Treatment of Anxiety and Mood Disorders

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Disclosure: John T. Walkup, MD

	Consultant	Advisory Board	Speaker's Bureau	Research Contract	Royalties
Pfizer				X Drug and PBO	
Abbott				X Drug	
Lilly				X Drug and PBO	
Shire	X				
Tourette Syndrome Assoc.		X	X	X	
Oxford Press Guilford Press					X

Off Label Use

- Should consider all medication uses discussed as off label unless specifically noted otherwise

- Case example – details changed for confidentiality purposes

Anxiety Disorders in Children and Adolescents

- Specific Phobia
- Separation Anxiety Disorder
- Generalized Anxiety Disorder
- Social Phobia
- OCD
- Acute Stress Disorder
- Post-traumatic stress disorder
- Panic Disorder

Ages of Risk

- ASDs – 0-3 years or later for mild
- ADHD - 4-7 or later for mild but differential is broader
- Anxiety – 6-12 years
- Depression – 13-16 years
- Bipolar and psychosis - > 16 years
- Disruptive behavior – almost anytime

Key Features of the Anxiety Disorders

- Hypervigilant
- Reactive to novel stimuli
- Threat bias

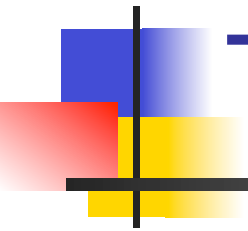
- Avoidance coping
- Catastrophic reactions
- Parental accommodation

Physical Symptoms – Provoked and Spontaneous

- Anxious children listen to their bodies
- Headache
- Stomachache – stomach and bowel problems
- Sick in the morning and can't fall asleep in the evening
- Frequent urge to urinate or defecate
- Shortness of breath
- Chest pain - tachycardia
- Sensitive gag reflex - fear of choking or vomiting
- Difficulty swallowing solid foods – growth inhibition?
- Dizziness, lightheaded
- Tension and tiredness – exhausted and irritable after a school day
- Derealization and depersonalization
- Avoidance to prevent above physical symptoms

Course of anxiety

- Onset in childhood
- "Prepubertal affective illness"
- Adolescence
  - Intense symptoms "burn out"
  - Generalized anxiety
  - Poor adaptation and coping – easily flooded and overwhelmed (pre-borderline)
  - Some morph to depression
- Young adulthood



Treatment of OCD

Serotonin Reuptake Inhibitors FDA Approvals

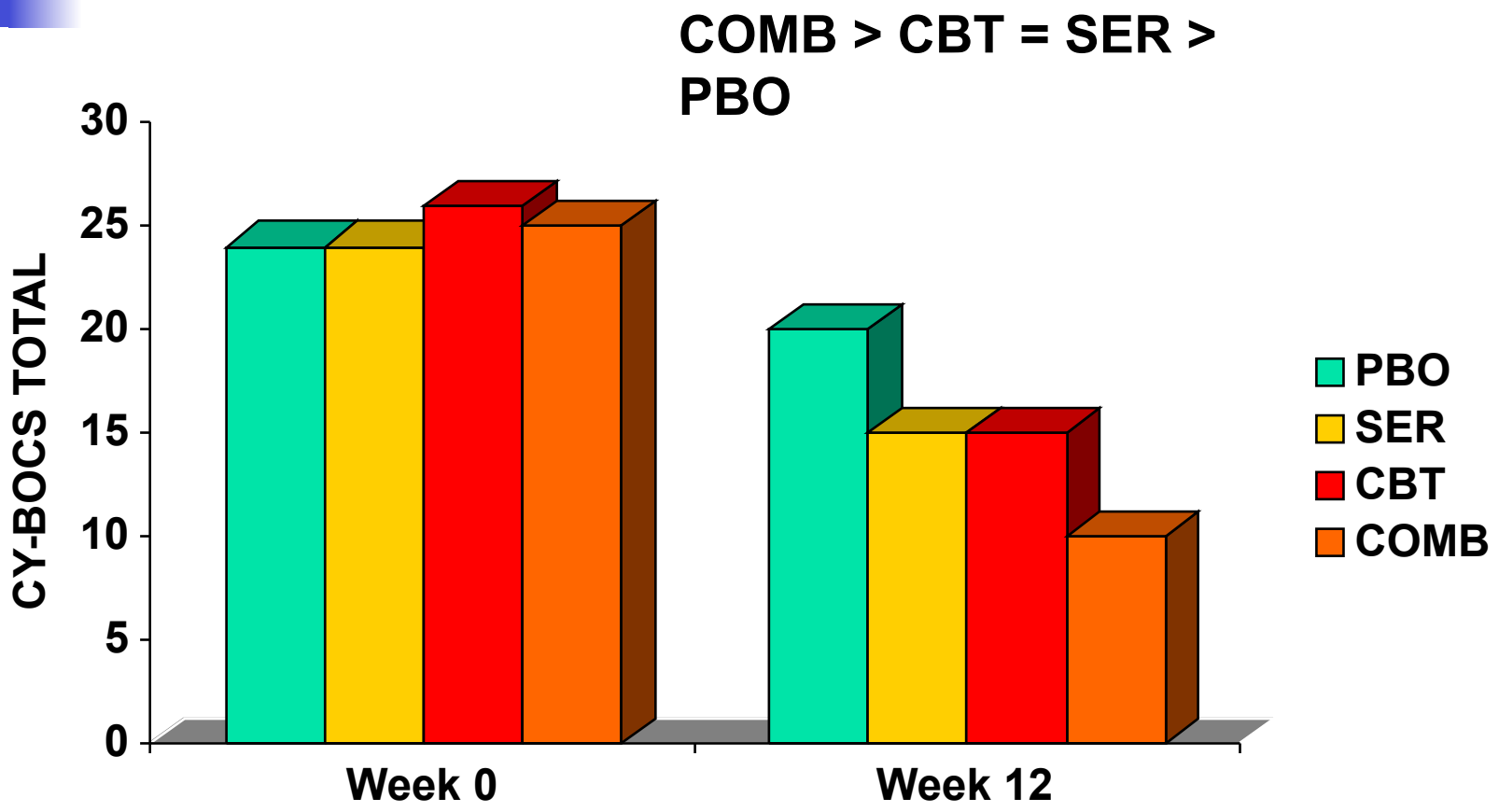
- Clomipramine - FDA approved to age 10 OCD
- Fluvoxamine - FDA approved to age 8 OCD
- Sertraline - FDA approved to age 6 OCD
- Paroxetine – effective for OCD and SoP
- Fluoxetine – effective for OCD; MDD to age 7
- Citalopram – No controlled trials in children
- Escitalopram – FDA approved to age 12 for depression
- Venlafaxine – Effective for SoP but $\pm$ GAD

Pediatric OCD Treatment Study - POTS

- N = 112
- Ages 7-17 years
- 3 sites, 12 weeks
- CBT, Sertraline, COMB and placebo

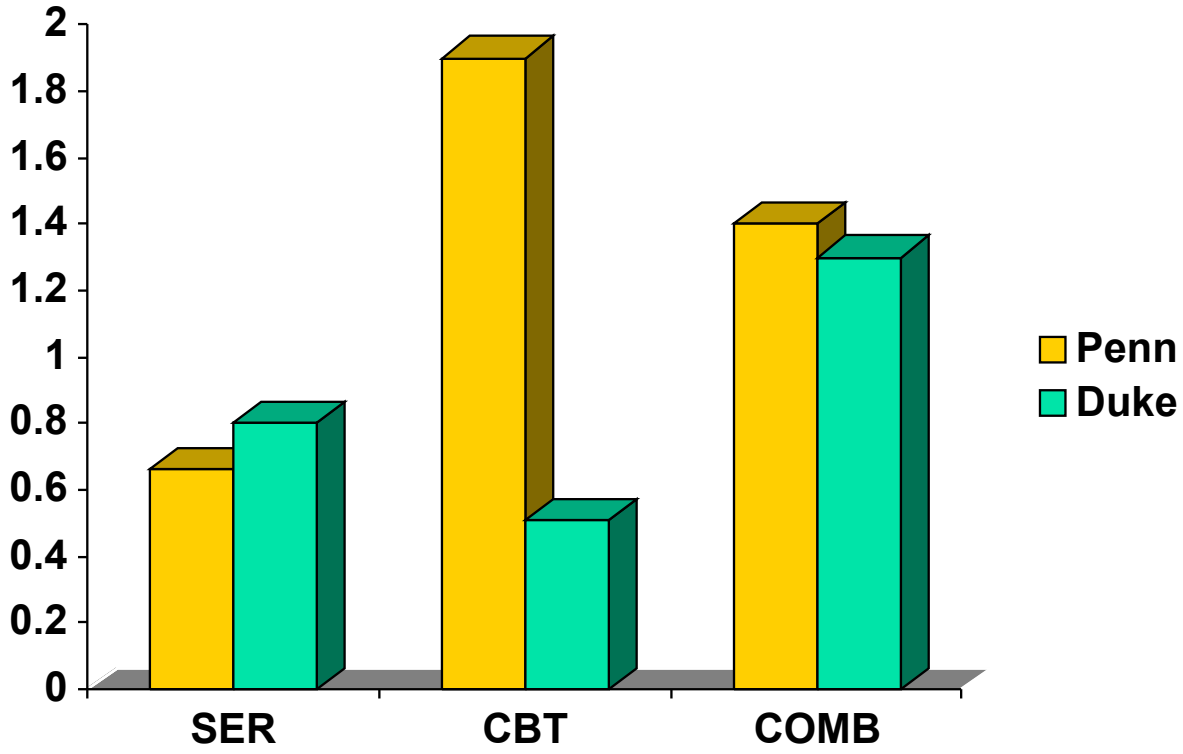
Pediatric OCD Treatment Study, 2004

CY-BOCS ITT Outcomes



Pediatric OCD Study Team (2004) *JAMA*.

Site x Treatment Interaction



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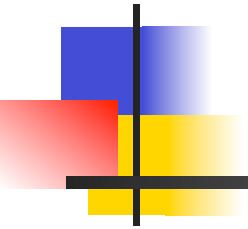

Treatment of Other Anxiety Disorders

Separation Anxiety Disorder
Generalized Anxiety Disorder
Social Phobia

- Pharmacotherapy
  - RUPP trial, 2001
  - Birmaher et al., 2003
  - CAMS, 2008
- Psychotherapy
  - Kendall, 1994
  - Kendal et al., 1997
  - Many others

Child/Adolescent Anxiety Multimodal Study (CAMS)

- NIMH-funded
- SAD, GAD and SoP
- N=488
- 12 weeks acute phase
- 6 month follow-up
- Results
  - COMBO 81%
  - CBT 60%
  - Sertraline 56%
  - PBO 24%
- Avg age 10-11
- Avg dose ~140 mg/day

Future Directions

- What to do with partial response?
  - Meds and CBT
- Augmentation strategies
- Dissemination of CBT
- Dissemination of good pharmacotherapy
- How long to treat? Can my child come off medication?
- Biological markers of treatment response

Depression and Bipolar Disorder

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Introduction

- Evidence Base for Teen Depression
  - Short-term outcomes
  - Long-term outcomes
  - Suicidal behavior

Treatment of Depressed Teens

- Treatment for Adolescents with Depression Study (TADS)
- Treatment of Resistant Depression in Adolescents (TORDIA)
- ADAPT
- Treatment of Adolescent Suicide Attempters (TASA)

Antidepressant Trials

- 2 NIMH-funded
  - Demonstrated efficacy
  - Low placebo response rates
  - Many quality indicators
- 15+ industry-funded
  - Multiple sites
  - High placebo rates
  - No quality indicators
  - FDAMA exclusivity
  - No investment in outcome

Placebo Response in C&A Antidepressant Trials

- Bridge et al. 2009
- 12 Studies – published and unpublished
- Placebo response correlated with number of sites
- Baseline severity inverse predictor of placebo response
- Younger subject had higher PBO response rate

e.g. Sertraline

- Wagner et al., 2003
- Pooled data of two multisite trials
- N=376 (Sites = 63)
- Ages 6-17 years
- 10 week, double-blind, placebo controlled trial
- Drug > placebo
- CDRS Responder 69% vs. 59%
- CGI-I Responder 63% vs. 53%

What is depression?

