Benzodiazepines: Safe Prescribing in the Era of Prescription Drug Abuse

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Disclosure

Dr. Hamilton is a
paid consultant & speaker for
Myriad Neuroscience.

Skin, Bones, Hearts & Private Parts

Learning Objectives

By the end of this presentation, attendees will be able to:

- differentiate between FDA approved & off-label uses of benzodiazepines for varied symptom presentations *(Rx)*
- review and reconceptualize neurobiological mechanisms that underlie anxiety symptoms
- identify & discuss the pharmacokinetics that lead to potential drug-drug interactions when patients concurrently use benzodiazepines with other medications *(Rx)*
- formulate rational, genomically-informed pharmacologic treatment approaches for anxiety disorders (including the appropriate use of benzodiazepines) *(Rx)*
- identify & discuss techniques to safely taper & discontinue benzodiazepines with minimal discomfort to the patient *(Rx)*

The Benzodiazepine Controversy

Spectrum of attitudes toward prescribing benzodiazepines

Conservative
Only for alcohol withdrawal and acute mania in supervised setting

Moderate
Short-term use for insomnia, panic in those without active substance use disorder (SUD)

Liberal
Long-term use for patients with psychosis or anxiety, even those with a SUD history.

http://www.psychiatrictimes.com/articles/religion-benzodiazepines

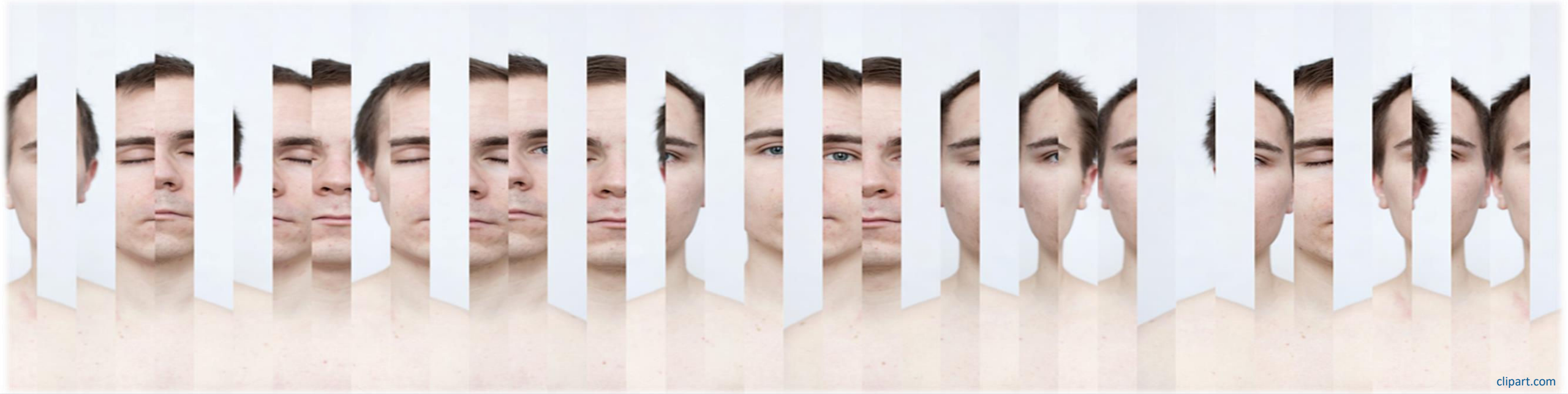
Benzodiazepines (BZDs)

- **Best for acute anxiety & specific phobias**
  - Flying, closed spaces, panic attacks, situational anxiety
- Rapid onset → Rapid relief
- Half-life of drugs varies widely
- May also be used for other conditions:
  - Seizures, acute psychosis, muscle relaxation, amnesic actions & insomnia
  - withdrawal from ETOH, BZDs & Barbiturates
- Enhances GABA-A, reducing excitability associated with anxiety states
- May contribute to feeling of euphoria
- May contribute to physiological dependency & psychological addiction

The brain doesn't care about the DSM-5!

Symptom-based treatment strategy:

1. Deconstruct into component symptoms
2. Match to brain circuits/NTs
3. Select therapies rationally



Neuroanatomy of Anxiety

- **Amygdala**
  - processing emotionally salient stimuli
- **Medial PFC**
  - modulation of affect
- **Hippocampus**
  - memory encoding & retrieval
- **CTSC**
  - “Worry loops”

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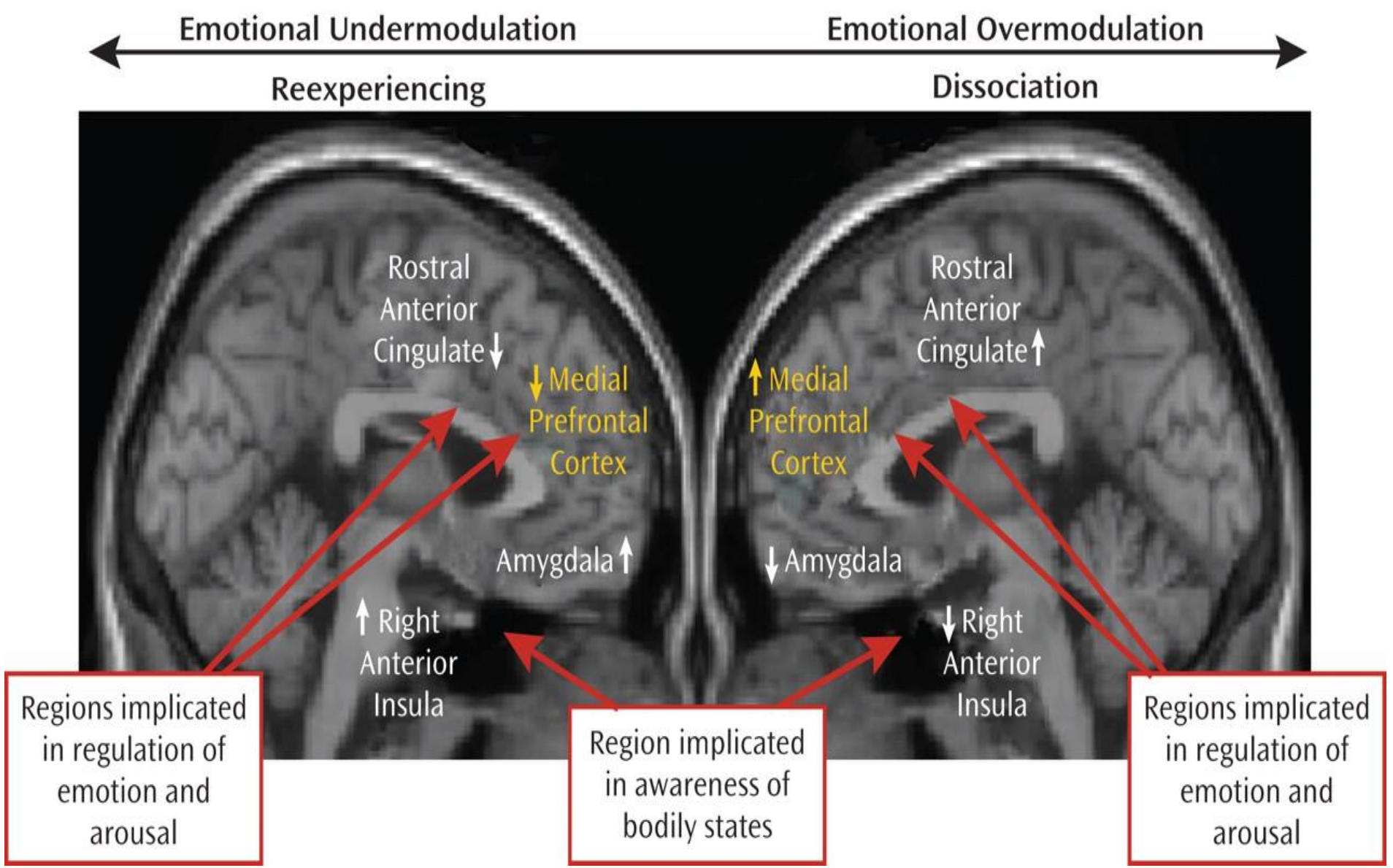

