What is anxiety and how do we understand and treat it?

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Poll Question

- True or False:
- Anxiety symptoms tend to occur in anxiety diseases, like generalized anxiety disorder and panic disorder.

Anxiety

- The fever of psychiatry
- Fever
  - An effect
  - Not a cause of itself
  - Causes: infections, cancer, heat stroke
  - Fever of unknown origin
- Anxiety is a symptom, not a disease

Causes of anxiety

- Personality trait: Neuroticism
  - Normal: Fight or flight response
  - Normal distribution
    - Too much: diagnosed with “GAD”
    - Too little: very calm person
- Mood states
  - Depression
  - Mania
    - Including mood temperaments
- Psychosis
- Other: PTSD, OCD, Eating disorders, Substance abuse

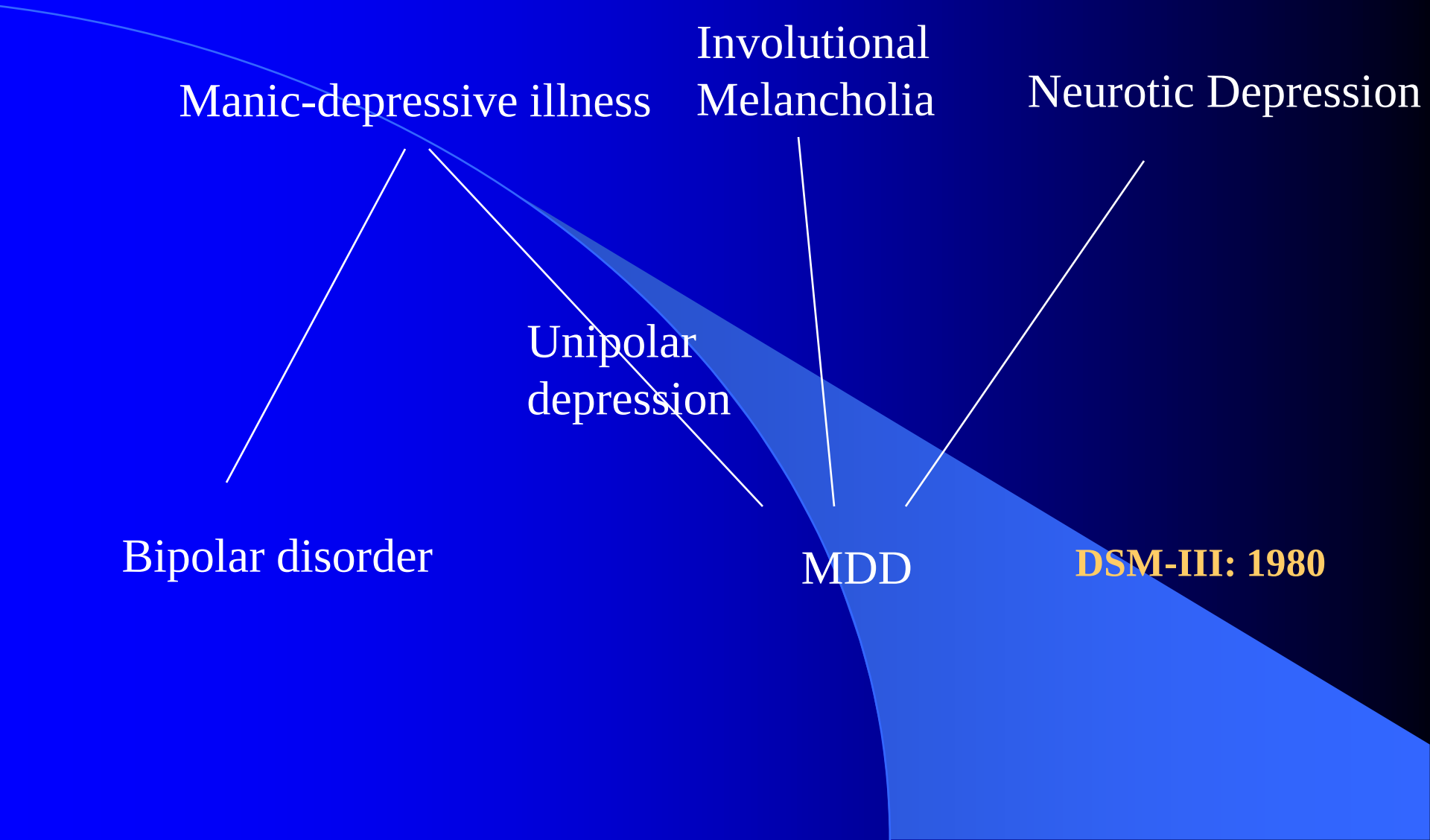
DSM anxiety states

- Anxiety “disorder” is meaningless
- “Generalized anxiety disorder”
  - Introduced in RDC and DSM-III in 1970s
  - Used to replace neurotic depression
  - Not validated as a legitimate scientific diagnosis
    - Diagnostic validators like genetics – does not differentiate MDD
- “Panic disorder” is not a disease
  - It’s a symptom, like anxiety in general

