mg. daily
ramipril (Altace)	1.25-2.5 mg. daily	5-10 mg. daily	20 mg. daily
trandolapril (Mavik)	1 mg. daily	4 mg. daily	4 mg. daily

ARB Indicated in ACE-I Intolerant Patients with ALVD and CHF with EF <40% in NYHA Class I-IV

ARB Goals	Initial Dose	Target Dose	Maximum Dose
Losartan	50 mg. daily	100 mg. daily	200 mg. daily
Valsartan	20 mg. 2/day	80 mg. 2/day	160 mg. 2/day
Candesartan	4 mg. daiily	16 mg. daily	32 mg. daily

Evidence-based doses of Heart Failure Medications - II

Beta blockers indicated in Patients with ALVD and CHF with EF < 40% in NYHA Class I-IV			
Beta Blocker Goals	**Initial Dose**	**Target Dose**	**Maximum Dose**
Metoprolol	12.5 mg. 2/day	25 mg. 2/day (< 85 kg) 50 mg. 2/day (> 85 kg)	50 mg. 2/day
Metoprolol LA	12.5 mg. daily	50 mg. daily (< 85 kg) 100 mg. daily (> 85 kg)	100 mg. daily
Carvedilol	3.125 mg. 2/day	12.5 mg.-25 mg. 2/day	25 mg. 2/day
Bisoprolol	1.25 mg daily	5 mg. daily	10 mg. daily
Aldosterone Angagonists in NYHA Classes II-IV	**Indicated In Patients**	**with CHF with EF**	**< 40%**
Aldosterone Antagonist Goals	**Initial Dose**	**Target Dose**	**Maximum Dose**
Spironolactone	12.5 mg. daily	25 mg. daily	50 mg. daily
Eplerenone	25 mg. daily	25 mg. daily	50 mg. daily

Questions?

Device Therapy for CHF

Cardiac Resynchronization Therapy

- In Heart Failure, synchronization of contraction of the right and left ventricles can result in substantially improved performance
- This is accomplished by biventricular pacing, coupled to atrial pacing (to optimize A-V intervals)

Cardiac Resynchronization Therapy

- From **MADIT-CRT** (N Engl J Med; published at www.nejm.org on September 1, 2009, 10.1056/NEJMoa0906431) , In Minimally symptomatic cardiac patients (NYHA I or II) with decreased EF and wide QRS, CRT-D reduced mortality or HF events (which ever comes first) when compared with ICD-only therapy by 41%.
- CRT may improve LV twist in some patients with CHF with Systolic dysfunction who will later improve LV end-systolic volume as well

Left Ventricular Assist Devices

- Implanted devices with external power source, which can be worn by patients with advanced HF
- Used both as bridge to cardiac transplantation and as "destination therapy"

Applying this to your patient

- CHF, like diabetes, COPD and hypertension, is a chronic disorder which is rarely cured but can be effectively managed with application of evidence-based therapies
- Critical role of education in the management of patients with CHF
- Critical role of careful monitoring of patients and actively engaging them in their mangement

Conclusions

- Important to understand classification and pathophysiology of congestive heart failure
- Treatment of Acute Decompensated Heart Failure evolving, but evidence-base not strong
- Treatment of Chronic Heart Failure due to Systolic Dysfunction has strong evidence base, favoring use of ACE-I/ARB, Beta Blocker, and sometimes digoxin, spironolactone, and/or hydralazine/ISDN

Conclusions (continued)

- Little data concerning effective treatment of HFNEF
- Good evidence base for treatment of ASLVD: again ACE-I/ARB and Beta Blocker
- Critical role of recognizing causes of decompensation and working with patient to anticipate and prevent them

Questions?