Lanius, Vermetten, Loewenstein, et al (2010). Emotion Modulation in PTSD. *Am J Psychiatry* (167): p 640-647.

Stress Diathesis & Anxiety

- **Neurohormonal responses to stress**
  - Pituitary ➔ adrenal cortisol
  - Catecholamine production
  - CRF produced in hypothalamus
  - Increased HPA activity ➔ stress reactivity

FEAR: Neurobiological Regulators

- GABA
- 5HT
- NE
- Voltage-gated calcium channels

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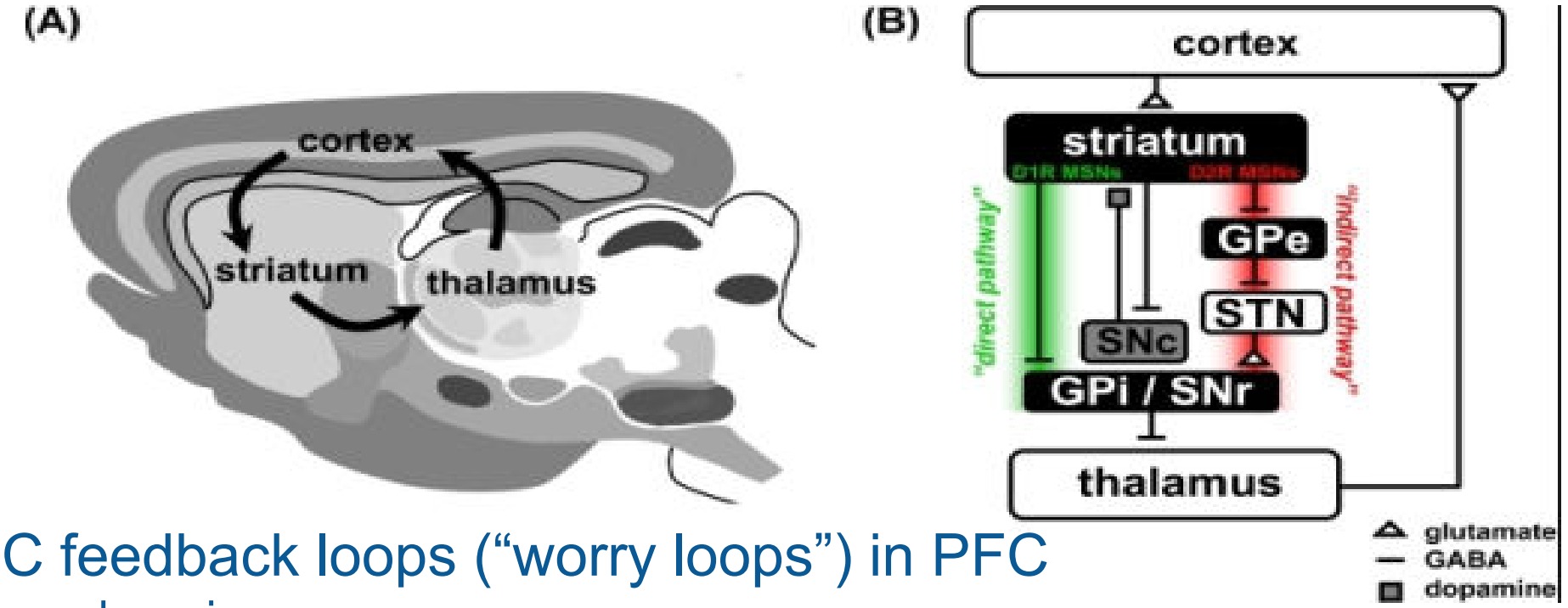
WORRY



- CTSC feedback loops ("worry loops") in PFC
  - Apprehension
  - Obsession
  - Catastrophizing
  - Anxious Misery
- Ruminations and delusions?