DSM: Adds comorbidities

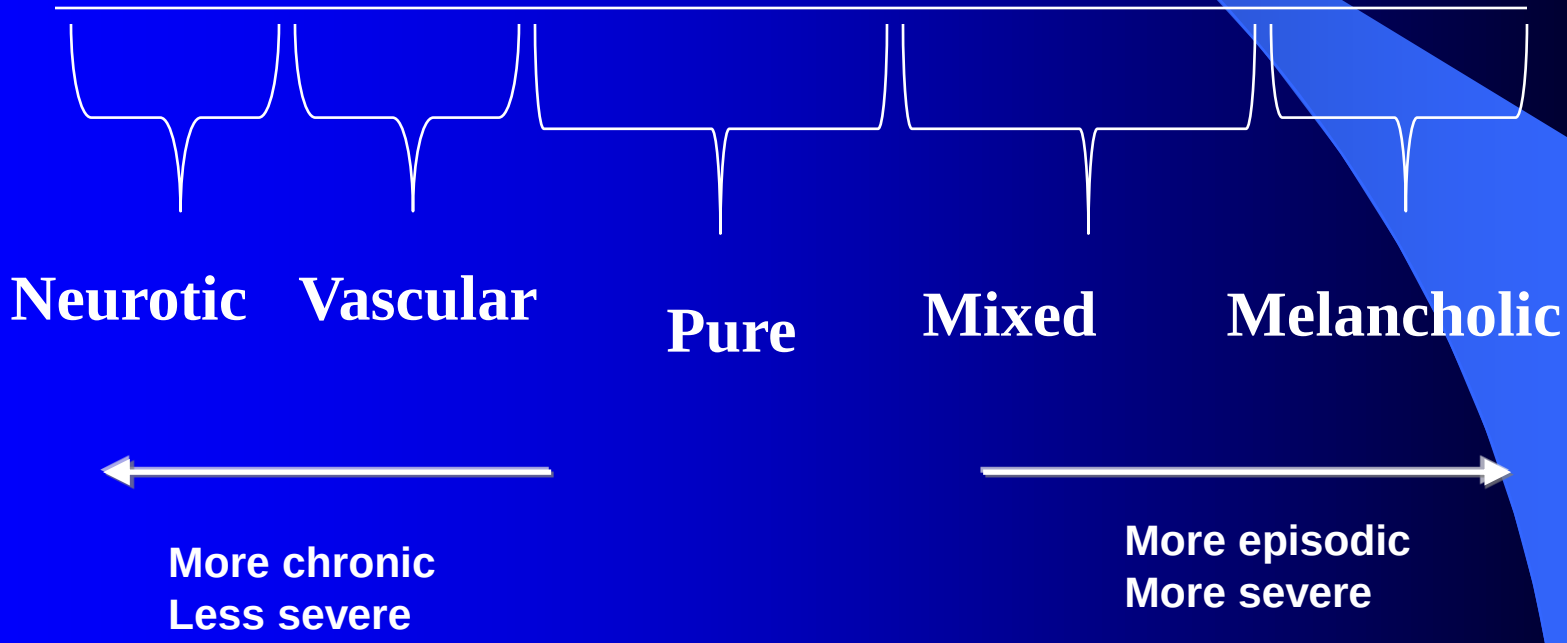
- Against the concept of the differential diagnosis or diagnostic hierarchy
- Add all diagnoses as you go along
  - All diagnoses are created equal
- Hermann van Praag: Nosologomania

