Treatment of Parkinson disease: lessons learned from cases

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Epidemiology

- 0.3 percent of the general population
- 1% of the population over the age of 60
- 500,000-1,000,000 persons in the U.S.
- Men slightly more affected than women
- Mean age of onset is ~ 60
- Young-onset PD: symptom onset before age 50
  - 10% of PD patients are young-onset

Samii, Nutt, Ransom. Lancet 2004;363(9423):1783-93

Signs of PD

Motor:
- asymmetric resting tremor (UEs>LEs)
- asymmetric cogwheel rigidity
- asymmetric bradykinesia (slowness)
- postural instability

Non-motor:
- rapid eye movement (REM) Sleep disorder
- hyposmia (reduced sense of smell)
- depression, anxiety, and cognitive problems
- dysautonomia: constipation, hypotension, urgency

Sinemet (carbidopa/levodopa)

- Still the most effective PD drug
- Various combinations of carbidopa/levodopa:
  - 25/100
  - 25/250
  - 10/100
  - 25/100 CR
  - 50/200 CR
- Many generic versions available
- Levodopa in the CR version is 30% less absorbed than regular version
Problems with carbidopa/levodopa

- Short half-life
- End-of-dose wearing off
- Fluctuations between off and on states
- Dietary protein may limit levodopa absorption
- Dyskinesia (fidgety/squirmy chorea)
- Side effects:
  - nausea alleviated by additional carbidopa (Lodosyn)
  - drop in blood pressure and dizziness
  - drowsiness, but less so than dopamine agonists

COMT Inhibition

- Comtan (entacapone) 200 mg used with each dose of carbidopa/levodopa up to 6 times daily
- Blocks COMT which breaks down levodopa, thereby increasing the duration of action of levodopa and increasing levodopa levels in the blood
- Helps alleviate end-of-dose wearing off
- Stalevo is a combination of carbidopa/levodopa/entacapone all in one pill with many available doses
- Entacapone makes urine bright orange, may cause diarrhea, and may exacerbate levodopa’s side effects like dyskinesia

Dopamine agonists

- Agonists bind directly on dopamine receptors
- Longer half-life (less fluctuations) than levodopa
- Less potent than Sinemet but more potent than MAO-B inhibitors
- Side effects:
  - nausea/vomiting and leg edema
  - dizziness and low blood pressure
  - somnolence and sleep attacks
  - hallucinations and psychosis
  - compulsive gambling and disinhibited behavior

Dopamine agonists

- Pramipexole (Mirapex) and ropinirole (Requip) are oral
- Rotigotine (Neupro patch) absorbed through the skin
- Effective for both early and advanced PD
- Less dyskinesia than levodopa
- Allow for lower dose of levodopa
- Dose ratio:
  - 1 mg pramipexole ~ 4 mg ropinirole ~ 4 mg rotigotine
- Ropinirole and pramipexole available in generic
- Once daily Mirapex ER and Requip XL available
- Apokyn (apomorphine) s.c. injection for quick rescue of severe off period
Monoamine Oxidase-B Inhibitors

- Used in early and advanced PD
- Disease modification/neuroprotection unproven
- Selegiline (generic)
  - 5 mg twice daily
  - stimulant byproducts may help alertness
  - second dose no later than noon
- Rasagiline (Azilect):
  - 1 mg once daily
  - no amphetamine byproducts
- Zelapar (orally disintegrating selegiline) 1.25 mg or 2.5 mg once daily as adjunct therapy

Deep brain stimulation

- Thalamic DBS improves contralateral tremor
- Pallidal (Gpi) DBS
  - improves most motor symptoms
  - less medication reduction compared to STN
- Subthalamic nucleus (STN) DBS
  - improves most motor symptoms
  - allows reduction in anti-PD meds
- Multi-center randomized study of bilateral Gpi vs. bilateral STN stimulation:
  - First phase (best medical therapy vs. surgery) showed significant benefit but more adverse effects with surgery
  - Second phase (STN vs. Gpi) showed equal efficacy but slightly more cognitive and mood problems with STN compared to Gpi but more medication reduction with STN

Who is a candidate for deep brain stimulation surgery?

- Improvement with medications but doses are maximized and cannot be increased because of side effects
- Disabling off periods or dyskinesias > 3 hours daily
- No serious medical conditions
- No serious memory or psychiatric problems
- Preferably less than 75 years old
- Can tolerate brain surgery awake
- Willing to return for frequent programming sessions
- Have realistic expectations from surgery

Case 1

- 74 y.o. woman with 6 months of LUE tremor
- PMHx: CAD, COPD, arthritis
- O/E: obese, reduced facial animation, LUE resting tremor, bilateral wrist cogwheel rigidity (L>R), mild postural instability
- Sinemet CR 50/200 1/2 qid improved tremor and mobility, but 1 qid caused nausea
- Settled on Sinemet CR 50/200 tid at 5 hr intervals with non-protein-rich snack
Case 1 lessons:
• In older patients with co-morbid conditions, it is safer to begin treatment with levodopa
• Taking anti-Parkinson meds with non-protein-rich meals can help reduce drug-induced nausea

Case 2
• 46 y.o. right-handed woman who presented for evaluation of left hemi-dystonia mostly involving the foot
• 6 months of left foot inversion, curling of left toes, clumsiness of the left upper extremity
• MRI: tortuous left vertebral artery, indenting brainstem, hence patient referred to neurosurgery
• Neurosurgery referred patient to neurology for management of dystonia

Case 2 (cont’d)
• O/E: LUE cogwheel rigidity, left foot dystonia, slow left finger tapping and alternating movements, but no tremor
• Started on dopamine agonist and dose titrated without side effects
• Motor improvement with resolution of left foot dystonia and improved mobility
• Diagnosis of Parkinson disease was made

Case 2 lessons:
• Tortuous vessels are common findings on MRI and do not necessarily cause symptoms
• Dystonia (especially of the foot) can be a presenting sign in Parkinson disease
• 1/3 of patients with PD don’t have tremor
• In young healthy patients, may begin treatment with a dopamine agonist or MAO-B inhibitor
• Medication responsiveness is a key feature of clinically-definite PD
Case 3
• 71 y.o. woman with 4 months of LUE tremor when lifting heavy objects and LUE clumsiness
• O/E: LUE tremor at rest and when holding objects, cogwheel rigidity at L wrist + L elbow, reduced L arm swing during ambulation
• Patient reported no response to Sinemet CR 50/200 1/2 qid
• Dose could not be increased because of nausea even when Sinemet was taken with food

Case 3 (cont’d)
• Tapering of Sinemet led to worsening of tremor and LUE clumsiness
• Resumed Sinemet CR this time with Lodosyn (extra carbidopa) 25 mg tabs with each dose of Sinemet
• Significantly improved motor symptoms on Sinemet CR 50/200 qid with no nausea on Lodosyn

Case 3 lessons:
• Action tremor may accompany resting tremor in Parkinson disease
• Some patients need a high dose of levodopa to initially respond: some suggest that at least 1,000 mg of immediate-release levodopa must be tried before concluding “medication failure”
• Tapering meds looking for motor deterioration can be more sensitive than dose increase in establishing medication responsiveness
• Lodosyn provides extra carbidopa (25 mg) and helps reduce levodopa-induced nausea

Case 4
• 62 y.o. man with one yr hx of RUE tremor
• 30 yr hx of mild essential tremor when anxious
• Tremor spread over 1 yr to head and all 4 limbs
• 4 yr hx of anxiety, depression, and palpitations
• O/E: resting and action tremor R>L, cogwheel rigidity, masked face, slow gait, and micrographia
• No improvement on Sinemet 25/100 2 tabs tid
• No deterioration after sudden cessation of Sinemet
Case 4 (cont’d)

- Pt was taking large amounts of protein in form of meat and dairy with each dose of Sinemet
- Sinemet re-trial:
  - titrate CR 50/200 1.5 tabs qid (1200 mg)
  - reduce protein intake and change timing of Sinemet
- Results:
  - improvement in tremor and mobility on Sinemet CR 50/200 6 tabs daily
  - started riding bicycle to UW campus again

Case 4 lessons:

- Essential tremor and Parkinson disease can occur in the same person
- Some patients need a higher dose of anti-parkinson meds to initially respond
- Protein intake may reduce the efficacy of levodopa because amino acids compete with levodopa in absorption and crossing the blood brain barrier

Case 5

- 47 y.o. man with young-onset PD transferring care:
  - Sinemet CR 50/200 t.i.d. (7:00, 13:00, 19:00)
  - Sinemet regular 25/100 5X/day at 3 hr intervals
- Main complaint: end-of-dose wearing off
- Medication changes:
  - Sinemet CR 50/200 1.5 tabs qid
  - Sinemet regular 25/100 qam for jump start
  - Added entacapone 200 mg qid with good results

Case 5 lessons:

- Levodopa in Sinemet CR is 30% less bioavailable than in immediate-release Sinemet, so use higher dose when switching to CR
- Use immediate release Sinemet in a.m. for “jump start” and as needed for added boost
- Some patients can’t do without the immediate-release Sinemet and like the “high” from it
- Comtan (entacapone) increases levodopa levels and helps relieve end-of-dose wearing off
Case 6

- 52 yo man with motor PD onset in at age 45 (R bradykinesia), started on ropinirole which caused vomiting
- Switched to carbidopa/levodopa CR 50/200 and entacapone which was titrated over years to 5 times daily
- Pramipexole was added with dose titration to 1.5 mg 5X/day
- Developed gambling and hypersexual behavior (pornography and placing ads on singles websites while married), which did not improve until pramipexole was completely stopped
- Bilateral STN DBS which improved motor fluctuations and dyskinesia
- Carbidopa/levodopa/entacapone dose reduction after DBS

Case 6 lessons:

- Some patients tolerate one dopamine agonist better than the others
- Impulse control disorder occurs more often in patients taking higher doses of dopamine agonists, younger male patients with pre-morbid history of novelty seeking behavior
- Dopamine agonist may have to be stopped entirely before impulse control disorder improves
- Always ask family members and caregivers about impulse control disorder, as patient may not recognize behavior or be willing to talk about it
- Bilateral STN DBS surgery tends to allow medication dose reduction
Sleep Disorders: In the Trenches

Oneil S Bains MD
Virginia Mason Sleep Disorders Center

Case History: 58 yo female

- 20 year hx of insomnia: initiation and maintenance
- Treatments: Sleep Hygiene
  - 1. Hypnotherapy: No Effect
  - 2. Relaxation Tapes: No Effect
  - 3. Only using bed for sleep and sex

- 4. Aromatherapy: No Effect
- 5. Melatonin: No Effect
- 6. Health Store Remedies: No Effect
- 7. Tylenol PM: Kept her awake
- 8. Sominex: No Effect
- 9. Diazepam: Effective but advised not to use more than once a week
- 10. Zolpidem: Effective for 4 hours
- 11. Zaleplon: Effective for 2 hours
- 12. Trazodone: Dizziness without sleepiness

How effective is sleep hygiene?

- A. No data
- B. Has been studied and moderately effective
- C. Not Effective
- D. Effective in combination with other techniques
Sleep Hygiene: Effective?
- Maintain a regular wake/sleep schedule.
- Refrain from taking naps.
- Avoid caffeine after mid-afternoon.
- Exercise - but not within 3 hours of bedtime.
- Establish a relaxing routine before bedtime.
- Use the bedroom for sleep activities.
- Set environment (light, noise, temperature) at comfortable levels.
- Avoid alcohol close to bedtime.

Sleep Hygiene Effectiveness
- No 2 studies use the same definition of sleep hygiene (SH)
- “Core” (SH) rules: caffeine, alcohol, and exercise
- No data on the role of poor SH on insomnia or that good sleep hygiene improves sleep in patients with insomnia

What is the next step in evaluation?
- A. Sleep study to evaluate for other disorders
- B. Sedating substance from another class (mirtazapine or quetiapine)
- C. Psychiatric evaluation
- D. Sleep restriction
- E. Zolpidem CR

Psychophysiologic Insomnia
- Not a “Sleep” Disorder
- Disorder of Heightened Arousal
- Patients do not describe daytime sleepiness
- Generally complain of daytime fatigue
- If daytime sleepiness is significant think of other sleep disorders
Factors Contributing to the Development of Insomnia

**Predisposing Factors**
- Personality
- Sleep-wake cycle
- Circadian rhythm
- Coping mechanisms
- Age

**Perpetuating Factors**
- Conditioning
- Substance abuse
- Performance anxiety
- Poor sleep hygiene

**Precipitating Factors**
- Situational
- Environmental
- Medical
- Psychiatric
- Medications


Model of Insomnia

Evaluation of Insomnia
- History: Sleep, Medical, Psychiatric
- Clinical Suspicion for Primary Insomnia
- Obtain:
  - Sleep Log/Diary

Sample Sleep Diary

<table>
<thead>
<tr>
<th>Complete in AM for previous night</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>Monday, 1/20</td>
</tr>
<tr>
<td>Bedtime</td>
<td>11 PM</td>
</tr>
<tr>
<td>Rise time</td>
<td>7:00 AM</td>
</tr>
<tr>
<td>Estimated time to fall asleep</td>
<td>60 min</td>
</tr>
<tr>
<td>Estimated no. of awakenings and time awake</td>
<td>4 times 2 hours</td>
</tr>
<tr>
<td>Estimated amount of sleep obtained</td>
<td>5 hours</td>
</tr>
</tbody>
</table>

Utility of Sleep Diary

- Sleep Efficiency (SE)
- SE = (Time Asleep / Time In Bed) x 100
- Normal sleep efficiency is > 85%
- In our example: 5 hours / 8 hours = 62.5%

Sleep Restriction Therapy

- Determine average amount of sleep based on sleep log for the past week (ex. 5 hours)
- Restrict time in bed to equal that duration for the following week (2am-7am)
- Evaluate Sleep Efficiency.
- Ex 4.5/5 = 0.9 x 100 = 90%
- If SE > 90% add 15 minutes to time in bed

Stimulus Control Instructions

- Do Not go to bed until sleepy
- If still awake after 15 min, leave the bedroom
- Return to bed only when sleepy
- If unable to return to sleep, leave the bedroom
- Fixed Wake Up Time
- Bed for sleep only
- Avoid Napping/Resting during the day

26 yo software engineer with insomnia

- Sleep initiation insomnia for 10 yrs
- Difficulty getting up for work, has been late and reprimanded
- Lights out at 11 pm, 2 hr sleep latency, alarm at 7 am, difficulty awakening
- Sleeps in on weekends until 11 am
- Has tried zolpidem but had complex behaviors, sleepwalking and eating
How would you treat?

