

Diagnosis and treatment of depression:

An advanced clinician's guide

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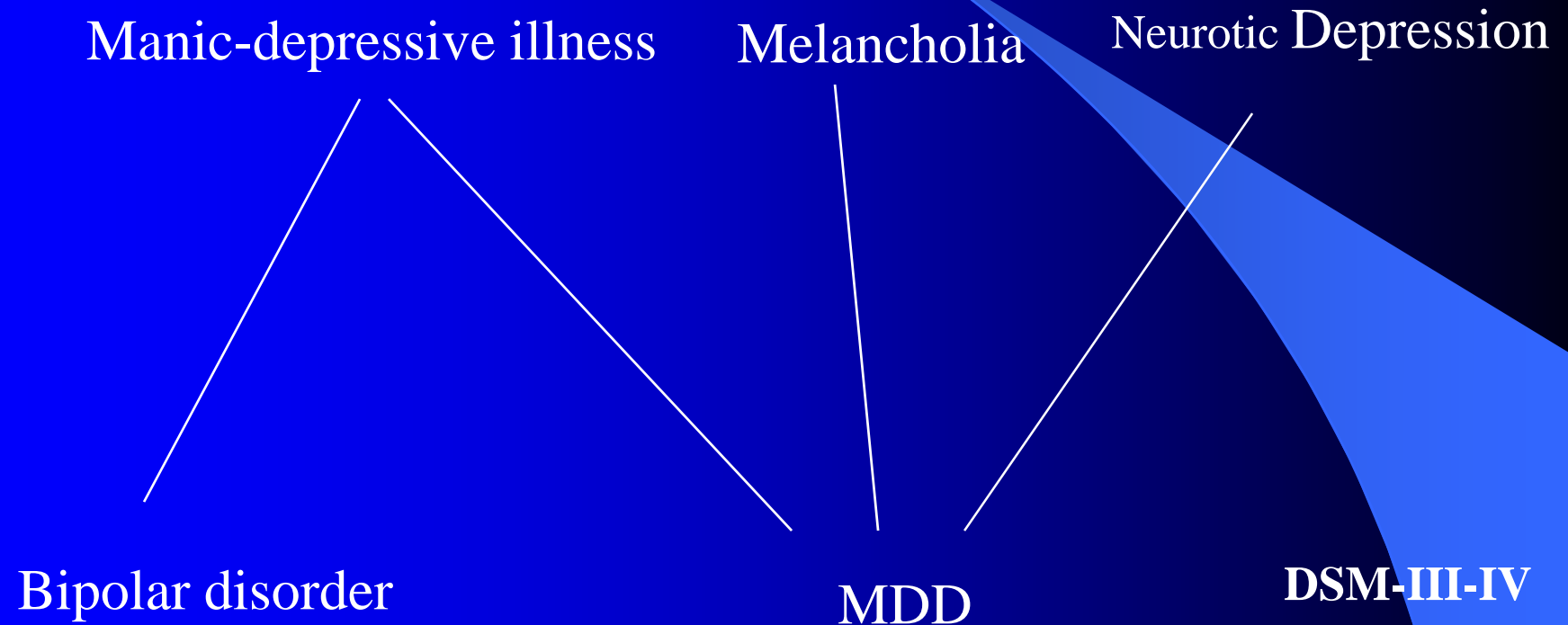
Validators of Diagnosis: No Gold Standard

- ❑ Phenomenology
 - cross-sectional symptoms
 - **DSM-IV** criteria
- ❑ Family History - genetics
- ❑ Course
 - Age of onset, # episodes, outcome
- ❑ Treatment Response
 - partial substitute for biological markers

E Shorter, Before Prozac, Oxford Univ Press, 2009

Ghaemi SN, Dalley S.. Australian and New Zealand J Psychiatry 48: 314-324, 2014.