MDI vs Bipolar/MDD



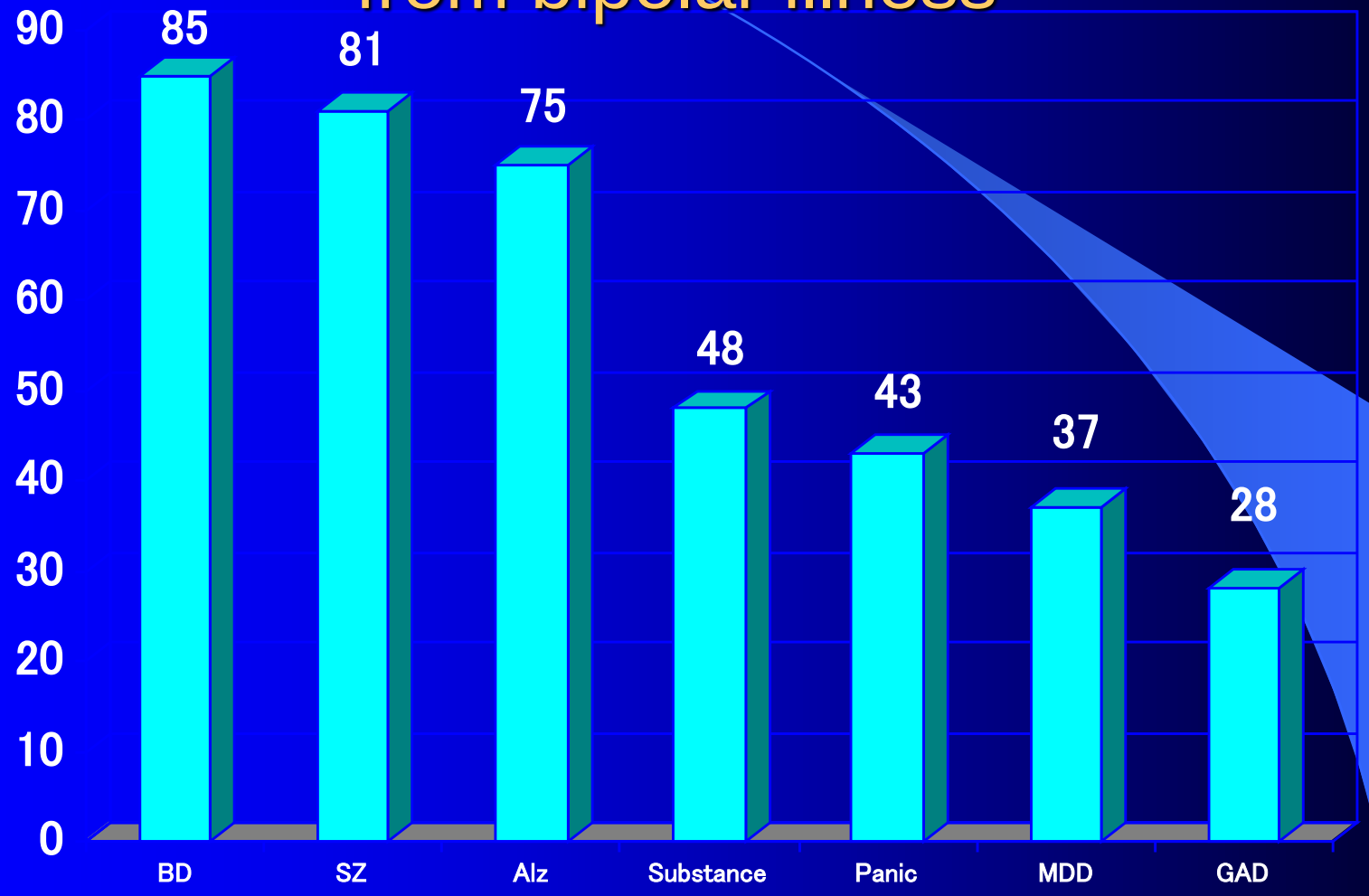
The MDD Spectrum

SN Ghaemi, PA Vohringer, D Vergne:
The varieties of depressive experience: Diagnosing depression
Psychiatric Clinics of North America, 2012



Ghaemi SN, Vohringer PA, Vergne D. Psych Clinics North Am 2012;35(1):73-86.

Genetics: Differentiates borderline PD from bipolar illness



OJ Bienvenu et al, 2011, Psychological Medicine, 41:33-40

Validators of Diagnosis: No Gold Standard

- Phenomenology
  - cross-sectional symptoms
  - DSM-IV criteria
- Family History - genetics
- Course
  - Age of onset, # episodes, outcome
- Biological markers
  - Treatment effects
    - Can be nonspecific

Modified from Robins and Guze 1970

GAD vs MAD

- No meaningful scientifically valid differentiation on diagnostic validators
- Therefore: they are the same

Validation of Neurotic Depression

- Symptoms
  - Mild to moderate anxiety and depression
  - Psychosocially responsive/reactive
- Genetics
  - Not very genetic – mostly environmental
  - Same genes predispose to “MDD” and “GAD”
- Course
  - Chronic, not episodic
- Treatment Response
  - Poor antidepressant response? (STARD)
  - Good psychotherapy response?

