ATYPICAL DEPRESSION

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Pre-Lecture Exam Question 1

1. **All of the following should be considered in validating a psychiatric syndrome except:**

   A. Family history
   B. Biology
   C. Course of illness
   D. Differentiation from other syndromes and disorders
   E. Number of syndrome symptoms a given patient has

Question 2

2. The concept of atypical depression was first described by:

A. DSM IV
B. Donald F. Klein
C. Donald Robinson
D. West and Dally
E. Hagop Akiskal

Question 3

3. **The DSM IV atypical features modifier defines a group of patients that**

   A. predictably respond to tricyclic antidepressants.
   B. have a biological disorder similar to melancholia.
   C. may be heterogeneous, some patients having a disorder similar to melancholia, others having a disorder unlike melancholia.
   D. do not have a biological disorder.
   E. do poorly when treated with pharmacologic agents.

Question 4

4. A possibly important post-DSM IV finding about depression with atypical features is that

A. depressed patients with atypical features have shortened REM period latency.

B. those who look least like patients with melancholia are those who experienced an early onset of their depressive illness and subsequently did not experience well-being.

C. those who look least like patients with melancholia are those who have a nonchronic course of illness.

D. epidemiologic studies have failed to find such patients.

E. they are likely to respond to placebo.

Question 5

5. **Depression with atypical features is**

   A. so labeled because it is rare in the population.
   B. so labeled because patients with it do not have typically melancholic features.
   C. common relative to melancholia.
   D. B and C
   E. None of the above

Question 6

6. Depression with atypical features

A. appears to be familial
B. is an early onset, chronic disorder
C. may be biological but does not demonstrate the abnormal biological features of melancholia
D. All of the above
E. None of the above

ATYPICAL DEPRESSION
Teaching Points

- West & Dally 1st described atypical depression as TCA-unresponsive/MAOI responsive in 1959
- Syndrome description, course of illness, biologic studies, family studies and pharmacologic dissection, differentiate atypical depression from melancholia and other depressions
- New criteria are proposed incorporating age of onset and chronicity requirements for DSM-V depression with atypical features

ATYPICAL DEPRESSION

- Historical perspective
- Validity
- Current context

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MELANCHOLIC PATIENTS ARE:

"dull or stern, dejected or unreasonably torpid, without manifest cause… And they also become peevish, dispirited, sleepless, and start up from a disturbed sleep."

Aretaeus of Cappadocia (AD 120-180)

A MELANCHOLIC PATIENT:

"In Thesus, a woman, of a melancholic turn of mind, from accidental cause of sorrow, while still going about, became affected with loss of sleep, aversion to food, and had thirst and nausea…"

Hippocrates (462-555 BC)

WEST AND DALLY – 1959

Characterized of patients who respond to MAOI but not TCA as not having typical endogenous symptoms

- Evening worsening
- Severe fatigue*
- Prominent anxiety
- Multiple phobias
- Somatic preoccupation
- Premenstrual tension

**A DSM-IV criterion for atypical features

A DSM-IV criterion for atypical features

West & Dally: *British Medical Journal 1*:1491-4;1959

WEST AND DALLY – 1959 (cont.)

- Emotional reactivity*
- Absence of endogenous vegetative symptoms
- Good premorbid functioning and personality

*A DSM-IV criterion for atypical features

*A DSM-IV criterion for atypical features

West & Dally: *British Medical Journal 1*:1491-4;1959

SARGENT – 1960
Atypical Depression

- Hysterical exaggeration*
- Emotional hyper-reactivity*
- Lethargy*
- Anxiety
- Good premorbid personality
- Depression in response to stress*
- Phobic fears

**A DSM-IV criterion for atypical features

A DSM-IV criterion for atypical features

Sargant W: *Psychosomatics 1*:14-17;1960

SARGENT – 1960 (cont.)