- A. Melatonin at bedtime
- B. Different sedative hypnotic, ie eszopiclone
- C. Fix the wake up time 7 days per week
- D. Write letter to his employer to change his work schedule
- E. Sedating antidepressant (trazodone)

Fundamentals for delayed sleep phase (DSPS)

- Wake up time has to be locked! 7 days per week
- Do not try to sleep unless sleepy
- Avoid PC, 2 hrs prior to bedtime
- Melatonin 1 mg, 6 hours prior to desired bedtime

\[\text{Circadian Rhythms}\]

**Suprachiasmatic Nuclei (SCN)**

**Output Rhythms**

**Physiology**

**Behavior**

*Figure 5. Schematic of the “components processes” mediating physiological sleepiness as a function of time of day. Sleep propensity increases in response to whichever imposed and/or experienced by the superchiasmatic pacemaker. Increasing levels of SCN-dependent cycling over the collective day oppose homeostatic sleep drive, both of which peak shortly before the habitual sleep phase. (From Ref. 66)*
42 yo female

- 10 yr history of insomnia
- Sleep initiation and maintenance insomnia
- Takes zolpidem 10 mg for the past 5 yrs
- Generally effective
- She wants to get off medications if possible but does not want to experience severe insomnia

How would you get her off of zolpidem

- A. Gradually taper over 1 month
- B. Substitute another sedating substance
- C. Sleep Restrict with zolpidem
- D. Sleep restrict without zolpidem
- E. Try to sleep without it and only take if unable to sleep

Female: recommendation to reduce zolpidem from 10 to 5mg

- A. Associated with complex behaviors
- B. Morning hangover
- C. Association with falling asleep driving
- D. More addictive in women

45 yo male with severe RLS

- RLS, severe, taking pramipexole started on 0.25 mg 4 yrs ago with benefit
- Increased by MD to 3 tabs at night
- He has started having daytime RLS and has increased to 6 tabs daily
- Pretty effective but he thinks the dose could be higher as still gets breakthrough
Next step in treatment

- A. Increase pramipexole dose to 7 tabs daily
- B. Discontinue pramipexole and change to gabapentin
- C. Change to ropinerole
- D. Start gabapentin and continue pramipexole initially

44 yo male with treated OSA

- Using cpap nightly for 6 hrs 93% of nights
- He takes off mask and sleeps the last 2 hrs without it
- AHI on his download of 1.8
- No snoring or mask leak present
- Continues to c/o daytime sleepiness

Percent of patients with EDS despite compliance with cpap

- A. 1%
- B. 10%
- C. 20%
- D. 30%

Next step in treatment?

- A. Increase sleep duration
- B. Nap during the day
- C. Modafinil
- D. Amphetamine stimulants
- E. Further sleep testing
Modafinil, which is FALSE

- A. Approved for treating residual edS in treated sleep apnea
- B. Shift workers
- C. Narcolepsy
- D. Reduces efficacy of birth control pills
- E. Mechanism of action well understood

Suvorexant (Belsomra)

- What Is Orexin (Hypocretin)? neurotransmitter
- Wake-promoting signaling involves many neurotransmitters.
  - These include serotonin, dopamine, noradrenaline, histamine, acetylcholine, and orexin.¹
  - Orexin is a central promoter of wakefulness.
- Orexin reinforces the activity of other wake-promoting neurotransmitters.²
- Orexin neurons are localized in the hypothalamus and project to the cerebral cortex

Blocking orexin receptors is thought to suppress wake drive. The therapeutic effect of BELSOMRA in insomnia is presumed to be through antagonism of orexin receptors.

BELSOMRA has no appreciable binding affinity at acetylcholine, dopamine, gamma-aminobutyric acid (GABA), histamine, melatonin, noradrenaline, opiate, or serotonin receptors.³

Antagonism of orexin receptors may also underlie potential adverse effects such as signs of narcolepsy/cataplexy. Genetic mutations in the orexin system in animals result in hereditary narcolepsy; loss of orexin neurons has been reported in humans with narcolepsy.
New Kids on the Block
New and Emerging Therapies for Diabetes Mellitus

Abe DeSantis, MD
Clinical Professor
Division of Metabolism, Endocrinology and Nutrition
University of Washington Medical Center

Disclosures

• Financial
  – NONE

Non- FDA approved indications
  SGLT2 inhibitor and Type 1 DM

Case

• 68 year old male with T2 DM for 8 years.
• No known complications
• Metformin 1000 mg po BID
• Glipizide 10mg po BID
• BMI = 38
• A1c = 8.6%

What to do?

Non-Insulin Pharmacologic Therapy for Type 2 Diabetes circa 1995

<table>
<thead>
<tr>
<th>Insulin secretagogues</th>
<th>Biguanides</th>
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<tr>
<td>Sulfonylureas</td>
<td>Metformin</td>
</tr>
<tr>
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<td></td>
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<tr>
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<td></td>
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<tr>
<td>– Glimepiride</td>
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Non-Insulin Pharmacologic Therapy for Type 2 Diabetes

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<tr>
<th>Category</th>
<th>Drugs</th>
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<tr>
<td>Meglitinides</td>
<td>Repaglinide, Nateglinide</td>
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<tr>
<td>DPP4 inhibitors</td>
<td>Sitagliptin, Saxaglitin, Linagliptin, Alogliptin</td>
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<tr>
<td>Amylin analogues</td>
<td>Pramlintide</td>
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<tr>
<td>SGLT2 Inhibitors</td>
<td>Canagliflozin, Dapagliflozin, Eeemagliflozin</td>
</tr>
</tbody>
</table>

α-Glucosidase inhibitors
- Acarbose
- Miglitol
- Lipase inhibitors
- Orlistat
- Dopamine Agonist
- Bromocriptine
- Insulin sensitizers
- Thiazolidinediones
  - Rosiglitazone
  - Pioglitazone
- Biguanides
- Metformin
- GLP1 Agonist
- Exenatide
- Linagliptide
- Bydureon
- Dapagliflozin
- Albiglutide

Sites of Action by Therapeutic Options Presently Available to Treat Type 2 Diabetes

Incretin-Based Therapies

The Incretin Effect in Healthy Subjects

*P<.05.
IV = intravenous.
GLP-1 Modulates Numerous Functions in Humans

Brain:
- Promotes satiety and reduces appetite

Stomach:
- Helps regulate gastric emptying

Alpha cells:
- ↓ Postprandial glucagon secretion
- ↓ Glucagon reduces hepatic glucose output

Beta cells:
- Enhances glucose-dependent insulin secretion

GLP-1 Secretion and Inactivation

Intestinal GLP-1 release

\[ \text{T}_{1/2} = 1 \text{ to } 2 \text{ min} \]

GLP-1 (7-36) active

DPP-4

GLP-1 (9-36) inactive (>80% of pool)

Exenatide (Byetta)

- Synthetic exendin-4
- In clinical studies, exenatide exhibited actions that are similar to those of GLP-1:
  - Stimulation of insulin secretion only when blood glucose concentrations are elevated
  - Suppression of postprandial glucagon secretion
  - Slowing of gastric emptying

Acute Meal Challenge Study: Postprandial Glucose and Glucagon Concentrations

Data from Kolterman OG, et al. J Clin Endocrinol Metab 2003;88:3082-3089

n=20  Mean ± SE
Proportion of Subjects Achieving A1C ≤7% at Week 30
Evaluable Population with Baseline A1C >7%

Placebo
5 µg exenatide
10 µg exenatide

DeFronzo R, et al. ADA 64th Annual Scientific Sessions, June 2004
Evaluable with baseline A1C >7%, N = 234 (Placebo, n = 77; 5 µg exenatide, n = 79; 10 µg exenatide, n = 84)
*P <0.01, **P <0.0001

Open-Label Study: Body Weight Over 24 Weeks

Mean (SE) Δ Study Weight (kg)

Baseline = 89 ± 2 kg
Δ -3.4 kg

Evaluable population (N=105)

Date from Poon T, et al. Diabetes Care 2005; 28(suppl 2):A45

Large Phase 3 Clinical Studies – Combined (ITT)
% Incidence of Nausea

Placebo (N = 483)
Exenatide 5 mcg BID (N = 480)
Exenatide 10 mcg BID (N = 483)

Dose increased from 5 mcg to 10 mcg at wk 4

Data on file, Amylin Pharmaceuticals, Inc.

Once-Weekly, Long-Acting Release Formulation of Exenatide over 15 Weeks in Type 2 Diabetes

BG = blood glucose.
GLP-1 Receptor Agonists: Liraglutide vs Exenatide

Change in HbA1c Change in Bodyweight

Patients receiving maximally tolerated doses of metformin, sulfonylurea, or both, stratified by previous oral therapy and randomized to liraglutide 1.8 mg qd vs exenatide 10 μg bid


Exenatide Plus Glargine: Change in Glucose Levels Over 30 Weeks

*P < .001 for between-group difference. †P < .010 for between-group difference.

PP = postprandial.


GLP1r agonists

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DEVICE</th>
<th>DOSE</th>
<th>FDA</th>
<th>A1c %</th>
<th>Wt. kg</th>
<th>A.E’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Pen</td>
<td>5 or 10 mcg SQ BID</td>
<td>Mono, oral, Basal insulin</td>
<td>1.2</td>
<td>1.5</td>
<td>Less Nausea</td>
</tr>
<tr>
<td>Bydureon</td>
<td>Pen and kit reconstit</td>
<td>2 mg SQ weekly</td>
<td>MonoRx, oral, Basal insulin</td>
<td>1.2</td>
<td>2.2</td>
<td>Same</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Pen</td>
<td>0.6-1.8 mcg SQ daily</td>
<td>Same + Wt. reduction</td>
<td>1.8</td>
<td>1.1</td>
<td>Same</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Pen with diluent</td>
<td>30 or 50 mg SQ weekly</td>
<td>Mono, oral, Basal insulin</td>
<td>1.2</td>
<td>1.1</td>
<td>Same</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Pen</td>
<td>0.75 or 1.5 mcg SQ weekly</td>
<td>Mono Oral</td>
<td>1.2</td>
<td>1.1</td>
<td>Less Nausea</td>
</tr>
</tbody>
</table>

Case

- 82 year old female. Type 2 DM x 6 years
- Metformin 1000 mg po BID
- A1c = 8.9%
- Polyuria related to higher BGs

What to do?
### Inhibition of DPP-4 Increases Active GLP-1

- **Intestinal GLP-1 release**
- **Mixed meal**
- **GLP-1 (7-36) active**
- **GLP-1 (9-36) inactive**
- **DPP-4 inhibitor**


### Glycemic, Incretin, and Islet Cell Response to a Meal After 4 Weeks of Treatment With Vildagliptin

- **Glucose**
- **Glucagon**
- **Insulin**
- **GLP-1 (7-36amide)**


### Combination of Vildagliptin and Metformin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vildagliptin/Metformin (extension, n = 42)</td>
<td>8.4 ± 0.2%</td>
</tr>
<tr>
<td>Placebo/Metformin (extension, n = 29)</td>
<td>8.0 ± 0.2%</td>
</tr>
<tr>
<td>Vildagliptin/Metformin (initial study, n = 56)</td>
<td>7.8 ± 0.2%</td>
</tr>
<tr>
<td>Placebo/Metformin (initial study, n = 51)</td>
<td>7.6 ± 0.2%</td>
</tr>
</tbody>
</table>


### DPP-4 Inhibitors
- **DPP-4 inhibitors approved**
  - Sitagliptin
  - Saxagliptin
  - Linagliptin
  - Alogliptin
- **Reduction in HbA1c ~0.6-0.8%**
- **Not associated with weight gain when glycemic control improved**
- **Well-tolerated with few adverse effects**
- **Dose adjustment for renal insufficiency for sitagliptin, saxagliptin, and alogliptin but not necessary for linagliptin**
- **Efficacious when used in combination with other oral antidiabetic agents**

Acute Pancreatitis in Exenatide, Sitagliptin, and Diabetes Control Groups

Retrospective Cohort Study of Medical and Pharmacy Claims Database
(38,615 Diabetic Patients: Exenatide 6345; Sitagliptin 15826; Control 16244)


Case

• 26 year old female with Type 1 DM
• Weight conscious.
• Insulin glargine and aspart with meals
• Withholds prandial insulin to keep weight down
• A1c = 8.8%
  
  What to do?

SGLT2 Inhibitors

Renal Handling of Glucose, Non-Diabetic Individual

Glucose filtered/day = 180 g

Virtually all the glucose filtered is reabsorbed and glucose does not appear in the urine.

SGLT = sodium-glucose cotransporter.

Renal Glucose Handling

SGLT2 Inhibition Results in Decreased Reabsorption and Increased Excretion of Glucose


**Effects of Canagliflozin from Baseline to Week 12 in Subjects with Type 2 Diabetes on Metformin**

*Mean Baseline HbA1c (%)*

- Placebo: 7.71
- Canagliflozin: 8.01, 7.81, 7.57, 7.70, 7.71, 7.62

- Sitagliptin

*Mean Baseline Weight (kg)*

- Placebo: 85.5
- Canagliflozin: 87.5, 87.7, 87.7, 87.8
- Sitagliptin: 86.3, 87

P < .001 vs placebo.
Canagliflozin Added to Metformin Study: Adverse Effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Cana 50 mg qd</th>
<th>Cana 100 mg qd</th>
<th>Cana 200 mg qd</th>
<th>Cana 300 mg qd</th>
<th>Cana 300 mg bid</th>
<th>Sita 100 mg qd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Tract Infections</td>
<td>4 (8%)</td>
<td>4 (5%)</td>
<td>2 (3%)</td>
<td>6 (9%)</td>
<td>2 (3%)</td>
<td>3 (5%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Vulvovaginal Myotic Infections</td>
<td>1 (3%)</td>
<td>6 (20%)</td>
<td>7 (25%)</td>
<td>4 (13%)</td>
<td>4 (14%)</td>
<td>7 (19%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>4 (6%)</td>
<td>0</td>
<td>2 (3%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>


SGLT2 Inhibitors

- SGLT2 inhibitors approved
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin
- Once daily oral dosing
- Reduction in HbA1c ~0.8%
- Modest weight reduction of 2-3 kg in long term studies
- Modest BP effect (SBP reduction 1.3 to 7.3 mmHg)
- Non-insulin dependent glucose lowering effect
- Dose adjustment for renal insufficiency
- Approval as monoRx or combination
- Increased risk of UTI’s and vulvovaginal candidiasis.
- Slight alterations in lipids


Average Reduction In HbA1C With Addition Of:

- Diet & Exercise 1.0%
- First Oral Agent 1.5-1.8%
- Second Oral Agent 1.0-1.2%
- Third Oral Agent 0.7%
- 4th
- 5th
- 6th?