Dealing with the new reality

SDAFP – 22 June 2012

PROZAC
fluoxetine hydrochloride
10 mg, 20 mg, and 40 mg pulvules
90 mg Weekly™ capsules

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It's difficult to make predictions - particularly about the future

Yogi Berra

San Diego County Medical Society

Outline

- Environmental scan
- Symptoms
- Diagnosis
- Prognosis
- Palliative treatment plan - *no systemic change*
- Radical treatment plan – *options for systemic* change
- So what can YOU do on Monday?
- Q&A

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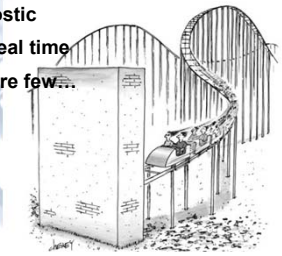
Four important comments

- This is not a good news story – my apologies
- I'm politically agnostic
- Ask questions in real time
- Actionable items are few…



I heard this is the scariest part of the ride!

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The Environmental Scan

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A political decision is one that is made in the absence of, or contravention of, the facts

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Supremes are warming up backstage!

Options

- Disneyland option - Total approval
- Armageddon option - Total dismissal (ignore severability)
- Neutron bomb option –
  - Perfect mandate, rest left standing
  - Perfect states' rights issue, rest left standing

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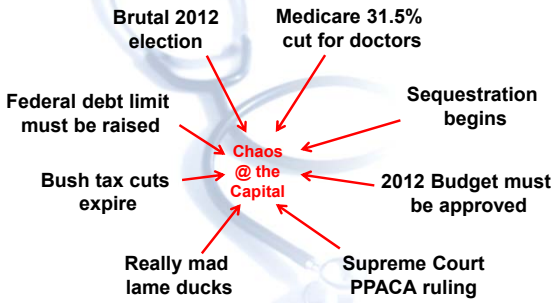
Fall 2012 – DC's 8 dimensional train wreck



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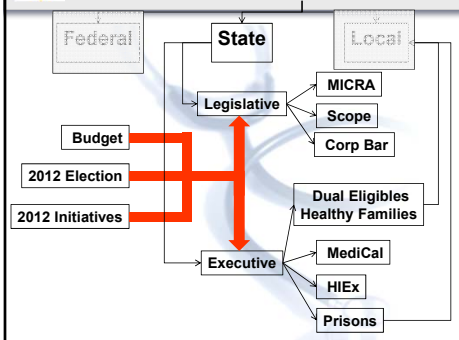
So what's next w/ State?



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PPACA simplified (impact on doctors)

2011

- MLR (85% or 80%) enforced
- No Physician owned hospitals
- GME changes for more PCPs
- Medicare EHR use + quality reporting – carrot and stick

2012

- ACOs & Bundled Payment pilots

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PPACA simplified (impact on doctors)

2013

- Health Insurance administrative simplification
- Increased Medicaid to PCP (2013/2014)

2014

- Individual mandate (weak)
- Guaranteed issue
- Community rating
- State based health insurance exchanges
- Multiple consumer friendly reforms to HI
- IPAB

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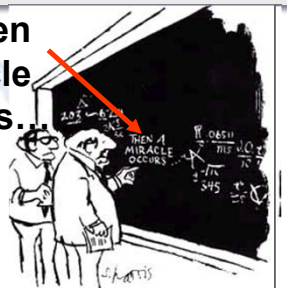
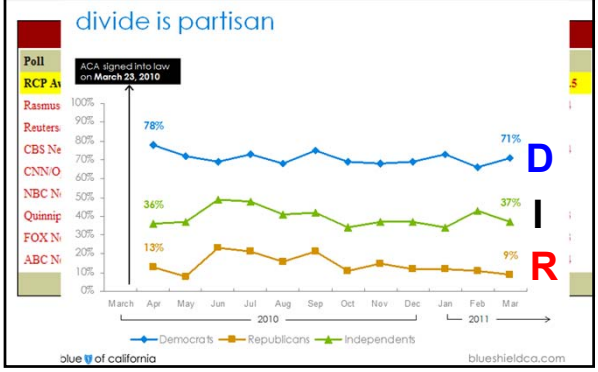
A little humor

And then a miracle happens…

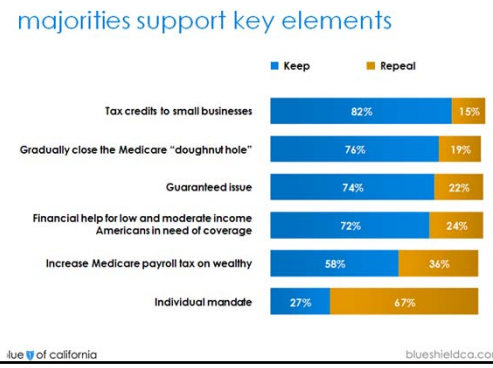


I think you should be more explicit in step 2!