- Lets go back a step

- Normal human sadness
- Demoralization
- Sadness without cause

- Horwitz and Wakefield…Loss of Sadness

What is depression?

- Depression before DSM-III
  - Sadness with cause
  - Sadness without cause
    - Black bile
    - “Groundless despondency”
    - Melancholy
- Depression after DSM-III
  - Change in mood
  - Other depressed symptoms
  - Context and quality of mood irrelevant

Consequence of DSM-III

- All unhappiness of sufficient severity can be depression
  - Increase rates of depression
  - Increased psychological care
  - Increased medication use
  - Increased failure rates of conventional treatments
  - Maybe increased use of somatic treatments

What is depression?

- Normal human sadness
  - Common
  - Expectable reaction to certain events
  - Can be severe, if event is severe
  - Time limited, but not episodic - moving on is expected
  - Can progress to an autonomous, excessive and disproportionate sadness

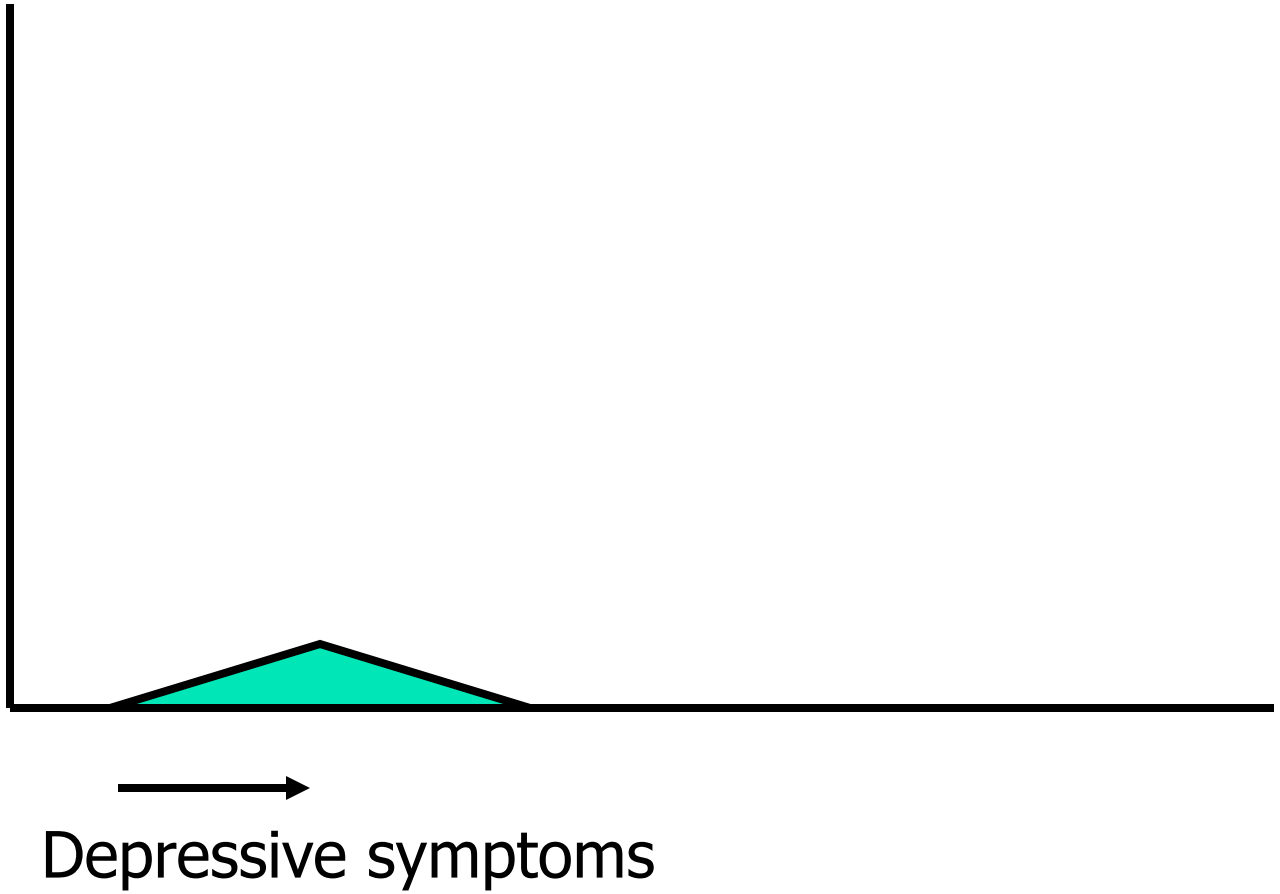
What is depression?

- Demoralization
  - Chronic unhappiness due to adverse circumstances
  - Depressive symptoms, but not anhedonia
  - Can be severe
  - Treated with a change in circumstances

What is depression?

- Sadness without cause
  - Depression with anhedonia
  - Many physical manifestations
  - Disproportionate and unexpected as to cause
  - Mood is distinct from normal sadness
  - Autonomous course – unaffected by changes in life circumstances

The Depression Severity Assessment Dilemma



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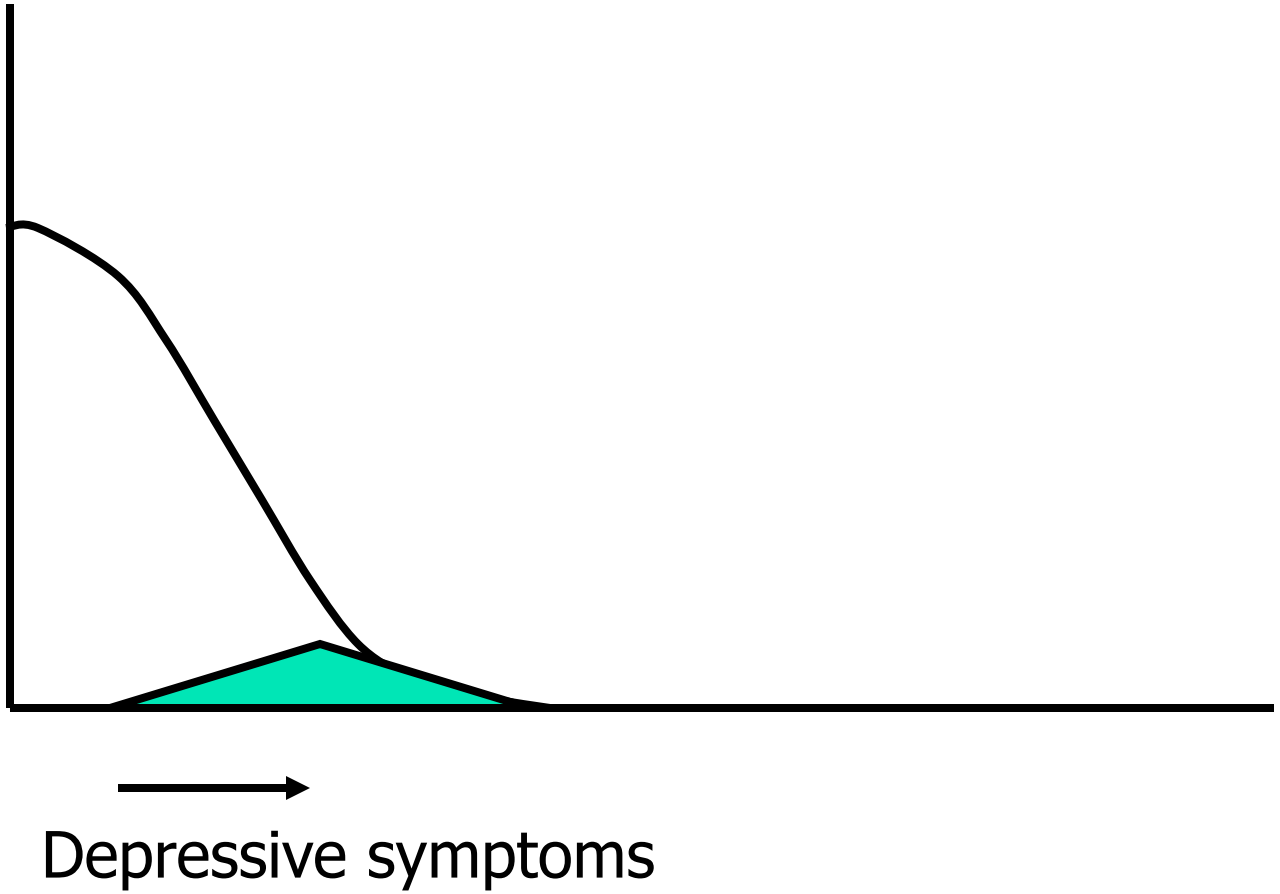

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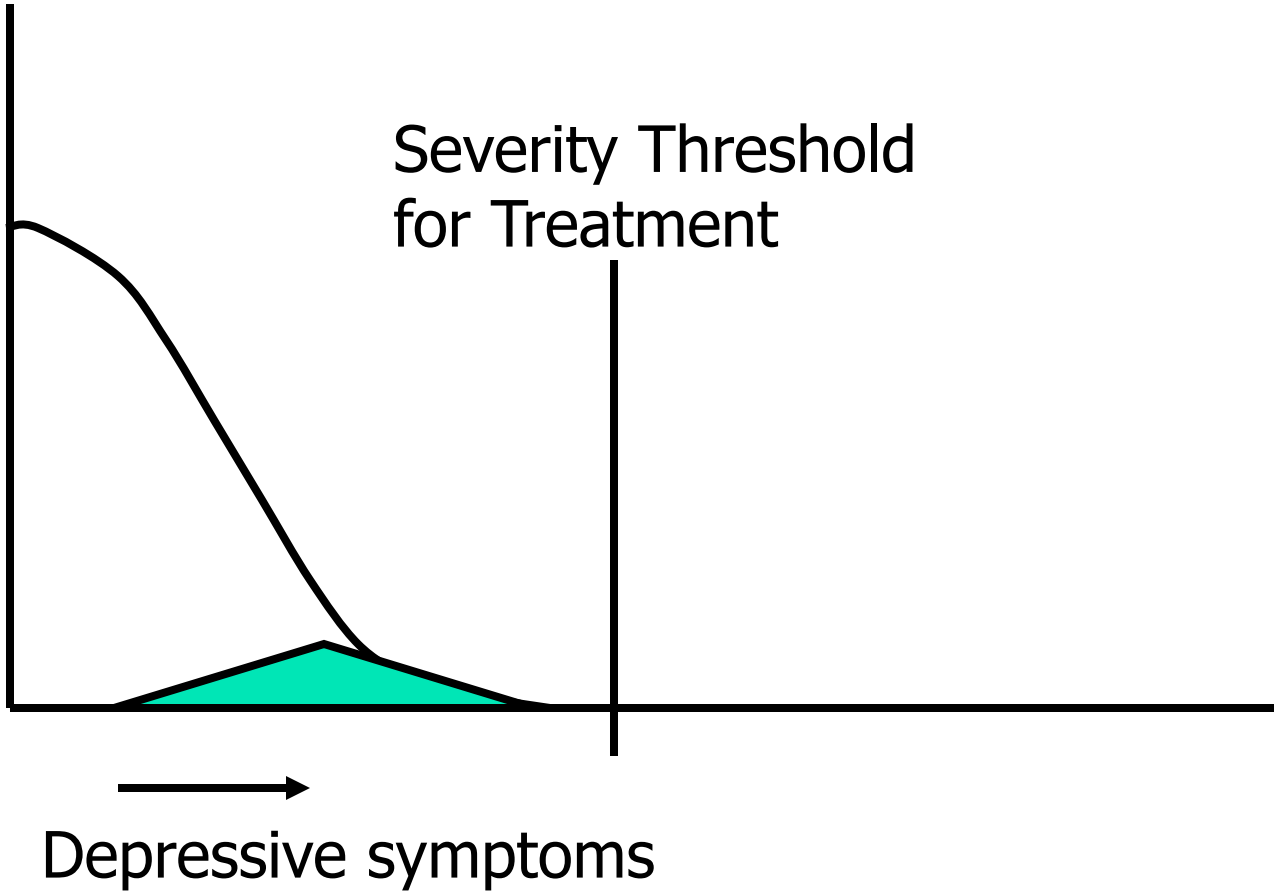