Natural History of Type 2 Diabetes

Inhaled Insulin

• Afrezza™ from MannKind
  – FDA approved, availability early 2015
• Technosphere platform to deliver recombinant human insulin as dry powder
• Shorter onset, similar duration RAA
• Similar efficacy, perhaps slightly lower hypoglycemia
• Higher risk DKA in Type 1 DM
• Requires basal insulin
• Pulmonary concerns

U300 Glargine insulin

3x concentrated insulin glargine
Leads to smaller SQ depot and longer PK profile
Similar hyperglycemia effects compared to U100 glargine
Improved hypoglycemia profile with less weight gain

Emerging Therapies for Type 2 Diabetes

Products in the Pipeline: Insulins
- Longer-acting basal insulins: overall similar HbA1c lowering with less hypoglycemia
  - Degludec: multihexamers, duration 42 hour
  - LY2605541: hepato-selective
  - Glargine U300: duration 36 hour
- More rapid acting prandial insulins
- Closed loop pumps “bionic pancreas”: insulin, insulin/glucagon
- Insulin patch-pumps
- Wireless CGMS data transfer- Dexcom Share

Products in the Pipeline: Noninsulin
- Additional agents of same types:
  - SGLT2 inhibitors
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
- Antigliugagon agents
  - Ranolazine
  - Ly2400921
  - LGD-6972
- Glucokinase activators
  - Decrease hepatic gluconeogenesis and increase glycogen synthesis
- Imeglimin
  - Decreases hepatic gluconeogenesis and increases muscle glucose uptake (? MOA)

Summary
- Incretin mimetics available as second line agents with insulin, solo, combination with orals
- SGLT2 inhibitors reduce glucose reabsorption in the kidney, resulting in decreased blood glucose levels, decreased weight, and slight increase in mycotic infections
- Additional drugs are being added to the classes currently available
- New longer-acting insulin analogs are coming that give similar glycemic lowering with less hypoglycemia
- New oral agents may be coming with novel mechanisms of action
Approaching Patients with Tricky to Treat Headaches

By Natalia Murinova, MD, MHA
Director, Headache Clinic at UW
Department of Neurology,
University of Washington
April 24, 2015

Why are we here today?

- Headache is one of the most common reasons for a medical visit
- Lifetime headache disorder is 93% in men and 99% in women
- Most people who have headaches do not go to the doctor, they self treat
- Appropriately recognizing and managing headache disorders is essential

Patient

- This is a first visit for 47 yo. lawyer who has a long history of migraine without aura and reports that her headaches occur few times monthly.
- The headaches resolves within 30 minutes to 2 hours with 50 mg oral sumatriptan.
- As you are writing medication refill, she asks for a medication override, allowing her 18 100 mg Imitrex tablets per month.
- You are surprised, if she has only migraines 3 to 4 times per month, why does she need so many pills?

More history

She had significant headaches since teenage years.
She tried numerous preventives, none of which worked apart from topiramate, but she did not like side effects.
She had an increase in both severity and frequency this year due to divorce and stress.
For the past 6 months she has been having much stronger migraine with hours of vomiting and debilitating pain.
47 year old needing 18 pills a month of sumatriptan

- She explains that even though the sumatriptan works well, the headache usually returns the same day, or the next day
- This cycle can continue for several days in a row
- Usually for 3 or 4 days or longer
- She does not have a headache diary

1. Ask number of headache days or number of free headache days

2. Ask specific medication use

3. I recommend using electronic diary or paper diary

"Document when you have a headache and how you are treating it."
General rules: headache lingers

- 1. Treat headache attack early within 40 minutes
- 2. Use higher dose: 100 mg sumatriptan not 25 mg or 50 mg
- 3. Use proper formulation: patient might have better response from nasal or injection form of triptan
- 4. Try another triptans or DHE

More than 15 days per month

- The patient was reporting 3 to 4 migraines, however her headache lasted usually for multiple days in a row.
- She was experiencing more than 15 days of headaches per month and she has chronic migraine
- The consideration of stepping up treatment to make acute treatment more effective
- Consider prophylactic treatment > 4 to 5 headache days a month
- Most research shows more likely progression to transformation into chronic migraine with more than 4 days per month of migraines

Add preventive medications in anticipation or during weaning

Chronic Headache

- 1 to 5% of general population is estimated to have chronic headache
- In Headache clinics more than 70% of patients are presenting with chronic headaches
- Chronic headache are usually associated with chronic comorbidities like anxiety, depression and phobias
The patient with sumatripan overuse

Topiramate:
- Week 1: 25 mg
- Week 2: 50 mg
- Week 3: 75 mg
- Week 4: 100 mg

Standard of Care in HA Clinics

- Combination therapy (not evidence-based)

Triptans or DHE

Anti-inflammatory

Anti nausea

Patient

- She opted to postpone daily prescription preventive medication due to past experience
- She started non-pharmacological daily feverfew tea for prevention and acute treatment - 1 cup 3 times
- We added diclofenac 50 mg for rescue combined with ondansetron 8 mg or phenergan 25 mg (at home)
- Within 2 weeks follow up she brought her electronic diary (iHeadache) that can be emailed and added to chart and it showed headaches that were now milder and occurring less often

iHeadache summary after first change in treatment

- 03/10/2015 to 03/20/2015: 6 headaches were reported.
  - Headache Type: 1 Migraines, 2 Probable Migraines, 3 Tension Headaches, 0 Unclassified Headaches
  - Medications: 1 doses of sumatriptan 100 mg for 1 headache, 1 doses of acetaminophen for 1 headache, 3 doses of ibuprofen for 3 headaches
- Disability - 0.00 hours of total disability
- Triggers - 2 Caffeine Decrease, 1 Overtired
EPICARE Message from last week

• “Things are going pretty well - I'm complying with directives (less coffee, more feverfew tea, more sleep, almost no Imitrex or OTC pain relievers, etc..) - and FAR fewer headaches overall, and NONE of the horrible variety!! No nausea whatsoever, which is really new and wonderful!”

Please give my best to Dr. M. Thanks

Male Patient Presentation

• First visit for a 38 year old male with history of headaches since teenage years for 20 years
• Worse since 2012 especially after MVA
• Continuous HA since May 2014
• 30 days per month
• Pain is 8/10, pressure and aching bilaterally in frontal, temporal and occipital regions
• Worse with heat, noise, light, exertion

Patient

• Aura equivalent: patterns of light change
• Associated symptoms: nausea, light sensitivity, noise sensitivity and dizziness
• Headache triggers include: Stress
• Headache pattern: continuous, worse in the evening
• Relieved by: OTC and prescription meds only

Patient

• Taking hydromorphone 2mg, initially for severe cases, but escalated to 6mg per day by May 2014
• Using Tylenol 2 grams per day since May 2014 daily
• Previous treatments: sumatriptan, rizatriptan, propranolol, verapamil, gabapentin, topiramate, amitriptyline, and citalopram
Breaking cycle of medication overuse Tepper


doi:10.3949/jcp.77u.09147

SYMON J. TOPPER, MD
Center for Headaches and Pain, Neurological Institute, Cleveland Clinic

DEBORAH K. TOPPER, MD
Center for Headaches and Pain, Neurological Institute, Cleveland Clinic

Patient

- At time of headache referral, patient’s referring provider educated him about typical headache clinic recommendations to stop opioids and Tylenol
- Patient then tapered himself off Tylenol rapidly within two weeks
- Also tapered himself off Hydromorphone 1mg/day over a week

Headaches after all these changes

- Patient reports feeling much better off hydromorphone and OTC meds
- Only medications now are propranolol and ketorolac rarely PRN
- Continues to have constant pain all around his head
- More severe migraine-like headaches every other day with visual auras, 6/10

Patient

- Patient suffered withdrawal symptoms, but headaches improved rapidly
- Using Sprix (nasal ketorolac) 4-5 times a month for symptom control
- Taking Propranolol 60 BID for prophylaxis
- Receiving Botox injections and supraorbital nerve blocks x 2
- 20# weight loss
- Massage therapy
CEFALEY Device

CEFALY Device

CEFALY for Migraines

- Transcutaneous Supraorbital Nerve Stimulator
- Acts as Trigeminal TENS unit
- May be used up to 20 minutes/day
- Available with prescription for $350
- In large randomized placebo-controlled trial, significantly reduced headache days


CEFALY USA is FDA approved with prescription

Last week our patient's visit

- Dr. M.: “How many headache days have you had since seeing you 6 weeks ago?”
- Patient: “You should be asking how many headache free days have I had last month?”
- Dr. M. “How many headache free days have you had last month?”
- Patient: “All apart from one!” “CEFALY and multimodal approach are working.”
Approach to refractory headaches

- Must make a diagnosis (>200 types of headaches)
- Is it secondary or primary?
- Medication overuse can confound any type of headache particularly prone to migraine (and can make hemicrania continua bilateral)
- Over time, headache due to low CSF pressure lose its temporal association with position

Why is the patient here?
Most patients fall into 1 of 3 groups

- The patient can no longer tolerate their typical recurrent headaches
- The patient has headaches regularly, but they are either so much different or so much worse that the patient is alarmed and came to the ED
- This is their first really severe headache

Diagnostic and therapeutic Pitfalls: What goes wrong?

- Wrong dose
- Excessive initial dose
- Inadequate final dose
- Duration of treatment too short
- Combination treatment required
- Non-compliance
- Unrealistic expectations
- The presence of CM/rebound/chronic daily HA

Adapted from Lipton RB, et al. Neurology. 2003;60(7):1064-1070
Does a response to therapy predict the etiology of an acute headache?


Gold standard in diagnosis
International Headache Society Criteria

- Part I: Primary Headaches
  - Migraine
  - Tension-type Headache
  - Cluster Headache and Trigeminal Autonomic Cephalalgias
- Part II: Secondary Headaches
- Part III: Cranial Neuralgias, Facial Pain
Medications Implicated in Transformation

- Opiates
- Combination analgesics
- Caffeine
- Barbiturate-containing medications
- Ergotamine tartrate, isomeptene
- Triptans
- Others

Chronic Daily Headache

- Transformed migraine treatment responds best to a multidisciplinary approach
- Identify and treat comorbid diseases
- Educate patient on trigger factors and lifestyle
- Eliminate overuse of acute drugs at the same time as patient begins preventative treatments

Ibuprofen can cause overuse

Slow weaning from certain medications like butalbital

Taper medication weekly, e.g., four butalbital tablets per day during the first week, three per day during the second week, and so on

Breaking the cycle STEWART, J. TEPPER, MD. Cleveland Clinic Journal of Medicine April 2010
Provide acute therapy during wean with limit of 6 days per month

- Provide acute medications
- (triptans or dihydroergotamine) for severe migraine no more than 2 days per week, fewer than 8 days/month

How Can Migraine Attacks Be Treated?

Pharmacotherapy
- Acute Treatments:
  - Triptans
  - Ergot compounds
  - NSAIDs
  - Anti-nausea
- Prophylactic Treatments:
  - Beta blockers
  - Calcium channel blockers
  - Antidepressants
  - Antiepileptics

Lifestyle modification and trigger reduction
- Sleep hygiene
- Daily exercise
- Nutrition
- Stress reduction
- Avoiding migraine triggers
- Behavioral therapy
- Physical therapy
- Massage therapy
- Acupuncture

Rescue Therapy for Headaches

Serotonin receptor agonists
- Dopamine antagonists
- NSAIDS

Prochlorperazine

- Prochlorperazine 10mg IV was shown to be superior to metoclopramide 10mg IV in treatment of HA in the ED in 70 patients.
- Commonly co-administered with Diphenhydramine 12.5 mg to prevent dystonia
- Combination of these two drugs shown superior to sumatriptan SQ


Prochlorperazine

- Dystonia

Metoclopramide

- Metoclopramide 10-20mg IV Q 20 minutes can be helpful in patients who can’t tolerate prochlorperazine
- Also frequently given with diphenhydramine

NSAIDs

- NSAIDs have shown efficacy for HA:
  - Ketorolac 30 mg IV or 60mg IM
  - Contraindicated in GI bleeding, renal impairment, and pregnancy
  - Diclofenac powder 50 mg (CAMBIA)

Corticosteroids

- Single dose Dexamethasone 10-25mg IV
- Short course oral prednisone
- No benefit for acute relief, however reduces HA recurrence 24-72 hours after discharge
- Host of side effects, including GI bleed, risk of osteoporosis and osteonecrosis
Corticosteroids

- Widely used, especially in IM form
  - Meperidine, tramadol and nalbuphine
  - Cause dizziness, sedation and nausea
- Should be avoided for at least 4 reasons:
  - Less effective, deals with pain, treating only a symptom
  - Sedation, respiratory depression
  - Opioids worsen headaches
  - Abuse potential
- Most useful in elderly and selected pregnant patients

Standard of Care in HA Clinics

- Preventive therapy every single day in patient who are missing work, requiring emergency room visits, have more than 4 days of migraine a month, can't tolerate acute medications

Goals of Headache Management of severe headaches

- Exclude Ominous Causes
- Find the Correct Diagnosis using IHS criteria
- Provide Adequate Relief of Pain
- Start preventive therapy
- Decrease headache triggers
- Address lifestyle
- Establish Trust
Controversies in Osteoporosis Management

Friday, April 24 ~ 10:40 AM to 11:10 AM

Elizabeth Reilly, MD

Handout Not Available at this Time
HCV – History

- before 1975 – 2 syndromes recognized
- serum hepatitis infectious hepatitis
- 1964 hepatitis B identified (serum)
- 1973 hepatitis A identified (infectious)
- 1975 description of non-A, non-B hepatitis
- 1989 identification of HCV
  - accounted for up to 96% of non-A, non-B hepatitis
- 1993 delineation of HCV genome

HCV – The Impact of Disease

- Nearly 3% of worldwide population has HCV

Most common blood-born infection in US

- Up to 75% of infected patients are unaware of infection until liver disease or cancer develops

HCV infection is associated with multiple diseases

- Diabetes
- Depression
- Liver Disease
- Kidney Disease
- Skin Conditions

- B-cell proliferative disorders
- Cognitive disorders
- Cancer

Lavanchy. Liver Int 2009;30:74
Shepard. Lancet Infect Dis 2005;5:59
HCV – The Impact of Disease

Baby Boomers account for 2 out of 3 cases of chronic HCV in the US

Number progressing to cirrhosis will continue to increase

PEARL

Prevalence (Millions)

Healthcare Cost ($ Billion)

Large Population Underscreened and HCV Patients Underdiagnosed

- Current screening practices fail to identify a large proportion of patients with chronic HCV infection
  - As few as 25% of patients are diagnosed
- Survey of 4000 primary care physicians
  - Only 59% of 1412 respondents asked all patients about HCV risk factors
- AASLD recommends that "as part of a comprehensive health evaluation, all persons should be screened for behaviors that place them at high risk for HCV infection"


CDC / USPSTF:

- All persons born from 1945 – 1965 should receive one time screening

HCV - Diagnosis

- Patients should routinely be tested if they have:
  - Known/possible risk factors
  - Born between 1945 - 1965
  - Elevated liver enzymes
    - ANY degree of enzyme abnormality
    - A single normal ALT doesn't rule out chronic hepatitis
- Utility of Tests
  - Has patient ever been infected? → antibody tests
  - Is infection still active or resolved? → RNA testing
  - What treatment should we use? → genotype testing

<table>
<thead>
<tr>
<th>Anti-HCV Antibody</th>
<th>HCV RNA</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>This patient is not infected with HCV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No further testing is needed</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>This patient has chronic HCV infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Early acute HCV infection (prior to antibody) OR HCV infection in severely immunocompromised setting (i.e., organ transplant, chemotherapy, HIV)</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>This patient has cleared the infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>spontaneous in 25% of exposed patients OR Following successful treatment</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>This patient has cleared the infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatocellular carcinoma, Decompenated cirrhosis</td>
</tr>
</tbody>
</table>

Natural History

Advanced Liver Disease in Chronic HCV-Infected US Population, 2009-2028

- The total number of patients with advanced liver disease in 20 yrs is projected to be >4-fold greater than it is today

HCV – Clinical Picture

- Clinical Presentation
  - majority
    - asymptomatic or nonspecific symptoms
  - normal to mild-moderate ALT elevations
- Liver Failure
  - very late in the course!!!
HCV – Assessing Disease Severity

Liver Biopsy = Gold Standard

Limitations:
- sampling error
- risk / complications
- expense

Noninvasive Liver Tests
- Transient Elastography, etc.
- MR Elastography
- Serum Fibrosis Markers, etc.

useful at the edges of disease – cirrhosis vs. mild disease
less helpful in between

Liver Stiffness Correlates with Fibrosis Stage

Yin et al. CGH 2007;5:1207-13

US Transient Elastography
FibroScan

- Vibration-Controlled Transient Elastography (VCTE™).
- Probe with small transducer, a 50-MHz wave is passed to measures the velocity of the shear wave
- Assess liver stiffness (measured in kPa correlated to fibrosis)
Factors affecting progression

- Age at infection (>40 years old)
- particularly if contracted via blood transfusion
- Male Gender
- Alcohol consumption
- Obesity
- Coinfection with HIV or HBV
- Iron in the liver, as detected via liver biopsy

Reminder: HCV progression has not been demonstrated to be influenced by viral load, genotype, serum ALT, or mode of transmission.