Ghaemi, Bipolar Disorders, 2008, 10:957-968

Neurotic depression vs MDI (including unipolar depression)

- Strong meaningful scientifically valid differentiation on diagnostic validators
- Therefore: they are the different and legitimate scientific diagnoses

The Return of Neurotic Depression: Proposed New Diagnostic Criteria (following Martin Roth)

- A. Depressed mood more intense or disabling, but not distinct, from normal sadness
- 2 or 3 neurovegetative criteria (not 1, not 4 or more)
  - Sleep changes, decreased interest or concentration, appetite changes, SI
- Chronic worry or anxiety most of the day nearly every day OR multiple somatic symptoms
- Duration $\geq$ 6 months
- Mood highly reactive to environment
- No marked psychomotor retardation or marked guilt
- Does not meet DSM-IV MDE criteria for most of the above duration

Ghaemi, Bipolar Disorders, 2008, 10:957-968

Anxiety in Mixed states: STARD

- Divide sample into high versus low anxiety symptoms
- High anxiety symptoms predicted worse antidepressant response
  - Due to mixed states?
- GAD:
  - Odds Ratio for remission = 0.59 versus no GAD
    - (95% confidence intervals: 0.38, 0.92)

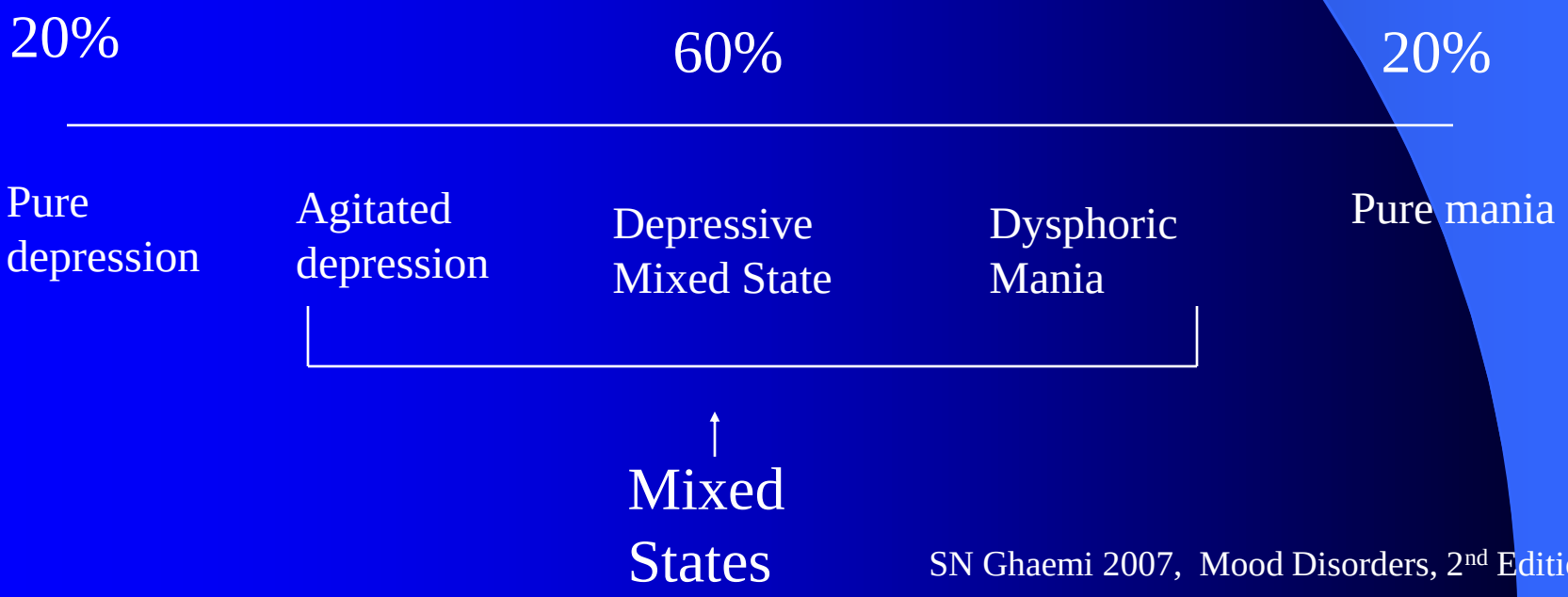
AJ Rush et al, Selection among second step antidepressant monotherapies, Arch Gen Psychiatry, 2008, 65:870-881