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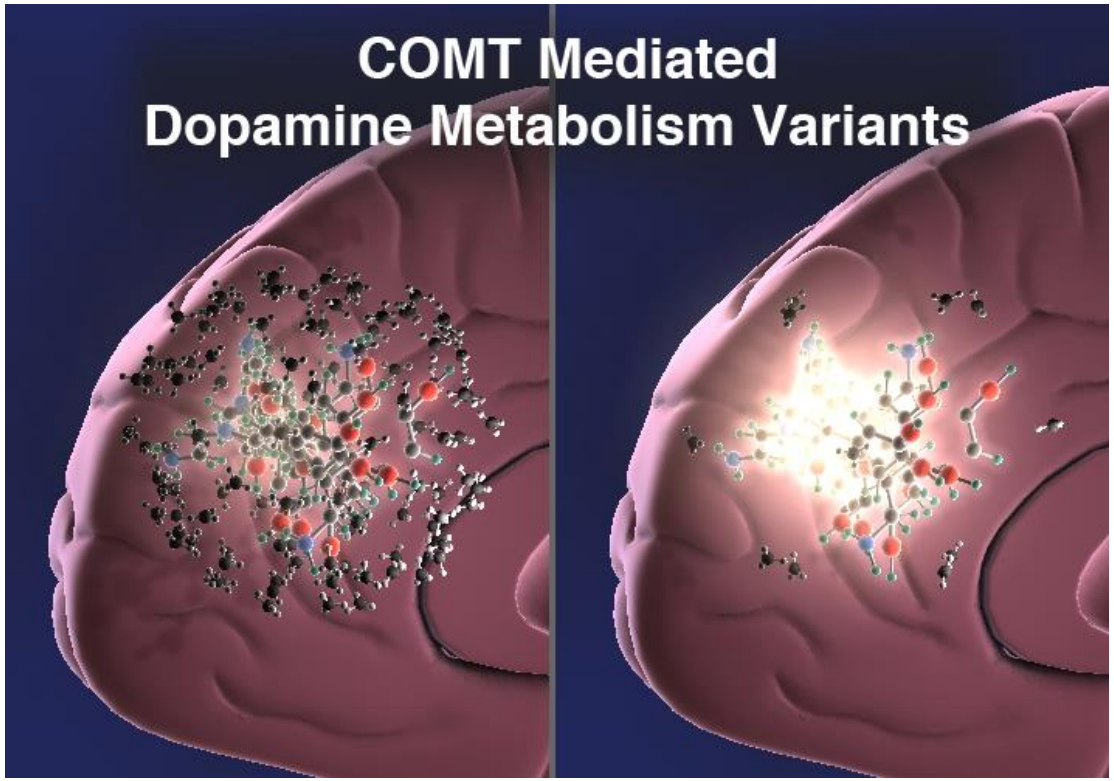
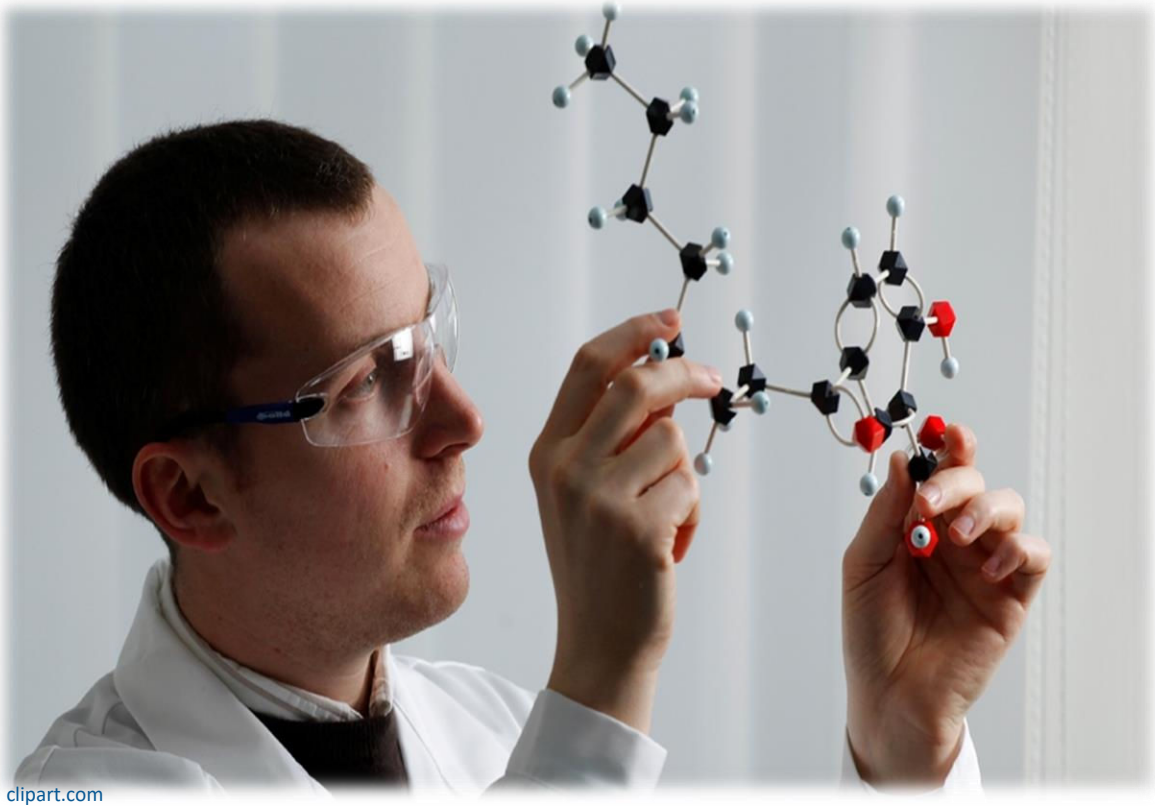
WORRY: Neurobiological Regulators

- 5HT
- GABA
- DA (COMT)
- NE
- Glutamate
- Voltage-gated ion channels



Pharmacotherapeutics for Anxiety



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$\alpha_2\delta$ ligands

- gabapentin
- pregabalin

Serotonergics

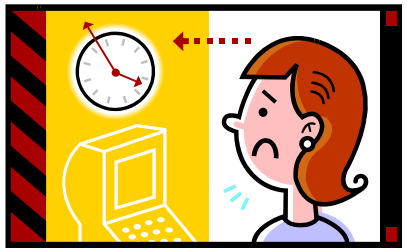
- SERT inhibitors
- buspirone (BuSpar®)

Noradrenergics

- α_1 blockers
- NET inhibitors

Benzodiazepines

Generalized Anxiety Disorder



Panic Disorder

Panic Disorder Etiology

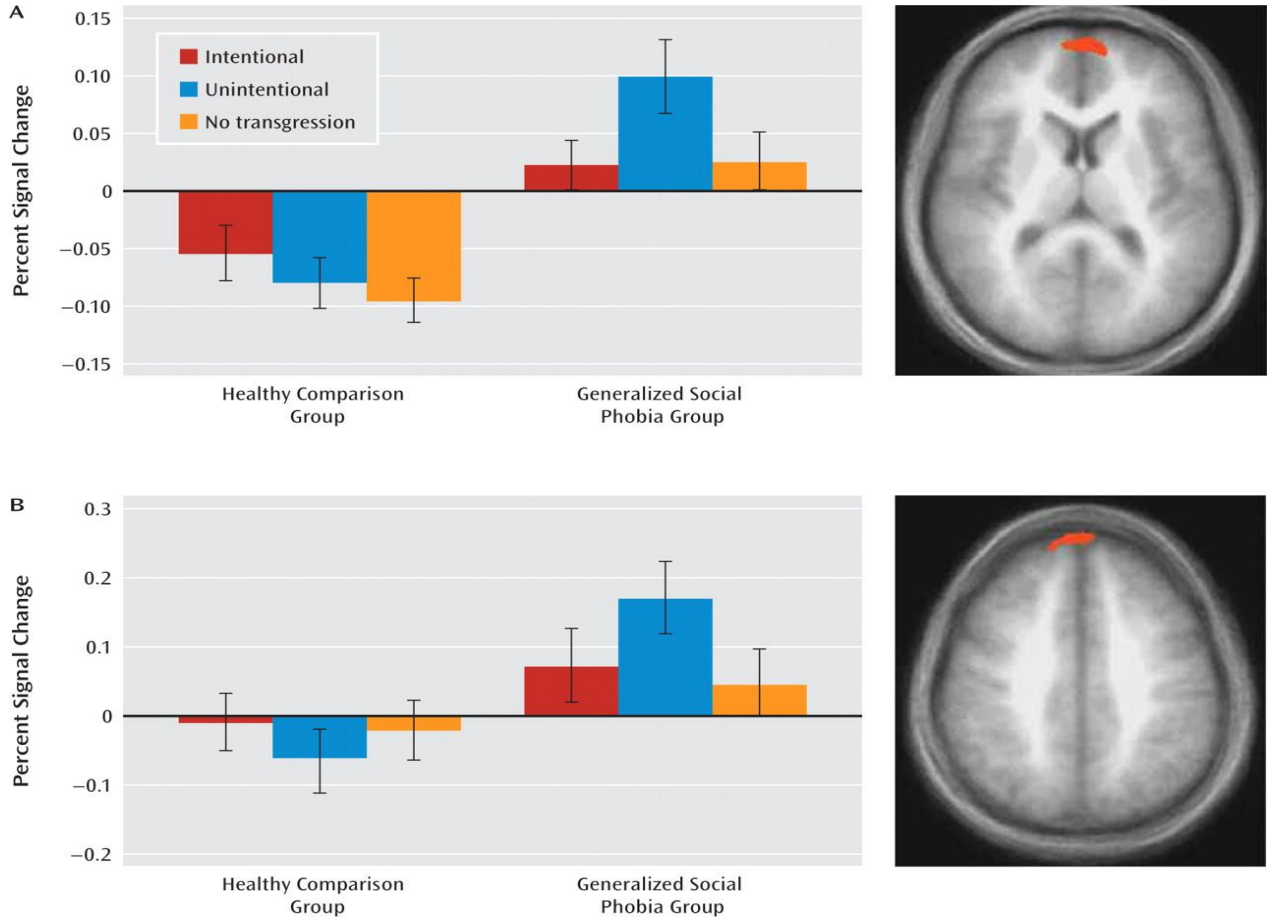
- Drug/Alcohol
- Genetics
- Social learning
- Cognitive theories
- Neurobiology/conditioned fear
- Psychosocial stressors
  - Prior separation anxiety