HCV Progression to Cancer

- Increased risk for Hepatocellular Carcinoma
  - cirrhosis (possibly bridging)
  - coinfection with HBV
  - alcohol consumption
  - iron overload (even small amounts)

**PEARL** – Cirrhotic HCV patients must undergo imaging surveillance every 6 months for hepatocellular carcinoma
Primary Care Objectives
• screen appropriate patients for HCV
• confirm the presence of viremia
• reassurance / supportive care
  • abstinence
  • weight loss
  • treatment of depression
• assess disease severity – a good time for referral
  • candidate for therapy?
• cirrhotics
  • don't forget the cancer screening!

Treatment - Goals
• Primary Goal
  • eradicate HCV
• Secondary Goals
  • decrease inflammation and necrosis
    • improve histology & halt progression to cirrhosis
  • reduce risk for hepatocellular carcinoma
  • improved health-related QOL
  • control extrahepatic manifestations

Treatment - Evolution
• Passive Immunization
  • Immune serum globulin
    • no evidence it works
    • use is not recommended
• Active Immunization
  • no effective vaccine is available
• Antioxidants
  • milk thistle
  • vitamin E
  • vitamin C
  • efficacy is unproven
• CAMs
  • herbal therapies, acupuncture, etc.
  • efficacy is unproven

Treatment - Evolution
• 1975 – non-A non-B identified
• 1989 – HCV identified
• 1991 – type-1 interferon approved for HCV
  • antiviral activity
  • antifibrotic activity
  • immunoregulatory activity
  • Cure rates – 10-22%
• 1992 – diagnostic ELISA test for HCV perfected
• 1998 – viral genotypes identified
Treatment – Evolution

- 1998 – ribavirin approved for HCV
- IFN/RBV became standard

<table>
<thead>
<tr>
<th>Cure rates</th>
<th>35% GT1 – 70% GT2/3</th>
</tr>
</thead>
</table>

- 2001 – first pegylated IFN approved
- Interferon now weekly – easier to take
- PEG-IFN/RBV became standard

<table>
<thead>
<tr>
<th>Cure rates</th>
<th>45% GT1 – 75% GT2/3</th>
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</table>

Treatment – Evolution

SVR = cure
SVR = improved outcomes

Treatment Limitations

- Not all patients could receive interferon
- Few options in those who failed
- SVR rates consistently lower among blacks, older patients, and individuals with advanced cirrhosis

Berg. Gastro 2006;30:1086
Poynard. Gastro 2009;37:6168
Huang. J Infect Dis 2010;201:751
Bitt. Hepatology 2010;52:2366

HCV Life Cycle and Targets for Direct-Acting Antivirals (DAAs)

- NS3/4 protease inhibitors
- NS5A inhibitors
- NS5B polymerase inhibitors
- Nucleos(t)ide Non-nucleoside

Treatment – Evolution

- 2002 – DAAs begin development
  - ISIS 14803 (Antisense)
  - UT-231B (Imino sugar)
  - VX-497 (IMPDH inhibitor)
  - Heptazyme (Ribozyme)
  - ACH-806/GS-9132 (NS4a)
  - ANA975 (TLR agonist)
  - BILN 2061 (Protease)
  - JTK-003 (Polymerase)
  - NM-283 (Polymerase)
  - CPG 10101 (TLR agonist)
  - RT025 (Interferon-alpha)
  - R803 (Polymerase)

- 2005 – HCV first replicated in the lab

Courtes of Nelson D. Adapted from 2008 Roche HCV Symposium

Direct-Acting Antivirals

- Directly target HCV
  - protease
  - polymerase
  - NS5A
  - NS5B

- Improve virologic response
  - in all patients


Treatment – Evolution

- 2011 – Approval of first DAAs
  - telaprevir
  - boceprevir

  Cure rates
  >80% GT1 – >90% GT2/3

- BUT
  - still needed interferon & ribavirin
  - horrible side effects
  - cure rates ranged from 14 – 85% depending on situation (genotype; prior treatment response)

Overall SVR
Treatment – Evolution

- 2013 – second generation DAAs approved
  - Sofosbuvir
  - Simeprevir
  - BUT
    - again, approved with interferon & ribavirin, or with ribavirin alone

Cure rates

>91% GT1 – 60-100% GT2
19-92% GT3

Sofosbuvir Phase 3 Studies

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment</th>
<th>SVR12 Overall</th>
<th>SVR12 Others</th>
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<tbody>
<tr>
<td>NEUTRINO</td>
<td>GT 1,4,5,6</td>
<td>Naive</td>
<td>GT1 91%</td>
<td>GT1 4.5.6</td>
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<td></td>
<td>GT4 96%</td>
<td>GT2.3 67%</td>
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<td>GT5,6 100%</td>
<td>GT2.3 4.5.6</td>
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<td>Cirrhosis – 80%</td>
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<td>Cirrhosis – 92%</td>
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<td>Cirrhosis – 91%</td>
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<td>Cirrhosis – 34%</td>
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Simeprevir Phase 3 Studies

<table>
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<th>Study</th>
<th>Population</th>
<th>Treatment</th>
<th>SVR12 Overall</th>
<th>SVR12 Others</th>
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<tbody>
<tr>
<td>QUEST-1</td>
<td>GT1</td>
<td>Naive</td>
<td>80%</td>
<td>GT1a 75%</td>
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<tr>
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<td></td>
<td>w/ QS68K – 84%</td>
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<td>w/ QS68K – 58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GT1b – 85%</td>
</tr>
<tr>
<td>PROMISE</td>
<td>GT1</td>
<td>Experienced</td>
<td>79%</td>
<td>GT1a 70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>w/ QS68K – 78%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>w/ QS68K – 41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GT1b – 85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F0–2 – 92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F3–4 – 73%</td>
</tr>
</tbody>
</table>
Paritaprevir/ritonavir + Ombitasvir + Dasabuvir + Ribavirin

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment</th>
<th>SVR12 Overall</th>
<th>SVR12 Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPPHIRE I</td>
<td>GT 1</td>
<td>Naïve</td>
<td>96%</td>
<td>GT 1a – 95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GT 1b – 98%</td>
</tr>
<tr>
<td>SAPPHIRE II</td>
<td>GT 1</td>
<td>Experienced</td>
<td>96%</td>
<td>GT 1a – 96%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GT 1b – 97%</td>
</tr>
<tr>
<td>PEARL IV</td>
<td>GT 1a</td>
<td>all</td>
<td>97%</td>
<td>Note: RBV needed; response without is 96%</td>
</tr>
</tbody>
</table>


Paritaprevir/ritonavir + Ombitasvir + Dasabuvir + Ribavirin

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment</th>
<th>SVR12 Overall</th>
<th>SVR12 Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEARL II</td>
<td>GT 1b</td>
<td>experienced</td>
<td>97-100%</td>
<td>Ribavirin not necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEARL III</td>
<td>GT 1b</td>
<td>naïve</td>
<td>99%</td>
<td>Ribavirin not necessary</td>
</tr>
</tbody>
</table>


Treatment – Evolution

- 2014 – several all oral regimens are now FDA-approved
  - Simeprevir + Sofosbuvir
  - Sofosbuvir + Ledipasvir
  - Sofosbuvir + ribavirin
  - Paritaprevir/ritonavir + Ombitasvir + Dasabuvir
  - Paritaprevir/ritonavir + Ombitasvir + Dasabuvir + ribavirin

Simeprevir + Sofosbuvir

<table>
<thead>
<tr>
<th></th>
<th>24 Wk</th>
<th>12 Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0-F2 Naïve/Nulls</td>
<td>93%</td>
<td>96%</td>
</tr>
<tr>
<td>F3-F4 Naïve/Nulls</td>
<td>91%</td>
<td>93%</td>
</tr>
</tbody>
</table>

FDA Approved:
- 24 weeks in noncirrhotics
- 24 weeks for cirrhotics
- no ribavirin

Sofosbuvir + Ledipasvir

<table>
<thead>
<tr>
<th>Subjects Without Cirrhosis</th>
<th>Treatment-Naïve</th>
<th>Treatment-Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>96%–99% SVR12 with 12 weeks of treatment</td>
<td>99% SVR12 with 12 weeks of treatment</td>
</tr>
</tbody>
</table>

| Subjects with Compensated Cirrhosis | 95% SVR12 with 24 weeks of treatment |

8-week duration can be considered in treatment-naïve patients without cirrhosis if pretreatment HCV RNA <6 million IU/mL.

Treatment-experienced patients who have failed treatment with Peg-IFN alfa + RBV ± HCV PI.


Paritaprevir/ritonavir + Ombitasvir + Dasabuvir ± Ribavirin

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>no cirrhosis</td>
<td>Viekira Pak + RBV</td>
<td>12 weeks</td>
</tr>
<tr>
<td>with cirrhosis</td>
<td>Viekira Pak + RBV</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Genotype 1b

- no cirrhosis: Viekira Pak + RBV for 12 weeks
- with cirrhosis: Viekira Pak + RBV for 24 weeks

Projected Timing for New Regimen Launches

<table>
<thead>
<tr>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
</table>

Summary

- SVR = cure
- SVR protects from liver related death (HR 0.06)
- SVR reduces, but doesn’t eliminate HCC (HR 0.19)
  - risk 8.5% over 8.5 years in cirrhotics
  - risk 1.8% over 8.5 years in severe fibrosis
- SVR eliminates liver failure (HR 0.07)
Summary

- Treatment-Naïve GT1 HCV Patients

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Noncirrhotic</th>
<th>Compensated Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regimen</td>
<td>Duration, Wks</td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td>LDV/SOF</td>
<td>12&quot;</td>
</tr>
<tr>
<td>GT1a</td>
<td>OMK/PTV/RTV + DSV + RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1b</td>
<td>OMK/PTV/RTV + DSV</td>
<td>12</td>
</tr>
<tr>
<td>GT1a</td>
<td>SMV + SOF ± RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1b</td>
<td>SMV + SOF</td>
<td>12</td>
</tr>
</tbody>
</table>

AASLD/IDSA HCV Guidelines: http://www.hcvguidelines.org

Summary

- Treatment-Experienced GT1 HCV Patients

<table>
<thead>
<tr>
<th>Population</th>
<th>Noncirrhotic</th>
<th>Compensated Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regimen</td>
<td>Duration, Wks</td>
</tr>
<tr>
<td>Prior PegIFN/RBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td>LDV/SOF</td>
<td>12</td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td>OMK/PTV/RTV + DSV + RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1a</td>
<td>OMK/PTV/RTV + DSV + RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1b</td>
<td>OMK/PTV/RTV + DSV + RBV</td>
<td>12</td>
</tr>
<tr>
<td>GT1a or 1b</td>
<td>SMV + SOF ± RBV</td>
<td>12</td>
</tr>
<tr>
<td>Prior SOF</td>
<td>Defer therapy</td>
<td></td>
</tr>
</tbody>
</table>

AASLD/IDSA HCV Guidelines: http://www.hcvguidelines.org

Summary

- Genotype 4
  - LDV/SOF x 12 weeks
  - OMK/PTV/RTV+RBV x 12 weeks
  - SOF+RBV x 24 weeks
  - SOF+SMV±RBV x 12 weeks
  - SOF+PEG+RBV x 12 weeks

AASLD/IDSA HCV Guidelines: http://www.hcvguidelines.org

Summary

- Genotype 5
  - LDV/SOF x 12 weeks
  - PEG+RBV x 48 weeks

- Genotype 6
  - LDV/SOF x 12 weeks
  - PEG+RBV x 48 weeks (naïve)
  - SOF+PEG+RBV x 12 weeks (experienced)

AASLD/IDSA HCV Guidelines: http://www.hcvguidelines.org

Summary

- Genotype 2
  - naïve
    - SOF+RBV x 12 weeks
    - SOF+RBV x 16 weeks (cirrhotics)
  - experienced
    - SOF+RBV x 12-16 weeks
    - SOF+PEG+RBV x 12 weeks

AASLD/IDSA HCV Guidelines: http://www.hcvguidelines.org

Summary

- Genotype 3
  - naïve
    - SOF+RBV x 24 weeks
    - SOF+PEG+RBV x 12 weeks
  - experienced
    - SOF+RBV x 24 weeks
    - SOF+PEG+RBV x 12 weeks

AASLD/IDSA HCV Guidelines: http://www.hcvguidelines.org
Nephrotoxicity and Electrolyte Complications of Common Drugs
Leah A. Haseley, MD

Case
A 59 year old woman with stage 3 CKD presents to your office c/o dysuria and bladder spasms. UA is loaded with WBCs. Prior urine cultures showed *coli* resistant only to ampicillin. You elect to treat with TMP-SMX.

