



Mood Disorders

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Objectives

- *Mood, affect, mood disorders (mood D/O's)*
- *Nosology, epidemiology, treatment (tx) of:*
 - Major depressive disorder (MDD)
 - Persistent depressive disorder
 - Premenstrual dysphoric disorder
 - Disruptive mood dysregulation disorder

-

- **Mood** - The subjective sense indicates the long, deep and constant feeling that affects a person, his functioning and his environment
- **Affect** - An objective impression of the examiner or other persons, and marks the passing and instantaneous emotion expressed in the present and observable
 - a. Not compatible or compatible with the content of thinking
 - b. The situation ...
 - In normal mode a person moves in range of MOODS with varying degrees of control
 - Mood disorders control the patient

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Mood v. Affect

“mood”

- a *sustained* emotional attitude
- typically garnered through pt self-report

“affect”

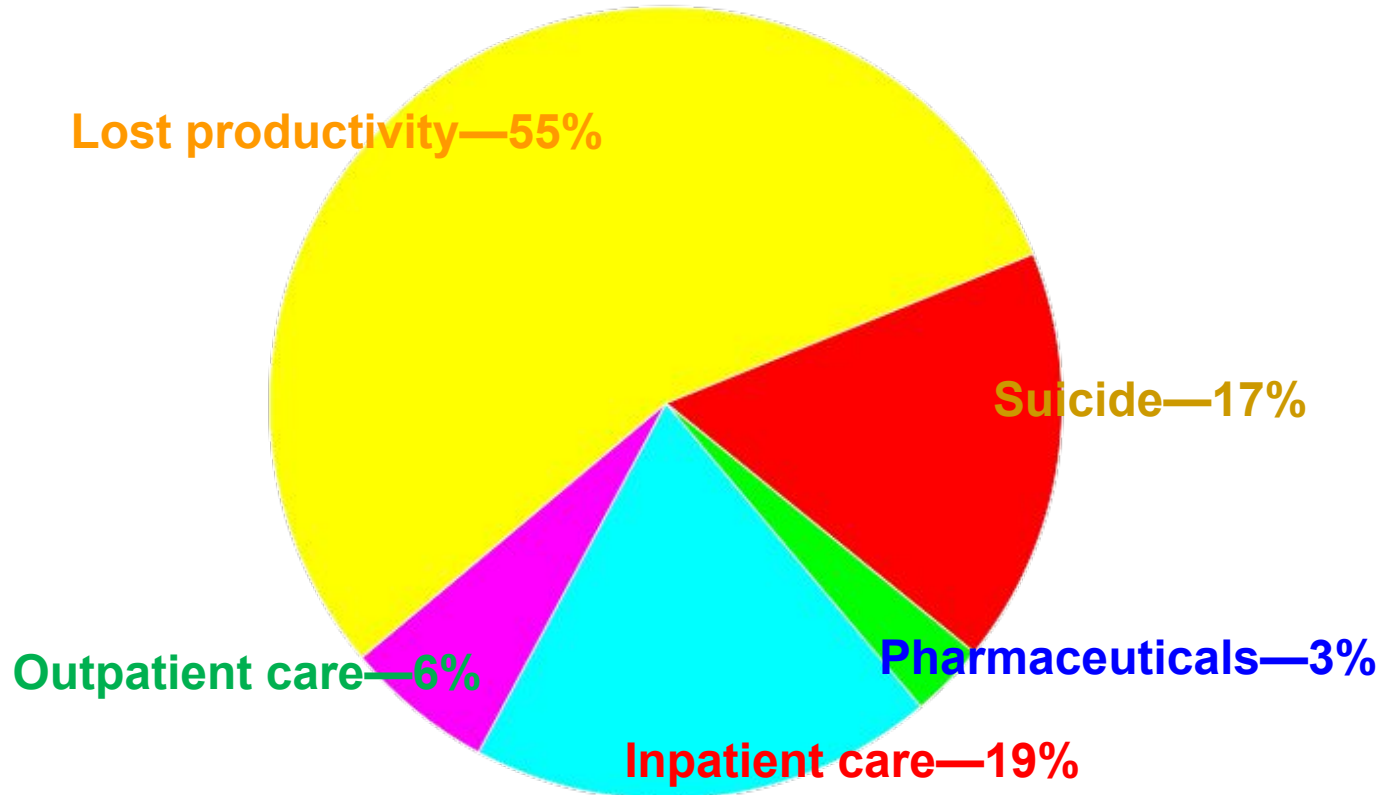
- the way a pt’s emotional state is *conveyed*
- relates more to *others’* perception of the pt’s emotional state, responsiveness

Mood disorders

Ψ conditions where mood is primary, the predominant problem.

Major Depressive Disorder

Economics of Depression — U.S.A. Data - Total Annual Cost ~\$44 Billion



Major Depressive D/O (MDD)

Epidemiology (Kendler et al, 1993; Schlessner & Altshuler, 1983)

- leading cause of disability among adults under 45y of age
- lifetime prevalence of 12% in ♂, 20% in ♀
- relative risk (RR) of 2-3 in 1^o relatives of probands; 41%:13% (monozygotic: dizygotic) concordance
- incidence peaks in 20s (but onset in late life not uncommon)

Sleep
Interest
Guilt

Energy

Concentration
Appetite
Psychomotor
Suicide

Question:

When does a major depressive episode (MDE) \neq Major Depressive Disorder?

Major Depressive D/O (MDD)

EXCLUSIONS:

- not attributable to a substance/**medication** or **another** medical condition
- no prior [endogenous] episodes of mania or hypomania

w/ seasonal pattern

w/ anxious distress

w/ mood-*[congruent, incongruent]*
psychotic features

Major depressive disorder

w/ mixed features

w/ peripartum onset

w/ catatonia

w/ atypical features

w/ melancholic features

≥2 of the following:

- keyed-up/tense
- unusually restless
- can't concentrate b/c of worry
- fear something awful may happen
- might lose control

w/ seasonal pattern

w/ anxious distress

w/ mood-*[congruent, incongruent]*
psychotic features

Major depressive disorder

w/ mixed features

w/ peripartum onset

w/ catatonia

w/ atypical features

w/ melancholic features

≥3 of the following nearly everyday during an MDE:

[drawn from list of sx's for a manic/hypomanic episode, minus distractibility;
this list includes elevated/expansive mood, insomnia, grandiose, flight of Ideas,
activity (goal-directed), sexual, talkative (i.e., pressured speech)]

