

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**

ATYPICAL DEPRESSION

- **Historical perspective**
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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

WEST AND DALLY – 1959 (cont.)

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

*A DSM-IV criterion for atypical features

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**

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

HORDERN – 1965

Atypical Depression

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

*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

HYSTEROID DYSPHORIA

Klein, 1969 (cont.)

- **Histrionic style of interaction**
- **Imipramine unresponsive**
- **MAOI responsive**

ENDOGENOMORPHIC DEPESSION

Klein - 1974

- Pervasive anhedonia is the hallmark of endogenous depression

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

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

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**

PHARMACOLOGIC DEPRESSION

Klein - 1989

- Different responses to the same treatment imply different underlying pathophysiologies

PHARMACOLOGIC DEPRESSION

Corollary

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

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

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

HYPOTHESES

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

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

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**

LABORATORY TESTING (%) ABNORMAL

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

VALIDATION OF ATYPICAL DEPRESSION

Family Study - Rate per 100 Relatives

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

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

23%

(12/52)

Imipramine

53%

(28/53)

Fluoxetine

51%

(25/49)

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., not approved by US FDA)

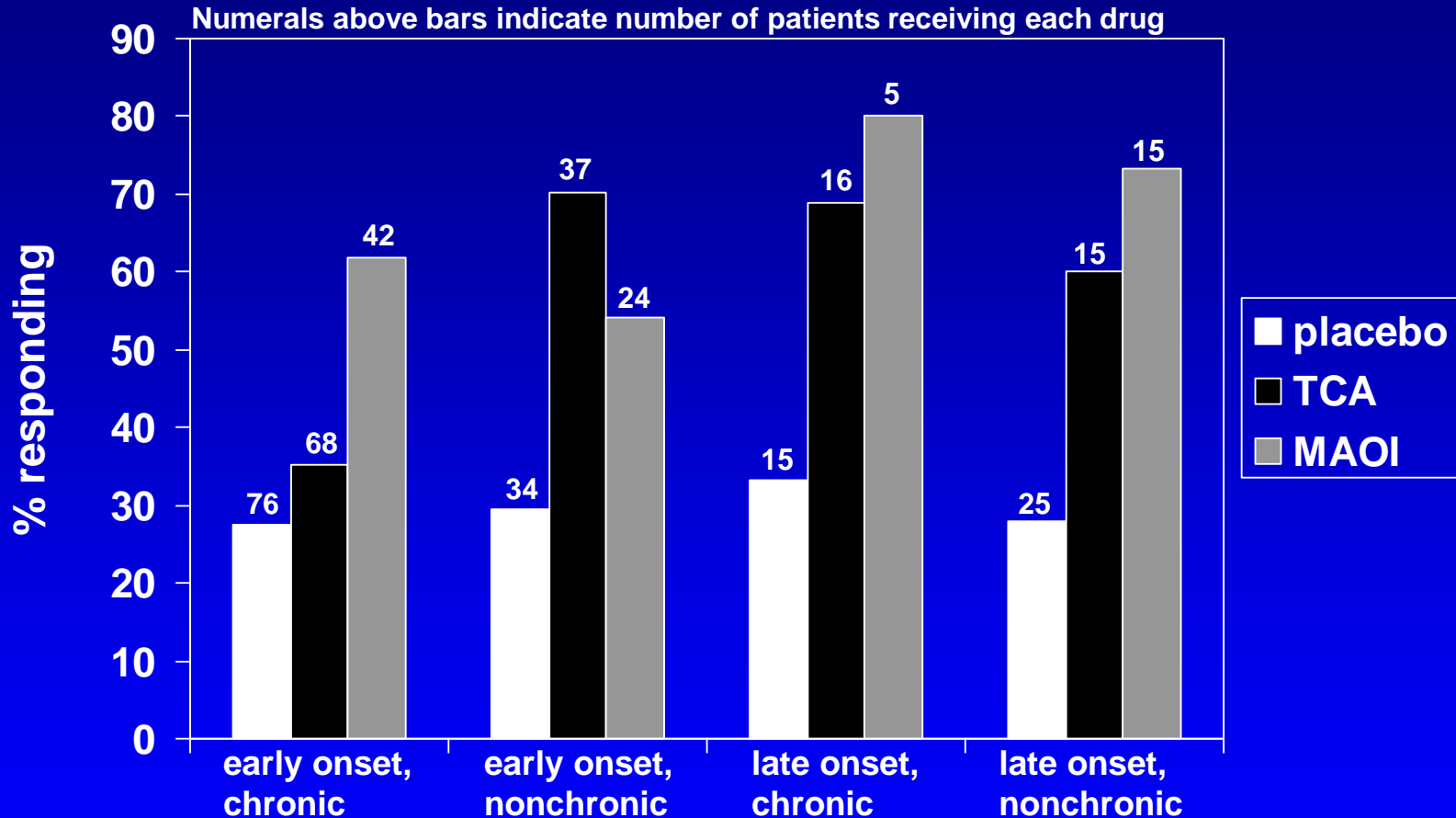
a Lonqvist et al: *Journal of Affective Disorders* 32:169-77;1994