Possible lab abnormalities that you might expect to see include:
- Hypocalcemia
- Hypernatremia
- Hyperkalemia and a small increase in creatinine
- None - you are just trying to scare me

Renal effects of TMP-SMX

"False" elevation in creatinine
Acute interstitial nephritis
Hyperlakemia

Drug-induced hyperkalemia

- Most common cause of hyperkalemia in everyday practice
- Highest risk:
  - CKD
  - Elderly
  - Multiple offending meds

**Drug -Induced hyperkalemia**

Blockade of ENAC
- Amiloride
- Triamterine
- Trimethoprim

Block intracellular shift
- Beta- blockers
- Digoxin Toxicity

Decreased Aldo
- ACEI
- ARB
- Spironolactone
- Heparin
- NSAIDs

Hyperkalemia from TMP-SMX:
- First described in 1983 (treatment for PCP pneumonia) NEJM 1990, 1993
- 76-100% of pts have a rise in potassium ranging 0.36-1.21 meq/liter
- Average onset: 4-5 days after treatment
- 10-20% develop K > 5.5

Hyperkalemia from TMP-SMX: Risk factors
- Creatinine > 1.2mg/dl
- High dose TMP
- Elderly
- Other meds
  - ACE
  - ARB
  - NSAIDs
  - Aldactone
TMP-SMX treatment results in....

- 2.46x Increased risk of sudden death among older pts on spironolactone (n= 328 on antibiotics)
- 3x Increased risk of hospitalization for high K among elderly woman treated for UTI (n = 393,039)
- 6x Increased risk of hospitalization for hyperkalemia among pt on ACE/ARB
- 1.33x Increased risk of sudden death among older pts on ACE/ARB

Trimethoprim causes a “false” rise creatinine

- Creatinine in healthy state
  Filtered 85% = glomerulus
  Secreted 15% = tubules through organic cation transporters (OCTs)

Trimethoprim also secreted via OCTs

Trimethoprim also secreted via OCTs

 TMP-SMX: What is a PCP to do?

- Do I need it...
- Avoid in elderly on RAAS inhibitors
- Check potassium after 3-4 days
- Accept a small rise in creatinine (< 0.5mg/dl), but if higher, need to consider interstitial nephritis
Case

A 67 year old woman with a long history of GERD has been lost to f/u for 6 years. She presents for routine care. GFR is normal. Medications include:

- Trazadone 50mg qHS
- Omeprazole 20mg BID
- Vitamin D 1000iu daily

Which of the following would be the most likely medication-induced electrolyte disturbance:

a) Hyperphosphatemia
b) Hypocalcemia
c) Hypomagnesemia
d) Hypoglycemia

PPIs and hypomagnesemia

- 2006: First cases reported of omeprazole in NEJM (Tetany with mg < 0.5mmol/liter)
- 2009: All PPIs have potential
- 2013: First meta-analysis
- Not the kidney’s fault

Drug causes of ↓ Mg

Renal loss
- Cisplatinum
- Diuretics
- Ampho B
- Cyclosporine
- ETOH
- EGF receptor inhibitors

GI loss
- PPI

PPIs and hypomagnesemia
Hypomagnesemia

- Tetany
- Arrythmia

Hypocalcemia (PTH resistance)
Hypokalemia  (renal wasting of K)

Hypomagnesemia from PPIs

<table>
<thead>
<tr>
<th>First Author</th>
<th>Design</th>
<th>Population</th>
<th>Patient #</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gau</td>
<td>Cross-sectional</td>
<td>Inpatient</td>
<td>487</td>
<td>+</td>
</tr>
<tr>
<td>El-Charabaty</td>
<td>Cross-sectional</td>
<td>Inpatient</td>
<td>421</td>
<td>+</td>
</tr>
<tr>
<td>Koulouridis</td>
<td>Case-control</td>
<td>Inpatient</td>
<td>804</td>
<td>-</td>
</tr>
<tr>
<td>Danaiger</td>
<td>Cross-sectional</td>
<td>ICU</td>
<td>11,490</td>
<td>+</td>
</tr>
<tr>
<td>Kim</td>
<td>Retro Cohort</td>
<td>Inpts/Outpts</td>
<td>112</td>
<td>+</td>
</tr>
<tr>
<td>Alhosaini</td>
<td>Retro Cohort</td>
<td>ESRD</td>
<td>62</td>
<td>+</td>
</tr>
<tr>
<td>Markovitis</td>
<td>Cross-sectional</td>
<td>Outpts</td>
<td>95,205</td>
<td>+</td>
</tr>
<tr>
<td>Van Ende</td>
<td>Cross-sectional</td>
<td>Outpts</td>
<td>512</td>
<td>-</td>
</tr>
<tr>
<td>Lindner</td>
<td>Cross-sectional</td>
<td>Inpatients</td>
<td>5118</td>
<td>+</td>
</tr>
</tbody>
</table>

PPIs and Hypomagnesemia

- Most pts on PPI > 1 year
- Majority asymptomatic, but tetany, seizure, arrythmias described
- Relapse after re-challenge with another PPI
- Refractory to magnesium repletion
- Got better quickly after stopping PPI

Famularo, Expert Opinion Drug Safety 2013:12
PPIs and Hypomagnesemia

- N = 11,490 ADMITTED TO ICU at single center
- Nested case control
- In pts taking diuretics on admission, use of PPIs was associated with a 0.028 mg/dl lower adjusted magnesium level
- In pts not on diuretics, PPI use did not associate with hypomagnesemia.
- Among pts taking diuretics:
  - Diuretics + PPI = 15.6 % hypomagnesemia
  - Diuretics no PPI= 11% hypomagnesemia


From the FDA...

- Consider obtaining serum magnesium levels prior to initiation of prescription PPI treatment and checking levels periodically thereafter for patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics).
- Advise patients to seek immediate care from a healthcare professional if they experience arrhythmias, tetany, tremors, or seizures while taking PPIs. These may be signs of hypomagnesemia.
- Consider PPIs as a possible cause of hypomagnesemia, particularly in patients who are clinically symptomatic.
- Be aware that consumers either on their own, or based on a healthcare professional’s recommendation, may take OTC PPIs for periods of time that exceed the directions on the OTC label. This is considered an off-label (unapproved) use. Healthcare professionals should communicate the risk of hypomagnesemia to patients if they are recommending prolonged use of an OTC PPI.

Case

- A 62 year old woman presents with sx of GERD. She is normotensive and otherwise healthy. Creat = 0.7 mg/dl.
- Rx: omeprazole
- Two months later she presents with fatigue and poor appetite.
  - Creatinine 3.4mg/dl.
  - UA: 1+ protein, few WBCs, no eos

UA: WBC cast
PPIs and Interstitial nephritis

- First described in 1992
- 1990s: primarily omeprazole
- To date: Omeprazole, pantoprazole, lansoprazole, ecomeprazole, rabeprazole
- Early studies: Eosinophilia, eos in biopsies
- Later studies: Renal failure >> hypersensitivity symptoms and signs

Biopsy –proven interstitial nephritis

\[ n = 133, \text{ Mayo Clinic}\]

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug induced</td>
<td>95 (71%)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>47</td>
</tr>
<tr>
<td><strong>PPIs</strong></td>
<td>13</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>10</td>
</tr>
<tr>
<td>Other drugs</td>
<td>11</td>
</tr>
<tr>
<td>Multiple drugs</td>
<td>14</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>27 (20%)</td>
</tr>
<tr>
<td>Malignancy, fungal, etc</td>
<td>Remainder</td>
</tr>
</tbody>
</table>

PPIs: Interstitial nephritis

- 2014 series
- 25 biopsy-proven cases of omeprazole AIN in UK center
- Presented with renal failure, sterile pyuria, mild proteinuria
- No one with extra-renal sx
- Biopsies with macrophages, lymphocytes, PMNs
- 88% did not recover full renal function

Causes of Urinary Eos

(please don’t routinely send this test!)

- Acute interstitial nephritis
- Atheroembolic disease
- Glomerulonephritis
- UTI/prostatitis
- Transplant rejection

Berney-meyer, Nephrology 2014
Different Flavors of AIN

<table>
<thead>
<tr>
<th>Beta lactam</th>
<th>Rifampin/ PPI</th>
<th>NSAID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extravascular symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fever + Rash + Eosinophilia < 10-15%

KI 2001

Case

37 year old man with HIV presents with a creatinine of 1.6mg/dl after starting HAART 5 months ago. His regimen: tenofovir, emcitritabine, efavirenz

The electrolyte complication you would be most likely to see is

- a) Hypophosphatemia
- b) Hypercalcemia
- c) Hyponatremia
- d) Hyperkalemia

Tenofovir: Most prescribed ARV

- Viread
- Truvada
- Atripla
- Complera
- Stribild

Drug-Induced Fanconi Syndrome

- Tenofovir
- Ifosphamide/Cisplatin
- Cidofovir/Adefovir
- Old tetracycline
- Suranam
- Alcohol
Fanconi Syndrome
Generalized proximal tubule dysfunction

- Aminoaciduria
- Glycosuria
- Phosphaturia
- Type II RTA

### Manifestation Clinical Consequences

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Clinical Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphatemia</td>
<td>Rickets, growth retardation</td>
</tr>
<tr>
<td>Type II RTA</td>
<td>Acidosis</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Concentrating defects</td>
</tr>
<tr>
<td>Salt wasting</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Osmotic diuresis</td>
<td>Polyuria/polydipsia</td>
</tr>
<tr>
<td>Aminoaciduria</td>
<td>Often none</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>Probably none</td>
</tr>
</tbody>
</table>

Fanconi Syndrome

Basolateral Blood

Apical Urinary

Proximal Tubule

Fanconi Syndrome

PO₄

HC₄ Glucose

Amino Acids

Proximal Tubule

Basolateral Blood

Apical Urinary

Tenofovir

Organic Anion Transporter

Tenofovir
**Tenofovir: Mitochondrial toxicity**

*Inhibits mitochondrial DNA synthesis*
*Upsets energy source of PCT*

- Atypical and Giant mitochondria in TDF Nephrotoxicity

**Vulnerability to tenofovir nephrotoxicity**
- Low body weight, advanced HIV
- Drug interactions: didanosine; ritonavir
- Pharmacogenetics- e.g. polymorphisms in genes coding for tubule transporters
- NOT traditional risk factors for CKD (diabetes, HTN)

---

**Is tenofovir nephrotoxic?**
- Subclinical tubular defects- YES
- Fanconi Syndrome- YES
- ATN (reversible)- YES
- CKD-???
  - RCT- NO
  - Industry sponsored- NO
  - Observational :
  - Yes- about 1% develop CKD

**Department of Veteran Affairs TDF study**

**Subjects**
- 10,842 HAART naive veterans 1997-2007
- Exclude: advanced CKD
- 4303 exposed to TDF for mean of 1.3 years (max 6.3 years)

**Results**
- 11% increase risk of rapid decline in renal function
- 10% increased risk of creatinine doubling
- 33% increased risk of GFR < 60.
- NO increased risk of GFR < 30
**Tenofovir: Monitoring**

- For the first year, check every 3 months:
  - Creatinine
  - Urinary markers of Fanconi syndrome: glycosuria, fractional excretion of phosphate, proteinuria (tubular proteins if available)
- After the first year, check every 6 months
- Speak to a nephrologist if in doubt about whether to stop the drug
Update in Men's Health

Friday, April 24 ~ 1:30 PM to 2:00 PM
Bradley Anawalt, MD

Handout Not Available at this Time
GOALS AND OBJECTIVES

1. Describe the role of intensive behavioral intervention in obesity management including recent recommendations and expected effects on body weight.

2. Recognize the potential impact on weight of common classes of medications.

3. Understand the indications, expected benefits and potential side effects of currently available medications for medical management of obesity.

PATIENT CASE

Sara

52 yo woman who presents for weight management for obesity.

Has been having slow steady weight gain for the last 20 years, especially after her children.

PMHx:
- T2DM
- HTN
- Depression

Medications:
- Metformin 1000 mg PO BID
- Glipizide 10 mg PO BID
- Lisinopril 10 mg PO daily
- Sertraline 100 mg PO daily
PATIENT CASE

Sara

Exam:
BP 138/74, P 85
Height 5'5", Weight 234 lb, BMI 39
- Normal heart and lung exam
- Acanthosis nigricans and skin tags posterior neck
- Abdomen obese, non-tender, no organomegaly

She is interested in losing weight and wants to talk about treatment options.

OBESITY-RELATED DISORDERS

- Heart disease
- Lung disease
- Diabetes mellitus
- High cholesterol
- Blood clots
- Gout
- Gallstones
- Cancer
- Fatty liver disease
- Infertility
- Sleep apnea
- Venous stasis
- GERD
- Stress urinary incontinence
- Osteoarthritis
- Chronic musculoskeletal pain
- Major depression

Reduced quality of life

RECOMMENDATIONS FOR WEIGHT MANAGEMENT

Weight management through intensive behavioral treatment is recommended for anyone with:

BMI >30 kg/m²

BMI >25 kg/m² with:
- Hypertension
- High cholesterol
- Heart disease
- Diabetes or Pre-diabetes
- Sleep apnea

Usual Services Task Force

Body Mass Index (BMI):

- Weight (kg)/Height (m)²

Endocrine Society Guidelines recommend lifestyle intervention for all overweight and obese patients (BMI >25 kg/m²).


USPSTF recommends all obese patients should be offered/referred for intensive, multicomponent behavioral interventions. (Grade B)

Sara would certainly qualify for weight management and intensive behavioral treatment is indicated.
LIFESTYLE INTERVENTION IS ASSOCIATED WITH WEIGHT LOSS

- Lifestyle
- Metformin
- Placebo

Change in weight (kg)

Year since DPP randomisation


LIFESTYLE INTERVENTION REDUCES INCIDENT TYPE 2 DIABETES

Cumulative incidence (%)

Year since DPP randomisation


THE DPP EXPERIENCE: EVERY KILOGRAM LOST REDUCED RISK OF DIABETES

- It doesn’t take much weight loss to improve health!

Diabetes incidence rate per 100 person-years

Change in weight from baseline (kg)

Adapted from Hamman et al., Diabetes Care (2006) 29: 2102-2107.

GUIDELINES FOR LIFESTYLE INTERVENTION

- Comprehensive lifestyle program that assists in adhering to a lower-calorie diet and increasing physical activity through the use of behavioral strategies.

- High-intensity (ie, ≥14 sessions in 6 mo) in individual or group sessions by a trained interventionist.

Reduce Calories  Increase Activity  Change Behaviors

BACK TO THE CASE

• Sara would benefit from an intensive behavioral intervention program.
• A diet to reduce calorie intake chosen based on her needs and preferences.
• Increased physical activity with an initial goal of 150 min/wk moderate activity.
• Counseling about behavioral change and frequent visits (ie ≥14 sessions in 6 mo).
• Goal 5-10% weight loss over next 6 months
• Consider other possible contributors to weight gain

How do common medications impact weight?