w/ seasonal pattern

w/ anxious distress

w/ mood-*[congruent, incongruent]*
psychotic features

Major depressive disorder

w/ mixed features

w/ peripartum onset

w/ catatonia

w/ atypical features

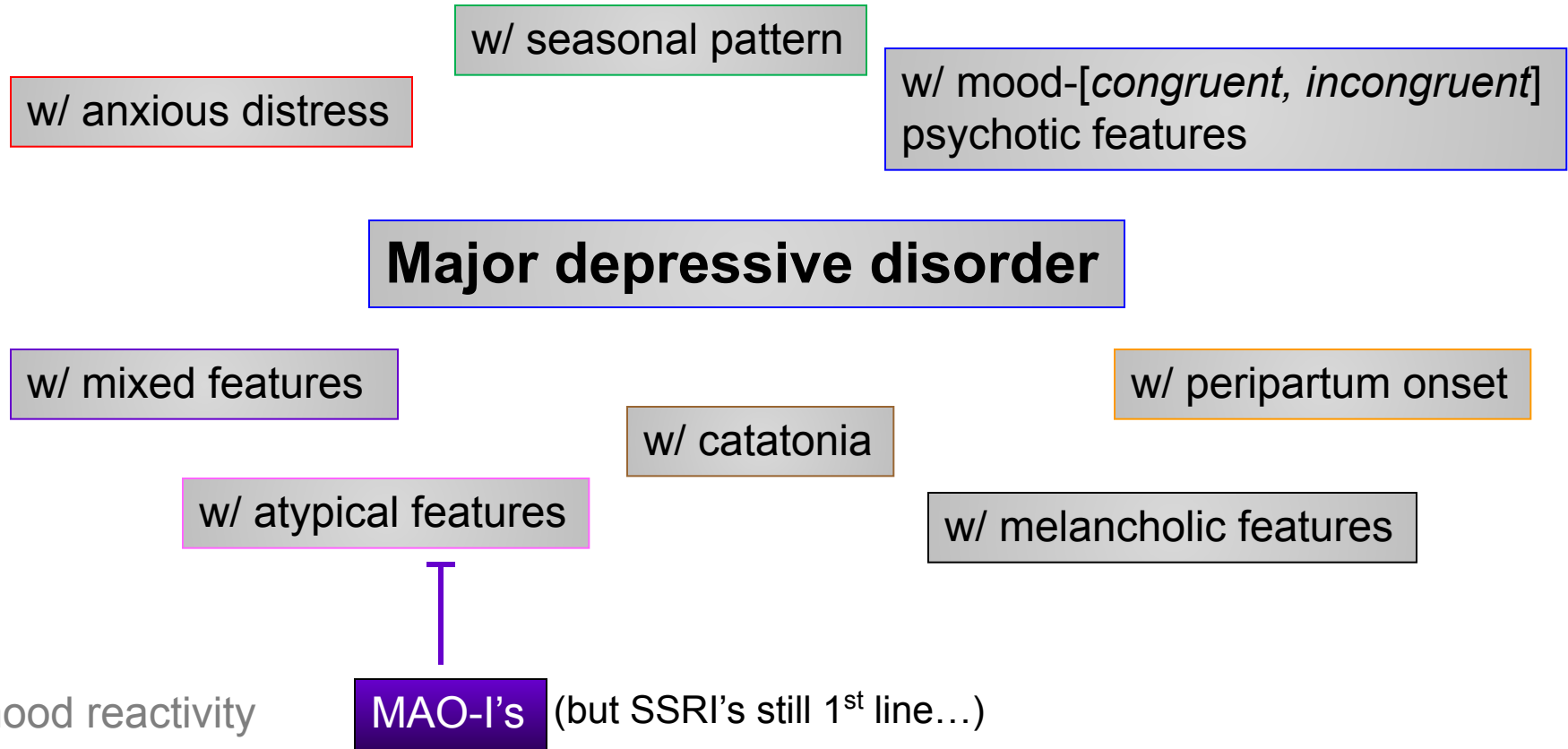
w/ melancholic features

≥1 of the following during the most severe portion of the current episode:

- absolute anhedonia or absolute mood non-reactivity

plus ≥3 of the following:

- a distinct quality of depressed mood (e.g., worse than prior MDEs)
- worse in the AM
- early AM awakening (by at least 2h)
- marked PMA or PMR
- significant appetite or wt loss
- excessive guilt



• mood reactivity

plus ≥ 2 of the following:

- significant appetite or wt increase
- hypersomnia
- long-standing interpersonal rejection sensitivity leading to social/work problems

w/ seasonal pattern

w/ anxious distress

w/ mood-*[congruent, incongruent]*
psychotic features

Major depressive disorder

w/ mixed features

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w/ melancholic features

- delusions &/or hallucinations
- examples of congruent delusions: personal inadequacy, guilt, death, nihilism, deserved punishment

w/ seasonal pattern

w/ anxious distress

w/ mood-*[congruent, incongruent]*
psychotic features

Major depressive disorder

w/ mixed features

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during most of the episode, ≥ 3 of the following:

- stupor
- catalepsy (passive induction of a posture held against gravity)
- waxy flexibility
- mutism
- negativism
- posturing (spontaneous, maintenance against gravity)
- mannerism (odd caricature of a normal action)
- stereotypy
- agitation (indep of external stimulus)
- grimacing
- echolalia or echopraxia

w/ seasonal pattern

w/ anxious distress

w/ mood-*[congruent, incongruent]*
psychotic features

Major depressive disorder

w/ mixed features

w/ peripartum onset

w/ catatonia

w/ atypical features

w/ melancholic features

- during pregnancy or in the 4wks after delivery

w/ seasonal pattern

w/ anxious distress

w/ mood-*[congruent, incongruent]*
psychotic features

Major depressive disorder

w/ mixed features

w/ peripartum onset

w/ catatonia

w/ atypical features

w/ melancholic features

- relapses and remissions occur at characteristic times of the year
- at least 2 seasonal MDE's in the last 2y (and no non-seasonal MDEs during this period)
- seasonal episodes outnumber non-seasonal episodes (lifetime)

If a patient always gets depressed with season unemployment (or the beginning of the school year), would we call this 'w/ seasonal pattern?' **No.**

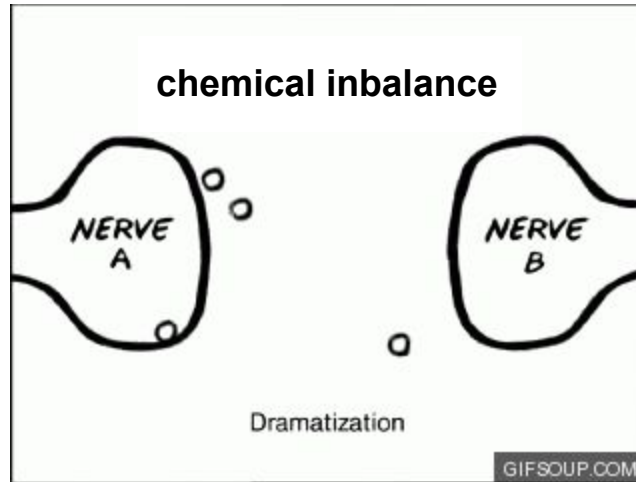
The monoamine hypothesis (1965)

iproniazid (1957)

imipramine (1959)

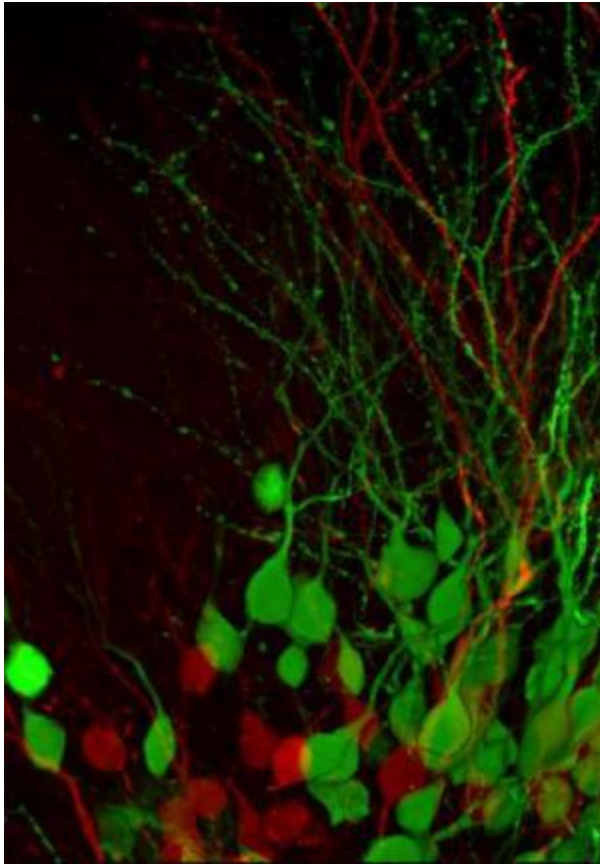


Joseph Schildkraut



Question:

Do antidepressants have additional actions besides inhibition of reuptake transporters?



[Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus.](#)

Malberg JE, Eisch AJ, Nestler EJ, Duman RS.
J Neurosci. 2000 Dec 15;**20**(24):9104-10

[Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants.](#)

Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R.
Science. 2003 Aug 8;**301**(5634):805-9.

[Depression and antidepressants: insights from knockout of dopamine, serotonin or noradrenaline re-uptake transporters.](#)

Haenisch B, Bönisch H.
Pharmacol Ther. 2011 Mar;**129**(3):352-68. Epub 2010 Dec 13. Review.

[Nicotinic acetylcholine receptor antagonistic activity of monoamine uptake blockers in rat hippocampal slices.](#)

Hennings EC, Kiss JP, De Oliveira K, Toth PT, Vizi ES.
J Neurochem. 1999 Sep;**73**(3):1043-50.

[Block of an ether-a-go-go-like K\(+\) channel by imipramine rescues egl-2](#)

[excitation defects in *Caenorhabditis elegans*.](#)

Weinshenker D, Wei A, Salkoff L, Thomas JH.
J Neurosci. 1999 Nov 15;**19**(22):9831-40.

Subsequent hypotheses about MDD

altered glutamatergic transmission

↓'d GABAergic transmission

monoamine-Ach imbalance

disruption of endogenous opioid signalling

neurosteroid deficiencies

thyroxine abnormalities

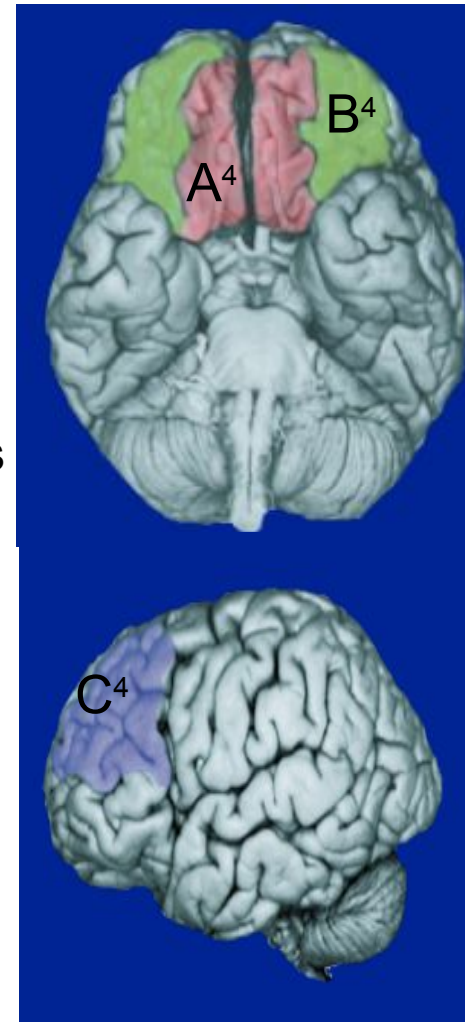
cytokine-mediated x-talk betw immune system & CNS

circadian abnormalities

(specific brain structure/circuit dysfxns...)

Key brain areas involved in regulation of mood

- **(A)** Ventromedial prefrontal cortex (VMPFC)¹
 - Modulates pain and **aggression**, and sexual and eating behaviors
 - Regulates autonomic and neuroendocrine response
- **(B)** Lateral orbital prefrontal cortex (LOPFC)²
 - **Activity is increased in depression**, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and panic disorder
 - Corrects and inhibits maladaptive, perseverative, and **emotional responses**
- **(C)** Dorsolateral prefrontal cortex (DLPFC)³
 - Cognitive control, solving complex tasks, and manipulation of information in working memory
 - **Hypoactivity of DLPFC in depression has been associated with neuropsychological manifestation**



1. Öngür D, Price JL. *Cereb Cortex*. 2000;10(3):206-219.
2. Drevets WC. *Annu Rev Med*. 1998;49:341-361.
3. MacDonald AW III, et al. *Science*. 2000;288(5472):1835-1838.
4. Davidson RJ, et al. *Annu Rev Psychol*. 2002;53:545-574

Key brain areas involved in regulation of mood (cont.)

- **(A) Amygdala:** regulates cortical arousal neuroendocrine response to surprising and ambiguous stimuli¹
 - Role in emotional learning and memory
 - **Activation of amygdala correlates with degree of depression²**

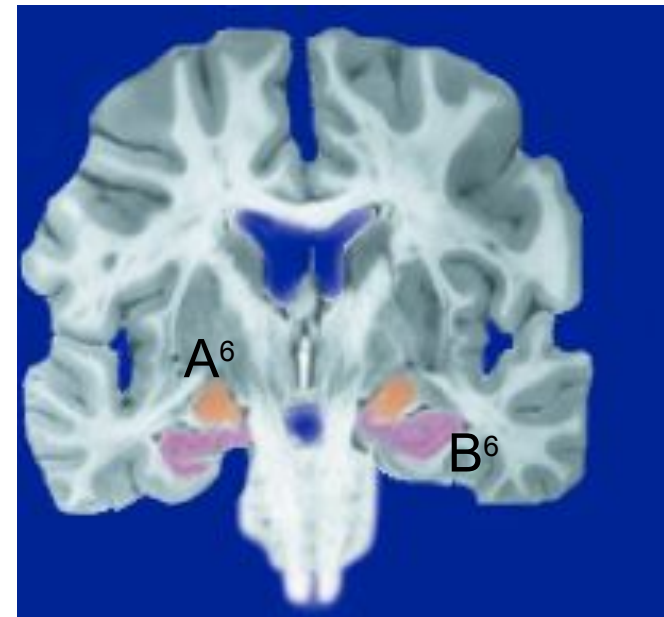
- Implicated in tendency to ruminate on negative memories²

- **(B) Hippocampus:** has a role in episodic, contextual learning and memory^{3,4}

- Rich in corticosteroid receptors⁵

- Regulatory feedback to hypothalamic-pituitary-adrenal axis

- Hippocampal dysfunction may be responsible for inappropriate emotional responses



Davidson RJ. *Psychophysiology*. 2003;40(5):655-665.

Drevets WC. *Curr Opin Neurobiol*. 2001;11(2):240-249.

Squire LR, Knowlton BJ. In: Gazzaniga MS, ed. *The New Cognitive Neurosciences*; 2000:765-779.