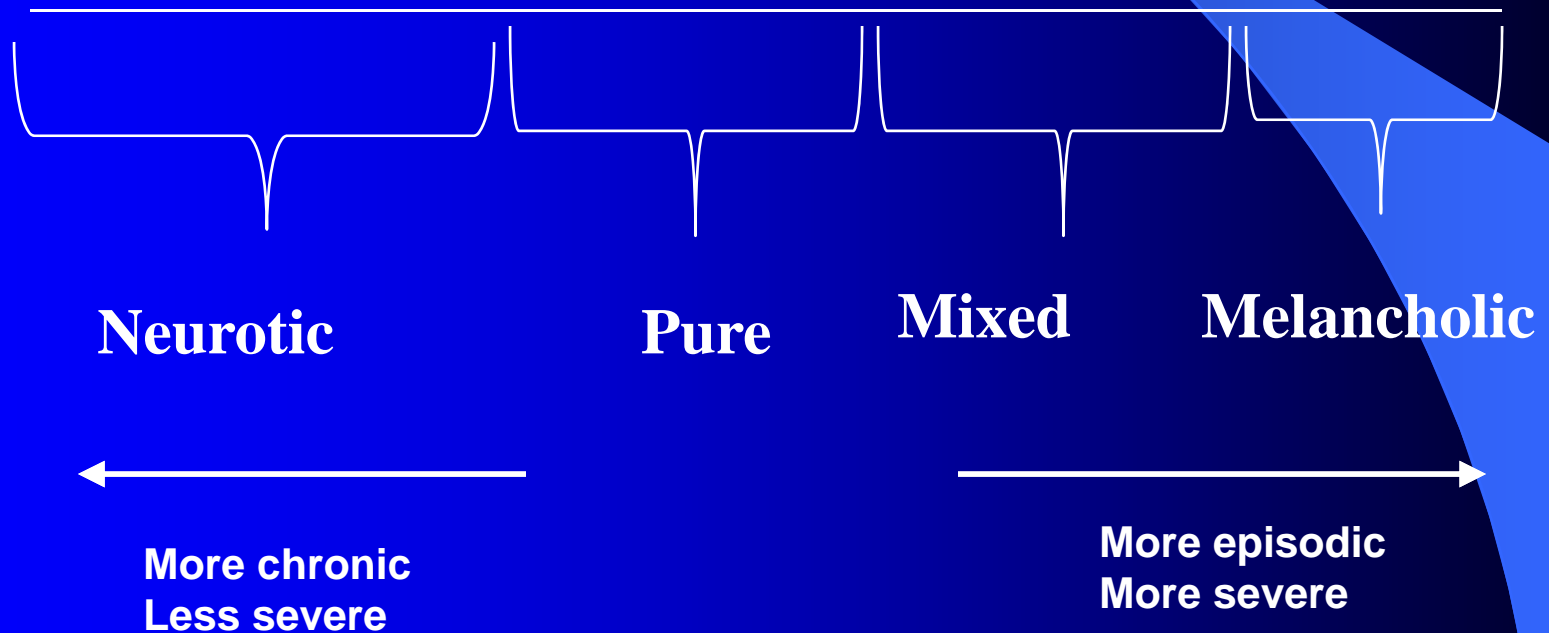
DSM-III: MDI vs Bipolar/MDD



Result: MDD epidemic

The MDD Spectrum

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



Heirarchy: Not Comorbidity

❑ Mood Disorders

- Bipolar
- Unipolar

❑ Psychotic Disorders

- Schizoaffective
- Schizophrenia

❑ Anxiety Disorders

❑ Other

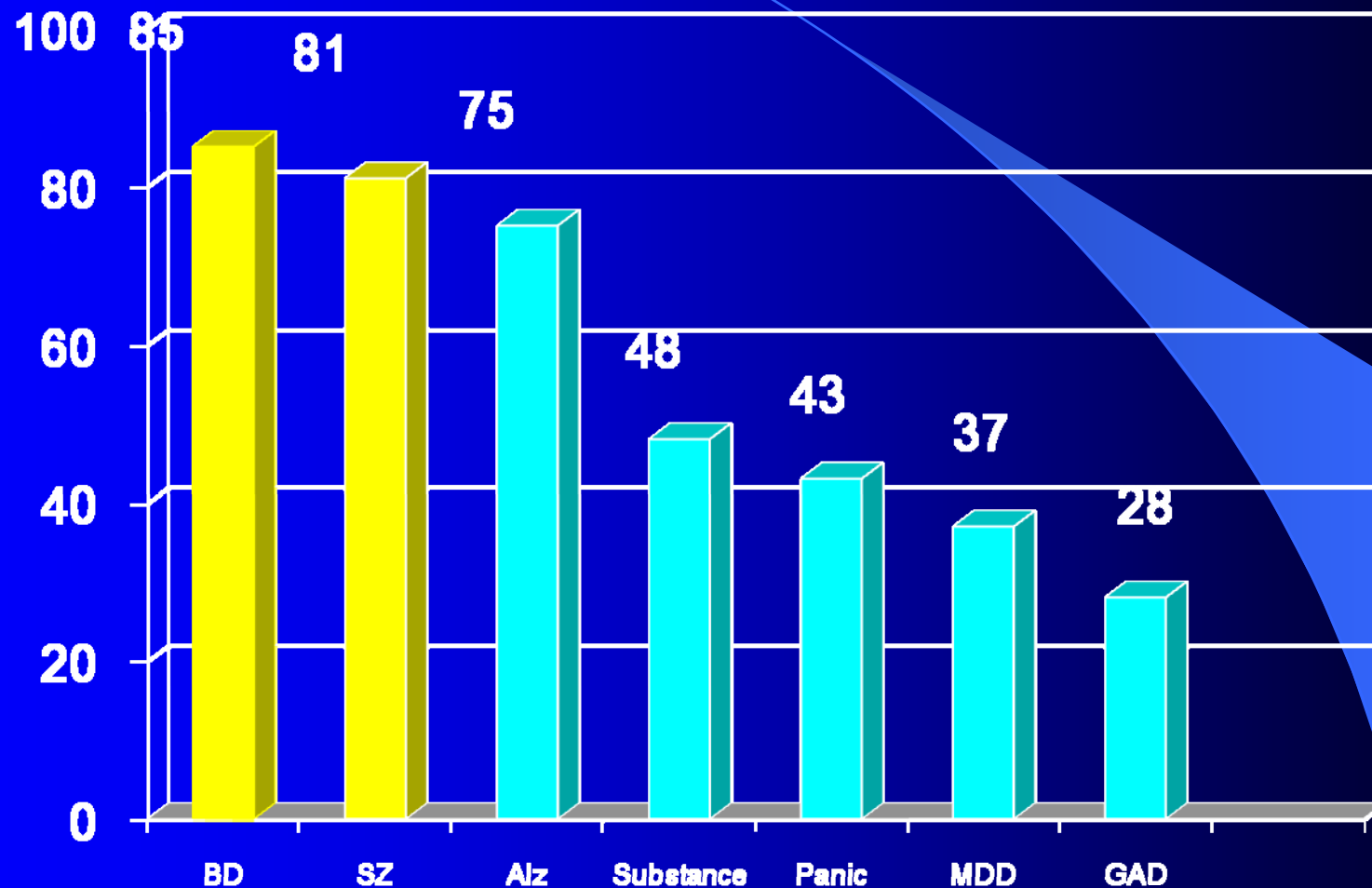
- Personality Disorders
- ADHD

PG Surtees, RE Kendell. Br J Psych, 1979, 135:438-443

Validators of Diagnosis: No Gold Standard

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Heritability: Disease vs Non-Disease*



OJ Bienvenu et al, 2010, in press

*Heritability is not necessarily purely genetics:
GE interactions, epigenetics

Increase in diagnosis of BD in youth

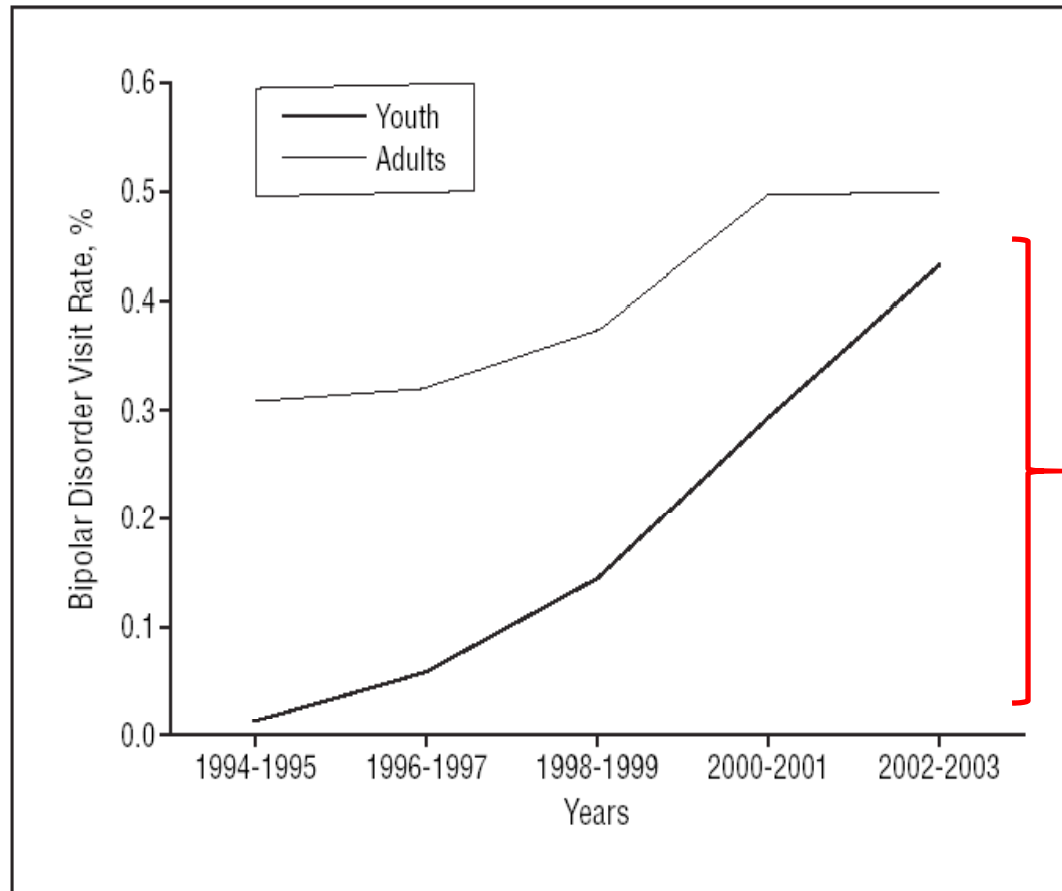
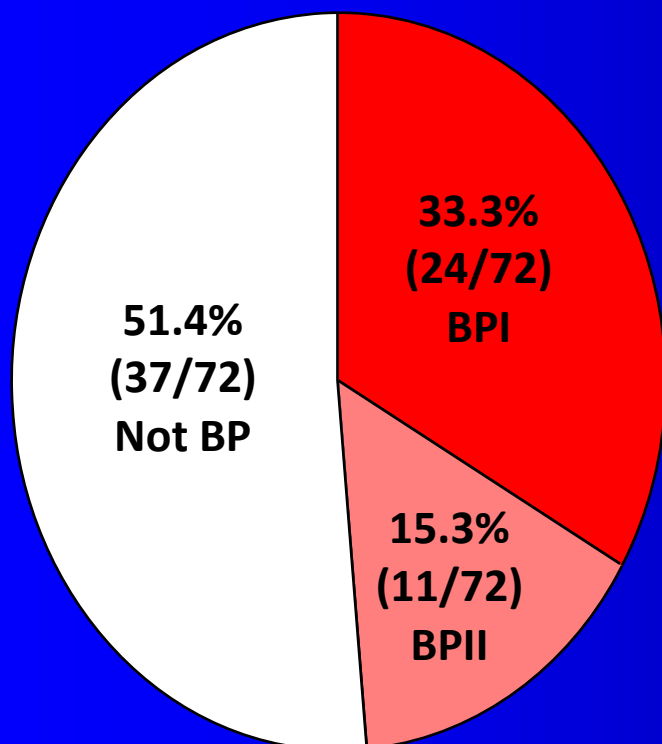


Figure. National trends in visits with a diagnosis of bipolar disorder as a percentage of total office-based visits by youth (aged 0-19 years) and adults (aged ≥ 20 years).

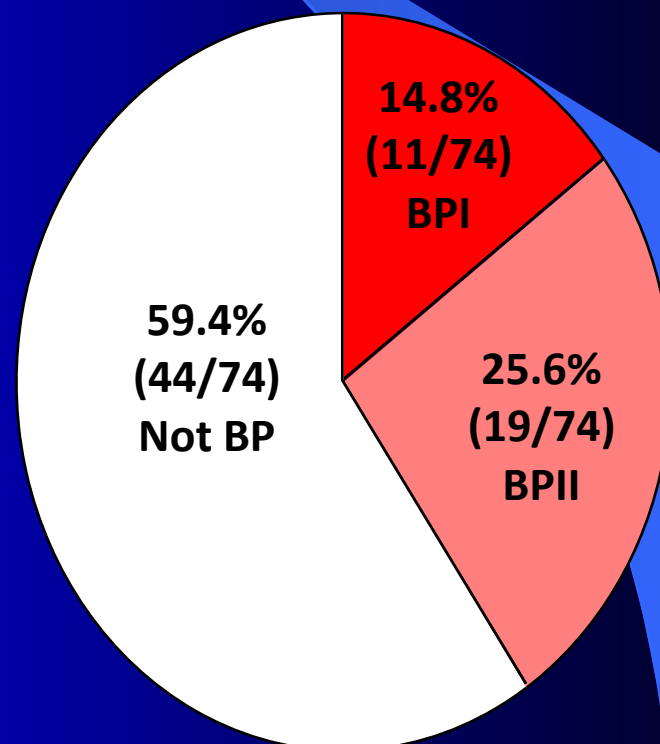
40-fold
increase in
rate of dx

High Bipolarity Risk in Prepubertal and Severe Adolescent / Young Adult Major Depression

Prepubertal Major Depression
(Age at intake 10.3 yrs)
49% Bipolar at 10-year Follow-up



Adolescents / Young Adults Hospitalized for Major Depression
(Age at intake 23.0 yrs)
41% Bipolar at 15-year Follow-up



Validators of Diagnosis: No Gold Standard

- ❑ Phenomenology
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Validation of Neurotic Depression

■ Symptoms

- Mild to moderate anxiety and depression
- Psychosocially responsive

■ Genetics

- Same genes predispose to depression and anxiety

■ Course

- Chronic, not episodic

■ Treatment Response

- Poor antidepressant response? (STARD)
- Good psychotherapy response?