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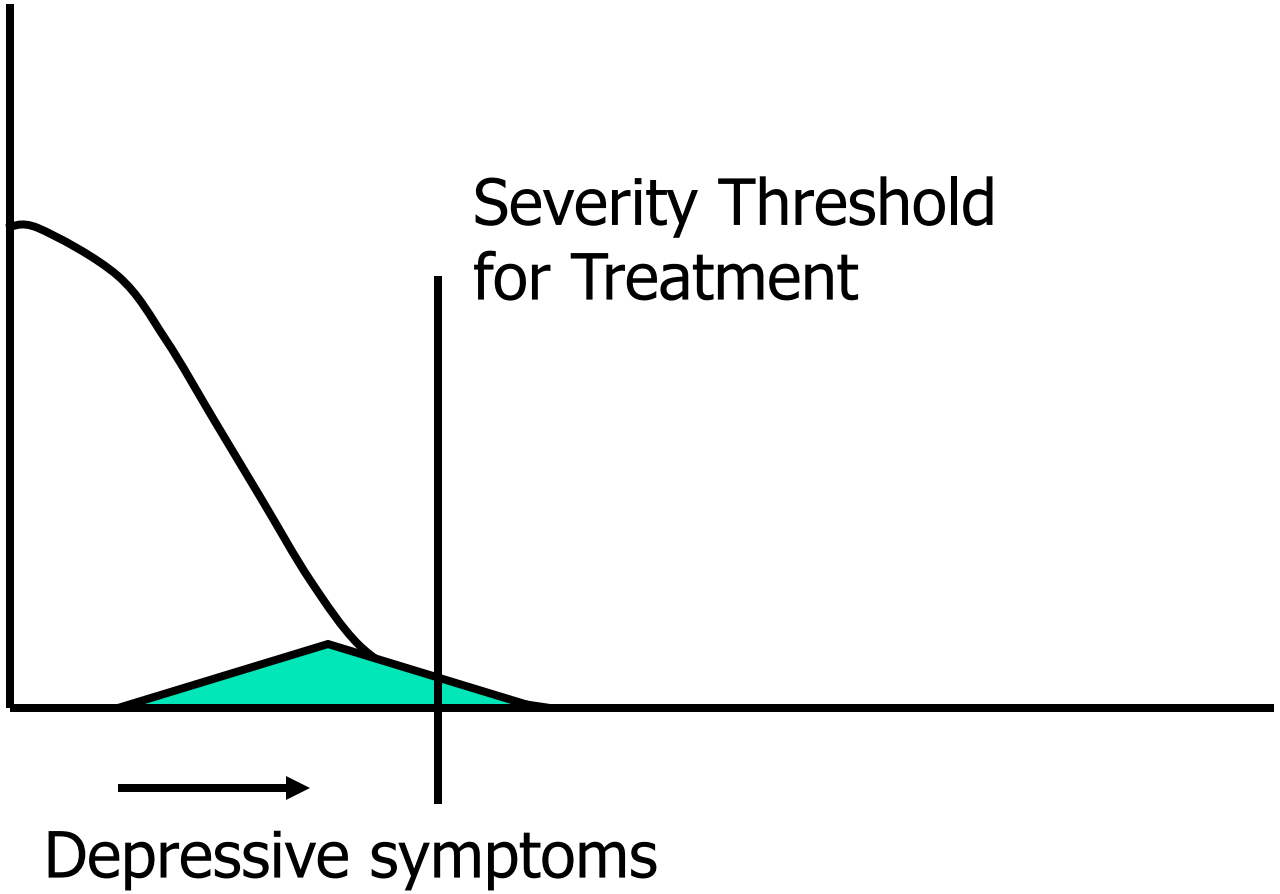

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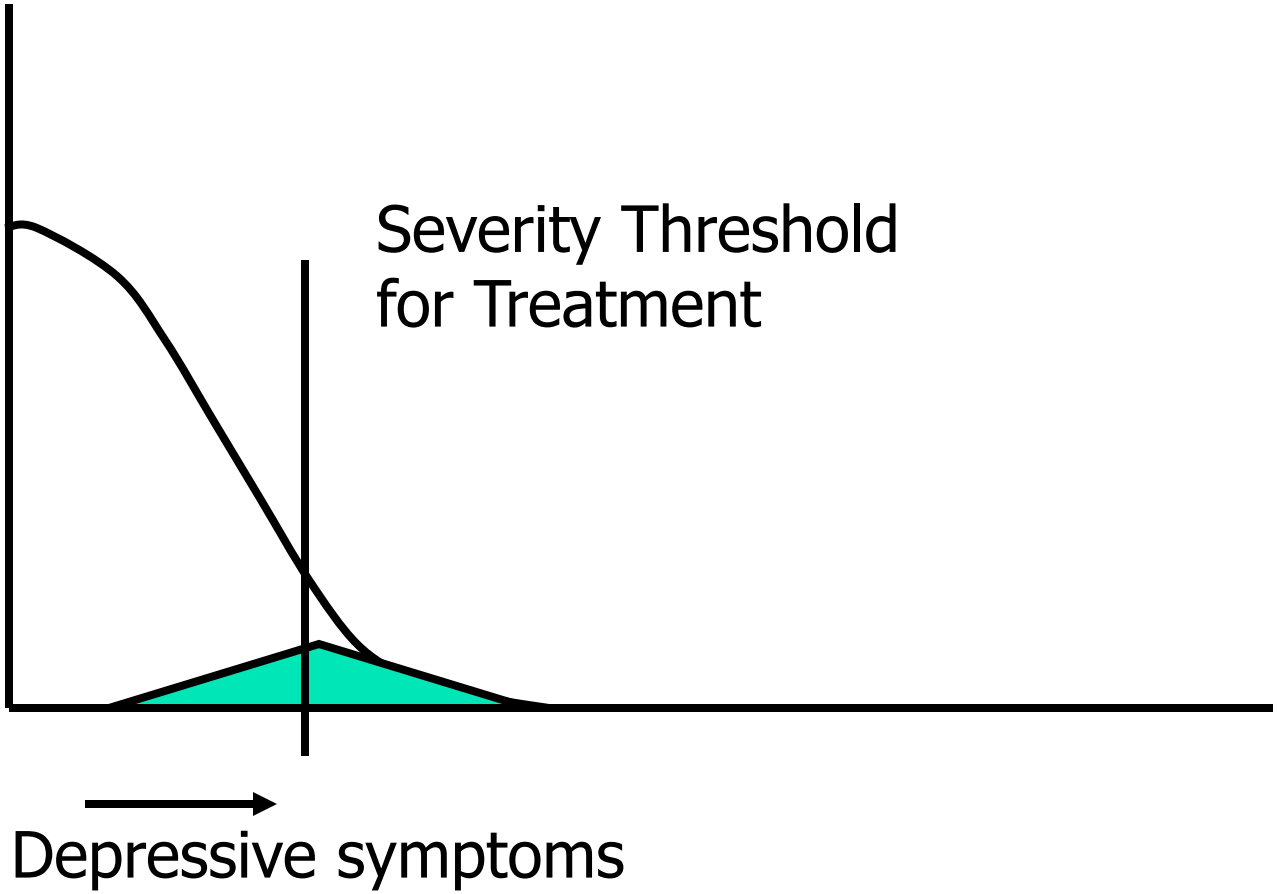

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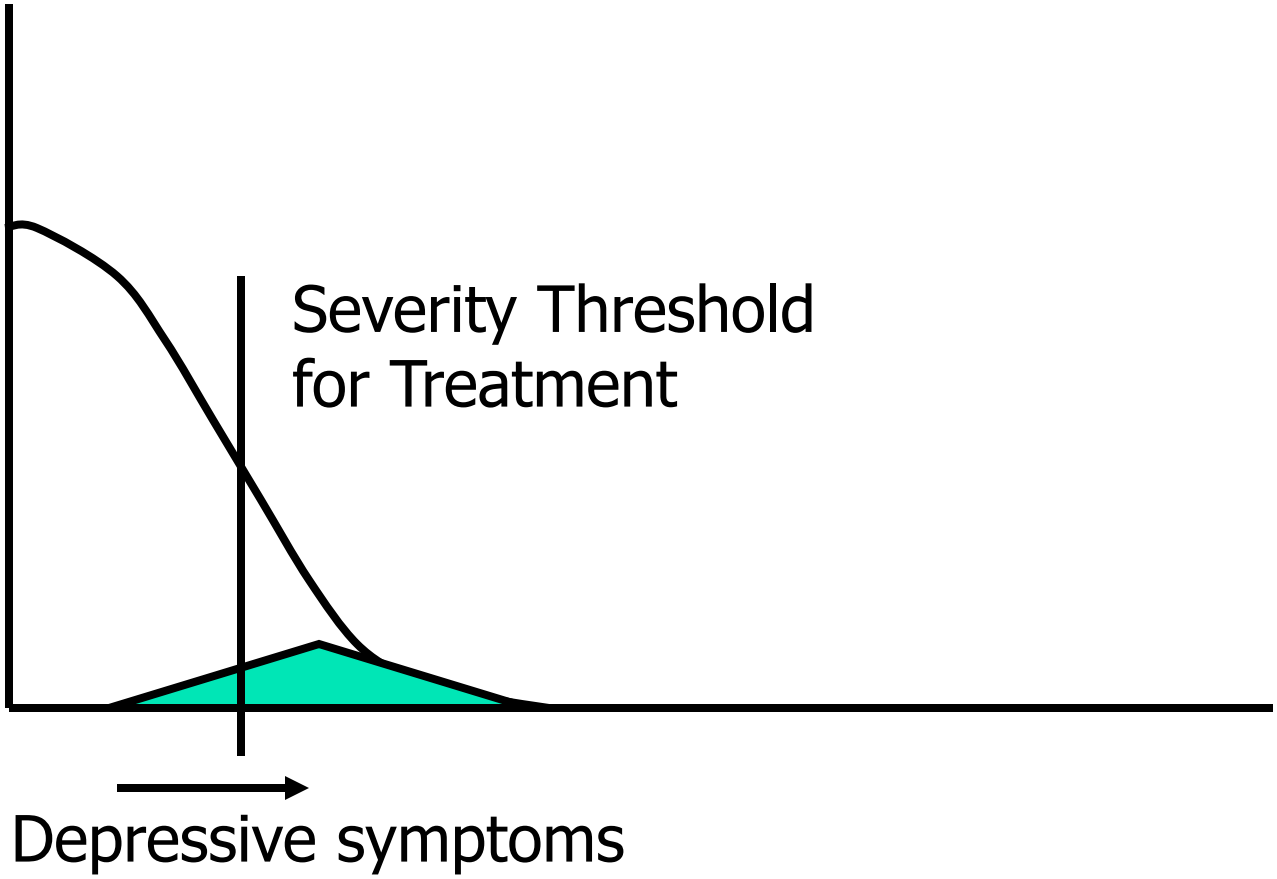