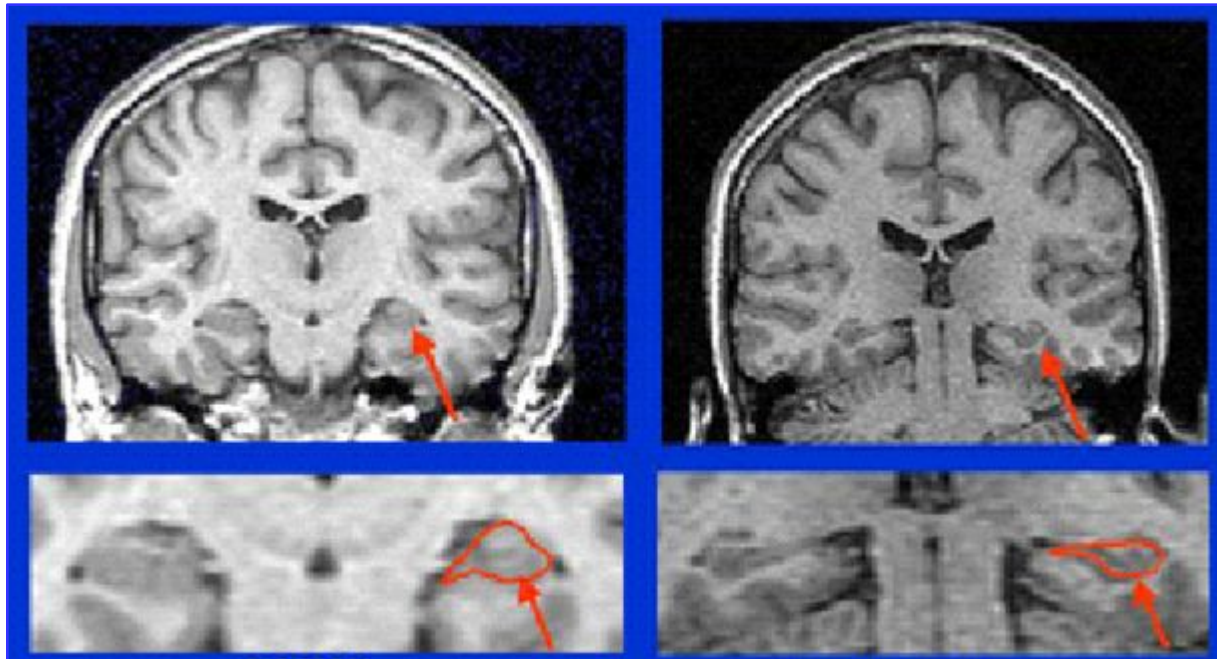
4. Fanselow MS. *Behav Brain Res*. 2000;110(1-2):73-81.

5. Reul JM, De Kloet ER. *J Steroid Biochem*. 1986;24(1):269-272.

6. Davidson RJ, et al. *Annu Rev Psychol*. 2002;53:545-574.

Brain atrophy in depression?

Atrophy of the Hippocampus in Depression¹



Normal²

Depressio

1. Bremner JD, et al. *Am J Psychiatry*. 2000;157(1):115-118.
2. Images courtesy of J Douglas Bremner, MD, Yale University.

Major Depression: Cognition

Learned helplessness (Seligman) (Seligman & Maier, 1967)

- Attribution of lack of control over stress leads to anxiety and depression
- Depressive attributional style is *internal, stable, and global*

Negative cognitive styles (Beck)

Depression is the result of negative interpretations (wearing gray instead of rose colored glasses, e.g. Eeyore in Winnie the Pooh)

Key Components of Negative Interpretations

- Maladaptive attitudes (negative schema) 'I'm no good' (self), 'Others can't be trusted' (others) and 'effort does not pay off' (world)
- Automatic thoughts
- Cognitive triad
- Errors

Seligman & Beck

Seligman

Attributions are:

- Internal
- Stable
- Global

I am inadequate **internal** everything (**global**) and I always will be (**stable**).

“Dark glasses about **why** things are bad”

Beck (**Negative Triad**)

Negative interpretations about:

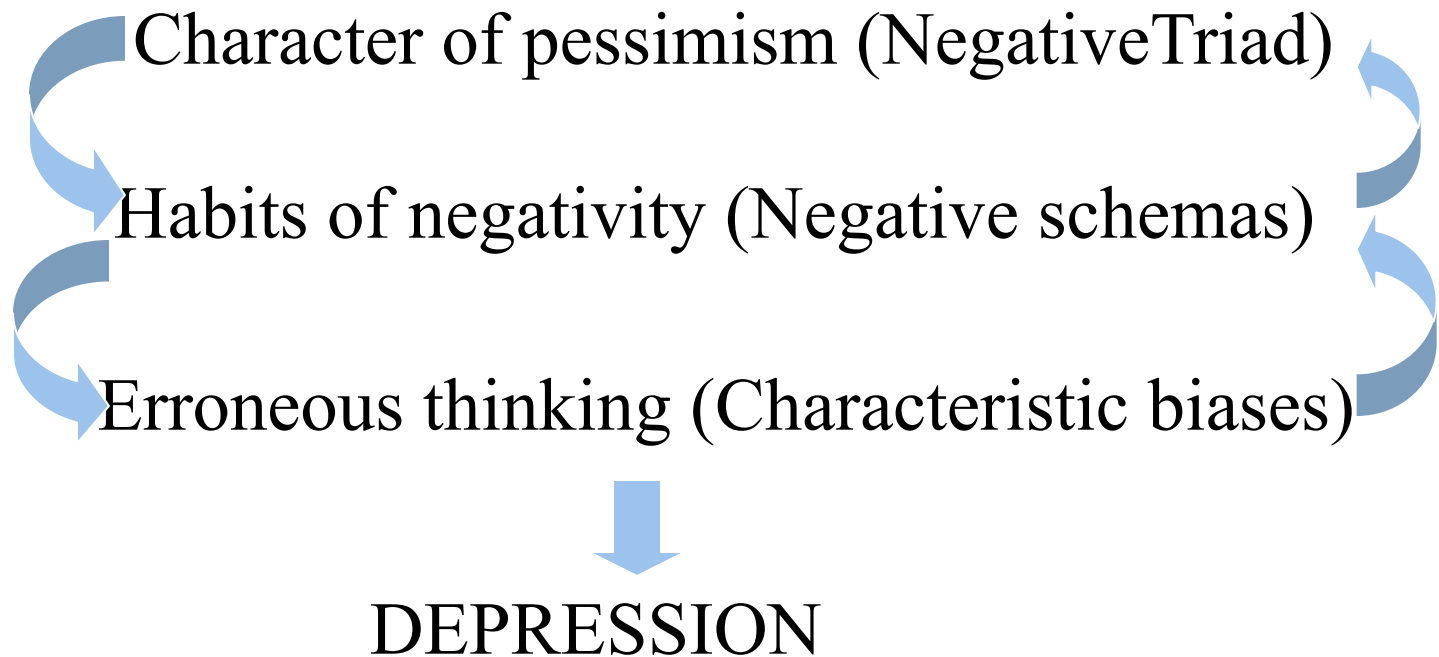
- Themselves
- Immediate world
- Future

I am not good at school (**self**). I hate this campus (**world**). Things are not going to go well in college (**future**).

“Dark glasses about **what** is going

Cognitive theories

- Beck's theory:



Characteristic biases

- Arbitrary inference
- Selective abstraction
- Overgeneralization
- Magnification and minimization

Behavioral theories

- Learned helplessness/hopelessness is a behavioral theory with a cognitive twist.
- Reduction in reinforcement leads to a reduction in activity.
- Depressive behaviors *are* reinforced.
- Depressed

Availability of reinforcers

- The amount of reinforcement available is a function of
 - Personal characteristics
 - Environment or milieu
 - Repertoire