- Irritability
- Hyper-reactive*
- PM worsening
- No insomnia or initial insomnia
- No psychomotor
- Worse with ECT

*A DSM-IV criterion for atypical features

*A DSM-IV criterion for atypical features

Sargant W: *Psychosomatics 1*:14-17;1960

HORDERN – 1965
Atypical Depression

- Phobic anxiety
- Reverse diurnal worsening
- Fatigue*
- Emotionality*
- Initial insomnia
- Tendency to blame others

*A DSM-IV criterion for atypical features

*A DSM-IV criterion for atypical features

Hordern A: *New England Journal of Medicine 272*:1159-69;1965

HYSTEROID DYSPHORIA
Klein - 1969

- Female
- Mood swings*
- Overidealize romances*
- Hyperphagia*
- Hypersomnia*
- Egocentric

*A DSM-IV criterion for atypical features

*A DSM-IV criterion for atypical features

Klein D: In Klein & Davis: *Diagnosis and Drug Treatment of Psychiatric Disorders*, 1968

HYSTEROID DYSPHORIA
Klein, 1969 (cont.)

- Histrionic style of interaction
- Imipramine unresponsive
- MAOI responsive

Klein D: In Klein & Davis: *Diagnosis and Drug Treatment of Psychiatric Disorders*, 1968

ENDOGENOMORPHIC DEPESSION
Klein - 1974

- Pervasive anhedonia is the hallmark of endogenous depression

Klein DF: *Arch Gen Psychiatry 31*:447-451;1974

ROBINSON – 1980
Description of patients likely to respond to MAOI's

- Evening worsening
- Hysterical personality*
- Weight gain*
- Psychic and somatic anxiety
- Initial insomnia
- Emotional reactivity*
- Somatic complaints

**A DSM-IV criterion for atypical features

Ravaris CL et al: *Archives of General Psychiatry 37*:1075-80;1980

DAVIDSON - 1982

- Required features - Mood reactivity, nonendogenous depression (by Newcastle Scale)
- A Type - Anxiety prominent
  - No required vegetative features
- V Type – Vegetative Symptoms prominent

  (one required)
  - *Hyperphagia
  - *Weight gain
  - Evening mood worsening

* A DSM-IV criterion for atypical features

* A DSM-IV criterion for atypical features

Davidson JR, et al: *Archives of General Psychiatry 39*:527-34;1982

ATYPICAL DEPRESSION

- Historical perspective
- **Validity**
- Current context

SYNDROMIC VALIDATION
Robins & Guze - 1970

- Syndrome description
- Laboratory findings
- Follow-up study
- Family history
- Delineation from other disorders

Robins & Guze: *American Journal of Psychiatry 126*:983-7:1970

PHARMACOLOGIC DEPRESSION
Klein - 1989

- Different responses to the same treatment imply different underlying pathophysiologies

Klein DF: In Robins L, Barrett J (eds.): *Validity of Psychiatric Diagnosis*, Raven, New York, 1989, pp 203-216

PHARMACOLOGIC DEPRESSION Corollary

- Different response to treatment is evidence that two syndromes have different underlying physiology

Klein DF: In Robins L, Barrett J (eds.): *Validity of Psychiatric Diagnosis*, Raven, New York, 1989, pp 203-216

SYNDROMIC VALIDATION
Robins & Guze + Klein

- Syndrome description
- Laboratory findings
- Follow-up study
- Family history
- Delineation from other disorders
- Pharmacologic dissection

ATYPICAL DEPRESSION
Syndrome Description

DSM-IV Criteria

- Meets criteria for major depression or dysthymia
- Significant mood reactivity
- At least two associated features
  - Hyperphagia
  - Hypersomnia
  - Leaden paralysis
  - Rejection sensitivity
- Does not meet criteria for melancholia or catatonic features

SYNDROME DESCRIPTION

	Atypical	Melancholia
Mood reactivity	Reactive	Pervasive anhedonia
Eating	Increased	Decreased
Sleep	Increased	Decreased
Energy	Leaden paralysis	Low without leaden paralysis
Premorbid personality	Rejection sensitive	Normal sensitivity

Stewart JW et al: *Psychiatric Clinics of North America 16*:479-495;1993

HYPOTHESES

- Patients with atypical depession will be more likely to benefit from phenelzine than from imipramine
- Imipramine will be no more effective than placebo for patients with atypical depession

INCLUSION CRITERIA

- 18-65 years
- Meets DSM-III criteria for depressive disorder
- Meets criteria for atypical depression
- Gives informed consent
- HAM-D $\geq$ 10

INCLUSION CRITERIA (cont.)