We can't make up our mind



And make THEM pay for it!



What are the symptoms?

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Health care is big and getting bigger

- Healthcare economy - $2.7T
- Healthcare economy % of GDP - 17+%
- Cost of HI for family of 4 - $12.6K (up 39% in 6 yrs)
- Cost of HI for single - $4.6K (up 41% in 6 yrs)

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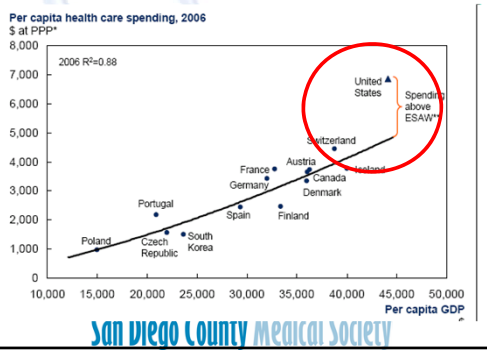
We spend more than we ought to be spending



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Huge geographic variations in spending

- Medicare spending per person
  - in Miami $18K
  - in Minneapolis-St. Paul $7K

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Many without health insurance

% uninsured >1 yr 15% (20% in California)

% uninsured 1 month or more in last year 30%

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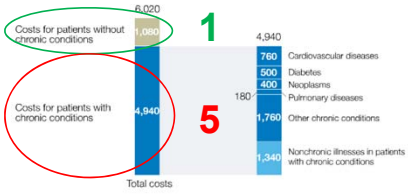
Chronic conditions are killing us

Chronic conditions account for the bulk of health care costs.

Share of costs for chronic and nonchronic conditions at a German SHI[1] fund, 2007, € million



[1]Statutory health insurance (public payor).

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Cost is mis-allocated

60-70% of HC cost from 10% of the population (in last 6-9 months of life)

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Government is huge player

% of HC Costs

- Non-Governmental 49%
  - Insurance 35-%
  - Out of Pocket 15-%
- Governmental 51%
  - Medicare 15+%
  - Medicaid (Medi-Cal) 15%
  - SCHIP 15%

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What's the diagnosis?

Bad news Dad – you're brain-dead!!

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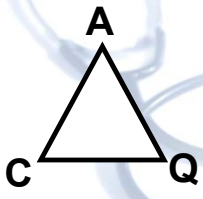
You cannot (simultaneously) improve quality, cost, AND access



Value=(QxA)/C

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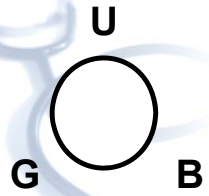
Someone else should pay for it



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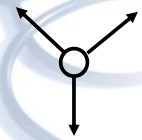
You cannot have insurance without more people in the pool

Insurance companies *not allowed to price discriminate* based on health conditions (Community Rating)

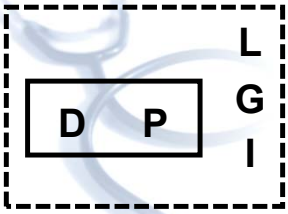
You *have to buy insurance* (Mandate)



You have to *right , to buy insurance – anytime*, irrespective of health (Guaranteed Issue)

San Diego County Medical Society

Who's in the ER/OR/Exam Room with you?



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What's the Prognosis

Your prognosis is tied to the outcome of the election!

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Unsustainable!

% of Mean Family Income for Health Insurance for family of 4

6 yrs ago 7%

now 17%

6 yrs in future 33%

Unsustainable!

San Diego County Medical Society

What's Mass. say about the future?