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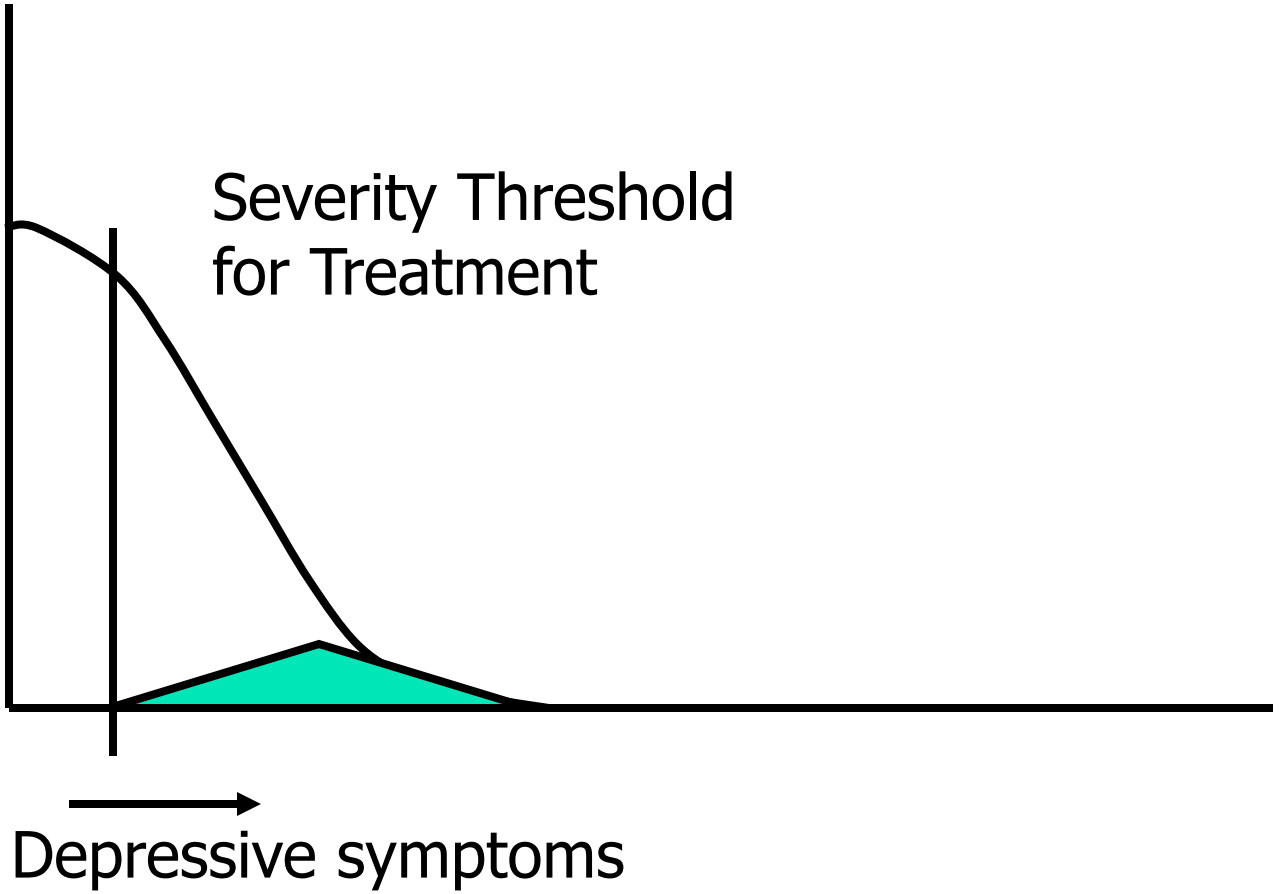

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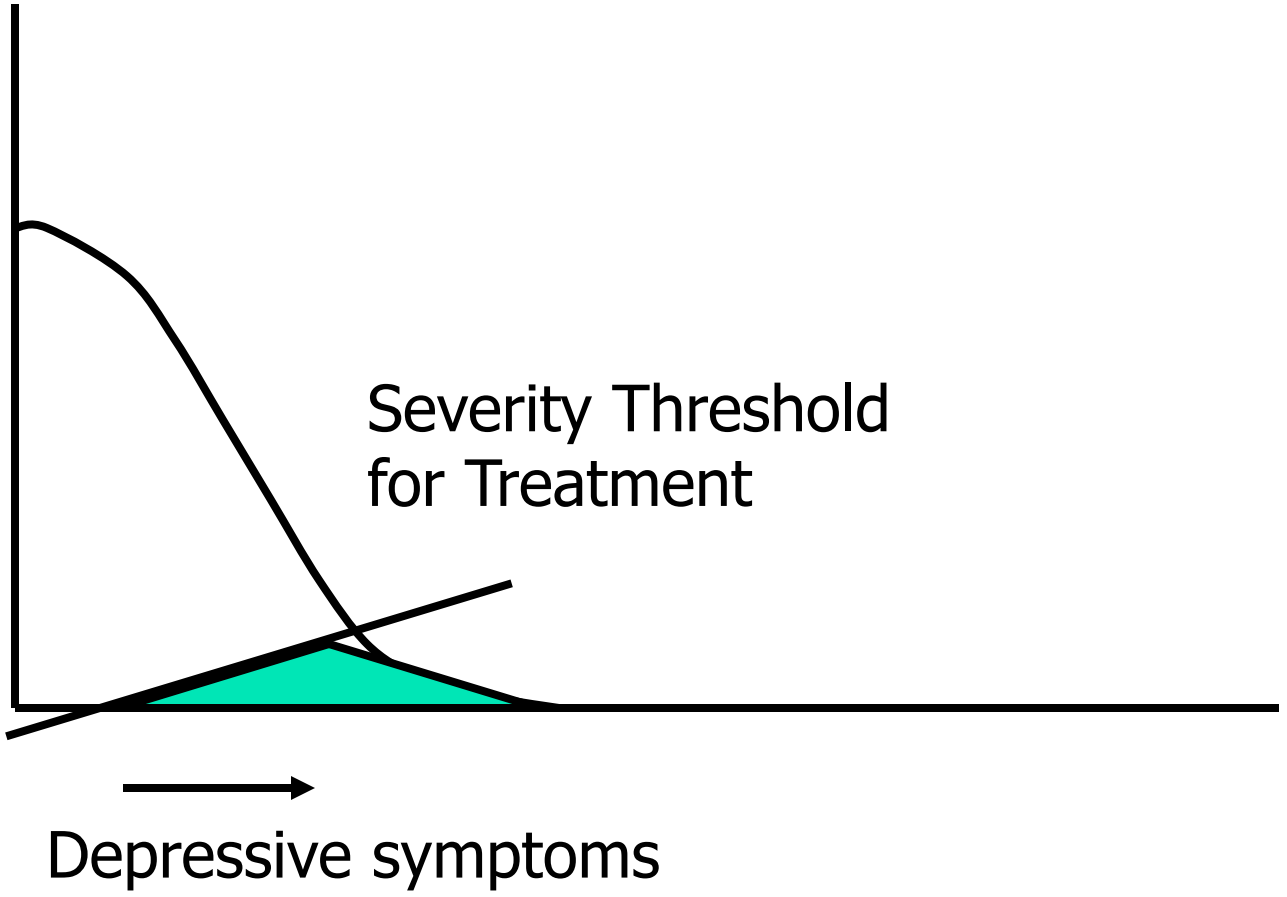
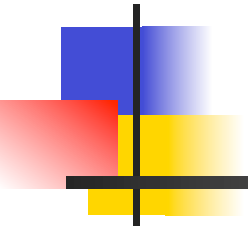
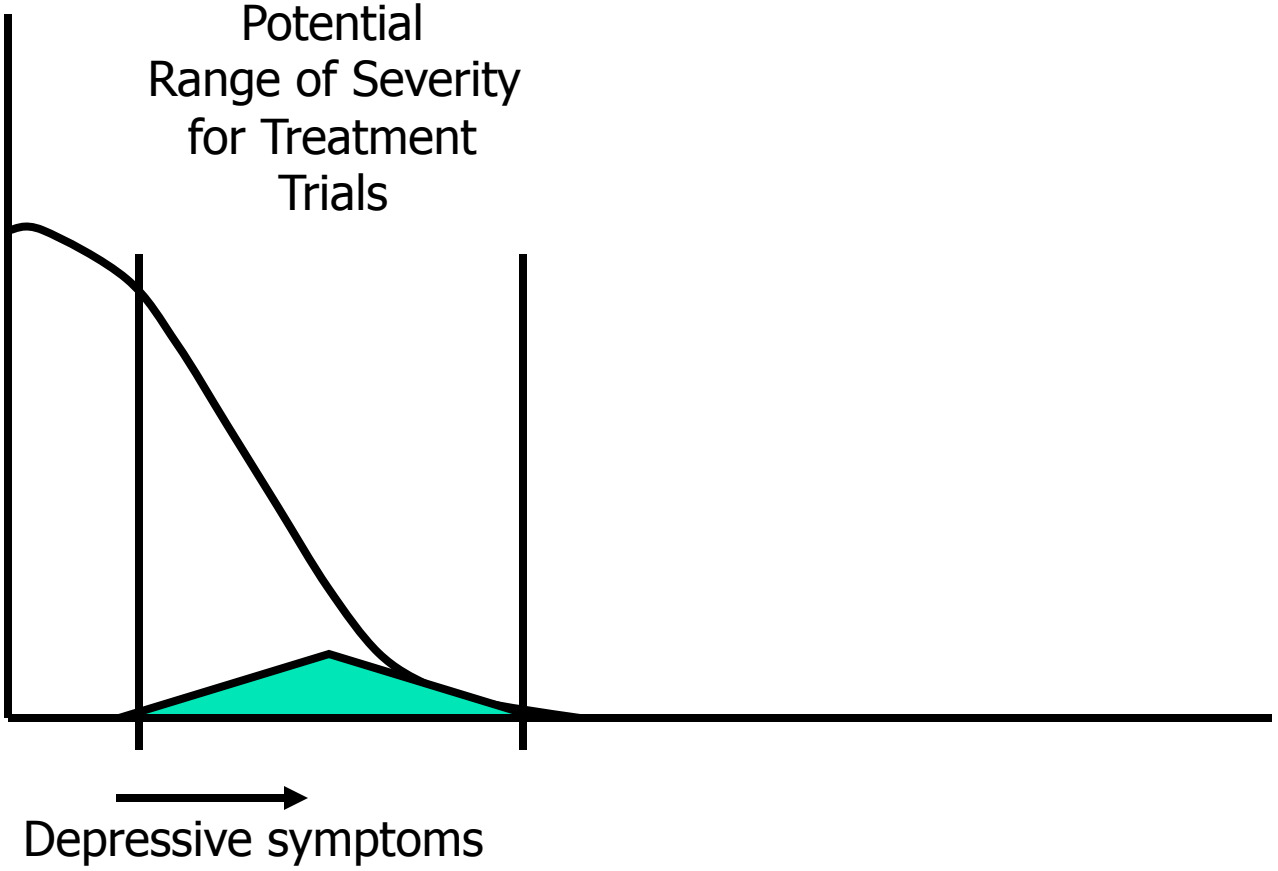




Impact on Clinical Trials

Who Should be Enrolled?



