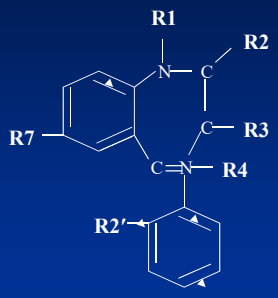
Anxiety Disorders, Insomnia, PTSD, OCD

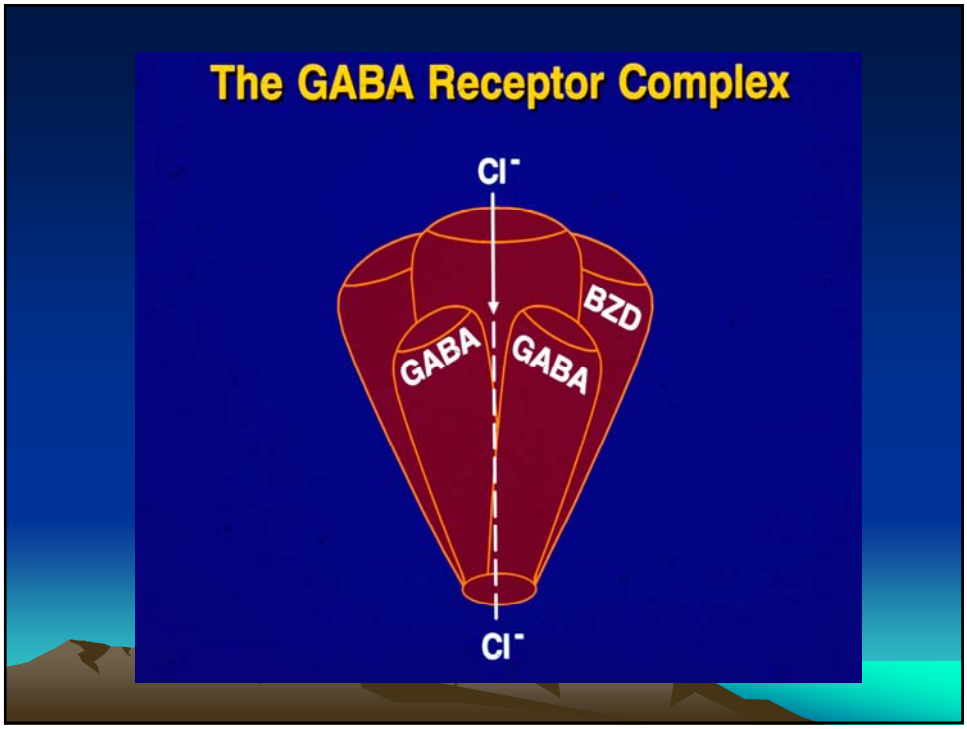
Steven L. Dubovsky, M.D.

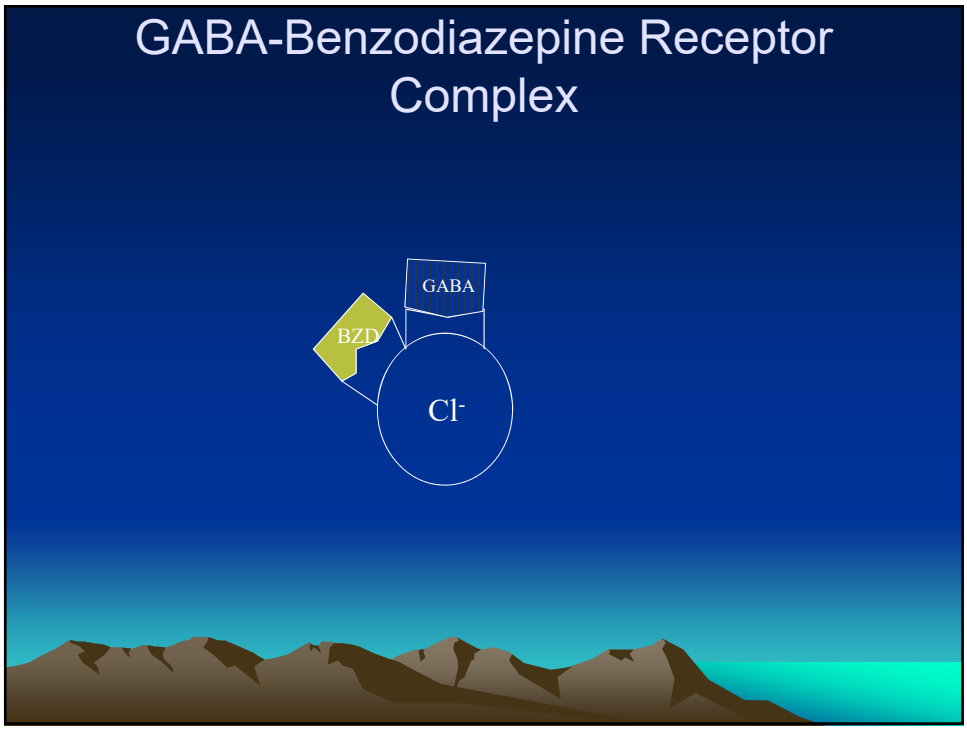
Pharmacotherapy of Anxiety

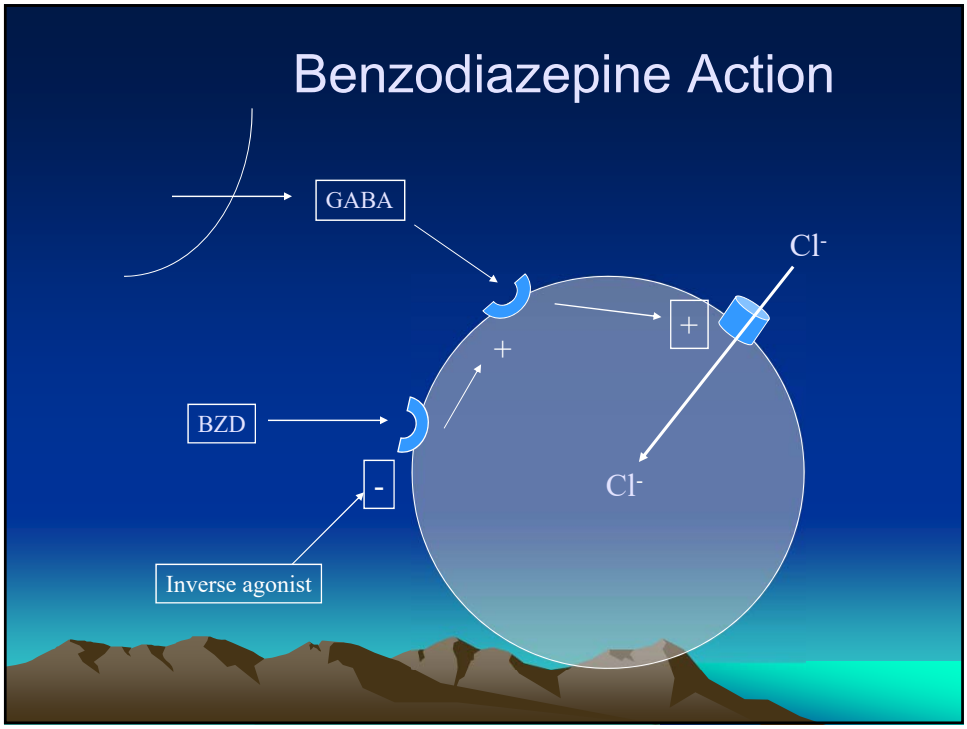
Basic Benzodiazepine Structure



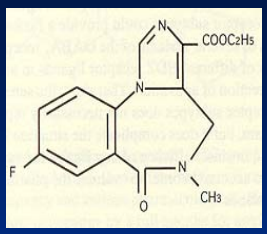
Benzodiazepine	R1	R2	R3	R7	R2'
Alprazolam	Fused triazolo ring		-H	-Cl	-H
Chlordiazepoxide	-	$-NHCH_3$	-H	-Cl	-H
Clonazepam	-H	=O	-H	NO_2	-Cl
Diazepam	$-CH_3$	=O	-H	-Cl	-H

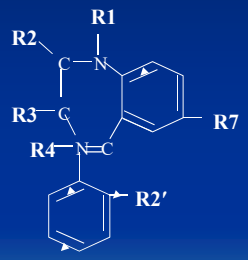

The GABA Receptor Complex
Cl-
BZD
GABA
GABA
Cl-


GABA-Benzodiazepine Receptor Complex
GABA
BZD
Cl-



Flumazenil





- Benzodiazepine receptor antagonist
- Therapeutic uses:
  - Benzodiazepine overdose
  - Reversal of conscious sedation
  - Reversal of hepatic encephalopathy symptoms
  - Facilitation of benzodiazepine withdrawal
- Can provoke withdrawal and induce anxiety

BZD Receptor Subtypes

- Type 1: Limbic system, locus coeruleus
  - Anxiolytic
- Type 2: Cortex, pyramidal cells
  - Muscle relaxation, anticonvulsant, CNS depression, sedation, psychomotor impairment
- Type 3: Mitochondria, periphery
  - Dependence, withdrawal

BZD Features

- Potency
  - High potency: Midazolam (Versed), alprazolam (Xanax), triazolam (Halcion)
  - Low potency: Chlordiazepoxide (Librium), flurazepam (Dalmane)
- Lipid solubility
  - High solubility: Alprazolam, diazepam (Valium)
  - Low solubility: Lorazepam (Ativan), chlordiazepoxide (Librium)
- Elimination half-life
  - Long half-life: Diazepam, chlordiazepoxide
  - Short half-life: Alprazolam, midazolam

Potency

- High potency
  - Smaller dose to produce same effect
  - More receptor occupancy
  - More intense withdrawal
- Low potency
  - Higher doses used
  - Less intense withdrawal

High Lipid Solubility

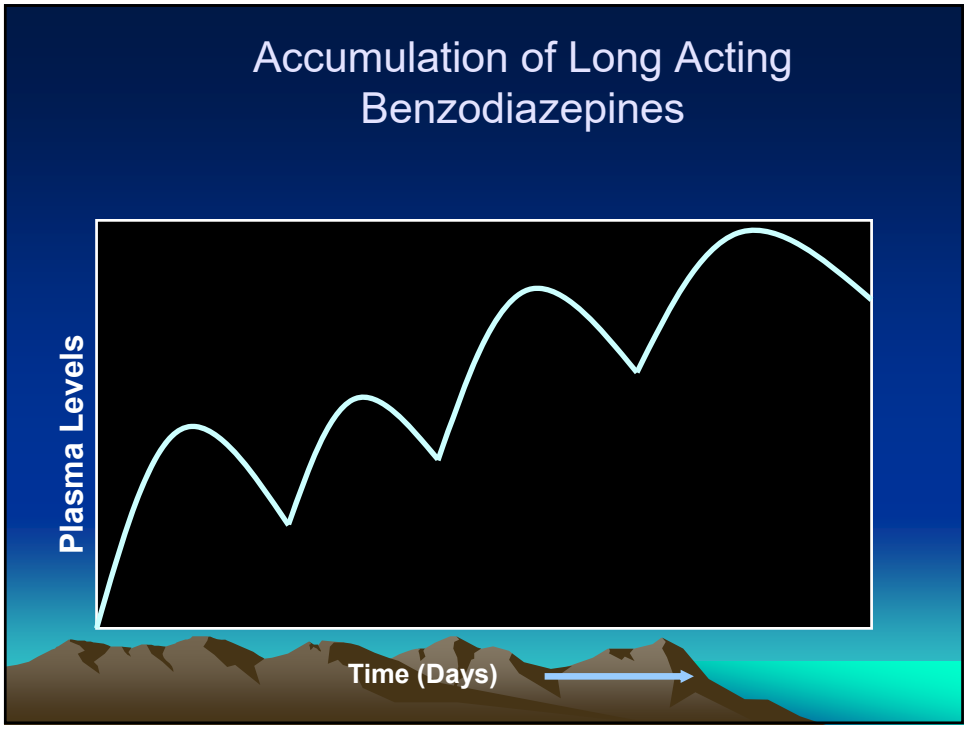
- Drugs get into brain fast and leave rapidly
- Preferable for patients who need rapid onset of action
  - Acute anxiety
- Bad for patients who do not like to feel that they are losing control
  - Can make patients feel spaced out
- More likely to produce a “buzz”
  - Can increase risk of dependence

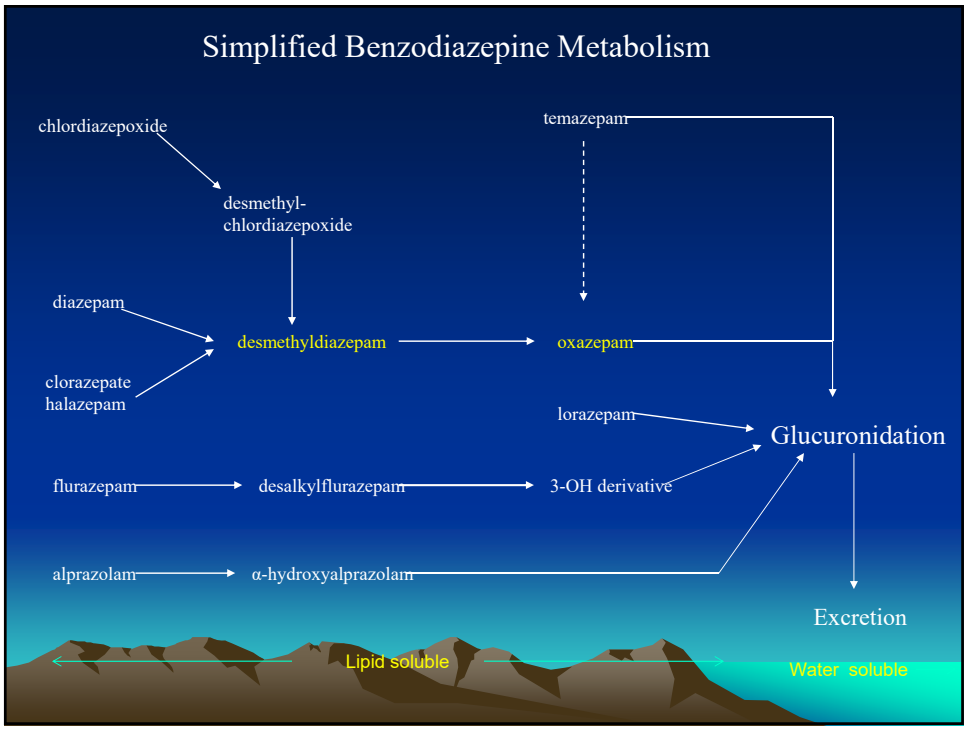
Low Lipid Solubility

- Get into and leave brain slowly
- Slow onset of action
- Effect lasts longer after a single dose
- Less likely to cause a “buzz”
  - Lower abuse potential