COMMON MEDICATIONS AFFECT WEIGHT

• Many medications commonly used in the management of diabetes, depression, chronic pain and other conditions can contribute to weight gain
• Choosing alternatives with a more favorable weight profile is important to consider

DRUGS THAT IMPACT WEIGHT

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Weight Neutral</th>
<th>Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine (+2.4 kg)</td>
<td>Ziprasidone may be weight neutral</td>
<td></td>
</tr>
<tr>
<td>Quetiapine (+1.1 kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone (+0.8 kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole (+0.6 kg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (+1.8 kg)</td>
</tr>
<tr>
<td>Bupropion (-1.3 kg)</td>
</tr>
<tr>
<td>Fluoxetine (-1.3 kg)</td>
</tr>
</tbody>
</table>

Domecq JP, et al. JCEM, Feb 2015, 100(2): 363-370
DRUGS THAT IMPACT WEIGHT

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Weight Neutral</th>
<th>Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin (+2.2 kg)</td>
<td>Lithium</td>
<td>Zonisamide (-7.2 kg)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Topiramate (-3.8 kg)</td>
<td></td>
</tr>
</tbody>
</table>

Anticonvulsants and mood stabilizers

No evidence of significant weight effect for any of anti-hypertensives reviewed.

Antihypertensive agents

Hormones

Gluocorticoids

Insufficient evidence for testosterone, -0.59 kg/m² at one year; medroxyprogesterone (may be weight neutral)

INSULIN | SGLT-2 inhibitors

**What's new in weight loss drugs for my patients?**
New Medications and How They Work

<table>
<thead>
<tr>
<th>Agent</th>
<th>Action</th>
<th>Approval</th>
<th>Scheduled Drug</th>
</tr>
</thead>
</table>
| Lorcaserin                 | • 5-HT₂ serotonin agonist  
• Little affinity for other serotonergic receptors                                                                                                                                                   | Approved 2012    | YES            |
| Phentermine/Topiramate ER  | • Sympathomimetic  
• Anticonvulsant (GABA receptor modulator carbonic anhydrase inhibitor, glutamate antagonist)                                                                                                | Approved 2012    | YES            |
| Naltrexone SR/             | • Opioid receptor antagonist  
• Dopamine/noradrenaline reuptake inhibitor                                                                                                                                                          | Approved 9/10/2014 | NO             |
| Bupropion SR               | • GLP-1 receptor agonist                                                                                                                                                                                 | Approved 12/13/2014 | NO             |

GABA: gamma-aminobutyric acid; SR: sustained release.

PHARMACOTHERAPY GUIDELINES

Pharmacotherapy can be considered for patients with:

BMI >30 kg/m²

BMI >27 kg/m² with:

• Hypertension
• High cholesterol
• Heart disease
• Diabetes or Pre-diabetes
• Sleep apnea

OBESITY DRUGS

• There is no magic bullet
• Guidelines recommend intensive lifestyle intervention for all patients who qualify for pharmacotherapy
• Important to consider side effects and contraindications
• Monitor for efficacy and discontinue if not demonstrating adequate weight loss
• Weight regain after discontinuation is common

CONTINUING MEDICATION BLOCKS WEIGHT REGAIN

**DRIVER OF WEIGHT GAIN: PHYSIOLOGY OF THE REDUCED OBESE STATE**

The metabolic handicap

In a review of 90 studies, mean daily decrease in REE was 15.4 ± 8.7 kcal/kg body weight lost.

Basal requirements:
- 1850 Kcal/day vs 2000 Kcal/day
- 90 kg (stable) = 2000 Kcal REE
- 100 kg → 90 kg = 1850 Kcal REE
- 90 kg (stable) = 2000 Kcal REE

**LEPTIN DECREASES WITH WEIGHT LOSS**

Leptin administration prevents weight regain

**LEPTIN DECREASES WITH WEIGHT LOSS**

![Graph showing leptin levels before and after weight loss](image)

Leptin decreases BEYOND expected based on weight loss alone

**DISEASE MODEL OF OBESITY**

We have to change our thinking about obesity...

This is chronic disease management!

**FDA APPROVED WEIGHT LOSS MEDICATIONS**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand Name</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Xenical (OTC Alli)</td>
<td>Lipase inhibitor</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Belviq</td>
<td>Serotonergic 5-HT2c receptor agonist</td>
</tr>
<tr>
<td>Naltrexone/bupropion</td>
<td>Contrave</td>
<td>Opioid antagonist / NE and dopamine reuptake inhibitor</td>
</tr>
<tr>
<td>Phentermine and diethylpropion (short term use only)</td>
<td></td>
<td>Sympathomimetic amine</td>
</tr>
<tr>
<td>Phentermine/topiramate ER</td>
<td>Qsymia</td>
<td>Sympathomimetic amine/anti-convulsant (acts on GABA and glutamate)</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Saxenda</td>
<td>GLP-1 agonist</td>
</tr>
</tbody>
</table>
**MONITOR BLOOD SUGARS**

- Counsel patients with DM to monitor BG closely while attempting weight loss
- Review hypoglycemia symptoms and management

**ORLISTAT**

- Gastrointestinal lipase inhibitor
- Reduces absorption of dietary fat

**ORLISTAT**

- Patients with T2DM on metformin or metformin+sulfonylurea.
- Calorie restricted diet
- Orlistat 120 mg PO TID. Followed for one year.

**ORLISTAT**

- Recommended dosing
  - 120 mg PO TID with each meal containing fat
  - OTC Alli 60 mg PO TID with each meal containing fat

**ORLISTAT**

- Side effects:
  - Flatus with discharge and oily spotting or fecal urgency
  - Reduced absorption of fat soluble vitamins
  - MV with fat soluble vitamins ≥2 h before or after orlistat
  - May interfere with absorption of some other drugs
  - Rare serious hepatotoxicity
  - Increased urinary oxalate

- Pregnancy category: X
**LORCASERIN (BELVIQ)**

- Serotonin 5-HT<sub>2C</sub> receptor agonist
- Thought to work in the hypothalamus to increase satiety and decrease food consumption

**LORCASERIN**

<table>
<thead>
<tr>
<th>Drug N</th>
<th>Mean (SD) Wt. loss (kg)</th>
<th>Plac. N</th>
<th>Mean (SD) Wt. loss (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidler 1564</td>
<td>5.8 (6.6)</td>
<td>1541</td>
<td>2.9 (6.4)</td>
</tr>
<tr>
<td>O'Neill 251</td>
<td>4.7 (6.3)</td>
<td>248</td>
<td>1.6 (6.3)</td>
</tr>
<tr>
<td>Smith 1538</td>
<td>5.8 (7.6)</td>
<td>1499</td>
<td>2.2 (3.9)</td>
</tr>
<tr>
<td>Total 3350</td>
<td></td>
<td>3288</td>
<td></td>
</tr>
</tbody>
</table>

Fidler, JCEM, 2012
O'Neill, Obesity, 2011
Smith NEJM, 2012

**Recommended dosing:**
- 10 mg PO BID
- Evaluate response at 12 weeks, if patient has not lost ≥ 5% baseline body weight discontinue treatment

**Side effects:**
- Headaches, fatigue, somnolence
- Serotonin syndrome (especially when used w/ other serotoninergic or dopaminergic agents)
- Do not use w/ other 5-HT<sub>2C</sub> receptor agonists (cabergoline), caution in heart failure

**Contraindications:** Pregnancy and breast feeding
**Pregnancy category:** X

**PHENTERMINE/TOPIRAMATE ER (QSYMIA)**

- Phentermine
  - sympathomimetic amine
  - Similar to amphetamines
  - Mechanism thought to be secondary to CNS effects including stimulation of hypothalamus to release NE
- Topiramate
  - anticonvulsant
  - Enhances GABA activity in brain, also acts on glutamate receptors
PHENTERMINE/TOPIRAMATE ER

- 130 subjects w/ T2DM from OR-20/DN-230 study (mean A1c 8.7%) plus 388 subjects with T2DM from CONQUER study (mean A1c 6.8%).
- Randomized to placebo vs Phen/Top (high dose).

Dosing

- Initial: Phentermine 3.75 mg/topiramate 23 mg once daily for 14 days. Increase to 7.5 mg/46 mg once daily for 12 weeks then evaluate weight loss.
- If 3% of baseline body weight has not been lost, discontinue use or increase dose to 11.25 mg/69 mg once daily for 14 days, and then to 15 mg/92 mg once daily.
- Evaluate weight loss after 12 weeks on 15 mg/92 mg; if 5% of baseline body weight has not been lost, gradually discontinue therapy.
- Discontinue gradually: 1 dose every other day for at least 1 week.

Side effects: increased heart rate, dry mouth, paresthesias, constipation, headache, insomnia, low potassium or bicarbonate, kidney stones

Avoid in patients with known heart disease or uncontrolled hypertension

REMS program (limited pharmacies)

Contraindications: pregnancy and breast feeding, hyperthyroidism; glaucoma; use during or within 14 days following MAO inhibitor therapy

Pregnancy category: X, monitor for pregnancy

NOTE topiramate is a teratogen
• Thought to affect food intake through hypothalamic and mesolimbic (reward) pathways

• Bupropion: inhibitor of dopamine and NE reuptake

• Naltrexone: pure opioid antagonist

**Dosing**

- Initial: One tab (naltrexone 8 mg/bupropion 90 mg) daily in the AM x1 week; then 1 tab BID x1 week; then 2 tabs AM and 1 tab PM x1 week; then 2 tablets BID.

- If the patient has not lost at least 5% of baseline body weight after 12 weeks at the maintenance dosage, discontinue.

**505 overweight or obese subjects with T2DM with or without diabetes drugs.**

- Baseline mean age 54, BMI 37 kg/m2, A1c 8.0%

- Randomized to NP/Bup or placebo

- All had standard lifestyle advice

- Side effects: headache, nausea, constipation, sleep problems

- Contraindications: chronic opioid/opiate agonist (eg, methadone) use; uncontrolled HTN; history of seizures; bulimia or anorexia nervosa; abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs; concomitant use of MAO inhibitors (or within 14 days)

- Pregnancy category: X
• Glucagon-like peptide-1 (GLP-1) agonist
  • increases glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, increases β-cell growth/replication, slows gastric emptying, and decreases food intake.

• Dosing (for obesity):
  • Initial: 0.6 mg q day x 1 week, increase by 0.6 mg daily at weekly intervals to a target dose of 3 mg once daily (low doses not demonstrated effective for weight loss).
  • Evaluate change in body weight 16 weeks after initiation of therapy; discontinue if have not lost at least 4% of baseline body weight.

LIRAGLUTIDE (SAXENDA)

LIRAGLUTIDE LEADS TO WEIGHT LOSS IN PATIENTS WITHOUT DIABETES

Astrup et al. Lancet 2009; 374: 1606–16

LIRAGLUTIDE (AT LOWER DOSES THAN SAXENDA) LOWERS A1C IN PATIENTS WITH T2DM


LIRAGLUTIDE

• Side effects:
  • Nausea, diarrhea, vomiting, headaches
  • Pancreatitis, increased heart rate
  • Black box: thyroid C-cell tumors

• Contraindications: medullary thyroid carcinoma or MEN syndrome
  • Not recommended for use w/ insulin

• Pregnancy category: X (Saxenda dose, category C for Victoza)
Agents Approved for Long-Term Use: Placebo-subtracted Weight Loss

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent weight loss at one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat1</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Lorcaserin1</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Lostiglitzide2</td>
<td>32/56 weeks</td>
</tr>
<tr>
<td>Naltrexone/bupropion1</td>
<td>56 weeks</td>
</tr>
<tr>
<td>PHEN/TPM2</td>
<td>56 weeks</td>
</tr>
</tbody>
</table>

1. Orlistat is a gastrointestinal enzyme inhibitor that reduces fat absorption. 2. Lorcaserin is a serotonin receptor agonist. 3. Naltrexone/bupropion is an opioid antagonist/nicotine replacement therapy. 4. Lostiglitzide is a GLP-1 receptor agonist. 5. PHEN/TPM is a SSRI and serotonin-norepinephrine reuptake inhibitor.

BACK TO THE CASE

- Screen for treatable causes (OSA, depression, binge eating)
- Offer comprehensive lifestyle intervention
- Consider changing glipizide to an alternative medication
- Consider adding or changing to bupropion
- Consider an adjunct weight loss medication after discussion of side effects. Discontinue if not effective.
- Follow-up, trouble shoot.

TAKE HOME POINTS

- Intensive lifestyle intervention is an important and effective part of weight management.
- Many medications we commonly use are linked to weight gain. Considering alternatives can be helpful for patients trying to lose weight.
- Many new drugs for weight management are available but side effects and long-term treatment plan must be considered.

Obesity is a chronic disease that we can treat, but not cure.
THE PROBLEM

Body weight is regulated

- The body resists weight loss and weight gain
- The faster and larger the weight loss...the more strongly the body resists
  - Appetite increases
  - Metabolism slows

We need energy and fat stores to survive

CURRENT RECOMMENDATIONS

Even modest weight loss improves your health:
- 7 percent weight loss results in 50 percent reduced risk of diabetes

A COMMITMENT TO YOUR HEALTH

Now

One year
SERVICES

- Intensive Behavioral Treatment
  - About 5-10% of body weight
- Medical Management
  - About 5-8% of body weight
- Weight-Loss Surgery
  - About 15-30% of body weight

UW Medicine
Pharmacology for Urinary Incontinence in Women

Current Concepts in Drug Therapy
University of Washington
Leah Gordon, MD MPH
4/24/15

Presentation Goals

Medications
- Review anti-muscarinic medications
  - Focus on newer meds
- Introduce beta-adrenergic medications

A 60 year-old woman with urge incontinence has pursued behavioral modification and pelvic floor training but continues to be bothered by frequent episodes of incontinence and is interested in pharmacologic treatment. She has no other medical problems. She has heard these medications can be expensive and is worried about the potential cost.

Question 1

Which medication would be most appropriate to start for her?

a. Oxybutynin (Ditropan XL) 30mg po daily
b. Fesoterodine (Toviaz) 4mg po daily
c. Tolterodine (Detrol LA) 2mg po daily
d. Mirabegron (Myrbetriq) 25mg po daily
Answer 1

Which medication would be appropriate to start for her?

a. Oxybutynin (Ditropan XL) 30mg po daily
b. Fesoterodine (Toviaz) 4mg po daily
c. Tolterodine (Detrol LA) 2mg po daily
d. Mirabegron (Myrbetriq) 25mg po daily

Anti-muscarinics

Primary Outcomes in Most Studies:
- Complete Continence = NO incontinent episodes
- Clinically Important Improvement = reduction in frequency of incontinent episodes by at least 50%
- Quality of Life

All Anti-Muscarinics:
- Many large, well-done RCTs
- BEST effects reduced incontinence or have clinically important improvement in 20% of women
- NO big differences in efficacy across meds
An Approach
Start low
Start Cheap
Side Effects?
Specific Cases

Anti-muscarinics

Answer 1
Which medication would be appropriate to start for her?