Interpersonal theory

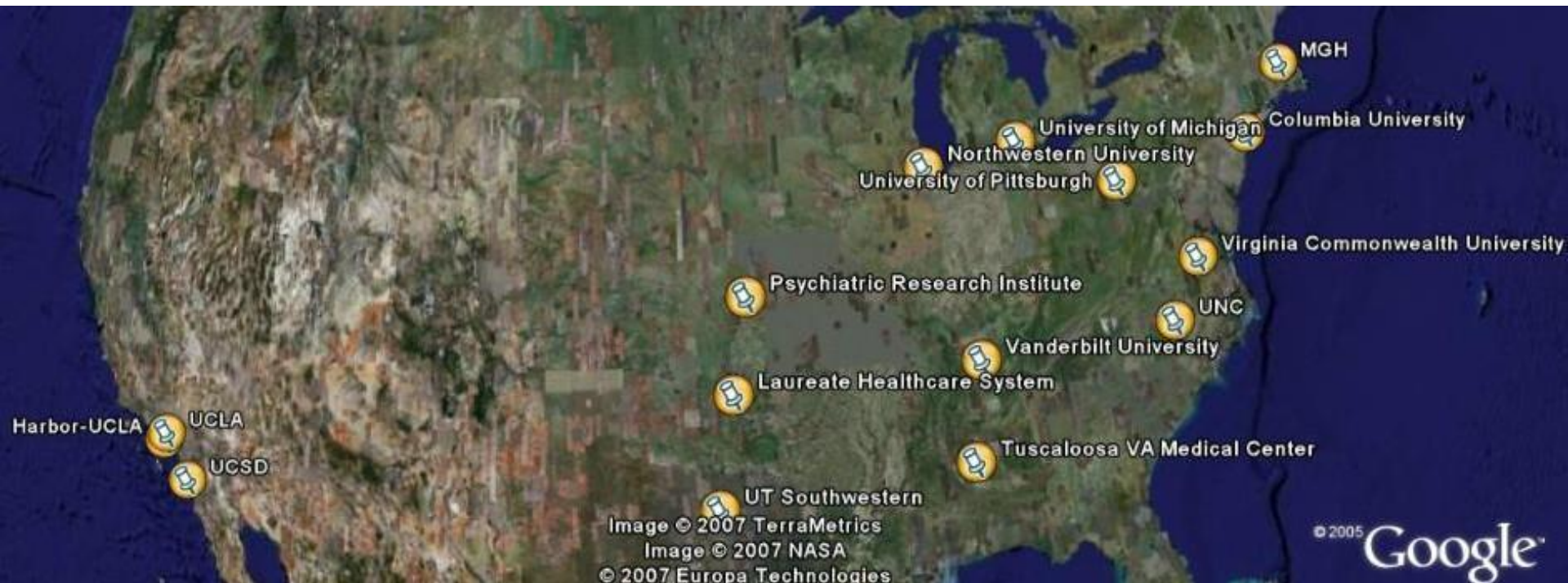
- Reduced interpersonal support
- Experiences of rejection
 - Due to social structure
 - Inadequate social networks
 - Others may dislike them
 - Elicited by patient
 - Consequences of behavioral choices
 - Critical comments by spouse
 - Poor social skills and seeking reassurance

MDD tx options

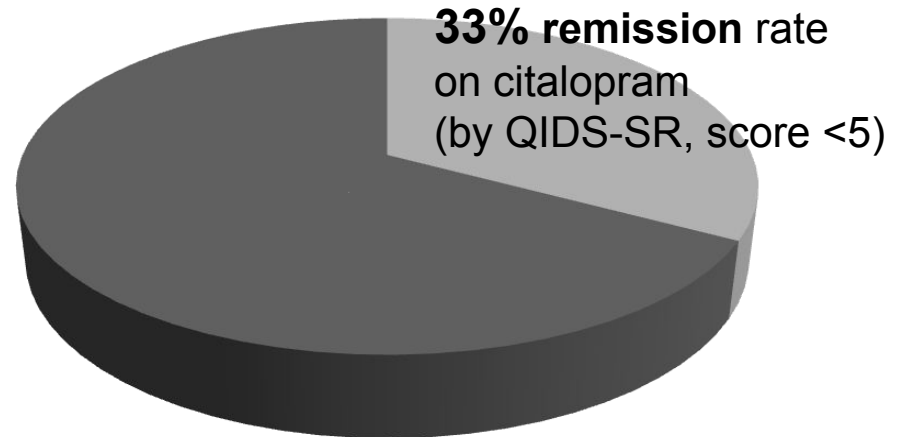
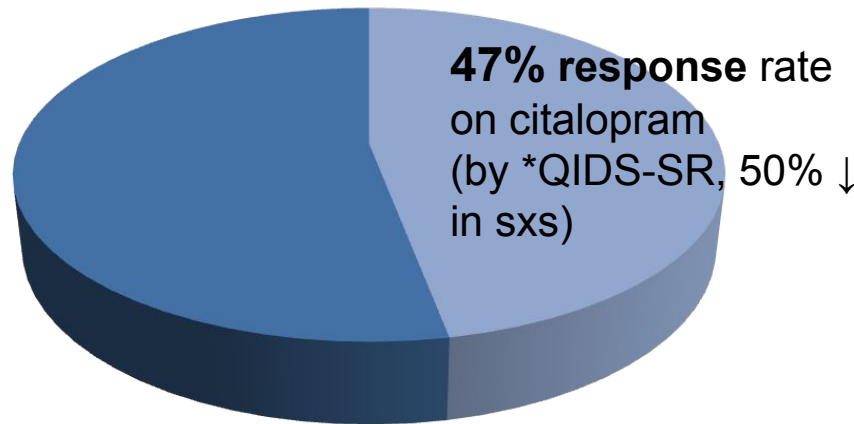
- selective serotonin reuptake inhibitors (SSRIs)
 - fluoxetine (PROZAC), 20-80 mg/d
 - citalopram (CELEXA), 20-40 mg/d
 - escitalopram (LEXAPRO), 10-20 mg/d
 - sertraline (ZOLOFT), 50-200 mg/d
 - paroxetine (PAXIL), 20-50 mg/d
- serotonin-norepinephrine reuptake inhibitors (SNRIs)
 - venlafaxine XR (EFFEXOR XR), 37.5-225 mg/d
 - desvenlafaxine (PRISTIQ)
 - duloxetine (CYMBALTA), 30-120 mg/d
- others
 - bupropion SR, XL (WELLBUTRIN)
 - 100-200 mg BID (SR)
 - 150-450 mg/d (XL)
 - mirtazapine (REMERON), 15-45 mg/d
 - trazodone, 50-200mg/noc (for sleep)
 - nefazodone
- tricyclic antidepressants (TCADs)
 - amitriptyline nortriptyline
 - imipramine desipramine
- monoamine oxidase inhibitors (MAO-Is)
 - typically, non-selective & irreversible
 - MAO-A (NE, EPI, 5HT, DA)
 - MAO-B (trace amines, DA)
 - why we “wash-out”
 - 5HT syndrome
 - HTNsive crisis
 - selegiline (EMSAM)
- [additional] augmenting agents
 - Li⁺
 - T3, 25 mcg/d
 - buspirone (BuSPAR), 5-30 mg BID
 - atypical antipsychotics

Sequenced Treatment Alternatives for the Relief of Depression (STAR*D)

- major NIMH-funded study (PI: A. John Rush) w/ 14 regional centers & 41 clinical sites
- initial enrollment of 4,041 patients
- aim: which tx algorithms work best after an initial failure to remit non-psychotic depression w/ an antidepressant?



Sequenced Treatment Alternatives for the Relief of Depression (STAR*D), n = 2,876 (qualifying pts)



Rx choice:

- according to side effects (SE's), comorbid condn's / risks (GMC & Ψ), ?FmRxHx
- 6-8wk trials each (preferable)
- augmentation v. switch?

*QIDS-SR = Quick Inventory of Depressive Symptomatology, Self-Report (range 0-27)

<http://www.ids-qids.org/>

MDD tx options

- Ψtherapy

- cognitive bx therapy (CBT)
- interpersonal therapy (IPT)
- psychodynamic therapy

[A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression.](#)

Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, Markowitz JC, Nemeroff CB, Russell JM, Thase ME, Trivedi MH, Zajecka J.

N Engl J Med. 2000 May 18;342(20):1462-70.