Elimination Half-Life

- Long half-life
  - Less frequent dosing
  - More accumulation with divided dose
  - Slower onset of withdrawal
  - Longer, more attenuated withdrawal
- Short half-life
  - Dosed more frequently
  - Less accumulation
  - Faster onset of withdrawal
  - Shorter, more intense withdrawal


Accumulation of Long Acting Benzodiazepines
Plasma Levels
Time (Days)


Simplified Benzodiazepine Metabolism
chlordiazepoxide
desmethyl-
chlordiazepoxide
diazepam
clorazepate
halazepam
desmethyldiazepam
temazepam
oxazepam
lorazepam
Glucuronidation
flurazepam
desalkylflurazepam
3-OH derivative
alprazolam
α-hydroxyalprazolam
Excretion
Lipid soluble
Water soluble

Benzodiazepine Metabolic Pathways

- Complex
  - Diazepam (Valium)
  - Chlordiazepoxide (Librium)
  - Flurazepam (Dalmane)
- Simple
  - Midazolam (Versed)
  - Alprazolam (Xanax)
  - Lorazepam (Ativan)
  - Oxazepam (Serax)

Predictors of a Good Response to a Benzodiazepine

- Acute symptoms
- Precipitating stress
- High levels of anxiety
- Low levels of depression
- Previous good response
- Awareness that problem is mental
- Expectation of medication

Choosing a Benzodiazepine

- Anxious CCU patient
- Agitated medical/ neurological patient
- Chronic anxiety in healthy patient
- Medically ill patient
- Acute agitation

- Rapid onset drug
  - Diazepam, alprazolam, midazolam
- Drug that will not accumulate
  - Lorazepam, oxazepam, midazolam
- Long half-life, low lipid soluble drug
  - Chlordiazepoxide, clonazepam
- Drug with simple metabolic pathway and intermediate half-life
  - Oxazepam, lorazepam, temazepam (Restoril)
- Midazolam, lorazepam

Common Misconceptions About Benzodiazepines

- Therapeutic effects diminish over time.
- Long-term users tend to escalate their doses.
- Dependence is the usual reason for long-term use.
- BZDs produce euphoria in most people.
- BZDs are commonly abused by people who do not otherwise abuse substances
- Elimination half life equals duration of action

Problems with BZDs

- Sedation
- Psychomotor impairment
- Interdose withdrawal with short acting BZDs, especially alprazolam
- Interactions with other CNS depressants, especially alcohol
- Discontinuation syndromes
- BZDs can reinforce passive approach to illness and desire for immediate relief from a pill

Driving Impairment

- 225,796 patients over 20 years old who got a first prescription of a benzodiazepine were compared with 97,862 controls
- New use of a benzodiazepine associated with an increased risk of a traffic accident within the first 4 weeks
- Greatest risk was with flurazepam
- OR for an accident
  - 6.1 for those under 60
  - 3.4 for those over 60
- Alprazolam 1 mg or placebo were administered in a double-blind design and a 100 km driving test in normal traffic was performed an hour later and psychomotor tests were performed 2.5 hours later. Subjects were crossed over to the other condition 2 weeks later
- Driving was significantly impaired by alprazolam compared to placebo, especially more
  - Weaving
  - Speed variability
  - Excursions out of lane
  - Equivalent to impairment with BAL of 0.15%
- Alprazolam also produced impairment compared to placebo on cognitive testing of
  - Tracking
  - Reaction time
  - Attention
  - Memory scanning

Neutel 1998; Verster 2002

Zaleplon (*Sonata*)

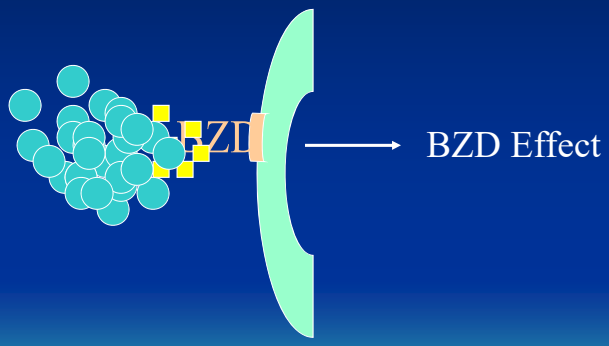
Zolpidem (*Ambien and Ambien CR*)

Eszopiclone (*Lunesta*)

Agents Selective for the BZD-1 Receptor

- Quazepam
  - Metabolized to desalkylflurazepam
- Zolpidem (Ambien), zalepon (Sonata)
  - Used as hypnotics
  - Not particularly effective as anxiolytic, muscle relaxant, anticonvulsant
  - Zolpidem has more next-day psychomotor impairment than originally thought
- Less effect on sleep architecture
- Antagonized by flumazenil

Partial Agonist Actions Depend on Agonist Availability



MVAs and Benzodiazepine Agonists

- Study of 72,685 French drivers involved in MVA with injury from 2005-2008
- Odds ratio for being responsible for the MVA with
  - Benzodiazepine hypnotics: 1.39
  - Zolpidem: 2.46
  - Zopiclone: not increased, but other studies indicate O.R. of 2.3

L. Orriols et al: Benzodiazepine-like hypnotics and the associated risk of road traffic accidents. Clin Pharmacol Ther2011;89:595

Alternatives to Benzodiazepine Receptor Agonists in the Treatment of Anxiety Disorders

- Antidepressants
  - Effective for GAD as well as panic and social anxiety
- Buspirone
  - Can be helpful at high doses
- Valproate
- Gabapentin, pregabalin
  - Helpful for depression as well as anxiety
- Antihistamines
  - One positive study of hydroxyzine
- Tiagabine
  - Studied only as augmentation
- Atypical antipsychotics
  - Can improve severe anxiety
  - Limited reliable data
  - Consider primarily for refractory anxiety in odd patients

Chamomile for GAD

- 57 outpatients with mild-moderate GAD
- Randomized to 880-1000 mg German chamomile extract or placebo
- 8 week double-blind trial
- HAM-A score decrease 6.29 greater with chamomile versus placebo
  - C: 15.5-8
  - P: 14-11.5

JD Amsterdam et al: J Clin Psychopharmacol 2009;29:378-382

Pharmacotherapy Studies in Pediatric Anxiety Disorders

- Most studies are with antidepressants, especially SSRIs
  - Separation anxiety, social anxiety, generalized anxiety
- Overall medication response
  - Active medication: 58-90%
  - Placebo: 32%
  - RR=1.9
  - NNT=4
  - Symptom improvement faster with medication
- CBT > antidepressants for remission and clinical significance in anxiety
  - 21 RCTs show that 39-80% improve with CBT
  - Medication effect levels off after 8 weeks; response to CBT continues to increase
- Most data for pediatric OCD
- Better response of non-OCD anxiety disorders than OCD
- No difference between SSRIs and SNRIs
  - Venlafaxine increases risk of deterioration in some reports
- Comorbid depression does not reduce treatment response of anxiety disorders
- Improvement of anxiety disorders not explained by improvement of concurrent depression
- Twice as many patients withdraw because of side effects from medication versus placebo

JC Ipser et al, 2009, CP Keeton, GS Ginsburg: Int Rev Psychiatry 2008;20:159

Psychotherapies

- CBT
- Relaxation
- Hypnosis
- Biofeedback
- Mindfulness
- All reduce tension, decrease helplessness, and increase sense of safety

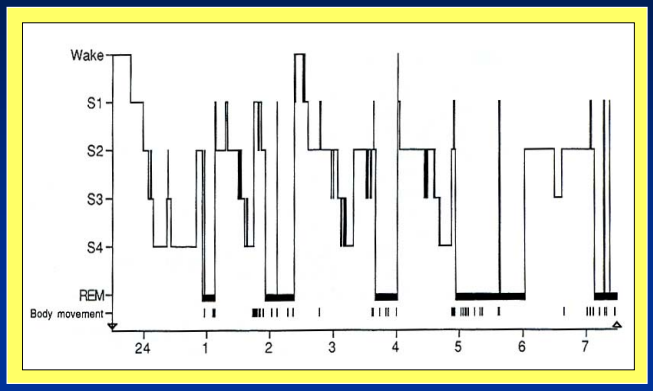
Combined Psychotherapy and Pharmacotherapy

- When to start medication first
  - Severe symptoms
  - Good but incomplete medication response
  - Plan to cross-taper to psychotherapy to avoid long-term medication use
- When to start psychotherapy first
  - Symptoms less acute
  - Patient preference
  - Less severe symptoms
  - Comorbidity
- When to start both together
  - Complex disorders
  - Family psychopathology
  - History of treatment resistance

CP Keeton, GS Ginsburg: Int Rev Psychiatry 2008;20:15

Insomnia

Sleep Architecture



TST: Total Sleep Time
TIB: Time In Bed
SE: Sleep Efficiency = TST / TIB x 100%
SOL: Sleep Onset Latency
WASO: Wake After Sleep Onset

Courtesy of N Sussman, M.D.

Epidemiology of Insomnia

- Occasional insomnia: 70% of population
- Frequent insomnia: 10%
- 60% increase in sleeping pill prescriptions to adults
- 85% increase in prescriptions to children

NY Times 10/19/05, 2/7/06

Common Causes of Insomnia

- Axis I disorders
  - Depression
  - Anxiety
  - Hypomania
  - PTSD
- Medication/substance effects
  - Side effects (e.g., caffeine, nicotine, stimulants)
  - Withdrawal/rebound (e.g., CNS depressants, alcohol)
- Medical disorders
  - GE reflux
  - Heart failure
  - MI
  - Dementias
  - Cancer
  - Pain
- Parasomnias
  - Periodic leg movements
  - Sleep disordered breathing
- Sleep phase change
- Psychophysiologic insomnia

Secondary insomnia

Common Treatments of Insomnia

- Alcohol
- Over the counter drugs
  - Diphenhydramine
  - Valerian
  - Doxylamine
  - Nyquil
- Someone else's medication
- Prescription hypnotics

Components of Primary Insomnia

- May be initial precipitating event or illness
- Hyperarousal
  - Elevated baseline or failure to down-regulate at night
  - Conditioning of arousal to being in bedroom
    - Increasing time spent in bed trying to get to sleep
    - Keeping TV on
    - Snacking at night
- Cognitive
  - Prone to worry, especially sleep-related worry
  - Selective attention to insomnia symptoms
- Circadian dysregulation
  - Initial insomnia: phase delay
  - Terminal insomnia: phase advance
  - Disturbance of timing or power of slow wave sleep
- Disrupted sleep "homeostat"
  - Inability to generate recovery sleep after sleep deprivation
  - Substantial sleep deprivation needed to reset homeostat
    - Should be a component of therapy

Pegeon and Perlis: Sleep Medicine Reviews 2006;10:247-254

Sleeping Pill Sales

- More than $300 million in advertising in 2005
  - Increase of 400% over previous year
    - Attributable to new Lunesta and Rozerem ads and doubled Ambien-CR ads to address increased competition
  - Lunesta manufacturer estimated it would eventually spend as much on advertising as McDonald's
- $2 billion/year in sales
- Best sellers: Ambien, Lunesta
  - Lunesta sales in first year: $329 million
    - 3.3 million prescriptions
    - $186 million in marketing by November 2005
    - Manufacturer's stock jumped $8.53 in one day

NY Times 10/19/05, 2/7/06

DTC Marketing

- FDA eased restrictions in 1997
  - Industry advertising increased from $55 million to $3 billion
- Since “the company’s potential markets [have] been limited to sick people,” [I hope] to “make drugs for healthy people”: Industry CEO
- Lunesta roll out tied to DTC campaign on “Desperate Housewives”
  - Audience 55% female
  - Women have insomnia > men
- Ambien CR released as patent for Ambien expires
- Initial FDA reaction to coupons for free introductory Ambien: “prescription drugs promoted with coupons or free trial offers may be seen as more widely indicated, more appropriate, and/or less risky than they really are”
  - Notice subsequently withdrawn as FDA studied the issue further

Moynihan and Cassels 2005; NY Times 2/7/06; Reuters: NY times, 8/14/06

Benzodiazepine Hypnotics

Drug	Usual adult oral dose (mg)	Tp (hrs)	T1/2 (hrs)	Protein binding (%)	Urinary excretion, unchanged (%)
Estazolam (Prosom®)	1-2	2	10-24	93	< 5
Flurazepam (Dalmane®)	15-30	0.5-1 (7.6-13.6)[1]	2-3/74-90[1]	97	< 1
Quazepam (Doral®)	7.5-15	2 (1-2)	41 (47-100)[1]	> 95	Trace
Temazepam (Restoril®)	15-30	1.2-1.6	3.5-18.4 (9-15)	96	0.2
Triazolam (Halcion®)	0.125-0.5	1-2	1.5-5.5	78-89	2

[1]N-desalkylflurazepam, active metabolite

Courtesy of N. Sussman, M.D.

Benzodiazepine Sleep Effects

- Reduced sleep latency, awakenings and duration of awakenings
- Increased total sleep time
- Prolonged REM latency
- Reduced REM in the first third of the night
- Increased duration of Stage 2
- Reduced duration of Stage 1
- Reduction or abolition of Stage 4

"Z" Drugs

Drug and Class	Half Life (hr)	Dose (mg)	Interactions
Eszopiclone (Lunesta) cyclopyrrolone	5-7	1-3	Drugs that inhibit CYP3A4, etoh, olanzapine
Zolpidem (Ambien, Ambien CR) imidazopyridine	3	5-10; 6.25-12.5 (CR)	Possibly drugs that inhibit CYP3A4
Zaleplon (Sonata) pyrazolopyrimidine	1-2	5-20	Possibly drugs that inhibit CYP3A4

Adapted from Silber M, NEJM 353;8: 806.