- Oxybutynin (Ditropan XL) 30mg po daily
- Fesoterodine (Toviaz) 4mg po daily
- Tolterodine (Detrol LA) 2mg po daily
- Mirabegron (Myrbetriq) 25mg po daily

Question 1
A 55 year-old woman with urge incontinence as well as atrial fibrillation, depression, and diabetes on Metformin, Fluoxetine, and Metoprolol is interested in starting a medication for her incontinence.

Question 2
Which medication would be most appropriate to start for her?

- Darifenacin (Enablex) 7.5mg po daily
- Trospium (Sanctura) 20 mg po daily
- Tolterodine (Detrol LA) 2mg po daily
- Solifenacin (Vesicare) 25mg po daily
Which medication would be most appropriate to start for her?

a. Darifenacin (Enablex) 7.5mg po daily
b. *Trospium (Sanctura) 20 mg po daily*

b. Darifenacin (Enablex) 7.5mg po daily

**Answer 2**

 Which medication would be most appropriate to start for her?

a. Darifenacin (Enablex) 7.5mg po daily
b. *Trospium (Sanctura) 20 mg po daily*
c. Tolterodine (Detrol LA) 2mg po daily
d. Solifenacin (Vesicare) 25mg po daily
A 65 year-old woman with mixed stress/urge incontinence and no other co-morbidities was previously on Trospium without improvement. She is now interested in trying a different medication.

Which medication would be most appropriate to switch to for her?

a. Oxybutynin (Ditropan) 5mg po daily
b. Trospium (Sanctura) 60mg po daily
c. Darifenacin (Enablex) 7.5mg po daily
d. Solifenacin (Vesicare) 25mg po daily

Which medication would be most appropriate to start for her?

a. Oxybutynin (Ditropan) 5mg po daily
b. Trospium (Sanctura) 60mg po daily
c. Darifenacin (Enablex) 7.5mg po daily
d. Solifenacin (Vesicare) 25mg po daily

Answer 3

Which medication would be most appropriate to start for her?

a. Oxybutynin (Ditropan) 5mg po daily
b. Trospium (Sanctura) 60mg po daily
c. Darifenacin (Enablex) 7.5mg po daily
d. Solifenacin (Vesicare) 25mg po daily

Anti-muscarinics

First-Line Therapy

Start low
Start Cheap
Side Effects?
Prior treatment?
Solifenacin
A 60 year-old woman with early Alzheimer’s disease on Donepezil is very bothered by urge incontinence and wants to start a medication.

Which medication would be most appropriate to start for her?

a. Mirabegron (Myrbetriq) 25mg po daily
b. Solabegron mg po daily
c. Oxybutynin (Ditropan) 5mg po daily
d. Trospium (Sanctura) 60mg po daily

Answer 4

Which medication would be most appropriate to start for her?

a. Mirabegron (Myrbetriq) 25mg po daily
b. Solabegron mg po daily
c. Oxybutynin (Ditropan) 5mg po daily
d. Trospium (Sanctura) 60mg po daily
Anti-muscarinics

First-Line Therapy

Start low

Caution:
- Cognitive Impairment
- Cholinesterase Inhibitors
- Combination with other strong anti-cholinergics
- Severe Hepatic Failure
- Dialysis

Beta-adrenergics

Beta-3-agonists

Mirabegron

Solabegron

Beta-3-agonists

Mirabegron

Solabegron

Not yet approved in US

Data
- Similar to anti-muscarinics
- About 20% response

Side Effects
- Increase in BP
- Headache
- Dizziness
- Tachycardia
- GI upset

NO: dry mouth, blurry vision

Beta-adrenergics

Beta-3-agonists

Mirabegron

Mechanism of Action
- Beta-3 agonism
- Relaxes detrusor muscle

Side Effects
- Increase in BP
- Headache
- Dizziness
- Tachycardia
- GI upset

NO: dry mouth, blurry vision
Which medication would be most appropriate to start for her?

a. Mirabegron (Myrbetriq) 25mg po daily
b. Solabegron mg po daily
c. Oxybutynin (Ditropan) 5mg po daily
d. Trospium (Sanctura) 60mg po daily

References

- Goode PS. Incontinence in Older Women. JAMA 2010;303:2172.
33 yr woman wants to start the pill
She has migraines (no aura) and is 3 wks postpartum, not breastfeeding.

What resources can you use to decide on a pill?
RESOURCE NEWSFLASH

- SAFETY: Medical Eligibility Criteria (MEC) updated 4th edition in 2010
- BARRIERS/NUANCES: Selected Practice Recommendations (SPR) provides evidence based solutions, released in 2013

SPR- Recommendations about:
- Initiation (tests to do before)
- Duration
- Managing unique problems

www.CDC.gov
(or just google “selected practice recommendations”)

MEC: Safety Scale 1-4

Back to the case: Which Pill to Start?
Tyra’s Steps:
1) “Must ask” safety questions (use MEC)
2) The basics
3) Tailor to special conditions (use SPR)
1) The “must asks” (3-4s on MEC).

- Smoking >35y old
- Pregnant / Postpartum
- Migraine: w aura or >35y
- Fam/PMH of VTE/clot dz
- Drug interactions (esp Abx/antivirals, AEDs)

2) The Basics:

- Choose a monophasic pill
- Favor levonorgesterol → slightly lower VTE risk
- Use 20-30mcg of estrogen
- EE 30mcg + 0.15mg LNG:
  - Nordette: (Levora, Portia $30)
  - Seasonale (~$300)
- EE 20mcg + 0.1mg LNG (more spotting):
  - Alesse ($35)

3) Tailor to side effects: USE SPR

- Postpartum? Progestogen only because of VTE risk for first 4-6 wks.

Initiation of POPs: Considerations: Postpartum; Not Breastfeeding
- Timing: start at any time if reasonably sure not pregnant.
- Need for back-up contraception for 2 days if:
  - ≥21d postpartum and cycles have not returned.
  - Cycles returned and >5d since bleeding started.

Outline

- Oral Contraceptive Pills
- LARC Methods
- Emergency Contraception
32 yr woman asks for IUD insertion today.
- Should you set her up for same-day insertion?
- Do you need any tests first?
- How long does she need to use a backup method?

IUD initiation - Use your Tools: SPR

<table>
<thead>
<tr>
<th>Method</th>
<th>When to start</th>
<th>Procedure to responsibly prevent pregnancy</th>
<th>Additional contraception needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper IUD</td>
<td>Any time</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>LNG IUD</td>
<td>Any time</td>
<td>P: &lt;10 days; 10 days if LMP: 7 days, use backup method for 7 days</td>
<td>n/a</td>
</tr>
<tr>
<td>Intrauterine Device</td>
<td>Any time</td>
<td>P: &lt;10 days; 10 days if LMP: 7 days, use backup method for 7 days</td>
<td>n/a</td>
</tr>
<tr>
<td>Injectable</td>
<td>Any time</td>
<td>P: &lt;10 days; 10 days if LMP: 7 days, use backup method for 7 days</td>
<td>n/a</td>
</tr>
<tr>
<td>Combined hormonal</td>
<td>Any time</td>
<td>P: &lt;10 days; 10 days if LMP: 7 days, use backup method for 7 days</td>
<td>n/a</td>
</tr>
<tr>
<td>Progestin-only pill</td>
<td>Any time</td>
<td>P: &lt;10 days; 10 days if LMP: 7 days, use backup method for 7 days</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Use your Tools: SPR
- Should you refer for same-day insertion? Yes!
- Do you need any tests first? Only a bimanual as long as she’s not pregnant
- How long is a backup method required? >7d since period: 7 days; <7d: none needed.
IUD Newsflash (4)

**Mirena**
- Good for 7 yrs
- FDA approved for menorrhagia (reduces by 90%)

**Skyla**
- Good for 3 yrs
- Smaller, ? better for nullips
- Lower levonorgestrel level: maybe more spotting?
- Much cheaper (~80% of Mirena cost!)

**Copper**
- Good for 10 yrs
- No delay in fertility return
- 50% d/c in 5 yrs because of dysmenorrhea and pain

Outline

Oral Contraceptive Pills

LARC Methods

Emergency Contraception

Main EC Timeline of Effectiveness:

- **Copper IUD**: 7-10 Days
- **Ulipristal**: 5 Days
- **Levo**: 3-5 Days

EC Newsflash:

- **Copper IUD still most effective and reduces future abortions**
- **Ulipristal Approved**
  Progesterone receptor modulator - also Approved for uterine fibroid/menorrhagia treatment!
- **Hormonal EC may not work as well in obese**
-1.4% Preg incidence - Effect holds up at 5 days - Rx required ($50) - Need to wait until after menses to re-start OCPs

-2.2% Preg incidence - Effect wanes after first day - OTC ($40-50) - Can restart OCPs in 7d

EC Take Home Points

- Offer a copper IUD as first-line therapy
- Use ulipristal over levonorgestrel
- Counsel overweight pts of the potentially reduced efficacy of hormonal methods.

Questions?

References

2) CDC Medical Eligibility Criteria (MEC)
3) NICE Clinical Guideline 30 “Long-acting reversible contraception (update)” issued: September 2014. guidance.nice.org.uk/cg30
NOT TONIGHT HONEY, I HAVE A HEADACHE....

FEMALE SEXUAL DISORDERS

Kim O'Connor, MD, FACP
Associate Professor
University of Washington
General Internal Medicine

Outline
- Sexual Response Cycle
- Categories of Female Sexual Dysfunction
- Biopsychosocial influences
- History
- Evaluation
- Treatment

Clinic Visit: Mrs. Jones

HPI
- 34 year old female
- 6 months post partum, vaginal delivery
- Breast feeding
- Feels exhausted all the time, slow to lose baby weight
- Husband upset because they aren’t having sex very often

PMHx
- Hx of depression
- Seasonal allergies and insomnia

Medications
- Norethindrone 0.35 mg po qd (Micronor) “Minipill”
- Citalopram (Celexa) 20 mg po qd for depression
- Diphenhydramine (Benadryl) 25 mg po qhs for allergies/insomnia

Traditional Model of Female Sexual Response Cycle
Screening For FSD

- Physicians do not regularly screen for FSD
  - Only 10-20% of women spontaneously volunteer info about FSD to their doctor

- Screening questions
  - “Sexuality is such an important part of our overall health. I’d like to ask you some questions about that now. Is that okay with you?”
  - Are you currently sexually active?
    - With men, women or both?
  - “Do you have any concerns about your sexual health?”

Female Sexual Dysfunction

- Symptoms MUST:
  - Be recurrent or persistent lasting > 6 months
  - Occur 75-100% of the time.
  - Cause significant personal distress

- Sexual complaints occur in 40% of women
  - Only about 12% are associated with distress

- Primary (lifelong) vs. Secondary (acquired)

- Situational vs. generalized
Classifications of FSD*

- **Desire**
  - Hypoactive sexual desire disorder - MOST COMMON
  - Sexual aversion disorder

- **Arousal**
  - Decreased arousal

- **Orgasm**
  - Difficulty achieving orgasm, anorgasmia

- **Pain**
  - Dyspareunia, vaginismus,

*Based on traditional linear model of female sexual response cycle, DSM-IV-TR

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DSM-5 Revisions to FSD criteria

- **Sexual interest/arousal disorder**
  - Merged desire and arousal disorders
  - Deleted sexual aversion disorder

- **Female orgasmic disorder**

- **Genito-pelvic pain/penetration disorder**
  - Merged dyspareunia and vaginismus

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Desire Disorders

<table>
<thead>
<tr>
<th>Hypoactive Sexual Desire Disorder</th>
<th>Sexual Aversion Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>History</td>
</tr>
<tr>
<td>-Infrequent sex</td>
<td>-Infrequent sex</td>
</tr>
<tr>
<td>-Absent/diminished interest</td>
<td>-Absent/diminished interest</td>
</tr>
<tr>
<td>-Usually doesn’t initiate sex</td>
<td>-Usually doesn’t initiate sex</td>
</tr>
<tr>
<td>-Not receptive to sexual activity</td>
<td>-Not receptive to sexual activity</td>
</tr>
<tr>
<td>-NO anxiety/aversion to sex</td>
<td>-SEVERE anxiety/aversion to sex</td>
</tr>
</tbody>
</table>

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Clinic Visit: Mrs. Jones

- Are you having problems with desire or interest in sex? Yes, tired all the time. I feel fat and unattractive.
- Does this bother you? Yes, I really enjoyed being sexually active in the past. It bothers me that I am not as interested in it now.
- In the past was your level of sexual desire or interest satisfying to you? Yes, it was fantastic.
- Is sexual activity pleasurable for you? Absolutely.
- Does it cause you severe distress or anxiety? No.
- What factors do you think may be contributing to your decreased interest or desire? The new baby, feeling depressed, breast feeding, no help from my husband...
You are concerned that she may have Hypoactive Sexual Desire Disorder (HSDD)

All of the following are likely contributing to HSDD EXCEPT?

A. Depression  
B. SSRI (Citalopram)  
C. Norethindrone (Micronor) "mini-pill"  
D. Stress  
E. Breast feeding

Desire Disorders

<table>
<thead>
<tr>
<th>Hypoactive Sexual Desire Disorder</th>
<th>Sexual Aversion Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential Causes</td>
<td>Potential Causes</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>Same</td>
</tr>
<tr>
<td>• Relationship issues/culture/religion</td>
<td>Same</td>
</tr>
<tr>
<td>• Sexual trauma</td>
<td>Same</td>
</tr>
<tr>
<td>Mental Health</td>
<td>Same</td>
</tr>
<tr>
<td>• Depression or anti-depressants (SSRIs)</td>
<td>Same</td>
</tr>
<tr>
<td>• Sleep deprivation/stress</td>
<td>Same</td>
</tr>
<tr>
<td>• Anti-psychotic medications</td>
<td>Same</td>
</tr>
<tr>
<td>Pregnancy or breast feeding</td>
<td>Same</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Same</td>
</tr>
<tr>
<td>• Weight gain, fatigue, constipation</td>
<td>Same</td>
</tr>
<tr>
<td>• Check TSH</td>
<td>Same</td>
</tr>
<tr>
<td>Post-menopausal/oophorectomy</td>
<td>Same</td>
</tr>
</tbody>
</table>
| * Combined Oral Contraceptives-conflicting data: Most often libido neutral. Can increase or decrease libido  
  * Progesterone only: neutral or increase |

Laboratory evaluation

- In general, laboratory evaluation is not helpful.
- Consider CBC, TSH, prolactin levels, STD screen, transvaginal US only if clinically indicated.
- Recommend AGAINST checking testosterone levels.