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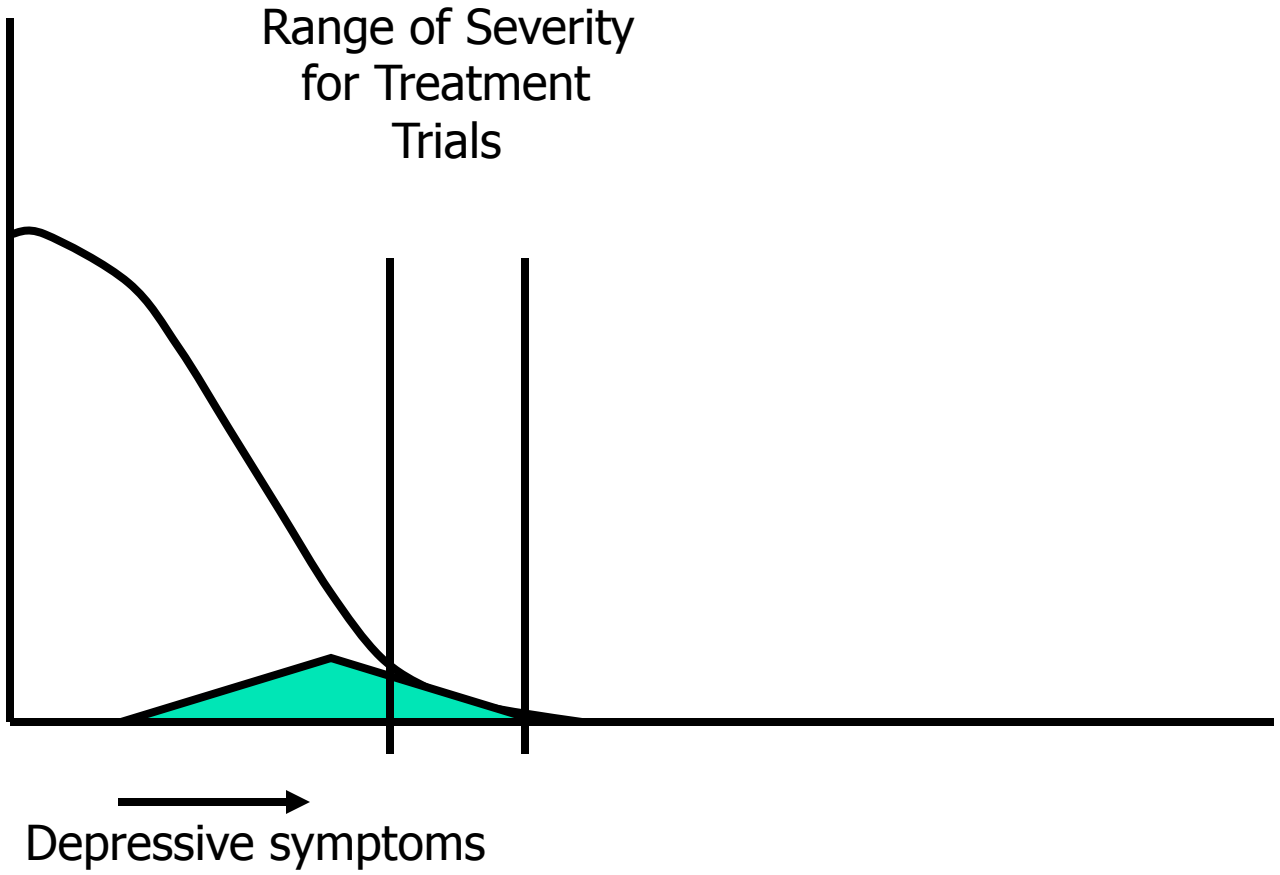

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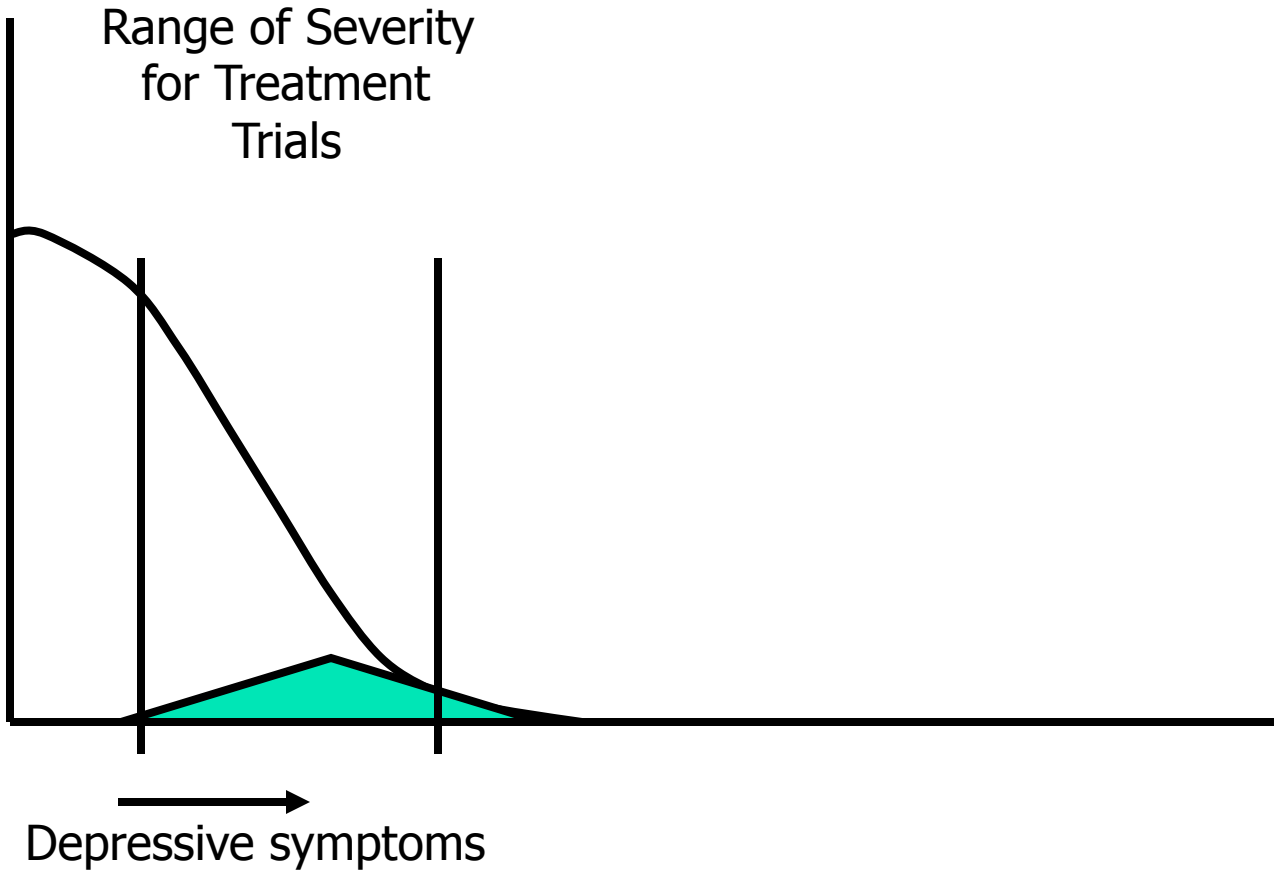

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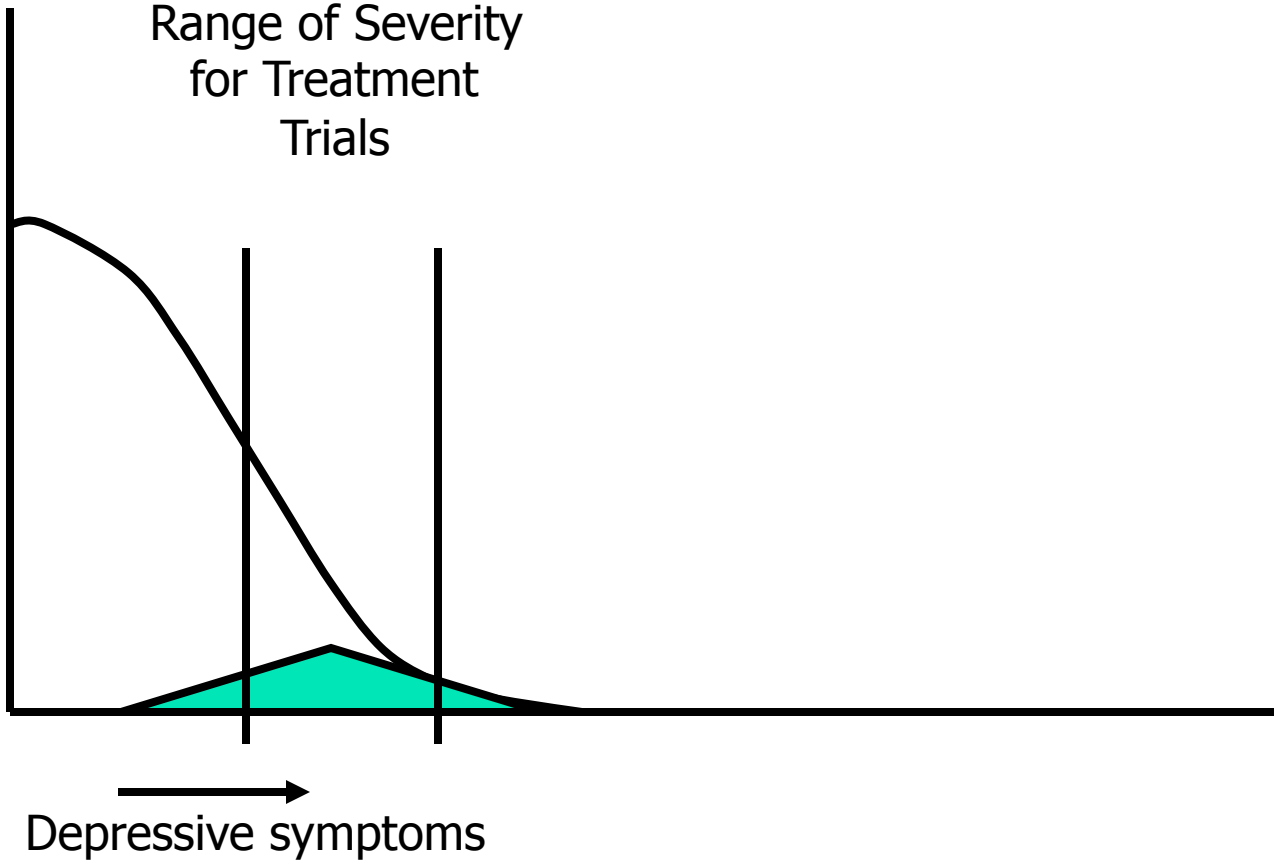