- Willing and able to follow tyramine-free diet
- Physically healthy

EXCLUSION CRITERIA

- History of psychosis
- History of prior adequate treatment with TCA or MAOI
- Medical disorder increasing risk of study medications
- BP> 140/90

ATYPICAL DEPRESSION
Study #1 (n=119)

Percent Responding

Placebo	**28%**
Imipramine	**50%**
Phenelzine	**71%**

Phenelzine > imipramine > placebo

Phenelzine > imipramine > placebo

Liebowitz MR et al: *Archives of General Psychiatry 45:*129-137;1988

ATYPICAL DEPRESSION
6 Week Outcome

	% Responding		
	Placebo	Imipramine	Phenelzine
Original Study (N=119)	28%	50%	71%
Replication Study (N=90)	19%	50%	83%

Liebowitz MR et al: *Archives of General Psychiatry 45:*129-137;1988
Quitkin FM et al: *Archives of General Psychiatry 47:*935-941;1990

LABORATORY STUDIES

- Sleep - Normal
- DST - Normal
- Tyramine - Normal
- Brain asymmetry - Normal vs. Right brain dysfunction
- Mood response to stimulants - Dysphoric

Stewart JW et al: *Psychiatric Clinics of North America 16*:479-495;1993

LABORATORY TESTING (%) ABNORMAL

	DST	Tyramine Excretion	Dichotic Listening	Dysphoria to Amphetamines
Atypical Depression	11	42	17	31
Melancholia	35	84	59	11

Stewart JW et al: *Psychiatric Clinics of North America 16*:479-495;1993

VALIDATION OF ATYPICAL DEPRESSION
Family Study - Rate per 100 Relatives

Proband	Atypical N=15	Nonatypical N=10	p
Relatives	22	30	
Major	59	33	0.06
Dysthymia	18	3	0.08
Atypical	27	7	0.04
Alcohol	0	10	ns

Stewart JW et al: *Psychiatric Clinics of North America 16*:479-495;1993

ATYPICAL DEPRESSION

- Historical perspective
- Validity
- **Current context**

TREATMENT RESPONSE OF ATYPICAL DEPRESSION TO FLUOXETINE

Inclusion Criteria

- Major depression
- Atypical depression
- 10 week double-blind, placebo-controlled
- Fluoxetine to 60 mg/d
- Imipramine to 300 mg/d

TREATMENT RESPONSE
Fluoxetine

Placebo	Imipramine	Fluoxetine
23%	53%	51%
(12/52)	(28/53)	(25/49)

McGrath PJ et al: *American Journal of Psychiatry 157*:344-350;2000

MOCLOBEMIDE

- Reversible type A inhibitor (RIMA)
- Not superior to SSRIs for atypical depression[a,b]
- Clinical impression[c]
  - works like traditional agents
  - better side effects profile
  - no diet
- 600-900 range most likely effective, appears safe
- Only available from foreign pharmacies (i.e., <u>not</u> approved by US FDA)

