

# **ATYPICAL DEPRESSION**

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# Pre-Lecture Exam

## Question1

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

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



# 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)*

**“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**

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

# WEST AND DALLY - 1959

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

# SARGENT - 1960

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

# SARGENT - 1960

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

# **HORDERN - 1965**

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

# **HYSTEROID DYSPHORIA**

## **Klein - 1969**

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



# HYSTEROID DYSPHORIA

- **Histrionic**
- **Imipramine unresponsive**
- **MAOI responsive**

# **SYNDROMIC VALIDATION**

## **Robins & Guze - 1970**

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

# **ENDOGENOMORPHIC DEPESSION Klein - 1974**

- **Pervasive anhedonia is the hallmark of endogenous depression**

# ROBINSON - 1980

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

# DAVIDSON - 1982

- **Required features - Mood reactivity, nonendogenous depression (by Newcastle Scale)**
- **A Type - Anxiety prominent**
  - **No required vegetative features**
- **V Type (one required) - \*Hyperphagia, \*Weight gain, Evening mood worsening**

# PHARMACOLOGIC DEPRESSION

## Klein - 1989

- **If two syndromes are different manifestations of the same disorder, they are likely to respond to the same treatment**
- **If two syndromes represent different disorders, they may improve with different treatments**

# PHARMACOLOGIC DEPRESSION

## Corollary

- **Similar responses to treatment is evidence that two syndromes may have similar underlying physiology**
- **Different response to treatment is evidence that two syndromes have different underlying physiology**

# ROBINSON - 1980

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



# ATYPICAL DEPRESSION

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

# **ATYPICAL DEPRESSION**

## **Syndrome Description: DSM-IV Criteria**

- **Significant mood reactivity**
- **At least two associated features**
  - **Hyperphagia**
  - **Hypersomnia**
  - **Leadens 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                | Leadens paralysis | Low without leadens paralysis |
| Premorbid personality | Rejection         | Good sensitivity              |

# **ATYPICAL DEPRESSION**

## **Columbia Criteria**

- **Mood reactivity (required)**
- **Associated features (2 required)**
  - **Hyperphagia**
  - **Hypersomnia**
  - **Leaden paralysis**
  - **Pathologic rejection sensitivity**

# **VALIDATION OF ATYPICAL DEPRESSION Syndrome Description**

- **Mood reactivity (required)**
- **Associated features (2 required) for definite, 1 for probable**
  - **Hyperphagia**
  - **Hypersomnia**
  - **Leaden paralysis**
  - **Pathologic rejection sensitivity**

# HYPOTHESIS

- **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**
- **Signs informed consent**
- **HAM-D  $\geq$  10**
- **Speaks English**

# INCLUSION CRITERIA

- **Willing and able to follow tyramine-free diet**
- **Physically healthy**
- **(Depressed all or almost all adult life)**



# EXCLUSION CRITERIA

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

# LABORATORY STUDIES

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

# LABORATORY TESTING (%) ABNORMAL

| <u>Short REM Latency</u> | <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                               |

# ATYPICAL DEPRESSION (n=119)

## Percent Responding

- Placebo 28%
- Imipramine 50%
- Phenyelzine 71%

# ATYPICAL DEPRESSION

## 6 Week Outcome

|                             | <u>% Responding</u> |                   |                   |
|-----------------------------|---------------------|-------------------|-------------------|
|                             | <u>Placebo</u>      | <u>Imipramine</u> | <u>Phenelzine</u> |
| Original Study<br>(N=119)   | 28%                 | 50%               | 71%               |
| Replication Study<br>(N=90) | 19%                 | 50%               | 83%               |

# VALIDATION OF ATYPICAL DEPRESSION

## Family Study - Rate per 100 Relatives

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

# **VALIDATION OF ATYPICAL DEPRESSION Syndrome Description**

- **Mood reactivity (required)**
- **Associated features (2 required for definite, 1 for probable)**
  - **Hyperphagia**
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# TREATMENT RESPONSE

## Fluoxetine

- 20 mg 58% (50/86)
- >20 mg 63% (15/24)