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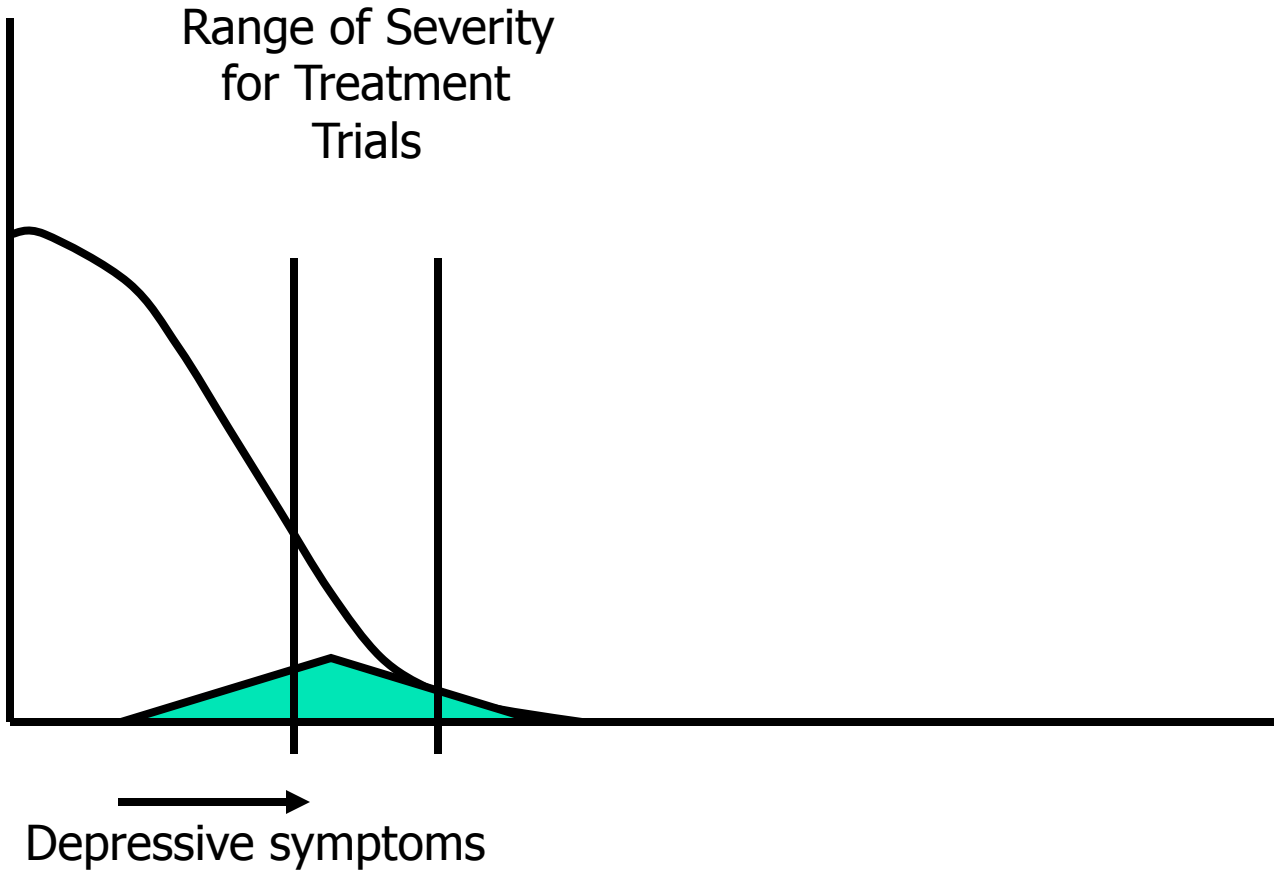

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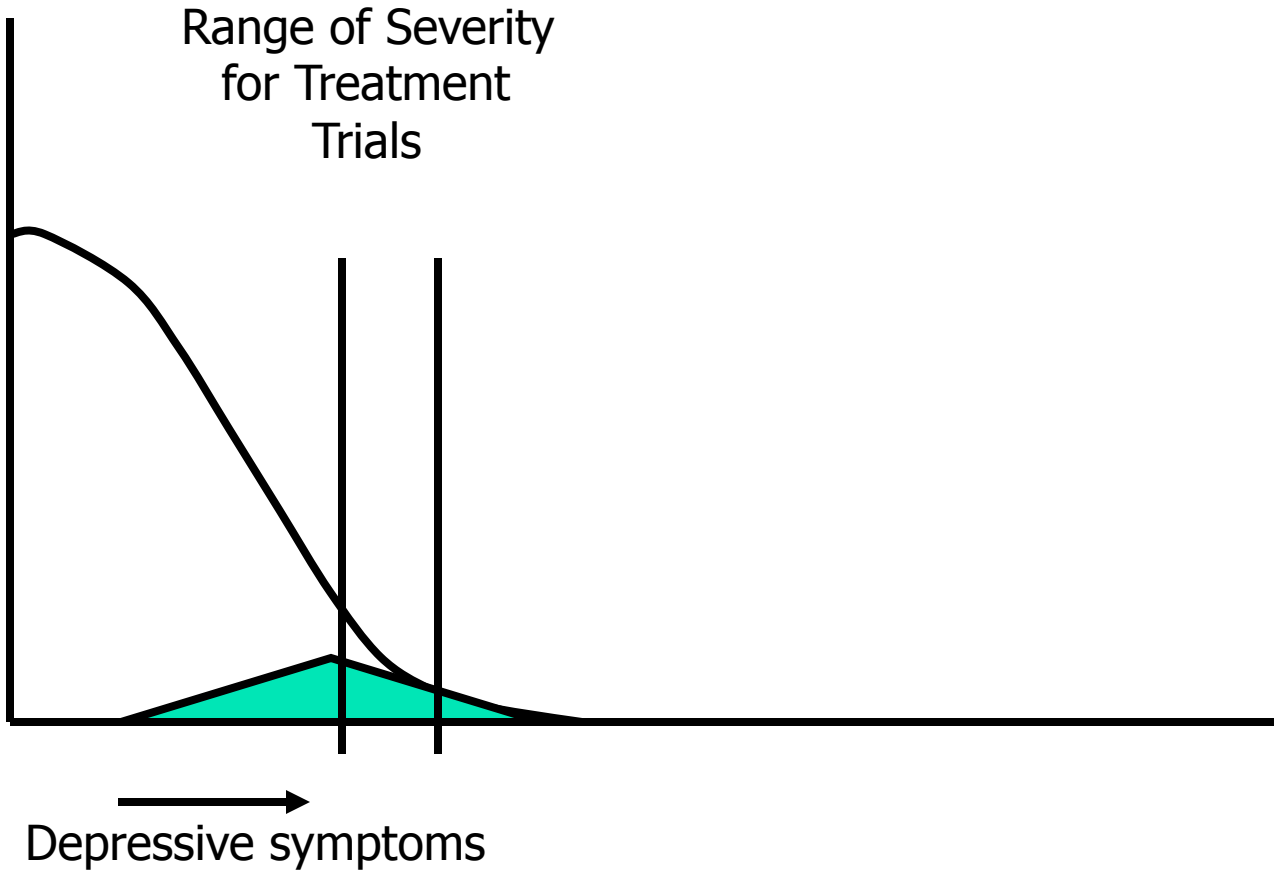

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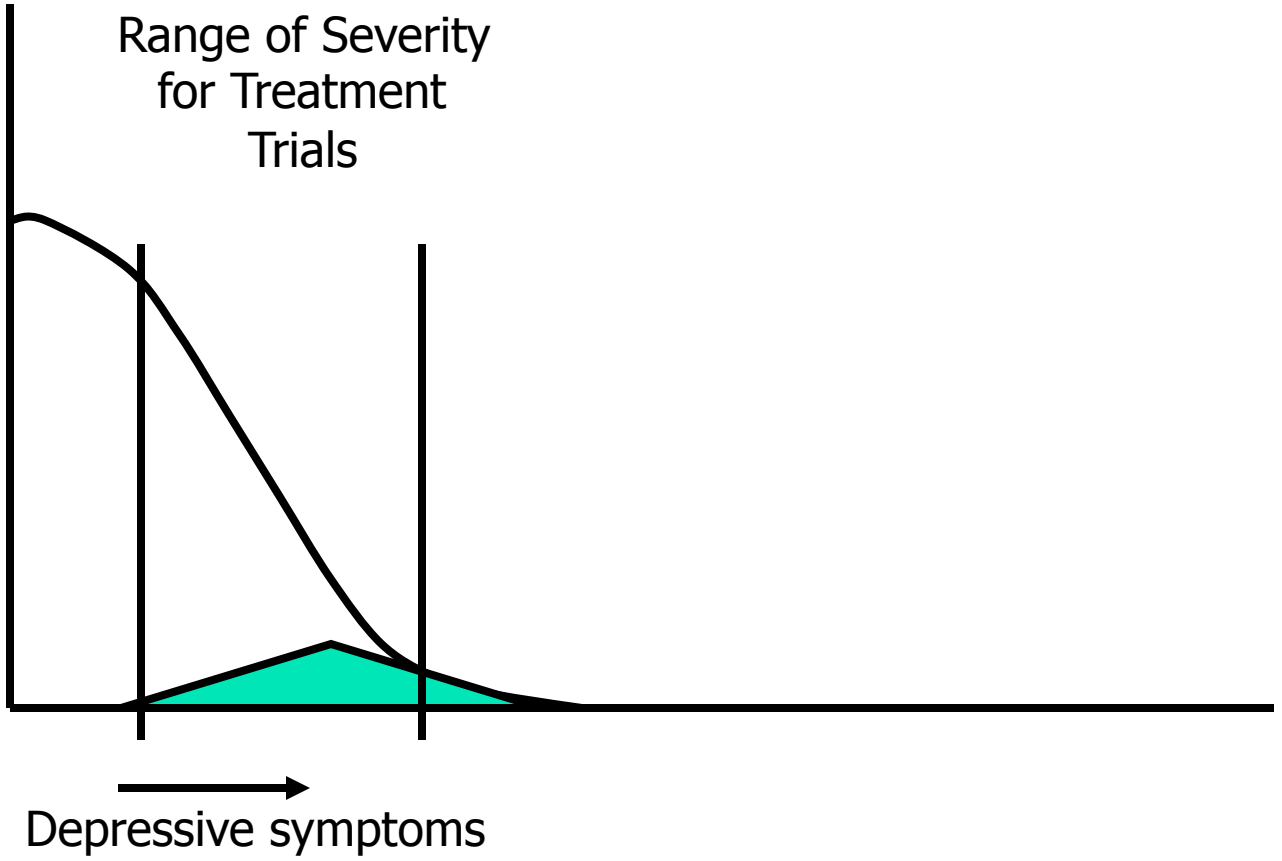
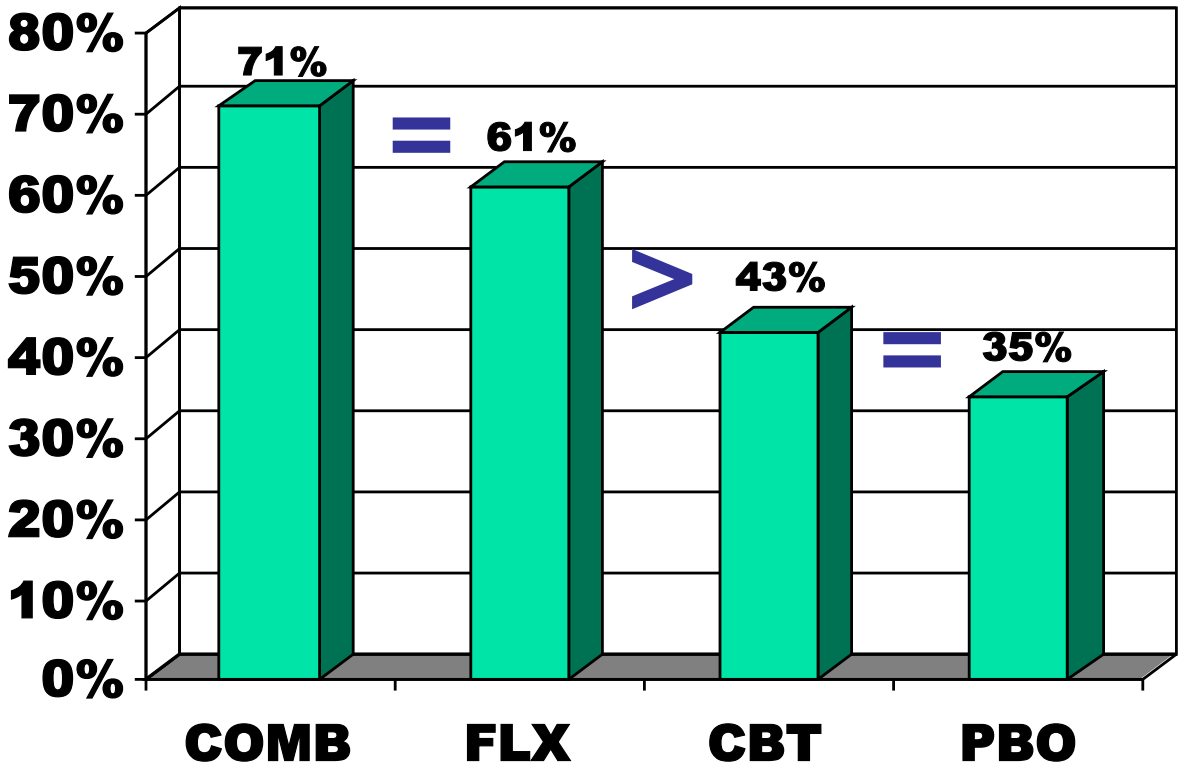