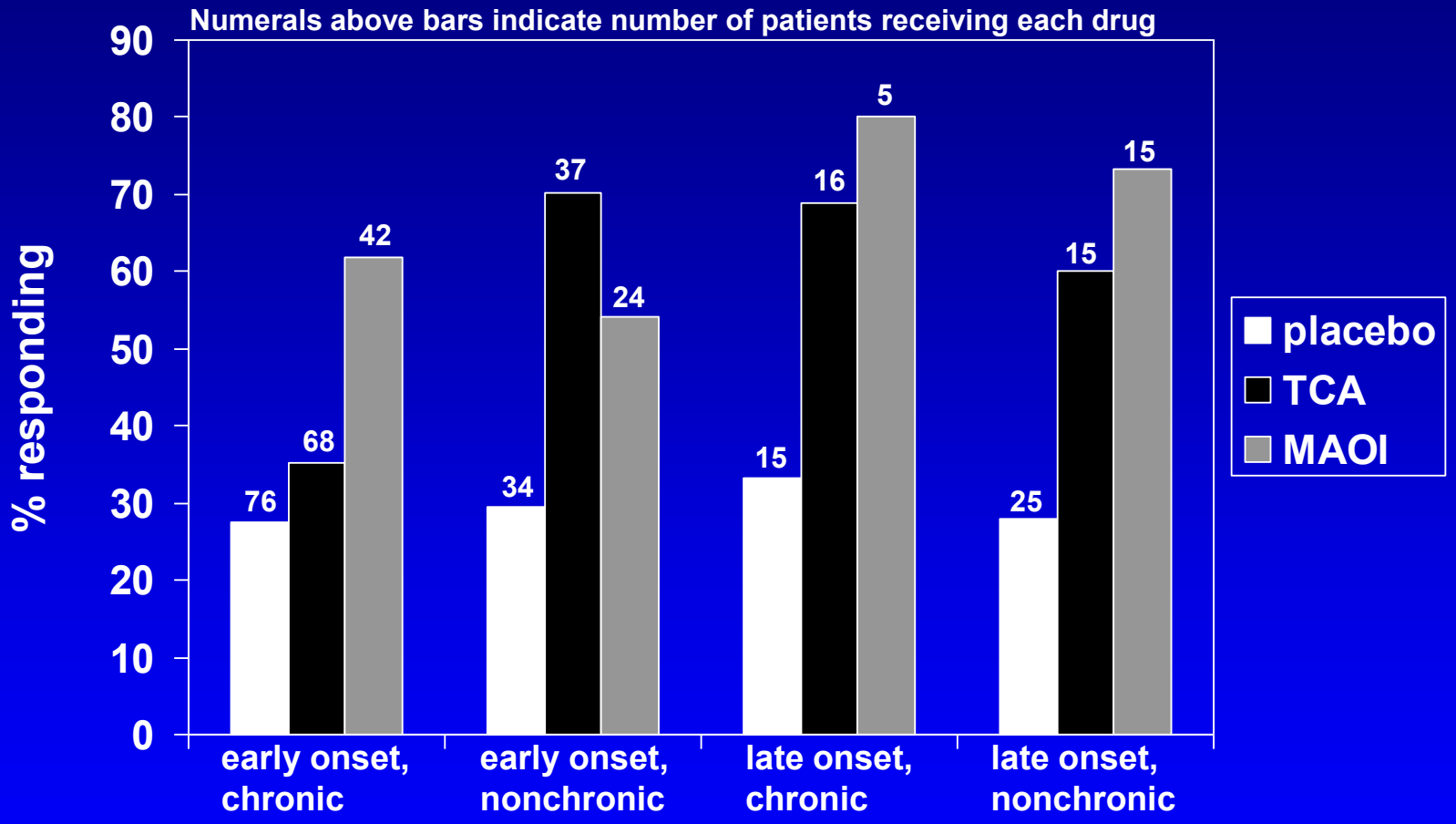
a Lonnqvist et al: *Journal of Affective Disorders* 32:169-77;1994

