PSYCHOPHARMACOLOGY MASTER CLASS 2021 :

ANXIETY MECHANISM & TREATMENT

Carl Salzman MD

ROLE OF AMYGDALA IN ANXIETY

- Amygdala is activated by fear, anxiety
  - Has arousal receptors: Norepinephrine and dopamine which increase CREB in the nucleus
  - Glutamate also stimulates CREB in central nuclei of the amygdala
- NE, DA, Glutamate--->activate and increase output from amygdala to HPA axis and cortex-->anxiety and depressive disorders
- Amygdala has oxytocin receptors

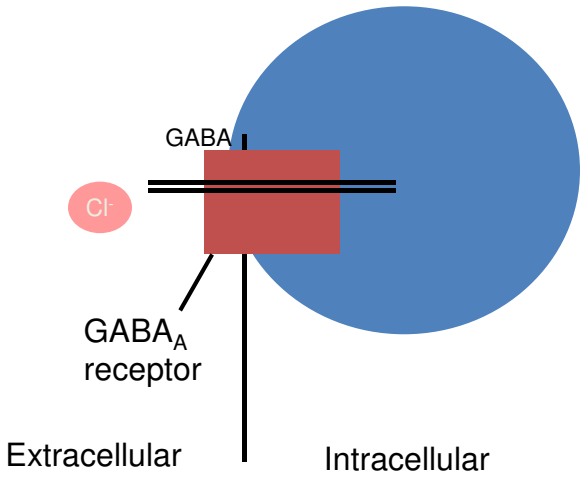
Mechanism of Anxiety
Hypothesis: Underactive Inhibitory Neurons

- Anxiety is related dysregulated or dysfunctional Gamma Butyric Acid (GABA) the primary inhibitory neurotransmitter :
  - dysfunctional inhibitory neurotransmitter (GABA); unlikely
  - Dysfunctional $GABA_A$ receptor

Neuronal Inhibition: *Role of $GABA_A$ Receptor*

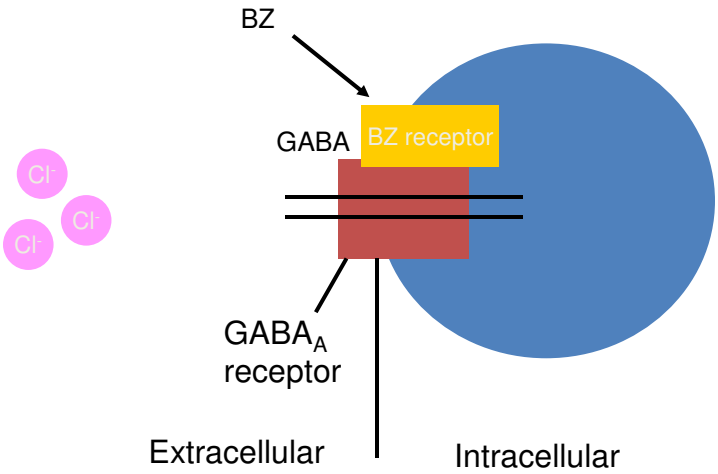
- Chloride channel within $GABA_A$ receptor admits Cl^- ions that hyperpolarize the neuron and decrease excitation
- Adjacent benzodiazepine receptor increases sensitivity of $GABA_A$ receptor
- BZ-GABA complex controls chloride ionophore regulating influx of negative ions

$GABA_A$ Receptor



BZ Receptor

Normally in "agonist sensitivity" position: enhances $GABA_A$ opening of Cl^- channel



LIGANDS FOR BZ RECEPTOR

- Agonist – (diazepam) –activates receptor
- Partial agonist – only partially activates receptor or receptors
- Inverse agonist (diazepam binding inhibitor; beta-carboline)- activates receptor but causes opposite effect
- Antagonist – (Flumazenil)- blocks all receptors (agonist and inverse agonist)

Mechanism of Anxiety II:
Hypothesis: *Role of Inverse Agonist*

- Increased endogenous BZ inverse agonist
- BZ receptors shift from agonist sensitivity to inverse agonist sensitivity

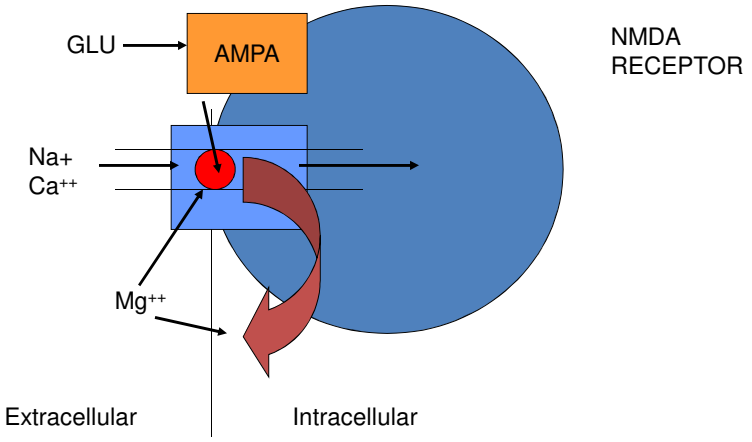
MECHANISM OF ANXIETY-III

- Dysfunctional (too much) stimulatory neurotransmitter;
  - Norepinephrine
  - Glutamate
  - serotonin
- Dysfunctional amygdala
  - All anxiety begins here
- Dysfunctional brain cortisol
  - Dysfunctional Cortisol releasing factor receptor

Neuronal Excitation: Hypothesis: *Role of Glutamate*

- Excitatory amino acid neurotransmitter
- Mediates excitatory neurotransmission
- Interacts with most synapses
- Stress activates cortical and limbic glutamate neurotransmission
- Increased neurotransmission is through NMDA receptor