Treatment of Adolescents with Depression Study (TADS)

- JAMA August 18, 2004
- N=439 teens at 13 sites
- Ages 12-17 years
- Treatment Comparisons
  - Meds (fluoxetine)
  - Cognitive-behavioral therapy (CBT)
  - Combination of medication + CBT
  - Medical Management with placebo
- Treatment duration - 12 weeks

TADS Response Rates



Treatment for Adolescents with Depression Study (TADS)

- Longer term outcome
  - Week 18
    - COMB 85%
    - FXT 69%
    - CBT 65%
  - Week 36
    - COMB 86%
    - FXT 81%
    - CBT 81%

ADAPT Trial

- Goodyer et al. 2006
- N=249
- MDD to age 17 years
- Design
  - Brief intervention (n=164)
  - SSRI vs SSRI + CBT (n=208)
- Result wk 12
  - Brief intervention - 25%
  - SSRI 45%
  - SSRI+CBT 43%

ADAPT Longer Term Outcomes

- Total of approximately 80% responded
- Approx 20% no change or worse by endpoint
- Approx 10% persistently refractory
- Some new onset responders between12-28 weeks

ADAPT Suicidal Adverse Events

- No increased events in either arm
- 15-20% had no baseline risk
- 45% had no risk at wk 6
- 65% had no risk at wk 28

- No between group differences

Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) Trial

- 334 adolescents with major depression resistant to ≥ 8 weeks of SSRI treatment
- Randomized to one of four treatments:
  - Switch to alternate SSRI (Paroxetine then Citalopram)
  - Switch to alternate SSRI + CBT
  - Switch to venlafaxine
  - Switch to venlafaxine plus CBT
- 12 week trial
- Unique context

(Brent et al, JAMA 2008;299:901-913)

TORDIA Wk 12 Outcomes

- Results
  - Antidep only - 50% response
  - Combo – 60% response
  - Moderators
    - Baseline - Lower depression, anxiety
    - Week 12 – lower depression, suicidal ideation, anxiety and family problems

TORDIA Adherence

- Blood levels
  - Low and high did worse
  - Medium did better
- Pill Counts (>30% of pills remaining)
  - Adherent did better 63% vs. 47%
  - Some 51% had evidence of nonadherence

TORDIA: Week 24 Outcomes

- Week 12 Non-responders didn't do more
  - Less than half stayed on original med
  - < 1/3 did something more with medication
  - <¼ switched to another med
  - Very few switched to a non-SSRI/NSRI
  - No Li or T3 Augmentation
- Non-response may require a special intervention to motivate participants for next steps.

TORDIA: Week 24 Outcomes

- Responders tailored their treatment even further between week 12 and 24
  - Response breeds additional interest in treatment

Treatment of Adolescent Suicide Attempters

- Brent et al., 2009
- N= 124
- Open trial
- Results
  - Depression – 72% responded
  - Suicidal events – 19%
  - Suicide attempts – 12%
  - Median time to suicidal event – 44 days

Summary of Studies

- Depression outcomes
- Moderators
- Suicidal behavior
- Role of psychotherapy

Longer Term Outcomes

- TADS
  - All active treatment converge – 80-85%
- ADAPT
  - Estimated 80+% responded; 10% persistently refractory
- TASA
  - 72% response
- TORDIA
  - 60% remitted
- **The earlier the response the better**

Moderators

- Severity
- Duration
- Comorbidity
- Family Issues
- Drugs and alcohol
- Adherence

Suicide Summary

- Treatment reduces risk
- Lack of response increases risk
  - Slow depression response
  - Predictors of poor response
- Only TADS had a finding supporting a relationship to SSRI treatment

Psychotherapy

- No additional benefit, if depression severe
  - TADS and ADAPT
- Small additional benefit in resistant dep
- Protective for suicidal behavior
  - Yes – TADS
  - No – TORDIA, ADAPT

Suicidality

- Risk Difference for Efficacy
  - Industry-spnsrd MDD (many) - 11.0% = NNT of 10
  - Investigator initiated MDD (2) – 35% = NNT of 3
  - OCD - 19.8% = NNT of 5
  - Non-OCD anxiety disorders - 37.1% = NNT of 3
- Risk Difference for Suicidality
- Significant overall - .7% = NNH 0f 143
  - But not for individual disorders
    - MDD - 0.9%; NNH=100
    - OCD - 0.5%; NNH=200
    - non-OCD anxiety disorders - 0.7% NNH=140

Bridge et al., 2007

Summary

- We have come a long way in the past 25 years!!
- Diagnosis, diagnosis, diagnosis
- Pick treatments to match the condition
- Early response breeds good outcomes and engagement in treatment
- Suicidal behavior risks and outcomes are better understood

Bipolar Disorder

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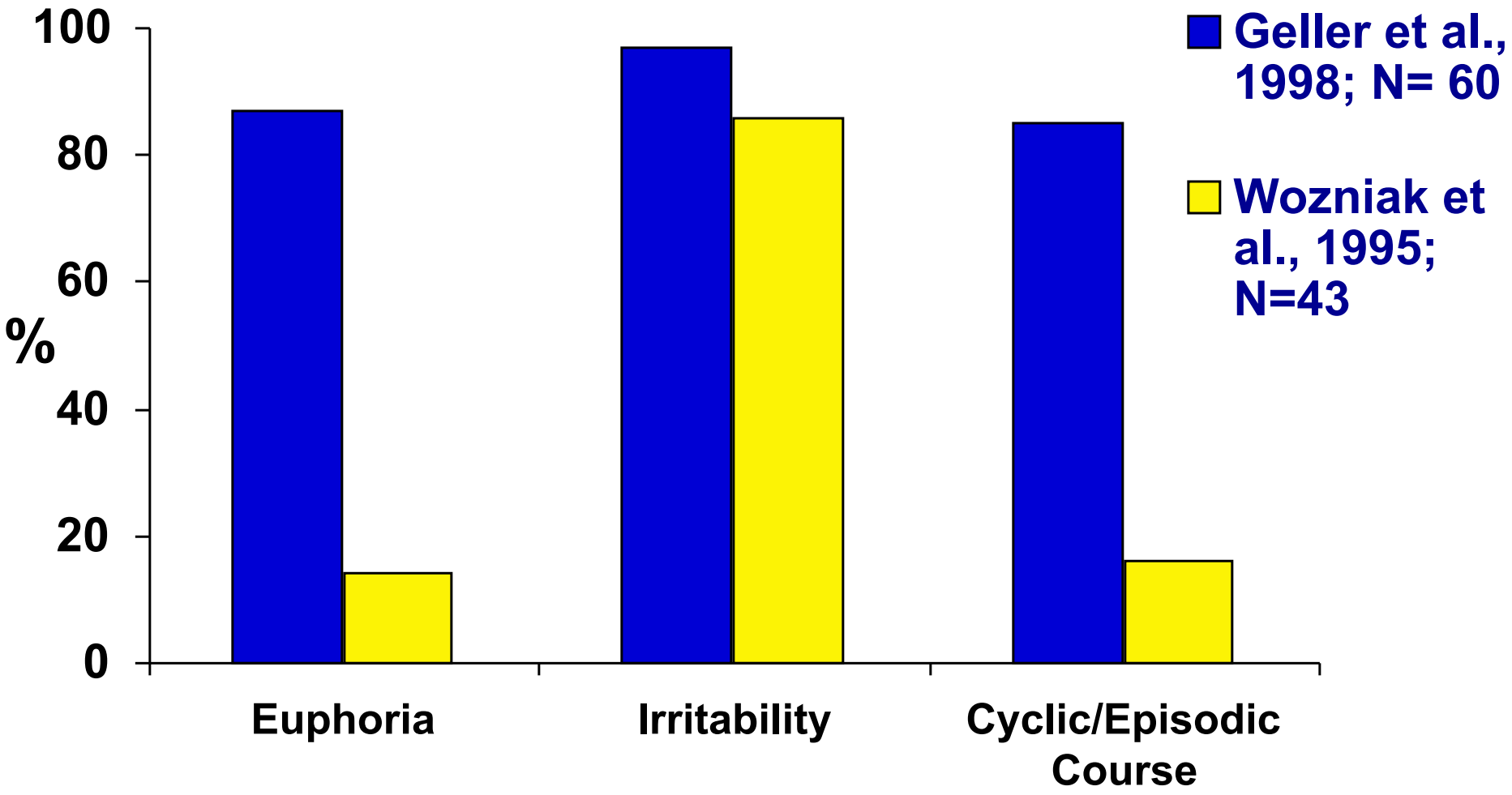
Diagnostic Issues in BPAD

Early-onset BPD



Children in a Community Study

(Cohen et al., 1993)

- Do episodic and chronic irritability differ in their associations with psychopathology?
- Longitudinal epidemiological study (N=776, T1-T3= 8 years)
- Age
  - Time 1 13.8 $\pm$ 2.5
  - Time 2 16.2 + 2.7
  - Time 3 22.1 + 2.7

Results

Episodic irritability (1) associated with:

Time 2: BPD, GAD, and phobia

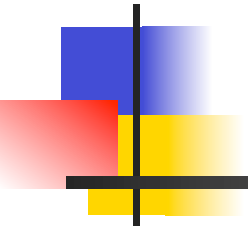
Time 3: BPD

Chronic irritability (1) associated with:

Time 2: ADHD, ODD

Time 3: MDD

Lessons from Pediatric Bipolar Disorder: Things may not be or become what they seem



Two studies by Lewinsohn et al.

- Study 1
  - 1507 youth ages 16-18 years
  - Prevalence of BP Disorder = 1% (10/1000)
  - Prevalence of *Subthreshold = 4.3% (43/1000)**
- Study 2 (follow up)
  - 893 young adults age 19-23 years
  - Prevalence of BP Disorder = 2.1%
  - Prevalence of *Subthreshold* = 5.3%

** Core symptoms + impairment*

Status at Follow-up

Bipolar Status

Study 1		Study 2	
BPD	→	Chronic (no remission)	35%
BPD	→	Recurrent episodes	27%
SUB	→	First full episode BPD	2%

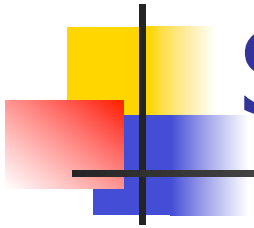
Status at Follow-up

Diagnostic Status

Study 1		Study 2	
SUB	➔	Anxiety Disorder	13%
	➔	Major Depression	41%

Bottom Line

- Episodic but not chronic irritability is a marker for bipolarity
- Chronic irritability is associated with depression
- Fear of precipitating a manic episode in the chronically irritable may result in under treatment of depression and anxiety.



So What is the Solution?