b Søgaard et al: *Journal of Pychopharmacology 13:406-14*;1999

c DF Klein, personal communication, 1999

Treatment Outcome of DSM IV Atypical Depression

Effect of Age of Onset and Chronicity

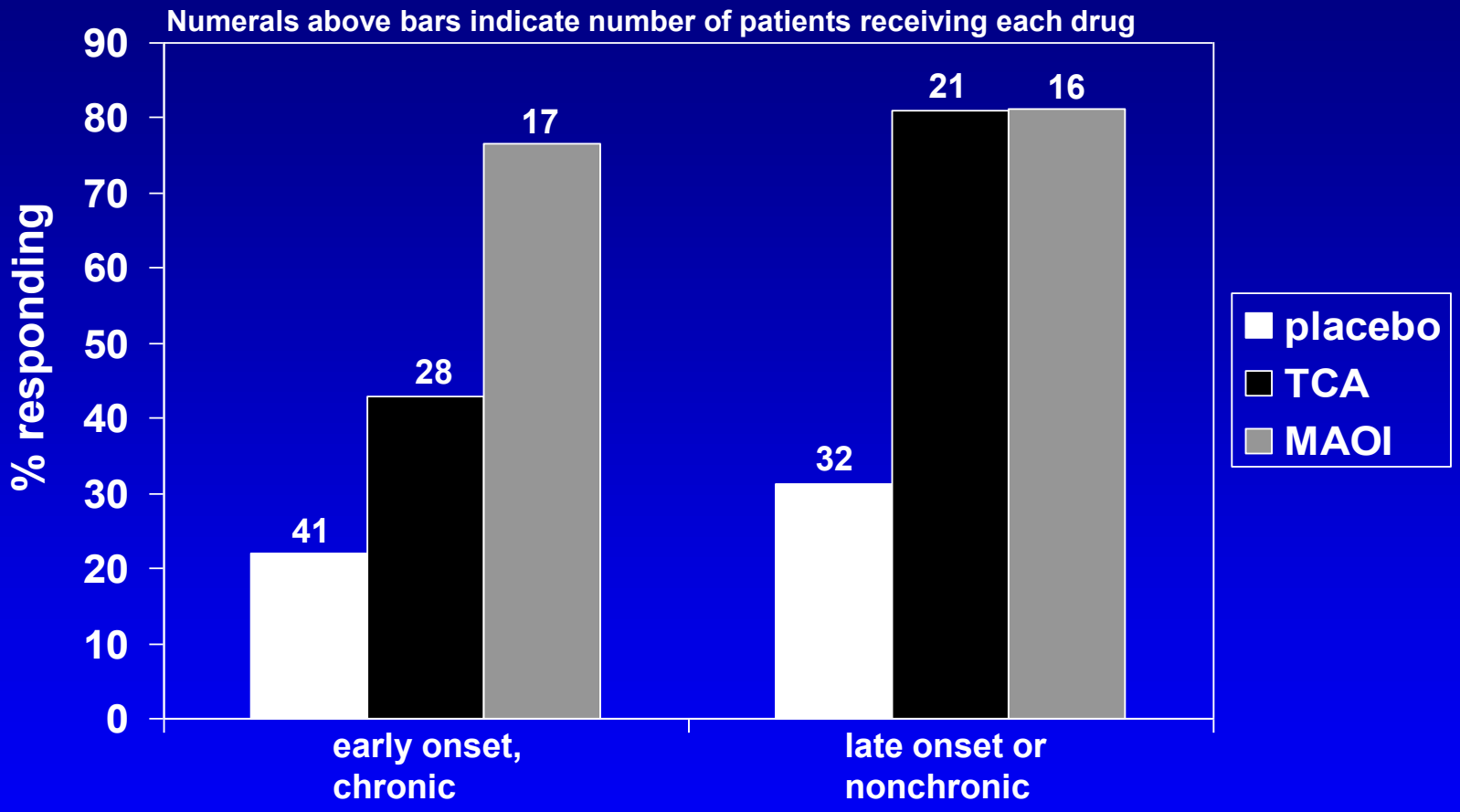


Early onset = first significant dysphoria prior to age 21
Late onset = first significant dysphoria after age 20
Chornic = duration > 2 years and no two month well-being following onset
Nonchronic = duration < 2 years or > two months well following onset