IONOPHORE RECEPTOR: glutamate



ROLE OF OTHER NEUROTRANSMITTERS HYPOTHESIS: ADENOSINE

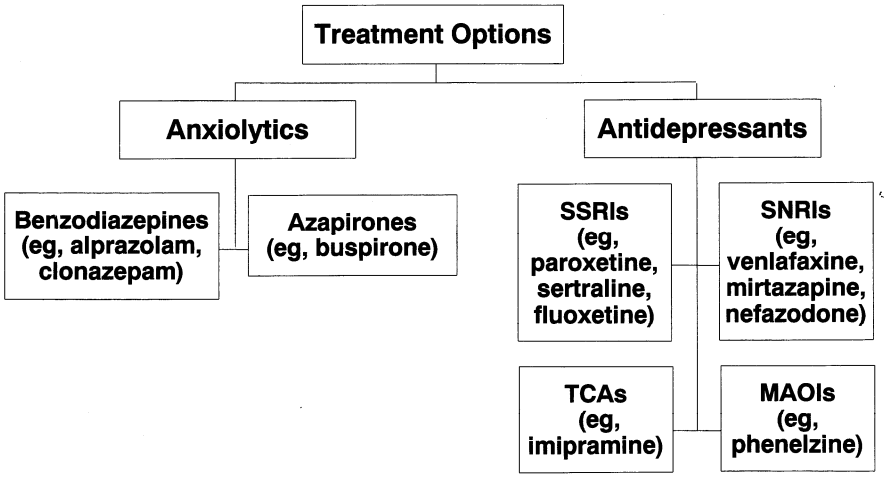
- Functions in postsynaptic second messenger systems
- Has sedative and hypnotic effects
- Has myorelaxant properties
- Adenosine antagonists (theophyllin and caffeine) increase anxiety (inhibit BZ binding to $GABA_A$ – BZ – Cl^- ionophore
- NO CAFFEINE for those with anxiety disorders

Role of Other Peptide Neurotransmission

- Cholecystokinin
- Corticotropin-releasing factor
- Neuropeptide Y
- Tachykinins
- Endogenous opiates

TREATMENT OF ANXIETY AND ANXIETY SPECTRUM DISORDERS

Pharmacologic Treatments for Generalized Anxiety Disorder



BENZODIAZEPINES: IN TODAY'S WORLD, A BLESSING OR A CURSE?

BENZODIAZEPINES FOR ANXIETY

- BZs continue to be the most widely prescribed class of pharmaco-therapeutic agents, often as adjuncts to SSRIs;
  - Most use is short term (3 weeks) and prescribed by non psychiatrists
- "With careful clinical evaluation…and careful monitoring for cognitive and psychomotor effects, (especially in older individuals), BZs are safe and highly effective"[2]

[1]Pollack 2014; Am J Psychiattry 171:44; 2Roy-Byrne 2014, ibid 1.

BENZODIAZEPINE CLASSIFICATION

- Short half-life/high potency:
  - Alprazolam
  - Lorazepam
- Long half-life/high potency:
  - Clonazepam
- Short half-life/low potency:
  - Oxazepam
  - Temazepam
- Long half-life/low potency:
  - Diazepam
  - Chlordiazepoxide

CHRONIC PSYCHIATRIC USE OF BENZODIAZEPINES

- Widespread use as primary and secondary treatment for anxiety & panic disorders
- Widespread use as add-on medication for anxiety spectrum disorders (SAD, OCD)
- Widespread use as add-on medication for affective disorders (mania, depression, dysthymia)
- Controversial use as chronic hypnotic

DOES CHRONIC BENZODIAZEPINE USE LEAD TO DOSE ESCALATION?

- Data do not suggest dose escalation over time for most patients who receive therapeutic doses.
- Dose escalation more likely in:
  - Substance abusers
  - Personality disorders

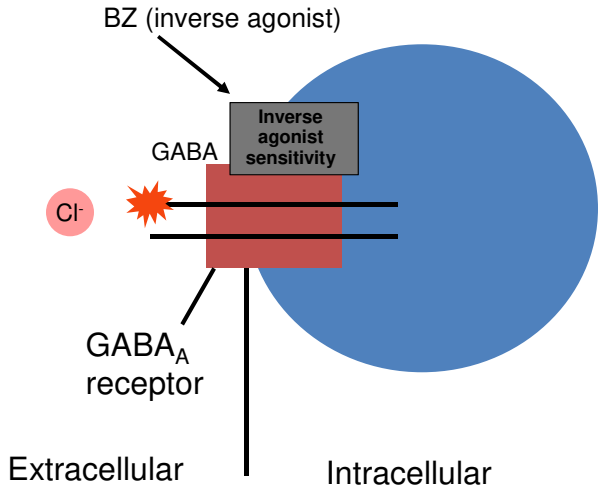
PROBLEMS WITH BENZODIAZEPINES

- Common dependence and withdrawal;
- Interact with alcohol & other sedative hypnotics:
  - Sedation
  - Impaired motor speed and coordination
  - Impaired cognition: short term memory (recent recall)
  - Falls (elderly)

MECHANISM OF BZ WITHDRAWAL

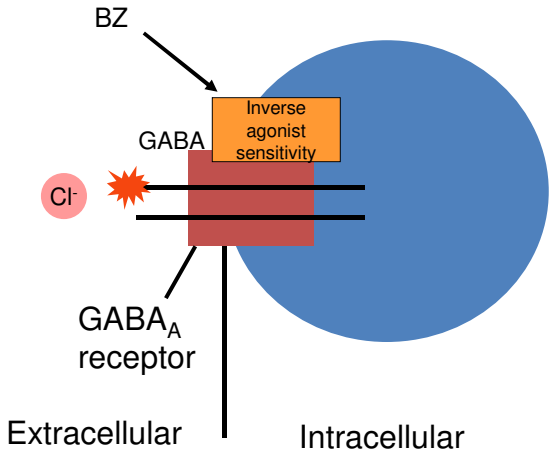
- Chronic exogenous BZs shift BZ receptor sensitivity from agonist to inverse agonist position;
- When exogenous BZs are suddenly withdrawn, receptors are left in inverse agonist sensitivity position;
- Takes 1 week for receptors to reset to agonist sensitivity
- BZ antagonist (flumazenil) blocks withdrawal

Role of "Inverse Agonist"



BZ Withdrawal

- When tonic BZ agonist is abruptly removed from receptor (ie, drug is discontinued), receptor shifts from agonist to inverse agonist sensitivity; Cl– channel shuts and anxiety increases



BENZODIAZEPINE SIDE EFFECTS

- Correlate with dose, duration of treatment, sensitivity of user:
  - Increased side effects in elderly; patients with damaged or dysfunctional CNS
- Sedation
- Impaired motor speed and coordination
- Impaired cognition: short term memory (recent recall)
- Falls (elderly)
  - Occurs with long- and short half-life drugs