Treatment of Panic Disorder

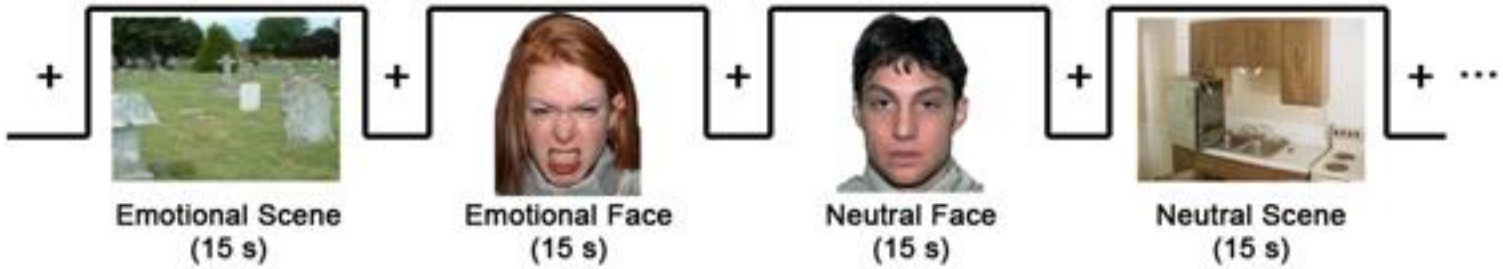
- ≥70% treatment response
- Educate, reassure, eliminate caffeine, AOD, stimulants
- CBT
- Medications
  - SSRIs/SNRIs
  - short-term “rescue” BZD
  - Neurontin, Lyrica
  - TCAs & MAOIs

Social Anxiety Disorder

What's going on in the brain?



What's going on in the brain?



- Both groups ↑ medial PFC activity in response to intentional vs. unintentional transgression.
- Social Anxiety Disorder:
  - significant response to unintentional transgression
  - significant increased activity in amygdala & insula

Treatment: Social Anxiety Disorder

- **Social skills, bx therapy, CBT**
- **Pharmacotherapy**
  - First-line BZD not generally accepted
  - Less evidence: sedating ADs & older ADs
  - β blockers (for discrete situations)
  - Naltrexone & acamprosate?

Obsessive-Compulsive & Related Disorders

- Obsessive-Compulsive Disorder
- Body Dysmorphic Disorder
- Hoarding Disorder
- Trichotillomania
- Excoriation Disorder

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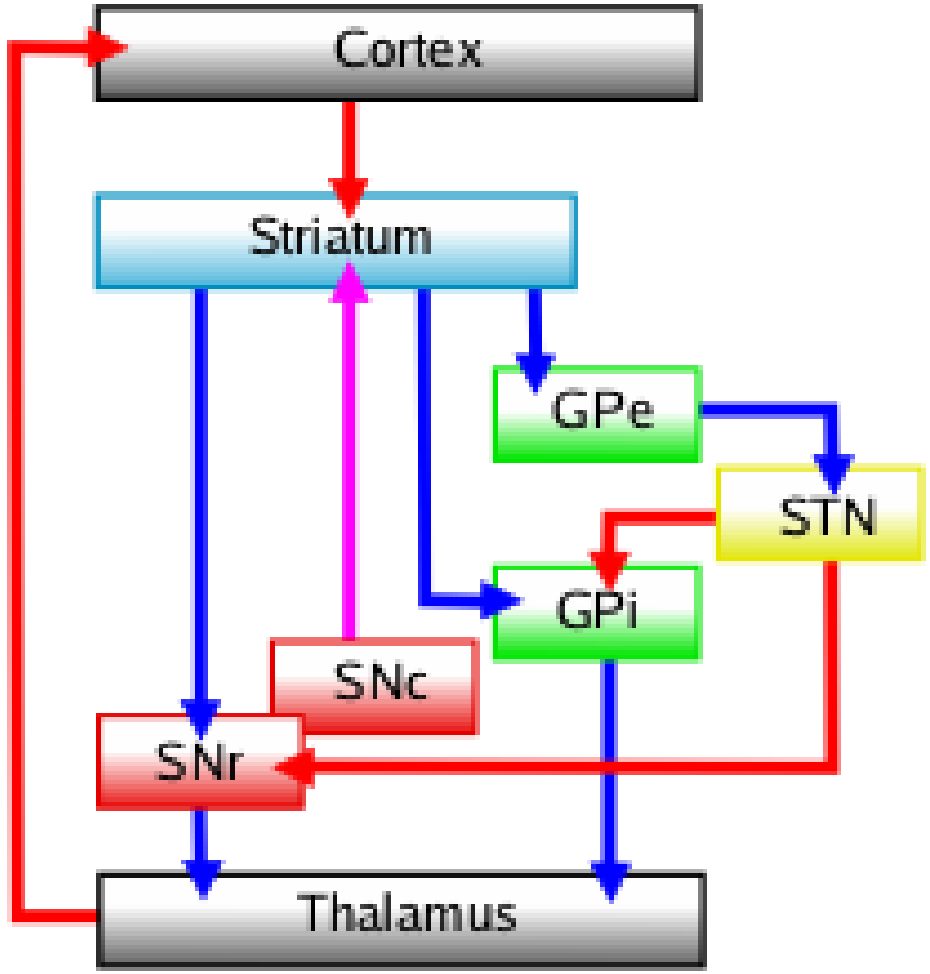
trichjournal.com

Obsessive-Compulsive Disorder

usanetwork.com/publicdomain

OCD Etiology

- Genetics
- Dopaminergic dysfunction
- Serotonergic dysfunction
- Cortico-striato-thalamo-cortical loop
- Autoimmune- PANDAS