Stewart JW et al: *Neuropsychopharmacology 26*:237-45;2002

Treatment Outcome of Probable Atypical Depression

Effect of Age of Onset and Chronicity



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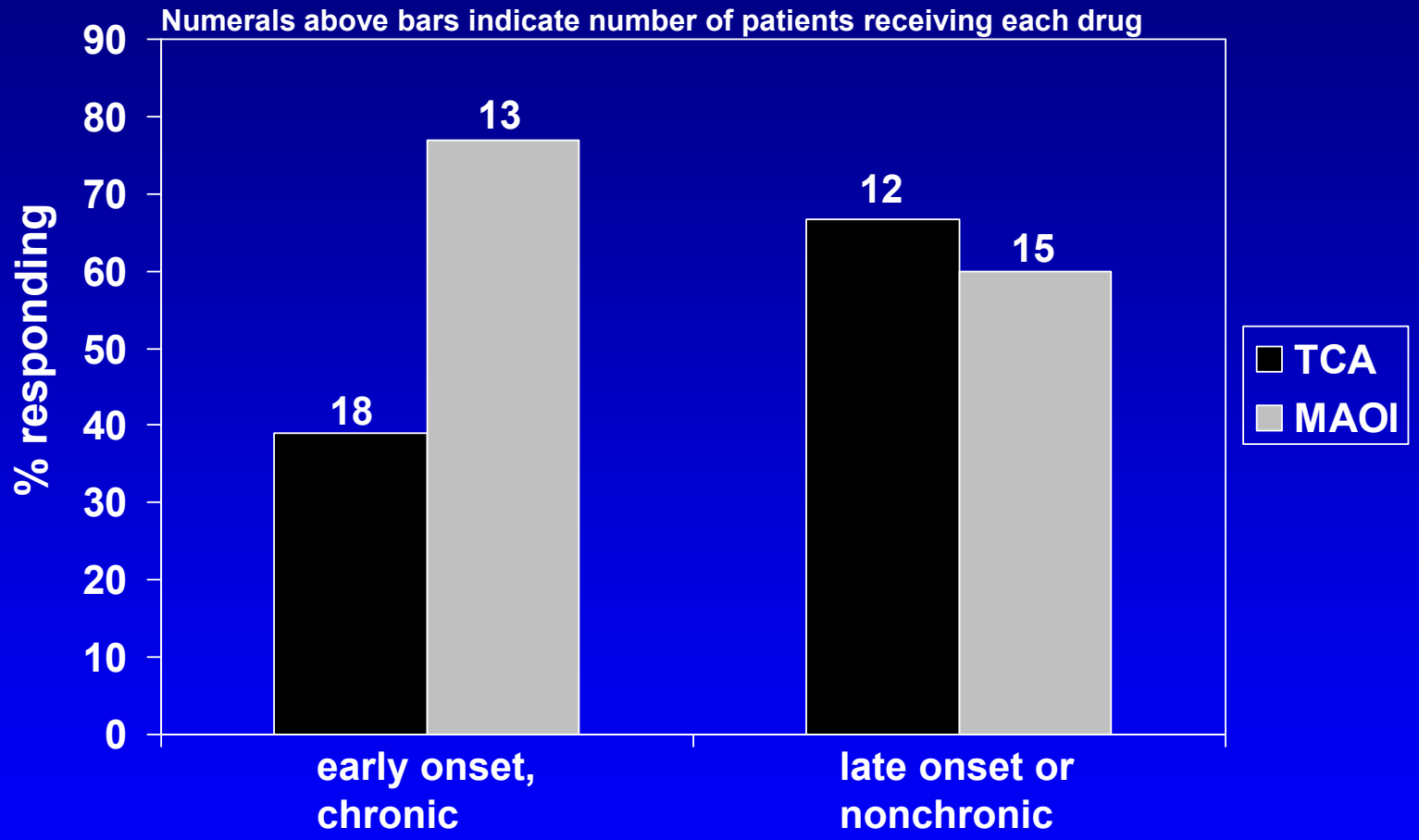
Treatment Outcome of Placebo Nonresponders with DSM IV or Probable Atypical Depression