- interventional Ψ

- electroconvulsive therapy (ECT)
- transcranial magnetic stimulation (TMS)
- vagal nerve stimulation (VNS)
- deep brain stimulation (DBS)

- 80-90% remission rate
- 50-80% relapse rate (6mos out)
- SEs: musculoskeletal, headache, *cognitive*
- mania, catatonia, NMS (other indixn's)

Devanand DP et al, 1991

- other

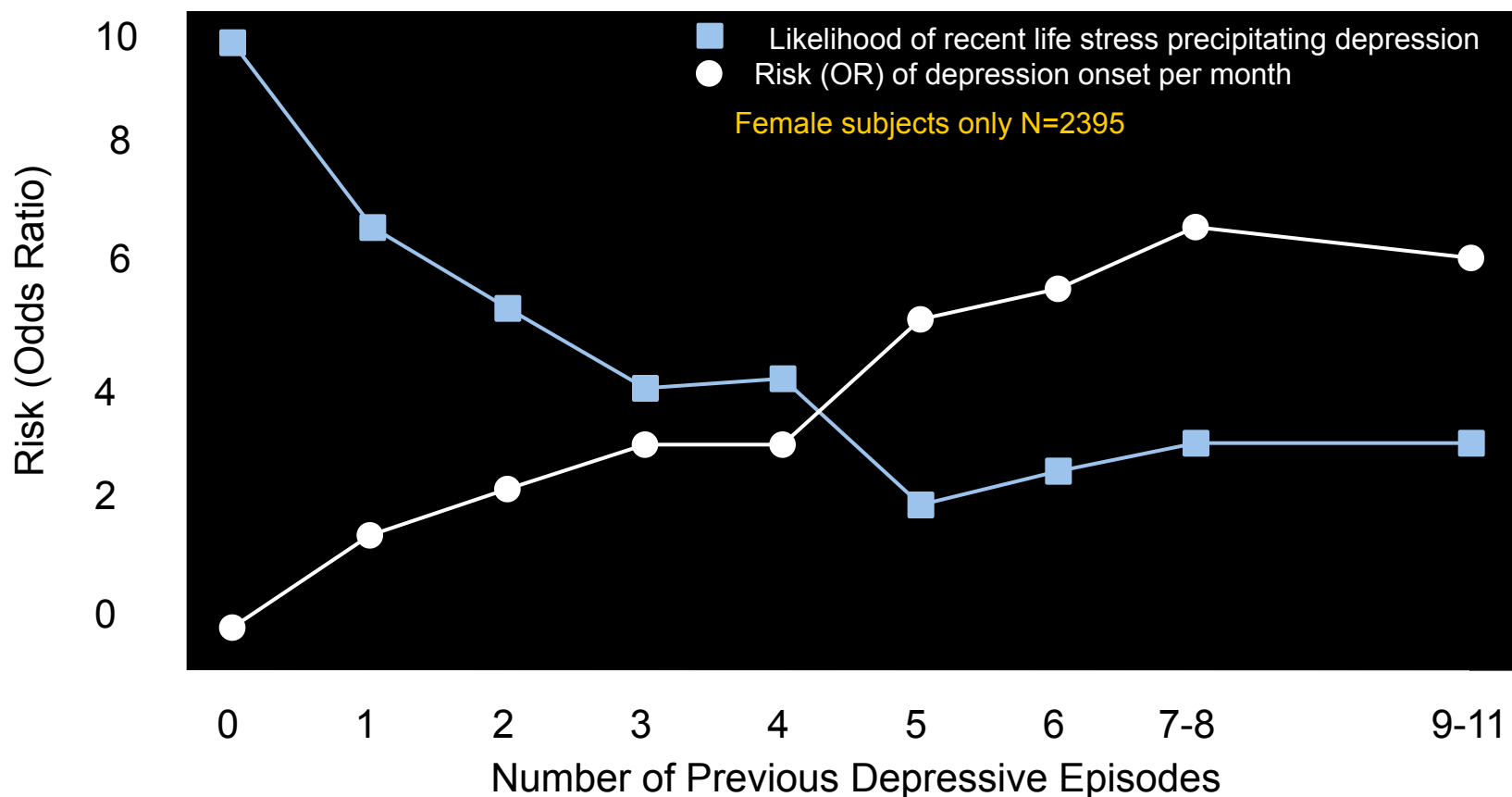
- lightbox therapy (mostly for MDD w/ seasonal features)

Major Depressive D/O (MDD)

NATURAL HISTORY (Frank E and Thase ME, 1999 & DSM-5)

- recovery usually begins:
 - w/in 3mos for two in five indivs
 - w/in 1y for four in five indivs

Progression of depression — “kindling” phenomenon: Adverse effects of each successive episode



Persistent depressive disorder (dysthymia)

- 2y of depressed mood (1y in children/adolescents) *most of the day, more days than not*, plus 2 of the following:
 - appetite disturbance (↓ or ↑) veg
 - sleep disturbance (↓ or ↑) veg
 - ↓energy E
 - ↓esteem E
 - poor [] C
 - hopeless H
- never sx-free for more than 2mos at a time
- **overlapping dx of MDD is now allowed**
- there has never been mania, hypomania, or cyclothymia

ersistent MDE

rmittent MDE's, w/ current episode

rmittent MDE's, w/o current episode

--

Persistent depressive disorder (dysthymia)

- may be more treatment-resistant (Tx^R) than straightforward MDD

EPIDEMIOLOGY

- lifetime prevalence = 6%
- 12-mo prevalence = 0.5%, compared w/ 1.5% for MDD
- high comorbidity w/ personality d/o's (particularly clusters B, C)

Case 1.

36yo F presenting w/ 3mos of ↓mood. She reports getting only ~4h of sleep/noc b/c of regular early AM awakenings. She feels drained everyday, all day long. She's gained about 4.5 kg in the last 2mos.

- What else would you like to ask?
- How would you work-up this patient?
- In the meantime, what would you dx and what would be your tentative tx plan?

She returns 1mo later and reports that her mood continues to spiral downward. Now, she adds that she's starting to think more morbid thoughts and that maybe it wouldn't be such a bad thing if she weren't around anymore.

- What would you ask now?
- How would you revise your tx plan?

The pt's sxs are finally stabilized and she returns at a later date w/ her sxs in remission x 1mo. "Doctor, I'm feeling so much better now. Do you think I can stop my psych Rx's?"

- How would you answer?

Premenstrual dysphoric d/o

Criterion A. In most menstrual cycles, ≥ 5 sx in the final week before onset of menses, w/ improvement w/in a few days after onset of menses, and near-absent in the week post-menses

Premenstrual dysphoric d/o

(M)ood (labile &/or irritable &/or anxious)

Sleep

Interest

Body

Energy

Concentration

Appetite

Out of control

Disruptive mood dysregulation disorder

- *severe recurrent temper outbursts (verbal or behavior) grossly disproportionate to the situation
- the outbursts are not developmentally appropriate
- on average, outbursts are $\geq 3x/wk$
- *inter-episode mood is typically irritable, corroborated by others

Bipolar disorder

Bipolar D/O (BD)

Epidemiology

	gender	prevalence	onset
BD I	♀ = ♂	0.4 – 1.6%	18yo
BD II	♀ > ♂?	0.5%	mid-20s
cyclothymic d/o	♀ = ♂	0.4 – 1.0%	adolescence / early adulthood

Bipolar D/O (BD)

Manic episode:

- elevated mood & ≥1wk of at least 3 of the following sx's (4 if mood irritable)

Distractible
Insomnia (actually, ↓'d need for sleep)
Grandiose

Flight Of Ideas
Activity (goal-directed)
Sexual (or spending or other activities w/
↑↑potential for painful consequences)
Talkative (i.e., pressured speech)

Bipolar Disorder (BD)

EXCLUSIONS:

- **another** medical cause
- substance/**medication** causes

Bipolar Disorder (BD)

MORE on 'w/ mixed features'...