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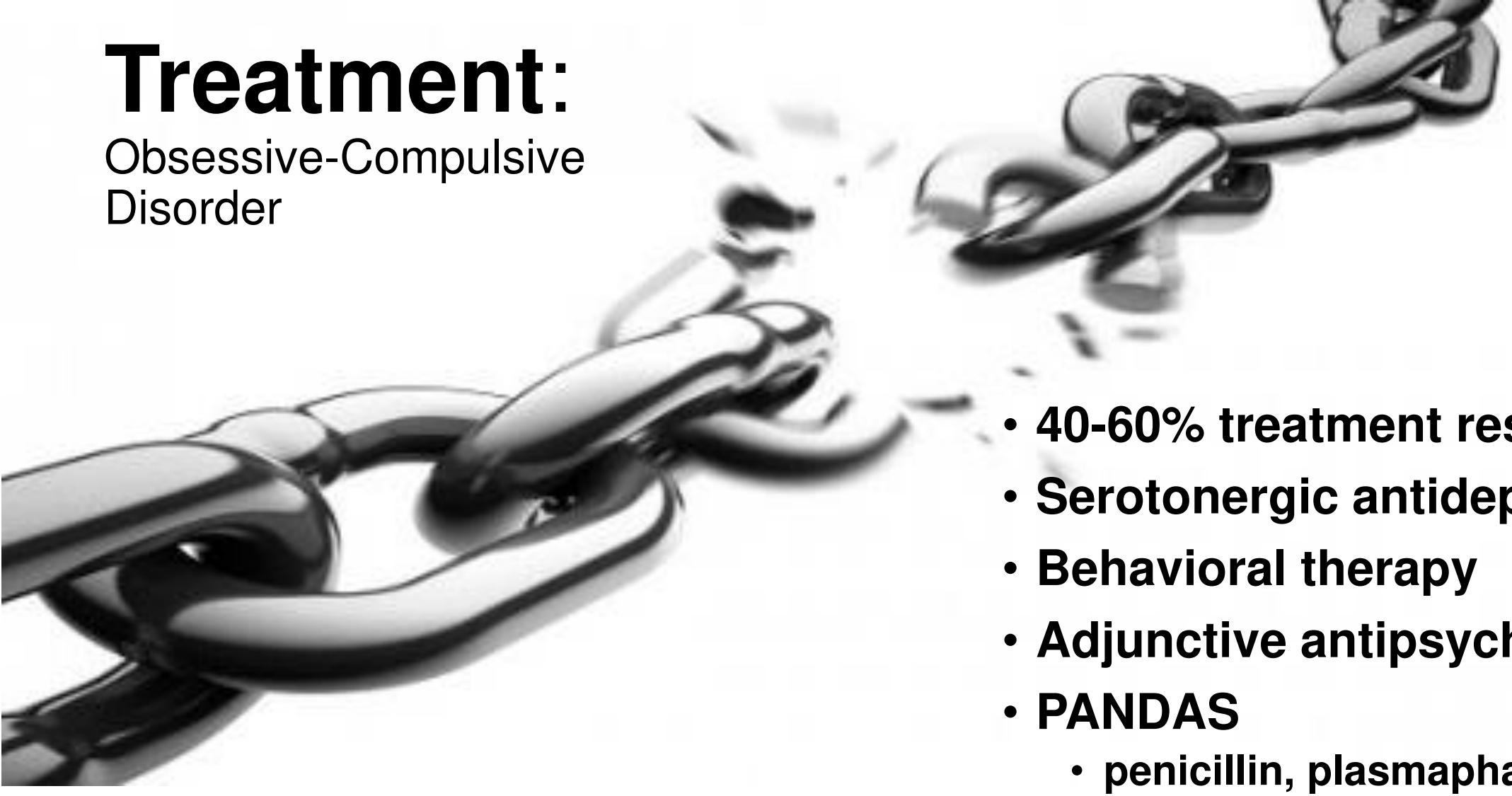
Functional Imaging & OCD

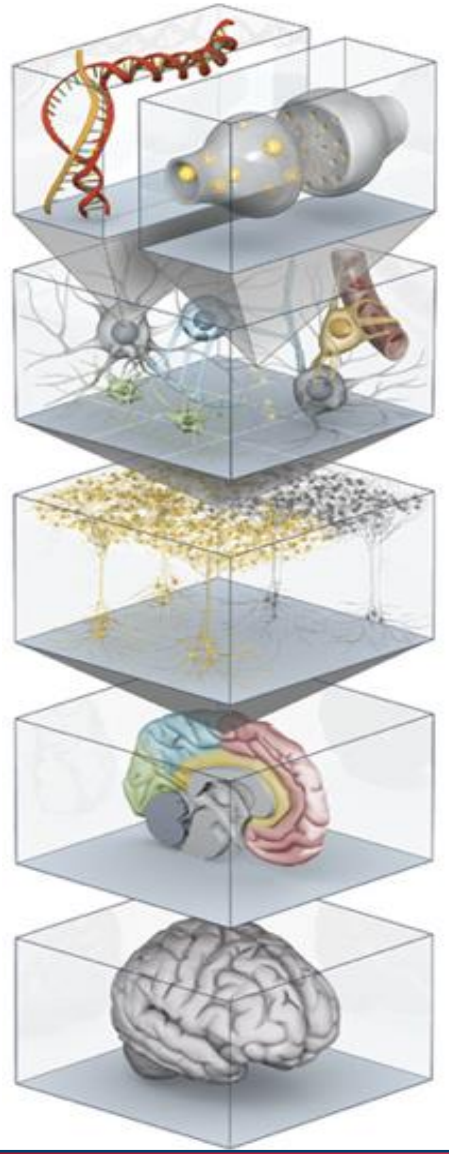
- Increased activity in right caudate
- CBT reduces resting state glucose metabolism & blood flow in right caudate (for responders)
- Similar results obtained with pharmacotherapy

Treatment:

Obsessive-Compulsive Disorder



- **40-60% treatment response**
- **Serotonergic antidepressants**
- **Behavioral therapy**
- **Adjunctive antipsychotics, DBS**
- **PANDAS**
  - **penicillin, plasmapharesis, immunotherapy**



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Symptom-Based Selection

- Build a multi-agent “portfolio”
- Treat all residual symptoms to sustained remission
  1. **Construct** symptoms into a diagnosis
  2. **Deconstruct** into specific symptom list
  3. **Match** symptoms to *brain circuits*
  4. **Consider** known *neuropharmacology* of **circuits**
  5. **Match** agents to *neuropharmacology*; **fine tune**