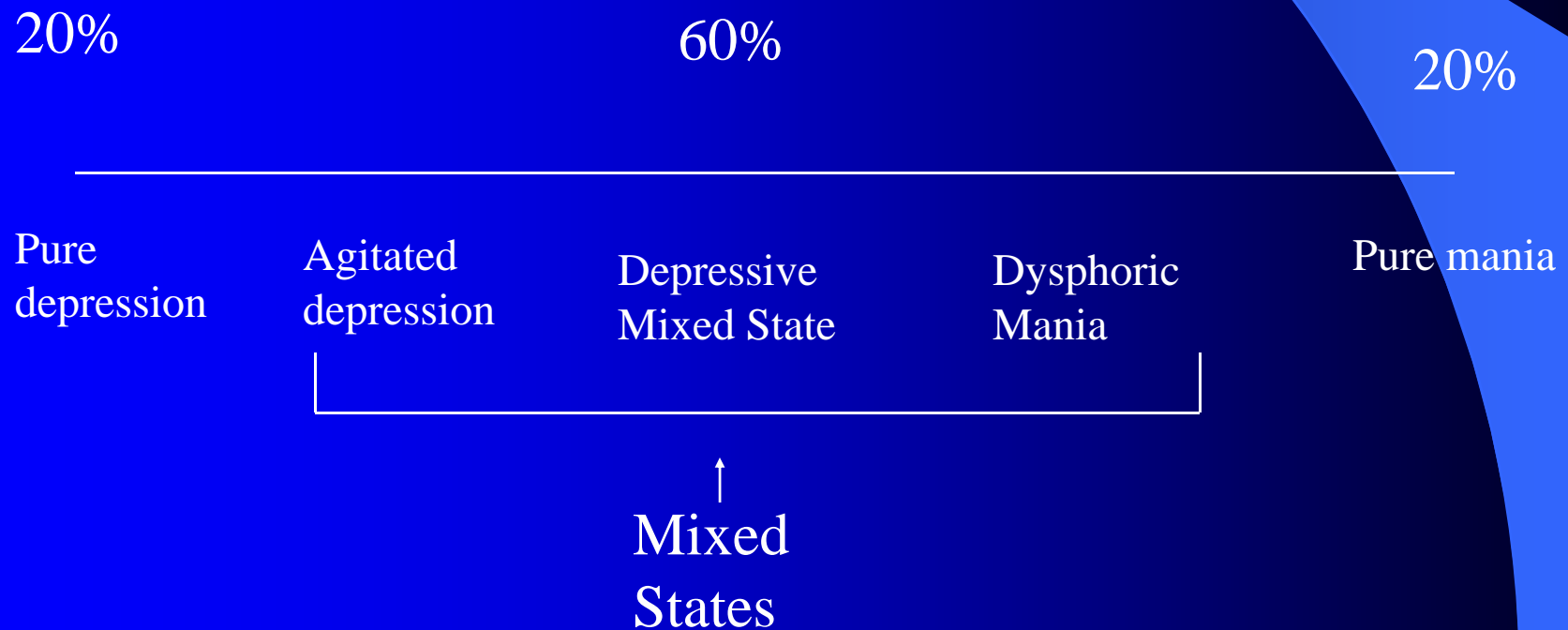
Melancholia

- ❑ NO reactivity of mood
- ❑ Marked psychomotor retardation
- ❑ NO anxiety/agitation
- ❑ Marked suicide risk
- ❑ Bipolar > Unipolar
- ❑ Responsive to short term AD treatment
 - TCAs and Venlafaxine over SRIs
- ❑ ECT effective but NOT in maintenance

HA Sackheim et al, JAMA, 2001, 285:1299-1307

A Koukopoulos, Psychiatric Clinics of North America, 1999, 22:547-564
SN Ghaemi, Mood Disorders: A Practical Guide, 2nd edition, Wolters Kluwer, 2007
F Cassidy et al, Neuropsychopharm, 2001 Sep;25(3):373-83;

Mixed states



The Primacy of Mania: A reconsideration of mood disorders

- ❑ Athanasios Koukopoulos
- ❑ MDI cycle
- ❑ Mixed states
- ❑ Temperaments
 - Hyperthymic, Cyclothymic
- ❑ Mania broadly defined
 - Includes anxiety and agitation

Mixed Depression – Koukopoulos criteria

■ Major depression + 6 of 9 criteria

- Mood lability
- Marked irritability
- Absence of psychomotor retardation
- Flight of ideas
- Increased libido
- High blood pressure
- Marked anxiety
- Marked insomnia
- Sexual impulsivity

Koukopoulos et al,
Melancholia Agitata and
Mixed Depression
Acta Psychiatr Scand
Suppl. 2007;(433):50-7.

Mixed Depression (Koukopoulos criteria): Rome study

- N= 219, Rome
 - Using DSM-IV: 12% BDI, 20.5% BDII, 46% MDD
- Age: 45 years, 11% rapid-cycling
- Temperament:
 - 63% hyperthymic, 16% cyclothymic, 7% dysthymic
 - 10% normal
- 51% antidepressant-induced Mixed depression
 - More in BP II than MDD, 45% TCAs, 38% SRIs
 - Suicide attempts: 2.5x more than non-AD MxD

Rome Study: Follow-Up 1.3 years

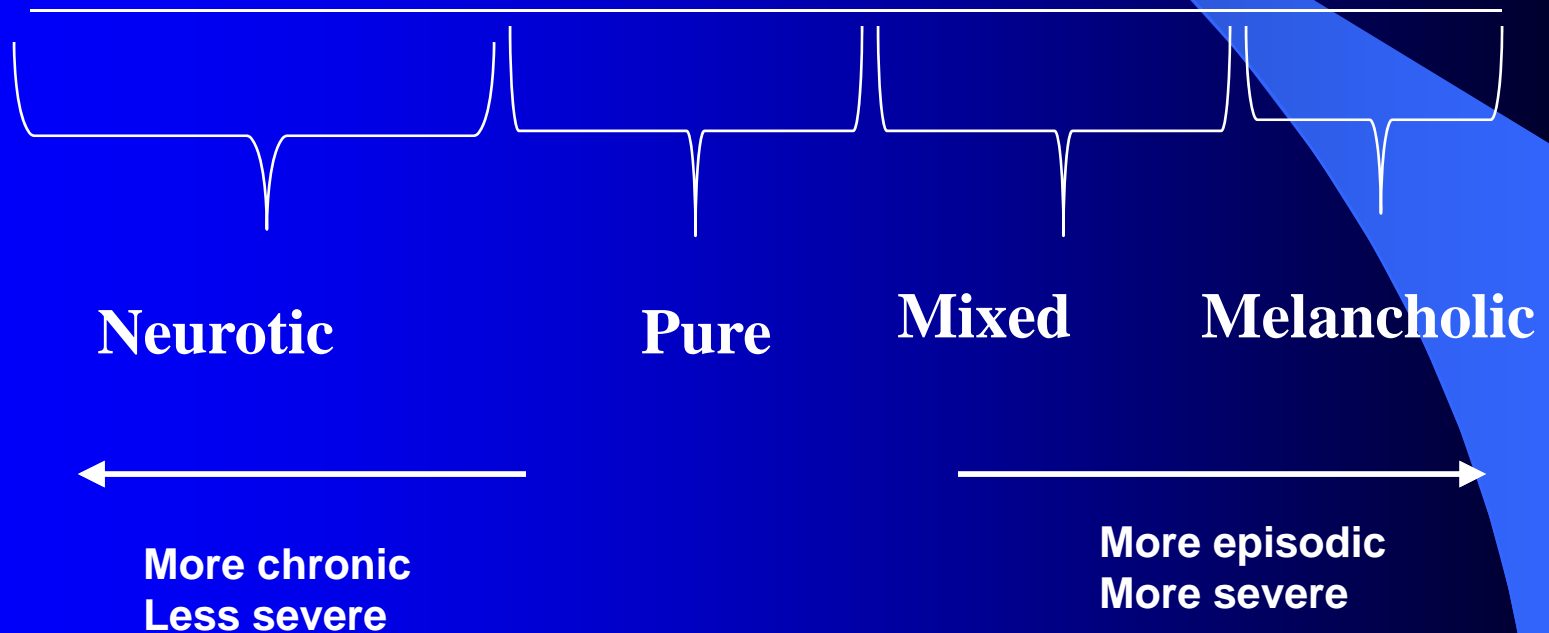
- 31.5% mood stabilizers, 30% dopamine blockers, 25% ECT
- **ONLY 2.7%** given antidepressants
- HDRS 27.9 to 8.0
- Episodes: **45% NONE**, 19% minor depressive, 17% pure depressive, 8% hypomanic, 7% mixed depressive, 1% suicide attempt