# ATYPICAL DEPRESSION: Treatment Response Sertraline (N=18)

| <u>Dose (mg)</u> | <u>Number<br/>Responding (N=16)</u> |
|------------------|-------------------------------------|
| 50               | 10                                  |
| 75               | 1                                   |
| 100              | 2                                   |
| 150              | 1                                   |
| 200              | 2                                   |

Total Response Rate (81%) (16/18)

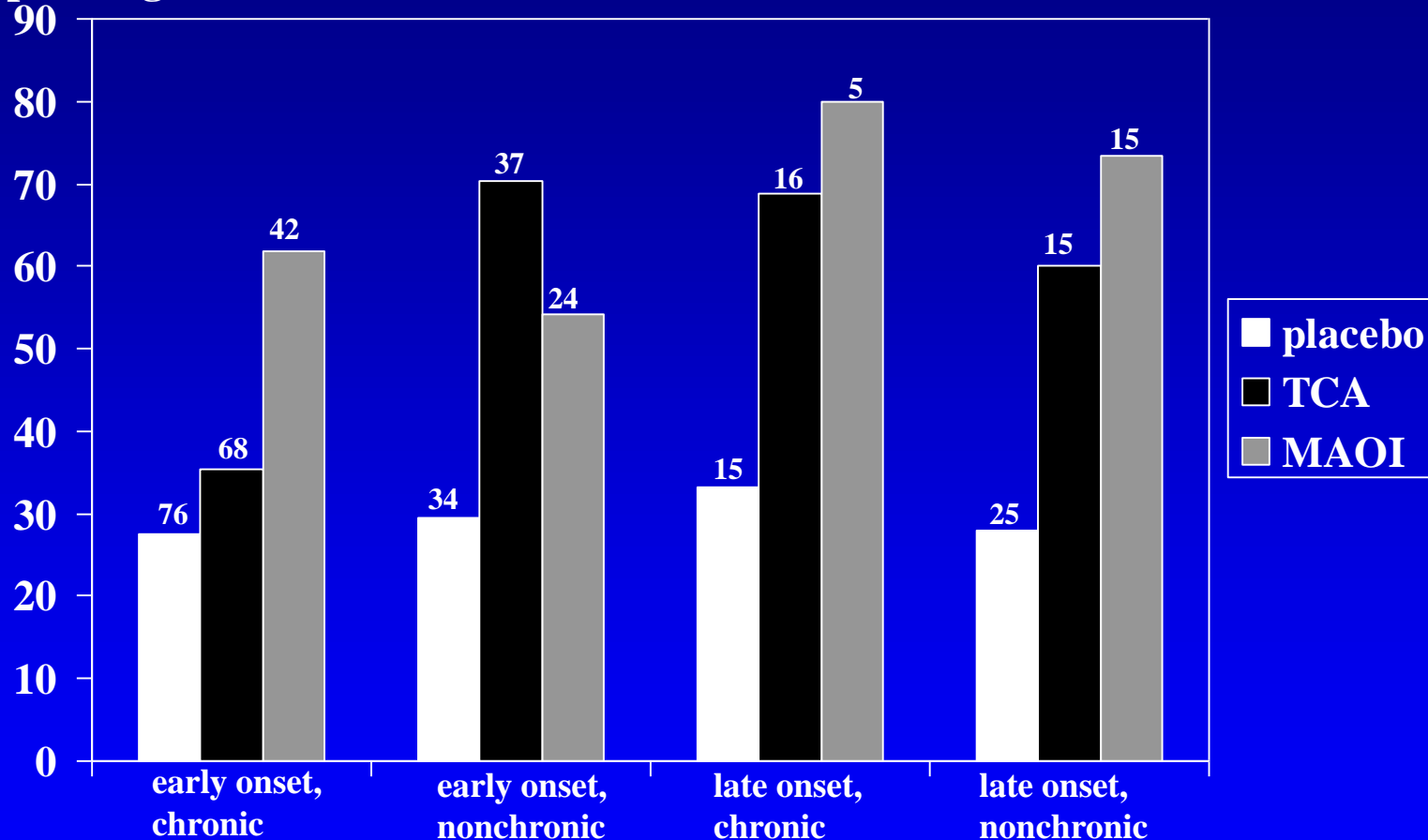
# MOCLOBEMIDE

- **Reversible type A inhibitor (RIMA)**
- **Not tested in atypical depression**
- **Clinical impression is that it works like traditional agents , better side effects profile, no diet\***
- **600-900 range most likely effective, appears safe**
- **Can be imported legally from Canada on case-by-case humanitarian use basis**