BENZODIAZEPINE EFFECT ON COGNITION

- Acute effect:
  - May decrease recent/immediate recall
  - Does not affect long-term storage/retrieval
  - Dose/potency dependent
- Chronic effect:
  - Reversible
  - Decrease short-term recall

LONG-TERM EFFECT OF BENZODIAZEPINES ON COGNITION - II

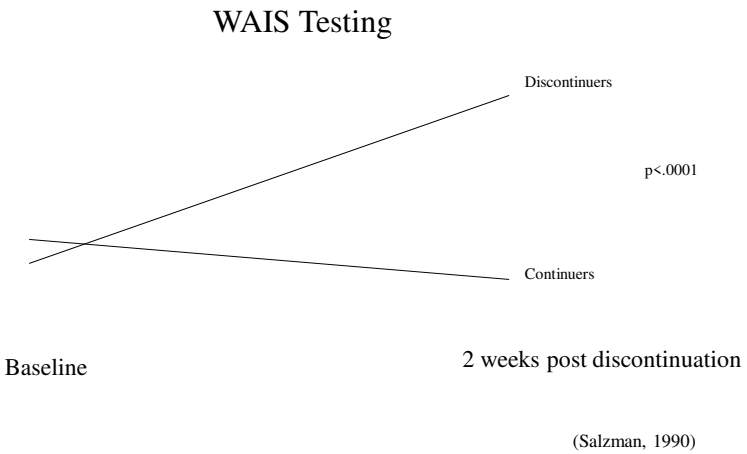
- Recent data suggest long-term decline in cognition with therapeutic usage
- Is reversible
- Benefit vs. risk: memory vs. reduced anxiety and enhanced sleep

Table 2 Moses illusions: Mean number of Illusions (I) and of detections followed by a correct answer (F) and criterion I/(I+F) for target word impostors

	Placebo	Lorazepam
Illusion (I)	3.8 (2.2)	8.4 (4.2)
Detection (F)	15.3 (2.9)	10.6 (3.9)
I/(I+F)	0.20 (0.12)	0.44 (0.21)

Izaute,2004

EFFECT OF DISCONTINUING BENZODIAZEPINES ON COGNITION IN THE ELDERLY



(Salzman, 1990)

BENZODIAZEPINES DO NOT CAUSE DEMENTIA

- Prospective study covering a 10 year period of benzodiazepine use
  - Multiple ratings of cognitive function
  - Careful diagnosis of Alzheimer's disease
- CONCLUSION: Results do not support a causal association between benzodiazepine use and dementia.

Gray, 2016; Salzman 2020,
Am J Psychiatry June

ANTIDEPRESSANTS FOR ANXIETY

- SSRIs, venlafaxine, mirtazepine, nefazodone are increasingly used for anxiety
- SSRIs approved for panic, social anxiety disorder, OCD, GAD
- Venlafaxine approved for GAD

CONCLUSIONS ABOUT ANTIDEPRESSANTS

- Not effective for acute treatment of anxiety
- Not superior to benzodiazepines for chronic treatment of generalized anxiety disorder
- Usefulness limited to anxiety-spectrum disorders
- Significant sexual side effects limit usefulness
- Significant drug interactions limit usefulness

GABAPENTIN (NEURONTIN)

- Not a benzodiazepine; does not work at BZ receptor
- Increases nonsynaptic release of GABA from glia
- Useful for decreasing agitation, rage, irritability
- Excellent sleeping pill
- No data on anxiolytic effect; may be helpful for social phobia, rage outbursts

ANTIANXIETY DRUGS THAT DO NOT AFFECT GABA

- Gabapentin (Neurontin)
- Pregabalin (in development)
- Buspirone
- Beta blockers
- Kava kava
- Cortisol releasing factor antagonists (in development)
- Neurosteroid stimulating drugs (in development)
- CCK antagonists (theoretical)
- Adenosine agonists (theoretical)
- Low dose antipsychotics
- Non stimulating antidepressants

BUSPIRONE

- An azapirone, not a benzodiazepine; effects serotonin, not GABA
- Delayed onset of action; not as effective as benzodiazepines either acutely or chronically
- No dependence or cognitive impairment
- Not popular with psychiatrists; used more by primary care physicians
- Not useful for acute anxiety; more useful for chronic anxiety states
- Therapeutic failure may be due to under dosing; may need 50 mg/d or more.

Treatment of Anxiety: *Alter Monoamines*

- Alter NE neurotransmission
  - Block postsynaptic β receptors
  - Stimulate presynaptic α_2 receptors
- Alter 5-HT neurotransmission
  - Block postsynaptic 5-$HT_{2A/C}$ receptors
  - Stimulate presynaptic 5-HT_{1A} and 5-HT_{1D} receptors

B BLOCKERS FOR ANXIETY

- Not effective for inner subjective experience of dread
- Very effective for autonomic, objective symptoms

PANIC DISORDER

- 3% lifetime prevalence
- High anxiety-spectrum comorbidity
  - GAD 16%; MDD 23%
- High substance abuse (10-20%)
- Etiology theories:
  - Dysregulated NE and 5HT autoreceptors
  - Hypersensitive cholecystokinin receptors
  - Suffocation hypothesis: increased sensitivity to CO_2 and lactate

BENZODIAZEPINES FOR PANIC DISORDER

- High potency BZs still used to treat panic, alone or as adjunctive medication:
  - Alprazolam
  - Clonazepam
- BZ and antidepressants equally effective
- Combination CBT and BZ used for most severely symptomatic patients