SRIs for anxiety

- Very effective
- Effect sizes (Cohen's d; clinical meaningful effect = 0.5, a medium effect)
  - Depression, MDD: 0.3
  - Anxiety, GAD: 0.4-0.5
- SRIs are anxiolytics, not antidepressants

Mood Episode Spectrum

A Koukopoulos, SN Ghaemi. The Primacy of Mania, European Psychiatry
F Benazzi, HS Akiskal, J Aff Disorders, 2001, 67:115-122
GB Cassano et al, Am J Psychiatry. 2004 Jul;161(7):1264-9
M Berk et al, Australian and New Zealand Journal of Psychiatry 2005; 39:215–221



SN Ghaemi 2007, Mood Disorders, 2nd Edition

Neurotic Depression: Psychotherapy?

- NEO, N = 280, Duration 16 weeks
- Randomized to CBT or SRIs (clinician choice)
- Openness to experience
  - Trend toward improvement overall vs other personality traits
- High neuroticism
  - Better depression symptom response with antidepressants than with CBT

RM Bagby et al, Personality and differential response in depression Canadian Journal of Psychiatry, June 2008, 53: 361-370

Neurotic Depression: Psychotherapy

- James McCullough (Virginia Commonwealth Univ)
  - Mixture of CBT with existential and Sullivanian methods
    - Cognitive Behavior and Associated Systems of Psychotherapy
  - Aimed at treatment of borderline PD
- Only RCT of Chronic MDD (Keller et al)
  - Nefazodone vs CBASP vs Combo vs Placebo RCT
  - CBASP = AD > placebo
- In subgroup with most childhood trauma, CBASP > antidepressant

Freud: Neurosis

- The expectation that every neurotic phase can be cured may be derived from the belief that the neuroses are something quite unnecessary, whereas they are constitutionally fixed characteristics that persist

1894

"Neurosis" – 19th-20th centuries

- American psychiatry
  - Freudian/psychoanalytic
  - Childhood unconscious experiences that led to later adult anxiety/depression symptoms
    - Neurosis: If childhood experiences were Oedipal (around age 5)
      - Normal: We all have the Oedipal stage of development
    - Psychosis: If childhood experiences were pre-Oedipal (before age 5; oral/anal stages of development)
      - Abnormal by definition
- European psychiatry (Roth)
  - Purely descriptive: chronic mild anxiety and depression

Wrong distinctions

- Reactive, Exogenous
  - Mild to moderate
  - Life stressor caused
  - No underlying illness or biological susceptibility
  - “Normal”
- Biological, Endogenous
  - Severe
  - Not life stressor caused
  - Underlying disease or biological susceptibility
  - Abnormal
  - Usually genetic
  - Defined as manic-depressive illness

20th century debates

- One depression – "MDD"
  - Aubrey Lewis, RDC group (George Winokur)
  - Severity and life events did not distinguish
  - Psychoanalytic etiology is not scientifically valid
- Two depressions – neurotic depression vs MDI
  - Martin Roth
  - No psychological etiology is claimed
  - Severity and life events are nonspecific and not relevant to validity

Temperaments

- Dysthymia
- Cyclothymia
- Hyperthymia
- Introduced by Kahlbaum, extended by Kretschmer, revised by Akiskal
- Biologically and genetically related to MDI
  - Forme fruste
- TEMPS scale

Typical scenario

- Mood temperament
  - *Mild* constant mood traits
    - Mild chronic depression and/or mania
      - Misdiagnosed MDD, treated with SRI
- Effects
  - *Severe* constant anxiety
    - Misdiagnosed GAD
    - Treated with benzodiazepines
  - *Severe* constant attentional impairment
    - Misdiagnosed ADD
    - Treated with amphetamines, which worsen anxiety

MDD + GAD + ADD = Cyclothymia

DSM: Diagnosis based on severity

- All diagnoses require high severity
- Contradicts standard medical practice and science
  - Conditions with mild symptoms: mild chest pain can be a very severe heart attack
  - Conditions with no symptoms:
    - Hypertension
    - Cancer
- Why not psychiatry?

Temperaments

- Constant, not episodic
- Family members of persons with MDI
- Baseline personality in persons with MDI in between mood episodes
- Predictor of future depressive or manic episode
- Risk factor for antidepressant-induced mania
- Responsive to low dose mood stabilizers
  - Low dose valproate especially is anxiolytic (500 mg/d)

TEMPS Scale: 50 item

Temperament Scale of Memphis, Pisa, Paris and San Diego-Autoquestionnaire Version (TEMPS-A) – Psychiatry Letter version (2019)

Name: _____ Date: _____ Sex: **M F** Age: _____

Directions: Circle T (True) for all items that are true about you MOST OF THE TIME IN THE DISTANT PAST, meaning years ago, not how you currently feel.