Manic Episode: Hallmark Symptoms

- Distinct period of abnormal elevated, expansive or irritable mood lasting > 7 days
- Three of the following if euphoric, four if irritable

  1) grandiosity

  2) decreased need for sleep

  3) distractibility

  4) pressured speech

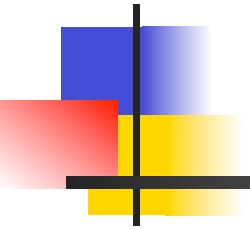
  5) flight of ideas/ racing thoughts

  6) increased goal-directed activity or psychomotor agitation

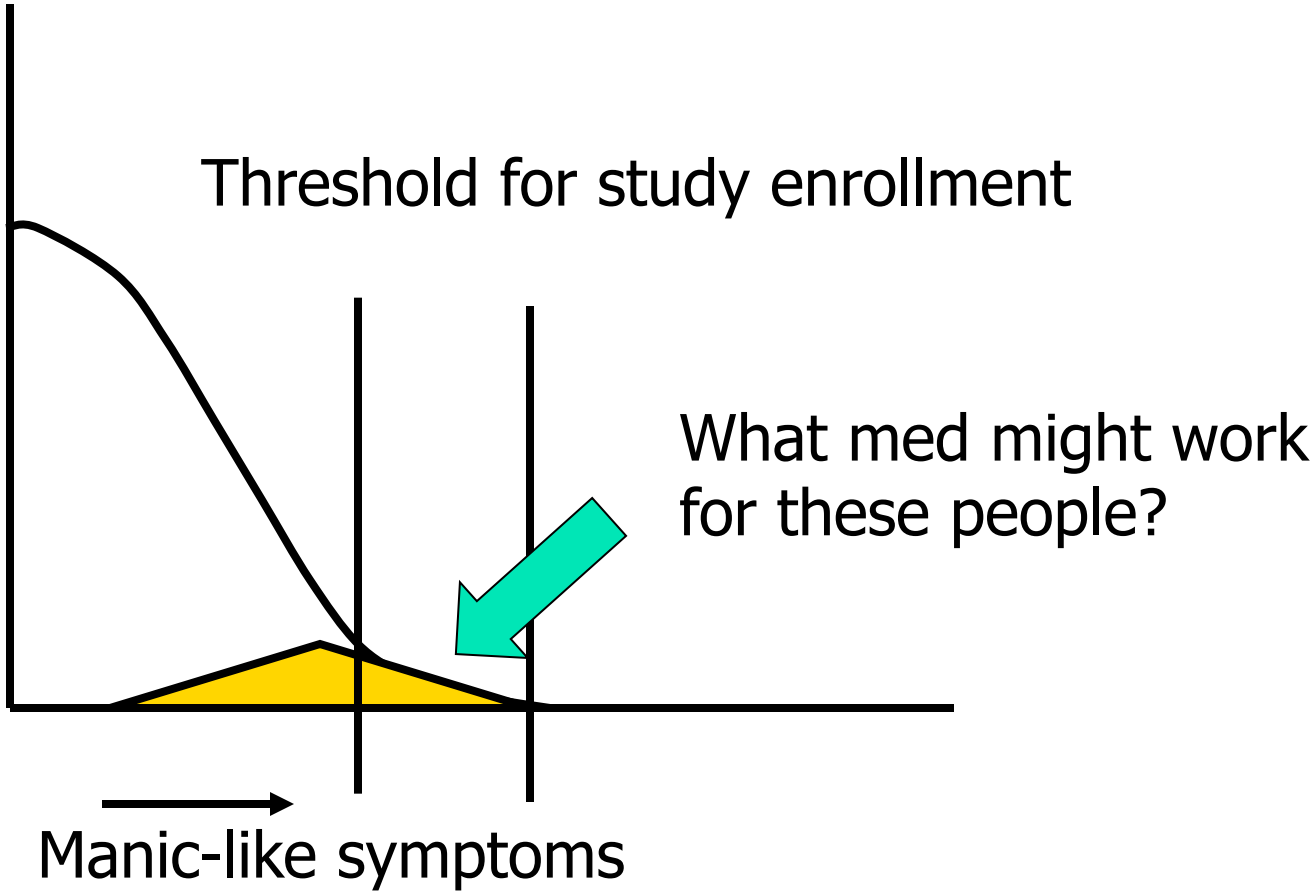
  7) increased involvement in pleasurable activities with potential for painful consequences

Leibenluft et al. 2003

Pharmacotherapy for Bipolar Disorder in Children and Adolescents



The Bipolar Disorder Treatment Dilemma



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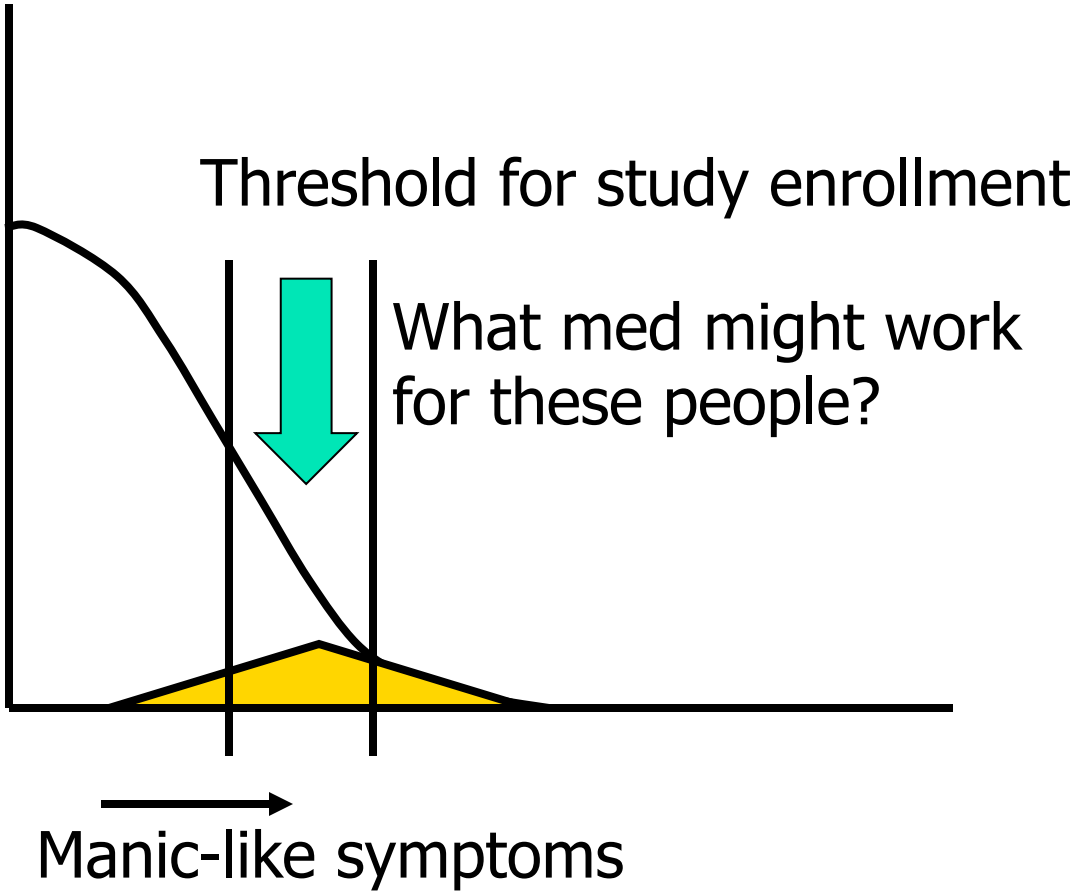

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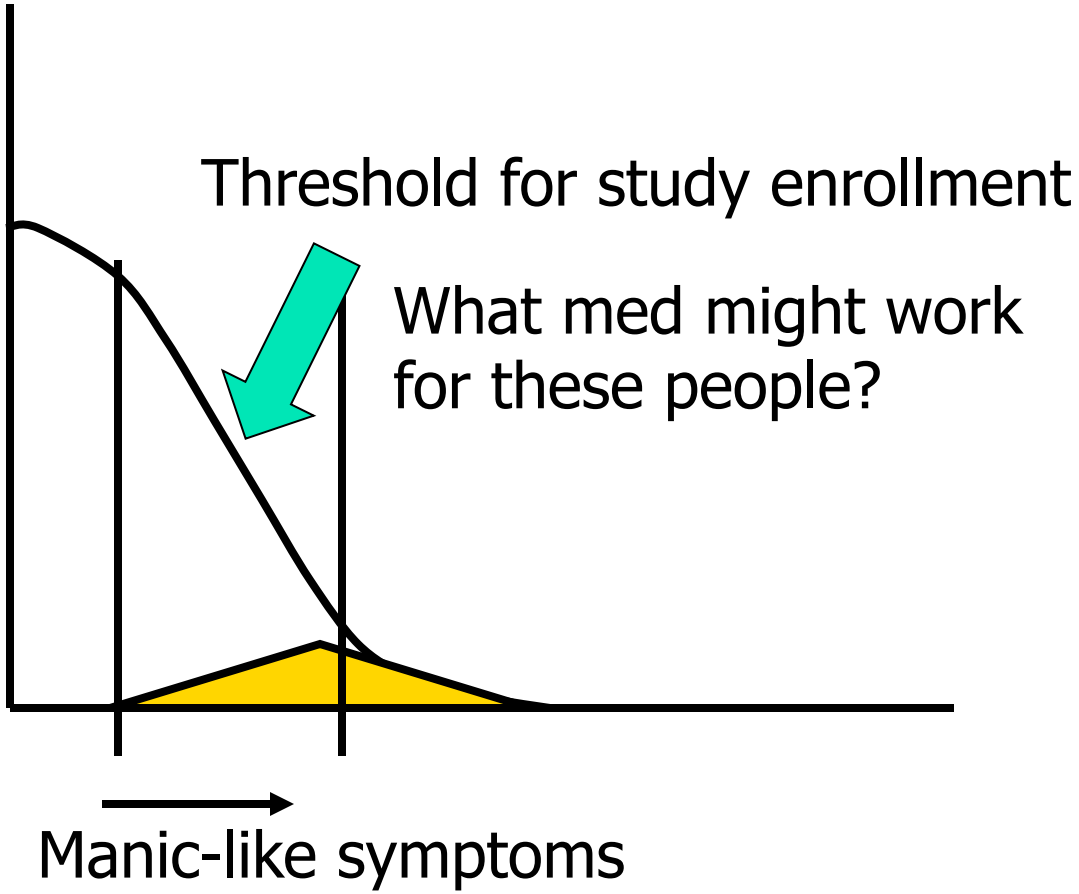

Negative Trials*

- Divalproex ER - Wagner et al, J Am Acad Child Adolesc Psychiatry 2009; 48(5):519-532
- Olanzapine - Wagner et al, Am J Psychiatry 2006;163:1-8;
- Topiramate - DelBello et al, J Am Acad Child Adolesc Psychiatry 2005;44:539-547

* Didn't differentiate from placebo

Positive Trials

- Olanzapine - Tohen et al, Am J Psychiatry. 2007 Oct; 164(10):1547-56
- Risperidone - Hass M, Bipolar Disorders 2009; 11:687-700
- Aripiprazole - Findling RL et al. J Clin Psychiatry. 2009 Oct;70(10):1441-51
- Quetiapine - DelBello et al, Presented at AACAP 2007 Annual Meeting, Boston MA
- Ziprasidone - DelBello et al, Presented at AACAP 2008 Annual Meeting, Chicago IL

Treatment of Early Age Mania Study

- Geller – Wash U
- Luby – Wash U
- Walkup – Hopkins and Weill Cornell
- Joshi and Robb – Children's National
- Axelson – Pittsburgh
- Wagner and Emslie - Texas

TEAM Summary

- Strengths
  - Large study of young BPAD I
  - Required elevated mood or euphoria
  - Well-characterized for mania and comorbid conditions
  - Multistep review of video tapes
  - Open design allowed for entry of more severely ill children
  - Opportunity to assess initial monotherapy as well as add-on and switch strategies
  - Maximized opportunity to respond to monotherapy
- Challenges/Limitations
  - Some ongoing issues with what prepubertal mania is
  - Blind ratings only at week 8; lack of blind ratings for dropouts and at intermediate treatment steps

TEAM Results

- Treatment naive (6-16 years)
  - Risperidone > Li
  - Risperidone > Divalproex
  - Li = Divalproex
- Non or partial responders to initial rx
  - Risperidone > Li
  - Risperidone > Divalproex
  - Li = Valproate

TEAM Adverse Events

- Wt gain with all medications
- Mild metabolic changes w Risp
- Thyroid changes with Li

Summary

- Much to be pleased about!!!!
- Efficacious treatment for high prevalence conditions – anxiety and depression
- A ways to go to understand bipolar disorder and what is best for whom
- Need to simplify and enhance psychological treatments…