Bruce, 2003; Pollack, 2003; Stahl, 2002; Starcevic, 2004

MAINTENANCE THERAPHY FOR ANXIETY SPECTRUM DISORDERS

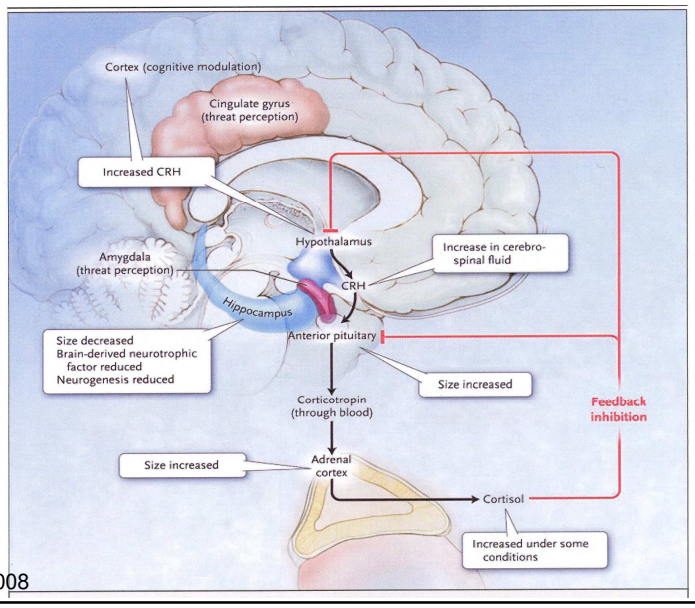
- All anxiety disorders have high relapse rates when drug treatment is discontinued;
- Recommended approach:
  - Keep patients on effective doses for as long as possible;
  - If discontinuing medication, taper doses very slowly.

PSYCHOPHARMACOLOGY MASTER CLASS 2021 :

PTSD; STRESS & STRESS DISORDERS

Carl Salzman MD
modified, final

THE STRESS AXIS



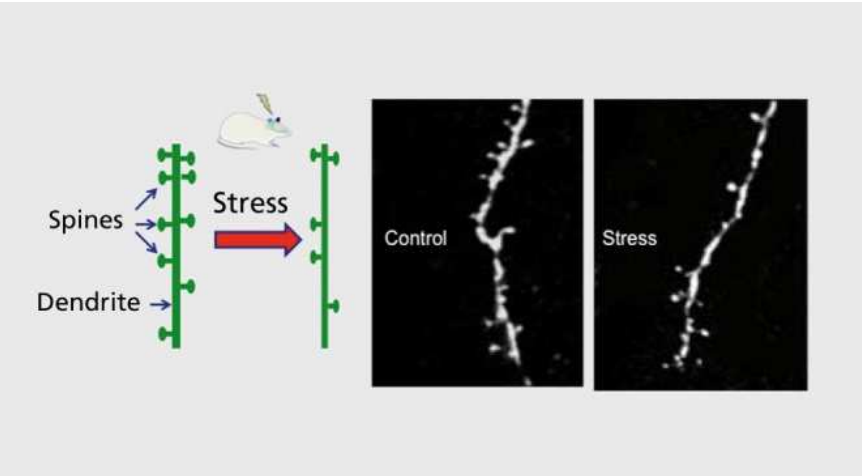
Belmaker, 2008

ROLE OF AMYGDALA IN STRESS

- Amygdala is a critical site for effects of stress and stress hormones on affective behaviors
  - Chronic stress causes hyperexcitability of lateral amygdala pyramidal neurons
  - Results in enhanced affective behavior
- Mediates physiological (autonomic reactivity) and behavioral effects of stress
- mPFC and oPFC integrate amygdala mediated arousal and down regulate amygdala reactivity

Rosenkranz 2010; Biol Psychiatry 67:1128

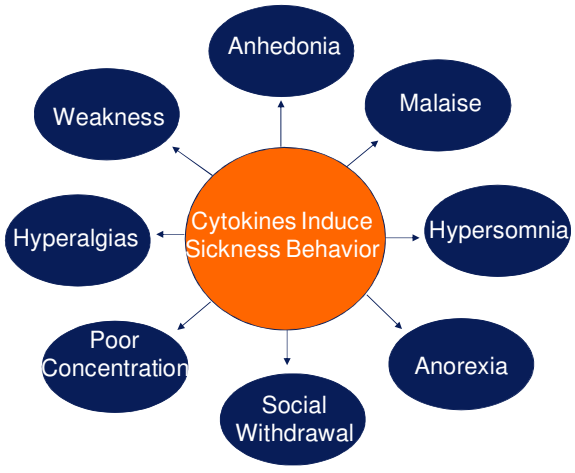
NEURONAL ATROPHY FROM STRESS



Duman 2014; Dialogues in Clin Neurosci 16:11

EFFECT OF STRESS ON THE IMMUNE SYSTEM

Effects of Immune Activation Resemble Depressive Symptoms



PREDICTORS OF STRESS EFFECTS

EFFECTS OF ADOLESCENCE STRESS:BULLYING, ISOLATION, NEGLECT

- Chronic stress increases vulnerability to cognitive impairments after inflammation
  - Decreased CNS cortisone, increased illness, decreased social behavior
- Mechanism: early onset chronic stress leads to decreased mitochondrial function, increased disease risk and accelerated biological aging
- All effects are worse in females

PARENTAL STRESS CAN AFFECT OFFSPRING NEURODEVELOPMENT

- Pre-conception stress in either parent can affect germ cells, influencing development in one or more generations.
  - During pregnancy, maternal stress alters the maternal milieu which can affect fetal development
  - Germ cell alterations may alter sperm as paternal causes of offspring neurodevelopment.

Chan 2018; Biological Psychiatry 83:886

STRESS, INFLAMMATION AND PSYCHIATRIC DISORDERS-I

- Inflammation is associated with alcohol use disorder: increased glial activity and increased pro-inflammatory cytokines;

EARLY LIFE STRESS

RISK FACTOR FOR PTSD

EFFECT OF MATERNAL PRENATAL STRESS ON FETAL BRAIN & ADULT VULNERABILITY TO STRESS

- May have long-term effects on brain development and later behavior
  - Degree of maternal stress correlates with significance of later developments
- Maternal stress during pregnancy:
  - Disrupts maternal immune response and increases cytokines
  - Increased stress response in offspring (as much as 40 years later)

EPIGENETIC REGULATION BY EARLY-LIFE TRAUMA

- Quality of postnatal parent-offspring interactions directly alter gene transcription by altering epigenetic mechanisms
- Inadequate mothering can lead to hypermethylation→decreased gene expression→increased vulnerability to stress

CNS CONSEQUENCES OF EARLY LIFE STRESS

- Maternal separation:
  - CRF activates locus ceruleus (LC) & increases norepinephrine release
  - Decreases dendrite arborization in limbic-LC axis
  - Increases arousal and a shift from focused to scanning attention (primates)
  - Decreases glucocorticoid receptors in hippocampus
    - Predisposes to adult onset depression