Zaleplon (Sonata)

- Used for initial insomnia
- Effect does not last long
- Does not increase total sleep time or decrease awakenings versus placebo

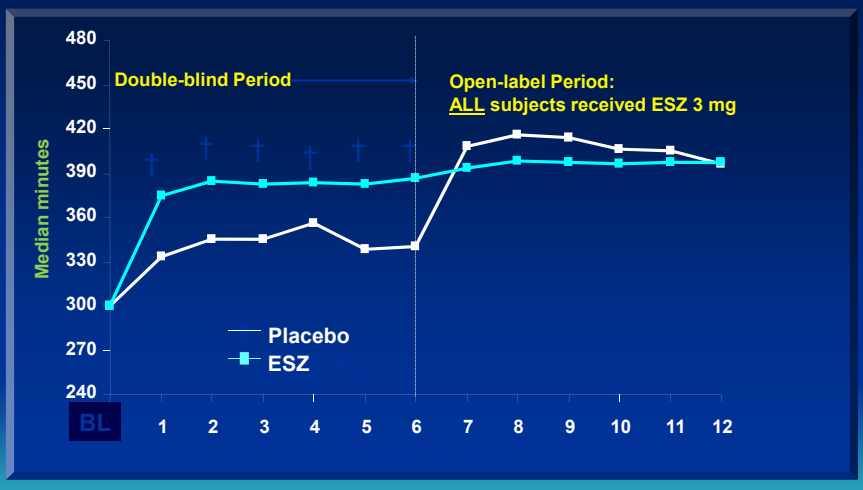
Zolpidem (Ambien CR)

- Reasons for development
  - Improve sleep maintenance as well as sleep induction
  - Extend patent
- Bi-layered tablet
  - First layer dissolves quickly to induce sleep
  - Second layer is released more gradually into the body to help provide more continuous sleep
  - Same time to peak onset as the immediate-release (IR), but concentrations are slightly lower
- Serum concentrations higher from 2.5 to 8 hours after the dose
- 12.5 mg of CR is more sedating than 10 mg IR
- Zolpidem associated with increased risk of falls in inpatients
- Daytime impairment common

Nonselective Partial BZD Receptor Agonists

- Zopiclone (Not available in U.S.)
- Eszopiclone (Lunesta)
  - S-enantomer of zopiclone
- Weaker acute effect than benzodiazepines
- Minimal effects on sleep architecture
- Minimal to no anxiolytic, anticonvulsant, muscle relaxant properties
- Less dependence and withdrawal
  - These can still occur
- Approved for longer-term use for insomnia
  - No data > 6 months

Eszopiclone (ESZ): Effects on Total Sleep Time--*Long-term Study*



†$P \leq 0.0001$ vs PBO.
Krystal et al. *Sleep*. 2003;26:793-799.

"Z" Drug Side Effects

- Next day somnolence
- Rebound insomnia on first night of discontinuation
- Tolerance
- Headache
- Dizziness
- Amnesia
  - Especially at higher doses
- Abuse in those with history of substance abuse (mainly zolpidem)
- Hallucinations at recommended doses (mainly zolpidem)
- Sleep automatisms with next day amnesia

"Z" Drugs: *The Medical Letter* Conclusions

"The main difference between all of them, except for half-life, is that the manufacturer of *Lunesta* sponsored a 6-month trial and submitted the results to the FDA, while the other 2 manufacturers did not."

The Medical Letter. February 28, 2005

Sleeping Pills and Risk of Death

- 10,529 patients who received hypnotics compared to 23,676 matched controls
  - Mean age 54
  - Followed for 2.5 years
- Data adjusted for age, gender, smoking, body mass index, ethnicity, marital status, alcohol use and prior cancer
- H.R.s for dying in patients taking hypnotics compared with no hypnotics:
  - <18 doses/year: 3.6
  - 18-132 doses/year: 4.43
  - >132 doses/year: 5.32

Slide 1

DF Kripke et al: BMJ Open *2012;2:e000850 doi:10.1136/bmjopen-2012-000850*

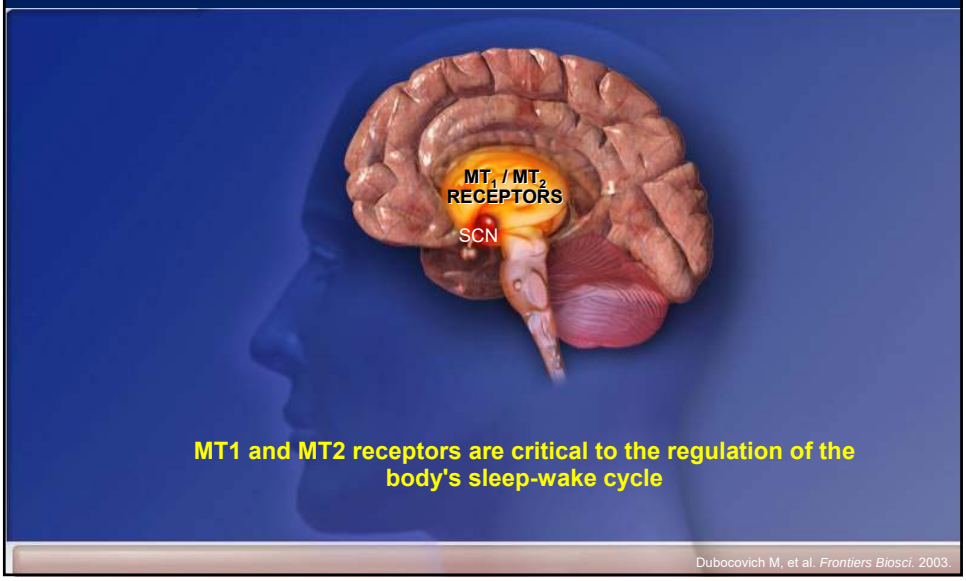
Sleeping Pills and Risk of Death

- Increased H.R.s individually for
  - Zolpidem
  - Eszopiclone
  - Zaleplon
  - Benzodiazepines
  - Sedating antihistamines
- Not attributable to pre-existing illness
- Insomnia requiring hypnotic could be an indicator of vulnerability to disease

Slide 2

DF Kripke et al: BMJ Open *2012;2:e000850 doi:10.1136/bmjopen-2012-000850*

Melatonin (Hormone of Darkness)
–Secreted from pineal gland during darkness/ indirectly feedbacks to SCN
–High levels secreted prior to sleep -- Levels low during wakefulness



MT1 and MT2 receptors are critical to the regulation of the body's sleep-wake cycle

Dubocovich M, et al. *Frontiers Biosci*. 2003.

Suprachiasmatic Nucleus

MT_1 agonism
- Attenuates SCN alerting signal
- Sleep-promoting effect

MT_2 agonism
- Synchronizes circadian clock
- Phase-shifting effect

Dubocovich M et al: Frontiers Biosci 2003; Lieu C et al: Neuron, 1997

Melatonin

- Can shift sleep-wake cycle but does not increase total sleep
- In nine of 10 controlled trials, melatonin taken close to the target bedtime at the destination decreased jet lag when crossing 5 or more time zones
  - Doses of 0.5 and 5 mg were equally effective except that sleep onset was sooner with 5 mg
  - Doses >5 mg are no more effective
  - Slow-release melatonin was not as effective, suggesting that a short lived high peak level is important
  - NNT for meaningful benefit = 2
- Mixed data on benefit for sleep disorder of dementia

Herxheimer, 2002

Ramelteon (Rozerem)

- Approved for the treatment of sleep onset insomnia
- MT1 and MT2 receptor agonist
- No abuse potential

Ramelteon (Continued)

- Pharmacokinetics:
  - T ½ 2-5 hours
  - Dose: 8 mg, 30 minutes before going to bed
  - Metabolized by CYP1A2
    - CYP2C and CYP3A4 minor paths
  - Should not be used in severe hepatic impairment or with fluvoxamine
  - Do not take with a high fat meal
- Adverse Events & Safety
  - Drowsiness
  - Dizziness
  - Increased prolactin levels
  - Cessation of menses
  - Galactorrhea
  - Decreased libido
  - Problems with fertility

Orexin (Hypocretin)

- In glutaminergic neurons in lateral hypothalamus
  - Diffuse projections to locus coeruleus arousal center
- Orexin-A and –B
- Hcrt 1 and 2 receptors
- Generate and maintain wakefulness
  - Sleep-to-wake transition
- Narcolepsy associated with loss of orexinergic neurons
- Animal studies suggest orexin-1 and -2 antagonists induce sleep at doses that do not impair cognition

JM Uslaner: Science Transl Med 2013;179:1; M Mieda and T Sakura: CNS Drugs 2013;27:83; L de Lecea et al: Biol Psychiatry 2012;71:1046-1052

Suvorexant (Belsomra)

- Dual orexin receptor antagonist (DORA)
- May reduce mesolimbic dopamine signaling
  - Possible decreased risk of dependence
- Industry sponsored 3-month studies
  - Decreased sleep latency by 10-22 minutes
  - Decreased WASO by 38-42 minutes
- 1-year study of 30 or 40 mg suvorexant (N=522) versus placebo (N=259)
  - 2-month double-blind discontinuation phase
  - 62-63% completed study
  - Insomnia improved more on suvorexant than placebo
    - At 1 year, subjective total sleep time increased 60 minutes versus 33 minutes on placebo
      - No objective sleep measures
  - Discontinuation of suvorexant associated with relapse of insomnia
- No effect on mood; no narcolepsy symptoms noted
- FDA insists on 15 mg maximum dose, which "may not be low enough for safe use"
  - Current labeling recommends 10 mg, with increase to 20 mg if necessary
    - Impaired driving the day after 20 mg HS dose
- Almorexant withdrawn due to adverse effects

D. Michelson et al: Lancetneurology 2014;13:461; ; M Meda and T Sakurai: CNS Drugs 2013;27:83

Lemborexant (Dayvigo)

- Dual orexin receptor antagonist
- 2.5-10 mg studied
- No impaired driving 9 hours after dosing
- Improves sleep efficiency and subjective sleep
- Daytime sedation not excessive

P. Murphy et al: J Clin Sleep Med 2017;13:1289

Sedating Antidepressants as Sleeping Pills

- Tertiary amine TCAs
  - Doxepin, trimipramine
    - H1 antihistamine
  - Amitriptyline
    - Useful for chronic pain
- Trazodone
  - Equivalent to zolpidem for sleep latency and subjective sleep duration
  - Priapism risk not dose related
- Nefazodone
- Mirtazepine

Walsh JK et al. Hum Psychopharmacol 1998;13:191-198)

Olanzapine as a Sleeping Pill

- Structurally similar to benzodiazepines
- Subjectively sedating
- Sleep effects:
  - Increased SWS
  - Increased Stage 2
  - Increased sleep quality
  - Decreased wakefulness
  - Decreased Stage1
  - Decreased REM

Sharpley AL et al. Biol Psychiatry 2000;47:468-470; Sain-Pascual RJ et al. Biol Psychiatry 1999;46:141-143

Anticonvulsants as Sleeping Pills

- Tiagabine (Gabatril)
  - Selective GABA reuptake inhibitor
  - Acts selectively at GAT-1 transporter
  - T_{max} = 45 min, $T_{1/2}$ = 7-9 hours
  - Improves sleep efficiency
  - Modest increase in Stage 3/4
- Gabapentin (Neurontin)
  - Alpha-2-delta ligand
- Pregabalin (Lyrica)
  - Alpha-2-delta ligand
  - Improves sleep latency, efficiency and time
  - Increases Stage 3/4 sleep
- Valproate (Depakote)
  - Improves sleep in manic and anxious patients

Prazosin

- Alpha-2 agonist antihypertensive
- Very sedating
- Reduces nightmares and insomnia in PTSD

Gamma Hydroxybutyrate (GHB, Xyrem)

- Aqueous solution - variable concentration
- Rapid onset, short half-life (20 minutes)
- Causes relaxation, disinhibition, euphoria
- Dependence and withdrawal significant risks
- Narrow therapeutic window
  - Dizziness, nausea, emesis, decreased respiration, coma
  - Additive with ETOH and other sedative-hypnotics
- Risks generally outweigh benefits

AASM Hypnotic Recommendations

Drug	Initial Insomnia	Sleep Maintenance	Not Recommended
Diphenhydramine			X
Doxepin		X	
Eszopiclone	X	X	
L-tryptophan			X
Melatonin			X
Ramelteon	X		
Suvorexant		X	
Temazepam	X	X	
Tiagabine			X
Trazodone			X
Triazolam	X		
Valerian			X
Zaleplon	X		
Zolpidem	X	X	

Placebo Effects on Sleep

- Self-ratings and PSG in 10 subjects at baseline and after two lactose pills
  - Patients told they were getting sleeping pills
- Placebo nights rated as more restful, with decreased awakenings compared to baseline
- PSG after placebo showed
  - Decreased wakefulness
  - Increased delta power during NREM sleep
  - Decreased beta during REM sleep
  - Improved morning functioning

Fratello F et al: Psychopharmacology 2005;181:761-770

Concerns about Long-Term Hypnotic Use

- Primary causes may be overlooked and untreated
- Chronic efficacy not supported by research
  - Longest study 6 months
- Potential for tolerance, accumulating psychomotor impairment, covert dependency
- Need for chronic use may be related to interdose rebound insomnia
- Encouragement of belief that solution to one's problems is outside oneself

Legal and Ethical Issues

- Informed consent requires informing patients about all proven therapies
  - CBT generally superior to hypnotics
- Society is stressful
  - Patients and society are not strengthened by omitting opportunities to learn to deal with stress
- People want to solve all problems with a pill
  - Sleeping well is a right
- Prescriber may have significant liability exposure despite reassurances from manufacturer
  - MVAs
  - Amnesia/automatic behavior
  - Drug dependence
- Clinicians are more likely to be sued for prescribing a sleeping pill that causes harm than for not prescribing it

Considerations Before Prescribing a Sleeping Pill

- Assess substance use carefully
- Inform patient about alternatives
- Sleeping pills still most appropriate for
  - Acute insomnia in response to
    - Stress
    - Acute illness
    - Hospitalization
      - Ask if patient wants a hypnotic
  - Short-term treatment of insomnia in depressed or anxious patients until antidepressant or anxiolytic effect begins
- Recommend behavioral treatments
- Chronic hypnotic treatment only if
  - Treatment of primary disorder is appropriate
  - Other measures have failed
  - The medication helps
  - Careful risk/benefit analysis has been performed

Meta Analysis of Behavior Therapy of Insomnia

- Meta analysis of 23 RCTs
- 3 modalities studied
  - CBT
  - Relaxation
  - Behavior therapy
- Equivalent benefit for all treatments on
  - Sleep quality
  - Sleep latency
  - Nighttime awakenings
- Similar benefit in older and younger patients

Irwin MR et al: Health Psychology 2006;25:3-14

Components of CBT for Insomnia

- Sleep hygiene
  - Correct environmental factors, exercise, alcohol use, diet
- Sleep restriction
  - Only in bed when asleep
  - Strict bedtime and waking schedule
- Stimulus control
  - Break association between being in bedroom and stimuli that promote arousal
    - Most activities except sleep
- Cognitive therapy
  - Address global assumptions and negative expectation about sleep
    - If I don't sleep well tonight, I'll never sleep again
- Progressive relaxation
  - Practice with recording every day
- Relapse prevention