b Sogaard et al: *Journal of Psychopharmacology* 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

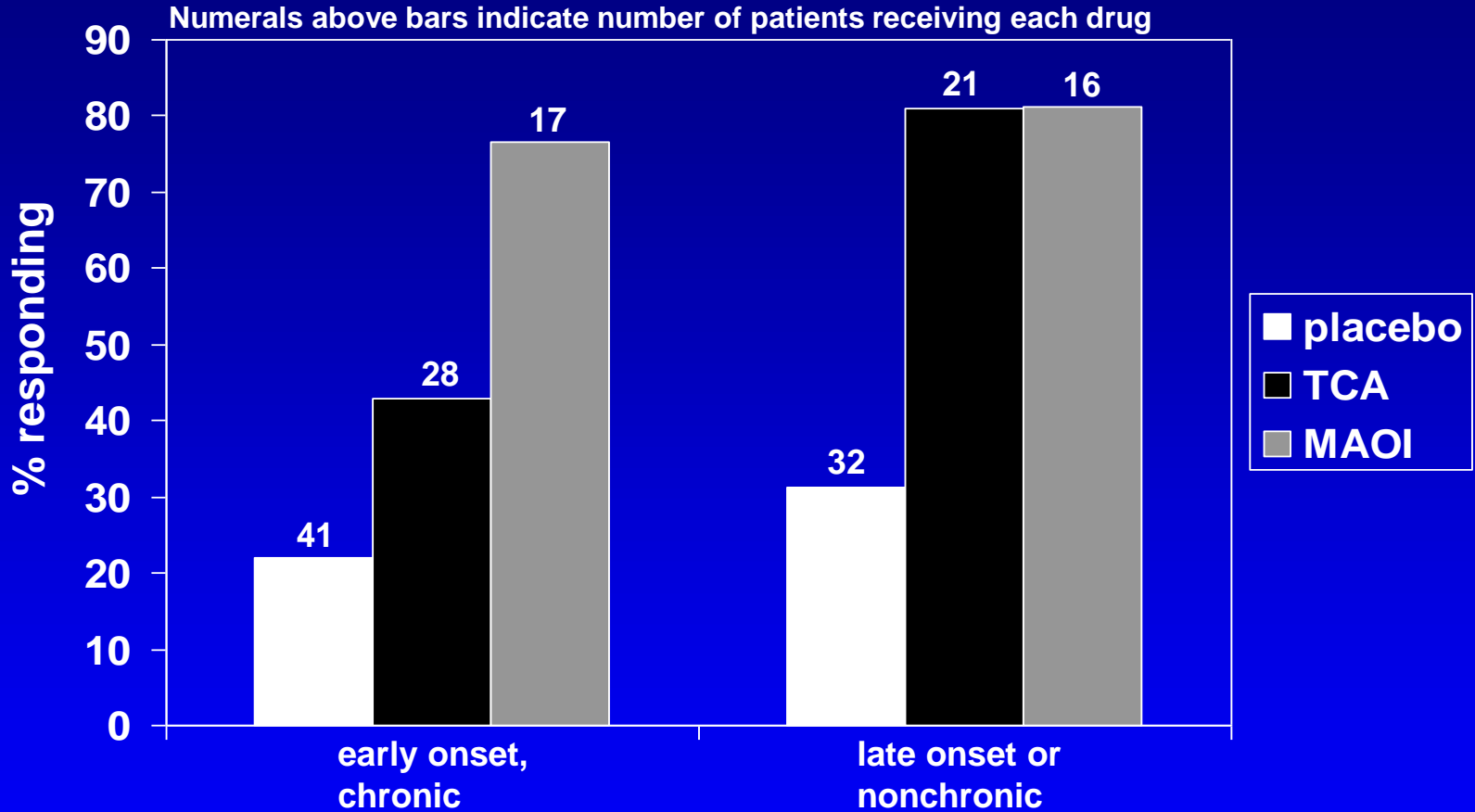
Late onset = first significant dysphoria after age 20