Swinney 2010, Int J Neuropsychopharmacology 13:515;
Arabadizisz 2010, Biol Psychiatry 67:1106

EFFECT OF EARLY CHILDHOOD NEGLECT

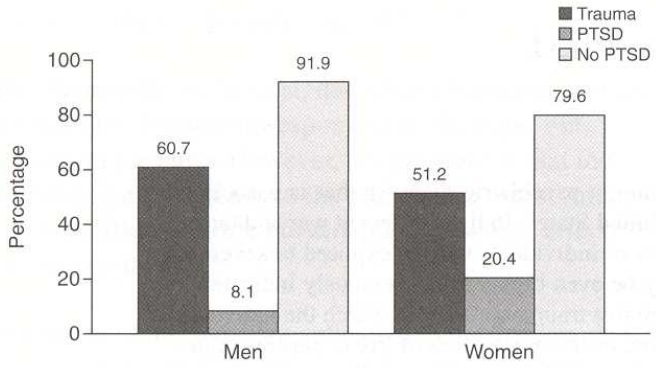
- Childhood neglect (& institutional rearing) constitute a deprived environment with reductions in quantity and quality of caregiver interactions;
  - Limited synaptic stimulation promotes decreased dendrite branching & spine development;
  - This leads to increased synaptic pruning with greater cortical shrinkage (age-specific cortical thickness.
  - Results in lower brain volume, reductions in cortical gray matter, and widespread cortical thinning

McLaughlin 2017; Biol Psychiat 82:462

POST TRAUMATIC STRESS DISORDER

(PTSD)

Figure 1. Prevalence of Trauma and Posttraumatic Stress Disorder (PTSD) by Gender[a]



[a]Data from Kessler et al.[2] 91.9% of men and 79.6% of women exposed to trauma do not develop PTSD.[2]

SEROTONIN TRANSPORTER PROMOTER POLYMORPHISM AND DEPRESSION AND EARLY STRESS

- **S/S genotype** influence on subsequent depression depends on early environment:
  - Is **protective against depression in a supportive early or current environment**
  - **Enhances risk for depression in a high-stress early or current environment**
- Negative events within 6 prior months also correlate with depression in s/s individuals

Taylor, 2006; Biol Psychiat 60:671

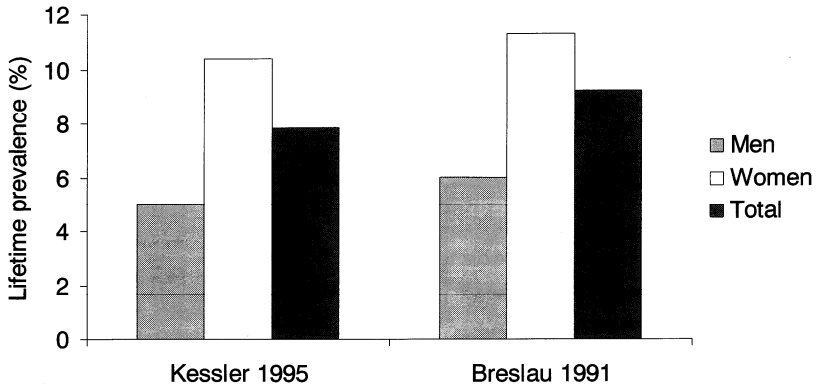
NEW CTE INFORMATION

- Chronic traumatic encephalopathy (CTE):
  - May have a genetic vulnerability explaining why not all cases of head trauma are associated with the development of CTE;
- Vulnerability may be associated with increased tau;
  - The transmembrane protein TMEM106B protects against tau;
  - A minor allele (single SNP) may not perform this protection leading to increased vulnerability to CTE.

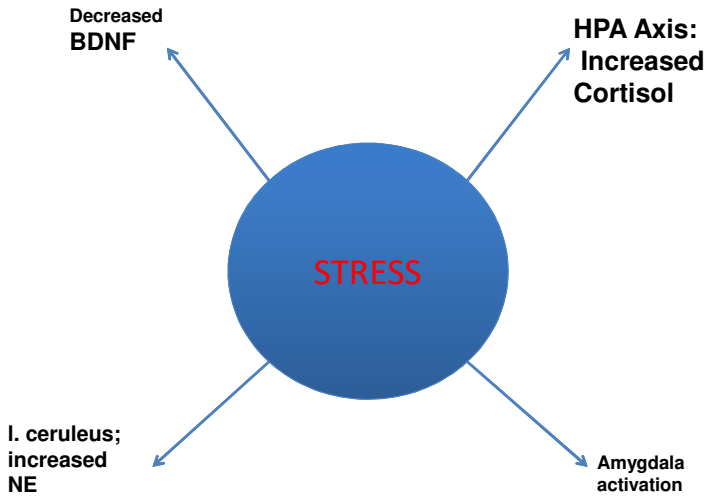
Treatment of PTSD

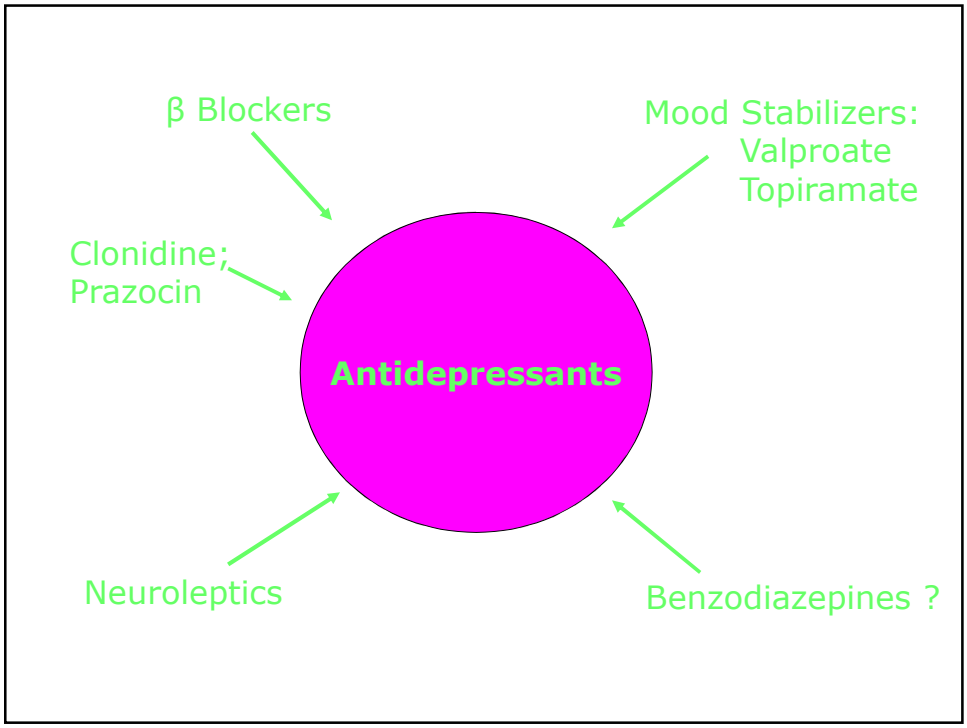
- **Education**
- **Support**
- **Lifestyle modification**
- **Psychosocial**
- **Pharmacotherapy**