CBT Effectiveness

- CBT benefits 70-80% of middle aged adults with insomnia
- CBT more effective than sleep hygiene alone
- CBT equal to temazepam acutely and superior long-term in geriatric primary insomnia
- Group CBT with telephone followup as effective as individual CBT
- RCTs show sustained improvement of insomnia in patients with chronic pain, arthritis, coronary artery disease, pulmonary disease, fibromyalgia, Alzheimer's disease, alcoholism, PTSD, depression, anxiety
- American Academy of Sleep Medicine recommends CBT as first line treatment for insomnia
  - Including secondary insomnia

Siversten B et al: JAMA 2006;295:2851-8; Stepanski and Rybarczyk: Sleep Medicine Reviews 2006;10:7-19; Edinger et al: Arch Intern Med 2005;165:2527-35

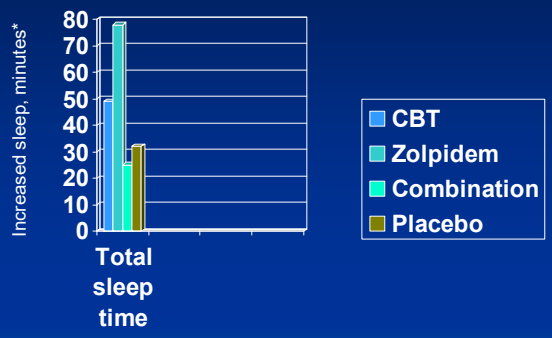
CBT vs Zolpidem

- 63 patients (54 completers) age 45-49 with sleep-onset insomnia randomly assigned to 8 weeks of
  - Zolpidem 10 mg/night for 4 weeks, 5 mg/night for 1 week, then 5 mg every other night for 1 week
  - CBT 3 individual sessions/week for 3 weeks, 1 individual session 2 weeks later, then 1 telephone session 2 weeks after last individual session
  - Zolpidem + CBT
  - Pill placebo + nonspecific management
- Outcome measured by sleep diaries and sleep lab
  - Diaries always overestimated improvement

Slide 1

Jacobs GD et al: Arch Intern Med 2004;164:1888-96

CBT vs Zolpidem

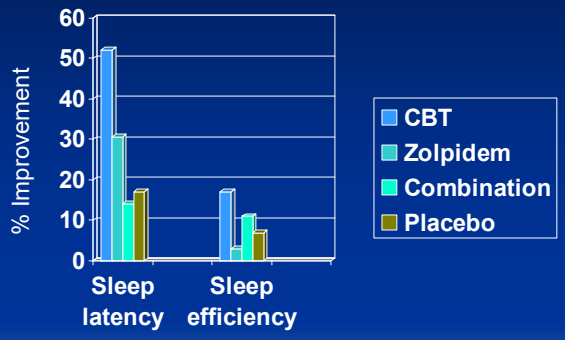


*Differences not statistically significant

Slide 2

Jacobs GD et al: Arch Intern Med 2004;164:1888-96

CBT vs Zolpidem



Slide 3

Jacobs GD et al: Arch Intern Med 2004;164:1888-96

CBT vs Zopiclone in Older Insomniacs

- Older adults (N=48; mean age 60) randomized to CBT (6 sessions), zopiclone or placebo
  - 7.5 mg zopiclone=3.75 mg eszopiclone (active enantomer)
    - Zopiclone 45% of hypnotic sales in Norway
  - 6 month study
- 6-week effects
  - Total wake time reduction: CBT>zopiclone=placebo
  - Total sleep time: no significant change with any treatment
  - Sleep efficiency improvement: CBT>placebo; CBT=zopliclone, but zopiclone=placebo
  - Increase in slow wave sleep: CBT>zopiclone and placebo
    - Slow wave sleep decreased with zopiclone (p=0.01)

Siversten B et al: JAMA 2006;295:2851-8

6-Month Effect Sizes

	Time awake	Total sleep time	Sleep efficiency	Slow wave sleep
CBT	1.7	-0.1	1.2	0.7
Zopiclone	0.2	-0.9	0	-0.5

Siversten et al 2006

Sleep Healthy Using the Internet (SHUTi)

- Automated seld-administered version of CBT for insomnia (CBTi)
- 330 subjects recruited over internet
  - Self-reported insomnia
    - >30 minutes sleep latency or WASO
    - Total sleep time ≤ 6.5 hours
    - Distress or impairment
- 6-week random assignment to SHUTi or automated sleep education program
  - "Single-blind" but easy to guess which program you had

Slide 1

LM Ritterband et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.3249

Sleep Healthy Using the Internet (SHUTi)

- SHUTi effect sizes
  - Post-treatment: 0.79-1.90
  - 1-year
    - Insomnia severity: 2.32
    - Sleep latency: 0.95
    - WASO: 1.41
- Control effect sizes
  - Post-treatment 0.37-0.77
  - 1-year
    - Insomnia severity: 1.53
    - Sleep latency: 0.64
    - WASO: 0.86

Slide 2

LM Ritterband et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.3249

Sleep Healthy Using the Internet (SHUTi)

- Insomnia remission based on severity measure
  - SHUTi
    - Post-treatment: 41%
    - 1-year: 57%
  - Control
    - Post-treatment: 11%
    - 1-year: 27%
- Caveats
  - No direct assessment
    - All measures self-rated
  - All subjects came from internet
    - White middle class
    - Experienced with internet
  - No sleep-lab correlation
  - No objective measures of daytime sleepiness/impairment

Slide 3

LM Ritterband et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.3249

Digital CBT for Insomnia in Pregnancy

- 208 pregnant women with self-reported insomnia
  - Mean age 34
  - Mean gestation 18 weeks
- Random assignment to dCBT-I (Sleepio) or usual care
  - 6 sessions on website or iPhone
  - Animated therapist
  - Reminders to go to the next session
  - Components: sleep restriction, stimulus control, cognitive therapy, relaxation techniques, education, sleep hygiene

Slide 1

JN Felder: JAMA Psychiatry 10.1001/jamapsychiatry.2019.4491

Digital CBT for Insomnia in Pregnancy

- dCBTi>usual care for
  - Insomnia severity (ES=1.03)
  - Remission of insomnia (44% vs 22%)
  - Improvement of symptoms of anxiety and depression symptoms
    - Patients did not have comorbid mood or anxiety disorder
- Improvement maintained 2 months after treatment ended
- Many more patients screened than treated
  - Most rejected because insomnia not severe enough
- No direct contact with or observations of patients

Slide 2

JN Felder: JAMA Psychiatry 10.1001/jamapsychiatry.2019.4491

Intensive Sleep Retraining

- Restrict sleep to 5 hours on night before treatment
  - Increases homeostatic sleep drive
- Series of 50 half-hourly sleep-onset opportunities in sleep lab
- Try to sleep
  - If no sleep in 20 minutes, get out of bed
  - If sleep occurs, awake after 3 minutes
    - Patient compares perception of sleep to PSG data
    - Remain quiet in a chair until next sleep session
- One night of recovery sleep at home
- Combined with sleep hygiene

Slide 1

J Harris et al: Sleep 2012;35:49

Intensive Sleep Retraining

- 25-hour protocol
- Study of 79 patients assigned to ISR, Stimulus Control Therapy, ISR+SCT or sleep hygiene only
  - Improvement after one treatment session
  - Maintained after 6 months
  - ISR+SCT had largest effect size
    - 1.26-2.20 for perception of sleep and dysfunctional attitudes
    - 0.79-1.34 for sleep onset, sleep efficiency, total sleep time, WASO

Slide 2

J Harris et al: Sleep 2012;35:49

Artificial Bright Light

- Best cue to time of falling asleep is exposure to bright light at time of awakening
- Especially useful for sleep phase delay
  - Consider for patients who cannot fall asleep at desired hour and feel sleepy or impaired in the morning
- Reduces night time confusion and wandering in demented patients

Prevention of Jet Lag

- Go to sleep at time corresponding to bedtime at destination
  - Short acting hypnotic helpful but not definitive
  - If previous jet lag and traveling east, skip dinner
- Wake up at time corresponding to time of awakening at destination
- Go outside or use artificial bright light after waking
- Do not go to sleep on first day at destination until appropriate bedtime

Behavior Therapy for Insomnia in Alzheimer's disease

- NITE-AD: Nighttime treatment and education for Alzheimer's disease
  - 6 weekly sessions
  - Develop individualized sleep hygiene program
    - No naps after 1 PM
    - Regular times of going to bed and waking up
  - Instructions to walk for 30 minutes/day
    - Accompanied by caretaker
    - Outside in daylight if possible
  - Increase daily exposure to light
    - Decrease light at night
  - Address problems with treatment adherence (e.g., pets in bedroom, noise at night, etc)
- Compared to nonspecific advice, NITE-AD had significantly
  - Fewer nighttime awakenings
  - Less total time awake
  - Less depression
  - More daytime exercise
  - Lower ratings of daytime sleepiness
  - Gains maintained at 6 months follow-up

McCurry SM et al. J Am Geriatr Soc 2005;53:793-802

Limitations of Behavioral Treatments

- Time and labor intensive
  - Group and automated formats reduce therapist time
- True expertise and protocol adherence uncommon
- Patients expect doctors to prescribe
  - Doctors expect themselves to prescribe
    - "Brain based" psychiatry
  - Nothing else seems like a real treatment
- Discussing treatment takes longer than a "med check"
- No payment for evidence based behavioral therapies

What if CBT is Not Available?

- Advise no caffeine after noon
  - Even decaf contains enough caffeine to interfere with sleep
- No alcohol at bedtime
  - Initial sedation balanced by long-term disruption of sleep architecture
  - Withdrawal in middle of night causes arousal
- Stop smoking if possible
- Review sleep hygiene in detail
  - Consider written instructions
  - Keep a log of times in bed
  - Start by decreasing time in bed below usual time asleep
  - Only use bed for sleep
  - Get out of bed for 20-30 minutes if awake for 20-30 minutes
  - Stick to strict time of going to bed and waking up
    - Wake up at same time each morning even if no sleep last night
    - Keep same hours weekends as week days

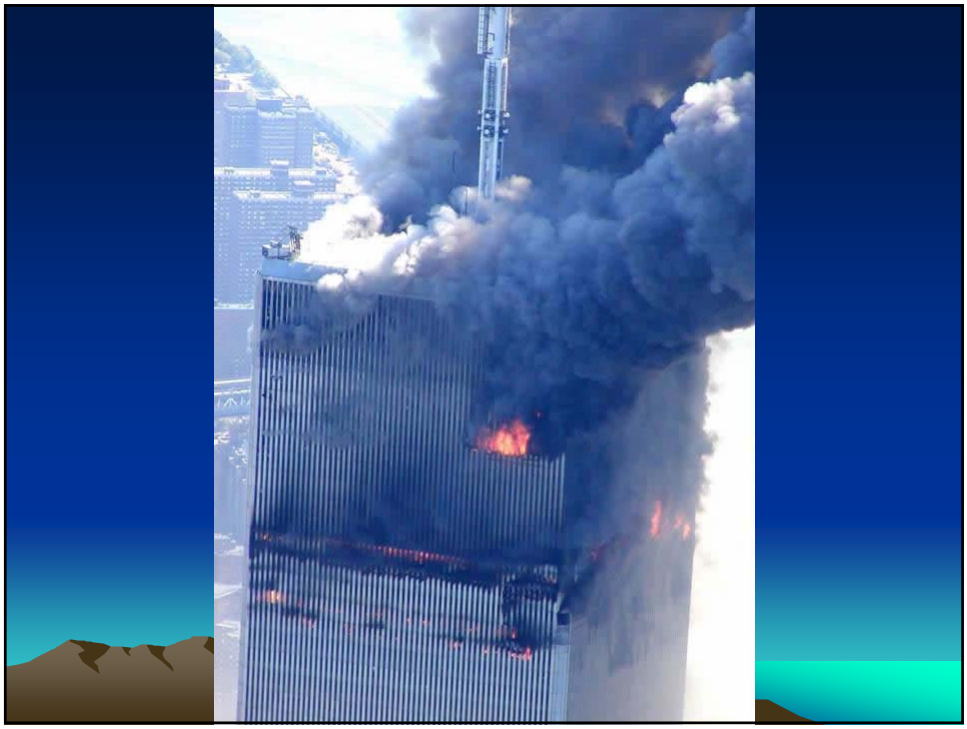
Slide 1

What if CBT is Not Available?