Common Meds Causing FSD

- Psychiatric
  - 17-26% of women with FSD are depressed
  - Anti-depressants, anti-psychotics, anxiolytics
    - SSRI cause sexual side effects in 30-70% pts
    - Other culprits: venlafaxine, duloxetine, TCA, MAOI
    - Can affect desire, arousal, orgasm
- Hormonal
  - COC data conflicting
    - Most often libido neutral but may increase or decrease
    - Variations in COC progesterone formulations do NOT appear to influence sexual effects
  - Progesterone only forms: neutral or improvement

* Items in red are present in our patient C.
Treatment for Desire Disorders

<table>
<thead>
<tr>
<th>Hypoactive Sexual Desire Disorder</th>
<th>Sexual Aversion Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Education</td>
<td>-Same</td>
</tr>
<tr>
<td>• Average frequency of sex</td>
<td></td>
</tr>
<tr>
<td>• Stress reduction</td>
<td></td>
</tr>
<tr>
<td>-Treat underlying medical disorders</td>
<td>-Same</td>
</tr>
<tr>
<td>• Thyroid replacement therapy</td>
<td></td>
</tr>
<tr>
<td>• Treat depression</td>
<td></td>
</tr>
<tr>
<td>Counseling</td>
<td>-Same</td>
</tr>
<tr>
<td>• Therapy (individual, couples, sex)</td>
<td></td>
</tr>
<tr>
<td>• Psychiatric evaluation/treatment</td>
<td></td>
</tr>
</tbody>
</table>

Clinic Visit: Mrs. Jones

She continues to feel she needs an anti-depressant but wonders if there are any treatment options for depression that may improve her sexual function.

Do you think adding bupropion to her citalopram may help with symptoms of HSDD?

A. Yes

B. No

Anti-depressants and FSD

If treatment of depression needed
- Try non-SSRI
  - Bupropion, mirtazipine, nefazodone
- Augment SSRI with bupropion
  - 5 high quality RCT. 579 participants
  - Improvement in sexual rating scores with bupropion 150 mg BID but not sustained release 150 mg Qd
- Drug holiday?
  - Stop taking the SSRI on the days of planned sexual activity.

Anti-depressants and FSD

What if your patient isn’t depressed?
- RCT 75 premenopausal women with HSDD
  - Patients were not depressed at baseline
  - Bupropion SR 300 mg/d x 16 weeks vs. placebo
  - Increased pleasure, arousal, orgasm vs. placebo
- RCT 232 premenopausal women with HSDD
  - Patients not depressed at baseline
  - Bupropion SR 150 mg/d x 12 weeks vs. placebo
  - Greater improvement in sexual fxn scores vs. placebo

Cochrane Review 2013. Taylor

PMID: 15118489, 20151970
Clinic Visit: Mrs. Jones
She is worried that the bupropion might make it difficult to sleep. A friend suggested she try androgen therapy.

Which of the following are FDA approved for treatment of Female Sexual Dysfunction?

A. Compounded testosterone 1% cream, 0.5 grams daily  
B. AndroDerm patch, cut down to 1/8 size  
C. AndroGel 1% gel, less than ½ pump per day  
D. Intrinsa 300 mcg testosterone patch 2 x per week  
E. None

Androgen Therapy

Do low androgen levels cause FSD?
- No correlation b/t endogenous androgen levels & FSD

Efficacy
- Some data supporting improvement in sexual function in post menopausal (natural/surgical) women +/- HRT
  - Vehicles: oral, transdermal, topical gel  
  - PMID: 22392827

Safety/Risks
- Hirsuitism, acne, deep voice, enlarged clitoris
- Decreased HDL
  - Effects of testosterone on CV events remains inconclusive.
- Possible increased risk breast cancer, uterine bleeding

Review of 20 RCTs. Longest studies 24 weeks
- Mostly postmenopausal (natural or surgical)
- Most pts on estrogen +/- progesterone
- Largest trials were with 300 mcg/d patch vs. placebo
- Statistically significant improvement in sexual fn
- Unclear if clinically significant.
  - Baseline events 3/mo. Increased by 2 vs. 1 event/mo

No FDA approved androgen Tx for FSD
- "Intrinsa" (300 mcg patch) NOT approved by FDA
- Ongoing trial of "LibiGel" testosterone gel  
  - PMID: 24714838

Data limited
- Uncertain regarding long term efficacy or safety
- Unclear if can be used w/o concomitant estrogen tx
- Dose in studies is approx 1/10th of male dosing
- The following doses are NOT FDA approved and NOT recommend but patients may already be on them.

Compounded
- 1% testosterone ointment/cream = 0.5 grams daily

Gel
- 1% gel. AndroGel. Male dose 50 mg = 4 pumps
- 1% gel. Female dose 5mg = < ½ of one pump
Androgen Therapy

- Transdermal
  - Androderm = 2mg/24h
  - 300 mcg/24 female dose = 1/8th of Androderm patch
  - Unclear if safe to cut. Not recommended.

- DHEA
  - 25-50 mg orally per day
  - 1% topical intravaginally if mod-severe vaginal atrophy

Clinic Visit: Mrs. Jones

Additional history from Mrs. Jones...

- She reports that even if she wants to have sex her body just doesn’t seem to respond.
- She also complains of poor lubrication.

Medications

- Norethindrone. 0.35 mg po qd (Micronor) “Minipill”
- Citalopram (Celexa) 20 mg po qd
- Diphenhydramine (Benadryl) 25 mg po qhs

Arousal Disorder

- Persistent or recurrent inability to attain or maintain sufficient sexual arousal
  - MUST occur in the setting of ADEQUATE stimulation

Arousal Disorders

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Psychosocial</td>
</tr>
<tr>
<td>- Stress, relationship issues, culture, religion</td>
</tr>
<tr>
<td>- Medication side effects</td>
</tr>
<tr>
<td>- Tricyclic anti-depressants, SSRI</td>
</tr>
<tr>
<td>- Anti-histamines</td>
</tr>
<tr>
<td>- Anti-cholinergics</td>
</tr>
<tr>
<td>- Anti-hypertensives (α-blockers, β-blockers, Ca-channel blockers, diuretics)</td>
</tr>
<tr>
<td>- Mental Health</td>
</tr>
<tr>
<td>- Depression</td>
</tr>
<tr>
<td>- Pelvic neurogenic or vascular impairments</td>
</tr>
<tr>
<td>- Local nerve damage (pelvic surgeries, spinal cord injury)</td>
</tr>
<tr>
<td>- Peripheral nerve disease (diabetes, Multiple Sclerosis)</td>
</tr>
<tr>
<td>- Vascular impairment (diabetes, HTN, hyperlipidemia, smoking)</td>
</tr>
</tbody>
</table>

* Items in red are present in our patient
Treatment for Arousal Disorders

<table>
<thead>
<tr>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>-Education</strong></td>
</tr>
<tr>
<td>• Physiology</td>
</tr>
<tr>
<td>• Lubrication</td>
</tr>
<tr>
<td><strong>-Counseling</strong></td>
</tr>
<tr>
<td>• Individual, couples, sex therapy</td>
</tr>
<tr>
<td><strong>-Stimulation</strong></td>
</tr>
<tr>
<td>• Eros Clitoral Therapy Device</td>
</tr>
<tr>
<td>• Vibrators</td>
</tr>
</tbody>
</table>

Eros Clitoral Device

- Prescription only
- Improves blood flow to clitoris and genitalia
- Kit includes: Eros device, 2 CAREss cups, one extension tubing, two AAA batteries, satin pouch for storage: $179
- Replacement CAREss cups. Good for 10 uses each: $58 for 21 cups
- Might just consider a vibrator. Cheaper!

Clinic Visit: Mrs. Jones

So she decided she didn’t want to try any kind of testosterone therapy. Her husband has used Viagra on occasion and she wonders if that might help her too? Meds: citalopram, diphenhydramine, norethindrone

Do you think sildenafil (Viagra) might be useful in treating her sexual dysfunction?

A. Yes  
B. No

Treatment of arousal disorder

- **Sildenafil (Viagra)**
  - Not effective for FSD alone
    - RCT 800 women pre/post menopausal, +/- ERT
    - Sildenafil 10-100 mg/d PRN x 12 week
    - No more effective than placebo
  - May be effective as augmentation to SSRI
    - 49 women on SSRI and FSD
    - 50-100mg before sexual activity. Study lasted 8 wks
    - Improved global sexual fxn and orgasmic response
    - Unclear if clinically significant.
      - Difference of 0.8 in favor of sildenafil on scale 1-7

PMID 12150499
PMID 18647982
Clinic Visit: Mrs. Jones

Additional history from Mrs. Jones...

- She hasn’t yet tried the Viagra but she did cut back on her diphenhydramine use and her vaginal lubrication issue has improved.
- She is frustrated because she is having difficulty reaching orgasm.
- This was rarely a problem for her in the past.
- She wonders if the vaginal delivery damaged any of the nerves “down there”

Which of the following conditions is UNLIKELY to contribute to an orgasm disorder?

A. Type 2 Diabetes Mellitus
B. Vaginal delivery
C. Hypertension
D. Spinal cord injury
E. Multiple Sclerosis

Orgasm Disorders

- Lack of orgasm, marked diminished intensity or delay of orgasm DESPITE self-reports of high sexual arousal or excitement.

- Primary vs. Secondary Disorder
  • Has the patient ever achieved orgasm with their partner or via self-stimulation?

Orgasm Disorders

Causes

- Psychosocial factors
  • Stress, relationship issues, culture, religion
  • Inadequate stimulation

- Medications
  • SSRI anti-depressants
    - occurs in 50% of patients on SSRIs
    - delayed rather than absent orgasm is often biggest issue

- Pelvic neurogenic or vascular impairments
  • Local nerve damage (pelvic surgeries, spinal cord injury)
  • Peripheral nerve disease (diabetes, Multiple Sclerosis)
  • Vascular impairment (diabetes, HTN, hyperlipidemia, smoking)

* Items in red are present in our patient
Treatment for Orgasm Disorders

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normalize the experience</td>
</tr>
<tr>
<td>• Orgasm not necessary for sexual fulfillment</td>
</tr>
<tr>
<td>• Education</td>
</tr>
<tr>
<td>• Teach women about their anatomy</td>
</tr>
<tr>
<td>• Recommend position changes</td>
</tr>
<tr>
<td>• Recommend self-stimulation</td>
</tr>
<tr>
<td>• May need prolonged stimulation to reach orgasm</td>
</tr>
<tr>
<td>• Counseling</td>
</tr>
<tr>
<td>• Therapy (individual, couples, sex)</td>
</tr>
<tr>
<td>• Medications</td>
</tr>
<tr>
<td>• Discontinue SSRI's</td>
</tr>
<tr>
<td>• Switch to alternate anti-depressant</td>
</tr>
<tr>
<td>- bupropion, mirtazapine, nefazadone</td>
</tr>
</tbody>
</table>

Basic approach to counseling

PLISSIT Model

P: Permission
• Normalize certain sexual practices

Li: Limited Information
• Educate about normal aspects of arousal
• Importance of foreplay
• Medication side effects or medical illnesses

SS: Specific Suggestions
• Use of topical estrogen, lubricants, environmental changes

IT: Intensive Therapy
• Refer to sex therapy

Clinic Visit: Mrs. Jones

Additional history from Mrs. Jones...
• Describes having pain with intercourse, especially with insertion
• Denies itching or discharge. No sex until post partum.

Based on her history and physical exam findings, what is the most likely cause of her pain with intercourse?

A. Herpes Simplex Virus
B. Atrophic vaginitis
C. Candidiasis
D. Lichen sclerosis
D. Lichen simplex chronicus
Pain Disorder

- Genitopelvic pain/penetration disorder
  - Recurrent or persistent pain with intercourse or sexual activity after ruling out other causes
  - Superficial
    - Initial penetration
  - Vaginal
    - Introitus to cervix
  - Deep
    - Cervix to pelvic/abdominal cavity

* Items in red are present in our patient

Causes of Pain Disorders

<table>
<thead>
<tr>
<th>Causes of Vaginal/Pelvic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Psychologic</td>
</tr>
<tr>
<td>- Inflammation/Irritation</td>
</tr>
<tr>
<td>- Atrophic vaginitis</td>
</tr>
<tr>
<td>- Breast feeding, &quot;mini-pill&quot;</td>
</tr>
<tr>
<td>- Low weight athletes</td>
</tr>
<tr>
<td>- Decreased lubrication</td>
</tr>
<tr>
<td>- Contact irritants</td>
</tr>
<tr>
<td>- Genitopelvic/pain disorder (vaginismus/dyspareunia, vulvodynia)</td>
</tr>
<tr>
<td>- Anatomic</td>
</tr>
<tr>
<td>- Scar (episiotomy)</td>
</tr>
<tr>
<td>- Endometriosis</td>
</tr>
<tr>
<td>- Uterine Prolapse, tumors</td>
</tr>
<tr>
<td>- Infectious</td>
</tr>
<tr>
<td>- Candidiasis</td>
</tr>
<tr>
<td>- STIs/ Pelvic inflammatory dz</td>
</tr>
</tbody>
</table>

* Items in red are present in our patient

Treatment of Pain Disorders

Treatments for Vaginal/Pelvic Pain

- Psychotherapy: Address fears
- Physiotherapy: Biofeedback, Vaginal Dilators, Pelvic floor PT
- Treat underlying causes
  - Lubricants
  - Topical vaginal estrogen/SERM
  - Treat infections
  - Treat inflammation
- Other interventions
  - Topical anesthetics
  - Oral medications
  - Surgical interventions

Treatment of Atrophic Vaginitis

- Vaginal moisturizers, lubricants
  - Moisturizers last longer than lubricants
  - Water-based, silicone-based, oil-based
    - Oil based not for use with latex condoms
    - Use natural oils (olive, corn, avocado, peanut)
    - Avoid mineral oil or petroleum-based, irritating
  - Topical estrogen
    - Estradiol (tabs, cream), ring or CE cream
    - Add progesterone if using creams?
  - SERM
    - Ospemifene (Osphena)
Atrophic Vaginitis

- Ospemifene (Osphena) 60mg/day.
  - Selective estrogen receptor modulator (SERM)
  - FDA approved for mod-severe menopausal dyspareunia
  - Prevents bone turnover
  - FDA recommends progesterone if intact uterus
    - Evidence of endometrial hyperplasia but not cancer
    - No studies evaluating protective effects of progesterone
  - Unlikely to have negative breast effects
    - Safety not determined in pts with hx of breast cancer or VTE
  - Risk of hot flashes and possibly VTE
  - No comparisons to estrogen therapy

Summary of Case: Mrs. Jones

- 34 year old female
  - Post-partum, stressed, breast feeding, “mini-pill”
  - Depressed. Being treated with an SSRI
  - Taking anti-histamines for allergies/insomnia
  - Atrophic vaginitis on exam

- DX: Female Sexual Dysfunction due to:
  - Hypoactive Sexual Desire Disorder
  - Arousal Disorder
  - Orgasm Disorder
  - Pain Disorder

In Summary

- Ask about sexual health
- Remember that FSD is often multi-factorial
- History should address issues of:
  - Desire, Arousal, Orgasm, Pain
- Look for and treat any underlying causes
- Recognize psychosocial influences
- Opportunity to educate
- Refer for therapy when appropriate

Resources

- Find a sex therapist in your area
  - www.aasect.org
- Find a pelvic floor PT in your area
  - www.apta.org