Lifetime Prevalence of PTSD



Breslau N, et al. *Arch Gen Psychiatry*. 1991;48:216-222.
Kessler RC, et al. *Arch Gen Psychiatry*. 1995;52:1048-1060.





ANTIDEPRESSANTS FOR PTSD

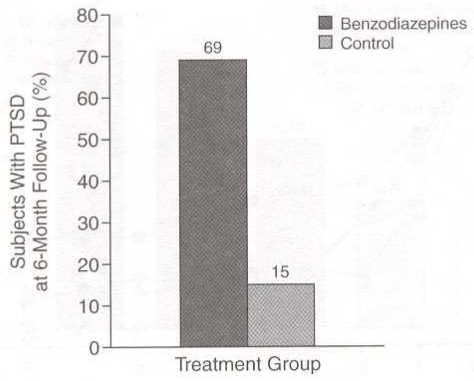
- Are the central position for polypharmacy treatment
- All antidepressants with serotonin properties are helpful; none are curative
  - SSRIs
  - Dual acting medications
  - tricyclics

BENZODIAZEPINES FOR PTSD

- Are prescribed for 30-50% of patients with PTSD
- Do NOT decrease the efficacy of prolonged exposure therapy
- May interact with other sedative hypnotics (e.g. alcohol) used as self medication
- Usually not suggested because of risk of abuse and dependence

Rosen 2013; J Clin Psychiatry 74:1241

Figure 5. Benzodiazepine Monotherapy in Posttraumatic Stress Disorder (PTSD)[a]



[a]Data from Gelpin et al.[16] Alprazolam (N = 3) or clonazepam (N = 10) vs. no treatment (N = 10).

TOPIRAMATE

- Reduces symptoms of PTSD
- Useful in decreasing nightmares
- Effective dose <200mg/d:
  - Usually <100mg

DECREASE STIMULATORY NEUROTRANSMITTERS (NOREPINEPHRINE)

- Post synaptic receptor blockade:
  - B blockers
  - Alpha 1 blocker (prazocin)
- Pre synaptic receptor agonist:
  - Clonidine (increases negative feedback of NE via alpha-2 stimulation

ROLE OF OXYTOCIN IN PTSD TREATMENT

- Dampens amygdala response to threatening stimuli
  - Combining oxytocin with psychotherapy improves therapeutic alliance and facilitates psychotherapy
  - Is termed “neruopsychotherapy”

BENZODIAZEPINES MAY PREVENT STRESS-INDUCED IMMUNE DYSREGULATION

- Animal studies of repeated social defeat:
  - lorazepam and clonazepam may be effective in attenuating increased CRH in the hypothalamus and cortisterone in plasma;
- Effect may be due to the enhancement of GABAergic neurotransmission
- These BZs also reversed anxiety-like and depressive-like behavior resulting from repeated social defeat.

Ramirez K, 2016; Brain Behav Immun 51:154

DOXAZOSIN FOR PTSD

- Is a "me-too" drug for prazocin (Minipress, an α_1 blocker)
- Is also an α_1 blocker, used for benign prostatic hypertrophy and for hypertension ("Cardura")
- Is like prazocin but has a longer half-life
  - (Prazocin: 2-3 hours and requires multiple daytime doses;
  - Doxazosin: half-life: 16-30 hours and can be taken once daily
- Doxazosin has less dizziness and sedation, but slightly more headache than prazosin

eCB SYSTEM AND STRESS

- Endocannabinoid system may regulate stress response
  - Cannabis consumption decreases stress; increases relaxation; dampens anxiety.
  - CB1 receptors are prominently expressed in the amygdala where they modulate excitatory and inhibitory signaling
- Interruptions of CB1 receptor function leads to HPA activation, increased anxiety, suppressed feeding, reduced responsiveness to rewarding stimuli hypervigilance, increased arousal, and impaired cognition

ADDITIONAL SLIDES
(not discussed in the lecture)

NEURAL MECHANISMS OF ANXIETY

- Anxiety is triggered by activating CRF_1 receptors in limbic brain regions.
  - This is part of the hypothalamic-pituitary adrenal axis and results in increased cortisol to the CNS;
- Anxiety is further modulated by the endogenous cannabinoid (eCB) system that attenuates the synaptic effects of stress.
  - Anandamide and 2-AG are endogenous cannabinoids that interact with each other and play a role in reducing anxiety and stress.

Natividad 2017; Biol Psychiat 82:500

OTHER DRUGS THAT AFFECT GABA

- None used to treat anxiety)
- Tiagabine (Gabatril)
- Barbiturates
- Non-barbiturate sedatives

TRIADIC STRESS CIRCUIT: AMYGDALA-mPFC-HIPPOCAMPUS

- Sensory information regarding external environment is processed by thalamus and sensory cortical centers →
- Funneled to amygdala where preconscious threat detection occurs, emotional valence is ascribed and reference to previous experiences occur through cross talk with the medial prefrontal cortex and hippocampus