Massachusetts

Uninsured to near zero

Increased demand => longer lines (initially)

Increased cost => Govt mandated cost cutting & revenue increase from providers

Decreased indirect cost (uninsured)

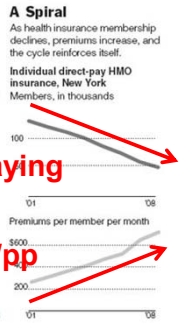
	FY06 Actuals	FY07 Actuals	FY08 Actuals	FY09 Estimated Spending
Commonwealth Care	0	133	628	800
MassHealth Coverage Expansions, Rate Increases and Benefit Restorations	0	224	355	452
Uncompensated Care Pool/Health Safety Net Trust Fund	656	665	416	406
Supplemental Payments to Medicaid MCOs (federal share)	385	0	0	0
Supplemental Payments to Safety Net Hospitals	0	287	287	287
Total	$1B	[illegible]	[illegible]	$1.8B

San Diego County [illegible]

What's New York say about the future?

New York

Weak mandate + guaranteed issue = unaffordable HI for individuals



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Greater demand

- More underinsured (MediCal ↑), but fewer uninsured
- Aging population (Medicare ↑)
- Demanding population (pressure to do more)
- More gizmos (pressure to do more)
- More drugs (pressure to do more)
- Everyone trying to make a living (pressure to do more)

DEMAND GOES UP

San Diego County Medical Society

Reduced supply

- Fewer docs (per person), plus wrong flavor of docs
  - But, lifetime employment
  - And, (theoretically) more economic power
- Scope of practice expansions by non-Physicians
- Not nearly enough PCPs
- Urban solo primary care is dead
- Urban specialist solo is on life support
- Not enough hospital capacity - same number of beds/nurses/etc...

SUPPLY GOES DOWN

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Longer lines

- PCP – demand driven
- Specialists – reimbursement driven
- ER – I-now-have-insurance driven

LONGER WAITS

San Diego County Medical Society

Increased macro-economic cost

- Demand driven cost increase (see MA, CO, WI)
- Fatally flawed insurance model cost increase (see NY)
- Consolidation driven market control cost increase

INCREASED COST

San Diego County Medical Society

Changing reimbursements

- Increased (willing or unwilling) integration – share the same or fewer $$$
- Reimbursements down to keep total cost down (see Mass. & Ca.)
- Reduce differences between specialty and PCP
- Premium for innovation
- Penalty for re-work/re-admit

San Diego County Medical Society

Increased quality

- Because it's the right thing to do for the patient
- But, understand macro-issue is to reduce cost
- Innovate locally

San Diego County Medical Society

What are *we* going to do?

We're going to negotiate first!

Patches, patches, and more patches

Current system is unsustainable

We are putting patches on top of patches

The cost will (eventually) bring the system to it's knees

We will either:

- Keep putting patches on top of patches on top of patches, or
- Revolutionary change (see 9/11 *or* FDR - March 1933 *or* Paris - 1793)

2016 (or perhaps 2020) election will be about a *revolutionary* approach to health care

San Diego County Medical Society

What's the second best medicine?

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What's next - move to Switzerland !

Universal mandate & guaranteed issue & national (community) rating

Citizens pay for insurance up to 8% of income – government subsidy if cost >8%

Insurance:

- Compulsory - standardized national minimum coverage at one price for all w/ no profit
- Complimentary (additional) insurance – risk based, competitive

No first dollar coverage – annual minimums

Bad behavior penalized

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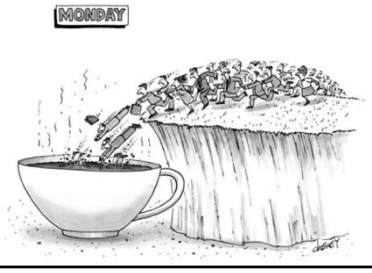
What are *you* going to do on …



Medicare & Medi-Cal "they are a'changing"

Medicare

- SGR
- EHR

Medi-Cal

- Dual Eligibles
- Healthy Families => Medi-Cal
- Expansion (or contraction) w/ the SCOTUS decision

San Diego County Medical Society

Run a better business

Automate (implement EHR), if and only if:

- Ready to change your workflow
- Ready to spend more time and money to get there
- Thoughtfully evaluated all options (ROI)
- Stop thinking about "penalty", think about ROI

San Diego County Medical Society

Run a better business

Become more efficient

- Make data based business decisions
  - ✓ Eliminate stupid expenses
  - ✓ Get rid of low revenue, high cost customers
  - ✓ Find high revenue, low cost customers
- Eliminate NVA steps
- Evaluate your Medicare & Medi-Cal options

San Diego County Medical Society

Run a better business

Accept that you are running a business

- Can't outsource thinking – YOU have to engaged
- Take advantage of your Medical Society
  - Seminars
  - NYCU
  - Web site
- Spend time on the business side
- Learn how to run a business

San Diego County Medical Society

Tell the story

Document the "consequential stories about the impact to your patients" – send 'em to SDCMS

Contact your Congressperson/State Legislators – tell them directly

San Diego County Medical Society

Educate – Pay attention

Read the paper/twitter/blog/…..

"Holler" when we need you to

Engage with your patients when we need you to!

San Diego County Medical Society

Collaborate

Medical Society

- Join/stay joined
- Listen/stay plugged in
- NYCU

Aggregate with your peers – legally

Get onboard an HIE

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Remember why you go it medicine!

It's not just a job - Remember the magic!

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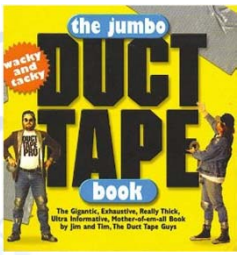
What's next?

We are almost out of



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Questions?

"Americans can always be counted on to do the right thing...

….after they have exhausted all other possibilities"

Churchill

San Diego County Medical Society

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San Diego County Medical Society

Quick Reference Chart for the WHO Medical Eligibility Criteria for Contraceptive Use –

to initiate or continue use of combined oral contraceptives (COCs), depot-medroxyprogesterone acetate (DMPA), progestin-only implants, copper intrauterine device (Cu-IUD)

CONDITION		COC	DMPA	Implants	Cu-IUD
Pregnancy		NA	NA	NA	
Breastfeeding	Less than 6 weeks postpartum				NC
	6 weeks to < 6 months postpartum				
	6 months postpartum or more				
Postpartum	Less than 21days, non-breastfeeding				NC
	< 48 hours including immediate post-placental	NC	NC	NC	
	≥ 48 hours to less than 4 weeks				
	Puerperal sepsis				
Postabortion	Immediate post-septic				
Smoking	Age ≥ 35 years, < 15 cigarettes/day				
	Age ≥ 35 years, ≥ 15 cigarettes/day				
Multiple risk factors for cardiovascular disease					
Hypertension	History of (where BP cannot be evaluated)				
	BP is controlled and can be evaluated				
	Elevated BP (systolic 140 - 159 or diastolic 90 - 99)				
	Elevated BP (systolic ≥ 160 or diastolic ≥ 100)				
	Vascular disease				
Deep venous thrombosis (DVT) and pulmonary embolism (PE)	History of DVT/PE				
	Acute DVT/PE				
	DVT/PE, established on anticoagulant therapy				
	Major surgery with prolonged immobilization				
Known thrombogenic mutations					
Ischemic heart disease (current or history of) **or stroke** (history of)				I C	
Known hyperlipidemias					
Complicated valvular heart disease					
Systemic lupus erythematosus	Positive or unknown antiphospholipid antibodies				
	Severe thrombocytopenia		I C		I C
	Immunosuppressive treatment				I C
Headaches	Non-migrainous (mild or severe)	I C			
	Migraine without aura (age < 35 years)	I C			
	Migraine without aura (age ≥ 35 years)	I C			
	Migraines with aura (at any age)		I C	I C	
Vaginal bleeding patterns	Irregular without heavy bleeding				
	Heavy or prolonged, regular and irregular				
	Unexplained bleeding (prior to evaluation)				I C