Manic/hypomanic, w/ mixed features	Depressed, w/ mixed features
Full criteria met for manic or hypomanic.	Full criteria met for depressive.
≥3 from SIG E CAPS (<u>minus appetite, sleep</u> sxs)	≥3 from DIG FAST (<u>minus distractibility</u> , which is replaced by elevated mood)

		Sleep
		Interest
		Guilt
		Energy
	Flight Of Ideas	Concentration
	Activity (goal-directed)	Appetite
	Sexual (or spending or other activities w/ ↑↑potential for painful consequences)	Psychomotor
	Talkative (i.e., pressured speech)	Suicide
Distractible		
Insomnia (actually, ↓'d need for sleep)		
Grandiose		

Case 1 - continued

Prior hx to date:

- 36yo F w/ 3mos of depressed mood
- tx'd w/ an SSRI
- sxs improved, asked if she could DC her SSRI, and advised against doing so

After your intervention, the pt agrees to remain on her Rxs and continues to do well for the next wk. Sometime later, you receive a call from her husband who reports that the pt has been up all night every night for about 3 or 4 nights in-a-row, making consecutive (and very uncharacteristic) \$500-1,000 purchases on eBay--and has drilled two large holes in the ceiling of their home (without checking with anyone else first) to create some new "skylights."

- How would you revise your dx?
- What changes would you make to your tx plan?

Case 1 - continued

Per DSM-5:

“A full manic/hypomanic episode that emerges during antidepressant tx but persists at a fully syndromal level beyond the physiological effect of that tx is sufficient evidence for a manic/hypomanic episode dx. However, caution is indicated so that one or two symptoms are not taken as sufficient...nor necessarily indicative of a bipolar diathesis.”

Biology of Bipolar D/O (BD)

- failure of linkage studies



- Janice Egeland – 2 decades of work w/ Old Order Amish, BAD []'d in particular Fm's



- David Housman – restriction fragment length polymorphism (RFLP) approach; started w/ chr11 (b/c of concurrent work w/ anemias, thalassemias)



Pedigree 110:

19 of 81 members w/ mood d/o;
14 w/ mania + depression;
5 w/ only depression

Bipolar affective disorders linked to DNA markers on chromosome 11

Janice A. Egeland*, **Daniela S. Gerhard^{†||}**, **David L. Pauls[‡]**, **James N. Sussex***,
Kenneth K. Kidd[§], **Cleona R. Allen***, **Abram M. Hostetter*** & **David E. Housman[†]**

* Department of Psychiatry, University of Miami School of Medicine (D-29), PO Box 016960, Miami, Florida 33101, USA

[†] Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

[‡] Child Study Center and Department of Human Genetics and [§] Departments of Human Genetics and Psychiatry, Yale University School of Medicine, New Haven, Connecticut 06510, USA

An analysis of the segregation of restriction fragment length polymorphisms in an Old Order Amish pedigree has made it possible to localize a dominant gene conferring a strong predisposition to manic depressive disease to the tip of the short arm of chromosome 11.

*'s

- 2 accompanying papers (same issue of *Nature*) unable to replicate chr11 assocn's in independent pedigrees

• Linkage across five loci (differentiation) across 1 new class to men

Re-evaluation of the linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish

John R. Kelsoe^{*}, Edward I. Ginns^{*}, Janice A. Egeland[†], Daniela S. Gerhard[‡], Alisa M. Goldstein[§], Sherri J. Bale[§], David L. Pauls^{||}, Robert T. Long^{*}, Kenneth K. Kidd[¶], Giovanni Conte^{*}, David E. Housman[#] & Steven M. Paul^{††}**

Reanalysis of an Old Order Amish pedigree, to include several new individuals and two changes in clinical status, markedly reduces the probability of linkage between bipolar affective disorder and the Harvey-*ras-1* oncogene and insulin loci on chromosome 11. This linkage can be excluded using a large lateral extension of the original Amish pedigree.

Biology of Bipolar D/O (BD)

Linkage studies

- 6q (LOD 4.19 narrow), 8q (LOD 3.40 broad) (still hold-up in meta-analyses – e.g., McQueen et al, 2005)

Genome-wide association studies (GWAS)

- Wellcome Trust (2007) – strongest signal at rs420259 (chr16p12)
 - intronic to *PALB2* (partner & localizer of *BRCA2*), assoc'd w/ medulloblastoma
 - same signal might be more relevant to *DCTN5* (dynactin 5)



More on select GWA-identified candidates

- *CACNA1C*
 - α_1 subunit of a voltage-dependent Ca^{2+} channel
 - per citations in PGC paper, separate literature has associated mutations w/ brain imaging changes (both strux and fxnl)
 - also an assoc'n finding in schizophrenia, MDD (not genomewide-significant)
- *ANK3*
 - ankyrin G
 - isoforms specific to nervous system
 - localization in axonal initial segments, nodes of Ranvier
 - fxn in ion channel maintenance? cell adhesion?
- *SYNE1*
 - synaptic nuclear envelope protein 1
 - not emphasized in PGC paper, but has prior literature in syndromes r/t ataxia, muscular dystrophy, mental retardation
- *ODZ4*
 - odd oz / ten-m homolog 4
 - pair-rule gene
 - cell-surface signalling, neuronal pathfinding

Bipolar Disorder (BD) – treatment

The old standard:

- mood stabilizer + reuptake blocker



FDA-approved Rx's for BD

Generic Name	Trade Name	Manic	Mixed	Maintenance	Depression
Valproate	<i>Depakote</i>	X			X
Carbamazepine extended release	<i>Equetro</i>	X	X		
Lamotrigine	<i>Lamictal</i>	X		X	
Lithium		X		X	
Aripiprazole	<i>Abilify</i>	X	X	X	
Ziprasidone	<i>Geodon</i>	X	X		
Risperidone	<i>Risperdal</i>	X	X		
Asenapine	<i>Saphris</i>	X	X		
Quetiapine	<i>Seroquel</i>	X			X
Chlorpromazine	<i>Thorazine</i>	X			
Olanzapine	<i>Zyprexa</i>	X	X	X	
Olanzapine/fluoxetine Combination	<i>Symbyax</i>				X

Debunked:

- gabapentin (NEURONTIN)
- topiramate (TOPAMAX)

from <http://emedicine.medscape.com/article/286342-treatment>



John Cade.

- Psychiatrist at a provincial hospital in Australia
- figured mania was 2/2 an abnormally secreted hormone
- collected urine from human pts (manic) □ injected into guinea pigs □ seizures (SZ's)
- focused on urate, and began utilizing Li-urate (since Na-urate was more insoluble)
- Li-urate □ sedated guinea pigs
- Li-carbonate □ sedated guinea pigs
- human trials...

Bipolar Disorder (BD) – treatment (cont'd)

Li⁺ v. Depakote / valproate (VPA) (Bowden CL, 2001)

- Li⁺ tends to have a more favorable response in tx-naïve cases than in BD indivs w/ longer tx hxs
- VPA may be >successful in tx'ing mixed episodes, BD indivs w/ comorbid substance issues

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Bipolar Disorder (BD) – treatment (cont'd)

How many agents to use?

- combination tx often helpful in acute stabilization
- antipsychotics REQ'D when there are psychotic features to mood episode

Adjuncts

- benzos

Bipolar Disorder (BD) – natural history

- 60% of manic episodes immediately precede an MDE
- MDE's usually significantly outnumber hypomanic and manic episodes
- ~10% of BD II's □ BD I
- episodes tend to increase in frequency/duration w/ age

Cyclothymic D/O

- 2y of fluctuating mood (1y in children, adolescents)
 - hypomanic **symptoms (but NOT episodes)**
 - dysthymic symptoms (but no MDEs)
 - \geq half the time & (no more than 2mos sx-free)
- EXCLUSIONS
 - no manic/hypomanic episodes
 - no depressive episodes

Differential diagnosis

Phenocopies and gray areas...