Effect of Age of Onset and Chronicity



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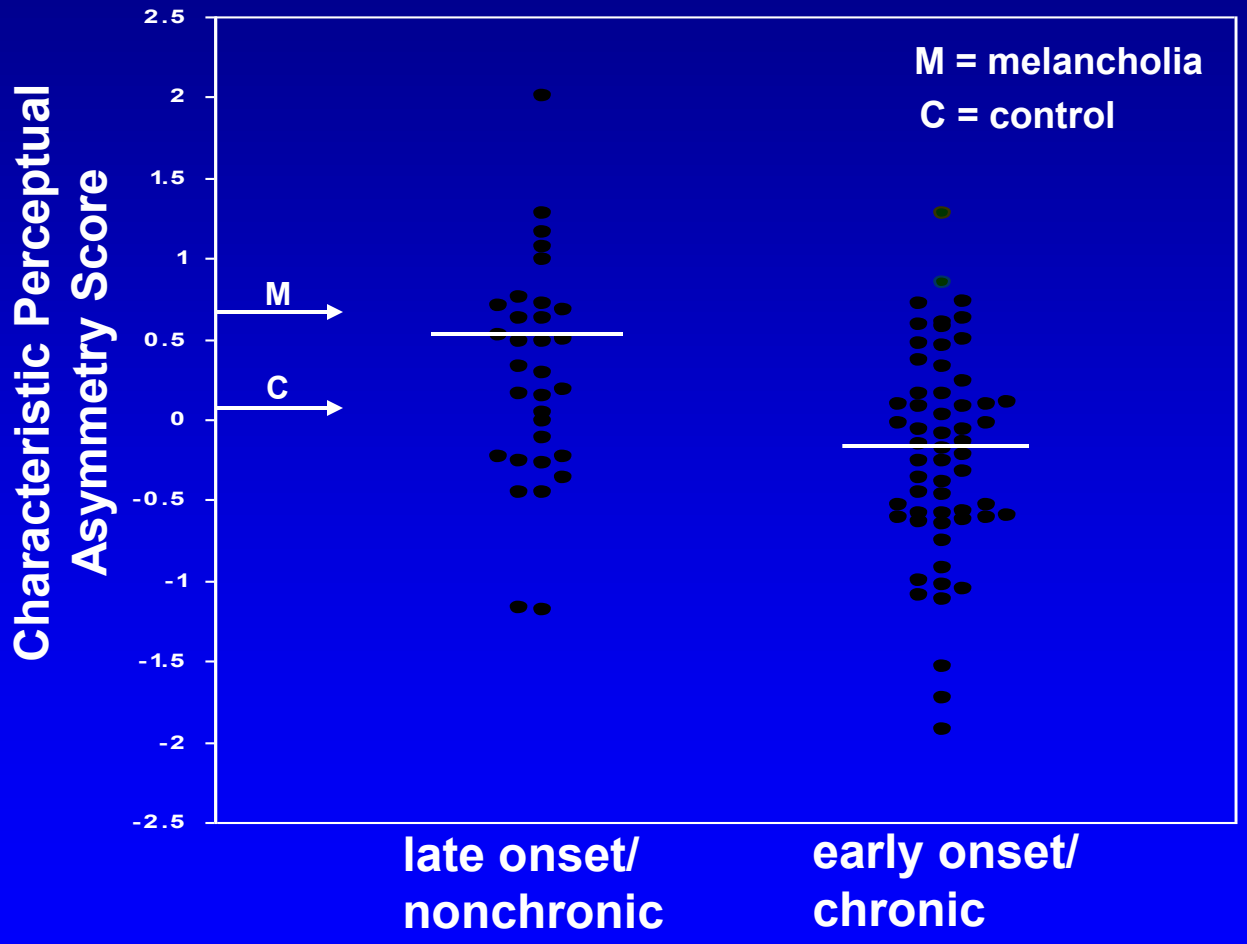
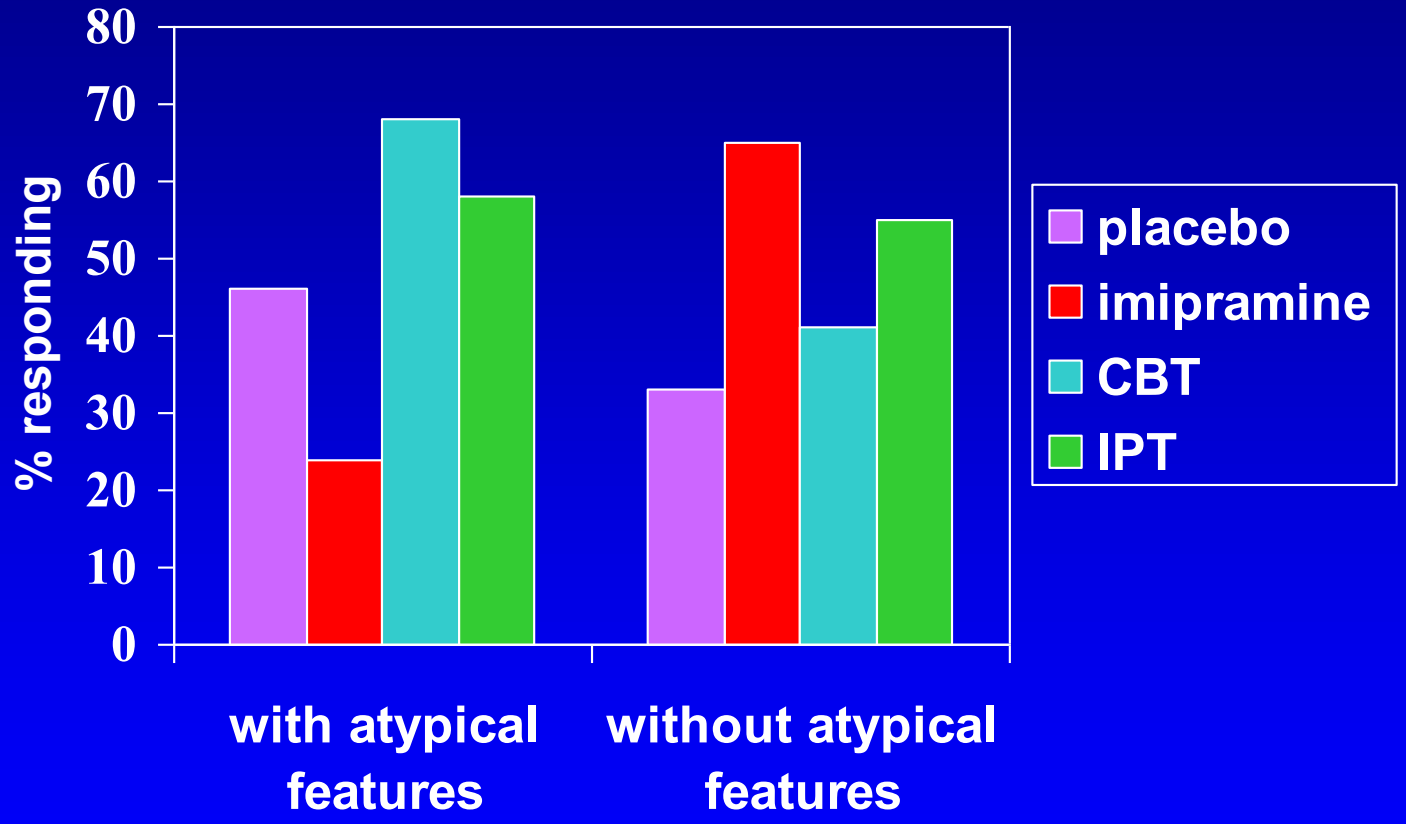
Dichotic Testing in Patients with DSM IV or probable Atypical Depression According to Age of Onset and Chronicity