BRIDGE study

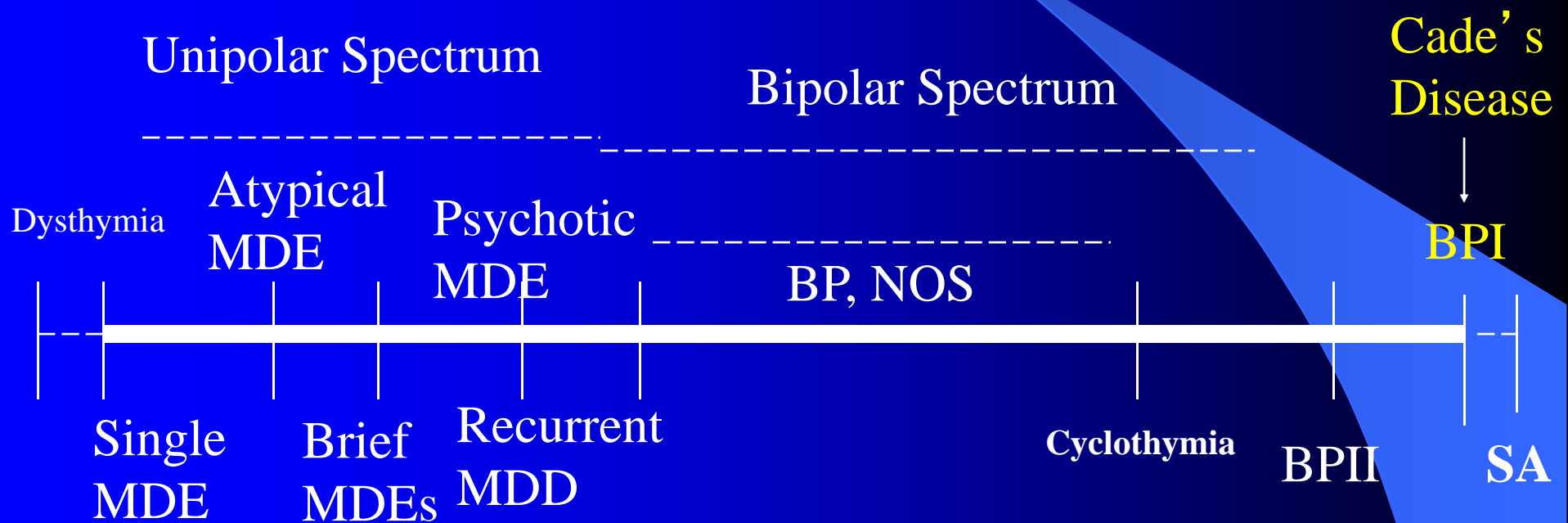
- N = 5635 with clinical depression
- DSM-IV criteria for BD = 16.0%
- Bipolarity specifier = 47.0%
 - 3 or more manic symptoms
 - No duration criterion
 - Marked impairment of functioning or unequivocal and observable change from usual behavior
- Bipolarity specifier highly associated with AD-induced mania (OR=9.5) and FH BD (OR=3.8)

The MDD Spectrum

SN Ghaemi, PA Vohringer, D Vergne:
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The Manic-Depressive Spectrum



BP, NOS= bipolar disorder, not otherwise specified. This could include mania or hypomania only on antidepressants, recurrent MDD with underlying hyperthymia, or recurrent MDD with a first-degree relative with bipolar disorder.

SA=schizoaffective disorder, bipolar type, can be seen as a more severe version of MDI.

Mood Temperments

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Personality

- ❑ Personality disorders - Freud
 - DSM: Categorical
 - Psychoanalytic tradition
- ❑ Temperaments – Kahlbaum/Kretschmer
 - Dysthymia, **Hyperthymia**, **Cyclothymia**, Schizothymia
 - Euthymia
- ❑ Traits - Eysenck
 - Neuroticism, Extraversion, Openness to Experience (NEO)
 - Tridimensional Personality Questionnaire (TPQ) - Cloninger

Temperaments

- ❑ Dysthymia
- ❑ Cyclothymia
- ❑ Hyperthymia
- ❑ Schizothymia (Schizotypal)
- ❑ Introduced by Kahlbaum, extended by Kretschmer, revised by Akiskal
- ❑ Relates to extremes of normal personality traits
 - Eysenck/Cloninger: Neuroticism, Extraversion, Openness to Experience (Novelty-seeking)

Temperaments versus Personality “Disorders”

■ Psychopathology

- Similar mood and behavioral presentations
- Temperaments are dimensions, extremes of normal personality traits
- PDs are categorical

■ Biology/genetics

- Temperaments are related to mood disorders
 - 50% genetic, environmental causes are nonspecific
- PDs stand alone and have specific traumas

■ Sexual trauma

- In Borderline PD – 50-76%
 - One-third report no abuse, meta analysis $r = 0.27$
 - Necessary but not sufficient
- In bipolar illness – 24-30%
- In general population – 15-22%

■ Self-cutting/self-harm

- In borderline PD 63-69%
- In bipolar illness (adult, without borderline PD comorbidity) 0.9%-36%
 - 0.9% rate in NCS study (n=5877)

Clinical example

- Hyperthymic temperament from childhood
- Workaholic, productive, successful, businessperson
- Sociable, extraverted, lively, vigorous
- Episodic depression/episodic anxiety
- Unresponsive after some time to SRIs or other antidepressants/anxiolytics
 - DSM diagnosis: “MDD/GAD”
- Responsive to low dose mood stabilizers or neuroleptics

Temperament ≠ Illness

- ❑ Reverse Stigma – Positive benefits of mental illness and limitations of mental health

JF Galvez, SB Thommi, SN Ghaemi, J Affective Disorders, 2011, 128-185-190

- ❑ **Hyperthymic temperament** - Charisma
 - Creativity
 - Sociability
 - Energy and Productivity
 - Resilience to trauma – medical, psychological, social

SN Ghaemi, A First-Rate Madness: Exploring the Links Between Mental Illness and Stigma, 2011

BRIDGE study

- Four borderline criteria overlapped with bipolar (mood lability, unstable relationships, impulsivity, anger)
- Four borderline criteria did NOT predict bipolarity even broadly defined: abandonment, identity disturbance, recurrent suicidal or self-mutilating behavior, dissociative symptoms

Angst et al, Acta Psychiatrica Scandinavica, 2013, in press

ADHD at age 41

- ❑ 33 year prospective follow up of 8 year olds
- ❑ ADHD persisted in 22%
- ❑ ADHD was diagnosed in 5% of adult control group, who did NOT have childhood ADHD
- ❑ Antisocial personality: 14% ADHD vs 0% controls
- ❑ Substance abuse common: 14% ADHD vs 5%
- ❑ Mood disorders: 9% vs 6%
- ❑ Anxiety disorders 13% vs 9%
- ❑ My conclusions:
 - Almost 80% of childhood ADHD does not persist into adulthood
 - Epidemiological prevalence of “adult ADHD” is consistent with normal variations of cognitive function
 - The most clear adult outcome of ADHD is antisocial personality
 - Mood and anxiety disorders are one-third more common outcomes in adulthood for children with ADHD

DE Vergne et al, Adult ADHD and amphetamines:
a new paradigm. Neuropsychiatry 2011; 13: 583–586.