\*DF Klein, personal communication, 1999

# Treatment Outcome of Patients with DSM IV Atypical Depression According to Age of Onset and Chronicity

% responding



Early onset = first significant dysphoria prior to age 21

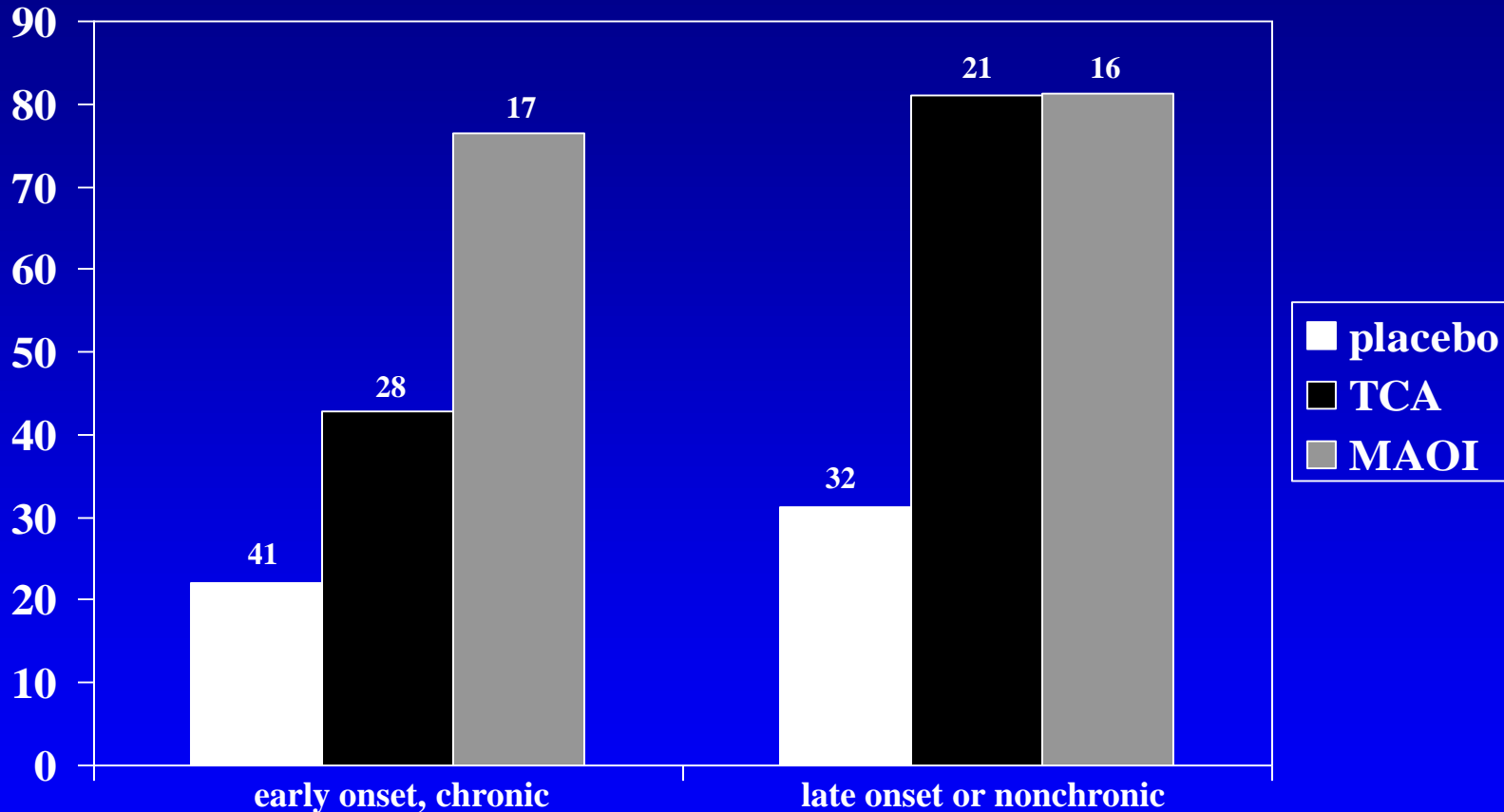
Late onset = first significant dysphoria after age 20