- Go outside or use artificial bright light in morning
- Ask patient to list worst fears about not sleeping
  - Then ask patient to think of possible counter arguments (e.g., "the worst that will happen if I don't sleep is that I'll feel tired")
- Have patient buy a relaxation tape
- Inform patient that sleep fluctuates normally
  - A decent night's sleep is usually no more than 2 or 3 days away
- Consider having patient sleep in a different bed for a while
- Refer patient to a self-help manual or SHUTi

Slide 2

PTSD

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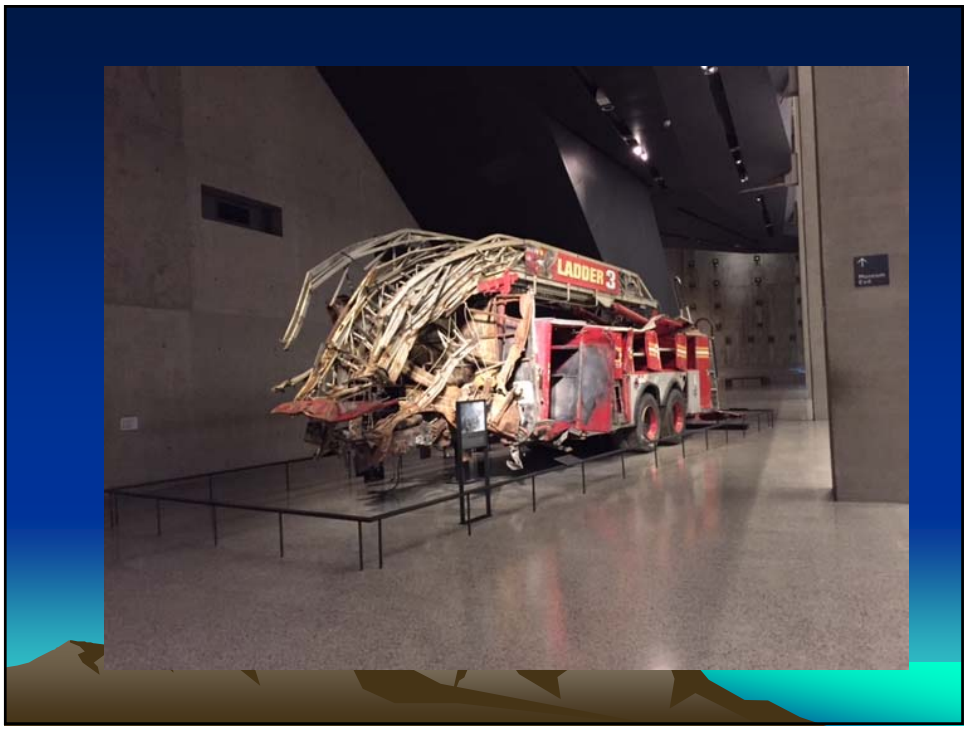
$10,000
CASH
REWARD
NYPD

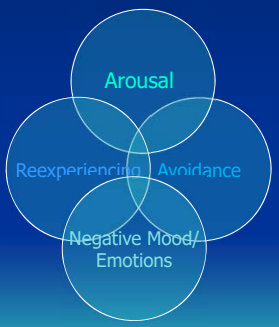

LADDER 3

History of PTSD

- Civil War: Soldier's heart/irritable heart (DaCosta)
- WWI: Shell shock
- WWII: Battle fatigue
- DSM I (1952): Gross stress reaction
- DSM II (1968): No diagnosis
- DSM III, DSMIV, DSM5: PTSD

Features of PTSD

Life Threatening Stress



PTSD

- Extreme stress
  - Experiencing, witnessing
  - Learning of a violent trauma to loved one
  - Repeated or extreme exposure to aversive details of event
    - Traumatic remains, child abuse
- Reexperiencing
  - Memories
  - Dreams
  - Flashbacks
  - Intense reactions to reminders

Slide 1 DSM5

PTSD

- Emotional numbing/avoidance
  - Avoidance of thoughts/memories
  - Avoidance of places or situations
- Hyperarousal
  - Hypervigilence
  - Irritability
  - Startling
  - Disturbed sleep
- Negative mood and thoughts
  - Blocking out memories
  - Self-blame
  - Negative view of the world
  - Detachment
  - Lack of enjoyment
  - Sense of foreshortened future

Slide 2

Problems with DSM-5 Criteria

- Requires avoidance
  - Many soldiers and first responders suppress avoidance
  - Avoidance more related to intrusive recall than a separate category
    - The more you try to suppress thoughts, the more intrusive they become
- Subsyndromal PTSD relegated to adjustment disorder
- Previous research used DSM-III-R and DSM-IV criteria
  - Not necessarily translatable to DSM-5

CS Hoge: JAMA Psychiatry 2015; published online 7/22/15

Risk Factors for PTSD

- Childhood trauma
- Family members with PTSD
- Poor premorbid functioning
- Family or past history of anxiety or mood disorder
- Low social support at time of trauma
- Lower intelligence
- Neurological impairment
- Stressful life events in preceding and following year
- Dissociation at time of trauma
- Resting tachycardia
- Decreased cortisol after trauma

Types of Trauma and PTSD

- WHO survey of 34,676 people from 20 countries
- Highest risk of PTSD with exposure to interpersonal violence
  - Kidnapped
  - Sexual violence
  - Witnessing atrocities
- Lower risk of PTSD with being civilian in
  - War zone
  - Terrorism zone
  - Natural disaster
  - Mainly explained by low risk of PTSD in those who moved to a better location and by recall of remote WWII experiences by well elderly adults
- Being in situations that promote mastery (e.g., military, first responder, even perpetrator) reduce risk of PTSD

H Liu et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.3783

PTSD and Dissociation

- Dissociation
  - Depersonalization
  - Derealization
- 14% of PTSD patients
- Associated with
  - Early onset
  - More prior trauma
    - Nature of trauma not specific for dissociation
  - More childhood adversity
- Outcome
  - More impairment
  - More suicidality
  - More severe symptoms
  - Harder to treat
    - Over-modulation of emotion may prevent habituation and fear extinction

DJ Stein et al: Biol Psychiatry 2013;73:302-312

Acute Stress Disorder

- Similar to PTSD in trauma and symptoms
- Develops right after the trauma
  - Always within one month
- Prominent dissociative symptoms may be present
- Lasts 3 days-4 weeks

Evolution of PTSD

- 1 year prospective study of 1138 patients in ED after traumatic injury
  - MVA, assault, work injury, other
  - 852 patients completed 1-year study
  - 490 had mild TBI
  - 82 had PTSD at 12 months
- Patients interviewed a week after injury and 1 year later
- Early network of symptoms related to fear conditioning and over-consolidation of fear memories
  - Re-experiencing, intrusive memories, avoidance of reminders, flashbacks, nightmares
  - Emotional numbing and social withdrawal a separate group of symptoms
  - Amnesia not linked to other symptoms

Slide 1

RA Bryant: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.3470

Evolution of PTSD

- After 1 year
  - Fear conditioning symptoms more closely linked
    - Startle response and hypervigilance added
  - Second strong constellation of dysphoric symptoms developed
    - Irritability, disturbed sleep, numbing, loss of interest, difficulty concentrating, sense of foreshortened future, amnesia
- Implications
  - Early treatment of fear conditioning may prevent later evolution of PTSD and advent of dysphoric dimension
  - Amnesia difficult to assess because of number of head injuries
    - However, not being able to remember past accurately interferes with planning for or conceiving of the future
  - Symptoms are not manifestations of psychiatric disorders: they ARE the disorders
  - Treatment addresses symptom clusters and their pathophysiology (e.g., fear conditioning), not the pathophysiology of the entire disorder

Slide 2

RA Bryant: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.3470

PTSD Epidemiology

- 50-85% of adults have had trauma exposure
  - 25% of those develop PTSD
  - 30-50% of traumatized children
  - 30% of disaster victims
  - 2-32% of accident victims
  - 27% of TBI patients
- 10-13% of middle east and Vietnam war veterans
- 10% of women and 5% of men
  - Lifetime prevalence of PTSD 7% overall
- Higher prevalence of PTSD symptoms without formal diagnosis
- 2/3 recover
  - 1/3 have chronic PTSD

PTSD 40 Years After Vietnam War

- National Vietnam Veterans Longitudinal Study
  - 1238 combat and non-combat veterans
  - 400 combat veterans had diagnostic interviews in addition to questionnaires
- Current/lifetime PTSD prevalence (DSM-5 + subthreshold)
  - Combat veterans
    - Men: 10.8%/26.2%
    - Women: 8.7%/25.7%

Slide 1

CR Marmer et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2015.0803

PTSD 40 Years After Vietnam War

- Current PTSD prevalence (DSM-5 + subthreshold)
  - Non-combat Vietnam-era veterans
    - Training accidents, civilian trauma
    - Men: 6.9%
    - Women: 7.8%
- About 25% had comorbid MDD
- Substance abuse not common
- 16% had clinically important increased symptoms over time
  - 7.8% had decreased symptoms
- 20% of representative sample died before study

Slide 2

CR Marmer et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2015.0803

PTSD After 9/11

- NYC population: 7-11%
- NYC school children: 10%
- Rescue workers:
  - Police: 6.2%
  - Volunteers: 21.2%
  - Overall: 12.4%
  - Higher prevalence in people who performed tasks not part of their profession
- Risk factors:
  - Prior trauma
  - Less disaster training
  - Volunteer
  - More time on site
- Significant stress symptoms: 44% of U.S. population

Slide 1

Perrin et al: Am J Psychiatry 2007;164:1385

PTSD after 9/11 (cont)

- Dose response curve for PTSD
  - Those closer to the event had more PTSD
  - Those who watched more TV had more PTSD
  - Debriefing team developed PTSD
- Most people considered this a personal attack
  - PTSD occurred in people distant from the event
  - National feelings of helplessness and overstimulation
  - People could not disconnect themselves from the attack
- Problems in addition to PTSD:
  - Grief
  - Survivor guilt
  - Shame at strong emotions
  - Relapse of substance abuse
  - Problems in relationships
- 87% of people had good functioning before the attack
- 55-68% returned to baseline functioning after the attack

Slide 2

Jackson et al: Psychiatric Services 2006;57:1283; Katz et al: Psychiatric Services 2006;57:1335

Comorbidity

- Mood disorders
  - Depression can be precipitated separately from PTSD following traumatic events
  - 50% of PTSD patients
- OCD
- Panic disorder and phobias in women
- Substance abuse
- Increased risk of Alzheimer's disease with aging
  - Could be common predisposing factors or impact of HPA axis changes on Aβ

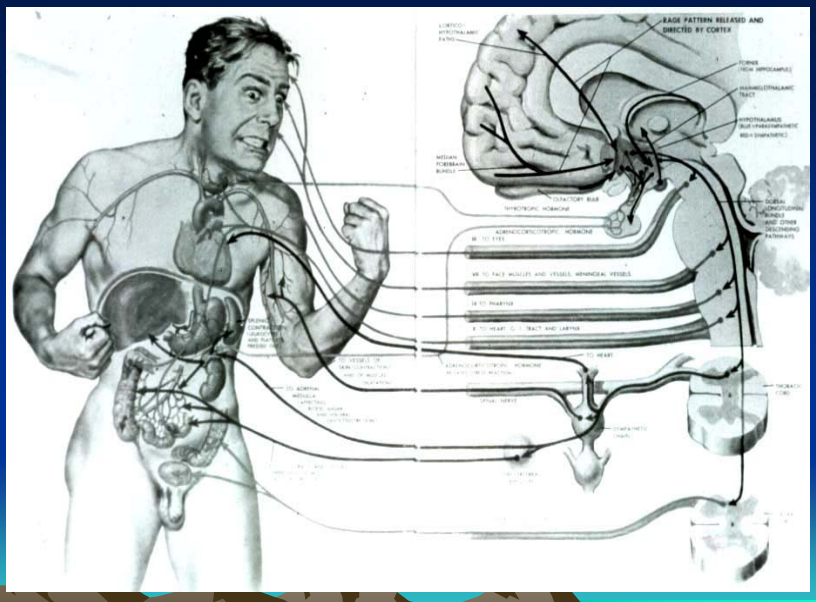
Psychotic PTSD

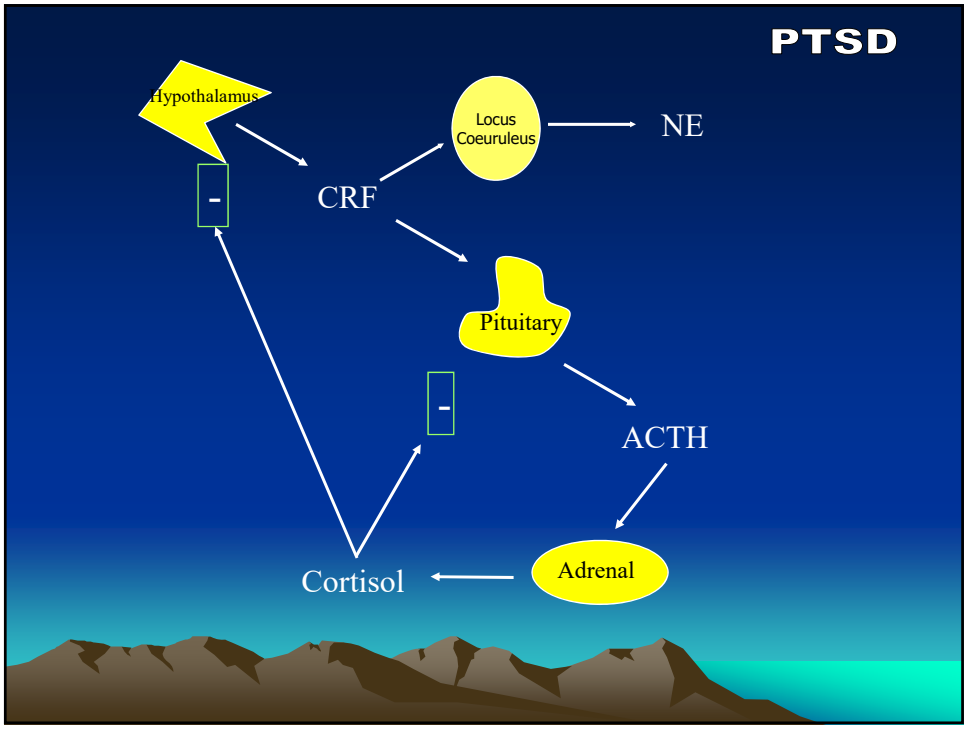
- Study of 45 combat veterans with combat related PTSD
  - 22 had psychotic features
- Severity of PTSD correlated with severity of psychosis
- Severity of psychosis did not correlate with severity of re-experiencing
  - Therefore not a re-experiencing symptom
  - Some symptoms were trauma congruent, some were not
- Psychosis occurred whether or not depression was present
  - Psychosis more severe if comorbid MDD
- Not known if antipsychotic drugs are necessary in psychotic PTSD

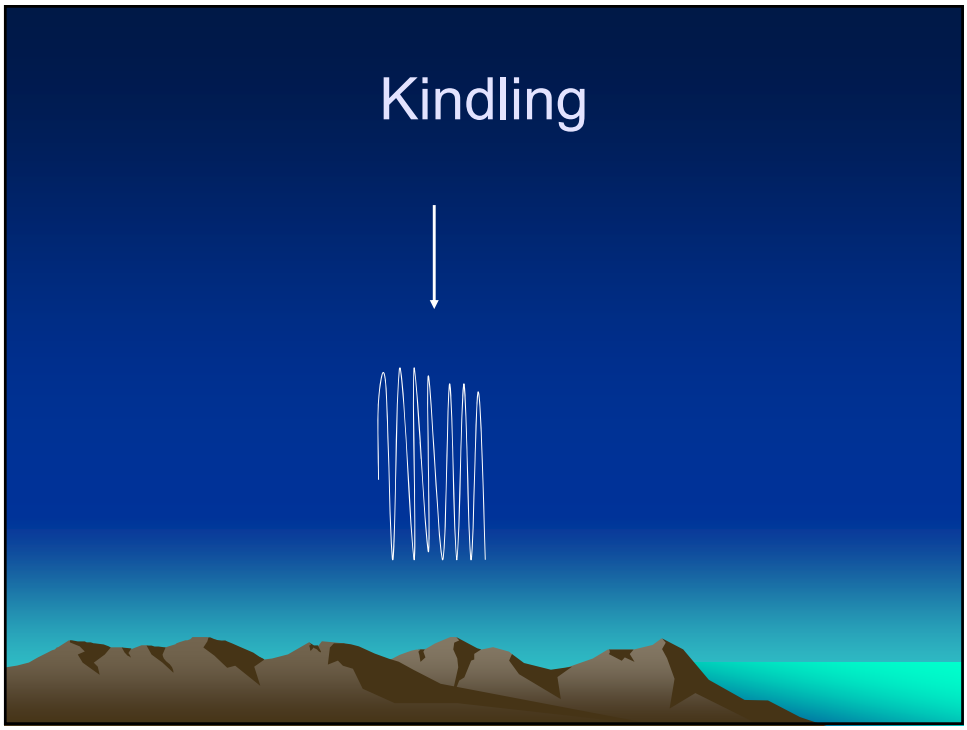
MB Hammer et al: Biol Psychiatry Biol Psychiatry 1999;45:846