CONDITION		COC	DMPA	Implants	Cu-IUD
Gestational trophoblastic disease	Regressing or undetectable β-hCG levels				
	Persistently elevated β-hCG levels or malignant disease				
Cancers	Cervical (awaiting treatment)				I C
	Endometrial				I C
	Ovarian				I C
Breast disease	Undiagnosed mass	*	*	*	
	Current cancer				
	Past w/ no evidence of current disease for 5 yrs				
Uterine distortion due to fibroids or anatomical abnormalities					
STIs/PID	Current purulent cervicitis, chlamydia, gonorrhea				I C
	Vaginitis				
	Current pelvic inflammatory disease (PID)				I C
	Other STIs (excluding HIV/hepatitis)				
	Increased risk of STIs				
	Very high individual risk of exposure to STIs				I C
Pelvic tuberculosis					I C
Diabetes	Non-vascular disease				
	Vascular disease or diabetes for > 20 years				
Symptomatic gall bladder disease (current or medically treated)					
Cholestasis (history of)	Related to pregnancy				
	Related to oral contraceptives				
Hepatitis	Acute or flare	I C			
	Chronic or client is a carrier				
Cirrhosis	Mild				
	Severe				
Liver tumors (hepatocellular adenoma and malignant hepatoma)					
HIV	High risk of HIV or HIV-infected				
AIDS	No antiretroviral therapy (ARV)				I C
	Clinically well on ARV therapy	see drug interactions			
	Not clinically well on ARV therapy	see drug interactions			I C
Drug interactions, including use of:	Nucleoside reverse transcriptase inhibitors				
	Non-nucleoside reverse transcriptase inhibitors				
	Ritonavir, ritonavir-boosted protease inhibitors				
	Rifampicin or rifabutin				
	Anticonvulsant therapy**				

Source: Adapted from *Medical Eligibility Criteria for Contraceptive Use*. Geneva: World Health Organization, updated 2008.
Available: http://www.who.int/reproductive-health/family_planning/guidelines.htm

Category 1 There are no restrictions for use.

Category 2 Generally use; some follow-up may be needed.

Category 3 Usually not recommended; clinical judgment and continuing access to clinical services are required for use.

Category 4 The method should not be used.

Unlike previous versions of the MEC Quick Reference Chart, this version includes a complete list of all conditions classified as Category 3 and 4 by WHO.

I/C (Initiation/Continuation): A woman may fall into either one category or another, depending on whether she is initiating or continuing to use a method. For example, a client with current PID who wants to initiate IUD use would be considered as Category 4, and should not have an IUD inserted. However, if she develops PID while using the IUD, she would be considered as Category 2. This means she could generally continue using the IUD and be treated for PID with the IUD in place. Where I/C is not marked, the category is the same for initiation and continuation.

NA (not applicable): Women who are pregnant do not require contraception.

NC (not classified): The condition is not part of the WHO classification for this method.

* Evaluation of an undiagnosed mass should be pursued as soon as possible.

** Anticonvulsants include: phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, and lamotrigine. Lamotrigine is a category 1 for implants.

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Contraception Updates, additional questions and answers

Also - a few clarifications of questions asked after the presentation.

1. OCP's and Obesity

OBGyn 2010 Aug

"Ovarian Suppression in normal-weight and obese women duringoral contraceptive use: a randomized controlled trial"

20mcg/100 mcg levonorgestrel

30mcg/150 mcg levonorgestrel

Consistent users of both pills had suppression of follicular development.

150/226 enrollees

Among consistent users, 2.7% ovulated (3/96 normal wt and1/54 obese women) 2 ovulations occurred with each formulation. Suggest that higher ocp failure amongobese women is not related to differences in OCP dosing.

2. MIGRAINES - Clarification for emphasis

Women who have migraine with aura should NOT use combinationhormonal contraceptives

3. OCP's and depression – worse on Yaz or Yasmin

Change to lowest relative progestational activity:

Norgestimate 0.3 (Ortho Cyclen, Ortho Tri-cyclen)

Levonorgestrel 0.5 (Alesse, triphasil, Nordette)

4. Nuvaring – confirmed – NO weight limit for Nuva-Ring