A few words about genetics…

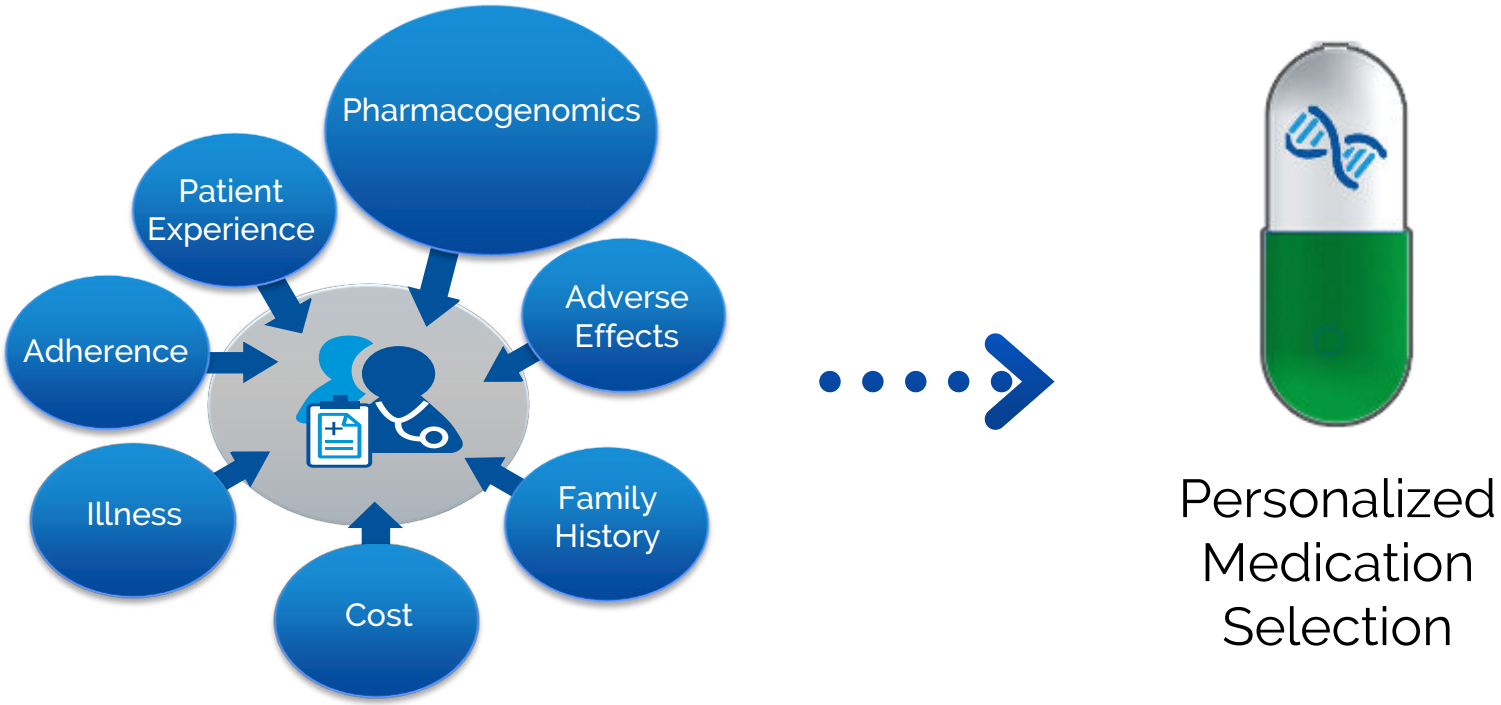
- Potential for diagnosis & treatment
- Genetic complexity of psych illness
- Response isn't "all or none"
- Predict non/response & side-effects
- CYP-450 genotypes
- "Equipoise"

Biomarker Testing in Clinical Settings

Genetic testing may aid in the treatment of patients with:

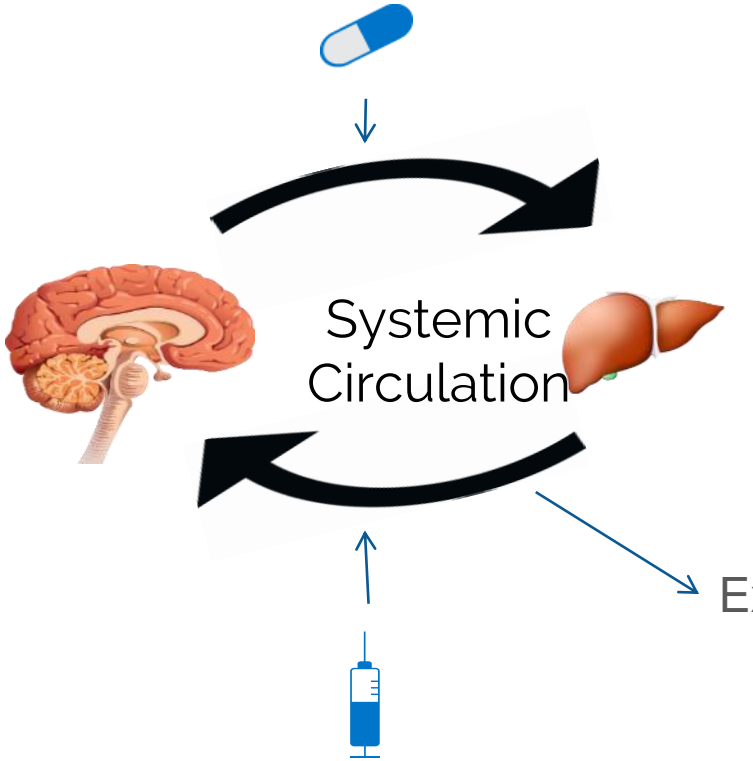
- Treatment resistance
- Previous failed treatment trials with adverse events or poor response
- Polypharmacy
- Comorbidity
- Noncompliance or issues with medication adherence

Personalized Medication Selection



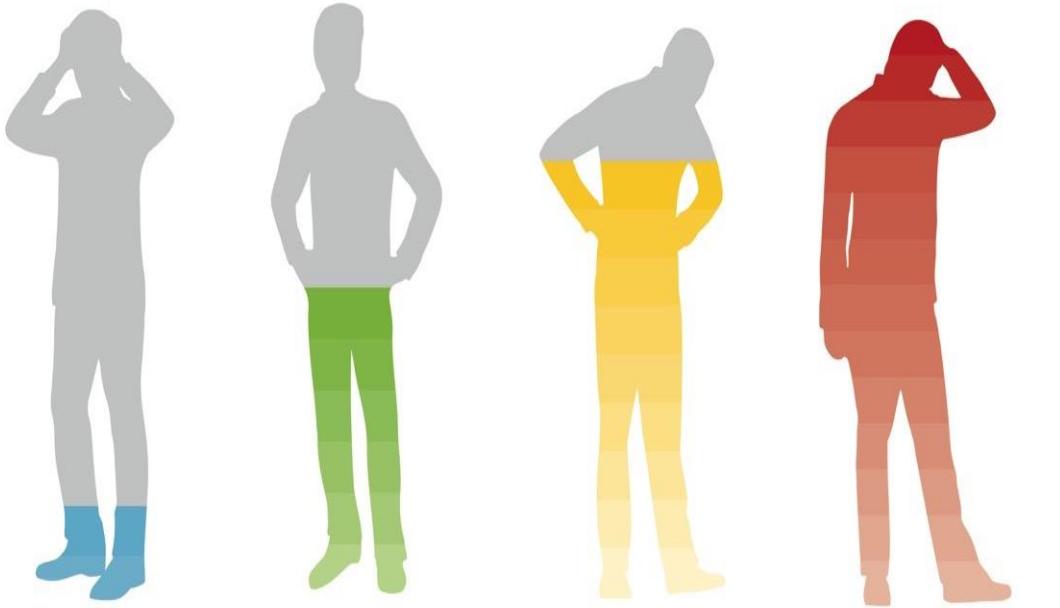
Pharmacokinetics & Pharmacodynamics

Polymorphisms in pharmacodynamic (PD) genes can affect drug action at its target (e.g. receptor binding).



Polymorphisms in pharmacokinetic (PK) genes (e.g. CYP450) can affect drug blood levels.

How Genetics Can Affect Medication Blood Levels



ULTRARAPID METABOLIZER

Breaks down medications rapidly. May not get enough medication at normal doses.