Animal Studies:

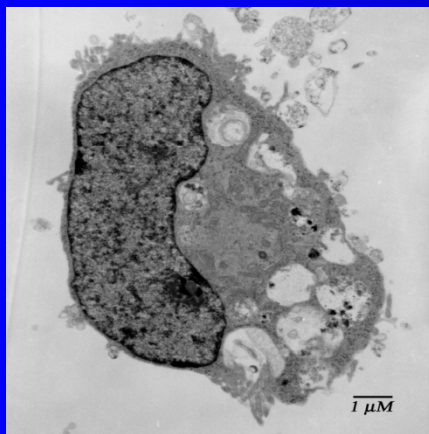
Harmful effects of amphetamines

- ❑ Decreased response to rewarding stimuli¹
- ❑ Increases in depressive and anxiety behaviors²
- ❑ Decreased dopaminergic neuronal activity³
- ❑ Enhanced corticosteroid response after stress¹
- ❑ Decreased long-term survival of new born cells in the temporal hippocampus⁴ (associated with depression)⁵

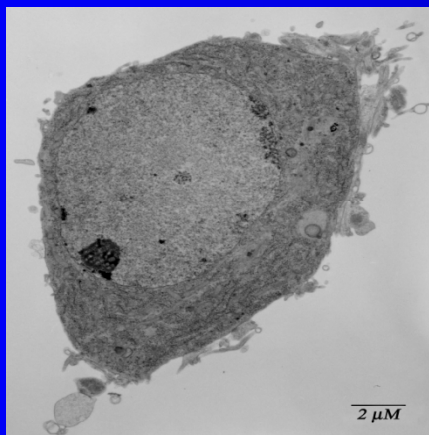
1. CA Bolanos et al, Biol Psych 2003;1317-1329; 2. WA Carlezon et al, Biol Psych 54: 1330-1337;
3. CL Brandon et al, Biol Psych 2003; 54: 1338-1344; 4. DC Lagace et al, Biol Psych, 2006; 60: 1121-1130;
5. RS Duman, Biol Psych 2004; 56:140-145; RS Duman et al Arch Gen Psych 1997; 54:597-606.

NMDA

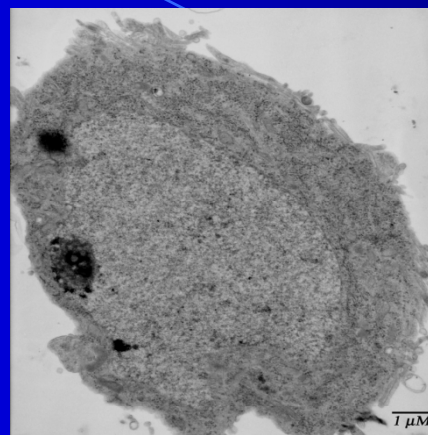
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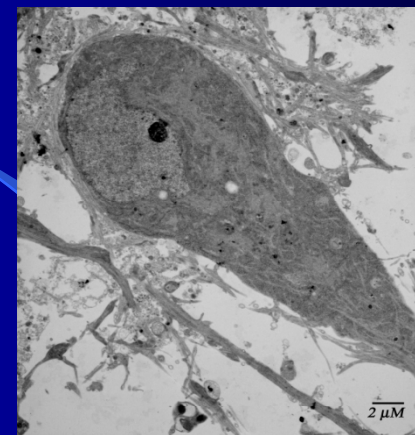
Ctl



Li Cl



VPA



The effect of Li and VPA on vacuolization induced by glutamate receptor agonist NMDA. Primary cultured hippocampus cells were pretreated with Li Cl (1 mM) and VPA (0.6 mM) for one week, and then incubated with NMDA 0.5 mM for 10 min. Vacuolization in the cells was detected using transmission electron microscopy.

CD Bown et al, Neuroscience, 2003;117(4):949-55

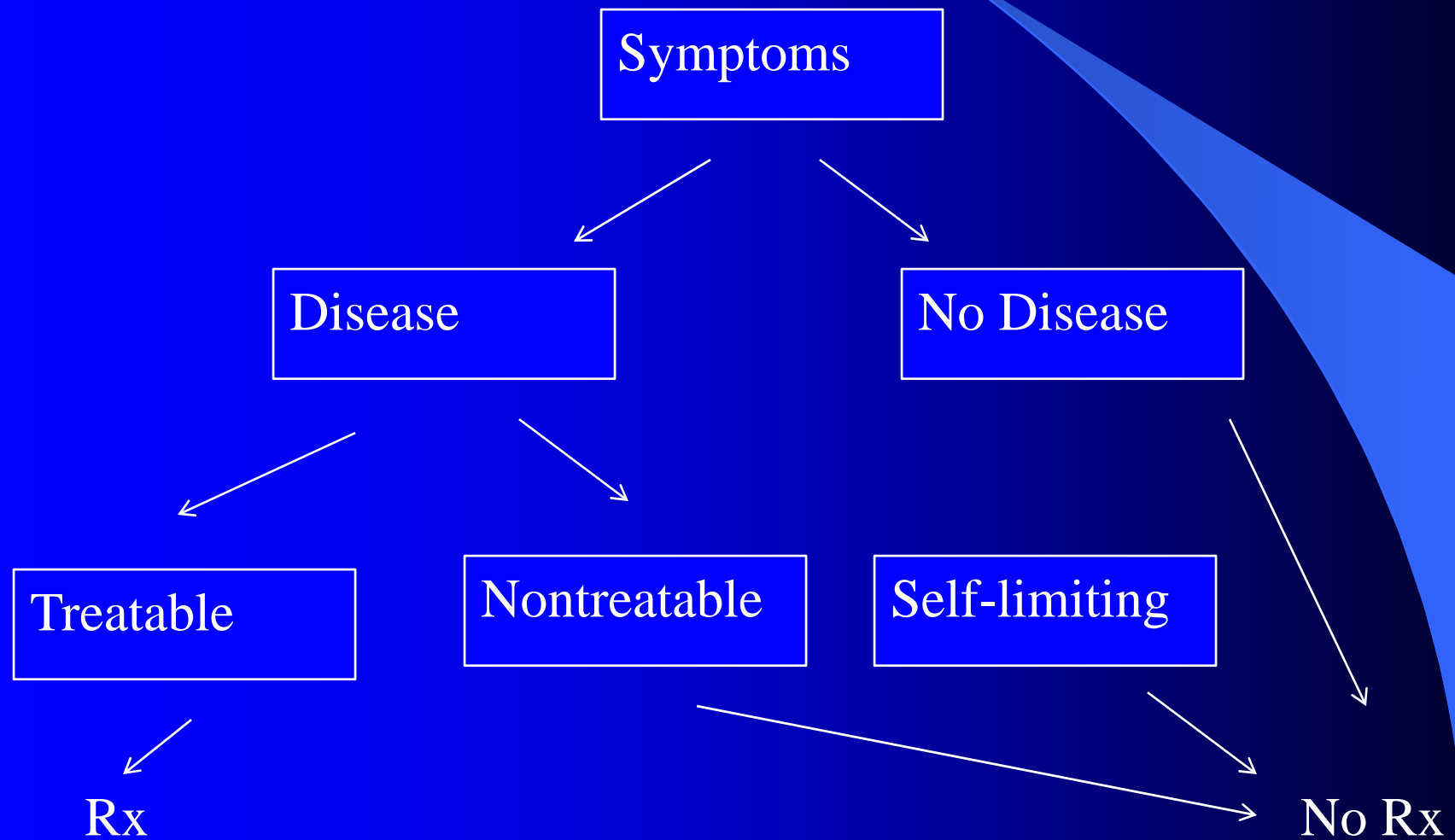
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Treatment