Stewart JW: *Abnormal Psychology 112*:253-62;2003

Treatment Response in the TDCRP* by Presence or Absence of Atypical Features



*TDCRP = Treatment of Depression Collaborative Research Project

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Stewart JW et al: *Journal of Clinical Psychopharmacology 18*:429-434;1998

Epidemiologic Validation: Twins

- Latent class analysis of 14 DSM-IV symptoms
- 1029 female-female twin pairs
- Three clinically identifiable types emerge:
  - Mild typical (8.9%)
  - *Atypical* (3.9%) or *26.9%* of clinically depressed subjects
  - Severe typical (1.7%)

Kendler et al: 1996 *Arch Gen Psychiatry* 53:391-399

Epidemiologic Validation: Twins

- Atypical subtype
  - Stable in repeated episodes (O.R. = 8.3, P < .0001)
  - Familial (MZ twin concordance O.R. = 5.4, P < .001)
  - Reverse vegetative features
  - Frequent fatigue and psychomotor retardation
  - Not characterized by anxiety
    - GAD 15% for atypical, 32% mild typical, 78% severe typical, all significantly different
  - *Least likely* to be precipitated by a stressful life event

Kendler et al: *Arch Gen Psychiatry* 53:391-399;1996

National Comorbidity Survey

- Latent class analysis
- N = 2,836 epidemiologic sample
- DSM III-R symptoms
- Results of twin study replicated
  - Four classes: mild and severe typical
    mild and severe atypical
  - *36.6%* of depressive episodes atypical

Sullivan et al: *Am J Psychiatry* 155:1398-1406;1998

ATYPICAL DEPRESSION
Suggested DSM-V Criteria

- Meets criteria for major depression or dysthymia
- Significant mood reactivity
- At least one associated feature
  - Hyperphagia
  - Hypersomnia
  - Leaden paralysis
  - Rejection sensitivity
- Onset prior to age 20
- At least two years duration
- No two months of spontaneous well-being since onset
- Does not meet criteria for melancholia or catatonic features

Stewart JW: *Acta Psychiatrica Scandanavia 115(Suppl 433)*:58-71;2007

Pre-Lecture Exam Question 1

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C. those who look least like patients with melancholia are those who have a nonchronic course of illness.

D. epidemiologic studies have failed to find such patients.

E. they are likely to respond to placebo.

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5. **Depression with atypical features is**

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   B. so labeled because patients with it do not have typically melancholic features.
   C. common relative to melancholia.
   D. B and C
   E. None of the above

Question 6

6. Depression with atypical features

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B. is an early onset, chronic disorder
C. may be biological but does not demonstrate the abnormal biological features of melancholia
D. All of the above
E. None of the above

Answers to Pre & Post Competency Exams

1. E
2. D
3. C
4. B
5. B
6. D