EXTENSIVE (NORMAL) METABOLIZER

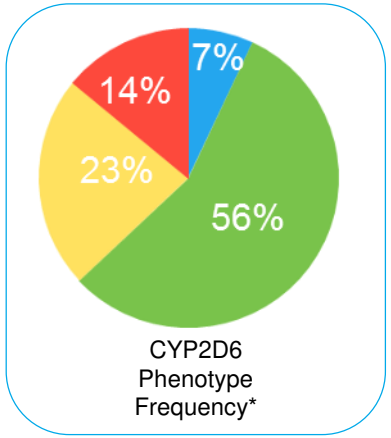
Breaks down medications normally. Has normal amounts of medication at normal doses.

INTERMEDIATE METABOLIZER

Breaks down medications slowly. May have too much medication at normal doses.

POOR METABOLIZER

Breaks down medications very slowly. May experience side effects at normal doses.



CYP2D6 Phenotype Frequency*

*Phenotype frequency is based on internal Asurex Health data of over 100,000 tested patients.

Adapted from selfhacked.com

“Mother’s Little Helpers”

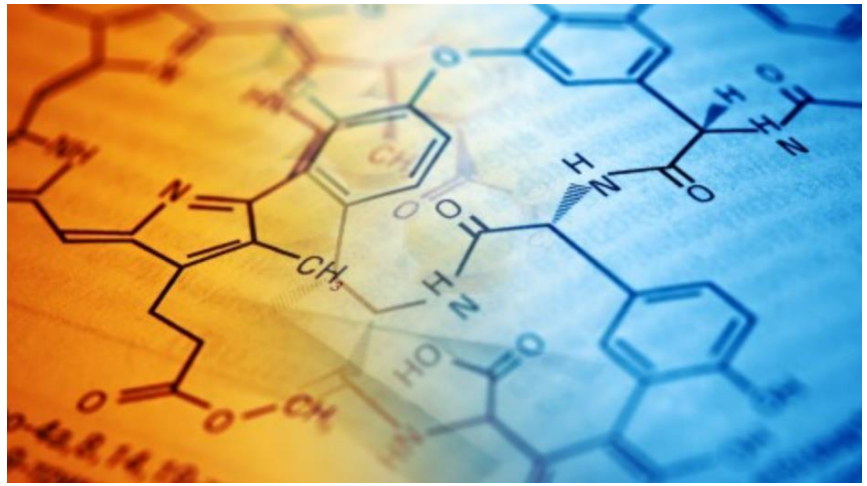
BZDs effective to ↓ anxiety sx

- risk of dependence; use with caution
- PRN basis or scheduled (depending upon specific patient)
- *Avoid alprazolam!*

Caution with history of addiction

- Especially if active AOD abuse or dependence

Benzodiazepines: Mechanism of Action



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- Endogenous GABA
- BZDs attach to benzodiazepine modulatory site
- Effect: decreased neuronal firing

BZD Pharmacokinetics

- Absorbed in 20-30 minutes
- Sublingual formulations bypass liver (first pass effect)
- Klonopin wafers (clonazepam)
- Duration of action determined by lipophilicity or “lipid solubility”

BZD Pharmacokinetics

- Metabolized by liver
- Lorazepam (L), oxazepam (O) and temazepam (T) ("LOT" acronym) metabolized by liver through glucuronidation:
  - Implications for clinicians: no active metabolites; rarely susceptible to drug-drug interactions
  - Appropriate for patients who are elderly, have cirrhosis, or have complex medical/pharmacological issues.

BZDs versus Non-BZDs

- Alpha-1 subunit of the GABA-A receptor mediates sedation.
- Alpha-2 subunit mediates anxiety.
- BZDs work on both, while non-BZDs work mostly on the alpha-1 (sedation) subunit.

Alcohol mediates GABA receptor sites…
but that's for another day!!

BZD Comparisons

Drug	Onset of Action	Peak Onset (hrs)	Half-life (hrs)	Elimination	Dose Equivalent
Long-Acting					
Chlordiazepoxide (Librium)	Int	2-4	5-30 (parent) 3-100 (metab)	Oxidation	10mg
Diazepam (Valium)	Rapid	1	20-50 (parent) 3-100 (metab)	Oxidation	5mg
Flurazepam (Dalmane)	Rapid	0.5-2	47-100 (metab)	Oxidation	30mg
Intermediate Acting					
Alprazolam (Xanax)	Int	0.7-1.6	6-20 (parent)	Oxidation	0.5mg
Clonazepam (Klonopin)	Int	1-4	18-39 (parent)	Oxidation	0.25mg
Lorazepam (Ativan)	Int	1-1.5	10-20 (parent)	Conjugation	1mg
Oxazepam (Serax)	Slow	2-3	3-21 (parent)	Conjugation	15mg
Temazepam (Restoril)	Slow	0.75-1.5	10-20 (parent)	Conjugation	30mg
Short Acting					
Triazolam (Halcion)	Int	0.75-2	1.6-5.5 (parent)	Oxidation	0.5mg

Onset of Action: Rapid=within 15 min; Intermediate=15-30min; Slow=30-60min

BZDs Approximate Daily Dose Equivalencies

• lorazepam	1 mg	• Ativan®
• clonazepam	0.5 mg	• Klonopin®
• chlordiazepoxate	10 mg	• Librium®
• oxazepam	15 mg	• Serax®
• clorazepate	7.5 mg	• Tranxene®
• diazepam	5 mg	• Valium®
• alprazolam	0.5 mg	• Xanax®
• alprazolam ER	0.5 mg	• Xanax XR®

Ciraulo, 2000 adapted from *Kaplan & Sadock.*

BZDs: Drug-Drug Interactions

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Antacids ↓ absorption & BZD levels