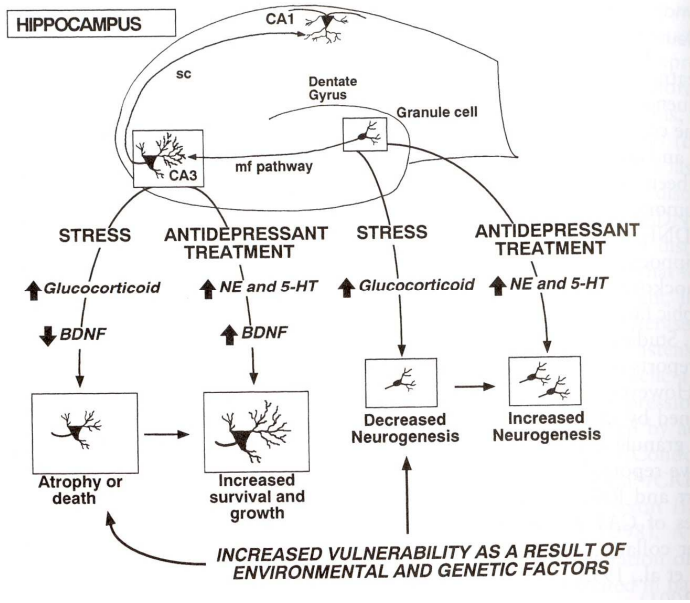
STRESS CIRCUIT-II

- Amygdala output contributes to HPA axis activation, anxiety, pain sensitivity, alterations in cognitive processes
- Excitatory inputs from from mPFC and hippocampus dampen amygdala output
  - Damage to either structure results in amplified responses to stress and impaired termination of stress response, increased anxiety, and increased sensitivity to stress.

STRESS CIRCUITRY-III

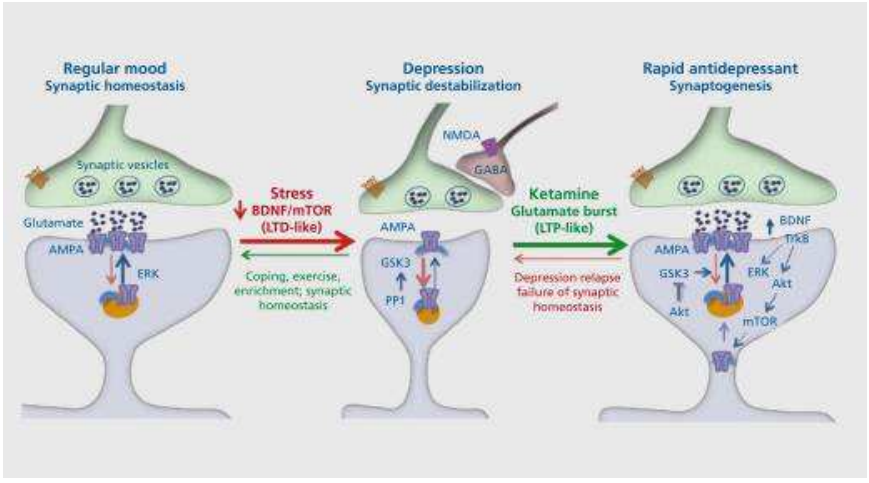
- Damage to either of these structures typically results in amplified responses to stress and impairments in termination of the stress response;
- In humans, reduced functional connectivity of these circuits, or hyperactivity of the amygdala, results in increased anxiety and sensitivity to stress.

EFFECT OF STRESS ON SYNAPTOGENESIS



Nemeroff, 2009

STRESS EFFECT ON SYNAPSE



Duman 2014, Dialogues in Clin Neurosci 16:11

*BDNF POLYMORPHISMS AND STRESS

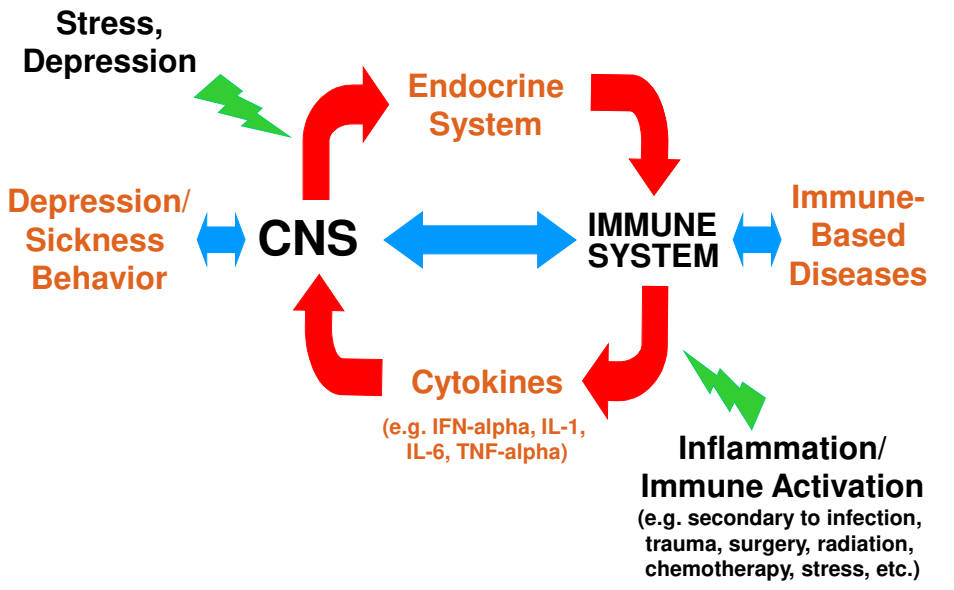
- BDNF regulates mesolimbic & accumbens dopamine
  - Pathway is involved with identification of, and response to emotional enviromental stimuli
  - Pathway is activated by positive (e.g. attachment) as well as negative social stimuli
- BDNF Val66Met polymorphism is associated with depression:
  - Requires presence of s/s 5HTTPLR
  - Also requires presence of childhood adversity

FKBP5 IN STRESS AND AGING

- Psychosocial stressors, such as childhood trauma, as well as stress-related psychiatric disorders, including major depressive disorder (MDD), increase risk for aging-related diseases
- Aging and stress-related phenotypes may together confer disease risk by increasing peripheral inflammation;
- Aging and stress synergize to epigenetically upregulate FKBP5, a protein implicated in stress physiology.
  - Higher FKBP5 promotes inflammation

NEUROBIOLOGY OF RESILIENCE TO STRESS

- Correlates of resilience:
  - Increased PFC activity
  - Stronger connections between hippocampus and anterior cingulate cortex
  - Higher levels of neuropeptide Y
  - Higher levels of oxytocin
  - Genetic Polymorphisms (e.g. FKBP5 gene)