IMPORTANT: DO NOT FOCUS ON HOW YOU FEEL NOW. DO NOT FILL THIS OUT BASED ON YOU HAVE FELT IN THE LAST FEW MONTHS OR IN THE PAST YEAR. FOCUS ON THE WAY YOU HAVE BEEN IN THE PAST FEW DECADES.

Circle F (False) for all the rest that don't apply to you for most of your life.

1.	**T**	**F**	I'm the kind of person who doesn't like change very much.
2.	**T**	**F**	I can really like someone a lot, and then completely lose interest in them.
3.	**T**	**F**	I often get many great ideas.
4.	**T**	**F**	I often feel wound up.
5.	**T**	**F**	I put the needs of others above my own.
6.	**T**	**F**	My moods and energy are either high or low, rarely in between.
7.	**T**	**F**	When angry, I snap at people.
8.	**T**	**F**	My mood often changes for no reason.
9.	**T**	**F**	My feelings are easily hurt by criticism or rejection.
10.	**T**	**F**	I am totally comfortable even with people I hardly know.
11.	**T**	**F**	I often give in to others.
12.	**T**	**F**	I'm the kind of person who believes everything will eventually turn out all right.

Download at

www.psychiatryletter.net

Anxiety as akathisia

- Subjective
  - Severe anxiety/agitation
- Objective
  - Motor restlessness
- Pseudoakathisia: just subjective severe anxiety
  - Severe suicidality
  - Like having a panic attack
- Associated with dopamine blockers
  - Stop the drug

Medication Treatment

Poll Question

- True or False:
- Serotonin reuptake inhibitors are stronger at treatment of depression symptoms than in treatment of anxiety symptoms.