Chronic = duration > 2 years and no two month well-being following onset

Nonchronic = duration < 2 years or > two months well following onset

Treatment Outcome of Probable Atypical Depression

Effect of Age of Onset and Chronicity



Early onset = first significant dysphoria prior to age 21

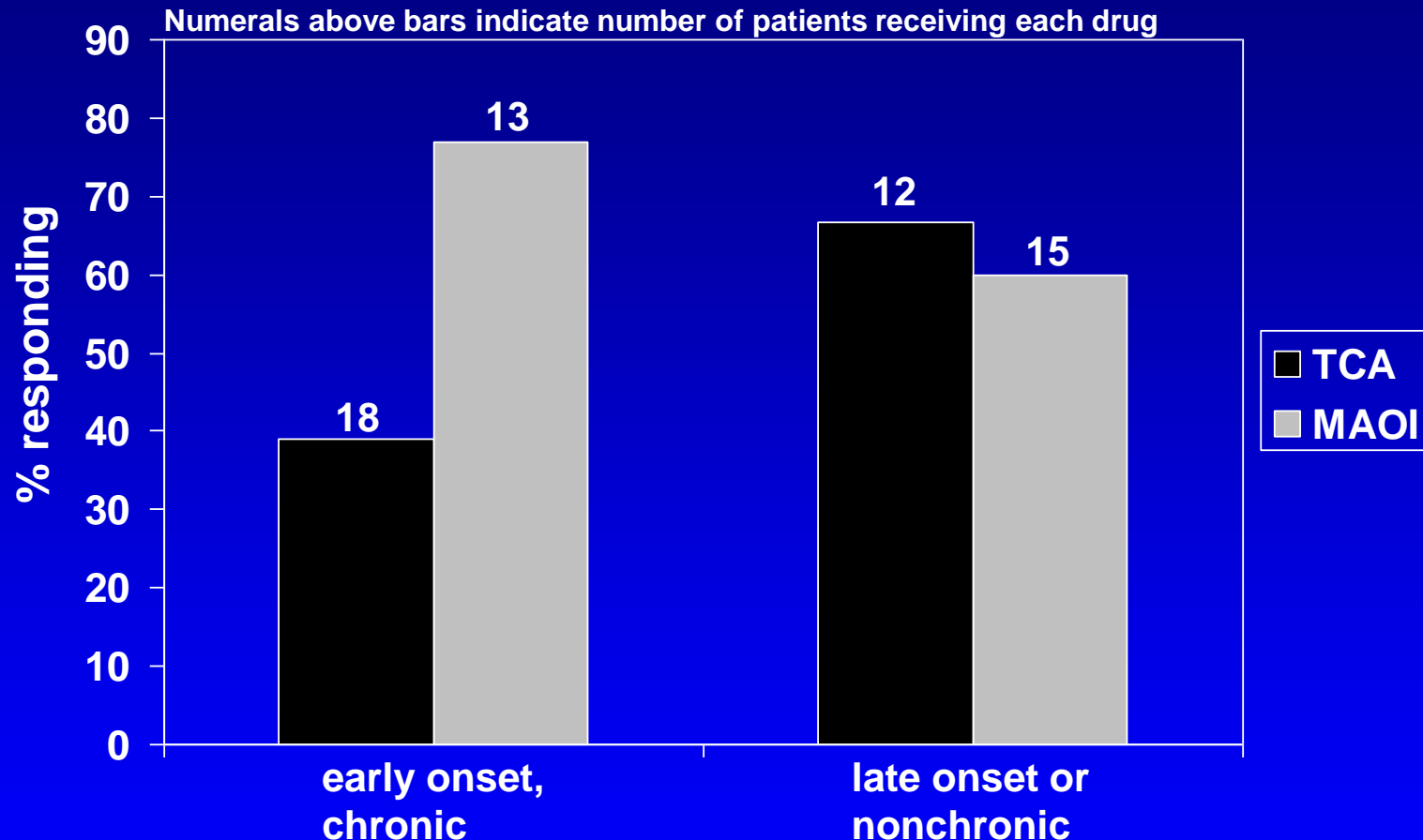
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Treatment Outcome of Placebo Nonresponders with DSM IV or Probable Atypical Depression