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 Patients with Probable Atypical Depression According to Age of Onset and Chronicity

% responding



Early onset = first significant dysphoria prior to age 21

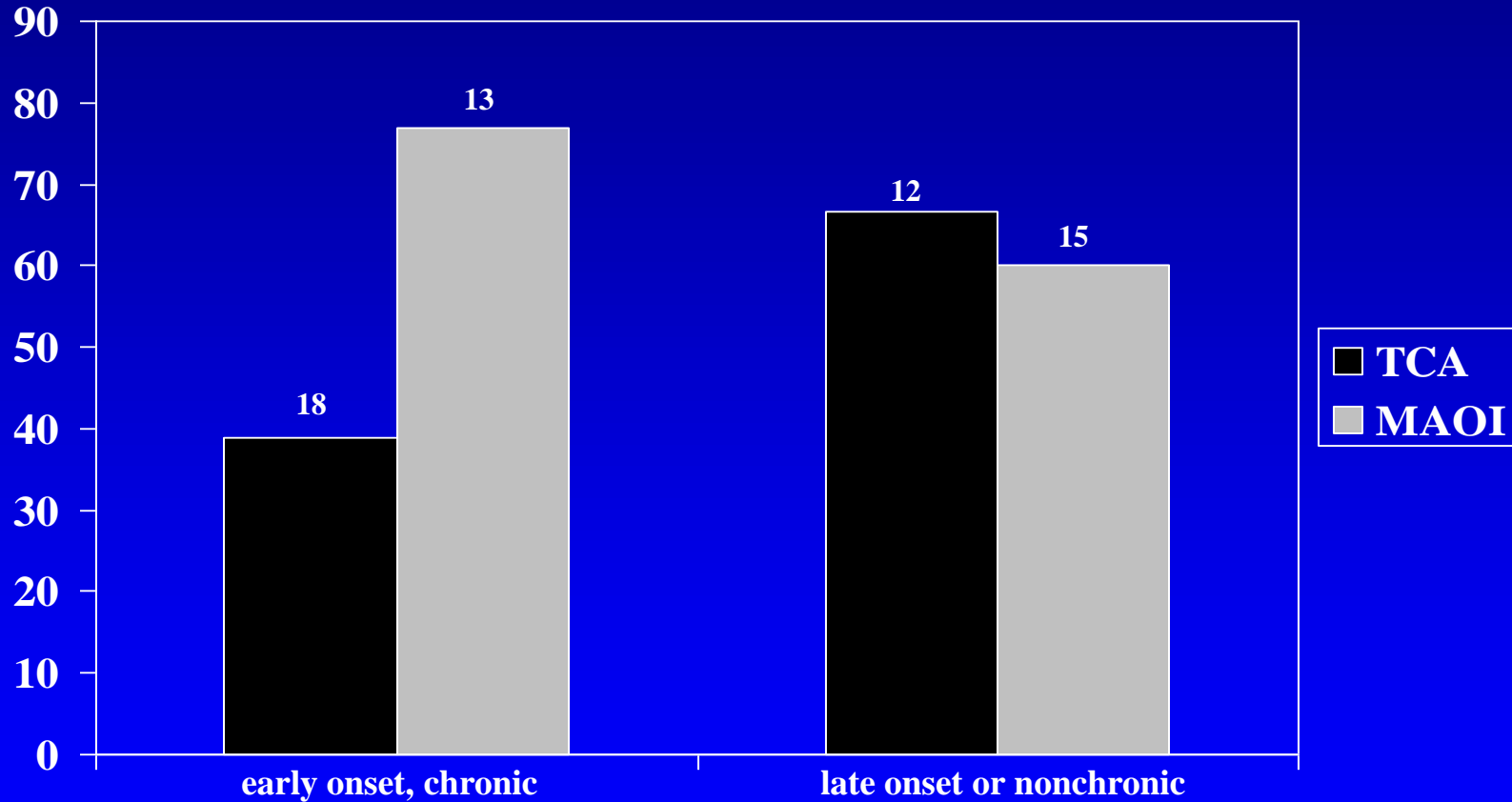
Late onset = first significant dysphoria after age 20