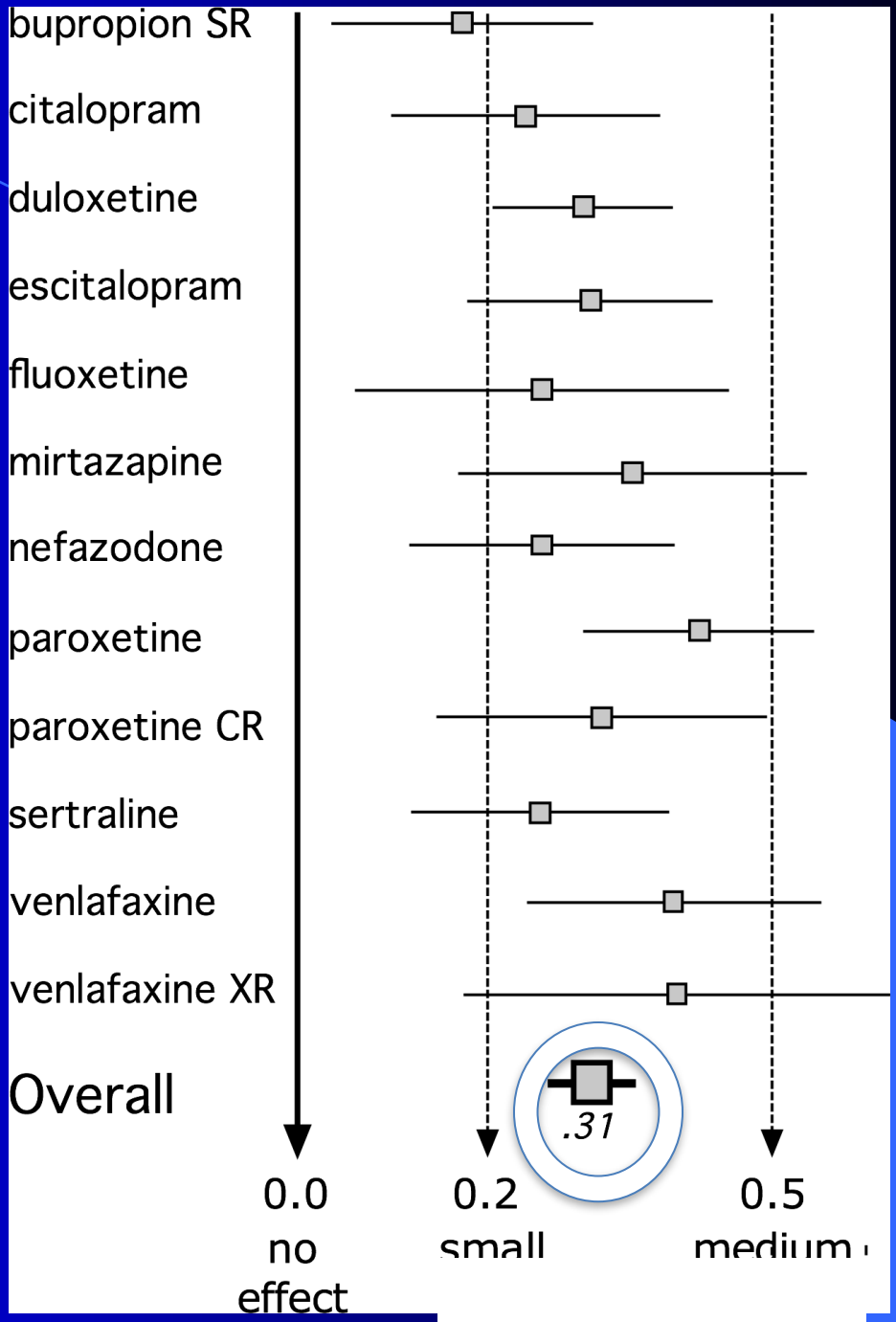
Drugs

- Symptomatic
  - Aspirin
- Disease-modifying
  - Lipitor

SRI "antidepressant" efficacy: Small effect size

EH Turner et al, NEJM, 2008; 358:252-260

Cohen landmarks:



SRIs – GAD meta-analysis

Table 3 Effect sizes by medication

Medication	ES ± SD	*p*-Value
Pregabalin	0.50 ± 0.24	$p < 0.0001$
Hydroxyzine	0.45 ± 0.18	$p < 0.0001$
Venlafaxine XR	0.42 ± 0.12	$p < 0.0001$
Benzodiazepines	0.38 ± 0.15	$p < 0.0001$
SSRI	0.36 ± 0.09	$p < 0.0001$
Buspirone	0.17 ± 0.21	NS
CAM	−0.31 ± 0.46	NS
All	0.39 ± 0.06	$p < 0.0001$
All (with outliers removed)	0.38 ± 0.06	$p < 0.0001$

ES: effect size; SD: standard deviation; NS: non-significant.

major depression with SS
drugs were compared, all
pattern was seen.

Compared with othe
response to treatment in
der, 0.45–1.48 (Greist *et*
2001); social phobia, 0.
somewhat similar to PTS
line (NICE, 2005).

Our ESs are also sligh
et al. (2005) in their meta
GAD (mean random ES
However, Mitte *et al.*'s wo
from our present investi
diagnostic criteria, includ
III), and they included s
anxiety and depression

RB Hidalgo et al Journal of Psychopharmacology 21 (2007) 864–872

Benzodiazepines: Clinical psychopharmacology

- All similar in mechanism
  - bind to “benzodiazepine receptors” located between alpha and gamma subunits of GABA-A receptor
- Differences mainly in half life and speed of onset
- Dose equivalence is important
  - Klonopin 1 mg/d = Ativan 4 mg/d = Valium 20 mg/d
  - Klonopin 4 mg/d = Ativan 16 mg/d = Valium 80 mg/d
- Benefits are much much more short term than long
- Alprazolam is has double-blind RCT data of efficacy for major depressive episodes (!!)

Benzodiazepines: 13 agents

Drug	T 1/2	Speed of onset	Dose equivalence	Daily dose (mg/d)	other
Alprazolam (Xanax)	**Short (6-12 h)**	**Very short (30 minutes)**	**0.5**	**0.5-3**	**Most addictive**
Lorazepam (Ativan)	**Medium (10-20 H)**	**Short (1 h)**	**1**	**0.5-3**	**Good prn**
Clonazepam (Klonopin)	**Long (20-50 h)**	**Long (1-4 h)**	**0.25**	**0.5-3**	**Least addictive but most potent and most sedating**
Diazepam (Valium)	**Long (20-100 h)**	**Short (1 h)**	**5**	**5-20**	**Addictive**

FDA indications

- NONE are for long-term management.
- Clonazepam
  - Lennox-Gastaut syndrome (petit mal variant) seizure disorder
  - Akinetic and myoclonic seizures
  - Absence seizures (petit mal) who have failed to respond to succinimides
  - NOT anxiety disorders
- Lorazepam
  - Treatment of status epilepticus
  - NOT anxiety disorders
- Alprazolam: GAD and panic disorders
- Diazepam: Anxiety disorders, convulsive disorders, skeletal muscle spasm

Efficacy in GAD

- Meta-analysis
- 23 RCTs, n= 2336
- Diazepam, lorazepam, alprazolam versus placebo
- RR 0.78 (0.62-1.00
- No Cochrane collaboration review
- Very little long-term data – I found none beyond 6 months

J Martin et al, J Psychopharmacol. 2007 Sep;21(7):774-82.