Nemeroff 2018

PRE-NATAL STRESS (PNS)

- Stress can be transmitted in the placenta to the fetus (animal studies):
  - Lead to long-term dysfunction in cognition, working memory, social behaviors;
- Mechanisms: PNS affects genes that control oxidative stress:
  - Increases vulnerability to inflammation, insulin resistance (type II diabetes), obesity, depression
- Humans: high correlation between childhood trauma and emotional dysregulation:
  - Increased vulnerability to illness, obesity;
  - Mechanism: oxidative stress

CHILDHOOD PREDICTORS OF ADULT PSYCHOPATHOLOGY

- Childhood irritability + depression: persists into adolescence:
  - Significant decrease in reward circuitry (striatum, ACC, Nacc,
- Impact of (ACE) adverse childhood experience:
  - Abuse, neglect, conflict, substance abuse
  - Combination with irritability leads to decreased cognition, mood, depression

CHILDHOOD PREDICTORS OF LATER PSYCHOPATHOLOGY

- Best predictors: poverty + childhood irritability + adverse experiences.
- Childhood depression: significant decrease in dopaminergic reward activation in corticostriatal circuit from n. accumbens;
  - Can occur in pre-school age children
  - Persists into adolescence
  - Is treatable (mother as co-treater)
- Mother's depression increases risk for childhood depression

EFFECT OF STRESS ON FETUS

PLACENTAL CRH

- CRH (corticotropin-releasing hormone)simulates the anterior pituitary to produce ACTH that ultimately increases the production of glucocorticoids (cortisol in humans)
- CRH is also produced in the placenta (pCRH)
  - Regulates fetal growth
  - Maternal cortisol levels early in pregnancy predict pCRH levels in 3rd trimester
  - high pCRH is associated with fearful temperament, emotional problems, depression, cognitive deficits and thinner PFC thickness.

Sandman 2018; Am J Psychiat 175:471

MATERNAL ANXIETY AFFECTS FETUS IN UTERO

- Vulnerability for anxiety disorders in children of affected parents may be moderated through genetic variations of the COMT gene.
  - This gene is well expressed in brain before birth;
  - Starts its PFC expression in infancy
  - Peaks during early adulthood
- Regulates catecholamine signaling in PFC, especially dopamine (val allele leads to lower DA in PFC)
- May explain variation in phenotypic outcomes in the offspring associated with maternal anxiety or wellbeing.

Qiu 2015; Am J Psychiatry 172:163

*EFFECT OF STRESS DURING PREGNANCY ON FETUS

- High stress during pregnancy decreases DNA methylation of genes
  - These genes are associated with increased
  - glucocorticoid transfer across the placenta
  - Cause elevated maternal cortisol transfer to fetus
- The specific gene codes for an enzyme that inactivates cortisol. More methylation of this gene leads to more fetal cortisol exposure and changes in brain-behavior development

Monk 2016; Am J Psychiatry 175:705

THE AMERICAN JOURNAL OF PSYCHIATRY

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OFFSPRING OF TRAUMA SURVIVORS ARE AT INCREASED RISK FOR MENTAL AND PHYSICAL ILLNESS

Am J Psychiatry. 2014;171(8):872-880. doi:10.1176/appi.ajp.2014.13121571

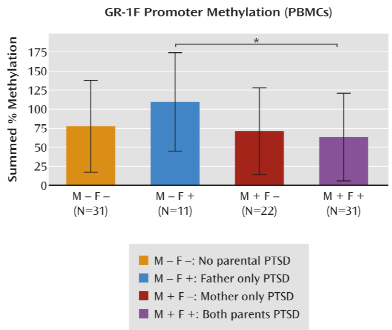

Figure Legend:

Percent Methylation in the Exon 1_F Promoter of the Glucocorticoid Receptor Gene in Peripheral Blood Mononuclear Cells (PBMCs) in Offspring[aa] Results are based on the presence or absence of maternal and paternal posttraumatic stress disorder, controlling for parental Holocaust exposure, age, smoking history, and PBMC type. The represented data (mean, standard deviation) are based on an analysis of covariance using raw data. The post hoc statistic (*) is from the analysis using transformed (natural logarithm) data.

Yehuda, 2014

EARLY LIFE STRESS

"Some children are like dandelions; they survive and thrive anywhere. Others are like orchids; they thrive under a nourIshing and caring environment but wither under neglect".

ELS can have enduring negative impact on the quality of life and social interactions that can contribute to lifelong risk for cognitive disability and mood disorders.

ELS may affect amygdala maturation.

ELS is a strong link between alcohol abuse and suicide.

Childhood adversity affects adult life

- Individuals who experienced threat histories had increased DNA methylation that correlates with advanced biological age;
  - Also correlates with early puberty
- Histories of deprivation do not correlate with increased DNA methylation, but had delayed puberty.
- Altered DNA methylation may be passed on to the next generation.

Roberts 2018; Transl Psychiatry

CNS CONSEQUENCES OF EARLY LIFE STRESS-II

- Childhood maltreatment is associated wih alterations in white-matter tracts
- History of child abuse and neglect show persistent neurobiological alterations:
  - Reduced hippocampal size
  - Cognitive dysfunction
  - Increased cortisol dysregulation
  - Increased risk for depression and anxiety disorders

EFFECT OF EARLY CHILDHOOD NEGLECT-I

- Human brain requires a wide variety if experiences and environmental inputs to develop normally
  - Typical early environment is rich in sensory, linguistic and social experiences that occur in the context of interactions with a caregiver and that provide a rich source of cognitive stimulation;
  - This shapes early learning by directing children's attention to important cues in the environment through vocalizations, facial displays, and tactile stimulation.

McLaughlin 2017; Biol Psychiat 82:462

INFANT TEMPERAMENT AND AMYGDALA SENSITIVITY

- The amygdala has a central role in the processing of novelty and emotion in the brain.
  - Four month old infants called high reactive (HR) demonstrate a distinctive pattern of vigorous motor activity and crying to specific unfamiliar visual, auditory and olfactory stimuli.
- The HR infant phenotype predicts greater amygdala reactivity to novel faces almost two decades later in adults.
  - Males who were HR infants show particularly high levels of reactivity to novel faces in the amygdala.

Schwartz, 2011, Molecular Psychiatry ,

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Schwartz, 2011, Molecular Psychiatry , 1–9