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

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# Treatment Outcome of Placebo Nonresponders with DSM IV or Probable Atypical Depression According to Age of Onset and Chronicity

% responding



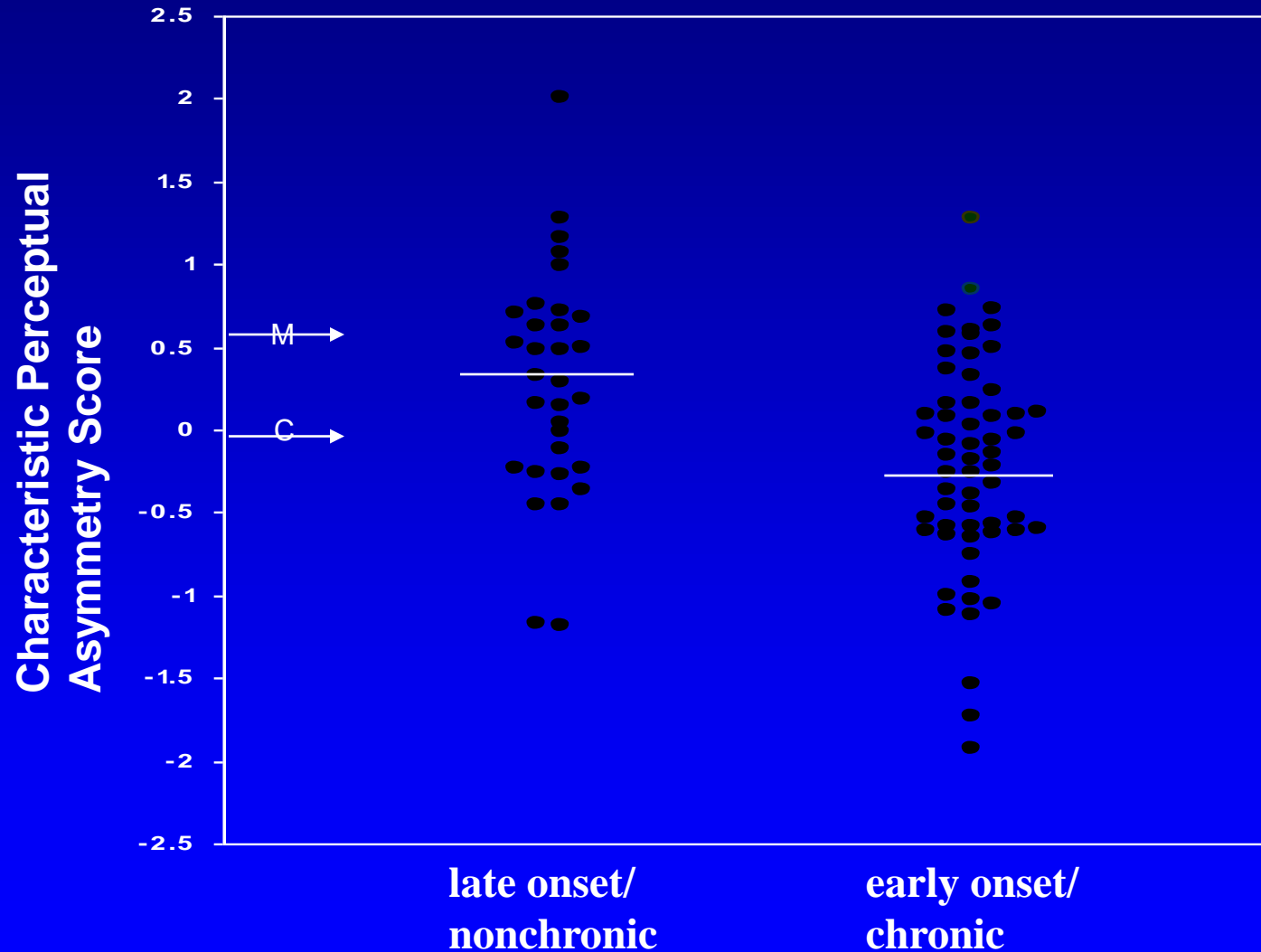
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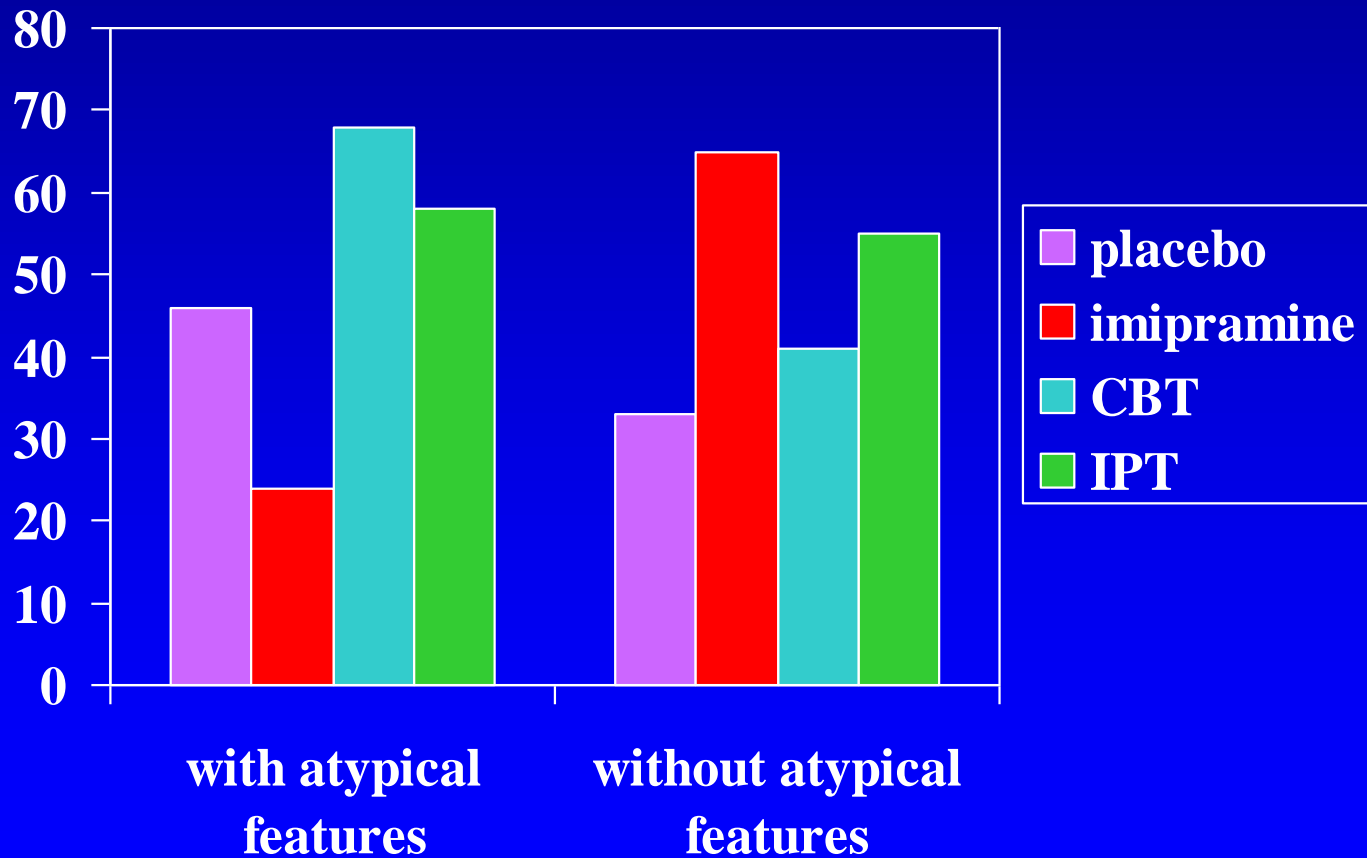
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# Dichotic Testing in Patients with DSM IV or probable Atypical Depression According to Age of Onset and Chronicity



## Treatment Response in TDCRP by Presence or Absence of Atypical Features



# 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

# Post Lecture Exam

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# Answers to Pre & Post Competency Exams

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