- Anxiety D/O's (esp. GAD, PTSD)
 - Schizoaffective D/O
 - Delirium
 - Dementia
 - Personality D/O's
-
- Substance/**Medication**-induced **Depressive D/O**
 - **Depressive D/O** d/t **Another** Medical Condition
 - **Other Specified Depressive D/O**
 - **Unspecified Depressive D/O**
-
- Substance/**Medication**-induced **Bipolar and Related D/O**
 - **Bipolar and Related D/O** d/t **Another** Medical Condition
 - **Other Specified Bipolar and Related D/O**
 - **Unspecified Bipolar and Related D/O**

Depressive, Bipolar & Related D/O d/t a Another Medical Condition

- Endocrine (e.g., thyroid, hypothalamic-pituitary-adrenal/HPA)
- Neurologic (e.g., multiple sclerosis, CVA, brain tumor, Parkinson's, Alzheimer's/other dementia, Huntington's, seizure d/o)
- Neoplastic (e.g., pancreas)
- TBI
- Autoimmune (e.g., neuropsychiatric systemic lupus erythematosus / NPSLE)
- Hematologic (e.g., acute intermittent porphyria / AIP)
 - typically: anx/depr >> s/t Ψ osis, mania (rare)
 - acute abdominal pain, muscle weakness
 - port wine-colored urine (porphobilinogen)
 - transient damage to nerve cells
- Nutritional (e.g., B12)
- Infectious (e.g., HIV, Syphilis)

Substance/Medication-induced **Depressive, Bipolar & Related D/O**

ILLICITS

- can be from intoxication or withdrawal phases
- EtOH – typically depressive
- stimulants – typically manic/hypomanic
- --good to ask about sx's during windows of sobriety (ideally, ≥ 6 mos)
- high substance comorbidity rates w/ endogenous Axis I Ψ d/o's, though (esp. BD I)

Prescription Rxs

- steroids
- IFN- $\alpha 2b$, RBV (HCV tx)
- β -blockers
- antidepressants
- α -TB drugs

Mood D/O's lab w/u

- CBC
- Chem panel
- TSH
- B12
- U-tox
- U-preg (dep on demographics)
- RPR (syphilis)
- HIV-1,2 ELISA (lower threshold for BD patients...)

Summary – cont'd

Diagnostic building blocks (not counting *mixed* feature possibilities...)

	depressive episode	depressive sxs	hypomanic sxs	hypomanic episode	manic episode
MDD	≥1	(possible)			
Persistent depressive D/O	(possible)	≥2 yrs			
BD I	(possible)	(possible)	(possible)	(possible)	≥1
BD II	≥1	(possible)	(possible)	≥1	
Cyclothymic D/O		≥2 yrs			

5 Myths and Facts About Suicide

Myth #1:

- People who talk about killing themselves rarely commit

Fact:

- Most people who commit suicide have given some verbal clues or warnings of their intentions

5 Myths and Facts About Suicide

Myth #2:

- The suicidal person wants to die and feels there is no turning back

Fact:

- Suicidal people are usually ambivalent about dying; they may desperately want to live but can not see alternatives to problems.

5 Myths and Facts About Suicide

Myth # 3:

- If you ask someone about their suicidal intentions, you will only encourage them to kill themselves.

Fact:

- The opposite is true. Asking lowers their anxiety and helps deter suicidal behavior. Discussion of suicidal feelings allow for accurate risk assessment.

5 Myths and Facts About Suicide

Myth # 4:

- All suicidal people are deeply depressed

Fact:

- Although suicide is usually associated with depression, not all suicidal people are obviously depressed. Once they make the decision, they may appear

5 Myths and Facts About Suicide

Myths # 5:

- Suicidal people rarely seek medical attention

Fact:

- 75% of suicidal individuals will visit a physician within the month before they kill themselves.

Socio-demographic Risk Factors

- Male
- > 60 years
- Widowed or Divorced
- White or Native American
- Living alone (social isolation)
- Unemployed (financial difficulties)
- Recent adverse life events
- Chronic Illness

Clinical Risk Factors

- **Previous Attempts**
- Clinical depression or schizophrenia
- Substance Abuse
- Feelings of hopelessness
- Severe anxiety, particularly with depression
- Severe loss of interest in usual activities
- Impaired thought process
- **Impulsivity**

Suicide:Treatment

- Problem-solving
- Cognitive behavioral therapy
- Coping skills
- Stress reduction

Additional case presentations

Case 2.

18yo M high school student who was BIB his parents to the ER after ingesting a bottle of 50 Tylenol pills. Recently, he has been isolating himself to his room more, sitting-out dinners with the family, and has been overheard at home talking about what a horrible “sinner” he is. He has shown increasing despondence and mood lability.

He is well-connected with friends at school, outgoing—and the above changes have occurred more in a matter of weeks than they have months/years.

On interview, the pt appears dysphoric, tearful, and internally preoccupied.

- What else would you like to know?
- How would you work-up this patient?
- In the meantime, what would you dx and what would be your tentative tx plan?

Case 3.

50yo F, under-employed and barely hanging-on with temp agency work, comes in for her first office visit to see you about “mood swings” that haven’t responded well to venlafaxine XR. She is dysphoric on presentation—but also quite irritable with your Q’s. This has been a lifelong issue for her, but she has managed to stay out of IP hospitalization through it all.

- What would you like to ask her?
- W/u and provisional dx & tx plan?

A U-tox comes back (+)for methamphetamine. A week later, you get an angry call from the pt’s E. Coast-based sister—who complains that you have the pt on the ‘wrong Rxs.’ She shares additional hx (in her voicemail) that the pt has had past episodes of elevated mood, sexual and financial indiscretions, and demands to know how you are going to modify the tx plan.

- What would you tell the pt’s sister?
- How does this change your working dx and tx plan?

TAKE – HOME POINTS

Major depressive disorder (MDD) – Key Points

- MDD can be a chronic, recurrent, and progressive condition^{1,2}
- MDD is associated with alterations in functional and structural changes in the brain²⁻⁴
- MDD, stress, and pain are all associated with similar suppression of neurotrophic factors and compromised neuroplasticity²⁻⁴
- **Remission** not response is the ultimate goal of treatment^{5,6}

1. Kendler KS, et al. *Am J Psychiatry*. 2000;157(8):1243-1251.
2. Maletic V, et al. *Int J Clin Pract*. 2007;61:2030-2040.
3. Duman RS. *Biol Psychiatry*. 2004;56:140-145.
4. Maletic V. *Prim Psychiatry*. 2005;12(suppl 10):7-9.
5. Keller MB, et al. *Arch Gen Psychiatry*. 1992;49(10

Summary

- Mood D/O's are Ψ conditions where emotional dysregulation is the primary issue.
- Mood d/o's can be endogenous, due to substances/medication, or due to another medical condition. There are additional phenocopies which should always be in your Ddx, including Anxiety D/O's, Schizoaffective D/O, Personality D/O's, Delirium, and Mild/Major Neurocognitive D/O's.
- The monoamine hypothesis of depression is only a preliminary framework for conceptualizing Mood d/o's and their tx, and requires significant theoretical revision.
- Mood D/O's, like other Ψ conditions in the DSM, are best conceived as syndromes rather than as unitary or homogeneous medical conditions.
- A little less than $\frac{1}{2}$ of tx-naïve pts will respond to their first antidepressant; only $\frac{1}{3}$ will remit without further intervention.
- Non-pharmacologic approaches to treating Mood D/O's include psychotherapy and interventional procedures (e.g., ECT).



Thank you for listening