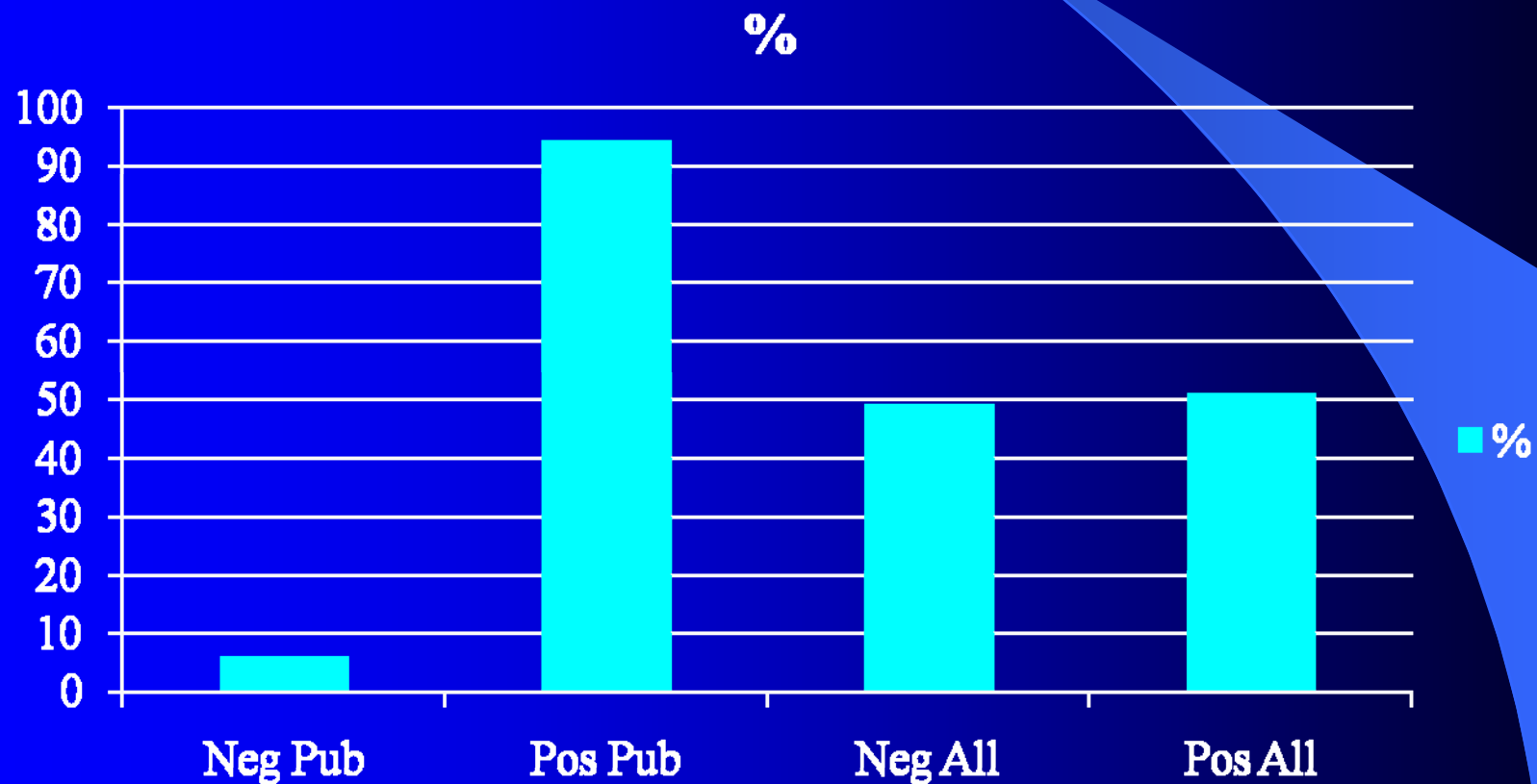
Proposed Psychopharm Nomenclature

Criteria	Monoamine agonists	Dopamine blockers	Direct second messenger modifiers	GABAergic agonists	Other
Clinical efficacy	Depression & anxiety syndromes & ADHD	Psychosis and mania	Prevention recurrences of depressive or manic episodes	Anxiety or insomnia	Anxiety or insomnia
Actions	Increase activity of dopamine, norepinephrine, or serotonin	Block dopamine receptors	Affect second messenger systems extensively	Stimulate GABA receptors and/or open chloride ion channels	Antihistaminic adrenergic antagonists, melatonin agonists

Hippocratic Practice

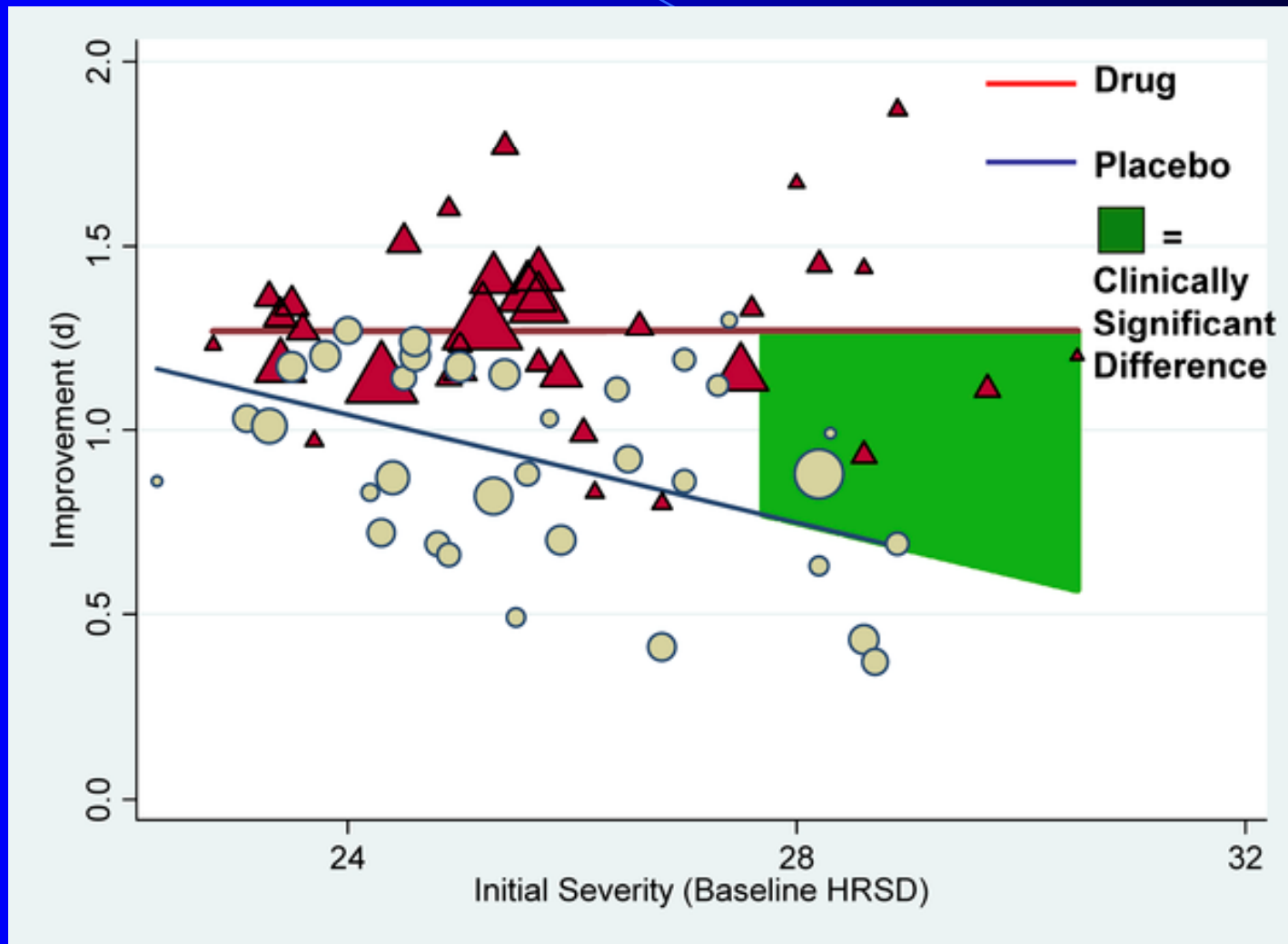


Negative Publications: Antidepressants



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

AD meta-analysis: Don't work?



Maintenance Designs: “Enriched” or Randomized Discontinuation Trials (RDTs)

- Give patients drug X
- If they do not respond, they go away
- If they respond, randomize them to the study
 - Stay on drug X
 - Come off and get nothing (placebo)
 - Come off and get another drug (active control)
- RDTs in psychiatry rarely if ever fail
 - Happily ever after assumption: What makes you well keeps you well
 - Works for almost ALL drugs
 - Poor falsifiability – **RDTs are invalid as used in psychiatry**

“Inverse” Enriched Design

■ Inverse enriched design:

- Take all AD maintenance RCTs and select acute placebo responders
 - Compare acute placebo responders who stay on placebo for maintenance (7 studies) versus
 - Acute AD-responders who switch to placebo for maintenance (39 studies)
- Maintenance relapse: Placebo (25%) < Drug (42%)

PA Vohringer, SN Ghaemi. Clin Ther. 2011 Dec;33(12):B49-61

PW Andrews et al, Front Psychol, 2011. 2(159): p. 1-24.

Maintenance Li studies: Enriched versus Non-enriched

- 9 RCTs, n= 1432, 705 prerandomization dropouts
- 341 RDT to lithium and 386 to placebo
- Two non-enriched RCTs: Odds Ratio = 3.2 (95% CI 0.65–15.46) lithium over placebo
- 3 enriched RDTs: OR = 22.0 (95% CI 7.0–68.7)
- 2 non-enriched RCTs (enriched for lamotrigine): OR = 1.9 (95% CI 1.2–2.8).
- 10-fold inflation of effect size: What if real effect size is 1? RDT result is 10!