Pathophysiology of PTSD

- Increased norepinephrine and epinephrine release
- Increased release of endogenous opioids
  - Elevated stimulus threshold
  - Analgesia
- ?dysregulated serotonin mediation of impulsivity and irritability
- Hyperactive stress response with burnout of stress hormones
  - Increased CRF
  - Blunted ACTH response to CRF
  - Decreased urinary cortisol
  - Increased dexamethasone suppression
  - Inability to muster appropriate response to daily stress
- Kindling and limbic sensitization
- Over-consolidation of fear memories




PTSD
Hypothalamus
Locus Coeuruleus
NE
-
CRF
Pituitary
-
ACTH
Adrenal
Cortisol


Kindling

Gene-Environment Interaction in PTSD

- COMT
  - Breaks down catecholamines
    - Norepinephrine, epinephrine, dopamine
  - Methionine (MET) instead of valine (VAL) at codon 158 of COMT gene decreases enzyme activity
    - More arousal in response to stress
- Study of 424 refugees from Rwanda genocide
  - Average of 13 different traumatic events per person
  - VAL/VAL and VAL/MET genotypes:
    - Increased traumatic load resulted in greater likelihood of PTSD
  - MET/MET genotype (lowest enzyme activity): High risk of PTSD regardless of traumatic load
  - More than 15 traumatic events: most people got PTSD regardless of genotype
- Implications:
  - Increased arousal predisposes to PTSD
  - Not everyone who is predisposed gets PTSD
  - Enough trauma will cause PTSD in anyone

Kolassa I-T et al: Biol Psychiatry 2010;67:304-308

Slide 1

Gene Environment Interactions in PTSD

- Study of 810 Ohio National Guard members
- Gene for β2 norepinephrine receptor
  - Greater activity + childhood adversity
    - Increased risk of PTSD
  - Low efficiency allele
    - Decreased sympathetic nervous system response to stress
    - Increased resilience
    - Resistance to PTSD
- Less responsiveness to stress conveys lower risk of PTSD

I Liberzon: JAMA Psychiatry 2014;71:1174-1182

Slide 2

Animal Studies of Stress Response Epigenetics

- Infants of mothers that groom a lot have
  - Smaller HPA axis response to stress
    - Less ACTH/corticosterone release
    - Better adaptation to stress
  - Increased grooming when they grow up
- Low grooming animals have more methylation of glucocorticoid receptor gene promoter
  - Decreases HPA axis modulation and increases stress response
- Cross fostering low groomed infants to high grooming mothers decreases methylation and moderates stress response
  - As adults, more grooming of their infants
- Implications: Genetic risk reduced by safe upbringing

SE Hyman: Nature Neuroscience 2009;12:241-243

Human Study of Stress Response Epigenetics

- Methylation of glucocorticoid receptor gene in hippocampus found in people with early trauma
- Results in decreased feedback inhibition of stress hormone release
- Leads to
  - Excessive response to all stresses
  - Decreased adaptation
  - Vulnerability to depression
  - Later burnout of HPA axis with PTSD
- Implication: Early trauma sensitizes the stress response system to later trauma

PO McGowan et al: Nature Neuroscience 2009;12:342-348

Epigenetics in Holocaust Families

- FKBP5 is a protein that regulates the glucocorticoid receptor (GR)
  - Decreases cortisol binding to GR
    - Increases stress response
- FKBP5 expression altered in PTSD and MDD
  - One site on FKBP5 (intron 7) is in region that alters GR response and influences FKBP5 transcription start site
    - Demethylated by cortisol and early trauma
- Study of 32 Holocaust survivors, 22 adult offspring and control parents and offspring
  - 52% had PTSD, 14% anxiety disorder other than PTSD, 31% mood disorder

Slide 1

R Yehuda et al: Biol Psychiatry 2016 doi:http://diagnosis.doi.org/10.1016/j.biopsych.2015.08.005

Epigenetics in Holocaust Families

- Parental Holocaust exposure predicted intron 7 methylation changes in parents and offspring, but in opposite directions
  - More methylation in Holocaust survivors
    - Less methylation in offspring
  - Not explained by early abuse of offspring
    - Physical abuse produced methylation at a different site
  - Less methylation associated with higher morning cortisol levels
    - Therefore offspring had more reactive cortisol stress response
    - Could create hyperactive HPA response to stress

Slide 2

R Yehuda et al: Biol Psychiatry 2016 doi:http://diagnosis.doi.org/10.1016/j.biopsych.2015.08.005

https://www.youtube.com/embed/3ZChSSw95Tg

Treatment Principles

- There is no definitive single treatment for PTSD
  - Multi-modal therapy aimed at different symptom networks
- Reduction of arousal necessary
- Medications alone are not sufficient
- Override fear conditioning
- Early re-exposure to traumatic situation with appropriate support can reduce symptoms
  - Reintegration with supports
  - Situation must be redefined as safe
  - Simply reliving stress aggravates distress
- Later reliving without mastery is often harmful
- Prolonged exposure most effective
- Mastery and control are crucial
- Adjunctive medications most useful after exposure sessions

Pharmacotherapy

- Beta blockers (e.g., propranolol)
  - Right after or during stress
  - During exposure therapy
- SSRIs
  - First line medication
  - Reduce arousal and intrusive thought and behavior
  - Facilitate fear extinction
  - Placebo controlled studies for sertraline, fluoxetine
  - Open studies for paroxetine, fluvoxamine
- MAO inhibitors
  - Older studies show efficacy, especially for arousal and intrusive recall
  - Potent REM suppression reduces nightmares
- Prazosin
  - Nightmares, insomnia, and arousal
  - Restores normal REM sleep for better processing of traumatic memories and reduces stage 2 traumatic nightmares

Slide 1

Pharmacotherapy

- Carbamazepine
  - Anti-kindling
  - Decreases anger, impulsivity, mood swings, recurrence
- Benzodiazepines
  - Can be helpful for arousal and insomnia
- Hydrocortisone
  - May enhance extinction when combined with fear reactivation
- Opioids (e.g., morphine)
  - Block fear conditioning
    - May be useful following trauma
  - Opioid signaling enhances fear extinction
- Clonidine
  - Open trials- helpful for arousal
  - Difficult to tolerate and to withdraw
- D-cycloserine
  - May facilitate prolonged exposure in people who do not respond to first few sessions
  - Better results with more severe PTSD
- THC, cannabinoids
  - Improve insomnia, nightmares, anxiety
  - May impair fear acquisition and enhance extinction

Slide 2

Fear Conditioning

Fear Extinction

Propranolol Treatment of Fear Conditioning

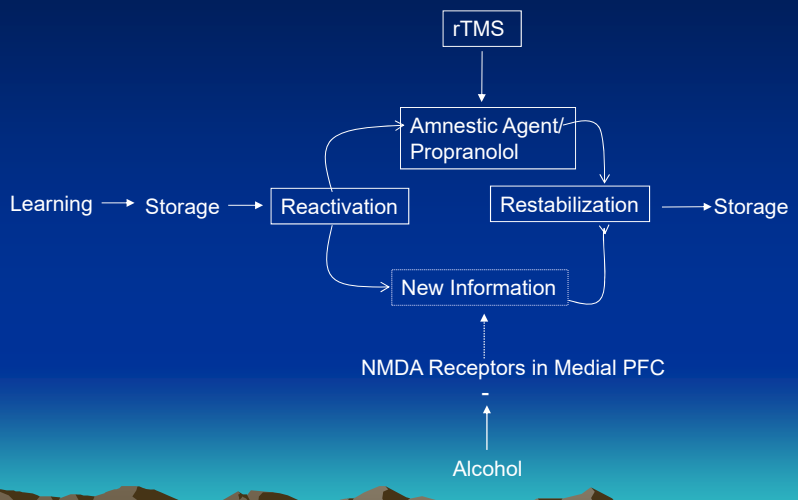
- Fear conditioning protocol
  - Measure startle response to loud noise
  - Fear acquisition: pair frightening stimulus (spiders) or neutral stimulus with noise
  - Memory reactivation: repeat association with or without 40 mg propranolol
  - Extinction/retesting
- Effect of propranolol during memory reactivation
  - No effect on acquisition of startle response or memory of association
  - Eliminated actual startle response after reactivation
- Conclusions
  - Fear conditioning can be reactivated into unstable state and then prevented from being consolidated again
  - Propranolol may decrease amygdala input into laying reactivated affective memory down as protein

M Kindt et al: Nature Neuroscience 2009;12:256-259

rTMS Promotes Fear Extinction

- Fear conditioning established by pairing light with finger shock in normal subjects
- Fear extinction by pairing light with no shock
  - rTMS over left posterior prefrontal cortex but not a nearby area when light presented enhanced extinction compared with no rTMS
- rTMS may alter amygdala output during fear rekindling to enhance extinction
- Could be adjunctive treatment during exposure therapy

Post Hoc Extinction Paradigm



S Kamboj, RK Das: JAMA Psychiatry 2/1/17

Psychotherapy

- Early re-exposure to traumatic situation can reduce symptoms
- Memory of fear conditioning can be overwritten when it is reactivated
  - Effective therapies reactivate fear memory and block reconsolidation
- Later reliving without fear extinction increases symptoms
- Provide safety but emphasize mastery
  - Model mugging
  - Increasing activity
- Reduce arousal
  - Learning is state dependent

Critical Incident Stress Debriefing

- Group approach
- 7 stages in one session
  - Introduction
  - Describe event
  - Describe what one thought after the event
  - Describe what one felt after the event
  - Describe specific symptoms such as anger or tremor
  - Education about stress management
  - Answer questions and end on positive note
- No evidence of efficacy
- May make symptoms worse
  - Reliving without resolution
  - No time or opportunity for processing of experience
  - Arousal and helplessness without mastery
  - No attempt to re-immerse in vivo with victim feeling safe
  - Increased guilt and shame at not recovering
- Practice guidelines recommend against routine use of CISD

Sijbrandij et al: Br J Psychiatry 2006;189:150

Crisis Counseling

- Most stress reactions are time-limited, normal responses rather than PTSD
- Brief counseling initial intervention
- Multiple sessions
- Education
- Mobilize supports
- Screen for PTSD
- Refer for persistent distress or complex symptoms

Evidence Based Psychotherapies

- Cognitive behavior treatments that attend to
  - Details of trauma
  - Associated emotions
  - Cognitions
- Trauma based therapies
  - Cognitive processing therapy
  - Prolonged exposure
  - Eye movement desensitization and reprocessing
- Stress inoculation training not specifically trauma focused

Cognitive Behavior Therapy (Cognitive Processing Therapy, CPT)

- 12 group or individual sessions
- Manualized
- Identifies, challenges and replaces maladaptive cognitions
- Discussion of treatment rationale
- Relaxation/deep breathing
- Imaginal exposure
- Gradual "in vivo" exposure
- Cognitive restructuring
  - Redefinition of situation
  - Elimination of global catastrophic thinking
- Relapse prevention
- Homework
  - Imaginal followed by in vivo exposure
  - 2 assignments involve writing about traumatic experience
  - Cognitive reprocessing
- Effective in controlled studies
- >TAU in World Trade Center disaster workers

Difiede et al: JNMD 2007;195:861

Controlled Studies of CPT in Combat PTSD

- 5 studies
  - 481 patients
  - 1 study compared group to telemedicine CPT
- Effect size 0.78-1.10
  - Compared with no treatment or TAU
- 2/3 had meaningful symptom improvement
  - Post-treatment symptoms still above clinical threshold
  - Most patients still had PTSD
- Marginally better than non-trauma focused therapies

MM Steenkamp et al: JAMA 2015;314:489-500

Group vs Individual Cognitive Processing Therapy

- 268 active duty servicemembers with PTSD
  - Random assignment to biweekly CPT for 6 weeks
    - Group (90 minute sessions)
    - Individual (60 minute sessions)
- Assessment at end of treatment and 6 months later showed
  - Individual had twice as much symptom reduction as group (ES 1.2 vs 0.6)
  - No difference in remission of PTSD
    - >51-63% still had PTSD
  - Only 58% completed at least 9/12 sessions
- Conclusions:
  - Individual>group CPT
  - Group still moderately effective
  - Longer and more comprehensive treatment probably necessary for remission

PA Resick et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2016.2729

Prolonged Exposure

- Targets trauma memories
- Confront rather than avoid feared memories and stimuli
- Promotes fear extinction
  - Replaces fearful association with safe association
- Repeatedly describe event with therapist
  - Record and then listen to description
  - Imaginal exposure
- In vivo exposure
- Affect management
- Cognitive restructuring
- Desensitization

Controlled Studies of PE in Combat PTSD

- 4 RCTs
  - 402 patients
- Effect size 0.80-1.80
- 70% had clinically meaningful symptom reduction
- 61% still had PTSD at end of treatment

MM Steenkamp et al: JAMA 2015;314:489-500

Written Exposure Therapy (WET)

- Five individual sessions
- Patients spend half of each session writing accounts of traumatic events and their reactions
- Written account then reviewed in session
- No homework
- Less therapist training required
- Less work for patient
- Randomized comparison to 12 session individual CPT
  - Equivalent reduction of PTSD symptoms
  - Equivalent remission of PTSD diagnosis (>50%)
  - Significantly fewer dropouts (6% vs 40%)

DM Sloan et al: JAMA Psychiatry doi:10.1001/jamapsychiatry.2017.4249

EMDR

- Brief sessions of attending to emotionally disturbing material
  - Focus on external stimulus (eye movements) at same time
- Identify sensations associated with image
- Identify aversive cognitions associated with trauma
  - Replace with alternative positive cognition