Carbamazepine/cimetidine ↓ BZD levels

BZDs ↑ ***digoxin*** levels

Erythromycin ↑ alprazolam levels

Ethanol ↑ sedation/respiratory depression

Nefazodone ↑ alprazolam/triazolam levels

Opioids ↑ sedation/respiratory depression

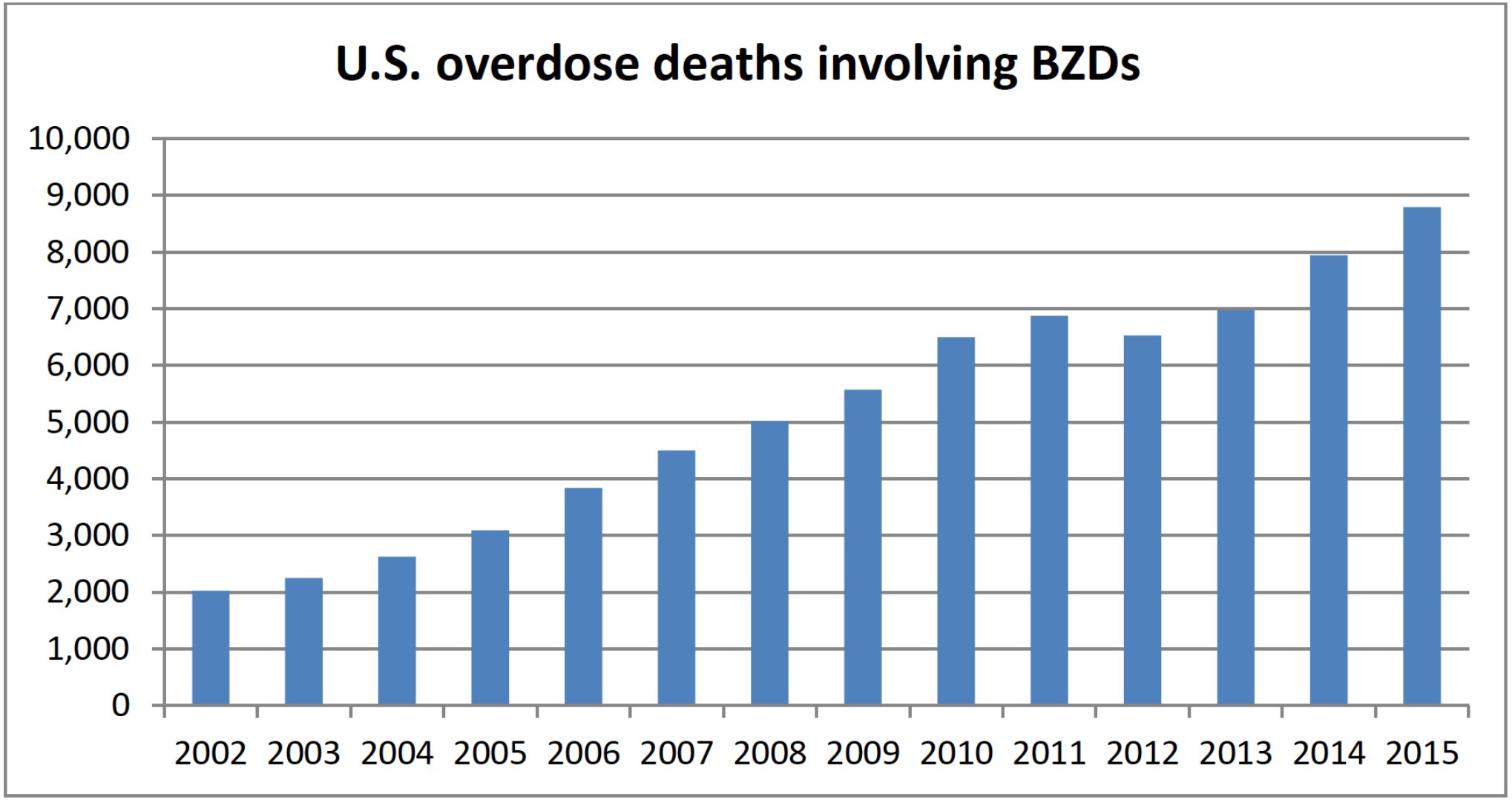
SSRIs (e.g. fluoxetine & fluvoxamine) ↑ diazepam/alprazolam level due to potent inhibition of CYP450 3A4

Valproic Acid ↑ BZD levels

How prone to *abuse* are BZDs?

- Most clinical trials with placebo have found little evidence for preference of BZDs over placebo. Arch Gen Psych 1986; 43:533-41

- Epidemiological studies consistently have shown that the overwhelming majority of patients in the community, even former substance abusers, take fewer BZDs than prescribed and rarely become “dose escalators.” They decrease rather than increase their dose over time. J Clin Psychopharmacology 1992; 12:316-21.



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Harm Reduction

Inpatient “ultrarapid detox”

Taper BZD to lowest dose possible; encourage only PRN or intermittent use

Advise & caution patients:

- Avoid mixing BZDs with other depressant drugs or alcohol.
- Never take other people’s prescribed medications.
- Avoid driving or other dangerous activities after taking BZDs.

DSM-5: Sedative, Hypnotic & Anxiolytic Use Disorder

APA, 2013.

- Continuing to use, despite negative personal consequences.
- Repeated inability to carry out major functions on account of use.
- Recurrent use in physically hazardous situations.
- Continued use despite recurrent/persistent social or interpersonal problems.
- Tolerance.
- Withdrawal (or use of the drug to avoid withdrawal).
- Using more of the drug or using for a longer period than intended.
- Persistent desire to cut down (or unsuccessful attempts to control use).
- Spending a lot of time obtaining/using the substance or recovering from use.
- Stopping/reducing important occupational/recreational activities due to use.
- Craving or strong desire to use.

Common *Acute* BZD Withdrawal Symptoms

Symptoms common to all anxiety states	Symptoms relatively specific to benzodiazepine withdrawal
Anxiety, panic attacks, agoraphobia	Perceptual disturbances, sense of movement
Insomnia, nightmares	Depersonalization
Depression, dysphoria	Hallucinations (visual, auditory), misperceptions
Excitability, jumpiness, restlessness	Distortion of body image
Poor memory and concentration	Tingling, numbness, altered sensation
Dizziness, light-headedness	Formication
Weakness, "jelly legs"	Sensory hypersensitivity (light, sound, taste, smell)
Tremor	Muscle twitches, jerks, fasciculation
Muscle pain, stiffness (limbs, back, neck, jaw, head)	Tinnitus
Sweating, night sweats	*Confusion, delirium
Palpitations	*Fits
	*Psychotic symptoms
*Usually confined to rapid withdrawal from high doses of benzodiazepines	

The Resource Site for Involuntary Benzodiazepine Tranquilliser Addiction, Withdrawal & Recovery [Internet]. [cited 2018 Oct 24]. Available from: https://benzo.org.uk/

Common *Protracted* BZD Withdrawal Symptoms

Symptoms	Usual course
Anxiety	Gradually diminishing over a year
Insomnia	Gradually diminishing over 6 to 12 months
Depression	A few months: responds to antidepressants
Cognitive impairment	Gradually improving but may last a year or more and occasionally incomplete
Perceptual symptoms tinnitus paresthesia - tingling, numbness, pain usually in limbs, extremities	Gradually receding, but may last at least a year and occasionally persist indefinitely
Motor symptoms muscle pain, weakness, tension, painful tremor, shaking attacks, jerks, blepharospasm	Gradually receding, but may last at least a year and occasionally persist indefinitely
Gastrointestinal symptoms	Gradually receding, but may last at least a year and occasionally persist indefinitely

The Resource Site for Involuntary Benzodiazepine Tranquilliser Addiction, Withdrawal & Recovery [Internet]. [cited 2018 Oct 24]. Available from: https://benzo.org.uk/

Withdrawal Scales

- Clinical Institute Withdrawal Assessment – BZDs (CIWA-B)
- Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)

Taper & Discontinuation of BZDs

Lemoine P, Touchon J, Billardon M. [Comparison of 6 different methods for lorazepam withdrawal. A controlled study, hydroxyzine versus placebo]. Encephale. 1997;23(4):290-9. PubMed PMID: 9417395.

Takes several months

Convert to longer-acting agent, then taper

25% dose reduction every 1-2 weeks

For high dose, long-term users, 10-25% q2-4 weeks x 6 months

Scheduled (NO PRN) dosing

Follow every 1-4 weeks

EMPOWER trial - www.criugm.qc.ca/fichier/pdf/BENZOeng.pdf

Clinical Pearls

Blunt	Blunt withdrawal symptoms: hydroxyzine, carbamazepine, pregabalin
Add	Add psychotherapy (CBT)
Give	Give clear, written instructions
Sign	Sign a treatment agreement
Do not increase	Do not increase a dose once taper has begun
Write	Write for 7 to 14 days only
Obtain	Obtain UDS before (and periodically during) taper
Monitor	Monitor GGT for ETOH use

Additional Reading

Web clip art (public domain) is used extensively throughout this presentation.

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