Happily ever after fallacy

■ Counterexamples in medicine

- Acutely response but no/less maintenance: antibiotics, steroids for autoimmune diseases
- Maintenance, but no/less acute: propranolol for migraine, lithium/lamotrigine for bipolar, antidepressants in MDD (STAR*D), antipsychotics in schizophrenia? (CATIE)

Acute AD efficacy in BD: Meta-analysis

- ❑ Cohn et al 1980, n = 86
- ❑ Shelton and Stahl 2004, n = 30
- ❑ Tohen et al 2003, n = 433
- ❑ Amsterdam et al 2005, n = 25
- ❑ Sachs et al 2007, n = 332
- ❑ **RR = 1.18 [0.99, 1.40]**

A Priori Subgroup Analysis: Rapid Cycling

- Excess of depressive recurrences/year was limited to AD-treated patients
 - **RC = 1.29 vs. nonRC = 0.42 major depressive episodes in the first year, a 3.1-fold excess; $z = -2.04, p=0.04$**
 - Not the AD-discontinued group (RC = 0.82 vs. nonRC = 0.70 episodes/year, only a 1.17-fold difference)

“Antidepressants” are mood destabilizers

- *Second messenger modifiers are less effective when combined with monoamine agonists*

Lithium and dementia: Zurich study

- Bipolar disorder ($N=220$) and major depressive disorder ($N=186$) enrolled 1959 and 1963
 - Up to 20 year follow up
 - Mean age at last observation 65.3 (BP) 68.6 (UP)
- 88 cases of dementia = 22%
 - Population norm < 5 %
- Lithium reduced dementia rates to population norm
 - OR = 0.23 (CIs 0.06-0.89)
 - level 0.7
 - NOT neuroleptics or antidepressants (except clozapine)

J Angst et al, International Journal of Psychiatry in Clinical Practice,
2007, Vol. 11, No. 1 , Pages 2-8

Low CSF lithium levels are somewhat neuroprotective in rats

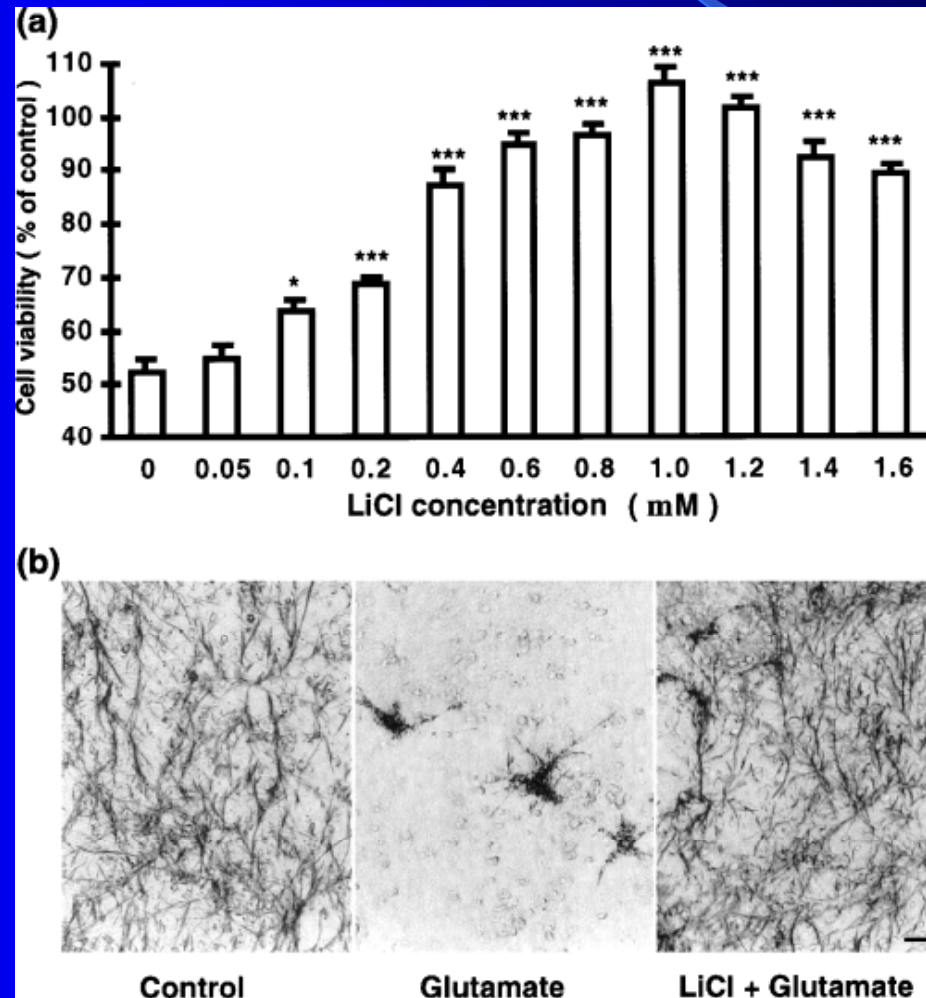
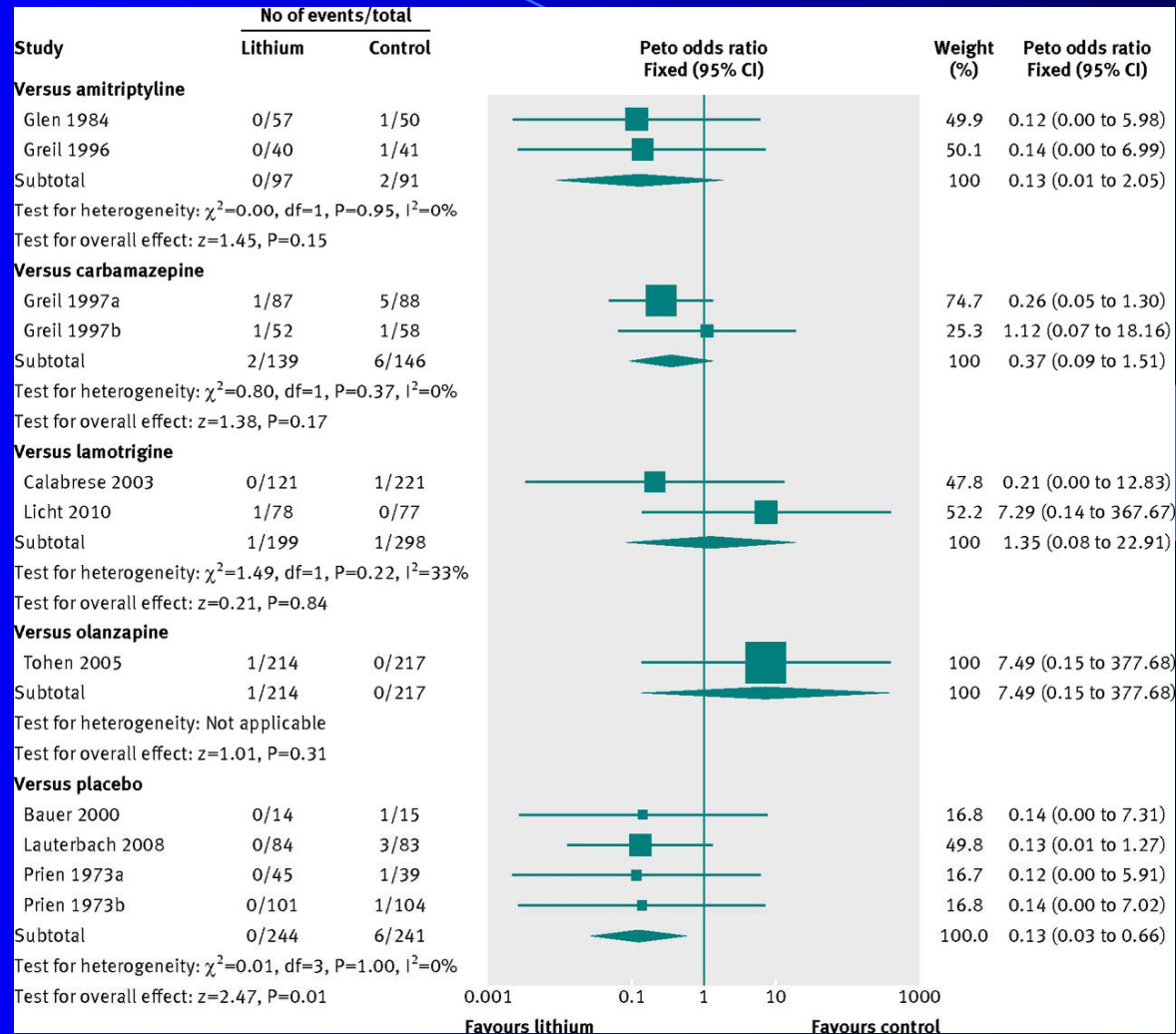


Fig 2 Forest plot showing meta-analysis of suicides in randomised trials comparing lithium with placebo or with active comparators.