Effect of Age of Onset and Chronicity



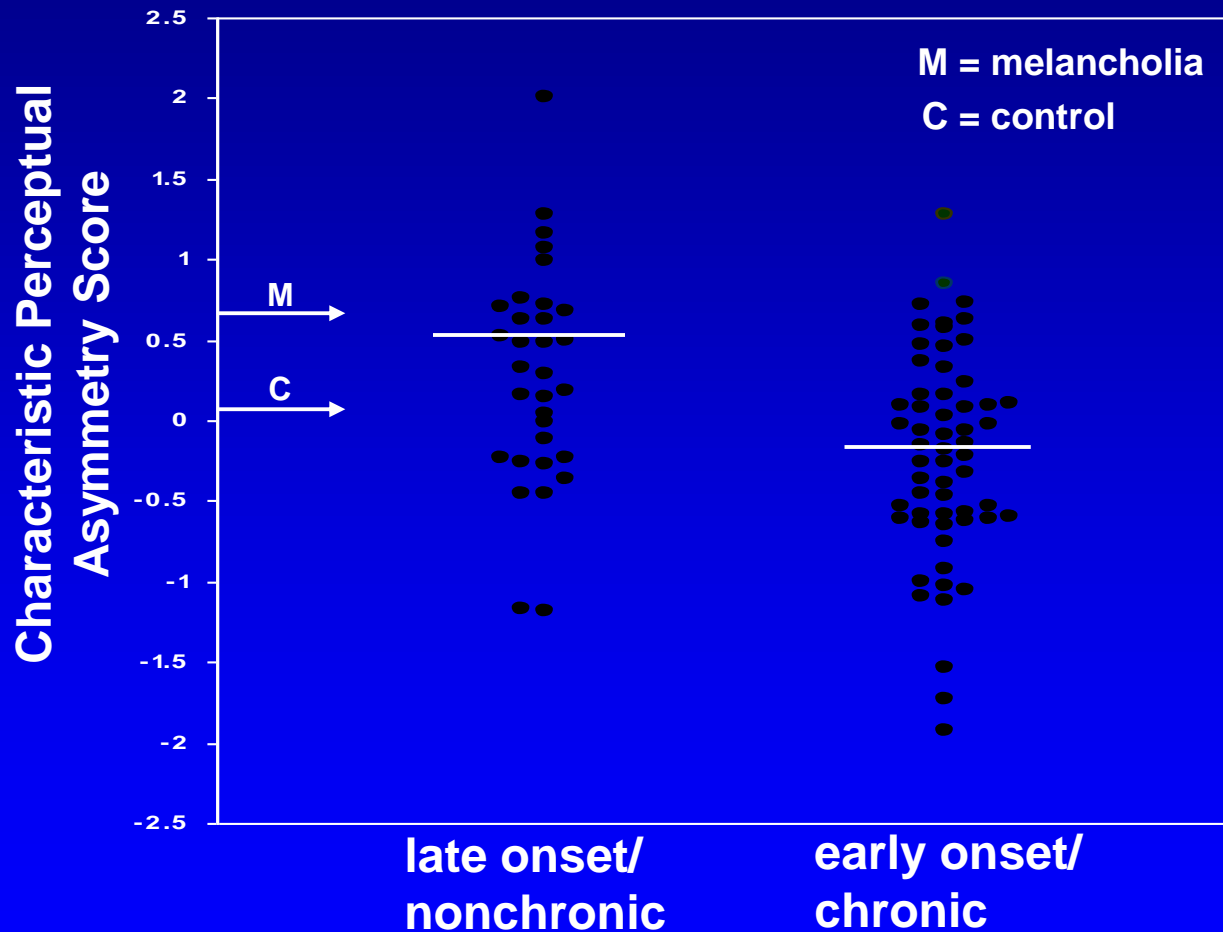
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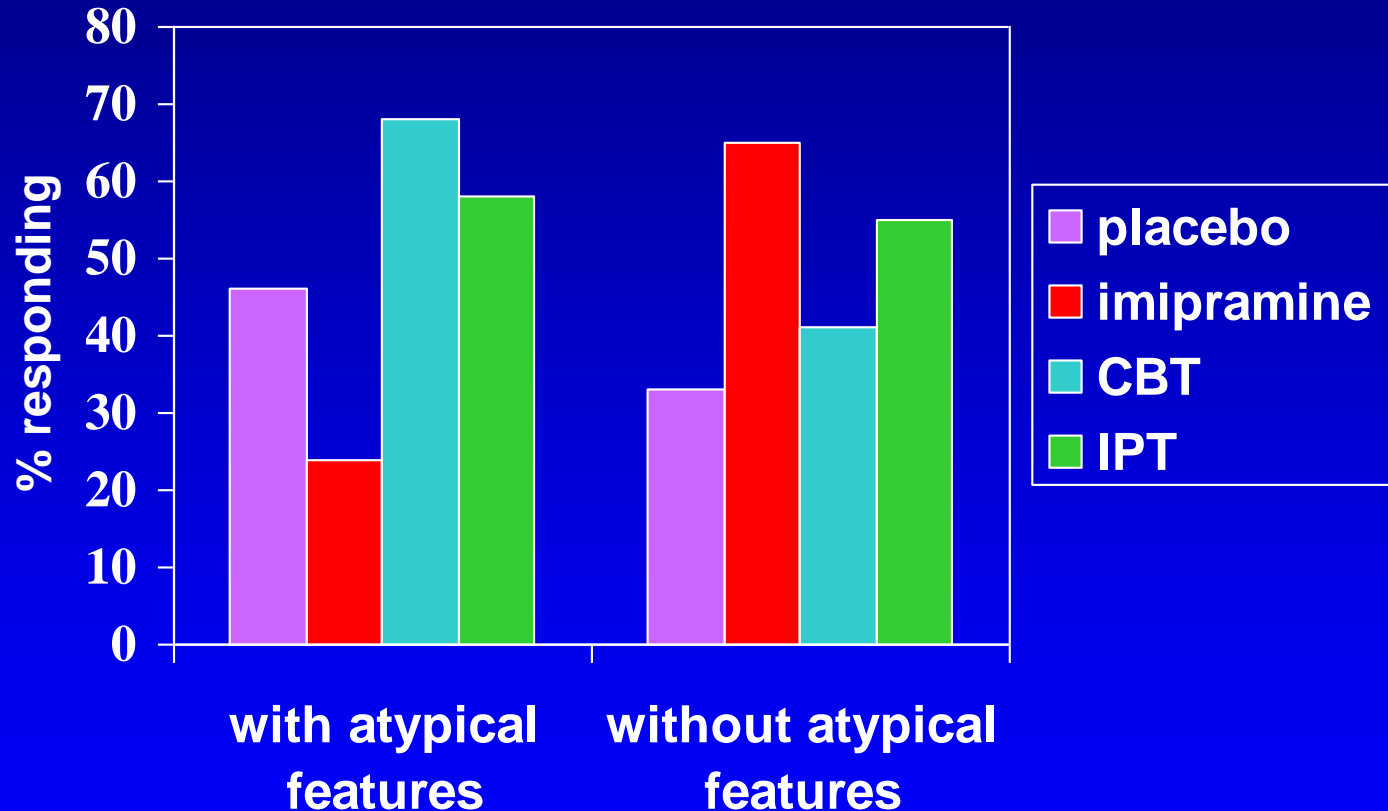
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Dichotic Testing in Patients with DSM IV or probable Atypical Depression According to Age of Onset and Chronicity



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



*TDCRP = Treatment of Depression Collaborative Research Project

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%)

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

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

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

Pre-Lecture Exam

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Answers to Pre & Post Competency Exams

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