Use in insomnia

- BNZ impair sleep architecture
  - increased alpha and beta activity, a decrease in K complexes and delta activity. Decrease in stage 1 NREM, NREM stage 3 and 4 sleep and REM sleep. Decrease in REM stage sleep.
- Meta-analysis
  - 24 studies, n=2417, RCTs, age > 60
- NNT = 13
  - Small effect size, r = 0.13 for sleep quality
  - Total sleep time increase mean 25 minutes
- NNH for adverse effects = 6
  - RR cognitive 4.76 [1.47, 15.47]

Bastien et al, SLEEP, Vol. 26, No. 3, 2003

J Glass et al, BMJ. 2005 Nov 19;331(7526):1169.

“Non-addictive” benzodiazepine alternatives

- Zolpidem (Ambien)
  - Onset 15-30 minutes, Half life 2-3 hours
  - Mechanism – binding to GABA-a receptors (like benzodiazepines), gamma-1 subunit
  - Maximum dose 10 mg/d, range 5-10 mg/d
  - Schedule IV: 40 mg/d in former drug abusers = 20 mg/d valium. 10 mg/d zolpidem = placebo
- Eszopiclone (Lunesta)
  - Active isomer of zoplicone (widely used in Europe)
  - GABA-a agonist
  - Onset 1 hour, half life 6 hours
  - Dose 1-3 mg/d
  - Schedule IV: 6-12 mg/d in former drug abusers = 20 mg/d valium. 3 mg/d = placebo
- Zaleplon (Sonata)
  - Same mechanism as zolpidem
  - Dose 5-20 mg/d
  - Ondry 15-30 minutes, Half-life 1 hour

http://products.sanofi.us/ambien/ambien.pdf

Hypnotics: Small effect sizes

- Lunesta RCTs
  - Fall asleep 15 minutes earlier
  - Sleep 37 minutes longer
  - Still meet insomnia criteria
- Revenue: $2.7 billion in 2005
- Rozerem
  - Fall asleep 14 minutes earlier, no improvement in sleep quality

Tolerance

- Proven in animal studies
  - 5 days led to more gabaergic and serotonergic activity versus rat controls, gone by 25 days
- Disputed in human studies but very few long-term randomized studies in anxiety disorders (22 weeks)

SV Vellucci, PSYCHOPHARMACOLOGY 62, 1 (1979), 61-65,
K Rickels, *JAMA*. 1983;250(6):767-771.

Withdrawal

- Anxiety
- Restlessness
- Insomnia
- Dizziness
- Nausea
- Headaches
- Seizures

Addictiveness potential

- Huge controversy
- It clearly happens – in animals and humans
- My view: More than coffee – Less than cocaine
- In polysubstance abuse, BNZs are primary drug of abuse in 32%
- If substance abusers are precribed BNZs, 15% eventually abuse it (versus 6% of controls not prescribed BNZs)
- Lower rate of abuse in non-substance abusing population

U Busto et al, British Journal of Addiction. 81, 1, pages 87–94, 1986
MF Brunette, Psychiatric Services, VOL. 54, No. 10, 2003

Other sleep alternatives

- Ramelteon (Rozerem)
  - Binds to melatonin 1 and 2 receptors in suprachiasmatic nucleus
  - 8 mg/d, half-life 2-6 hours
- Trazodone
  - 25-100 mg/d, can have unwanted antidepressant effects (cause mania), priapism
  - Half-life 3-6 hours
- Gabapentin
  - 300-900 mg/d
  - Half life 4-8 hours
- Hydroxyzine
  - 50-100 mg/d, antihistamine
  - Half-life 3 hours
- Quetiapine
  - 25-100 mg/d, most potent antihistamine, can have weight gain and metabolic effects
  - Half-life 4-8 hours

Summary

- Anxiety is like fever
  - It's an effect, not a cause
  - Can be severe, but not be the actual diagnosis
- Causes
  - Mood conditions
    - Neurotic depression
      - High neuroticism as a personality trait
    - Mood temperaments
  - Problems of living – not "GAD"
- GAD and panic disorder are not scientifically validated as diagnoses
- Anxiety as part of mixed states (agitation)