Cipriani A et al. BMJ 2013;346:bmj.f3646

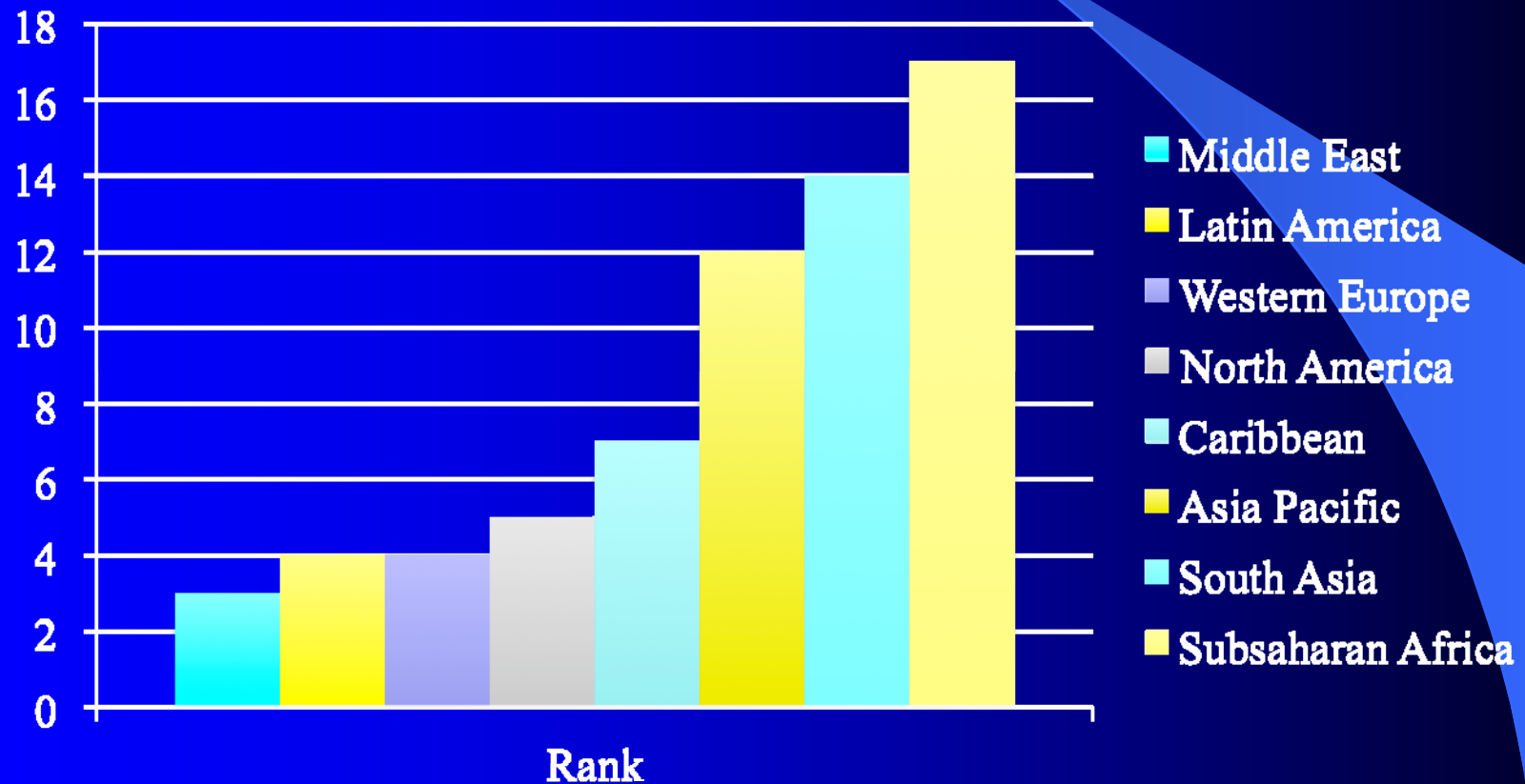
Lithium renal failure

- Sweden, 2.7 million population
- N=3369 lithium-treated
- N = 17 ESRD (0.5%)
 - Mean treatment time 23 years
 - 10 patients stopped lithium 10 years before dialysis
- Chronic renal disease prevalence 1.2%

Psychological and social aspects of depression

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Global Burden of Disease: Depression by Region



Theories of mental illness

- ❑ Kraepelin. Kretschmer
- ❑ Freud
- ❑ Existential school
 - Jung, Binswanger, Heidegger
 - Karl Jaspers

Personality

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 - Euthymia
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Validating ND

■ Phenomenology

- Quality of depressed mood
 - not different from normal sadness in ND, while “distinct” quality in melancholia (My view: “despair”)
- Absence of psychomotor retardation
- Presence of mood reactivity to changing circumstances

■ Psychosocial stress/life events

- More common in ND than unipolar/bipolar, but common also in the latter

■ Course – “Irregularly episodic”

- Chronic only if recurrence is not improved with treatment
 - Not invariable part of natural history

M Roth and TA Kerr, The concept of neurotic depression: A plea for reinstatement
In The Clinical Approach to Psychiatry, Edited by Pierre Pichot and Werner Rein
Collection Les Empecheurs de Penser en Rond, pp 339-368

Validating features of ND and relation to other depressions

■ Genetics

- No genetic liability to ND in twin studies, in contrast to strong liability in unipolar/bipolar depression
 - “one of the most impressive discriminating features from unipolar depression proper.”

■ Nonresponse to treatment

- More response in unipolar/bipolar, but still good response in ND in a large minority

M Roth and TA Kerr, The concept of neurotic depression: A plea for reinstatement
In The Clinical Approach to Psychiatry, Edited by Pierre Pichot and Werner Rein
Collection Les Empecheurs de Penser en Rond, pp 339-368

MDD = GAD

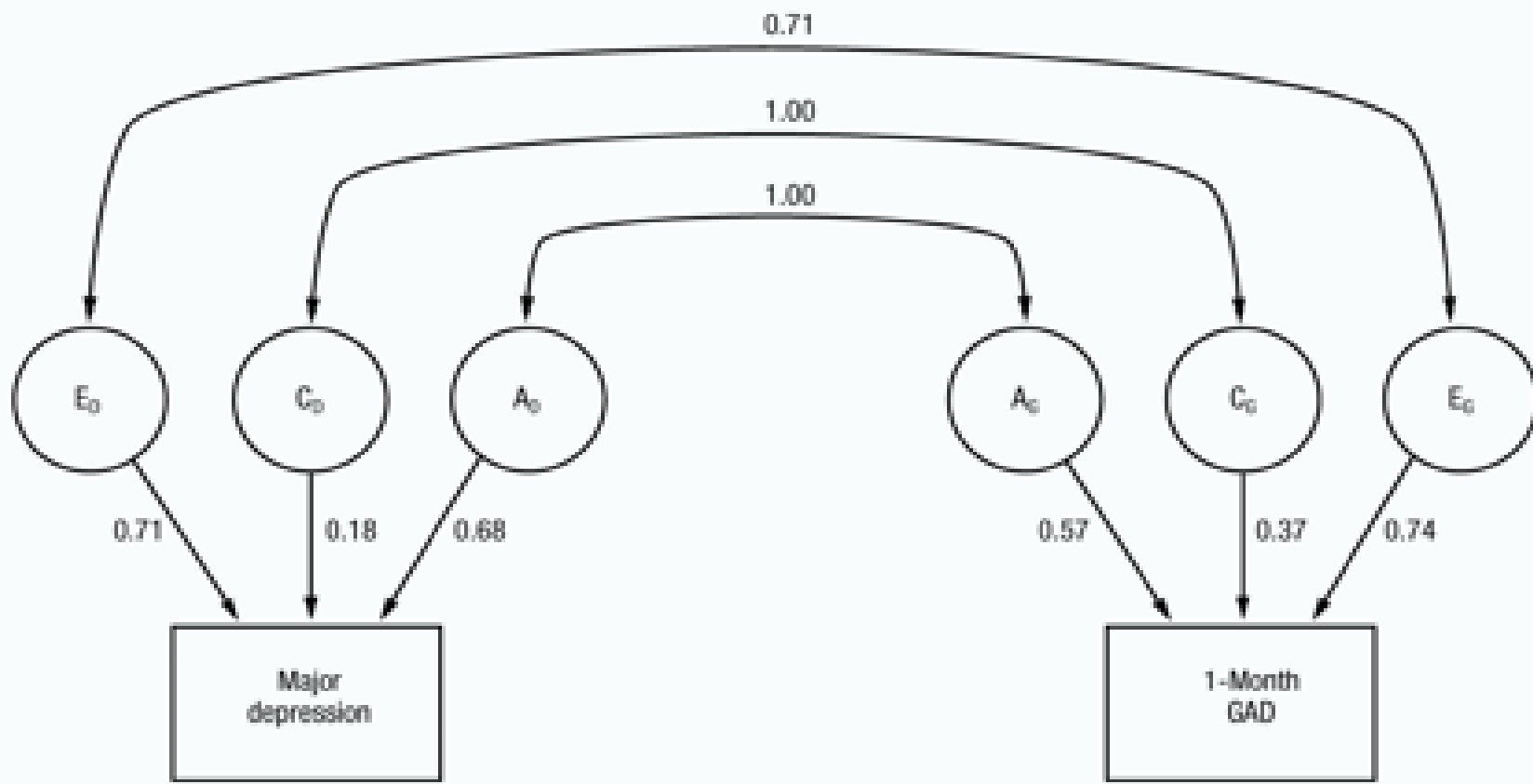
KS Kendler, Major depression and generalized anxiety disorder:

Same genes and (partly) different environments - revisited, British Journal of Psychiatry 1996; 168(suppl 30): 68–75.

Kendler, K. S., et al (1992b) Major depression and generalized anxiety disorder: same genes, (partly) different environments?

Archives of General Psychiatry, 49, 716–722

A. Full model



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

Theories of mental illness

- ❑ Kraepelin/Kretschmer
- ❑ Freud
- ❑ Existential school
 - Jung, Binswanger, Heidegger
 - Karl Jaspers