Controlled Studies of EMDR in Combat PTSD

- Small samples
- 1-3 sessions
- Poor methodology
- EMDR = similar therapy without eye tracking= non-trauma focused therapy>wait list

MM Steenkamp et al: JAMA 2015;314:489-500

Head to Head Comparison

- 207 patients with Iraq or Afghanistan combat related PTSD
- Random assignment to
  - PE (13 90-minute sessions) + pill placebo
  - Sertraline (mean dose 171 mg) + enhanced medication management
    - 30 minute medication management sessions
  - PE + sertraline
- 24 week trial

Slide 1

SAM Rauch: JAMA Psychiatry doi:10.1001/jamapsychiatry.2018.3412

Head to Head Comparison

- Equivalent CAPS score reductions with all treatment groups
  - Sertraline:
    - Initial 75.5
    - Final 41.7 (55% of baseline)
  - PE + placebo
    - Initial 80.9
    - Final 51.5 (64%)
  - PE + sertraline
    - Initial 76.0
    - Final 43.3 (57%)

Slide 2

SAM Rauch: JAMA Psychiatry doi:10.1001/jamapsychiatry.2018.3412

Head to Head Comparison

- Conclusions
  - Response of combat PTSD to standard therapies is limited
    - Combined treatment does not seem superior to medication
    - More dropouts with PE
  - Civilian PTSD may have different response pattern
  - Extended med management sessions could have facilitated patient self-exposure
  - We need more data on response of specific PTSD domains to different treatments

Slide 3

SAM Rauch: JAMA Psychiatry doi:10.1001/jamapsychiatry.2018.3412

Stress Inoculation Training

- Anxiety management skills
  - Relaxation training
  - Breathing retraining
  - Positive self-talk
- Assertiveness training
- Thought stopping
- Cognitive restructuring and exposure optional

Summary of PTSD Treatment Studies

- CPT and PE have large effect sizes
- 1/3-1/2 of patients do not have meaningful symptom change
- 2/3 still have residual PTSD symptoms
  - Remission uncommon
- Not always more effective than non-trauma focused therapies
- Outcomes not as good in veterans
  - Comorbidity
  - Compensation factors may inhibit response

MM Steenkamp et al: JAMA 2015;314:489-500

Medication Trials in Juvenile PTSD

- 3 DBPC studies of SSRIs
  - One negative study
  - Limited support for SSRIs as first line pharmacologic treatments in this population
- One controlled IMI study
- Open label studies of
  - Other antidepressants
  - Anti-adrenergics
  - Atypical antipsychotics
- Anti-adrenergics may be promising
  - Clonidine, propranolol for arousal
  - Prazosin for nightmares
  - More data needed
- Benzodiazepines not found to be helpful for PTSD symptoms
- Insufficient data on combined psychotherapy-pharmacotherapy
  - May be no benefit of early combined treatment even if comorbid MDD
  - Begin with CPT and add SSRI if incomplete response

JR Strawn et al: J Clin Psychiatry 2010;71:932; Cochrane Reviews 7: CD007316, 2010; AACAP: Journal of the Am Acad Child Adolesc Psychiatry 2010:49:414

Project Liberty

- FEMA funding
- Organized by NYS Office of Mental Health
- All services free
- Recipients remained anonymous
- Served 686,848 people
- Public education for another 550,000

Slide 1

Project Liberty

- Protocol
  - PTSD screening questionnaire
  - 10-12 sessions
  - CBT
    - Recognize post-disaster distress
    - Skills to deal with anxiety and depression
    - Cognitive reframing
  - Help with grief
  - Techniques for dealing with guilt
  - Homework assignments
- Specialized treatment for persistent PTSD and depression
  - Required by 9%

Slide 2

Donahue et al: Psychiatric Services 57:1298, 2006

President Bush as National Therapist

- Prompt exposure to stress
- Emphasize mastery
- Produce a sense of safety
- Express affect
- Promote attachment and affiliation
- Take action
- Maintain optimism

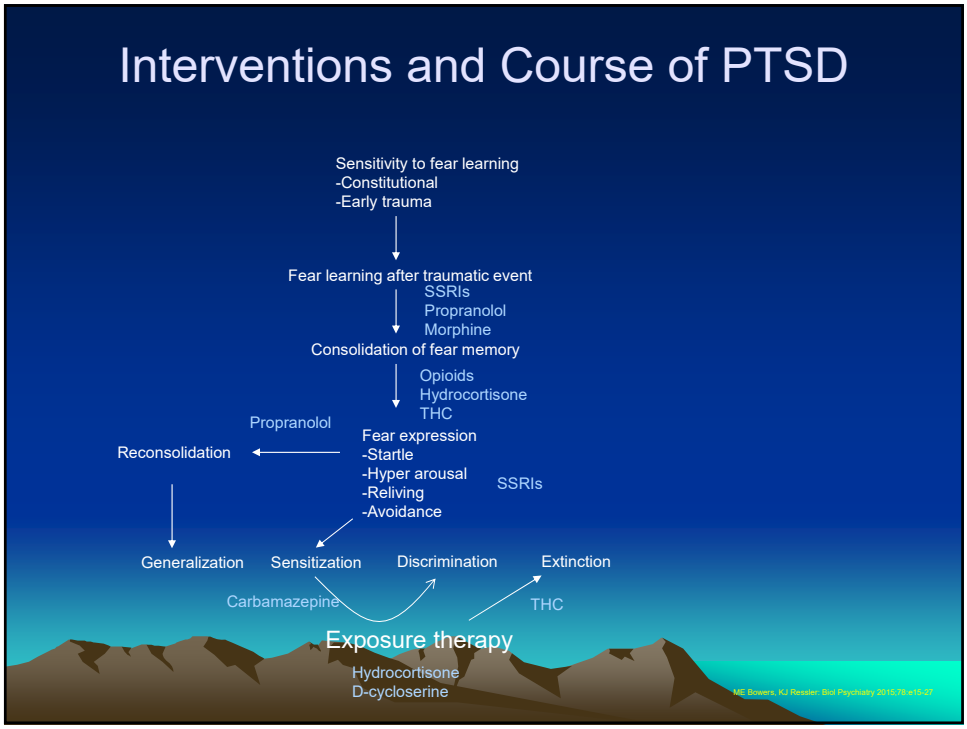
PTSD

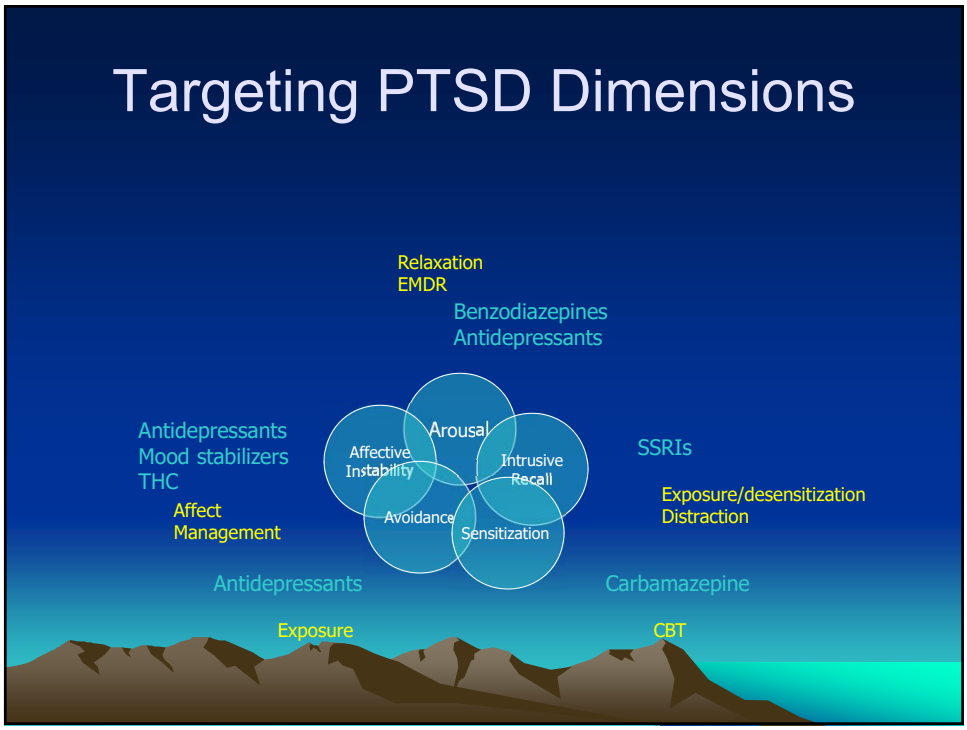
Danger
Tension
Excessive arousal
Helplessness
Passivity
Loss of control
Victimhood

CURE

Safety
Relaxation
Calm
Confidence
Activity
Mastery
Active engagement

Safe environment
Reduce arousal
Relaxation training
Exposure
Encourage active engagement
Competence skills
Move out of victim identity
Overcome; don't just survive


Interventions and Course of PTSD
Sensitivity to fear learning
-Constitutional
-Early trauma
Fear learning after traumatic event
SSRIs
Propranolol
Morphine
Consolidation of fear memory
Opioids
Hydrocortisone
THC
Propranolol
Reconsolidation
Fear expression
-Startle
-Hyper arousal
-Reliving
-Avoidance
SSRIs
Generalization
Sensitization
Discrimination
Extinction
Carbamazepine
THC
Exposure therapy
Hydrocortisone
D-cycloserine
ME Bowers, KJ Ressler: Biol Psychiatry 2015;78:e15-27


Targeting PTSD Dimensions
Relaxation
EMDR
Benzodiazepines
Antidepressants
Antidepressants
Mood stabilizers
THC
Affect
Management
Arousal
Affective
Instability
Intrusive
Recall
Avoidance
Sensitization
SSRIs
Exposure/desensitization
Distraction
Antidepressants
Carbamazepine
Exposure
CBT

What to Tell the Media

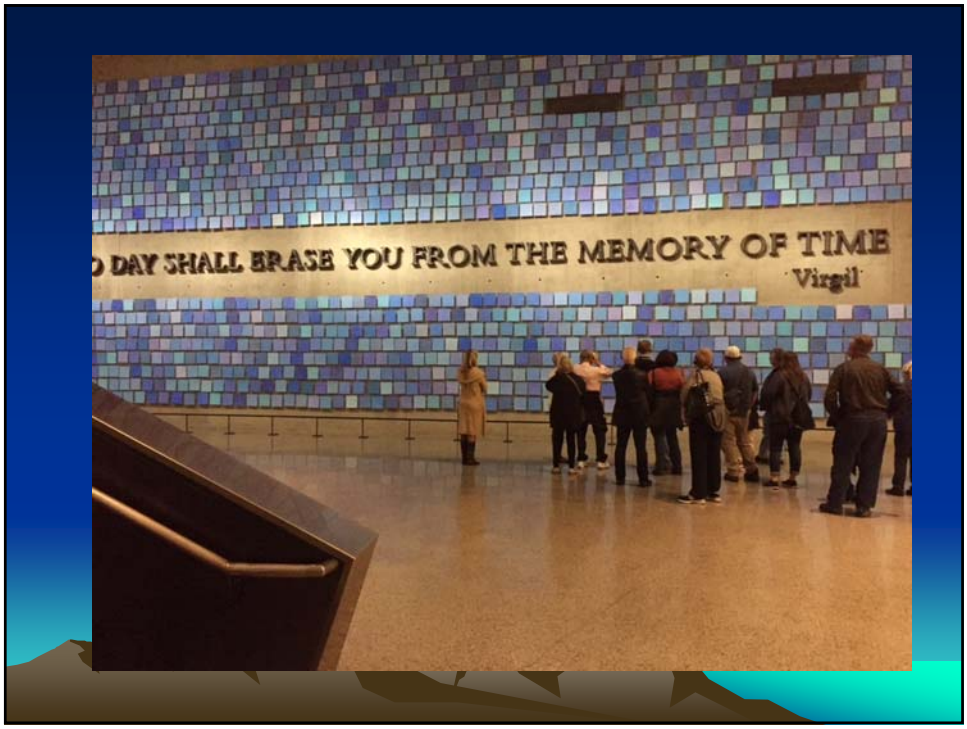
Nothing

Challenges to Clinicians, Helpers and Society

- It is impossible to avoid identifying with victim
  - Inhuman trauma
  - Overwhelmed victim
  - Sensitization to trauma by media coverage
- Complex goals
  - Safety and protection
  - Promote competence and independence
  - Confront negative attachments
  - Foster positive attachments
  - Empathize with emotions
  - Support strengths
  - Avoid victimhood
- You cannot provide comprehensive care by yourself

Conclusions

- Traumatic events are common
- PTSD is often overlooked or untreated
- Past trauma predisposes to future PTSD
- Treatments improve dimensions of PTSD
- Immediate exposure can reduce symptoms
- Living in the past can increase symptoms
- Anything that promotes mastery can help PTSD



OCD

Pathophysiology

- Hyperactivity of right caudate
  - Decreased by SSRIs and behavior therapy
- Increased frontostriatal connectivity
  - Nucleus accumbens to lateral and medial prefrontal cortex
  - Overrides environmental-responsive systems with internally generated drives
  - DBS decreases hyperactive connectivity

M Figee et al: Nature Neuroscience 2013;16:386

Treatment Efficacy in OCD

- SRIs
  - High doses usually needed
  - 40-50% improvement
  - Improvement abates with medication discontinuation
  - Meta analyses demonstrate greater efficacy of clomipramine than SSRIs
    - Earlier studies suggesting superiority of clomipramine probably biased by lack of alternative treatments
- One study suggested effectiveness of venlafaxine in 39 refractory OCD patients
- Exposure and response prevention with CBT
  - 70% improvement
  - Benefit persists after treatment discontinuation

Hollander 2003

Augmentation

- Antipsychotic drugs
  - Best for overvalued or delusional obsessions
- Benzodiazepines
  - May be helpful for severe anxiety with behavior therapy
    - State dependent learning could occur
- MAOIs
  - Early studies suggest some efficacy but cannot be combined with SRIs

Surgical Treatment of OCD

- Subcaudate tractotomy
- Cingulotomy
- Limbic leukotomy
- Capsulotomy
  - Most effective

Typical Surgical Patient

- Average duration of illness: 24 years
- Mean number of Axis I diagnoses: 3
- Average number of medication trials: 24
- Percent having had ECT: ¾ (mean number of treatments 15)
- Preoperative GAF score: 20-45
- Preoperative Y-BOCS score: 35/40

Ventral Capsulotomy for OCD

- 16 patients with refractory OCD randomized to real or sham bilateral gamma knife lesion in ventral internal capsule
- After one year, 4 sham surgery patients received open capsulotomy
- Overall response rate (35% improvement) 58% with active surgery over 4 years
- Response rate to sham surgery = 0

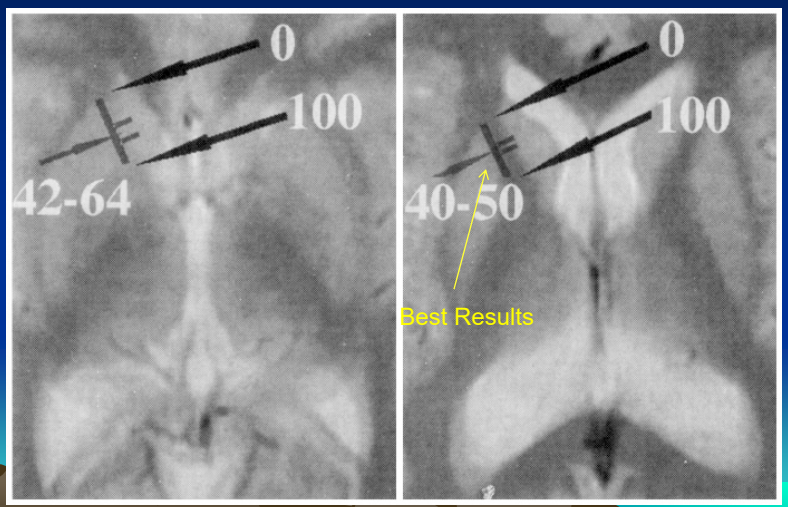
AC Lozano et al. JAMA Psychiatry doi:10.10100/jamapsychiatry.2014.1193

Capsulotomy for OCD

- Increased right caudate rCBF in prefrontal cortex
- Interruption of pathways in internal capsule between frontal lobe and thalamus
- Thermal lesion or gamma knife
- Right sided anterior lesion seems associated with best response
  - Extending lesion in case of nonresponse not helpful
- Several hundred patients with very refractory chronic OCD studied
  - All treatments tried
  - No controls
- 1/3-2/3 of patients improved

Lippitz BE et al: Neurosurgery 1999;44:452-460; Jenike MA: Br J Psychiatry 1998;173(35S):79-90

Capsulotomy- Anterior Limb of Internal Capsule



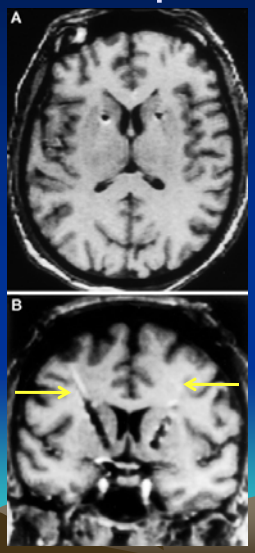
Deep Brain Stimulation for OCD

- Reversible
- Makes controlled studies possible
- Electrodes placed in anterior limb of internal capsule bilaterally
  - Similar to targets in capsulotomy
- Y-BOCS scores 35% lower with stimulation on versus off in blinded on-off paradigm in about 2/3 of patients followed
  - About 30 patients reported

Internal Capsule Deep Brain Stimulation for OCD

- Reversible
- Makes controlled studies possible
- Electrodes placed in anterior limb of internal capsule bilaterally
  - Similar to targets in capsulotomy
- Y-BOCS scores 35% lower with stimulation on versus off in blinded on-off paradigm in about 2/3 of patients followed
  - About 20 patients reported

Electrode in Anterior Limb of Internal Capsule



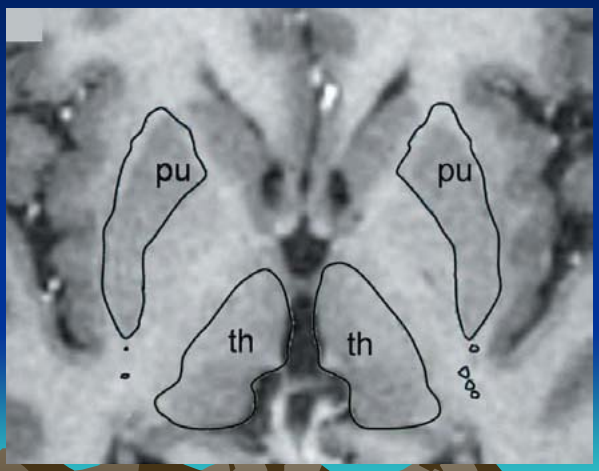
Subthalamic DBS

- Randomized double-blind multicenter crossover study
- 16 patients with very refractory OCD
  - Mean illness duration 18 years
  - Y-BOCS 27-37
  - CGI 6-7
  - GAF 25-37
  - All but 2 on SRI/SNRI with augmentation
- 3 months treatment, 1 month washout between treatments
- Real-washout-sham or sham-washout-real
- Electrode in anteromedial subthalamic nucleus
  - Border of associative and limbic regions
  - Bilateral stimulation for all but 2 patients

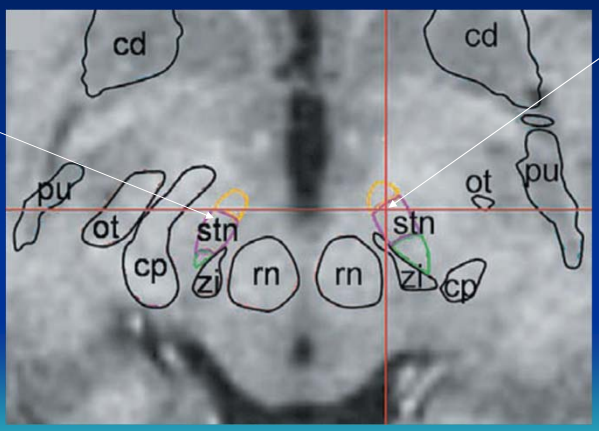
Slide 1

L. Mallet et al: NEJM 359:2121-2134, 2008

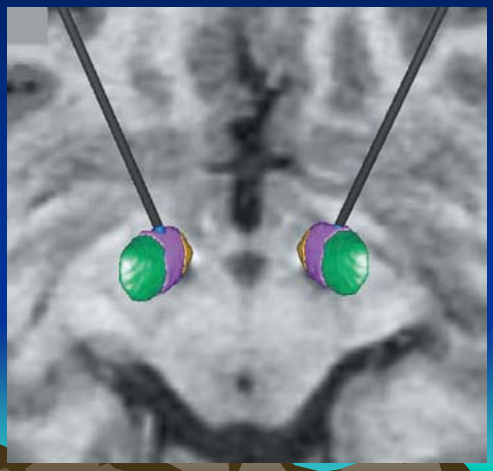
Target Area Showing Putamen and Thalamus



Electrode Target



Electrodes in Associative Area



Subthalamic DBS

- Y-BOCS change with stimulation
  - Sham: 28-30
  - Active: 30-19
  - Benefit lost with termination of stimulation
- GAF:
  - Sham: 40-41
  - Active: 39-52
- No change in depression, anxiety or disability
- Response (25% improvement)
  - YBOCS: 38% (sham) versus 75% (active)
  - GAF: 38% (sham) versus 100% (active)

Slide 2

L. Mallet et al: NEJM 359:2121-2134, 2008

Subthalamic DBS

- Adverse events
  - Intracerebral hemorrhage with paralysis of a finger: 1 patient
  - Infection: 2 patients
  - Transient hypomania: 4 patients
  - Transient anxiety: 2 patients
  - Transient dyskinesias: 1patient
  - Transient dysphagia: 1 patient

Slide 3

L. Mallet et al: NEJM 359:2121-2134, 2008

DBS of Ventral Internal Capsule/Ventral Striatum

- 8 years experience of 4 groups
  - Leuven/Antwerp
  - Butler Hospital
  - Cleveland Clinic
  - University of Florida
- 26 patients
- Mean follow-up 31 months
- More posterior targets more effective
- 20 point increase in GAF
  - >60% had clinically significant functional improvement
- HRSD decreased 43%
- Non-OCD anxiety scores decreased by 59%

Slide 1

BD Greenberg et al: Mol Psychiatry 2008;55:1-16

DBS of Ventral Internal Capsule/Ventral Striatum

- Complications
  - 2 intracerebral bleeds
    - Resolved spontaneously
  - 1 patient had a single seizure
  - One superficial wound infection
  - Two breaks in leads/wires
  - 3 patients had increased depression
  - Slight hypomania in 3
- No change in cognition

Slide 2

BD Greenberg et al: Mol Psychiatry 2008;55:1-16

DBS of Nucleus Accumbens

- 16 patients with refractory OCD
  - Duration of illness 8-48 years
  - 7-13 medication trials
  - Up to 8 CBT trials
- Bilateral DBS in nucleus accumbens
- 8 month open label treatment
- 2 weeks of double-blind random assignment to real or sham DBS followed by 2 weeks of opposite condition
- One year of open maintenance DBS

Slide 1

D Denys et al: Arch Gen Psychiatry 2010;67:1061-1068

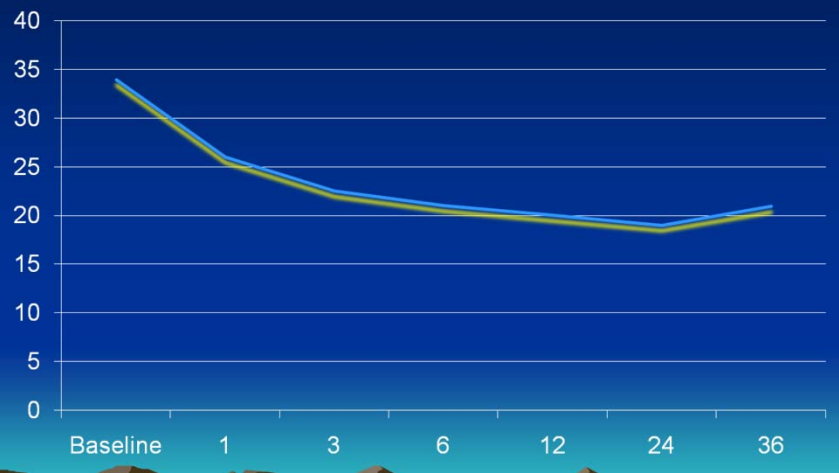
DBS of Nucleus Accumbens

- YBOC scores decreased overall by 52% over 21 month study
  - Half of patients were responders (≥35% decrease)
    - Mean decrease in YBOC in this group = 71%
- Worst response in patients with hoarding, perfectionism, symmetry
- Anxiety and depression decreased in responders and nonresponders
- Interrupting limbic or striatal circuits may be preferable for different OCD subtypes

Slide 2

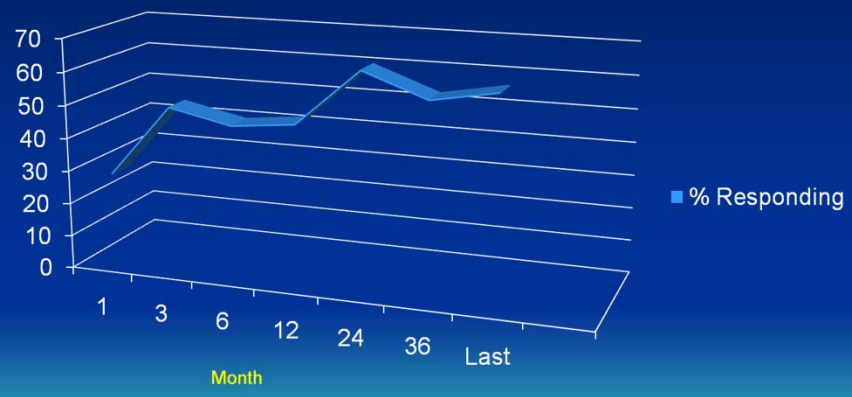
D Denys et al: Arch Gen Psychiatry 2010;67:1061-1068

YBOCS Severity Changes with DBS



BD Greenberg et al: Mol Psychiatry 2008;55:1-16

Percent Responding to DBS (35% Decrease in YBOCS)



BD Greenberg et al: Mol Psychiatry 2008;55:1-16

Cognitive Therapy of Childhood OCD

- CBT is initial treatment of choice
  - Exposure + response prevention
  - Cognitive therapy of expectations/beliefs
- Validated in younger patients
- 70% improvement
- Improvement persists after CBT discontinuation
- Cognitive therapy without behavioral component may be helpful for some children and adolescents
- Poor response to CBT predicted by
  - Low insight
  - Family accomodation
  - Comorbidity
  - Cognitive deficits

ME Franklin et al in Evidence based psychotherapies for chilren and adolescents. New York, Guilford, pp 80-92; TI Williams et al: Eur Child Adolesc Psychiatry 201

Pharmacotherapy of Childhood OCD

- Sertraline, fluoxetine and fluvoxamine approved in U.S. for pediatric OCD
- SSRIs are first-line pharmacotherapy
- Clomipramine reduced OCD symptoms by 50% over one year
  - Only one study of this medication in pediatric OCD
  - Second-line treatment because of adverse effects and need for cardiac monitoring
- Two long-term fluoxetine trials found no superiority over placebo for relapse prevention
- High rate of discontinuation of long-term SSRI treatment

Conclusions

- Benzodiazepines still the most effective anxiolytics
  - Risks of psychomotor impairment
- Hypnotics are most appropriate for acute, stress related insomnia
- In secondary insomnia, the primary disorder should be treated adequately before long-term hypnotic treatment is determined to be necessary
- DTC advertising and clinician symposia and reviews overestimate applications of sleeping pills
- Suvorexant studied in higher than approved doses in nonpsychiatric individuals
- Nonpharmacological interventions almost always beat medications in head-to-head comparisons in acute, chronic, primary and secondary insomnia

Slide 1

Conclusions

- Many clinicians are unfamiliar with structured therapies for insomnia
- Many patients confuse treatment of insomnia with living a better life
- A demand for a sleeping pill is not the same thing as a clinical indication
- Non-benzodiazepine medicatiions act on the benzodiazepine receptor
- Melatonin receptor agonists act on melatonin receptors; so does melatonin
- Single session debriefing is not effective for PTSD
  - CBT related therapies are effective
- Medications treat dimensions of PTSD, not the entire disorder
- Outcomes in PTSD remain incomplete
  - Especially combat PTSD
- Behavior therapy beats medications for OCD but more difficult to administer
  - Combinations may not be > behavior therapy alone
- Neurosurgical approaches appear promising, especially DBS

Slide 2